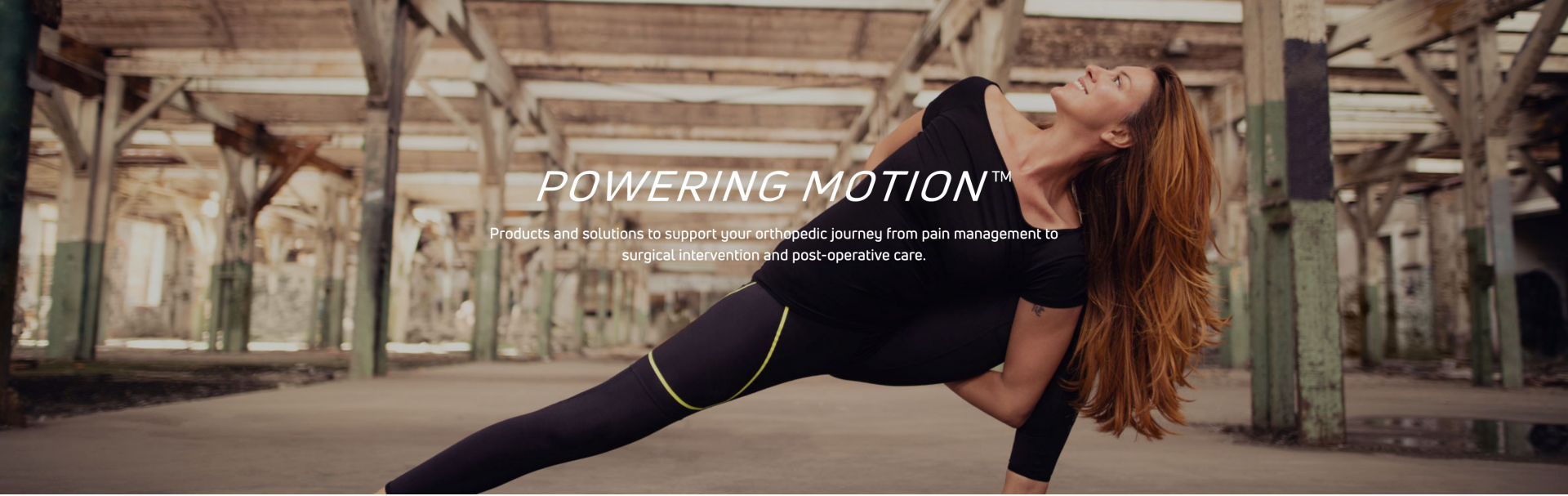

Presented by:
Kelly Yustat, Sr. Supervisor, Enovis Revenue Cycle Management
Willie Kaplan, Principal, Kronos Medical representing Enovis Utah

Supported by:
Tom Fortie, Territory Manager, Kronos Medical representing Enovis Utah
Steve Slack, National Director, Enovis Payer Development
Jim Garvin, Area Vice-President, Enovis

DJO, LLC is now…

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Creating Better Together™

DJO, LLC is a contracted provider with UT State Medicaid & the Managed Medicaid providers in Utah.
DJO, LLC is requesting a reimbursement rate on the fee schedule for E0747 & E0748 in Utah.

Electrical Bone Growth Stimulation (E0747, E0748)

About the Product	• FDA Class III medical devices, durable medical equipment
	• Insurance coverage: Spine E0748, Fracture E0748 – currently on Utah Medicaid fee schedule with no reimbursement rate
	  • Medicaid covered by 45/51 states, including all states neighboring Utah
	  • Medicare reimbursement rates for Utah: $5,207.87 & $5,174.14

Indications for Use & Prescribing Information	• **SPINE FUSION**: a non-invasive adjunct to lumbar spine fusion surgery to enhance bone consolidation, speed healing, and avoid repeat fusion[1,3] • **BONE FRACTURES**: a non-invasive therapy for use on “nonunion” fractures - fractures that are not healing successfully with standard orthopedic care[2]; frequently prescribed as an alternative to surgical intervention for patients that are poor surgical candidates (diabetics, sick patients)[3]
Patient Daily/Monthly Use	• 30 minutes per day[4] • 9 months (270 days)[4]

Science & Clinical Outcomes Data

How it Works – Technology/Science[5, 6, 7]	• Wolff's Law: bones in the body grow and remodel in response to the stress you place on them[5] • Piezoelectric Currents: the electrical current that occurs naturally within the body in response to mechanical stress (e.g. bone fracture/spine fusion)[6] • Given that piezoelectric currents can be measured and mimicked, electrical stimulation provides an external source of the natural frequencies emitted by the body under mechanical stress[7] • Non-invasive electrical stimulation mimics the body's natural electrical frequencies and thus aids in the formation of new bone (healing)[7]

Clinical Outcomes Summary – Published Data	• SPINE:
	  • Journal of Neurosurgery & John's Hopkins Level I, Meta-Analysis: significant improvement overall in rates of bone fusion with use of electrical stimulation in animal & human studies[8]
	  • Spine Journal: 21% increase in healing success rate observed when compared to patients that do not use stimulation[9]
	  • Journal of Orthopedic Surgery and techniques: 2.6 months earlier healing observed when compared to patients that do not use stimulation[10]
	• BONE FRACTURES:
	  • 35% reduction in chronic nonunion reported with use of stimulation vs. no stimulation[11]
	  • 75.6% heal rate reported in a study of bone fractures with an average age of 2+ years, 2.5 prior surgical procedures (fractures that would otherwise have not healed without further intervention)[12]

Economic Considerations & Benefits

Spine Fusion	• Agency for Healthcare Research & Quality (AHRQ, 2018) ranked spine fusion[13]:
	  • The MOST COSTLY principal OR procedure with stays totaling $14.1B in aggregate costs
	  • One of the five most costly principal OR procedures for both males and females in all age groups younger than 75 with aggregate costs ranging from $252M among males aged 0-17 yrs and $2.9B among females aged 45-64 yrs
	• Spine pseudoarthrosis (nonunion) has been reported in literature to be as high as 35% at 1 year post operatively[14]
	• Post-surgical readmission rates for spine fusion in low income communities were reported by AHRQ to be 7.5% which is 12% higher than high income communities with an additional average cost/stay of $13,400[15]

Bone Fracture Nonunion (unhealed fractures >90 days)	• AHRQ (2018) ranked three musculoskeletal procedures in the TOP FIVE most costly principal OR procedures[13]: • Fixation of leg and foot bones ($567M), bone fixation excluding extremities ($446M), and femur fixation ($443M) • An analysis of a large US claims database looking at long-bone fracture in 2012 reported the mean total care cost for non-union patients was more than double that of patients without a nonunion ($35,317 vs. $102,989, p = 0.0006)[16] • An economic outcomes real-world study of patients with fracture nonunion reported patients who used electrical bone growth stimulation had significantly lower predicted health care associated costs (>$2000) 1-year post index date when compared to patients that did not use stimulation[18] • A published cost analysis in England (2021) reported ~$1500 cost-savings with use of Enovis technology when compared with surgical intervention for individuals with nonunion tibial fractures[17]

In conclusion, electrical bone growth stimulation is proven to have both clinical & economic benefits, and over 30 years of clinical outcomes data showing potential for reduction in time to heal, reoperation, and chronic nonunion; all of which rank highest among healthcare utilization costs. We respectfully request your consideration to reimburse this highly effective technology for Utah's Medicaid patient population.

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2. P910066
3. Data on flle based on claims processed by Enovis.
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5. Rowe P, Koller A, Sharma S. Physiology, Bone Remodeling. [Updated 2023 Mar 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499863/Piezoelectric currents
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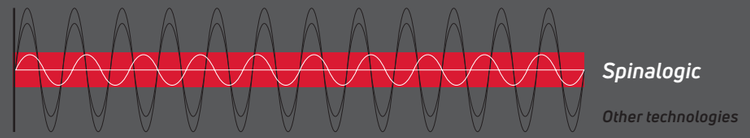
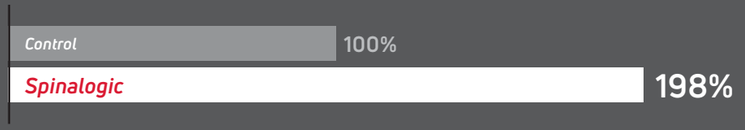
Early researchers determined that maximum bone cell response occurred within frequencies similar to those generated intrinsically by functional activity (0-150Hz). Further research showed 76.6Hz to be the more efficient frequency for bone healing—the frequency offered by the Spinalogic®.[1, 4]

Other bone growth technologies claim similar outcomes, but operate across a wider spectrum of frequencies. For example, imagine trying to catch water in a cup with a rotating lawn sprinkler. Ultimately, some of the water finds its way into the cup, but it is extremely inefficient. Spinalogic is like a steady stream of water focused exclusively on the cup.



FREQUENCY RANGES [2 7]

30 minutes of exposure to 76.6Hz increased the volume and number of IGF II molecules and receptors. An increase in both have been correlated to an amplified increase in bone cell proliferation.[3 4]



IGF-II S YNTHESIS[3]

SPINALOGIC® BONE GROWTH STIMULATION BRIEF PRESCRIBING INFORMATION

INDICATION: Spinalogic® is a portable, battery powered, microcontrolled, noninvasive bone growth stimulator indicated as an adjunct electromagnetic treatment to primary lumbar spinal fusion surgery for one or two levels.

CONTRAINDICATIONS: Demand-type pacemaker and implantable cardiovertor defibrillator (ICD) operation may be adversely affected by exposure to combined static and dynamic magnetic fields. Physicians should not prescribe Spinalogic® for patients with such devices. The safety and effectiveness of Spinalogic® in pregnant women have not been studied, and the effects of the device on the mother or the developing fetus are unknown. Thus, this device should not be used in pregnant women. If a woman becomes pregnant during treatment with Spinalogic®, treatment should be discontinued immediately.

PRECAUTIONS: The safety and effectiveness of the use of this device on individuals lacking skeletal maturity have not been established. The safety and effectiveness of this device in treating patients with the following conditions have not been established and therefore the safety and effectiveness of the device in these individuals are unknown: osseous or ligamentous spinal trauma, spondylitis, Paget's disease, severe osteoporosis, metastatic cancer, renal disease, and uncontrolled diabetes mellitus. Animal studies conducted to date do not suggest any long term adverse effects from use of this device. However, long term effects in humans are unknown. Compliance with the treatment schedule, timely battery change and proper care of the device are essential. The device will not perform properly and treatment may be unnecessarily prolonged if the patient fails to adhere to the care routine. This device should not be used if there are mental or physical conditions which preclude patient compliance with the physician and device instructions.

ADVERSE EFFECTS: No known significant adverse effects have resulted from the use of this device. Clinical studies, animal studies, and tissue culture experiments conducted with Spinalogic® Bone Growth Stimulator magnetic fields have not indicated any evidence of significant adverse effects.

CAUTION: Federal Law (USA) restricts these devices to sale by or on the order of a physician.

For full prescribing information, contact DJO, LLC.

1 McLeod, K.J., Rubin, C.T., The Effect of Low Frequency Electrical Fields on Osteogensis. J. Bone Joint Surg., 74A: 920-929, 1992.

2 Signal shown in red represents 76.6Hz frequency emitted by CMF Technology

3 Ryaby, J.T., et al., The Role of Insulin-like Growth Factor in Magnetic Field Regulation of Bone Formation, Bioelectrochemistry and Bioenergetics, 35: 87-91, 1994.

4 Fitzsimmons, R.J., Ryaby, J.T., Magee, F.P. and Baylink, D.J. (1995), IGF-II receptor number is increased in TE-85 osteosarcoma cells by combined magnetic fields. J Bone Miner Res, 10: 812-819.

5 Linovitz R, Pathria M, Bernhardt M, et al. Combined Magnetic Fields Accelerate and Increase Spine Fusion: A Double-Blind, Randomized, Placebo Controlled Study, Spine. 2002 July; 27(13):1383-1388.

6 Raiszadeh, Ramin, et al. "Effectiveness of combined magnetic field bone growth stimulation on lumbar spinal fusion outcomes: a single center retrospective analysis comparing combined magnetic field to no-stimulation." International Journal of Research in Orthopaedics 6.3 (2020): 1. A retrospective study that utilized radiographic fusion criteria, included data from 4 surgeons, consisted of a heterogenous patient population and had minimum 6 months follow up.

7 Based on actual frequencies of other technologies (1-50,000HZ, 60,000Hz)

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MKT00-10873 Rev B

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SMARTER TECHNOLOGY

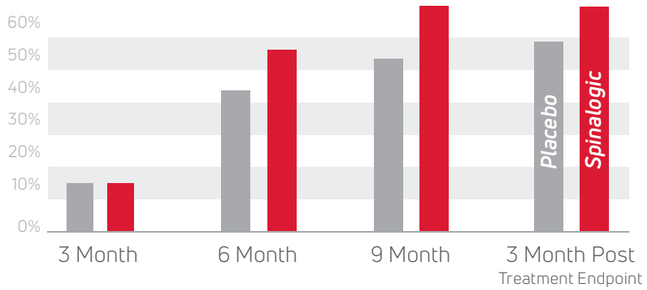
Spinalogic® helping to drive successful spine fusion[5]

Combined Magnetic Field Technology

PROCEED CONFIDENTLY

There are many variables that can prevent successful spinal fusion—from patient risk factors to post-op treatment compliance. Spinalogic® and its efficient bone growth technology has been shown to help increase the likelihood of lumbar fusions—giving your patients every advantage to support a full recovery.[5]

CLINICAL RESULTS OF SPINALOGIC [5]



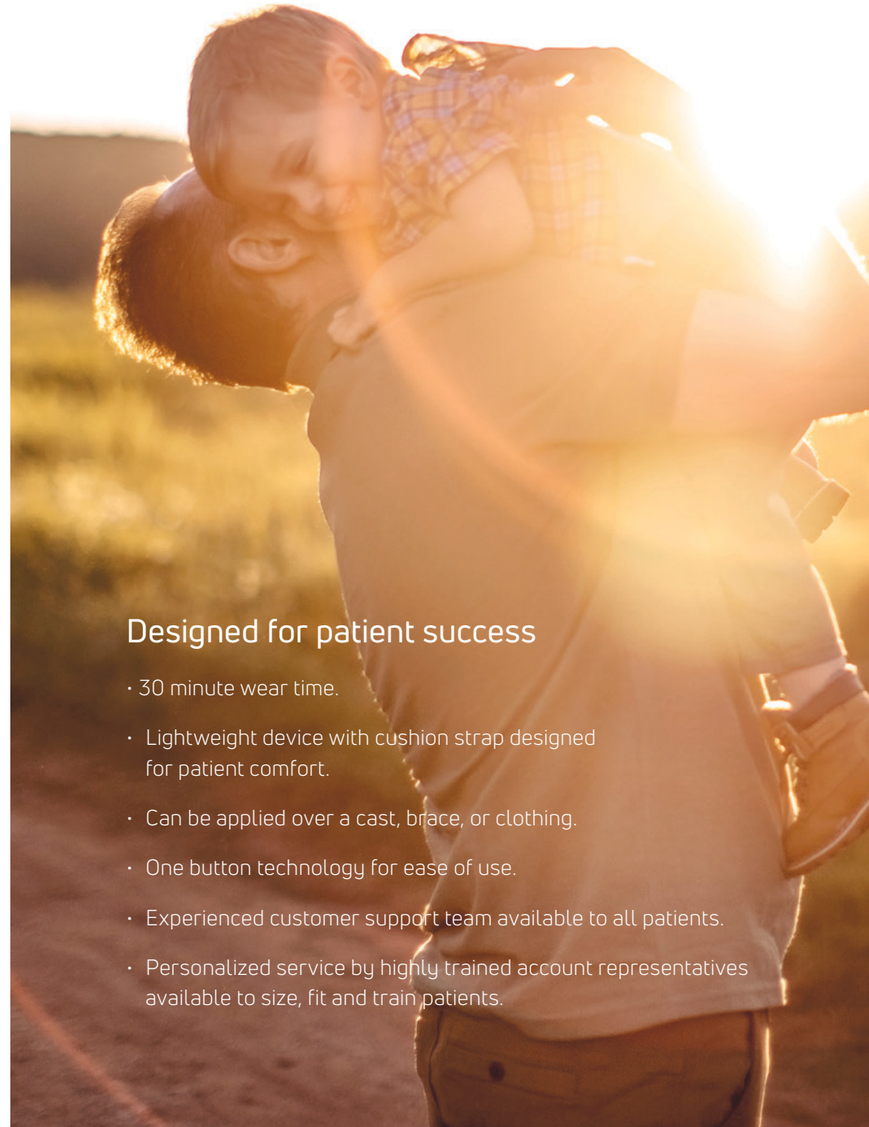
97%

Lumbar fusion success observed [6]

21%

Increase in lumbar fusions over placebo device [5]

djoglobal.com/Regeneration



Designed for patient success

- 30 minute wear time.
- Lightweight device with cushion strap designed for patient comfort.
- Can be applied over a cast, brace, or clothing.
- One button technology for ease of use.
- Experienced customer support team available to all patients.
- Personalized service by highly trained account representatives available to size, fit and train patients.

HOW DOES IT WORK?

The Spinalogic® bone growth stimulator is a nonsurgical treatment which your physician has prescribed to help the healing of your lumbar fusion. The stimulator uses a very low-strength Combined Magnetic Field (CMF™) to activate the body's natural healing process. The fusion may not mend properly. The bone growth stimulator provided by Enovis™ has proven to be successful in helping to treat lumbar fusions after surgery.[1]

You should not feel the CMF therapy during the 30 minute treatment. The Spinalogic unit is designed to be lightweight and adjustable for a comfortable fit. It is powered with a battery, which allows the unit to be portable. You can perform activities of daily living as recommended by your physician.

The unit will allow one 30 minute treatment per day, and you have the flexibility to receive your treatment at any time you choose. It is recommended to be worn approximately the same time each day.

Each device functions for 270 days. Your physician will closely monitor your progress, and will indicate when you no longer need to use Spinalogic. Normally, the device is used until your spine fusion has healed. To promote healing, it is very important that you wear Spinalogic daily, as prescribed. Your doctor may require that you bring your unit in on your follow-up visits to check your compliance with using the device.

1 Linovitz R, Pathria M, Bernhardt M, et al. Combined Magnetic Fields Accelerate and Increase Spine Fusion: A Double-Blind, Randomized, Placebo Controlled Study, Spine. 2002 July; 27(13):1383-1388.

CMF™ Spinalogic® BONE GROWTH STIMULATION BRIEF PRESCRIBING INFORMATION

INDICATION: CMF™ Spinalogic® is a portable, battery powered, microcontrolled, noninvasive bone growth stimulator indicated as an adjunct electromagnetic treatment to primary lumbar spinal fusion surgery for one or two levels.

CONTRAINDICATIONS: Use of this device is contraindicated in individuals having a synovial pseudarthrosis. Demand-type pacemaker or implantable cardiovertor defibrillator (ICD) operation may be adversely affected by exposure to magnetic fields. Physicians should not prescribe CMF™ Spinalogic® for applications that may place the treatment transducers in close proximity to the pacemaker. Further screening by the attending cardiologist is recommended (such as with an electrocardiogram). CMF™ Spinalogic® should not be used in the presence of external or internal fixation devices that are constructed from magnetic materials. (NOTE: Almost all fracture fixation devices implanted today are made from non-magnetic materials.)

WARNINGS: Do not use the CMF™ Spinalogic® near products that may have strong magnetic fields, such as audio speakers. The device may not work properly around these products.

- **WARNING!** This device is intended only for single patient use. Secondary use can cause serious injury, including infection.
- Care must be taken when operating this device adjacent to other equipment. Potential electromagnetic or other interference could occur with this or other equipment. Try to minimize this interference by increasing the separation between this device and nearby equipment, and by not using other equipment (i.e.cell phones, MRI, electro surgery, defibrillation, etc.) when you are using this device.
- The equipment should not be used adjacent to or stacked with other equipment and, if adjacent or stacked use is necessary, the equipment should be observed to verify normal operation in the configuration in which it will be used.
- Do not use the CMF™ Spinalogic® while smoking or near heat, fire or flammable gases because the device may be damaged.
- Do not use the CMF™ Spinalogic® if there are exposed wires or the device appears damaged.
- Do not modify or repair this device because you may damage it.
- Do not put the device or any of its parts in any liquid.
- Do not drop the device or bend the coils because this may damage it.
- Device is designed to comply with electromagnetic safety standards. However, there is no guarantee that interference will not occur in a particular installation. Harmful interference to other devices can be determined by turning this equipment on and off. Try to correct the interference using one or more of the following:
  - Reorient or relocate the receiving device
  - Increase the separation between the equipment
  - Contact Enovis™ Customer Care
- Some people, with very sensitive skin, may experience redness. Generally, this redness is totally harmless and usually disappears after 10 to 20 minutes. However, never start another treatment on the same area if the redness is still visible.
- If the performance of the device varies in any way from the described operation, call Customer Care.
- The use of other cables and accessories may affect EMC performance.
- This device and its accessories must be kept out of the reach of children, Pets, and Pests.
- Do not use device in contact with open wounds.
- Contamination by Patient could be sweat, expired gases, saliva, on the CMF™ Spinalogic®. Clean the applied part of the coil once a week using soap and a damp cloth.
- Do not use device while in bath or shower

CAUTIONS: DO NOT operate this unit in an environment where other devices are being used that intentionally radiates electromagnetic energy in an unshielded manner. Portable and mobile RF communications equipment can affect Medical Electrical Equipment.

ADVERSE EFFECTS: No known significant adverse effects have resulted from the use of this device. Clinical studies, animal studies, and tissue culture experiments conducted with the CMF™ Spinalogic®, which has the same treatment signal as the Spinalogic® and Spinalogic SC[1], have not indicated any evidence of significant adverse effects.

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MKT00-10875 Rev D

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30 MINUTES. ONCE DAILY.

Bone Growth Stimulation as an adjunct to spine fusion surgery.

Combined Magnetic Field Technology

WILL MY INSURANCE COVER IT?

Insurance policies are different depending on the plan you have. The Spinalogic® bone growth stimulator is covered by the majority of health plans including Medicare and workers compensation plans; specific coverage criteria must be met.

DOES Enovis™ PREAUTHORIZE THE DEVICE WITH MY INSURANCE COMPANY?

If pre-authorization is required, Enovis™ will verify your eligibility and benefit levels to obtain a pre-authorization from the payer of record.

WHAT HAPPENS IF MY INSURANCE COMPANY DENIES THE CLAIM?

In the event the insurance carrier denies coverage, the claim will be forwarded to our appeals processing department on your behalf. Depending on the outcome, you may contact us at 888-631-9587 option 3 to arrange payment options.

For more information, contact your local sales representative or call Enovis™ Customer Service at **(800) 263-6004**

enovis.com/regeneration

SPINALOGIC®

ARE THERE KNOWN SIDE EFFECTS OF CMF™?

There are no known side effects related to the use of this device. Thousands of patients have been prescribed Spinalogic® to help heal their spine fusions after surgery. Spinalogic may be safely used with non-magnetic fixation devices, such as screws, plates, or metal pins.

CAN I WEAR THE SPINALOGIC IF I AM PREGNANT?

The safety of the Spinalogic is not known if you are pregnant or nursing. Therefore, if you are pregnant or nursing, you should consult your doctor before using the Spinalogic.

CAN I USE THE SPINALOGIC IF I HAVE A PACEMAKER?

The operation of your pacemaker may be affected from exposure to the CMF Spinalogic magnetic fields. Please consult your prescribing physician to see if your device will be placed in close proximity to your pacemaker. Further screening by your attending cardiologist is also recommended such as with an electrocardiogram.

CAN I TRAVEL WITH MY SPINALOGIC?

Yes. Although not commonly required, in advance of your travel, you may request a letter from our Customer Service Support department or your Enovis™ Sales Representative that will explain what the device is and how it operates. You can also keep your user manual available to quickly and easily identify the device for any security personnel. We recommend administering your 30-minute treatment prior to going through security, this will ensure when moving through the x-ray and imaging devices, that the unit cannot be turned on for the magnetic fields to interfere.

HOW OFTEN WILL I NEED TO CHANGE THE BATTERY?

The Spinalogic will be delivered with a battery installed. A low battery symbol will appear on the LCD screen on your remote indicating when the batteries should be changed. There are additional 9V batteries included that should last for up to 9 months. If more are needed, please contact customer service.

WHAT DO I DO WITH THE DEVICE WHEN I AM DONE USING IT?

After your treatment is complete and your doctor says you no longer need to use your Spinalogic, you may dispose of the device yourself according to your local governing ordinances and recycling plans. You may also contact our Customer Support department for help with device disposal. The Spinalogic is not reusable. Each device is for single patient use only and cannot be re-sold or used on multiple patients.

89%

Success rate as high as 89.7% in treating nonunion fractures[2]

The risk of nonunion following a fracture is estimated to be up to 12% depending on the anatomical location of the fracture and patient-specific risk factors.[5]

At Enovis™, we love solving the difficult problems. It took time and commitment to offer doctors and patients dealing with a tough break another option than additional surgeries or living with the pain. High risk patients can have conditions that can inhibit proper bone unionization, causing nonunions. OL1000™ is a bone growth stimulator that is specifically designed to help heal nonunion fractures. [1]

Factors that increase risks of nonunion[4]

The American Academy of Orthopedic Surgeons notes the following factors that increase the risk of nonunion:

- Nicotine/Tobacco use
- Older age
- Severe anemia
- Diabetes
- Low Vitamin D levels
- Hypothyroidism
- Poor nutrition
- Certain medications
- Infection
- A complicated break that is open or compound

23%
Documented tibial nonunion fracture rate[3]

16%
Rate of open nonunion fractures with extensive soft tissue damage[5]

8%
Observed rates of femoral shaft nonunion with the use of IM nailing [3]

OL1000™ BONE GROWTH STIMULATION BRIEF PRESCRIBING INFORMATION

INDICATION: Noninvasive treatment of an established nonunion acquired secondary to trauma, excluding vertebrae and all flat bones. A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

CONTRAINDICATIONS: Demand-type pacemaker and implantable cardiovertor defibrillator (ICD) operation may be adversely affected by exposure to combined static and dynamic magnetic fields. Physicians should not prescribe OL1000 for patients with such devices. The safety and effectiveness of OL1000 in pregnant women have not been studied, and the effects of the device on the mother or the developing fetus are unknown. Thus, this device should not be used in pregnant women. If a woman becomes pregnant during treatment with OL1000, treatment should be discontinued immediately.

PRECAUTIONS: The safety and effectiveness of the use of this device on individuals lacking skeletal maturity have not been established. The safety and effectiveness of this device in treating patients with the following conditions have not been established and therefore the safety and effectiveness of the device in these individuals are unknown: osseous or ligamentous spinal trauma, spondylitis, Paget's disease, severe osteoporosis, metastatic cancer, renal disease, and uncontrolled diabetes mellitus. Animal studies conducted to date do not suggest any long term adverse effects from use of this device. However, long term effects in humans are unknown. Compliance with the treatment schedule, timely battery change and proper care of the device are essential. The device will not perform properly and treatment may be unnecessarily prolonged if the patient fails to adhere to the care routine. This device should not be used if there are mental or physical conditions which preclude patient compliance with the physician and device instructions.

ADVERSE EFFECTS: No known significant adverse effects have resulted from the use of this device. Clinical studies, animal studies, and tissue culture experiments conducted with OL1000 Bone Growth Stimulator magnetic fields have not indicated any evidence of significant adverse effects.

CAUTION: Federal Law (USA) restricts these devices to sale by or on the order of a physician.

For full prescribing information, contact Enovis™

1 Enovis™ CMF PMA: P910066/S005, May 1997
"Tough/Difficult fracture" defined per the following: Success rates obtained on fractures greater than 9 months post injury; Mean time since initial injury = 29.3 months; Mean number of prior surgeries = 2.5

2 Baumhauer Phillips M, Baumhauer J, Sprague S, Zoltan J. Use of Combined Magnetic Field Treatment for Fracture Nonunion. J Long Term Eff Med Implants. 2016;26(3):277-284. doi: 10.1615/JLongTermEffMedImplants.2016016818. PMID: 28134611.

3 Stewart SK. Fracture Non-Union: A Review of Clinical Challenges and Future Research Needs. Malays Orthop J. 2019;13(2):1-10. doi:10.5704/MOJ.1907.001

4 https://orthoinfo.aaos.org/en/diseases--conditions/nonunions

5 Thomas JD, Kehoe JL. Bone Nonunion. [Updated 2020 May 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554385/

6 McLeod, K.J., Rubin, C.T., The Effect of Low Frequency Electrical Fields on Osteogensis. J. Bone Joint Surg., 74A: 920-929, 1992.

7 Signal shown in red represents 76.6Hz frequency emitted by CMF Technology

8 Ryaby, J.T., et al., The Role of Insulin-like Growth Factor in Magnetic Field Regulation of Bone Formation, Bioelectrochemistry and Bioenergetics, 35: 87-91, 1994.

9 Fitzsimmons, R.J., Ryaby, J.T., Magee, F.P. and Baylink, D.J. (1995), IGF-II receptor number is increased in TE-85 osteosarcoma cells by combined magnetic fields. J Bone Miner Res, 10: 812-819.

10 Based on actual frequencies of other technologies (1-50,000HZ, 60,000Hz)

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MKT00-10872 Rev B

enovis™

TOUGH BREAK

Smarter electrical stimulation technology to help resolve nonunion fractures[1]

Combined Magnetic Field Technology

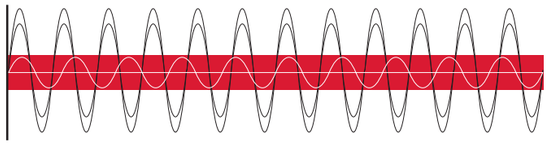
CHALLENGE ACCEPTED

OL1000™ was designed to help treat tough fractures[1]

OL1000™

Smarter Technology: Early researchers determined that maximum bone cell response occurred within frequencies similar to those generated intrinsically by functional activity (0-150Hz). Further research showed 76.6Hz to be the more efficient frequency for bone healing—the frequency offered by the OL1000™.[6,9]

Other electrical bone growth technologies claim similar outcomes, but operate across a wider spectrum of frequencies. For example, imagine trying to catch water in a cup with a rotating lawn sprinkler. Ultimately, some of the water finds its way into the cup, but it is extremely inefficient. OL1000™ is like a steady stream of water focused exclusively on the cup.



FREQUENCY RANGES [7,10]

30 minutes of exposure to 76.6Hz increased the volume and number of IGF II molecules and receptors. An increase in both have been correlated to an amplified increase in bone cell proliferation.[8,9]

Multiple sizes available to accommodate any anatomical variation

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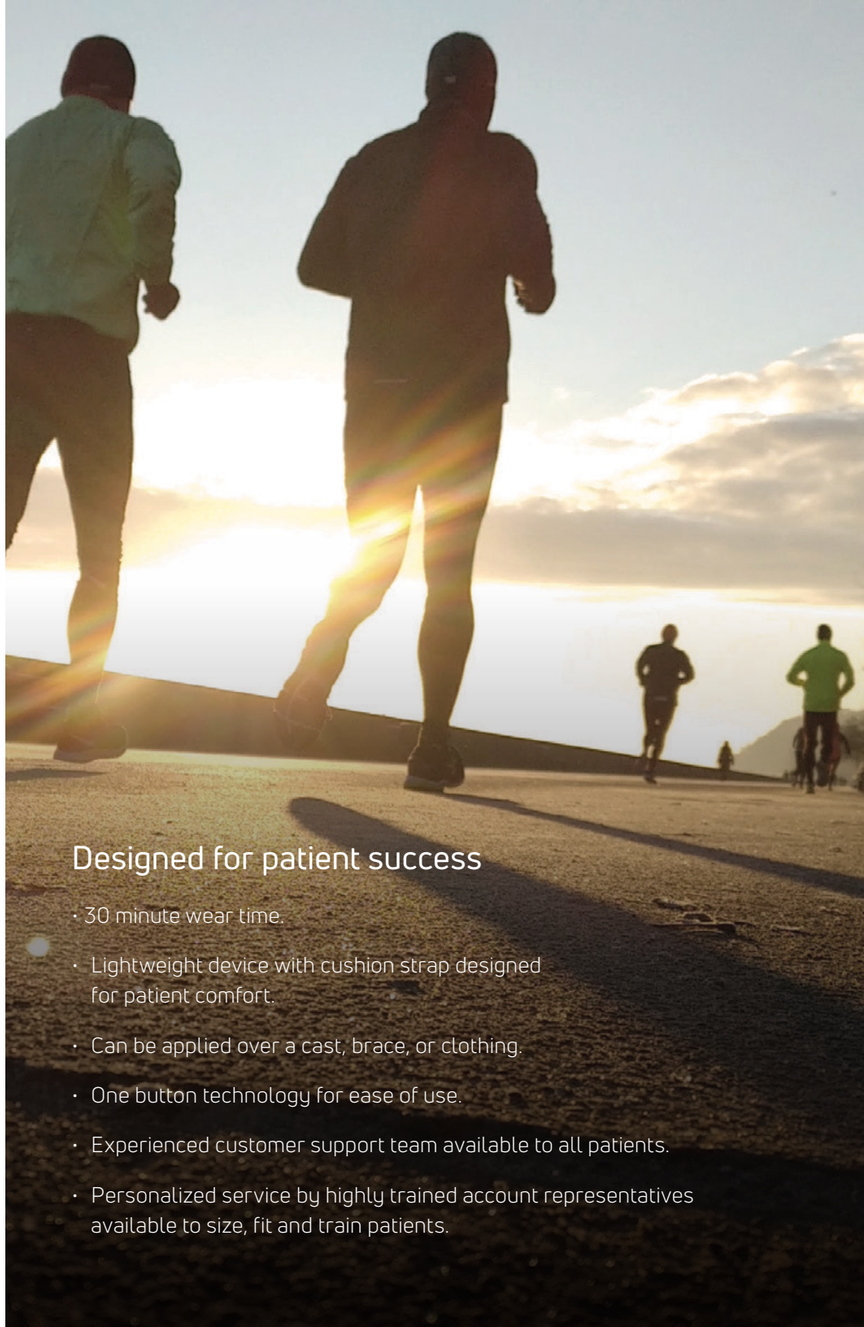

Designed for patient success

- 30 minute wear time.
- Lightweight device with cushion strap designed for patient comfort.
- Can be applied over a cast, brace, or clothing.
- One button technology for ease of use.
- Experienced customer support team available to all patients.
- Personalized service by highly trained account representatives available to size, fit and train patients.

HOW DOES IT WORK?

The OL1000™ bone growth stimulator is a nonsurgical treatment which your physician has prescribed to help the healing of your bone fracture. The stimulator uses a very low-strength Combined Magnetic Field (CMF™) to activate the body's natural healing process. In some patients, this healing process is impaired or absent. The fracture may not mend properly. The bone growth stimulator provided by Enovis™ has proven to be successful in helping to heal fractures that have progressed to nonunion.[1]

You should not feel the CMF therapy during the 30 minute treatment. The OL1000 unit is designed to be lightweight and adjustable for a comfortable fit. It is powered with a battery, which allows the unit to be portable. You can perform activities of daily living as recommended by your physician.

The unit will allow one 30 minute treatment per day, and you have the flexibility to receive your treatment at any time you choose. It is recommended to be worn approximately the same time each day.

Each device functions for 270 days. Your physician will closely monitor your progress, and will indicate when you no longer need to use OL1000. Normally, the device is used until your fracture has healed. To promote healing, it is very important that you wear OL1000 daily, as prescribed. Your doctor may require that you bring your unit in on your follow-up visits to check your compliance with using the device.

1 Enovis™ CMF PMA: P910066/S005, May 1997

CMF™ OL1000™ BONE GROWTH STIMULATION BRIEF PRESCRIBING INFORMATION

INDICATION: CMF™ OL1000™ is indicated for the Noninvasive treatment of an established nonunion acquired secondary to trauma, excluding vertebrae and all flat bones. A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

CONTRAINDICATIONS: Use of this device is contraindicated in individuals having a synovial pseudarthrosis. Demand-type pacemaker or implantable cardiovertor defibrillator (ICD) operation may be adversely affected by exposure to magnetic fields. Physicians should not prescribe CMF™ OL1000™ for applications that may place the treatment transducers in close proximity to the pacemaker. Further screening by the attending cardiologist is recommended (such as with an electrocardiogram). CMF™ OL1000™ should not be used in the presence of external or internal fixation devices that are constructed from magnetic materials. (NOTE: Almost all fracture fixation devices implanted today are made from non-magnetic materials.)

WARNINGS: Do not use the CMF™ OL1000™ near products that may have strong magnetic fields, such as audio speakers. The device may not work properly around these products.

- **WARNING!** This device is intended only for single patient use. Secondary use can cause serious injury, including infection.
- Care must be taken when operating this device adjacent to other equipment. Potential electromagnetic or other interference could occur with this or other equipment. Try to minimize this interference by increasing the separation between this device and nearby equipment, and by not using other equipment (i.e.cell phones, MRI, electro surgery, defibrillation, etc.) when you are using this device.
- The equipment should not be used adjacent to or stacked with other equipment and, if adjacent or stacked use is necessary, the equipment should be observed to verify normal operation in the configuration in which it will be used.
- Do not use the CMF™ OL1000™ while smoking or near heat, fire or flammable gases because the device may be damaged.
- Do not use the CMF™ OL1000™ if there are exposed wires or the device appears damaged.
- Do not modify or repair this device because you may damage it.
- Do not put the device or any of its parts in any liquid.
- Do not drop the device or bend the coils because this may damage it.
- Device is designed to comply with electromagnetic safety standards. However, there is no guarantee that interference will not occur in a particular installation. Harmful interference to other devices can be determined by turning this equipment on and off. Try to correct the interference using one or more of the following:
  - Reorient or relocate the receiving device
  - Increase the separation between the equipment
  - Contact Enovis™ Customer Care
- Some people, with very sensitive skin, may experience redness. Generally, this redness is totally harmless and usually disappears after 10 to 20 minutes. However, never start another treatment on the same area if the redness is still visible.
- If the performance of the device varies in any way from the described operation, call Customer Care.
- The use of other cables and accessories may affect EMC performance.
- This device and its accessories must be kept out of the reach of children, Pets, and Pests.
- Do not use device in contact with open wounds.
- Contamination by Patient could be sweat, expired gases, saliva, on the CMF™ OL1000™. Clean the applied part of the coil once a week using soap and a damp cloth.
- Do not use device while in bath or shower

CAUTIONS: DO NOT operate this unit in an environment where other devices are being used that intentionally radiates electromagnetic energy in an unshielded manner. Portable and mobile RF communications equipment can affect Medical Electrical Equipment.

ADVERSE EFFECTS: No known significant adverse effects have resulted from the use of this device. Clinical studies, animal studies, and tissue culture experiments conducted with the CMF™ OL1000™, which has the same treatment signal as the OL1000™ and OL1000™ SC[1], have not indicated any evidence of significant adverse effects.

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MKT00-10874 Rev C

enovis™

30 MINUTES. ONCE DAILY.

Bone Growth Stimulation for the treatment of fracture nonunion.

Combined Magnetic Field Technology

WILL MY INSURANCE COVER IT?

Insurance policies are different depending on the plan you have. The OL1000™ bone growth stimulator is covered by the majority of health plans including Medicare and workers compensation plans; specific coverage criteria must be met.

DOES Enovis™ PREAUTHORIZE THE DEVICE WITH MY INSURANCE COMPANY?

If pre-authorization is required, Enovis™ will verify your eligibility and benefit levels to obtain a pre-authorization from the payer of record.

WHAT HAPPENS IF MY INSURANCE COMPANY DENIES THE CLAIM?

In the event the insurance carrier denies coverage, the claim will be forwarded to our appeals processing department on your behalf. Depending upon the outcome, Enovis™ may contact you to arrange payment options.

For more information, contact your local sales representative or call Enovis™ Customer Service at **(800) 263-6004**

enovis.com/Regeneration

OL1000™

ARE THERE KNOWN SIDE EFFECTS OF CMF™?

There are no known side effects related to the use of this device. Thousands of patients have been prescribed OL1000™ to help heal their fracture nonunion. OL1000 may be safely used with non-magnetic fixation devices, such as screws, plates, or metal pins.

CAN I WEAR THE OL1000 IF I AM PREGNANT?

The safety of the OL1000 is not known if you are pregnant or nursing. Therefore, if you are pregnant or nursing, you should consult your doctor before using the OL1000.

CAN I USE THE OL1000 IF I HAVE A PACEMAKER?

The operation of your pacemaker may be affected from exposure to the CMF OL1000 or CMF OL1000 magnetic fields. Please consult your prescribing physician to see if your device will be placed in close proximity to your pacemaker. This would include fractures of the upper extremities (e.g. wrist, arm). Further screening by your attending cardiologist is also recommended such as with an electrocardiogram.

CAN I TRAVEL WITH MY OL1000?

Yes. Although not commonly required, in advance of your travel, you may request a letter from our Customer Service Support department or your Enovis™ Sales Representative that will explain what the device is and how it operates. You can also keep your user manual available to quickly and easily identify the device for any security personnel. We recommend administering your 30-minute treatment prior to going through security, this will ensure when moving through the x-ray and imaging devices, that the unit cannot be turned on for the magnetic fields to interfere.

HOW OFTEN WILL I NEED TO CHANGE THE BATTERY?

The OL1000 will be delivered with a battery installed. A low battery symbol will appear on the LCD screen on your remote indicating when the batteries should be changed. There are additional 9V batteries included that should last for up to 9 months. If more are needed, please contact customer service.

WHAT DO I DO WITH THE DEVICE WHEN I AM DONE USING IT?

After your treatment is complete and your doctor says you no longer need to use your OL1000, you may dispose of the device yourself according to your local governing ordinances and recycling plans. You may also contact our Customer Support department for help with device disposal. The OL1000 is not reusable. Each device is for single patient use only and cannot be re-sold or used on multiple patients.

JNS SPINE

LITERATURE REVIEW

J Neurosurg Spine 32:106–126, 2020

The effect of electrical stimulation therapies on spinal fusion: a cross-disciplinary systematic review and meta-analysis of the preclinical and clinical data

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OBJECTIVE Nonunion is a common complication of spinal fusion surgeries. Electrical stimulation technologies (ESTs)—namely, direct current stimulation (DCS), capacitive coupling stimulation (CCS), and inductive coupling stimulation (ICS)—have been suggested to improve fusion rates. However, the evidence to support their use is based solely on small trials. Here, the authors report the results of meta-analyses of the preclinical and clinical data from the literature to provide estimates of the overall effect of these therapies at large and in subgroups.

METHODS A systematic review of the English-language literature was performed using PubMed, Embase, and Web of Science databases. The query of these databases was designed to include all preclinical and clinical studies examining ESTs for spinal fusion. The primary endpoint was the fusion rate at the last follow-up. Meta-analyses were performed using a Freeman-Tukey double arcsine transformation followed by random-effects modeling.

RESULTS A total of 33 articles (17 preclinical, 16 clinical) were identified, of which 11 preclinical studies (257 animals) and 13 clinical studies (2144 patients) were included in the meta-analysis. Among preclinical studies, the mean fusion rates were higher among EST-treated animals (OR 4.79, $p < 0.001$). Clinical studies similarly showed ESTs to increase fusion rates (OR 2.26, $p < 0.001$). Of EST modalities, only DCS improved fusion rates in both preclinical (OR 5.64, $p < 0.001$) and clinical (OR 2.13, $p = 0.03$) populations; ICS improved fusion in clinical studies only (OR 2.45, $p = 0.014$). CCS was not effective at increasing fusion, although only one clinical study was identified. A subanalysis of the clinical studies found that ESTs increased fusion rates in the following populations: patients with difficult-to-fuse spines, those who smoke, and those who underwent multilevel fusions.

CONCLUSIONS The authors found that electrical stimulation devices may produce clinically significant increases in arthrodesis rates among patients undergoing spinal fusion. They also found that the pro-arthrodesis effects seen in preclinical studies are also found in clinical populations, suggesting that findings in animal studies are translatable. Additional research is needed to analyze the cost-effectiveness of these devices.

https://thejns.org/doi/abs/10.3171/2019.5.SPINE19465

KEYWORDS spinal fusion; electrical stimulation; pseudarthrosis; nonunion; surgical technique

Each year, approximately 400,000 Americans undergo a spinal fusion operation for the treatment of neck or back pain, radiculopathy, and/or myelopathy.[77] These operations account for the highest aggregate hospital cost of any surgical procedure in America, estimated at $13 billion in 2011.[89] Consequently, demonstration of clinical efficacy is paramount given increasing scrutiny of cost-effective care. Prior studies have suggested that clinical improvement following spinal fusion surgery is often in accordance with the radiological success of fusion, as defined by continuous bony union across the fusion site.[3,59,87] For this reason, emphasis has been placed on reducing the rates of nonunion, or pseudarthrosis, which are reported to be as high as 81% in some small series.[9,20,29,32,64,82] Interventions to accomplish this goal include preoperatively addressing risk factors (e.g., diabetes, chronic steroid use, and cigarette use)[51] and improving operative technique (e.g., adequate decortication, removal of interposing soft tissues, and sufficient bone graft).[12] Additionally, new technologies are continuously being investigated to enhance the fusion rate, including the use of recombinant human growth factors (e.g., bone morphogenetic pro-

ABBREVIATIONS CCS = capacitive coupling stimulation; DCS = direct current stimulation; ICS = inductive coupling stimulation; PEMF = pulsed electromagnetic field.

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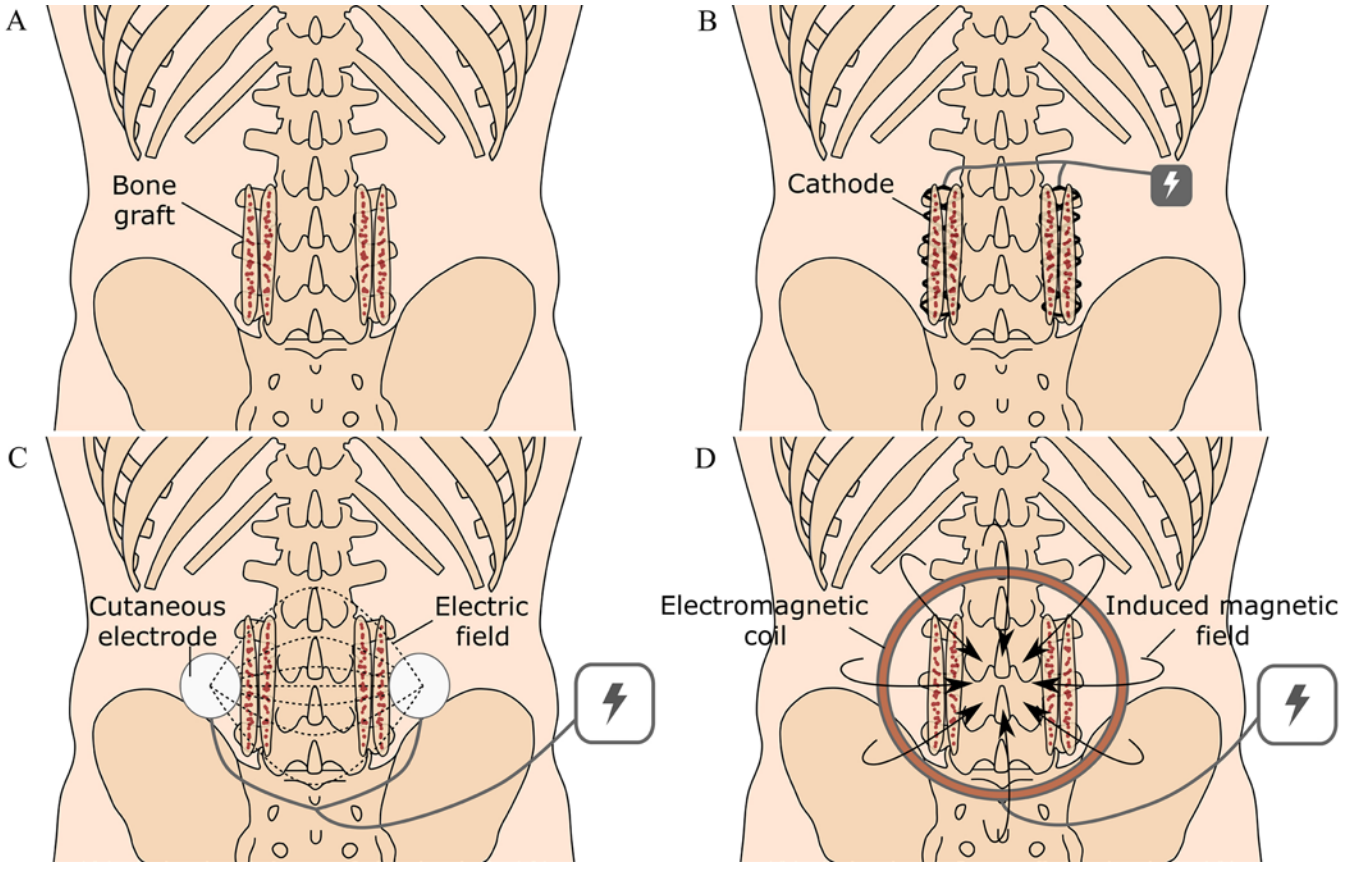

FIG. 1. Conceptual illustrations of the 3 types of electrical stimulation therapies used in spinal fusion. **A:** Posterolateral L3–5 inter–transverse process spinal fusion using bone graft, without electrical stimulation. **B–D:** Same procedure illustrating postoperative adjuvant therapy with DCS (B), CCS (C), or ICS (D), sometimes referred to as PEMF. In B, the electric generator is typically implanted subcutaneously. In C and D, the electric generators are externally located. Copyright Ethan Cottrill. Published with permission. Figure is available in color online only.

tein–2),[27,43,76] mesenchymal stem cells,[79] novel bone graft substitutes,[31,73] and dynamic instrumentation.[65,91] Postoperative electrical stimulation therapy has also been suggested as an attractive adjuvant therapy to enhance or accelerate bony union.[4,49]

The use of electrical stimulation therapy to induce fusion has been investigated clinically since at least 1812, when Birch successfully treated a patient with tibial nonunion using "[s]hocks of electric fluid . . . passed [daily] through the space between the ends of the bones both in direction of the length of the limb and that of its thickness."[50] A considerable body of evidence has since been generated to support the general concept that electrical energy influences living bone (as well as other biological tissues).[6] Notably, in the 1950s, Fukada and Yasuda described the piezoelectric effect of bone, defined as the generation of electric potentials in bone subjected to mechanical stresses. Using a custom galvanometer, they documented an electrical potential across the stressed bone, with the compressed bone being electronegative and the side under tension being electropositive.[44] Subsequently, Friedenberg and Brighton described the bioelectric potentials in bone, in which areas of bone undergoing active repair or growth are electronegative relative to areas at rest.[40,41] Therapeutic electrical stimulation devices are based on these biophysical principles—namely, that the external application of an electrical stimulus can stimulate bone growth through the induction of a negative bioelectric potential.

There are currently 3 types of electrical stimulation therapies used in spinal fusion: direct current stimulation (DCS), capacitive coupling stimulation (CCS), and inductive coupling stimulation (ICS), also known as pulsed electromagnetic field (PEMF) therapy (Fig. 1). Conventionally, DCS involves the implantation of cathodes (negative electrodes) into the prospective fusion mass and an anode (positive electrode) into the adjoining soft tissue. A continuous electrical current between 5 and 20 μA is then delivered to the fusion site via a subcutaneously implanted electric generator; the lifetime of this current is dictated by the charge size of the implanted battery, although most devices operate for a minimum of 6 months.[16,39,42] CCS, in contrast to DCS, is completely noninvasive and employs two capacitive plates placed on the skin on opposite sides of the fusion site. Alternating current is applied to the plates, setting up an oscillating electric field (1–100 mV/cm). As the battery pack is external, it may be replaced and recharged, allowing for continuous use (24 hours/day)

until there is radiological confirmation of fusion. Lastly, ICS employs electromagnetic coils placed over the fusion site. Alternating current applied to these coils induces an electromagnetic field covering the fusion site.[83] Compared to CCS, ICS devices require shorter daily usage, with only 30 minutes to 2 hours of continuous use required per day until radiological confirmation of fusion is established. The mechanisms of action and the relative technical advantages and disadvantages of these 3 therapies are summarized in Table 1.[1,7,8,10,11,16,17,19,21,23,30,37,66,85,88,92,93]

Although prior reviews have described the effects of electrical stimulation therapies on spinal fusion, none to date have systematically evaluated both the preclinical and clinical literature of all 3 available technologies. In this article, we perform such a review as a means of compiling the current evidence and validating the translatability of results achieved using these technologies in animal models. We set out to evaluate the available English-language literature for all 3 technologies, asking of each one: 1) To what degree does the technology improve bony fusion in animal models? 2) To what degree does the technology facilitate bony fusion in humans? Additionally, we report the results of a meta-analysis of the available clinical studies to provide an estimate of the overall effect at large and in subgroups.

Methods

Electronic Literature Search

A systematic review of the literature was performed using PubMed, Embase, and Web of Science databases. The search query was designed to obtain all of the available in vivo data (preclinical and clinical) examining the effect of electrical stimulation therapies on spinal fusion. The query for the PubMed database was as follows: (spinal fusion[mesh] OR spine fusion*[tw] OR spinal fusion*[tw] or spinal arthrodes*[tw] OR cervical fusion*[tw] OR lumbar fusion*[tw] OR lumbosacral fusion*[tw] OR interbody fusion*[tw] OR posterolateral fusion*[tw] OR cervical arthrodes*[tw] OR lumbar arthrodes*[tw] OR lumbosacral arthrodes*[tw] OR interbody arthrodes*[tw] OR posterolateral arthrodes*[tw]) AND (electric stimulation[mesh] OR electric stimulation therapy[mesh] OR electromagnetic fields[mesh] OR "electrical stimulation"[tw] OR "pulsed electromagnetic field*"[tw] OR "electromagnetic pulsing*"[tw] OR "magnetic fields*"[tw] OR "direct current stimulation*"[tw] OR "bone growth stimulation*"[tw] OR "electrical current*"[tw] OR "capacitively coupl*"[tw] OR "capacitive coupl*"[tw] OR "capacitive stimulat*"[tw] OR "inductively coupl*"[tw] OR "inductive coupl*"[tw] OR "inductive stimulat*"[tw]). This query was stylistically modified for use in the Embase and Web of Science databases. The bibliographies of the included studies were also queried for additional sources.

Included studies were preclinical or clinical peer-reviewed publications with full English-language text availability that evaluated the effects of one or more electrical stimulation therapies on spinal fusion. We defined electrical stimulation as the therapeutic use of electromagnetic energy (including direct current, capacitive coupling, and inductive coupling) with the expressed intent of promoting bony fusion after instrumented or noninstrumented spinal fusion. Studies were excluded if they examined a surgical model other than spinal fusion or if they mixed the results of spinal fusion with other surgical models. Eligible studies were screened against these criteria by two reviewers (E.C. and Z.P.); a third reviewer (A.K.A.) served as a referee, resolving any discrepancies between the first two reviewers. Critical Appraisal Checklists obtained from the Joanna Briggs Institute at The University of Adelaide were used to assess the quality of the clinical studies included in the meta-analysis.[71] Because preclinical studies are all classified as level of evidence V, a similar appraisal was not conducted for them. Additionally, the QUOROM (Quality of Reporting of Meta-analyses) checklist was used for this systematic review and meta-analysis.[70]

Data Extraction

Studies meeting the inclusion criteria were reviewed to extract details regarding the type of electrical stimulation, specifications of the electrical therapy, means of determining bony fusion, and the overall fusion rate at last follow-up. For preclinical studies, we also recorded details about the animal species and surgical model employed. For clinical studies, we included details on the patient demographics and the surgical approach.

For both preclinical and clinical studies, the primary endpoint was the fusion rate at last follow-up. In preclinical studies, we defined this as the total number of levels fused divided by the total number of levels included in the prospective fusion mass. In clinical studies, we defined the fusion rate as that derived from the proportion of patients experiencing a successful radiological fusion at the last follow-up visit. The definition and method of assessment of fusion were recorded for each study.

Statistical Analysis

Statistical meta-analyses were performed using R version 3.4.2 (The R Foundation for Statistical Computing). Separately for the preclinical and clinical studies, we generated mean fusion rates and odds ratios using the Freeman-Tukey double arcsine transformation, a previously established method for normalizing proportions with variance stabilization.[38] A random-effects meta-analysis was then employed to give a pooled estimate of the effect of electrical stimulation on fusion rates. We elected to forego a numbers-needed-to-treat analysis based on these results, as prior reports have demonstrated such estimates to be commonly misleading.[81] Using this methodology, we also performed subgroup analyses of the clinical data based on smoking status, surgical history (index vs revision procedure), use of interbody devices, region fused, type of bone graft, use of instrumentation, and number of levels fused. For all analyses, an α of 0.05 was used as the definition of statistical significance.

Results

Our search identified 340 unique articles, and 47 of these met our inclusion criteria (Fig. 2). After reviewing the full texts, we included 17 preclinical studies[15,22,25,28,

TABLE 1. Mechanisms of action and relative technical advantages and disadvantages of the 3 types of electrical stimulation therapies used in spinal fusion surgery

Electrical Stimulation Therapy	Mechanisms of Action	Relative Technical Advantages	Relative Technical Disadvantages
DCS	1) Electrochemical (faradic) reaction at the cathode lowers the oxygen tension & raises the pH, favoring net bone formation:[7,11,16] $2\,H_2O + 4\,e^- + O_2 = 4\,OH^-$. 2) Generation of H_2O_2 at the cathode stimulates macrophage secretion of vascular endothelial growth factor, a potent angiogenic agent involved in bone healing.[21] 3) Upregulation of osteoinductive growth factors (e.g., BMP-2, 6, & 7).[37]	1) Continuous, focal delivery of direct electric current for the life of the battery/device. 2) Virtually 100% pt compliance (requires no further action from the pt following implantation).	1) Risks associated w/ the surgical implantation of a medical device (e.g., infection, immune reaction, protrusion causing discomfort, device breakage or malfunction, release of toxic substances). 2) May require additional training by the surgeon for correct implantation. 3) May require an additional surgery for removing the electrical generator following successful fusion. 4) May be incompatible w/ MRI (contrast w/ CCS & ICS, which involve external, removable devices).
CCS	1) Direct activation of osteoblastic membrane-bound voltage-gated Ca channels leads to an increase in cytosolic Ca^{2+}, inducing downstream phospholipase-A_2– & calmodulin-mediated bone formation.[8,17,23,30,92] 2) Upregulation of osteoinductive growth factors (e.g., BMP-2, 4, 5, 6, & 7; & TGF-β1).[88,93]	1) Noninvasive & theoretically painless. 2) Relatively lightweight & discreet; wearable 24 hrs/day.	1) Requires active pt participation, w/ recommended usage of 24 hrs/day throughout the duration of therapy. 2) Possible device-related medical complications, including electric shock, burns, & immune reaction to the cutaneous electrodes (& undetermined carcinogenicity & mutagenicity).
ICS	1) Direct release of Ca^{2+} from intracellular stores, inducing downstream calmodulin-mediated bone formation.[17,23,92] 2) Modulation of osteoblastic PTH signaling at the plasma membrane, reducing inhibitory effects on collagen synthesis.[19,66] 3) Upregulation of osteoinductive growth factors (e.g., BMP-2 & 4; TGF-β1; & FGF-2).[1,10,85]	1) Noninvasive & theoretically painless. 2) Recommended usage is 30 mins to 2 hrs per day (compare to CCS).	1) Requires active pt participation throughout the duration of therapy. 2) Heavier & more obtrusive than CCS devices.

BMP = bone morphogenetic protein; Ca = calcium; FGF = fibroblast growth factor; pt = patient; PTH = parathyroid hormone; TGF = transforming growth factor.

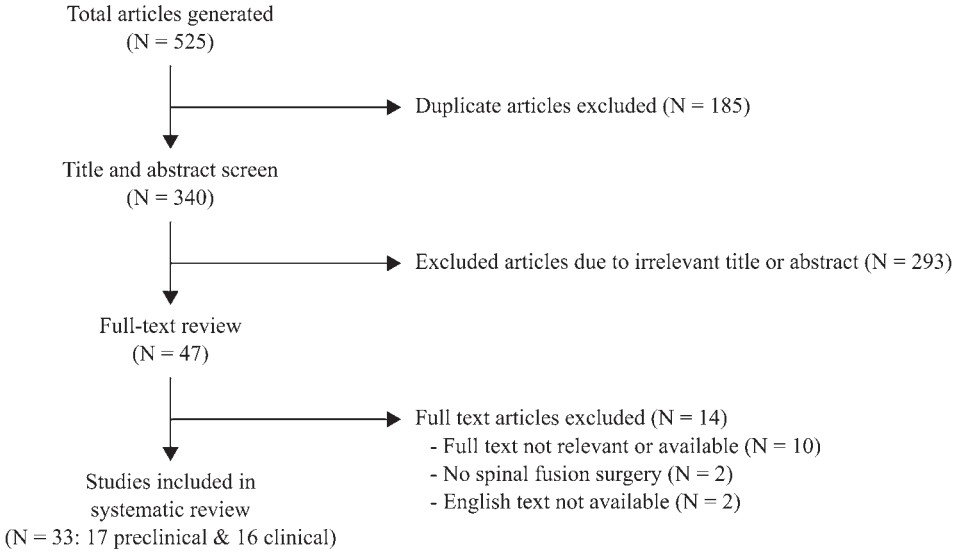

FIG. 2. Diagram of the consolidated standards of reporting trials for article selection.

[35–37,46,48,52,54–56,67,75,86,94] and 16 clinical studies.[5,14,26,34,47,53,57,60,63,68,69,72,74,78,84,90] Among the 14 excluded articles, the reasons for exclusion were lack of full-text availability (n = 10), surgical model other than spinal fusion (n = 2), and lack of an English-language translation (n = 2). Of these 33 articles, 11 preclinical (257 animals; 273 levels) and 13 clinical (2144 patients) studies were ultimately included in the meta-analysis. The clinical studies were deemed to have sufficient quality to be included in the meta-analysis (Critical Appraisal Checklists). The included articles are summarized in Tables 2 and 3, as well as in Supplemental Tables 1 and 2. Supplemental Fig. 1 plots these studies by year of publication, illustrating the dearth of recent studies.

Overall Effect of Electrical Stimulation Technologies on Spinal Fusion

In the preclinical literature, the mean fusion rates were higher among animals treated with electrical stimulation therapy (77.7%) than among controls (42.0%). Across all studies, the use of electrical stimulation produced a nearly fivefold increase in the odds of a successful fusion (OR 4.79 [95% CI 2.51–9.16], $p < 0.001$) (Table 4). In the clinical literature, electrical stimulation similarly was shown to produce higher rates of fusion versus controls in which no electrical stimulation therapy was administered (84.9% vs 73.4%, respectively), although the overall effect was smaller than in the preclinical literature (OR 2.26 [95% CI 1.48–3.44], $p < 0.001$) (Table 4). Figure 3A illustrates the random-effects meta-analysis of the fusion rates from all clinical studies.

Effect of DCS on Spinal Fusion

Eleven preclinical and 9 clinical studies investigating the effect of DCS on spinal fusion were identified, and 8 preclinical and 6 clinical studies were included in the meta-analysis.

Preclinical Data

The preclinical studies (Table 2) involved rat (n = 1), rabbit (n = 4), dog (n = 2), pig (n = 1), sheep (n = 1), goat (n = 1), and monkey (n = 1) spinal fusion models. All surgical models involved one-level fusions of the lumbar spine, with 3 using posterior facet joint fusion, 5 using posterolateral inter–transverse process fusion, and 3 using interbody fusion. Among these studies, 11 used autograft, 1 used allograft, and 1 used synthetic bone graft; 3 of the studies employed instrumentation in the fusion construct. All but one study used implantable electrodes in the fusion beds. The remaining study routed electrical current through pedicle screws and rods.[67]

The reported fusion rates ranged between 70% and 100% for the treatment group and between 0% and 73% for controls (Supplemental Fig. 2A). On meta-analysis, the mean fusion rate was found to be significantly higher in DCS-treated levels than in controls (OR 5.64 [95% CI 2.64–12.06], $p < 0.001$) (Table 4).

Clinical Data

Nine clinical studies examined the effects of DCS on spinal fusion: 8 studies in adult cohorts and 1 study in a pediatric cohort (Table 3). Four studies examined its use in patients with difficult-to-fuse spines using the following definitions: 1) age > 60 years;[5] 2) multiple prior spine surgeries, failed prior fusion, segmental instability, spinal stenosis, and/or spondylolisthesis;[60] 3) multilevel fusion, failed prior fusion, and/or grade II or worse spondylolisthesis;[84] and 4) age > 65 years, presence of rheumatoid arthritis, failed prior fusion, infection, and/or immunosuppression.[90] One study was restricted to index procedures, while 8 included both index or revision procedures. Only 1 study employed interbody fusion; the remaining 8 used solely posterior/posterolateral fusion. The spinal segments investigated were cervical in 1 study and lumbar/lumbosacral in 8. Six studies used autograft only, and

TABLE 2. Descriptive summaries of the identified preclinical studies (n = 17)

Authors & Year (LOE)*	Animal & Surgical Model	Study Groups		Postop Definition of Fusion Outcome	Fusion Rate
DCS					
Nerubay et al., 1986 (V)	Pig (n = 20): L5–6 posterior facet joint fusion w/ iliac crest autograft	A. DCS via Osteostim model S11; constant 20-μA current (n = 9)		NA	Fusion rate not reported; however, a "significant increase of osteoblastic activity with bone formation" favoring the experimental group was observed at 2 mos postop ($p = 0.037$)
		B. Control; implantation of the Osteostim device, w/o an active power source (n = 11)			
Kahanovitz & Arnoczky, 1990 (V)	Dog (n = 4): L1–2 & L4–5 posterior facet joint fusion w/ local autograft	A. DCS; 10 μA (n = 2; each animal had either L1–2 or L4–5 electrically stimulated)		Histological & radiographic evidence of complete bony fusion across the graft & both facets (defined as 1 level) at 12 wks postop	A. 100% (4/4 levels)
		B. Control; implantation of electrodes, w/o an active power source (n = 2; each animal had L1–2 or L4–5 electrically stimulated)			B. 0% (0/4 levels)
Bozic et al., 1999 (V)	Rabbit (n = 53): L3–4 posterolateral inter–transverse process fusion w/ bone graft	A. Coralline HA w/ autologous bone marrow aspirate & an implanted DCS device (SpF-100, Electro-Biology, Inc.) (100 μA) (n = 15)		Blind manual palpation of fusion segment (graded as fused or not) at 8 wks	A. 87% (13/15 levels) (significantly higher in group A than C)
		B. Coralline HA w/ autologous bone marrow aspirate & an implanted DCS device (SpF-XLIIb, Electro-Biology, Inc.) (40 μA) (n = 12)			B. 50% (6/12 levels)
		C. Coralline HA w/ autologous bone marrow aspirate (n = 12)			C. 25% (3/12 levels)
Toth et al., 2000 (V)	Sheep (n = 22): L4–5 discectomy & interbody fusion w/ Ti cage (Bagby & Kuslich) & iliac crest autograft	Ti interbody cage (Bagby & Kuslich) filled w/ iliac crest autograft & an implanted DCS device for 4 mos	A. 100 μA (SpF-100, Electro-Biology, Inc.) (n = 8)	Histological evidence of fusion defined as a continuous bony bridge from superior to inferior vertebrae at 4 mos	A. 100% (8/8 levels)
			B. 40 μA (SpF-XLII, Electro-Biology, Inc.) (n = 7)		B. 71% (5/7 levels)
			C. Control; 0 μA (n = 7)		C. 29% (2/7 levels); each group statistically different (Fisher's exact test, $p < 0.009$)
Dejardin et al., 2001 (V)	Dog (n = 5): L1–2 & L4–5 facet joint fusion w/ local autograft	Postop constant DCS for 12 wks	A. 10 μA/cm (n = 1.5 animals; 3 levels)	Histological & radiographic evidence of complete bony fusion across the graft & both facets (defined as 1 level) at 12 wks	A. 100% (3/3 levels)
			B. 4 μA/cm (n = 2 animals; 4 levels)		B. 100% (4/4 levels)
			C. 0.83 μA/cm (n = 1.5 animals; 3 levels)		C. 100% (3/3 levels)
France et al., 2001 (V)	Rabbit (n = 34): L5–6 posterolateral inter–transverse process fusion w/ iliac crest autograft	A. Postop local DCS (60 μA) for 5 wks (n = 12)		NA	Fusion rate not reported; however, via manual palpation scores & biomechanical testing, there was no statistically significant difference btwn the 3 groups
		B. Postop local DCS (20 μA) for 5 wks (n = 8)			
		C. Control; implantation of stimulator but no current (0 μA) (n = 14)			

CONTINUED ON PAGE 112 »

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TABLE 2. Descriptive summaries of the identified preclinical studies (n = 17)

Authors & Year (LOE)*	Animal & Surgical Model	Study Groups	Postop Definition of Fusion Outcome	Fusion Rate
DCS (*cont'd*)				
Cook et al., 2004 (V)	Nonhuman primate (n = 22): L5–6 anterior lumbar interbody fusion w/ iliac crest autograft & either a femoral allograft ring or Ti alloy fusion cage	A. Ti alloy cage w/ autograft & postop local DCS (SpF, Electro-Biology, Inc.) (19.6 μA/cm^2) for 26 wks (n = 4)	CT evidence of fusion defined as "bridging callus with trabeculations" at 26 wks	A. 100% (4/4 levels)
		B. Ti alloy cage w/ autograft & postop local DCS (SpF, Electro-Biology, Inc.) (5.4 μA/cm^2) for 26 wks (n = 7)		B. 86% (6/7 levels)
		C. Ti alloy cage w/ autograft alone (7)		C. 71% (5/7 levels)
		D. Femoral ring allograft w/ autograft (n = 4)		D. 75% (3/4 levels) (no statistical significance btwn groups)
France et al., 2006 (V)	Rabbit (n = 25) (nicotine & control models): L5–6 posterolateral inter–transverse process fusion w/ iliac crest autograft	A. Postop local DCS (SpF-100, Electro-Biology, Inc.) (100 μA) & continuous dose of nicotine via transdermal patch (10.5 mg) for 5 wks (n = 9)	Evidence of fusion by manual palpation, graded 3 separate times at 5 wks postop; fusion rate was calculated as the ratio of fused segments to total segments tested × 100	A. 85.3% ± 12.7% (approximately 7/9 levels) (significantly greater than that of group C)
		B. Postop continuous dose of nicotine via transdermal patch (10.5 mg) for 5 wks (n = 8)		B. 66.7% ± 7.2% (approximately 5/8 levels) (significantly greater than that of group C)
		C. Control; neither nicotine nor stimulator (n = 8)		C. 37.5% ± 12.5% (approximately 3/8 levels)
Fredericks et al., 2007 (V)	Rabbit (n = 5): L4–5 posterolateral inter–transverse process fusion w/ iliac crest autograft	A. Postop local DCS (SpF-100, Electro-Biology, Inc.) (100 μA) for 28 days (n = 2)	Radiographic evidence of bilat bridging fusion at 4 wks	A. 100% (2/2 levels)
		B. Control; no electrical stimulation (n = 3)		B. 33% (1/3 levels)
MacEwan et al., 2016 (V)	Goat (n = 2): L4–5 interbody fusion w/ local autograft & instrumentation permitting DCS (anodized Ti rods & pedicle screws)	A. Constant DCS (Varta Microbattery, Inc.) (40 μA) routed directly through the Ti rods & pedicle screws (novel "osteogenic spinal instrumentation") (n = 1)	Micro-CT evidence of fusion, defined as solid bridging of the vertebral bodies at 3 mos	A. 100% (1/1 level)
		B. Control; same system w/o DCS (n = 1)		B. 0% (0/1 level)
Cho et al., 2019 (V)	Rat (n = 60); L4–5 posterolateral inter–transverse process fusion w/ tubular nickel-Ti (nitinol) mesh containers filled w/ iliac crest autograft	A. Nitinol container filled w/ autograft & constant DCS (Cybermedic, Inc.) (100 μA) for 8 wks (n = 20)	Evidence of fusion by manual palpation & micro-CT, defined as no intersegmental motion & continuous bridging bone at 8 wks	A. 100% (20/20 levels)
		B. Nitinol container filled w/ autograft & pulsed DCS (Cybermedic, Inc.) (100 μA, 100 Hz, 200 μsec) for 8 weeks (n = 20)		B. 100% (20/20 levels)
		C. Control: nitinol container filled w/ autograft alone (n = 20)		C. 70% (14/20 levels) (significantly less than A & B; $p < 0.01$)
ICS				
Kahanovitz et al., 1984 (V)	Dog (n = 2): L2–4 posterior lumbar fusion w/ local autograft & instrumentation	A. Postop local ICS (positive pulse: 200 μsec @ 1.1 mV/cm; negative pulse: 200 μsec @ 9.6 mV/cm; repeated for 5 msec @ 12 Hz); 12 hrs of stimulation/day (n = 1)	NA	Fusion rate not reported; however, radiographically & histologically "no demonstrable objective differences" btwn the groups observed at 15 wks postop
		B. Control: no postop ICS (n = 1)		

CONTINUED ON PAGE 113 »

» CONTINUED FROM PAGE 112

TABLE 2. Descriptive summaries of the identified preclinical studies (n = 17)

Authors & Year (LOE)*	Animal & Surgical Model	Study Groups		Postop Definition of Fusion Outcome	Fusion Rate
ICS (*cont'd*)					
Guizzardi et al., 1994 (V)	Rat (n = 6): L4–6 posterolateral inter–transverse process fusion w/ local autograft	A. Postop ICS (via coils fixed to the outside of the animals' cages); mean 2.5 mV for 12 hrs/day (n = 3)		NA	Fusion rate not reported; however, histological analysis showed an acceleration of bony callus formation in the experimental group
		B. Control; no postop ICS (n = 3)			
Kahanovitz et al., 1994 (V)	Dog (n = 12); L1–2 & L4–5 posterior facet joint fusion w/ local autograft & wire to secure the graft in place	Postop local ICS (pulse burst frequency: 1.5 Hz; pulse burst duration: 30 msec)	A. 30 mins/day for 12 wks (n = 4)	Histological & radiographic evidence of complete bony fusion across graft & both facets (defined as 1 level) at 12 wks	A. 0% (0/8 levels)
			B. 60 mins/day for 12 wks (n = 4)		B. 0% (0/8 levels)
		C. Control; no postop ICS (n = 4)			C. 0% (0/8 levels)
Ito et al., 1997 (V)	Dog (n = 26): L5–6 posterolateral inter–transverse process fusion w/ iliac crest autograft	Postop local ICS (American Medical Electronics, Inc.) (positive pulse: 195 µsec; negative pulse: 65 µsec; peak change in positive flux density: 9 T/sec; peak change in negative flux density: 3 T/sec; pulses/burst: 99; burst interval: 670 µsec)	A. w/ Steffee (variable screw placement plate) (n = 6)	NA	Fusion rate not reported; however, the authors noted no statistically significant effect of pulsed electromagnetic field on the BMD or biomechanical properties of the fusion mass at 24 wks postop
			B. w/o Steffee plate (n = 7)		
		Control; no postop local ICS	C. w/ Steffee plate (n = 6)		
			D. w/o Steffee plate (n = 7)		
Glazer et al., 1997 (V)	Rabbit (n = 20): L5–6 posterolateral inter–transverse process fusion w/ iliac crest autograft	A. Postop external ICS (Orthofix, Inc.) (via coils fixed to the outside of the animals' cages); peak change in positive flux density: 9 T/sec; peak change in negative flux density: 3 T/sec; pulse burst: 26 msec; burst interval: 670 msec; 4 hrs/day for 6 wks (n = 10)		Radiographic evidence of bilat fusion, defined as the presence of a continuous trabecular pattern across the fusion mass at 6 wks	A. 80% (8/10 levels)
		B. Control; no postop external ICS (n = 10)			B. 60% (6/10 levels) ($p > 0.05$)
Zhuo et al., 2018 (V)	Rabbit (n = 32): L5–6 posterolateral inter–transverse process fusion w/ bone graft	A. Postop ICS (CMF SpinaLogic device, DJO Global; affixed to the cage) for 30 mins/day for 8 wks & nano-HA–coated biphasic Ca phosphate bone graft substitute (n = 8)		Radiographic evidence of bilat fusion at 9 wks	A. 100% (8/8 levels)
		B. Postop ICS (CMF SpinaLogic device affixed to the cage) for 30 mins/day for 8 wks & biphasic Ca phosphate bone graft substitute (n = 8)			B. 62.5% (5/8 levels)
		C. Nano-HA–coated biphasic Ca phosphate bone graft substitute alone (n = 8)			C. 75% (6/8 levels)
		D. Biphasic Ca phosphate bone graft substitute alone (n = 8)			D. 38% (3/8 levels) (significant improvement w/ nano-HA–coated biphasic Ca phosphate, $p < 0.05$)

BMD = bone mineral density; cont'd = continued; HA = hydroxyapatite; LOE = level of evidence; NA = not applicable; Ti = titanium.
* Each preclinical study was classified as level V evidence according to guidelines of the North American Spine Society.

TABLE 3. Descriptive summaries of the identified clinical studies (n = 16)

Authors & Year, Study Design (LOE)*	Inclusion Criteria	Surgical Model	Study Groups (no. of pts)	Definition of Fusion Outcome	Fusion Rate (pts) (p value)
DCS					
Nerubay & Katznelson, 1984, case series (IV)	Pediatric pts w/ spondylolisthesis	Posterior lumbar fusion w/ iliac crest autograft w/ or w/o instrumentation	Osteostim model S11; direct current of 20 μA over 4 cathodes (5 μA/cathode); 105-mA/hr battery capacity for at least 6 mos (n = 5)	Radiographic evidence of solid bony fusion at 1 yr	100% (5/5)
Kane, 1988, nonrandomized, multicenter (III)	NA	Posterior lumbar fusion w/ autograft	DCS via Osteostim HS1 (BGS Medical Corp.); 20 μA over 4 cathodes; active for 22 wks (n = 82)	NA	91.5% (75/82) (p = 0.02)
			Historical control: no DCS (n = 159)		80.5% (128/159)
Kane, 1988, prospect RCT nonblinded (II)	Pts w/ difficult-to-fuse spines: failed prior fusion, grade II or worse spondylolisthesis, multilevel fusion, &/or other high-risk medical condition (e.g., gross obesity)	Posterior lumbar fusion (1–4 levels fused) w/ autograft	DCS via Osteostim HS1; 20 μA over 4 cathodes; active for 22 wks (n = 31)	Radiographic evidence of fusion at 18 mos	81% (25/31) (p = 0.026)
			Matched control: no DCS (n = 28)		54% (15/28)
Kane, 1988, nonrandomized, multicenter (IV)	NA	Posterior lumbar fusion w/ autograft	DCS via Osteostim HS1; 20 μA over 4 cathodes; active for 22 wks (n = 116)	Radiographic evidence of fusion (no time point given)	93% (108/116)
Meril, 1994, retro comparative cohort (III)	Adult pts undergoing primary or revision anterior or posterior lumbar interbody fusion	Single-level or multilevel anterior or posterior lumbar interbody fusion w/ or w/o instrumentation & w/ autograft &/or allograft	DCS device (EBI Medical Systems); 20 μA over 2 cathodes; active for 24 wks (n = 122)	CT evidence of fusion, defined as unequivocal incorporation of the graft into the adjacent vertebral endplates on at least half of the curved coronal views, at ≥21 mos	93% (113/122) (p < 0.001)
			Control: no DCS (n = 103)		75% (77/103)
Rogozinski & Rogozinski, 1996, prospect comparative study (III)	Adult pts undergoing instrumented lumbosacral PLF	Lumbosacral posterolateral instrumented fusion w/ autograft (not interbody)	DCS via SpF-2T (EBI Medical Systems); 20 μA over 2 cathodes w/ 220-mA/hr battery (n = 53)	Radiographic evidence of fusion, defined as mature trabeculated bone across instrumented levels w/ no movement on stress views & no loss of fixation, at ≥19 mos	96% (51/53) (p >0.05)
			Control: no DCS (n = 41)		85% (35/41)
Tejano et al., 1996, retro case series (IV)	Pts w/ difficult-to-fuse spines: multilevel fusion, previous failed fusion, &/or grade II or worse spondylolisthesis	Posterior or posterolateral lumbar fusion w/ iliac crest autograft w/o instrumentation	DCS device (EBI Medical Systems); 20 μA over 4 cathodes for a minimum of 24 wks (n = 118)	Radiographic evidence of fusion, w/ no motion btwn vertebrae at ≥2 years	92% (108/118)
Kucharzyk, 1999, prospect comparative series (II)	Pts w/ difficult-to-fuse spines: multiple prior spine surgeries, failed prior fusion, segmental instability, spinal stenosis, &/or spondylolisthesis	Posterolateral lumbar fusion w/ Rogozinski hardware (early pedicle screw system) & autograft	DCS device (model not given) (n = 65)	Radiographic evidence of fusion, defined as the presence of bridging trabeculae, consolidation of bone graft, no pseudarthrosis lines, absence of spine-specific pain, & no failure of instrumentation, at a mean 3.8 yrs of follow-up	95% (62/65) (p > 0.05)
			Control: no DCS (n = 65)		86% (56/65)

CONTINUED ON PAGE 115 »

» CONTINUED FROM PAGE 114

TABLE 3. Descriptive summaries of the identified clinical studies (n = 16)

Authors & Year, Study Design (LOE)*	Inclusion Criteria	Surgical Model	Study Groups (no. of pts)	Definition of Fusion Outcome	Fusion Rate (pts) (p value)
DCS (*cont'd*)					
Jenis et al., 2000, RCT (II)	Adult pts undergoing primary or revision lumbar or lumbosacral PLF	Primary or revision lumbar or lumbosacral PLF; single-level or multilevel w/ instrumentation & iliac crest autograft	DCS via SpF-2T; 20 μA over 2 cathodes (n = 17)	Radiographic evidence of fusion, defined as solid arthrodesis w/ trabecular bridging bone at 1 yr	59% (10/17) (p > 0.05)
			Control: no DCS (n = 22)		82% (18/22)
Welch et al., 2004, retro case-control study (III)	Pts w/ difficult-to-fuse spines: age >65, rheumatoid arthritis, prior failed fusion, infection, &/or immunosuppressed	Posterior cervical fusion from the occiput to C3 w/ instrumentation & autograft &/or allograft	DCS via SpF-2T (EBI Medical Systems); 20 μA over 2 cathodes w/ 220-mA/hr battery (n = 16)	Radiographic evidence of fusion, defined as the incorporation of osteosynthetic bone into the lateral masses, facet joints, & lamina; the absence of movement btwn fused segments on dynamic studies; & the preservation of implant integrity, at a mean of 19 mos	94% (15/16)
Andersen et al., 2009, RCT (II)	Pts w/ difficult-to-fuse spines: age >60 eligible for spinal fusion	Posterolateral lumbar fusion (1–4 levels) w/ local autograft &/or allograft, w/o instrumentation	DCS via SpF-XL IIb stimulator (BiometSpine) 100 μA (n = 8)	CT evidence of fusion, defined as "a continuous bony bridge either between the transverse processes or at the lateral side of the facet joints on at least 1 side or a bilateral fusion of the facet joints," at 24 mos	50% (4/8)
			DCS via SpF-XL IIb stimulator (BiometSpine) 40 μA (n = 40)		32.5% (13/40)
			Control: no DCS ("dummy electrodes" implanted) (n = 36)		33% (12/36) (all groups, p > 0.05)
CCS					
Goodwin et al., 1999, double-blind RCT (I)	Adult pts undergoing lumbar spinal fusion	1- or 2-level lumbar fusion (anterior interbody, posterior interbody, &/or posterolateral) w/ autograft &/or allograft & any type of internal fixation except interbody fusion cages; w/ or w/o instrumentation	CCS via Bioelectron device (early generation of current Biomet Orthopak [Zimmer Biomet]); instructed to use 24 hrs/day until healing occurred, or for 9 mos (average actual = 15.7 hrs/day) (n = 85)	Radiographic evidence of fusion, w/ ≥50% integration of interbody & vertebrae (interbody fusion) or uninterrupted bone masses on AP & lat radiographs (PLF), at 12 mos	90.6% (77/85) (p > 0.05)
			Control: inactive stimulator (n = 94)		81.9% (77/94)
ICS					
Mooney, 1990, double-blinded RCT (II) (<80% of cohort included due to noncompliance)	Adults pts undergoing index interbody fusion via anterior or posterior approach	1- or 2-level anterior or posterior lumbar interbody fusion w/ autograft &/or allograft, w/ or w/o instrumentation	ICS via custom brace (specifications not provided); 8 hrs/day (n = 64)	Radiographic evidence of fusion, defined as >50% assimilated at ≥12 mos	92% (59/64) (p < 0.005)
			Control: nonfunctioning brace (n = 53)		68% (36/53)

CONTINUED ON PAGE 116 »

» CONTINUED FROM PAGE 115

TABLE 3. Descriptive summaries of the identified clinical studies (n = 16)

Authors & Year, Study Design (LOE)*	Inclusion Criteria	Surgical Model	Study Groups (no. of pts)	Definition of Fusion Outcome	Fusion Rate (pts) (p value)
ICS (*cont'd*)					
Marks, 2000, retro comparative (III)	Adult pts w/ discogenic low-back pain	Anterior lumbar interbody &/or PLF w/ autograft &/or allograft, w/ or w/o instrumentation	ICS via Spinal-Stim (Orthofix, Inc.) for ≥4 hrs/day while awake beginning 2 days postop (n = 42)	Radiographic evidence of fusion, defined as incorporation of the graft w/ no radiolucency btwn the graft & vertebral bone & no motion at each level, at a mean of 15.6 mos	97.6% (41/42) (p < 0.001)
			Control: no ICS (only thoracolumbosacral brace) (n = 19)		52.6% (10/19)
Jenis et al., 2000, RCT (II)	Adult pts undergoing primary or revision lumbar or lumbosacral PLF	Primary or revision lumbar or lumbosacral PLF; 1-level or multilevel w/ instrumentation & iliac crest autograft	ICS via Spinal-Stim model 8212 (Orthofix, Inc./American Medical Electronics, Inc.) w/ in 30 days of op; at least 2 hrs/day on at least 90% of the 150 consecutive treatment days after op (actual average = 182.7 ± 59 days) (n = 22)	Radiographic evidence of fusion, defined as solid arthrodesis (AP views) w/ trabecular bridging bone at 1 yr	64% (14/22) (p > 0.05)
			Control: no ICS (n = 22)		82% (18/22)
Bose, 2001, retro cohort (IV)	Pts w/ difficult-to-fuse spines (poorly defined): herniated nucleus pulposus, degenerative disc disease, spondylolisthesis, spinal stenosis, &/or prior failed fusion	PLF w/ instrumentation & autograft &/or allograft	ICS via Spinal-Stim (Orthofix, Inc.) w/in 4 wks of op; recommended usage 4 hrs/day until fusion; Boston Overlap Brace for support (n = 48)	Radiographic evidence of fusion, defined as 2-point bridging, no radiolucency, & intact hardware, at ≥6 mos (mean 16 mos)	98% (47/48)
Linovitz et al., 2002, RCT (I)	Adult pts undergoing index noninstrumented PLF of 1 or 2 levels btwn L3 & S1	Index posterolateral lumbar 1- or 2-level fusion (btwn L3 & S1) w/o instrumentation, either w/ autograft alone or in combination w/ allograft	ICS via SpinaLogic, w/in 30 days of op; 30-min treatment per day for 9 mos	Radiographic evidence of fusion, defined as continuity of fusion mass, at 12 mos	63% (66/104) (p > 0.05)
			Control: w/o active PEMF therapy		49% (48/97)
Foley et al., 2008, RCT nonblinded for FDA IDE (II)	Pts w/ difficult-to-fuse spines: smokers &/or undergoing multilevel fusion w/ allograft	ACDF w/ allograft & plate	ICS via CervicalStim (Orthofix, Inc.) w/in 7 days postop; recommended use 4 hrs/day for 3 mos	Radiographic evidence of fusion, defined as ≥50% bony bridging through surfaces of the graft-vertebra interface, no radiolucency at any portion of the graft-vertebra junction, & ≤4° of motion btwn adjacent fused vertebrae at 12 mos	92.8% (116/125) (p > 0.05)
			Control: no ICS		86.7% (104/120)
Coric et al., 2018; retro multicenter cohort compared to historical data from trial for initial FDA approval (III)	Pts w/ difficult-to-fuse spines: age ≥65, active smoker, multilevel fusion, prior failed fusion, diabetic, &/or osteoporotic	Single- or multilevel ACDF w/ no restrictions on the interbody implant, graft material, or surgical procedure	ICS via CervicalStim (Orthofix, Inc.); 4 hrs/day for 3–6 mos	Radiographic evidence of fusion, defined as the presence of continuous bridging bone on plain films, at 12 mos	92.6% (201/217) (p < 0.05)
			Historical controls: no ICS		82.6% (76/92)

ACDF = anterior discectomy and fusion; AP = anteroposterior; FDA = Food and Drug Administration; IDE = investigational device exemption; PLF = posterolateral fusion; prospect = prospective; RCT = randomized controlled trial; retro = retrospective.

* Levels of evidence classified according to guidelines of the North American Spine Society.

TABLE 4. Mean fusion rates and odds ratios for the preclinical and clinical studies determined by random-effects meta-analysis*

Type of EST	Type of Study & Authors & Year	Fusion Rate (no. fused/total)†		Cochran's Q	OR (95% CI) & p Value
		Stimulation Group	Control Group		
DCS	Preclinical				
	Kahanovitz & Arnoczky, 1990	4/4	0/4	5.45	**5.64 (2.64–12.06); p < 0.001**
	Bozic, 1999	19/27	11/26		
	Toth et al., 2000	13/15	2/7		
	Cook et al., 2004	10/11	8/11		
	France et al., 2006	7/9	8/16		
	Fredericks et al., 2007	2/2	1/3		
	MacEwan et al., 2016	1/1	0/1		
	Cho et al., 2019	40/40	14/20		
	Overall (95% CI)	**87.6% (74.2–96.5%)**	**45.3% (30.0–61.1%)**		
	Clinical				
	Kane, 1998	208/229	143/187	13.60	**2.13 (1.08–4.21); p = 0.03**
	Meril, 1994	113/122	77/103		
	Rogozinski & Rogozinski, 1996	51/53	35/41		
	Kucharzyk, 1999	62/65	56/65		
	Jenis et al., 2000	10/17	18/22		
	Andersen et al., 2009	17/48	12/36		
	Overall (95% CI)	**82.2% (65.8–94.1%)**	**73.9% (61.7–84.4%)**		
CCS	Clinical			0	2.12 (0.87–5.21); p > 0.05
	Goodwin et al., 1999	77/85	77/94		
	Overall (95% CI)	90.6% (88.3–95.8%)	81.9% (72.6–89.1%)		
ICS	Preclinical				
	Kahanovitz et al., 1994	0/16	0/8	0.03	3.08 (0.88–10.72); p > 0.05
	Glazer et al., 1997	8/10	6/10		
	Zhuo et al., 2018	13/16	9/16		
	Overall (95% CI)	47.8% (1.1–97.8%)	35.7% (4.9–75.9%)		
	Clinical				
	Mooney, 1990	59/64	36/53	16.17	**2.45 (1.20–4.99); p = 0.014**
	Marks, 2000	41/42	10/19		
	Jenis et al., 2000	14/22	18/22		
	Linovitz, 2002	66/104	48/97		
	Foley et al., 2008	116/125	104/120		
	Coric et al., 2018	201/217	76/92		
	Overall (95% CI)	**86.0% (74.2–94.6%)**	**71.2% (56.2–84.1%)**		
All	Preclinical				
	Overall (95% CI)	**77.7% (54.2–94.3%)**	**42.0% (27.5–57.2%)**	6.15	**4.79 (2.51–9.16); p < 0.001**
	Clinical				
	Overall (95% CI)	**84.9% (76.8–91.4%)**	**73.4% (65.4–80.8%)**	29.92	**2.26 (1.48–3.44); p < 0.001**

Boldface type indicates statistical significance.

* Only studies reporting the fusion rates for both the intervention (i.e., electrical stimulation) and control groups were included in the meta-analysis.

† For preclinical studies, the fusion rate was defined as the number of bilateral vertebral levels fused divided by the total number of levels attempted. For clinical studies, the fusion rate was defined as the number of patients experiencing successful fusion divided by the total number of patients undergoing surgery. For the analysis of preclinical data, where the fusion rate was 0 in some cases, delta was set to 0.5 (Haldane-Anscombe correction). For clinical studies, where the fusion rate was always greater than 0, delta was set to zero.

the remaining 3 used autograft and/or allograft. Instrumentation was placed in all patients in 4 studies and in some patients in 2 studies; 3 studies used in situ fusion only (Table 3).

The fusion rate ranged from 35% to 96% for treated patients and from 33% to 86% in controls (Supplemental Fig. 3A). In the meta-analysis, patients treated with DCS were found to have a significantly higher fusion rate at the last follow-up than the control patients (OR 2.13 [95% CI 1.08–4.21], p = 0.03) (Table 4 and Fig. 3B).

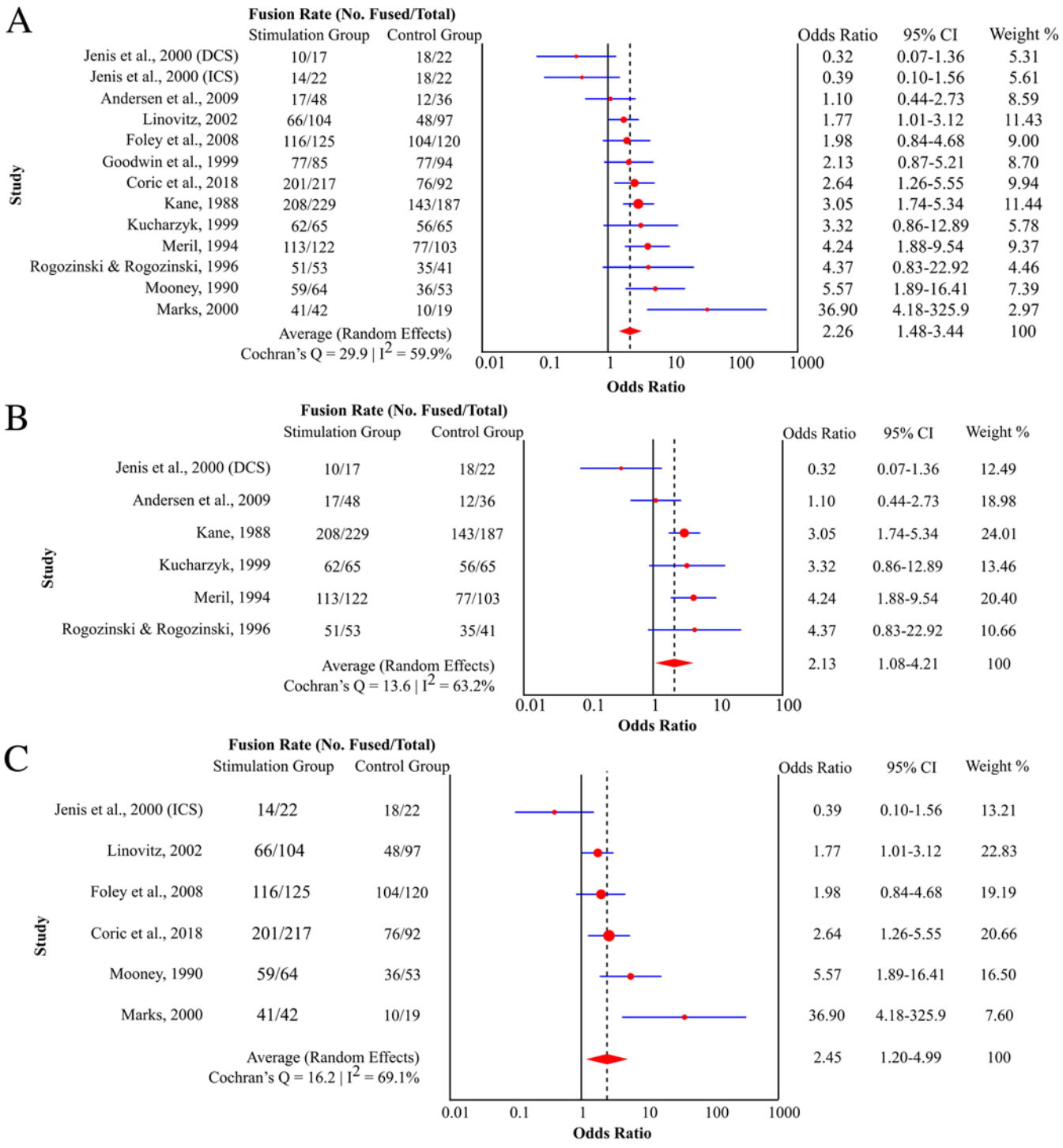

FIG. 3. Forest plots demonstrating random-effects meta-analysis of the fusion rates from all clinical studies (**A**), only clinical studies examining the effect of DCS on spinal fusion (**B**), and only clinical studies examining the effect of ICS on spinal fusion (**C**). Only studies reporting fusion rates for intervention (i.e., electrical stimulation) and control groups are included. Figure is available in color online only.

Effect of CCS on Spinal Fusion

No preclinical studies were found that described the use of CCS in a spinal fusion model, and only 1 clinical study met our inclusion criteria (Table 3). In that double-blind randomized controlled trial, Goodwin et al. examined the use of CCS in 179 adults undergoing one- or two-level fusions in which one of the following techniques was used: anterior lumbar interbody fusion, pos-

terior lumbar interbody fusion, or posterolateral lumbar fusion.[47] All patients were instructed to use the stimulation device (precursor of the Biomet OrthoPak [Zimmer Biomet]) for 24 hours/day for 9 months or until fusion was confirmed radiologically. At the 12-month follow-up visit, no significant difference in fusion rates was detected between CCS-treated (90.6%) and control (81.9%) patients (Table 4).

Effect of ICS on Spinal Fusion

Thirteen total studies—6 preclinical and 7 clinical—describing the results of ICS met our inclusion criteria. Of these, 3 preclinical and 6 clinical studies were included in the meta-analysis.

Preclinical Data

Preclinical studies described the effects of ICS in dog (n = 3), rabbit (n = 2), and rat (n = 1) models using posterior facet fusion (n = 2) or posterolateral inter–transverse process fusion (n = 4) of the lumbar spine. Four studies involved one-level procedures, whereas 2 involved multilevel fusions (≥ 2 levels). All studies used either autograft (n = 5) or synthetic bone graft (n = 1); 2 studies used instrumentation (Table 2).

The fusion rate varied widely across studies, ranging from 0% to 81% in treated groups and from 0% to 60% in controls (Supplemental Fig. 2B). In the aggregate, the included studies failed to show a significant difference in fusion rates between ICS-treated animals and controls (OR 3.08 [95% CI 0.88–10.72], p > 0.05) (Table 4).

Clinical Data

All clinical studies investigating the effect of ICS on spinal fusion examined adult patients (Table 3). Three of the studies examined the effects in only patients with difficult-to-fuse spines, defined by the studies as 1) patients with a herniated nucleus pulposus, degenerative disc disease, spondylolisthesis, spinal stenosis, and/or those who had undergone a prior failed fusion;[14] 2) those who smoked and/or were undergoing multilevel fusion with an allograft;[34] or 3) those who were age ≥ 65 years, actively smoked, were undergoing multilevel fusion, had undergone a prior failed fusion, had diabetes, and/or had osteoporosis.[26] Two studies restricted patients to those without a history of spine surgery, while the remaining 5 included both index and revision procedures. Three studies involved only posterior/posterolateral fusion procedures, 3 involved only interbody procedures, and 1 involved either type of procedure. The spinal segments investigated were cervical (n = 2) and lumbar/lumbosacral (n = 5). Autograft alone was used in 1 study, allograft alone in 1 study, and autograft and/or allograft in 5 studies. Instrumentation was used in all patients in 4 studies, some patients in 2 studies, and none of the patients in 1 study.

Fusion rates varied between 63% and 98% in the ICS group and between 49% and 87% in the control group (Supplemental Fig. 3C). Patients receiving ICS were found to have significant improvements in overall fusion rate relative to control patients (OR 2.45 [95% CI 1.20–4.99], p = 0.014) (Table 4 and Fig. 3C).

Subanalysis of Clinical Data

On meta-analysis, patients receiving some form of electrical stimulation were found to have a 126% increase in the odds of a successful fusion by last follow-up compared to controls (Fig. 3A). Table 5 summarizes the subgroup meta-analyses of the clinical data. The variables investigated include those listed as characteristic of patients with difficult-to-fuse spines, patients with a history of smoking, those undergoing revision surgery, those in whom interbody fusion is performed, and those undergoing a multilevel fusion, as well as the surgical level that was treated, the type of graft material used, and whether instrumentation was placed.

Notably, one or more electrical stimulation therapies resulted in statistically significant increases in the fusion rates compared to no stimulation in the following subgroups: patients with difficult-to-fuse spines, smokers, nonsmokers, patients undergoing index procedures, and those undergoing interbody fusions, single-level fusions, multilevel fusions, cervical fusions, lumbar/lumbosacral fusions, fusions with allograft alone, fusions with instrumentation, and fusions without instrumentation. In contrast, significant differences could not be detected between the fusion rates of patients receiving electrical stimulation therapy and controls in the following subgroups: revision surgery, posterior/posterolateral fusion subgroups, and autograft alone (Table 5).

Discussion

Spinal fusion is performed in the treatment of spinal pathologies of hundreds of thousands of Americans annually. Although most patients experience good outcomes, many experience nonunion, which can be associated with pain, persistent neurological compromise, and need for revision surgery.[24] One class of surgical adjuvant therapies designed to avoid this outcome is electrical stimulation, including DCS, CCS, and ICS. In the current article, we have reported on the results of a systematic review and meta-analysis that evaluated the existing preclinical and clinical literature with the goal of addressing two questions: 1) To what degree does the technology improve bony fusion in animal models? 2) To what degree does the technology facilitate bony fusion in humans? We found that both DCS and ICS lead to significant improvements in fusion rates in humans and that DCS also produces significant increases in fusion rates in preclinical studies. Considering all electrical stimulation modalities as a whole, we found that electrical stimulation can significantly increase fusion rates among patients undergoing open fusion operations for a range of spinal pathologies. Subanalyses suggested that this effect persists in patients with difficult-to-fuse spines, smokers, those undergoing index procedures, and those undergoing interbody fusion. Further analyses investigating the effects based on the number of levels fused and whether instrumentation was used suggested that these variables do not alter the fusion benefits of electrical stimulation devices (Table 4).

The merits of any technology can be winnowed down to two questions: 1) Does it work? 2) Is it an economical means of achieving the goal? For medical technologies,

TABLE 5. Random-effects subgroup meta-analysis of the clinical data*

Variable	Type of EST	Authors & Year	Fusion Rate (no. fused/total)		Cochran's Q	OR (95% CI) & p Value
			Stimulation Group	Control Group		
Studies limited to difficult-to-fuse spines†	DCS	Andersen et al., 2009	17/48	12/36	3.21	2.14 (0.94–4.86); p > 0.05
		Kucharzyk, 1999	62/65	56/65		
		Kane, 1988	25/31	15/28		
		Overall (95% CI)	73.3% (31.3–98.8%)	59.2% (24.9–89.0%)		
	ICS	Foley et al., 2008	116/125	104/120	0.25	**2.34 (1.33–4.10); p = 0.003**
		Coric et al., 2018	201/217	76/92		
		Overall (95% CI)	**92.4% (89.4–95.0%)**	**84.6% (79.5–89.1%)**		
	All	Overall (95% CI)	**82.5% (64.1–95.2%)**	**70.8% (52.2–86.3%)**	3.59	**2.18 (1.43–3.32); p < 0.001**
Smoker	DCS	Meril, 1994	85/92	42/59	4.44	2.46 (0.71–8.55); p > 0.05
		Rogozinski & Rogozinski, 1996	24/26	14/18		
		Jenis et al., 2000	5/10	8/13		
		Overall (95% CI)	83.1% (62.5–96.6%)	70.5% (60.9–79.3%)		
	ICS	Mooney, 1990	24/27	12/20	8.05	4.48 (0.45–44.26); p > 0.05
		Marks, 2000	18/19	0/3		
		Jenis et al., 2000	6/12	8/13		
		Overall (95% CI)	80.3% (55.2–96.6%)	47.0% (20.2–74.7%)		
	All	Overall (95% CI)	**82.2% (68.6–92.5%)**	**62.5% (49.3–74.8%)**	12.50	**2.84 (1.00–8.11); p = 0.05**
Nonsmoker	DCS	Meril, 1994	26/28	14/20	1.45	3.79 (0.99–14.53); p = 0.05
		Rogozinski & Rogozinski, 1996	27/27	21/23		
		Jenis et al., 2000	6/7	8/9		
		Overall (95% CI)	94.1% (82.8–99.6%)	81.9% (67.1–93.0%)		
	ICS	Mooney, 1990	35/37	24/33	6.37	3.66 (0.34–39.8); p > 0.05
		Marks, 2000	23/23	10/16		
		Jenis et al., 2000	7/10	8/9		
		Overall (95% CI)	91.5% (74.4–99.6%)	71.7% (59.9–82.2%)		
	All	Overall (95% CI)	**93.1% (85.0–98.2%)**	**77.0% (67.3–85.4%)**	7.81	**3.58 (1.09–11.8); p = 0.04**
Index surgery (no prior back surgery)	DCS	Meril, 1994	101/109	69/92	0.50	**3.69 (1.69–8.07); p = 0.001**
		Rogozinski & Rogozinski, 1996	32/34	24/27		
		Overall (95% CI)	**92.4% (87.6–96.2%)**	**80.1% (66.1–91.1%)**		
	CCS	Goodwin et al., 1999	77/85	77/94	0	2.12 (0.87–5.21); p > 0.05
		Overall (95% CI)	90.6% (82.3–95.8%)	81.9% (72.6–89.1%)		
	ICS	Mooney, 1990	59/64	36/53	9.78	**5.52 (1.17–25.95); p = 0.03**
		Marks, 2000	38/38	6/14		
		Linovitz et al., 2002	66/104	48/97		
		Overall (95% CI)	**88.5% (60.6–100%)**	**55.0% (40.7–69.0%)**		
	All	Overall (95% CI)	**90.0% (78.9–97.3%)**	**69.2% (55.6–81.2%)**	11.14	**3.24 (1.69–6.21); p < 0.001**
Revision surgery (prior back surgery)	DCS	Meril, 1994	12/13	8/11	0.24	6.56 (0.98–44.0); p = 0.05
		Rogozinski & Rogozinski, 1996	19/19	11/14		
		Overall (95% CI)	95.7% (83.4–100)	74.2% (56.4–88.6%)		
	ICS	Marks, 2000	3/4	4/5	0	0.75 (0.03–17.51); p > 0.05
		Overall (95% CI)	75% (19.4–99.4)	80% (28.4–99.5%)		
	All	Overall (95% CI)	92.0% (75.2–99.7%)	74.4% (58.4–87.6%)	1.58	3.68 (0.72–18.73); p > 0.05

CONTINUED ON PAGE 121 »

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TABLE 5. Random-effects subgroup meta-analysis of the clinical data*

Variable	Type of EST	Authors & Year	Fusion Rate (no. fused/total)		Cochran's Q	OR (95% CI) & p Value
			Stimulation Group	Control Group		
Posterior or postero-lateral fusion	DCS	Kane, 1988	208/229	143/187	11.34	1.77 (0.78–4.01); p > 0.05
		Kucharzyk, 1999	62/65	56/65		
		Andersen et al., 2009	17/48	12/36		
		Jenis et al., 2000	10/17	18/22		
		Rogozinski & Rogozinski, 1996	51/53	35/41		
		Overall (95% CI)	79.4% (56.7–95.1%)	73.6% (57.4–87.1%)		
	ICS	Jenis et al., 2000	14/22	18/22	3.94	0.95 (0.22–4.11); p > 0.05
		Linovitz et al., 2002	66/104	48/97		
		Overall (95% CI)	63.3% (54.8–71.4%)	64.7% (32.7–90.6%)		
	All	Overall (95% CI)	77.1% (56.3–92.6%)	74.7% (60.8–86.4%)	16.57	1.51 (0.82–2.79); p > 0.05
Interbody fusion	DCS	Meril, 1994	113/122	77/103	0	**4.24 (1.88–9.54); p < 0.001**
		Overall (95% CI)	92.6 (86.5–96.6%)	74.8% (65.2–82.8%)		
	ICS	Foley et al., 2008	116/125	104/120	5.68	**3.54 (1.71–7.31); p = 0.001**
		Coric et al., 2018	201/217	76/92		
		Mooney, 1990	59/64	36/53		
		Marks, 2000	19/20	6/14		
		Overall (95% CI)	**92.3% (89.6–94.7%)**	**74.1% (59.9–86.2%)**		
	All	Overall (95% CI)	**92.3% (90.0–94.4%)**	**74.8% (64.4–84.0%)**	6.08	**3.56 (2.08–6.11); p < 0.001**
Single-level fusion	DCS	Kane, 1988	14/16	10/16	0.05	**4.96 (2.32–10.63); p < 0.001**
		Meril, 1994	85/93	49/73		
		Rogozinski & Rogozinski, 1996	16/16	18/20		
		Overall (95% CI)	**92.0% (84.6–97.2%)**	**72.7% (56.3–86.4%)**		
	ICS	Mooney, 1990	43/46	29/40	1.32	**8.77 (1.70–45.28); p = 0.01**
		Marks, 2000	18/18	6/12		
		Overall (95% CI)	**95.2% (87.0–99.5%)**	**64.1% (42.7–82.8%)**		
	All	Overall (95% CI)	**93.1% (88.5–96.6%)**	**69.6% (58.8–79.4%)**	1.68	**5.56 (2.91–10.64); p < 0.001**
Multilevel (≥2) fusion	DCS	Kane, 1988	11/15	5/12	0.34	**3.40 (1.15–10.0); p = 0.03**
		Meril, 1994	23/24	26/28		
		Rogozinski & Rogozinski, 1996	35/37	17/21		
		Overall (95% CI)	**89.2% (76.1–97.5%)**	**74.6% (45.5–95.0%)**		
	ICS	Mooney, 1990	16/18	7/13	0.34	**9.46 (2.16–41.43); p = 0.003**
		Marks, 2000	23/24	4/7		
		Overall (95% CI)	**91.4% (81.4–97.8%)**	**54.6% (34.0–74.4%)**		
	All	Overall (95% CI)	**90.4% (83.4–95.6%)**	**68.0% (46.3–86.2%)**	1.88	**4.86 (2.03–11.62); p < 0.001**
Cervical fusion	ICS	Foley et al., 2008	116/125	104/120	0.25	**2.34 (1.33–4.10); p = 0.003**
		Coric et al., 2018	201/217	76/92		
		Overall (95% CI)	**92.4% (89.4–95.0%)**	**84.6% (79.5–89.1%)**		
Lumbar or lumbosacral fusion	DCS	Kane, 1988	208/229	143/187	13.60	**2.13 (1.08–4.21); p = 0.030**
		Meril, 1994	113/122	77/103		
		Rogozinski & Rogozinski, 1996	51/53	35/41		
		Kucharzyk, 1999	62/65	56/65		
		Jenis et al., 2000	10/17	18/22		
		Andersen et al., 2009	17/48	12/36		
		Overall (95% CI)	**82.2% (65.8–94.1%)**	**73.9% (61.7–84.4%)**		

CONTINUED ON PAGE 122 »

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TABLE 5. Random-effects subgroup meta-analysis of the clinical data*

Variable	Type of EST	Authors & Year	Fusion Rate (no. fused/total)		Cochran's Q	OR (95% CI) & p Value
			Stimulation Group	Control Group		
Lumbar or lumbosacral fusion (*cont'd*)	CCS	Goodwin et al., 1999	77/85	77/94	0	2.12 (0.87–5.21); p > 0.05
		Overall (95% CI)	90.6% (82.3–95.8%)	81.9% (72.6–89.1%)		
	ICS	Mooney, 1990	59/64	36/53	15.90	2.84 (0.76–10.72); p > 0.05
		Marks, 2000	41/42	10/19		
		Jenis et al., 2000	14/22	18/22		
		Linovitz et al., 2002	66/104	48/97		
		Overall (95% CI)	81.6% (59.9–96.0%)	62.2% (47.6–75.7%)		
	All	Overall (95% CI)	**82.9% (72.3–91.4%)**	**70.9% (61.6–79.4%)**	29.68	**2.25 (1.34–3.80); p = 0.002**
Autograft	DCS	Kane, 1988	208/229	143/187	8.86	2.03 (0.73–5.65); p > 0.05
		Meril, 1994	51/53	35/41		
		Kucharzyk, 1999	62/65	56/65		
		Jenis et al., 2000	10/17	18/22		
		Overall (95% CI)	89.4% (79.7–96.2%)	80.4% (75.1–85.2%)		
	ICS	Mooney, 1990	23/25	14/19	10.07	2.88 (0.28–29.58); p > 0.05
		Marks, 2000	19/20	5/11		
		Jenis et al., 2000	14/22	18/22		
		Overall (95% CI)	84.0% (63.6–97.0%)	68.9% (49.5–85.3%)		
	All	Overall (95% CI)	87.4% (78.9–93.9%)	78.5% (72.0–84.4%)	19.39	2.14 (0.85–5.37); p > 0.05
Allograft	ICS	Mooney, 1990	25/27	16/22	2.28	**2.86 (1.18–6.95); p = 0.02**
		Marks, 2000	11/11	4/7		
		Foley et al., 2008	116/125	104/120		
		Overall (95% CI)	**92.8% (88.3–96.2%)**	**76.7% (59.2–90.4%)**		
With instrumentation	DCS	Meril, 1994	24/24	51/63	9.15	2.25 (0.50–10.1); p > 0.05
		Rogozinski & Rogozinski, 1996	51/53	35/41		
		Kucharzyk, 1999	62/65	56/65		
		Jenis et al., 2000	10/17	18/22		
		Overall (95% CI)	91.4% (77.7–98.9%)	83.2% (77.6–88.1%)		
	ICS	Mooney, 1990	44/48	28/39	7.37	1.92 (0.94–3.93); p > 0.05
		Marks, 2000	9/10	1/1		
		Jenis et al., 2000	14/22	18/22		
		Foley et al., 2008	116/125	104/120		
		Coric et al., 2018	201/217	76/92		
		Overall (95% CI)	88.5% (81.4–94.1%)	82.4% (77.3–86.9%)		
	All	Overall (95% CI)	**89.8% (83.8–94.6%)**	**82.8% (79.3–86.1%)**	16.44	**1.94 (1.01–3.73); p = 0.05**
Without instrumentation	DCS	Kane, 1988	208/229	143/187	5.92	**2.64 (1.20–5.81); p = 0.02**
		Meril, 1994	89/98	26/40		
		Andersen et al., 2009	17/48	12/36		
		Overall (95% CI)	**75.9% (45.3–96.3%)**	**59.3% (34.1–82.2%)**		
	ICS	Mooney, 1990	15/16	8/14	8.07	7.71 (0.86–69.38); p > 0.05
		Marks, 2000	32/32	9/18		
		Linovitz et al., 2002	66/104	48/97		
		Overall (95% CI)	88.2% (54.7–99.9%)	50.4% (41.9–58.9%)		
	All	Overall (95% CI)	**82.2% (63.7–95.0%)**	**56.0% (40.7–70.7%)**	14.03	**3.01 (1.56–5.84); p = 0.001**

CONTINUED ON PAGE 123 »

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TABLE 5. Random-effects subgroup meta-analysis of the clinical data*

EST = electrical stimulation technology.
Boldface type indicates statistical significance.
* Only studies reporting the fusion rates for both the intervention (i.e., electrical stimulation) and control groups were included in the meta-analysis.
† These studies included only patients with known risk factors for pseudarthrosis: 1) age > 60 years;[5] 2) failed prior fusion, grade II or worse spondylolisthesis, multilevel fusion, and/or other high-risk medical condition (e.g., gross obesity) (select cohort within study);[57] 3) multiple prior spine surgeries, failed prior fusion, segmental instability, spinal stenosis, and/or spondylolisthesis;[60] 4) age ≥ 65 years, active smoker, multilevel fusion, prior failed fusion, diabetic, and/or osteoporotic;[26] or 5) active smokers and/or multilevel fusion.[34]

we also consider the safety of the technology. Our review mainly addresses the first of these questions—namely, whether electrical stimulation is an effective means of promoting bony fusion. On the whole, our results suggest that the answer to this question is yes, as the results of our pooled analysis demonstrated significantly higher odds of fusion in patients treated with electrical stimulation (OR 2.26, $p < 0.001$). However, more in-depth investigation suggests that the majority of these results are driven by DCS and ICS. Between these 2 technologies, though, there appears to be no difference in efficacy.

This brings us to considering the questions of economics and safety profiles: 1) Are ICS and DCS economical means of promoting bony fusion? 2) Are they safe? The latter is most easily answered as both implantable DCS and noninvasive ICS devices have been approved under the relatively stringent FDA premarket approval process (class III devices) based on results of randomized controlled trials.[5,34,47,53,57,72] The former question, i.e., whether the DCS and ICS devices are economical, is one that is harder to answer.

At present there are no high-quality studies evaluating the cost-effectiveness of electrical stimulation devices in the spine literature. However, back-of-the-envelope calculations are possible using estimates of device cost, pseudarthrosis rates, and cost of revision surgery. Prior studies of pseudarthrosis have found that the direct surgical costs of a revision operation are approximately $21,113 ± $11,895 for cervical operations[58] and $28,069 ± $2508 for lumbar operations.[2] To a gross approximation, this reduces to $25,000 per reoperation. Based on the present results, the approximate pseudarthrosis rate among patients receiving electrical stimulation therapy is 15%, compared to 27% in the control population. Of these patients, approximately half may require surgical revision for pseudoarthrosis.[24,45,61,62,80] Accounting for this, the cost of surgical revisions for pseudarthrosis averaged across patients receiving electrical stimulation therapy is $1875, compared to $3375 for controls. For patients receiving electrical stimulation therapy, though, the cost of the stimulation device is an estimated additional $4000–$5000. Therefore, from a strictly financial standpoint, electrical stimulation devices may be a cost-ineffective means of improving fusion rates, except in patients with a high risk of nonunion.

The overall risk of pseudarthrosis among patients with difficult-to-fuse spines—commonly defined as those in whom prior fusion has failed, smokers, and those undergoing multilevel fusion procedures—has been reported to exceed 40%.[5,13,18,57,62] Accordingly, the cost of revision operations averaged across these patients may exceed $10,000, suggesting that the use of electrical stimulation devices in this patient population may be cost-effective. Consistent with this, Medicare—the largest single insurer in the US—covers these devices only for patients with a history of multilevel fusion or a history of one or more prior failed fusion operations. This analysis does not consider the effect of nonunion on indirect costs, namely, days of lost work and decreased quality of life; however, it is likely that consideration of indirect costs will only increase the cost-effectiveness of these stimulation devices. Additional, high-quality investigation is warranted to evaluate this point.

Study Limitations

There are several limitations to this study. First, we were forced to exclude 6 preclinical and 3 clinical studies from the meta-analysis as they lacked control groups for estimation of odds ratios. This produces a potential selection bias that may limit the generalizability of the data. Second, the results of the study are based on a combination of prospective and retrospective studies. Retrospective studies are limited in the quality of the data they provide, which consequently limits the generalizability of the results of the present study. Nonetheless, we evaluated the quality of the clinical studies included in the meta-analysis (using the Critical Appraisal Checklists) and deemed each to have sufficient quality to be included in the present review. Additionally, although we provide estimates of the overall effect of electrical stimulation therapies at large and in subgroups, the heterogeneity of the included studies prevents us from answering the following questions: 1) Which patients will benefit most from electrical stimulation technologies? 2) For how long should treatment be continued? Furthermore, the definition of fusion varied between studies, suggesting that the outcome may have been distinct across studies, which would limit the validity of our meta-analysis. We describe this heterogeneity by presenting the definition and method of assessment of spinal fusion used by each study. All clinical studies employed plain radiograph– or CT scan–based radiological assessment, both of which are considered valid techniques in the clinical literature. Although a CT scan provides higher-resolution imaging and is therefore often considered the gold standard for fusion assessment, relative to standard radiography it is more expensive, exposes the patient to high radiation levels, and often provides no additional information.[33] Nevertheless, the different assessment modalities impart heterogeneity to the results, which we attempted to address by employing random-effects versus fixed-effects models. Lastly, we pooled the results of several different electrical stimulation technologies. Though our results suggest that

ICS and DCS have similar effects, they employ distinct technologies and have widely different patient compliance levels given that the latter is an implanted device, whereas the former is a wearable device. It is therefore possible that limitations in patient compliance among the ICS group limited the ability of our analysis to see differences in efficacy between the technologies. Given these limitations, it is apparent that future studies are necessary to directly compare the effectiveness of these different electrical stimulation technology modalities.

Conclusions

Here we report the results of the first systematic review and meta-analysis analyzing the effectiveness of electrical stimulation devices on spinal fusion in the preclinical and clinical literature. We found that these devices lead to significant increases in fusion rates, with a nearly fivefold increase in the odds in preclinical studies and a more than twofold increase in clinical studies. Subanalysis suggested that among the clinical population, DCS and ICS lead to significant decreases in pseudarthrosis rates, whereas CCS does not. Additional research is needed to analyze the cost-effectiveness of electrical stimulation devices to identify those patients in whom these devices are likely to be not only practically effective but also cost-effective.

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Disclosures

Dr. Goodwin reports being a consultant for Augmedics and ROM3, having an ownership stake in AOSpine/NREF, and receiving textbook royalties from Kendall Hunt. Dr. Theodore receives royalties from DePuy and Globus Medical Inc.; he is a consultant for Globus. Dr. Witham reports receiving non–study-related grant support from the Gordon and Marilyn Macklin Foundation and Eli Lilly and Company; he is a consultant for DePuy Synthes Spine. Dr. Sciubba is a consultant for Baxter, DePuy Synthes, Globus, K2M, Medtronic, NuVasive, and Stryker. Mr. Cottrill reports receiving non–study-related grant support from the National Institute on Aging (F30AG063445).

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Conception and design: Sciubba, Cottrill, Pennington. Acquisition of data: Cottrill, Pennington. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sciubba. Statistical analysis: Cottrill, Pennington, Ahmed. Administrative/technical/material support: Sciubba, Theodore, Witham. Study supervision: Sciubba, Theodore, Witham.

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Combined Magnetic Fields Accelerate and Increase Spine Fusion

A Double-Blind, Randomized, Placebo Controlled Study

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Study Design. The clinical study conducted was a prospective, randomized, double-blind, placebo-controlled trial.

Objectives. The purpose of this study was to evaluate the effect of combined magnetic fields on the healing of primary noninstrumented posterolateral lumbar spine fusion.

Summary of Background Data. Combined magnetic fields, a new type of biophysical stimulus, have been shown to act by stimulating endogenous production of growth factors that regulate the healing process. This is the first placebo-controlled study to assess the effect of an electromagnetic stimulus on primary noninstrumented posterolateral lumbar spine fusion surgery as well as the first evaluation of combined magnetic fields as an adjunctive stimulus to lumbar spine fusion.

Methods. This multicenter investigational study was conducted at 10 clinical sites under an Investigational Device Exemption from the United States Food and Drug Administration. Eligible patients had one-level or two-level fusions (between L3 and S1) without instrumentation, either with autograft alone or in combination with allograft. The combined magnetic field device used a single posterior coil, centered over the fusion site, with one 30-minute treatment per day for 9 months. Randomization was stratified by site and number of levels fused. Evaluation was performed 3, 6, and 9 months after surgery and 3 months after the end of treatment. The primary endpoint was assessment of fusion at 9 months, based on radiographic evaluation by a blinded panel consisting of the treating physician, a musculoskeletal radiologist, and a spine surgeon.

Results. Of 243 enrolled patients, 201 were available forevaluation. Among all patients with active devices, 64% healed at 9 months compared with 43% of patients with placebo devices: a significant difference ($P = 0.003$ by Fisher's exact test). Stratification by gender showed fusion in 67% of women with active devices, compared with 35% of those with placebo devices ($P = 0.001$ by Fisher's exact test). By contrast, there was not a statistically significant effect of the active device in this male study population. In the overall population of 201 patients, repeated measures analyses of fusion outcomes (by generalized estimating equations) showed a main effect of treatment, favoring the active treatment ($P = 0.030$). In a model with main effect and a time by treatment interaction, the latter was significant ($P = 0.024$), indicating acceleration of healing. Performed in the full sample of 243 patients, results of the intent-to-treat analysis were qualitatively the same as in the evaluable sample of 201 patients.

Discussion. This investigational study demonstrates that combined magnetic field treatment of 30 min/d increases the probability of successful spine fusion, and statistical analysis using the generalized estimating equations model suggests an acceleration of the healing process. This is the first randomized clinical trial of noninstrumented primary posterolateral lumbar spine fusion, with evaluation by a blinded, unbiased panel. This is the first double-blind study performed to date assessing noninstrumented fusion outcome with extremely critical radiographic criteria. The lower overall fusion rates in this study are attributed to the high-risk patient group with an average age of 57 years, the use of noninstrumented technique with posterolateral fusion only, and the reliance on extremely critical radiographic and clinical criteria and blinded panel for fusion assessment without surgical confirmation.

Conclusions. In conclusion, the adjunctive use of the combined magnetic field device was statistically beneficial in the overall patient population, as has been shown in previous studies of adjunctive bone growth stimulation for spine fusion. For the first time, stratification of fusion success data by gender demonstrated that the female study population responded positively to the adjunctive combined magnetic field treatment, with no statistically significant effect observed in the male study population. Adjunctive use of the combined magnetic field device significantly increased the 9-month success of radiographic spinal fusion and showed an acceleration of the healing process. [Key words: combined magnetic fields, electromagnetic stimulation, posterolateral lumbar fusion, placebo-controlled trial, randomized trial] **Spine 2002;27:1383–1389**

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Electrical and electromagnetic fields have been shown to promote the healing of delayed union and nonunion of

bone. Their use as noninvasive therapeutic devices began with their first approval by the U.S. Food and Drug Administration (FDA) in 1979. The concepts underlying electrical and electromagnetic stimulation have fostered the development of several FDA-approved noninvasive bone growth stimulation devices for the treatment of fracture nonunion[2,20,21] (also J.D. Zoltan and J.T. Ryaby, unpublished data), and additional clinical work has been performed on avascular necrosis.[1,3,22] The use of these devices for adjunctive stimulation of spinal fusion began in the 1970s.

Initially, this technology, as applied to clinical spine fusion, was with surgically implantable direct current stimulation devices, as reported by Dwyer et al.[7] in 1974 and later by the randomized trial of Kane.[13] However, although the Kane study was randomized, neither of these studies had a placebo control.

The first use of a noninvasive electromagnetic technology was the study by Mooney, who reported on a double-blind placebo-controlled trial of pulsed electromagnetic fields for stimulation of interbody fusions.[16] However, the study was not controlled for use of instrumentation, daily treatment time, or type of graft.

The present study evaluates combined magnetic fields for the noninvasive adjunctive treatment of primary noninstrumented spine fusion. Combined magnetic fields, a new type of biophysical stimulus, are effective with only 30 min/d of stimulation. The use of combined magnetic fields is based on theoretic calculations that predicted coupling to calcium-dependent cellular signaling processes in tissues.[8,15] Combined magnetic fields have been shown to stimulate bone formation and fracture healing in animal model systems.[6,17] They are believed to act by stimulating endogenous production of growth factors that regulate the healing process.[9,10] The first clinical application of combined magnetic fields was on long bone nonunion healing and received FDA approval in 1994. This is the first placebo-controlled study to assess the effect of any electromagnetic stimulus on primary noninstrumented posterolateral lumbar spine fusion surgery as well as the first evaluation of combined magnetic fields as an adjunctive stimulus to lumbar spine fusion.

■ Methods

The clinical study was a prospective, randomized, double-blind, placebo-controlled trial[14] conducted under an Investigational Device Exemption (IDE) from the US Food and Drug Administration. The purpose of this clinical study was to investigate the effect of combined magnetic fields as an adjunct to spinal fusion. All patients signed an informed consent and were informed that they would be randomized to receive either active or placebo devices. The investigational sites in this study all received institutional review board approval before initiation of this study. Randomization was accomplished by a computer-generated randomization code provided by an independent third party. A six-block randomization code was used to eliminate bias between investigational sites based on enrollment rates.

Table 1. Study Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Primary, noninstrumented intertransverse fusion	Use of instrumentation
One or two vertebral levels	Prior fusion surgery
Between L3 and S1	Malignancy
≥18 years of age	Metabolic bone disease
Autograft ± allograft	Severe osteoporosis
Device application within 30 days postsurgery	Spondylitis
	Implanted cardiac pacemaker
	Pregnancy

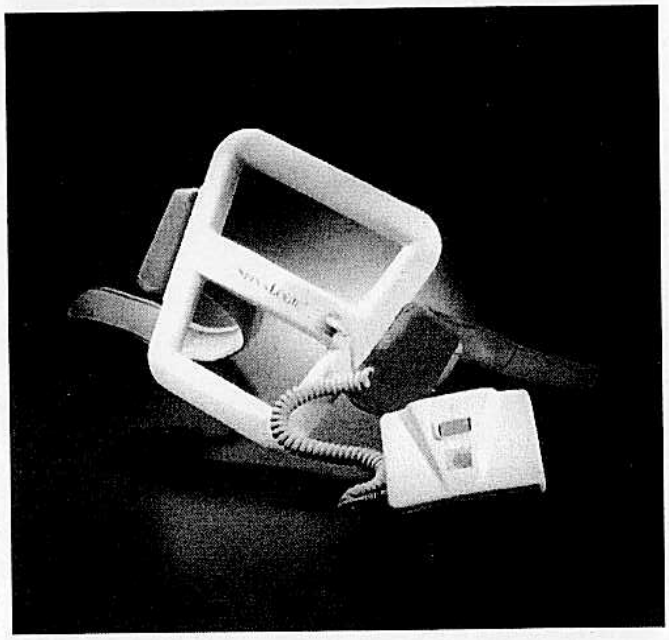

Figure 1. The combined magnetic field device (SpinaLogic) uses a single posterior coil centered over the fusion site.

Specific inclusion/exclusion criteria are provided in Table 1. The inclusion criteria included patients over 18 years of age, with primary intertransverse fusion without internal fixation of one or two vertebral levels between L3 and S1 within the past 30 days, with autograft alone or in combination with allograft. The major exclusion criterion was no use of internal fixation. Additional exclusion criteria were skeletal immaturity (age ≤18 years), pregnancy, vertebral trauma or scoliosis, diagnosis of metastatic cancer, metabolic bone disease, spondylitis, Paget's disease, moderate to severe osteoporosis, renal dysfunction, uncontrolled diabetes mellitus, or having an implanted cardiac pacemaker. Patients were prescribed with a lumbosacral orthotic and instructed to use it for a minimum of 2 months after surgery.

The patients were enrolled and randomized within 30 days of their fusion surgery. Active and placebo combined magnetic field devices were identical in appearance. The combined magnetic field stimulation was delivered by a portable, microprocessor-controlled, noninvasive device (SpinaLogic, OrthoLogic, Tempe, AZ) that was placed over the spine fusion site. The device is a single coil worn posteriorly (Figure 1) that produces low-energy combined magnetic fields with an integral timer programmed to turn the device off after 30 minutes of treatment. The patient was prevented from using the device for more than one 30-minute treatment in a 24-hour period by microprocessor control. Patient compliance was assessed by a built-in compliance monitor showing the number of completed

Table 2. Criteria for Radiographic Assessment of Fusion

Grade	Status	Percent Continuity	Motion	Description
0	No fusion	0 to <25	Motion	Discontinuity of the fusion mass with motion
1	Minimal fusion	≥25 to <50	Motion	A narrow band of continuity in the fusion mass with motion
2	Moderate fusion	≥50 to <75	None	Continuity of the fusion mass without motion
3	Solid fusion	≥75 to 100	None	Extensive continuity of the fusion mass without motion

treatments for the previous 30 days of use as well as the total number of completed treatments since initial application of the device. Placebo devices were programmed to not generate the combined magnetic fields and were identical in appearance to the functioning active devices.

Clinical and radiographic follow-up evaluations were performed 3, 6, and 9 months after surgery. Routine imaging of the fusion site included anteroposterior, lateral, and oblique radiographs. Computed tomography was performed at 9 months, and lateral flexion-extension radiographs were taken when clinically indicated by the investigator.

The endpoint for the determination of effectiveness was fusion status after 9 months of treatment. The evaluation of fusion outcome was performed by a blinded radiographic review panel composed of the investigator (treating orthopedic spine surgeon) and two reviewers blinded to the device status: a musculoskeletal radiologist and an orthopedic spine surgeon. All treating physicians, reviewers, patients, and the sponsor were blinded as to the activity status of all devices. Safety was determined by evaluating all reports of device-related complications and adverse events.

Fusion status was graded into one of four categories, from no fusion (0) to solid fusion (3) (Table 2). When two levels were involved, the lowest grade at either level was used for the fusion assessment. As defined in the protocol, the grades 0 and 1 were combined into a single category: no fusion (failure). Grades 2 and 3 constituted fusion (success). If the investigator and the radiologist disagreed, the independent spine surgeon reviewer's rating was used to define fusion status. For this investigation, the treating surgeon had access to all radiographic imaging, clinical, and surgical information. Consistently with clinical practice, the radiologist was provided the radiographic data alone, and the independent spine surgeon was provided radiographic data as well as pertinent patient information, including demographic, clinical, and operative information.

Effectiveness was defined by a statistically significant difference between fusion status outcomes in the active and placebo groups. Effectiveness by gender was also performed. Statistical analysis was performed using Fisher's exact test and the Generalized Estimating Equations (GEE) method of Zeger and Liang.[24] The latter analysis makes full use of data at 3 and 9 months, thereby assessing time trends in healing rate.

To examine the sensitivity of our findings to missing or excluded values, series of tabular analyses were run to examine 9-month outcomes in an intent-to-treat analysis. When out-

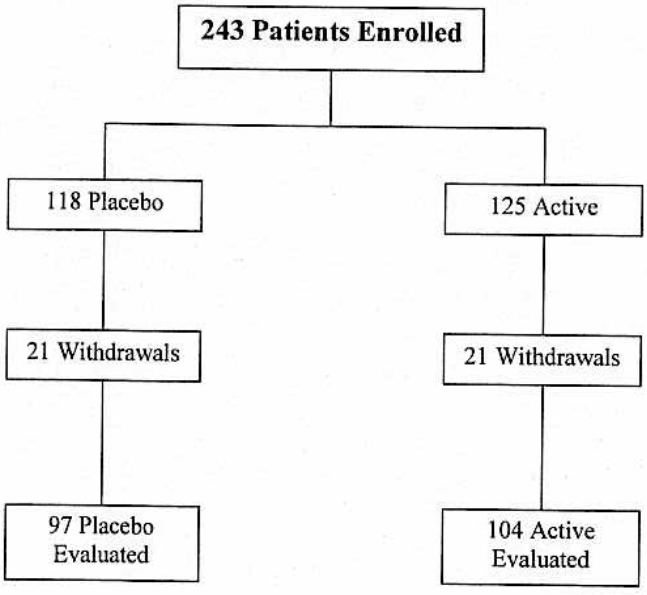

Figure 2. Study design diagram.

Table 3. Patient Demographics by Randomization Group

Demographics	Placebo	Active	Test: *P* Value
Age, y (calculated)			
N	118	124*	Student *t* (240.0): 0.92
Mean	56.58	56.77	
SD	15.03	15.47	
Median	57.00	57.00	
Minimum	26.00	22.00	
Maximum	82.00	87.00	
Sex			
Male	43	51	Exact: 0.51
Female	75	74	
Height, in			
N	118	124	Student *t* (240.0): 0.44
Mean	66.67	66.26	
SD	4.02	4.19	
Median	66.00	65.00	
Minimum	57.00	60.00	
Maximum	76.00	76.00	
Weight, lb			
N	118	124	Student *t* (240.0): 0.25
Mean	171.47	176.98	
SD	35.25	38.58	
Median	170.00	177.00	
Minimum	105.00	95.00	
Maximum	285.00	279.00	
Girth, in			
N	118	124	Student *t* (240.0): 0.15
Mean	34.73	35.73	
SD	5.33	5.47	
Median	34.00	36.00	
Minimum	24.00	24.00	
Maximum	54.00	52.00	
Currently smoke			
No	104	105	Fisher exact: 0.46
Yes	12	16	
Prior discectomy			
No	92	100	Fisher exact: 0.64
Yes	26	24	

*One patient did not have demographic information.

Table 4. Patient Diagnosis by Randomization Group and Gender

	Total	Percentage	Placebo (n)	Active (n)
Men				
Degenerative disk disease	16	17.0	8	8
Instability	3	3.2	2	1
Spondylolisthesis	48	51.1	21	27
Spinal stenosis	23	24.5	11	12
Miscellaneous	4	4.3	1	3
Total	94		43	51
Women				
Degenerative disk disease	29	19.46	14	15
Instability	7	4.70	5	2
Spondylolisthesis	91	61.07	44	47
Spinal stenosis	17	11.41	8	9
Miscellaneous	5	3.4	4	1
Total	149		75	74

comes were missing, in separate analyses, fusion status was imputed as fused or not fused, or assigned its most recent known value (LVCF). Using each of the three imputation schemes, tabulations were done separately for all subjects, men and women.

■ Results

From February 1993 through database closure in July 1998, 243 patients were enrolled in the study at 10 investigational sites (Figure 2). Patient demographics are provided in Table 3 for active and placebo device patients. Of the 243 patients, 201 patients completed the study (83%). Of the 42 nonevaluable patients, 16 patients (8 active, 8 placebo) voluntarily withdrew from the study before the 9-month visit. Ten patients (5 active, 5 placebo) were withdrawn by their physician(s) from the study before the 9-month follow-up. Two patients (one active, one placebo) died during their course of treatment. Both deaths were caused by natural causes, and in neither case was the death considered by the investigator to be related to the application of the SpinaLogic device. An additional 2 patients (placebo) violated the inclusion/exclusion criteria, and the remaining 12 patients missed their follow-up visits or had out-of-window follow-up visits. No patients were withdrawn because of device-related problems. Intent-to-treat analysis considered the withdrawn patients to represent failure. The statistical test results demonstrated that the randomized assignments of patients to the two treatment arms resulted in a well-balanced distribution of patient diagnosis between placebo and active devices (Table 4). No statistically significant differences were found for the clinical variables

Table 5. Percent Fusion Success as Determined by the Panel at 9 months

	Placebo	Active	*P* Value
All patients	43% (42/97)	64% (67/104)	0.003
Men only	55% (22/40)	61% (24/41)	0.656
Women only	35% (20/57)	67% (42/63)	0.001

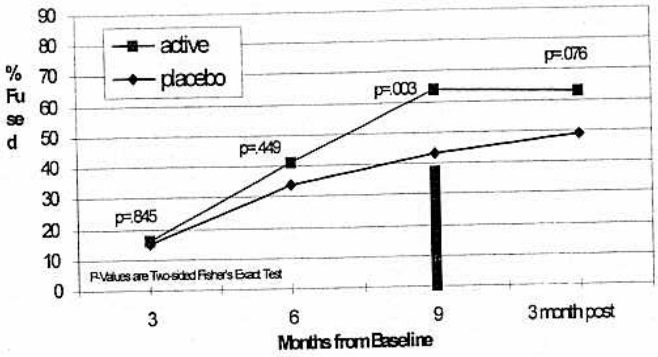

Figure 3. Effect of combined magnetic field treatment compared with placebo on fusion success at each follow-up time point in all patients (n = 201). The treatment endpoint was 9 months.

cited. The average time after surgery for treatment initiation was 19 days.

The data in Table 5 demonstrate a positive effect of the active device in the overall and female patient population. The data show that the treatment did not have a statistically significant effect in the male population. Fusion percentages in the overall patient population increased over the 9-month treatment period in both active and placebo groups (Figure 3). For the 201-patient evaluable population, repeated-measures analysis of fusion outcomes by GEE (Figure 4) demonstrated a main effect of treatment, favoring the active treatment ($P = 0.030$) and, in a separate model, a significant time by treatment interaction ($P = 0.024$), indicating acceleration of healing. Both this analysis and that of the overall patient population (sample size 243, with qualitatively similar results) revealed good agreement between the data and the GEE model. For both active and placebo patients, the proportion of healed patients increased linearly over time, but the V-shaped plot showed that healing was more rapid among active treated patients. For the female population (Figure 5), there was a strongly statistically significant difference between the active and placebo groups at the 6-month, 9-month (study end-

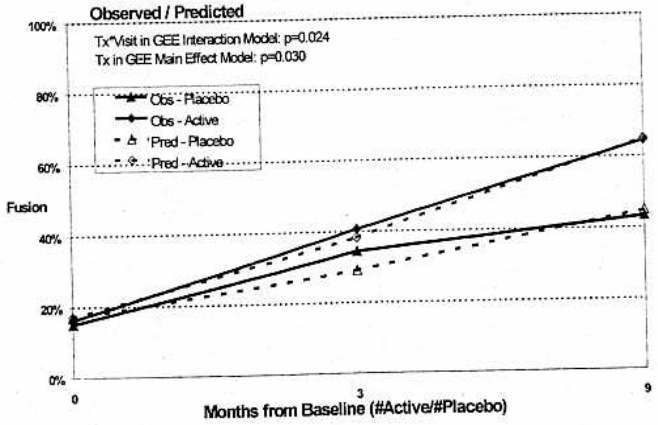

Figure 4. Observed and predicted fusion proportions, from baseline to 9 months, for all 201 patients. The predicted line is based on a generalized estimating equations model with a time by treatment interaction term.

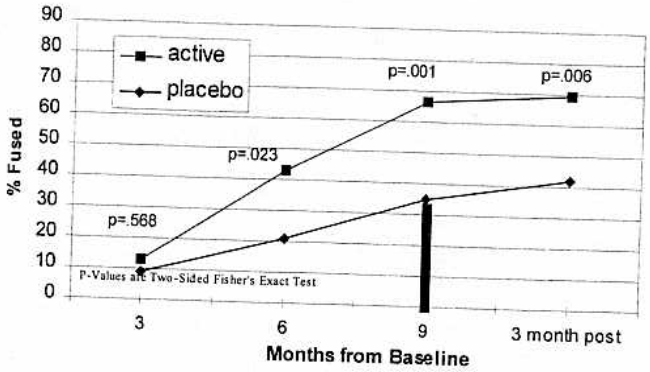

Figure 5. Effect of combined magnetic field treatment compared with placebo on fusion success at each follow-up time point in female patients (n = 120).

point), and 12-month (3 months after treatment) time points. The 12-month data show that the increase in fusion percentage was maintained beyond the treatment endpoint. The fusion results for the male population showed no statistically significant difference between the active and placebo groups at any time point (Figure 6). The results shown in Table 6 stratify the data by number of levels fused. One-level fusions were significantly improved in the active device group, with an increase of 24% over placebo. Two-level fusions were improved by 18%; however, this difference did not reach statistical significance. The data in Table 7 show the results in the smoking patient population. Only 28 patients were current smokers, and the difference between active and placebo devices did not reach statistical significance.

The results of the intent-to-treat analysis show a statistically significant treatment effect in favor of the active device for all patients: *P* values were 0.006, 0.015, and 0.007 for imputation as fused, not fused, and LVCF, respectively. For women, there was a statistically significant treatment effect in favor of the active device: *P* values were 0.004, 0.0005, and 0.0003 for imputation as fused, not fused, and LVCF, respectively. For men, there was no statistically significant treatment effects: *P* values were 0.521, 0.684, and 0.838 for imputation as fused, not fused, and LVCF, respectively.

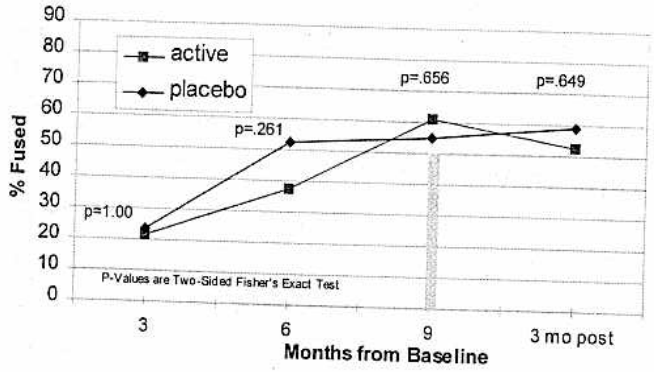

Figure 6. Effect of combined magnetic field treatment compared with placebo on fusion success at each follow-up time point in male patients (n = 81).

Table 6. Effect of Levels Fused on Fusion Outcome

Level	Placebo	Active	*P* Value
1	45% (30/66)	69% (46/67)	0.009
2	39% (12/31)	57% (21/37)	0.153

■ Discussion

This prospective, double-blind, placebo-controlled study demonstrates that combined magnetic field treatment of 30 min/d increases the probability of achieving a successful one-level or two-level posterolateral spine fusion. In addition, statistical analysis using the GEE model shows an acceleration of the healing process (Figure 4). Intent-to-treat analysis, which considers patient dropouts to be failures, still resulted in a statistically significant benefit of the active device compared to placebo.

There have been no previous studies of adjunctive bone growth stimulation in noninstrumented posterolaterally fused patients. Noninstrumented posterolateral fusions are more difficult to achieve than instrumented fusions and therefore provide a more rigorous test of the efficacy of adjunctive stimulation. In addition, the mean age in this patient population (57 years) provided an additional challenge to successful outcome. Additional information on other technologies for adjunctive stimulation of spine fusion can be found in recent review articles.[5,17,19]

This noninvasive technology is unique in requiring only 30 minutes of treatment per day. Previous studies using the other noninvasive technologies required much longer daily treatment times. The study of Mooney[16] evaluating pulsed electromagnetic fields required a minimum of 4 hours per day of treatment to be included in the compliant users group. In patients who used the pulsed electromagnetic fields device less than 4 hours per day, there was no statistically significant difference between active and placebo device recipients. In the study by Goodwin et al[11] of capacitively coupled field stimulation, patients were required to use the device 24 hours per day. However, patients used the device for an average of only 15–16 hours per day, and 2.6% of patients withdrew because of adverse effects from skin irritation with the electrodes. The relatively low dropout rate of 17% in the study reported here, compared with the 20% dropout rate of Mooney[16] and the unspecified dropout rate of the Goodwin study[11] as noted by Kahanovitz,[12] is likely related to a daily use time of only 30 minutes. This is the first double-blind study performed to date assessing noninstrumented fusion outcome with extremely

Table 7. Percent Fusion Success in Current Smokers

	No Fusion	Fusion	*P* Value
Placebo	75% (9/12)	25% (3/12)	NA
Active	50% (8/16)	50% (8/16)	0.253

NA = not available.

critical radiographic criteria. Some other studies, however, have shown similar fusion rates in noninstrumented patients. In the study by Dwyer et al,[7] fusion occurred in the noninstrumented control group at a rate of 53.6%. Similarly, Brodsky[4] reported a success rate of 68.5% with no instrumentation, corresponding to the success rate of 65% reported by Zdeblick[23] in a randomized study. The lower overall fusion rates in this study compared with many other reports may have been caused by the high average age of 57 years, the use of noninstrumented technique with posterolateral fusion only, and reliance on extremely critical radiographic and clinical criteria using a blinded panel for fusion assessment. Surgical confirmation was not performed, which may have altered the absolute results. However, this most likely would have similar effects on both populations.

The overall patient population data presented here are analogous to data presented in previous studies of bone growth stimulation for adjunctive spine fusion.[7,11,13,16] In addition, for the first time in the literature, data stratified by gender are presented, demonstrating an increase in the fusion success rate from 35% to 67% in women with the device. No statistically significant effect of the device was noted in the male patient population in this study. The number of patients in this study did not allow stratification by diagnosis at patient entry. Neither this study nor the surgical literature provides any explanation for this finding. These findings should be considered in designing clinical protocols for future studies in spine fusion.

In conclusion, the adjunctive use of the combined magnetic field device for posterolateral fusions was shown to be beneficial in this study. The beneficial results were strongest in the female population included in the study, whereas the male population showed no statistical significance. Adjunctive use of the combined magnetic field device significantly increases the 9-month success rate of radiographic spinal fusion and accelerates the healing process.

■ Key Points

- First evaluation of combined magnetic fields for spine fusion.
- First double-blind, placebo-controlled evaluation of an adjunctive stimulation device on noninstrumented fusion.
- Higher mean age of the patients in this study than in other published fusion studies.
- Use of a blinded panel, providing for rigorous assessment of fusion.

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Increased Spinal Lumbar Fusion with Combined Magnetic Field (CMF) Bone Growth Stimulation

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Abstract

The aim of this study was to assess the efficacy of bone growth stimulation (BGS), specifically Combined Magnetic Field (CMF) stimulation, in the recovery of lumbar spinal fusion patients. Electrical BGS devices are prescribed post-operatively to help with the healing of spinal fusion patients by promoting fusion. This retrospective cohort analysis examined 316 patients who received lumbar spinal fusion surgery at Brain & Spine Surgeons of New York between the years 2013 and 2018. Patients were divided into 4 groups according to type of BGS used: Combined Magnetic Field (CMF), Capacitive Coupling (CC), Pulsed Electromagnetic Field (PEMF) and No Stimulation (No-Stim). The average time-to-fusion for the CMF group was 5.5 months compared to 8.1 months for the No-Stim group ($p = 0.003$). Patients receiving CMF stimulation fused 75 days faster than patients receiving PEMF stimulation ($p = 0.02$) and 42 days faster than patients receiving CC stimulation. Smokers and spinal stenosis patients using the CMF stimulator also fused the fastest in their respective subgroups. The CMF group displayed the highest overall fusion rate at 95.7% and had the highest fusion rates for all patient subgroups studied. Electrical bone growth stimulation in general resulted in faster fusion times and greater fusion rates.

Keywords

Lumbar, Spine, Spinal, Spinal fusion, CMF, Combined magnetic field, Electrical bone growth stimulation

Introduction

Lumbar spinal fusions are being performed at increasing frequency, with almost two-hundred-thousand cases performed in the United States in 2015, a 62.3% increase in volume since 2004. Fusion procedures performed for disc degeneration, disc herniation and spinal stenosis accounted for 42% of the total elective lumbar cases in 2015. Rapidly rising costs of spinal surgery have resulted in over $10.2 billion dollars in yearly hospital costs for these procedures, amounting to more than $50,000 per patient admission [1], a 177% increase since 2004. The mean age of lumbar fusion patients continues to rise. The mean age in 2001 was 52 and this rose to 54.6 in 2004, 57 in 2013 and 59.9 in 2015 [1,2]. This rising average age has been linked to a greater comorbidity burden and an increase in risks for perioperative complication outcomes [2]. Patients with degenerative spinal conditions may require lumbar fusion if they do not respond to non-operative treatment and have abnormal and/or excessive motion at a vertebral segment resulting in severe pain and/or inability to function. Other conditions that may require fusion include a weak or unstable spine, possibly caused by infections or tumors, fractures, scoliosis and spinal deformities.

Spinal fusion surgery is designed to decrease pain generated from the joints by stopping the motion at a painful vertebral segment. The approach to fusion includes adding a bone graft or bone graft substitute to the spine segment which, through a biological response, causes bone growth and fusion between the vertebra, resulting in the formation of a single, solid bone. Historically a patient's hip bone, the iliac crest, was harvested for spinal fusions but due its donor site morbidity physicians have shifted toward using allograft, non-iliac crest autograft and bone graft substitutes [3].

Failed solid bony fusion, known as pseudarthrosis, is a serious, prevalent and costly complication of spinal fusion procedures [4]. It is known to cause persistent or recurrent pain and disability, as shown by Kornblum, et al. [5] in a prospective, randomized study focused on the long-term influence of pseudoarthrosis on clinical outcomes in patients who

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received posterior lumbar fusion. It was found that patients who presented with pseudoarthrosis were significantly less likely to have a clinical outcome of excellent to good and had significantly higher back and lower limb pain than patients without pseudoarthrosis. Lumbar pseudarthrosis causes quality of life challenges in the patient's physical and mental experience and can result in severe morbidity [6].

Pseudoarthrosis is often suspected when a fusion patient presents with recurrent or neurological symptoms during long-term follow-up. A significant rate of pseudoarthrosis has been reported in the literature ranging from 15 to 43% [7,8], and rates at 1-year can be as high as 35% [9]. The prevalent rate of symptomatic pseudoarthrosis in lumbar spinal fusions is 10-15% [10,11]. This high incidence rate is significant as pseudoarthrosis is one of the most common indications for repeat surgery, and one of the most common revision surgery indications is when symptomatic non-fusion occurs [12]. There are certain risk factors associated with pseudoarthrosis which include smoking, obesity, diabetes, multilevel fusions, previously failed fusion, and osteoporosis [13,14].

The best treatment for pseudarthrosis is to prevent it from occurring after the initial operation [13]. Because of the complications caused by pseudoarthrosis and the fact that fusion has been shown to be positively correlated to improved clinical and functional outcomes [1], achieving a solid fusion is the ultimate goal of spinal fusion procedures. Given the number of patients undergoing lumbar spinal fusion procedures and the percentage of failed fusions, consideration of adjunctive therapies to further enhance the probability of fusion is warranted [15].

One of these adjunctive therapies is electrical stimulation. The clinical benefits of electrical stimulation as adjuncts to spinal fusions have become increasingly recognized over the last 30 years. Scientific studies have better defined their mechanisms of action, thus supporting the validity of these treatments. Bone formation and fusion involves a complex series of cellular interactions and molecular pathways [16]. Learning how to heal injured bone and induce and accelerate bone growth and repair has led to the creation of bone growth stimulator (BGS) devices which employ various technologies that revolve around electrical stimulation. These devices are prescribed post-operatively to help mimic the body's natural healing environment by generating electric fields that activate the body's internal repair mechanism which promotes bone growth [16].

Three types of electrical stimulation technologies have been FDA approved for clinical use. These technologies are direct current (DC), capacitive coupling (CC), and inductive coupling (IC) such as pulsed electromagnetic fields (PEMF) and combined magnetic fields (CMF) [17].

Previous generations of electrical stimulation technologies like DC have been shown to be effective fusion adjuncts, but these technologies are invasive, which has led to the more frequent use of newer, external non-invasive technologies such as CC and IC. An external electrical stimulation device is worn for a specified number of hours a day for a period of approximately 3 to 9 months following the surgery. With the CC device, metal electrodes with conductive gel are applied to the skin and are connected to an alternating current signal generator. With the IC device, an electromagnetic field, either CMF or PEMF, is created by an electrical current and transmitted through treatment coils that are placed into a brace and externally onto the fusion site. CMF treatment can promote bone cell proliferation through the release of IGF-II, which acts as a feedback loop [18]. Modelling for both the interbody and posterolateral fusion models showed that CMF therapy has a robust 100% coverage of the L1 to L5 vertebrae and all the intervertebral disc spaces [15]. Both CMF and PEMF involve the use of low energy, low-frequency magnetic field pulses, however CMF treatment differs from PEMF treatment by using a combination of static and alternating dynamic electromagnetic fields instead of one static electromagnetic field that pulses on or off.

External non-invasive therapeutic electrical BGSs have been shown to be successful when evaluated as an adjunct to spinal fusion surgery to enhance the chances of obtaining a solid spinal fusion or to treat a failed fusion. However, there is still controversy regarding which stimulation technology is most effective under certain clinical scenarios [9,19]. The main focus of this retrospective study is to evaluate the relationship between using a BGS, especially the CMF SpinaLogic BGS, and the success of bone fusion after lumbar spinal surgery. This study provides an overview of external BGS stimulation as an adjunct to spinal fusion and summarizes indications while focusing on the CMF stimulation technology.

Materials and Methods

Study design and patients

This study was a retrospective review of lumbar spinal fusion surgeries performed between 2013 and 2018 by 11 surgeons at Brain and Spine Surgeons of New York (BSSNY). The data was prospectively collected in BSSNY's Centricity PMS system through chart abstraction.

It was an all-comers study with the one inclusion criteria being that there was sufficient information in the patient's chart to assess the patient's fusion status. There were no exclusion criteria. All lumbar fusion procedures performed used instrumentation. The statistical tests utilized were ANOVA, Chi-squared test and Tukey's HSD range test.

There was a total of 316 patients examined with an average follow-up of 6 months. Patients were stratified into one of four cohorts. In three of the cohorts a particular non-invasive BGS was used as an adjunct to fusion (CMF, PEMF or CC) and in the fourth cohort no stimulation (No-Stim) was used. The PEMF device was worn for 8 hours a day and the CC device was worn for 24 hours a day. The CMF SpinaLogic ®Bone Growth Stimulator (DJO Global, Dallas, Texas) was worn by patients for 30 minutes a day. This stimulator is shaped to accommodate spine curvature and promotes fusion at one or two levels.

A stimulator was used in 72% (226/316) of patients and 28% (90/316) received no stimulation. The stimulator brand

Table 1: Patient demographics.

Patient Demographics		Distribution % (Patient Count)				
Group (% patients unknown)	**Group**	**No-Stim**	**CMF**	**PEMF**	**CC**	**Total**
		n = 90	**n = 115**	**n = 54**	**n = 57**	**n = 316**
Gender	Female	54.4% (49)	40.9% (47)	48.1% (26)	57.9% (33)	49.1% (155)
	Male	45.6% (41)	59.1% (68)	51.9% (28)	42.1% (24)	50.9% (161)
Smoking History (8.5%)	Current/Former	52.3% (47)	57.4% (66)	59.3% (32)	45.6% (26)	54% (171)
	No	29.8% (26)	40% (46)	38.9% (21)	43.9% (25)	37.3% (118)
Diabetes History (11.7%)	Yes	14.4% (13)	16.5% (19)	7.4% (4)	10.5% (6)	13.3% (42)
	No	70% (63)	73% (84)	88.9% (48)	73.7% (42)	75% (237)
Age	Age < 55	55.6% (50)	43.5% (50)	33.3% (18)	43.9% (25)	45.3% (143)
	Age ≥ 55	44.4% (40)	56.5% (65)	66.7% (36)	56.1% (32)	54.7% (173)
	Age 61-70	23.3% (21)	29.6% (34)	37% (20)	28.1% (16)	28.8% (91)
BMI (11.1%)	≤ 29	45.6% (41)	54.8% (63)	50% (27)	45.6% (26)	49.7% (157)
	≥ 30	34.4% (31)	42.6% (49)	44.4% (24)	35.1% (20)	39.2% (124)
Exercise History (24.1%)	Never	13.3% (12)	17.4% (20)	18.5% (10)	10.5% (6)	15.2% (48)
	Rarely	16.7% (15)	35.6% (41)	29.6% (16)	40% (23)	30.1% (95)
	Weekly	18.8% (17)	27.8% (32)	33.3% (18)	12.3% (7)	23.4% (74)
Previous Spine Surgery	0	48.9% (44)	59.1% (68)	57.4% (31)	43.9% (25)	53.2% (168)
	1	24.4% (22)	25.2% (29)	25.9% (14)	35.1% (20)	26.9% (85)
	2	18.9% (17)	11.3% (13)	9.3% (5)	8.8% (5)	12.7% (40)
	3+	2.2% (2)	3.5% (4)	5.6% (3)	5.3% (3)	3.8% (12)

Table 2: Diagnosis demographics.

Diagnosis	**Distribution %** **(Patient Count) n = 316**
Adjacent Segment Disease	1% (4)
Degenerative Disc Disease	28% (88)
Disc Herniation	36% (114)
Instability	4% (14)
Prior Discectomy	2% (7)
Prior Fusion Surgery	5% (17)
Pseudoarthrosis	2% (5)
Spondylolisthesis	27% (86)
Stenosis	47% (147)

distribution percentage of the 226 patients using a BGS was as follows: CMF with 51% (115), PEMF with 24% (54), and CC with 25% (57). Patient demographic and baseline characteristic data is presented in Table 1. Table 2 shows the diagnosis demographics and Table 3 displays the surgical demographics.

The risk profile for the total patient population consisted of 55% aged 55 and over, 39% with a BMI of 30 or greater, 54% who are current or former smokers, 1.6% with osteopenia, 4.4% with osteoporosis and 13% with diabetes. The CMF patient risk profile was as follows: 57% aged 55 and over, 43% with a BMI of 30 and above, 57% who are current or former smokers, 3% with osteopenia, 5% with osteoporosis, and 17% with diabetes.

Fusion Status was determined by both radiographical and clinical evidence. The patient was documented as "Fused" if this status was explicitly stated in imaging reports and/or if the trusted surgeon's post-operative notes stated that the patient was doing clinically well and did not need further follow-up. One of the reasons patients do not follow up after surgery is because they are recovering well and feel that they no longer need medical care. Typically, patients would return for a follow-up visit if they were experiencing recurrent or new symptoms. If the imaging reports clearly articulated pseudoarthrosis, the patient's status was labeled as "Not Fused", and 100% of the not-fused patients were deemed so by radiography.

Results

Fusion rate and fusion time (time-to-fusion) are the two outcome measures used in this study to assess treatment success of patients receiving lumbar fusion surgery. Fusion rate was determined according to the definition outlined in the Methods/Materials section. Fusion time was treated as a continuous variable. Overall fusion rate and fusion time are reviewed, as well as the fusion rate and fusion time of specific patient subgroups. Due to a lack of consistent documentation in the patients' charts, for several of the patient factors there is no information available for the PEMF and CC patient groups. Below we summarize the findings for each outcome measured and compare results among the patient groups (when information is available).

Table 3: Surgical demographics.

Surgical Demographics		Distribution % (Patient Count/Total)				
Group (% patients unknown)	**Group**	**No-Stim**	**CMF**	**PEMF**	**CC**	**Total**
Operative Distribution	Minimally Invasive	50% (17/34)	26% (9/34)	9% (3/34)	15% (5/34)	11% (34/316)
	Open	26% (73/282)	38% (106/282)	18% (51/282)	18% (52/282)	89% (282/316)
Level Distribution	Single-Level	57% (51/90)	53% (61/115)	N/A	N/A	55% (112/205)
	Multi-Level	43% (39/90)	47% (54/115)	N/A	N/A	45% (93/205)
Surgical Approach (1%)	Posterior	29% (63/221)	34% (74/221)	18% (40/221)	20% (44/221)	70% (221/316)
	Anterior	30% (8/27)	33% (9/27)	22% (6/27)	15% (4/27)	9% (27/316)
	Lateral	26% (12/46)	57% (26/46)	9% (4/46)	9% (4/46)	15% (46/316)
	Posterior and Anterior	20% (3/15)	33% (5/15)	20% (3/15)	27% (4/15)	5% (15/316)
Bone Graft (2%)	Allograft	24% (15/62)	40% (25/62)	15% (9/62)	21% (13/62)	20% (62/316)
	Autograft	29% (36/123)	33% (40/123)	24% (30/123)	14% (17/123)	39% (123/316)
	Allograft + Autograft	27% (33/122)	39% (48/122)	12% (15/122)	21% (26/122)	39% (122/316)

Table 4: Overall fusion rate and time-to-fusion.

Device	Fused/Total Patient Count	Overall Fusion Rate %	Overall Fusion Time: Mean Days-to-Fusion
No-Stim	83/90	92.2	244
CMF	110/115	95.7	166*
PEMF	50/54	92.6	241
CC	54/57	94.7	208

*Statistically Significant, p = 0.002.

Table 5: Fusion rates by high risk factors.

High Risk Factors	Device Fusion Rates (Patient Count Fused/Total) %			
	No-Stim	**CMF**	**PEMF**	**CC**
Smokers-Overall	89.4% (42/47)	92.4% (61/66)	87.5% (28/32)	92.3% (24/26)
Age 61-70	90.5% (19/21)	100% (34/34)	95% (19/20)	93.8% (15/16)
Previous Spine Surgery	92.7% (38/41)	95.7% (44/46)	90.9% (20/22)	92.9% (26/28)

Fusion rate

Overall fusion success rates were higher in patients receiving electrical stimulation, and CMF stimulation resulted in the highest overall fusion rate at 95.7% (110/115) with the No-Stimulator group having the lowest fusion rate at 92.2% (83/90) (Table 4).

The CMF stimulator group also had the highest fusion rate for patients with known risk factors for lumbar fusion surgery, specifically smokers (current or former), patients between the ages of 61-70, and patients with a history of previous spine surgery. For overall smokers, 92.4% (61/66) fused when using the CMF stimulator compared to 92.3% (24/26) when using the CC stimulator, 89.4% (42/47) when using no stimulator, and 87.5% (28/32) when using the PEMF stimulator. Regarding patients between the ages of 61-70, the CMF stimulator group had a 100% (34/34) fusion rate and the fusion rates for the PEMF, CC and No-Stim groups were 95% (19/20), 93.8% (15/16) and 90.5% (19/21), respectively. For these patients, fusion success rates were higher in those receiving electrical stimulation. Approximately ninety-six percent of patients (44/46) who received CMF stimulation and had a history of previous spine surgery fused. This was the highest fusion rate among all cohorts for this patient subgroup. The CC No-Stim and PEMF cohorts had fusion rates of 92.9% (26/28), 92.7% (38/41), and 90.9% (20/22), respectively (Table 5).

Other patient factors investigated include gender, diagnosis, return-to-work ability, and pre-operative exercise history. When compared to the other stimulator groups and the no-stimulator group, the CMF group had the greatest fusion rates for patients who are female and patients who have a primary diagnosis of spinal stenosis; fusion rates for the CMF group were 95.7% (45/47) and 100% (28/28), respectively. Female patients who received no stimulation and patients with a primary diagnosis of spinal stenosis who received no stimulation displayed the lowest fusion rates in their respective subgroups at 87.8% (43/49) and 88.9% (16/18) (Table 6 and Table 7).

Fusion data for patients who returned to work and

Table 6: Fusion rate by patient factors.

Other Patient Factors	Device Fusion Rates (Patient Count Fused/Total) %			
	No-Stim	**CMF**	**PEMF**	**CC**
Spinal Stenosis	88.9% (16/18)	100% (28/28)	92.9% (13/14)	90.9% (10/11)
Female	87.8% (43/49)	95.7% (45/47)	88.5% (23/26)	93.9% (31/33)
Never Exercise	92% (11/12)	100% (20/20)	N/A	N/A
Rarely Exercise	80% (12/15)	95.1% (39/41)	N/A	N/A
Ability to Return to Work Overall	84% (16/19)	100% (26/26)	N/A	N/A

Table 7: Fusion time by patient factors.

Patient Factors	Device Fusion Time - Mean Days-to-Fusion (Patient Count)			
	No-Stim	**CMF**	**PEMF**	**CC**
Smokers Overall	242 (42)	175 (61)	219 (28)	216 (24)
Spinal Stenosis	267 (16)	152* (28)	356 (13)	203 (10)

*Statistically Significant, $p < 0.001$.

Table 8: Overall fusion time ANOVA.

Statistical Comparison	ANOVA				
	Sum of Squares	**dF**	**Mean Square**	**F**	**Sig.**
Between Groups	350519.479	3	116839.826	5.178	0.002
Within Groups	6588501.275	292	22563.361		
Total	6939020.753	295			

Significant difference, $p = 0.002$.

Table 9: Overall fusion time Tukey HSD.

Tukey HSD		
Multiple Comparisons		
Dependent Variable: Time to Fusion		
(I) Brand of stimulator	(J) Brand of stimulator	Sig.
No-Stim	PEMF	1.000
	CMF	0.003
	CC	0.525
PEMF	No-Stim	1.000
	CMF	0.020
	CC	0.676
CMF	No-Stim	0.003
	PEMF	0.020
	CC	0.343
CC	No-Stim	0.525
	PEMF	0.676
	CMF	0.343

CMF was significantly lower than No-Stim, $p = 0.003$; CMF was significantly lower than PEMF, $p = 0.02$.

those with known pre-operative exercise history information was only available for the CMF and No-Stim groups. Patients in the CMF stimulator group who returned to work fused at 100% (26/26), 16% more than patients in the No-Stim group. For those patients stating that they never or rarely exercised, ones that used the CMF stimulator fused more than those using no stimulator, with CMF fusion rates of 100% (20/20) and 95.1% (39/41), respectively (Table 6).

Fusion time

Overall, patients in the electrical stimulation groups had shorter times-to-fusion (fused faster) than patients in the group receiving no electrical stimulation. The CMF stimulator group had a mean fusion time of 166 days (SD 112.21), or 5.5 months, shortest among any of the patient groups. The mean fusion time for the CC, PEMF and No-Stim groups were 208 days (SD 136.11), or 7 months, 241 days (SD 175.68), or 8 months, and 244 days (SD 183.30), or 8.1 months, respectively (Table 4). ANOVA tests revealed a statistically significant difference between the groups ($p = 0.002$) (Table 8), and Tukey's HSD tests showed that patients using the CMF stimulator fused significantly faster (time-to-fusion was significantly less) than patients using no stimulator ($p = 0.003$) and patients using the PEMF stimulator ($p = 0.02$) (Table 9).

This held true for patients with a primary diagnosis of spinal stenosis. Patients who had this stenosis diagnosis and received CMF stimulation had a mean fusion time of 152 days (SD 99.28), which was significantly shorter than the mean fusion times of stenosis patients receiving no stimulation ($p = 0.061$) and PEMF stimulation ($p < 0.001$) by 115 and 204 days, respectfully. The CMF group also had a shorter fusion time when compared to the CC group, although this difference was

Table 10: Spinal stenosis fusion time ANOVA.

Statistical Comparison	**ANOVA**				
	Sum of Squares	**dF**	**Mean Square**	**F**	**Sig.**
Between Groups	402515.568	3	134171.856	6.617	0.001
Within Groups	1277351.208	63	20275.416		
Total	1679866.776	66			

Significant main effect, $p < 0.001$.

Table 11: Spinal stenosis fusion time Tukey HSD.

Tukey HSD		
Multiple Comparisons		
Dependent Variable: Time to Fusion		
(I) Brand of stimulator	(J) Brand of stimulator	Sig.
No-Stim	PEMF	0.343
	CMF	0.061
	CC	0.685
PEMF	No-Stim	0.343
	CMF	0.000
	CC	0.061
CMF	No-Stim	0.061
	PEMF	0.000
	CC	0.771
CC	No-Stim	0.685
	PEMF	0.061
	CMF	0.771

CMF was significantly lower than No-Stim, $p = 0.061$; CMF was significantly lower than PEMF, $p < 0.001$.

not statistically significant (Table 7, Table 10 and Table 11).

The other patient subgroup studied for this outcome was overall smokers. For these patients, the CMF group had a mean fusion time of 175 days (SD 113.05), which was 67 days faster than the No-Stim group and the fastest among all patient groups. The mean fusion times for the CC, PEMF and No-Stim groups were 216 mean days (SD 128.38), 219 mean days (SD 185.52), and 242 mean days (SD 161.37), respectively, (Table 7).

Adverse events

In patients for which we could obtain complication data, it was found that the overall post-op complication rate was 15.5% (46/297). There were no significant differences in the occurrence of these events between any of the groups. According to the CMF SpinaLogic company, no known significant adverse events have resulted from the use of their BGS device in ether clinical or preclinical studies. None have been reported in the literature either. The same was found for the PEMF and CC technologies. Because of the latter and former, and the fact that the complication rates for all the patient cohorts hovered around 15.5%, we have reason to believe that these complications occurred because of the surgery and are not attributable to the use of bone growth stimulators.

Discussion

We conducted this retrospective review to better understand the effectiveness of bone growth stimulators in promoting lumbar spinal fusion under different clinical scenarios. Use of any of the BGS technologies was safe and did not result in a significant increase in adverse events. When looking at the overall patient population, all of the BGS technologies (CMF, PEMF or CC) resulted in an increase in fusion rate when compared to no stimulation. This result is corroborated in the literature. A systematic review which examined the effect of electrical stimulation on lumbar fusions reported fusion rates following PEMF stimulation to be in the range of 64% to 83% while fusion rates following no stimulation ranged from 43% to 81%. Similarly, the fusion rate following CC stimulation was 91%, which was greater than the fusion rate of 82% following no stimulation [19].

A randomized prospective study completed by Linovitz [8] looked at the effect of CMF stimulation on fusion rate and reported a statistically significant 21% increase in fusion rates when using CMF stimulation compared to placebo. In our study, among patients receiving electrical stimulation, those receiving CMF stimulation had the highest fusion rates. While the Linovitz study showed CMF's superiority to no stimulation, and a study by El Hashemi [20] showed higher solid fusion rates for patients receiving CMF stimulation compared to PEMF stimulation, there is no current literature which shows a higher fusion rate following CMF stimulation when compared to CC stimulation.

Patients receiving any type of electrical stimulation also fused faster than patients receiving no stimulation. Our study is the first to show a decrease in fusion time following CMF stimulation when compared to PEMF stimulation and CC stimulation. The difference in fusion time was 75 days ($p = 0.02$) between the CMF and PEMF groups, 42 days between the CMF and CC groups, and 78 days between the CMF and No-Stim groups ($p = 0.003$). Although the Linovitz [8] study reported an accelerated time-to-heal for patients receiving CMF stimulation, the study only compared CMF patients to those receiving placebo.

In addition to having the highest fusion rates and shortest times-to-fusion among all cohorts for the overall patient population, the CMF group also had the highest fusion rates and shortest times-to-fusion for all patient subgroups. Smoking is an established spinal indication for the use of electrical bone growth stimulators [16]. It is a

known high risk factor for lumbar spinal surgery and has been repeatedly shown to be associated with an increased risk of pseudoarthrosis and poor recovery [6]. Our results show that for patients with a smoking history, CMF stimulation resulted in the greatest fusion rate and fastest time-to fusion. It has been shown in the literature that PEMF stimulation can enhance smoker fusion rates [21] which held true in our study, but to date no comparison has been made in the literature between the BGS technologies or between CMF and no stimulation in regards to the fusion success of smokers.

Diagnosis is another patient-specific factor reported on in the literature in relation to bone growth stimulators' effect on fusion. Grade II+ spondylolisthesis is the only diagnosis shown in the literature to be a spinal indication for the use of electrical bone growth stimulators [16]. When investigating the relationship between various diagnoses and fusion success in the different patient cohorts, we discovered that for patients with a primary diagnosis of spinal stenosis, the CMF group had the highest fusion rate and fastest time-to-fusion.

In fact, spinal stenosis patients receiving CMF stimulation fused more than 200 days faster than patients receiving PEMF stimulation ($p < 0.001$) and more than 100 days faster than patients receiving no stimulation (not statistically significant). To our knowledge, no studies to date have discussed spinal stenosis as a possible indication for using a BGS. Given the fact that spinal stenosis is one of the most common indications for lumbar fusion surgery [1] and patients receiving fusion with this diagnosis have been shown to be at an increased risk of reoperation and complications [22], the potential for bone growth stimulators to promote fusion success in this subgroup has significant implications. Other patient factors investigated in this study in which there was data for all patient groups include gender, age and history of previous spine surgery.

As seen in the literature, use of electrical stimulation in the current study resulted in an increase in fusion rates for females but not males [7,8]. No comparisons are made among the BGS technologies in the literature. In our study, females receiving CMF stimulation had the greatest fusion rates compared to females receiving PEMF or CC stimulation. The CMF stimulator group also had the highest fusion rates among all patient groups for patients aged 61-70 and patients with a history of previous spine surgery, both of which are known risk factors for lumbar fusion surgery [23,24]. Literature could not be found on the effect of electrical bone growth stimulation on lumbar fusion success in these patient subgroups.

The current study demonstrates that electrical bone growth stimulation post-operatively results in an increase in fusion rate and a decrease in fusion time. The CMF BGS proved to be the most effective among the BGS technologies studied, both for the overall patient population and all stratification groups. It is important to recognize that the CMF stimulator has a much shorter wear-time than the PEMF or CC stimulator. Patients used the CMF stimulator for 30 minutes/day as opposed to 8 hours/day for the PEMF stimulator and 24 hours/day for the CC stimulator. Wear time is important since the duration of commitment could put patient compliance in jeopardy. Without consistent schedule adherence, the benefits from BGS treatment may not be realized. A low maintenance device, such as the CMF SpinaLogic, requiring only 30 minutes a day makes the patient more apt to comply with the necessary home self-care.

Bone healing, or fusion, is the ultimate goal of spinal fusion procedures. A delay or failure in healing (pseudoarthrosis) can cause serious patient morbidity and often results in secondary procedures that are expensive and invasive, resulting in societal and personal costs such as postponements in returning to work, diminished productivity and lost wages [25]. To combat bone healing complications, there has been an increase in good surgical practices, knowledge and design which have improved fusion rates [16]. The use of BGSs for spinal fusions has been shown to be a cost-effective adjunctive treatment option [16], and a review of the literature indicates that treatment with CMF is clinically beneficial for lumbar spinal fusions, reducing the occurrence of pseudoarthrosis, and may be economically advantageous because of less time away from work and reduced risk of reoperation [1]. Spinal fusions and their recovery are a significant burden on patients, their caregivers, and the healthcare system. The benefits of electrical stimulation for certain populations such as the elderly, postmenopausal women, and smokers, all of who demonstrate a greater fusion response to CMF treatment [18], should not be overlooked.

Our findings are strengthened by the large scope of the study, the wide range of clinical eligibility criteria, the number of participating surgeons, and the comparative and comprehensive nature of the study. Limitations of our study include its retrospective nature, limited data availability, heterogeneity of the patient and physician populations, and the fact that fusions were not entirely determined by radiography.

Conclusions

Lumbar spine surgery demand in the U.S. will increase due to a rise in the aging population. Spinal surgery costs are increasing and with the constellation of care options available, the need to optimize treatment is more important now than ever. The data in this study shows that non invasive electrical bone growth stimulation is beneficial in promoting fusion success. We conclude that the integration of a BGS, specifically the CMF SpinaLogic BGS, in the aftercare healing of lumbar spinal fusion patients can potentially move the lumbar fusion field towards a higher expected fusion rate and a decreased time-to-fusion.

CMF stimulation was found to be the most effective bone growth stimulator technology among all those studied, as use of this stimulator resulted in the shortest fusion times and highest fusion rates. Given the short wear time of the CMF product, using it as an adjunct to lumbar spinal fusion surgery is very appealing. Choosing the right BGS is important for the wellbeing and quality of life of the patient.

These results provide a platform for future real-world evi-

dence-based studies and help provide an example of the value of evidence-based decision making in the post-operative management of spinal fusion patients.

Author Contributions

Conceptualization: Rae Stegall and Rami Elsabeh; Methodology: Rae Stegall and Rami Elsabeh; Investigation: Rami Elsabeh and John Abrahams; Data Curation: Rae Stegall; Writing -Original Draft Preparation: Rae Stegall and Rami Elsabeh; Writing - Review and Editing: Rami Elsabeh and John Abrahams.

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Conflicts of Interest

Rami Elsabeh and John Abrahams declare no conflict of interest. Rae Stegall is a paid consultant for DJO Global.

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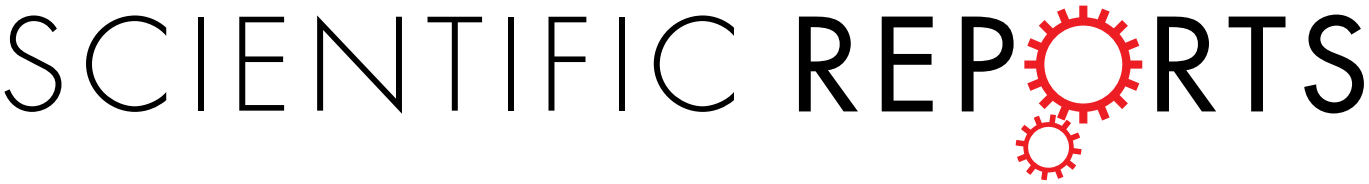

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Efficacy of Electrical Stimulators for Bone Healing: A Meta-Analysis of Randomized Sham-Controlled Trials

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Electrical stimulation is a common adjunct used to promote bone healing; its efficacy, however, remains uncertain. We conducted a meta-analysis of randomized sham-controlled trials to establish the efficacy of electrical stimulation for bone healing. We identified all trials randomizing patients to electrical or sham stimulation for bone healing. Outcomes were pain relief, functional improvement, and radiographic nonunion. Two reviewers assessed eligibility and risk of bias, performed data extraction, and rated the quality of the evidence. Fifteen trials met our inclusion criteria. Moderate quality evidence from 4 trials found that stimulation produced a significant improvement in pain (mean difference (MD) on 100-millimeter visual analogue scale = −7.7 mm; 95% CI −13.92 to −1.43; p = 0.02). Two trials found no difference in functional outcome (MD = −0.88; 95% CI −6.63 to 4.87; p = 0.76). Moderate quality evidence from 15 trials found that stimulation reduced radiographic nonunion rates by 35% (95% CI 19% to 47%; number needed to treat = 7; p < 0.01). Patients treated with electrical stimulation as an adjunct for bone healing have less pain and are at reduced risk for radiographic nonunion; functional outcome data are limited and requires increased focus in future trials.

Bone healing is a complex physiological process and is the end goal in the treatment of patients with fractures, surgical osteotomies and spinal fusion procedures. Failure or delays in bone healing often require further intervention and may result in serious morbidity such as increased pain and functional limitations[1]. Secondary procedures to promote bone healing may be invasive, expensive, and result in significant patient morbidity. The socioeconomic burden associated with bone healing complications such as delayed union or nonunion is substantial and includes direct treatment costs as well as personal and societal costs, such as lost wages, decreased productivity and delays returning to work[2–4].

Electrical stimulation is a popular adjunctive therapy used to promote bone healing across a range of indications[5,6]. Basic science research suggests that electrical stimulation enhances the process of bone healing by stimulating the calcium-calmodulin pathway secondary to the upregulation of bone morphogenetic proteins, transforming growth factor-β and other cytokines[3,7–11]. Clinical evidence to support the use of electrical stimulators for bone healing has been inconclusive. Prior systematic reviews of electrical stimulation have been limited by narrow scope, poor methodologic quality, and a focus on radiographic healing over patient-important outcomes[12–19]. We performed a meta-analysis of randomized sham-controlled trials to determine the effect of electrical stimulation on bone healing, focusing on patient-important outcomes.

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Methods

We report this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[20] and the protocol for reviews outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[21].

Identification of Studies. We systematically searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library from inception of the database to March 6, 2016. We used MeSH and EMTREE headings in various combinations and supplemented with free text to increase sensitivity (**Appendix 1**). Manual searches of the reference lists of included trials were conducted to identify any additional articles. We hand-searched major orthopaedic conference proceedings from March 2013 to March 2016 to identify unpublished studies that were potentially eligible.

Assessment of eligibility. Two authors independently screened all titles and abstracts and applied eligibility criteria to the methods section of potentially eligible trials using an electronic screening form. All discrepancies were resolved by consensus.

We included all studies fulfilling the following criteria:

1) Adult patients >16 years of any sex undergoing operative or nonoperative treatment for a fresh fracture, nonunion, delayed union, osteotomy, or symptomatic spinal instability requiring fusion.
2) Trials comparing direct current (DC), capacitive coupling (CC), or pulsed electromagnetic field therapy (PEMF).
3) Randomized sham-controlled trials (RCT) only[22].

No restrictions were made for publication date, language, presence or absence of co-interventions, or length of follow-up. Studies using multiple bones in the same patients as the unit of randomization, rather than patients were excluded due to lack of independence[23].

Assessment of risk of bias. Two reviewers independently performed outcome-specific assessment of risk of bias using the Cochrane Collaboration's tool for risk-of-bias assessment[21]. Attempts were made to contact study authors to resolve any uncertainties when required. When the issues bearing on the risk of bias were identical across outcomes within a study, a single risk of bias assessment was reported[24].

Data extraction. Two reviewers independently extracted data using a piloted electronic data extraction form. Extracted data included author names, journal names and publication year, funding source, sample size, mean ages and proportion of each sex in treatment and control groups, descriptions of the interventions in each group, all reported outcomes and follow-up times, and loss to follow-up. We attempted to contact study authors for clarification if important data were unclear or not reported.

Radiographic healing was determined according to the methods implemented in each trial. When multiple criteria for union were described, we recorded the most conservative estimate of union. For each trial we determined whether radiographic assessment was blinded or independently assessed and judged by consensus whether the determination of union was reasonable or not reasonable. We converted radiographic union rates to the number of nonunions by subtracting from the total number of patients in each group. For patients already presenting with a nonunion or delayed union, we recorded the number of patients with persistent or on-going nonunions. In trials that reported union based on CT-scan and plain radiographs, we recorded plain film radiographic healing for consistency.

Statistical Analyses. We calculated agreement for reviewers' assessments of study eligibility with the Cohen's kappa coefficient and agreement for assessments of risk of bias using the intraclass correlation coefficient (ICC). Kappa values $\geq$0.65 were considered adequate[25].

Among eligible trials we found substantial diversity in the types of bone lesions targeted for treatment. Although baseline bone healing time differs by size of bone and the site of lesion, the biologic process of healing is consistent across all bone lesions[26–29] and the effect of electrical stimulation compared with control on the time to bone healing is therefore likely to be similar. We reasoned that pooling trials exploring the effect of electrical stimulation for different bone lesions would increase the generalizability of our results[30]. We explored the validity of this assumption. We further anticipated that different forms of electrical stimulation may produce different effects, and explored this issue.

We utilized the conservative random-effects model of DerSimonian and Laird to pool effect estimates[21,31]. Our primary meta-analysis was an intention-to-treat analysis in which all patients were analysed in the groups to which they were originally randomized. We reported pooled estimates as risk ratios (RR) with 95% confidence intervals (CIs). The Absolute Risk Reduction (ARR) was used to calculate the Number Needed to Treat (NNT) when applicable to aid interpretability[32,33]. Continuous outcome instruments measuring the same constructs were summarized using mean differences (MDs) with 95% CIs[21]. If standard deviations were not available, they were estimated from trials with similar outcomes[21,34]. We transformed pain scores expressed in different units to the 0 to 100 mm visual analogue scale to facilitate pooling as a weighted mean difference. When there were at least 10 studies in a particular meta-analysis, we examined publication bias by using funnel plots comparing sample size versus treatment effect across the included trials[21]. All tests of significance were two-tailed and p-values of <0.05 were considered significant.

Evaluation of heterogeneity. We quantified heterogeneity using the X^2 test for heterogeneity and the I^2 statistic[21]. I^2 values were interpreted according to the Cochrane Handbook[21] as: 0–30% might not be important, 30–60% may represent moderate heterogeneity, 50–90% substantial heterogeneity and 75–100% considerable heterogeneity. We prespecified the following two subgroup hypotheses to explain potential heterogeneity[35].

(1) Clinical indication: fresh fractures, delayed union or nonunion, spinal fusion, or surgical osteotomy.
(2) Type of stimulation: direct current (DC), capacitive coupling (CC), or pulsed electromagnetic fields (PEMF).

For each subgroup, we performed tests for interaction using a chi-square significance test[36].

Sensitivity Analyses. Our main reported analysis is a complete case analysis in which participants with missing data were excluded from both the numerator and denominator. To explore the effects of missing outcome data, we performed sensitivity analyses. For the control group, we assumed the event rate to be the same for patients with missing data and those successfully followed; for the treatment group we assumed plausible ratios of event rates in patients with missing data compared with those who were successfully followed at ratios of: 1.5:1, 2:1, and 2.5:1[37]. As such, we tested the robustness of the results of the primary meta-analysis under relatively extreme assumptions with variable degrees of plausibility[37,38]. When only total losses to follow-up were reported and not specific numbers of losses in each arm, we assumed that losses in each arm were equal.

Given potential variability in the methods used to evaluate radiographic union[39–41] we performed three further sensitivity analyses: (1) including only trials in which an independent assessor was used to determine radiographic union; (2) including only trials in which consensus judgment was reasonable with regards to overall determination of union; (3) including only trials that defined union as >70% of bony continuity, or three of four cortices, as the most conservative estimate of bony union.

GRADE quality assessment and summary of findings. We utilized the GRADE approach to summarize the quality of the evidence for or against the use of electrical stimulation by each outcome. Data from randomized controlled trials were considered high-quality evidence, but could have been rated down according to risk of bias, imprecision, inconsistency, indirectness, or publication bias[42].

Results

Eligible and Included Studies. Of 2025 potentially eligible articles, 1664 titles and abstracts were screened and 17 were eligible for our review. However, the authors of one trial[43] clarified that the same patients were included in a more recent manuscript[44] and Anderson *et al.* reported different outcomes of the same patient population in two separate publications[45,46]. Thus 15 trials that were reported in 16 manuscripts[44–59] with a total of 1247 patients were included (Fig. 1). No additional trials from conference proceedings were identified. Agreement between the reviewers for eligibility based on title and abstract screening was very high (kappa = 0.85, 95% CI 0.78–0.93).

Study characteristics. Mean age of study participants was 45 years in the experimental and control arm. The proportion of male patients in the experimental and control arm was 58.3% and 56.3%, respectively. Mean follow-up was 8.2 (SD 3.4) months for radiographic outcomes and 8.6 (SD 3.7) months for pain and function **(Appendix 2).**

Four trials included patients undergoing a spinal fusion[45,46,49,52,55], five trials evaluated fresh fracture treatment[44,47,50,51,54,60], five trials examined treatment of delayed or nonunions[48,56–59] and one study included patients undergoing surgical osteotomy[53]. Trials of the appendicular skeleton assessed patients with tibial or femoral fractures[47,48,53,54,57,59], femoral neck[44], scaphoid fractures[50,51], and other long-bone fractures[56,58].

Twelve trials reported use of pulsed electromagnetic field (PEMF) therapy, one trial reported direct current (DC) stimulation and two trials reported continuous current (CC) stimulation. Details with regards to specific stimulator type, frequency and treatment duration for each study are reported in **Appendix 3**.

Radiographic union was described in all 15 of the included trials **(Appendix 4)**. Consensus judgment with regards to the overall determination of union was deemed to be reasonable in all but four studies[48,54,56,59]. Sharrard[57] reported results of radiographic union read by both orthopaedic surgeons and radiologists separately.

Pain was reported in four trials using either the Visual Analogue Scale (VAS)[44], Dallas Pain Questionnaire (DPQ)[46] or a categorical pain scale[48,57]. The lower and upper limits of the categorical pain scale reported in one study[57] (with demised single author) was assumed to be 0 to 5 based on the reported mean and standard deviations and a statistical simulation. Functional outcome was reported using components of the Short Form 36 (SF-36) health survey in two trials[46,47].

Risk of bias. Risk of bias assessments are presented in Fig. 2. The funnel plot for radiographic nonunion at last follow-up was symmetric and did not suggest publication bias (Fig. 3)[21].

Pain and function. Pain was reported across four trials[44,46,48,57] including a total of 195 patients. The pooled estimate of effect between electrical stimulation and sham control showed a statistically significant difference in pain (MD on the 100 mm visual analogue scale = −7.67 mm, 95% CI −13.92 to −1.43; p = 0.02; I^2 = 0%; Fig. 4). In the GRADE quality assessment (Table 1) pain was rated as moderate quality due for imprecision given that the 95% CI includes values below and above the minimal important difference (MID) of 10 mm[61]. We found no evidence to support a difference in treatment effect due to treatment indication (interaction p = 0.41) or stimulator type (interaction p = 0.19).

Functional outcomes were compared in two trials that reported SF-36 scores (n = 316 patients). The pooled estimate of effect between electrical stimulation and control was not statistically significant (MD −0.88, 95% CI −6.63 to 4.87, p = 0.76) (Fig. 5). In the GRADE quality assessment, functional outcome was rated as low quality evidence due to risk of bias (high losses to follow-up in both studies[46,47]) and inconsistency due to unexplained heterogeneity (I^2 = 57%)[62].

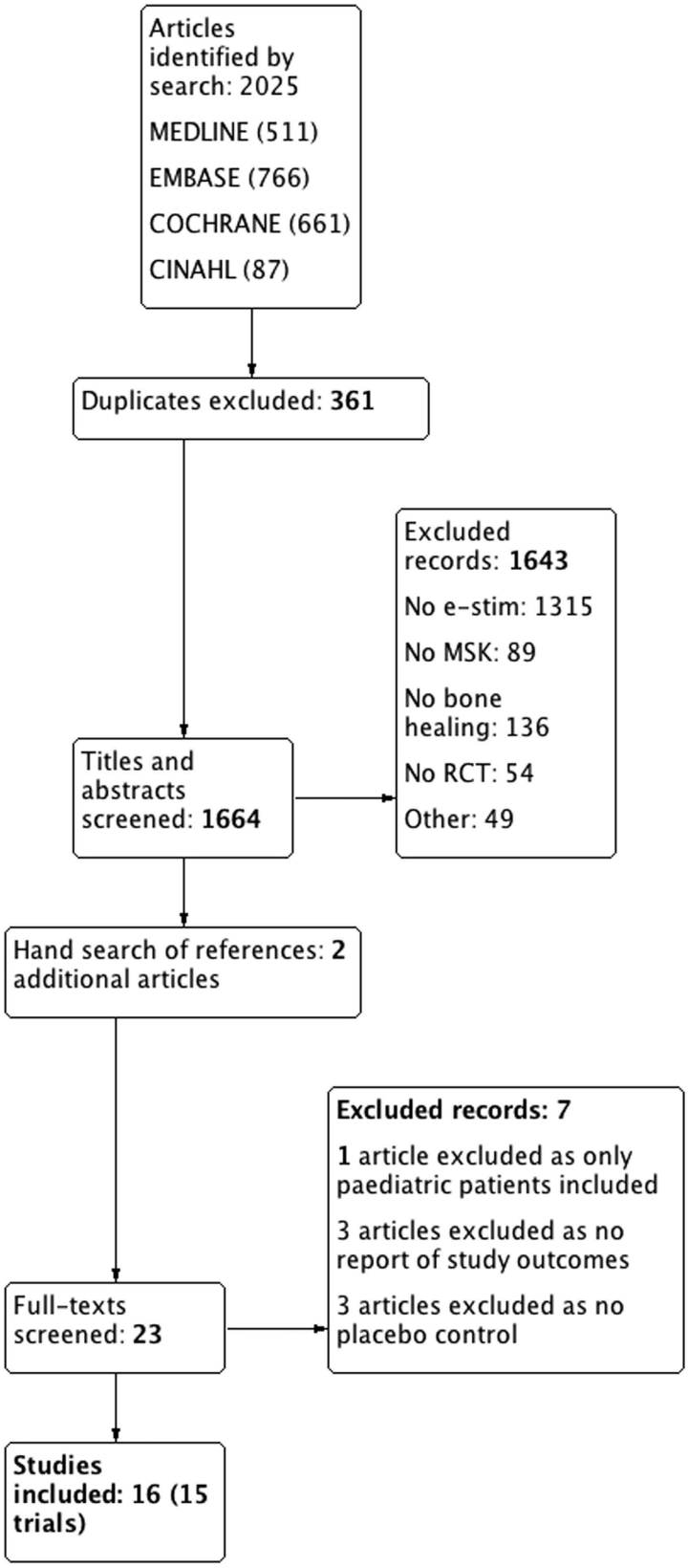

Figure 1. Flow of articles included in the study.

Radiographic nonunion. Radiographic nonunion was compared across 15 trials with 1247 patients. The pooled estimate of effect between electrical stimulation and sham controls at last reported follow-up up to 12

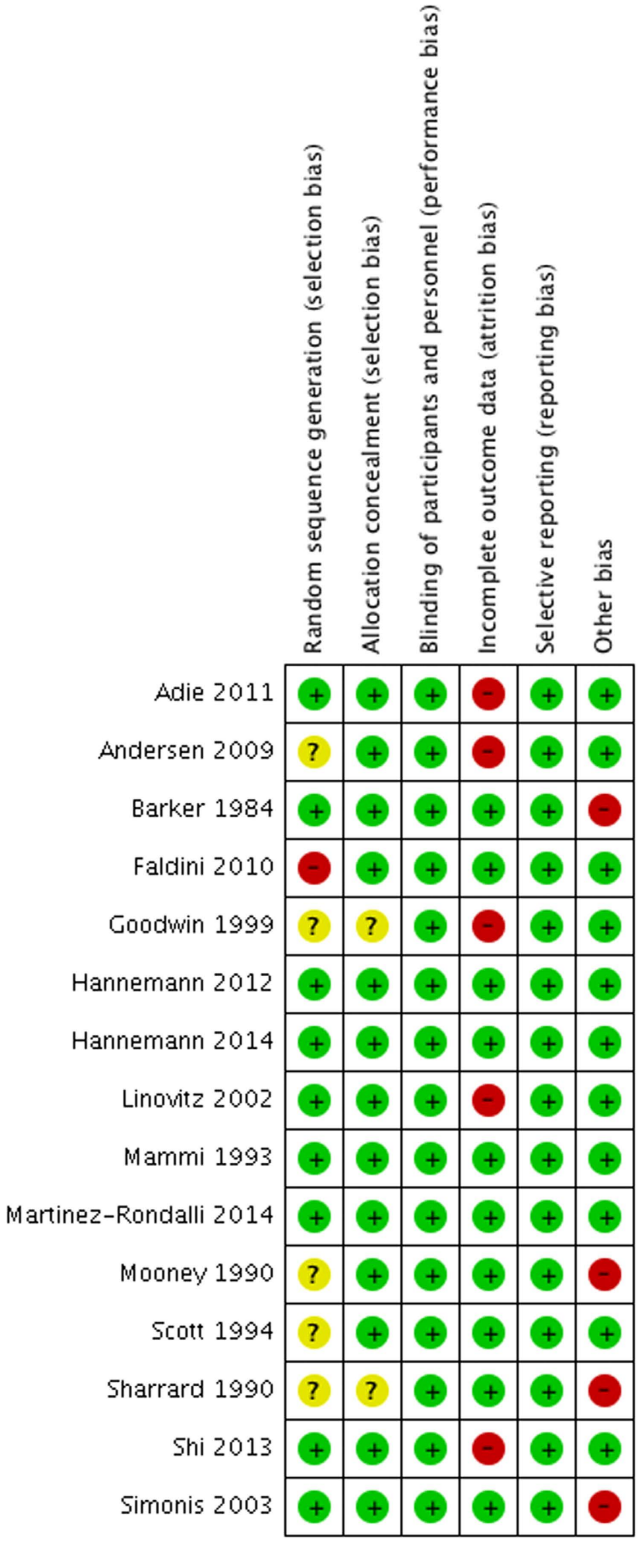

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for included trials. Green circles indicate low risk of bias and red circles indicate high risk of bias.

months found that electrical stimulation reduced the relative risk for nonunion or persistent nonunion by 35% (RR 0.65, 95% CI 0.53 to 0.81, $p < 0.01$, moderate certainty) and the absolute risk by 15%. Overall between-study heterogeneity was moderate ($I^2 = 46\%$; $p = 0.02$) (Fig. 6). Interpreted another way, for every 7 patients treated with electrical stimulation, 1 nonunion or persistent nonunion could be averted (NNT = 7). In the GRADE quality assessment radiographic nonunion was rated as moderate quality evidence due to indirectness (Table 1). We found no evidence to support a difference in treatment effect due to treatment indication (interaction $p = 0.75$)

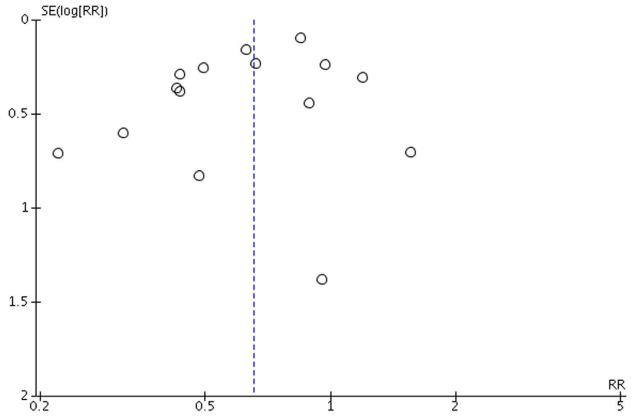

Figure 3. Funnel plot of Standard Error (log(relative risk)) against relative risk to assess for publication bias.

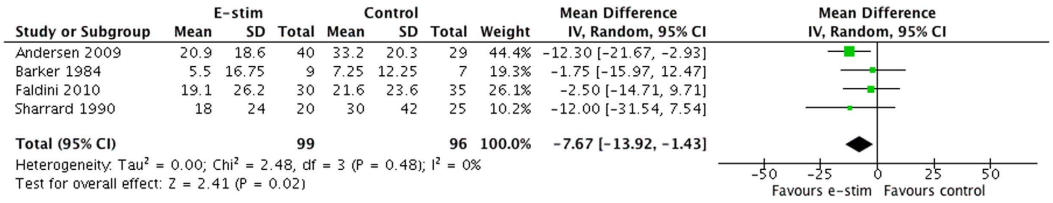

Figure 4. Pooled pain score (mean difference).

or stimulator type (interaction p = 0.05) **(Appendices 5 and 6)**. An analysis conducted with the spine studies removed still showed a significant pooled treatment effect in favor of electrical stimulation for acute fracture, nonunion or delayed union, and osteotomy (RR 0.68, 95% CI 0.50 to 0.91, p = 0.01).

Sensitivity Analyses. Our complete case analysis showed a significant difference (RR 0.66, 95% CI 0.55 to 0.80) that remained robust when assumed nonunion rates in patients with missing data were 1.5:1 and 2:1. When the assumed nonunion rates in patients with missing data went up to 2.5:1 the pooled estimate of effect was no longer significant **(Appendix 7)**.

In only trials in which an independent assessor was used to determine union, a significant difference in favor of electrical stimulation was found (RR 0.69, 95% CI 0.54 to 0.87, $p < 0.01$). Trials in which consensus judgment deemed the definition and assessment as reasonable showed a significant difference in favor of electrical stimulation (RR 0.68, 95% CI 0.55 to 0.85, $p < 0.01$). Finally, the most conservative estimate in only those trials[44,47,50–53,57,58] explicitly defining union as >75% of bony continuity also favored electrical stimulation (RR 0.73, 95% CI 0.58 to 0.91, $p < 0.01$).

Discussion

Our systematic review and meta-analysis of eligible randomized controlled trials found moderate quality evidence for electrical stimulation in reducing patient-reported pain and radiographic nonunion or persistent nonunion. Low-quality functional outcome data showed no difference with electrical stimulation compared to sham treatment.

Our findings are strengthened by our comprehensive search and broad clinical eligibility criteria, and by including only randomized sham-controlled trials. We hypothesized the effect of electrical stimulation on bone healing would be similar across different types of stimulation and different clinical lesions, and our subgroup analyses support this assumption. We found no evidence to support a difference in treatment effect due to treatment indication (interaction p = 0.75). In keeping with other orthopaedic trials of bone healing, most trials reported only surrogate end points. Limited reporting of patient-important outcomes is highlighted in this review and has been identified as a significant problem in the surgical literature[63,64]. The calculation of Minimally Important Differences (MIDs) can further aid the interpretation of treatment effects, but they are often context- or instrument- specific and may have limited generalizability across clinical indications or varying pain measures[65,66]. Although we found the mean difference in pain statistically significant, it is possible that this may not represent a difference important to patients[67].

A Cochrane review published in 2011 reported non-significant differences for electrical stimulation in improving union rates in four trials involving 125 patients[15]. Two reviews done in 2014 also showed an inconclusive benefit of electrical stimulation. Hannemann *et al.*[51,60] performed a systematic review evaluating the effects of low-intensity pulsed ultrasound (LIPUS) and electrical stimulation specifically in acute fractures; results for

Quality assessment							Number of patients		Effect		
# of trials	Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	E-stim	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
15	Radiographic nonunion	Not serious	Not serious	Serious[4]	Not serious	None	162/625 (25.9%)	255/622 (41.0%)	RR 0.65 (0.53 to 0.81)	143 fewer per 1000 (from 78 fewer to 193 fewer)	⊕⊕⊕⊖ MODERATE
								35.0%		123 fewer per 1000 (from 73 fewer to 163 fewer)	
4	Pain	Not serious	Not serious	Not serious	Serious[3]	Not serious	307	305	—	SMD 0.34 lower (0.62 lower to 0.05 lower)	⊕⊕⊕⊖ MODERATE
2	Functional outcome	Serious[1]	Serious[2]	Not serious	Not serious	None	161	155	—	SMD 0.07 higher (0.33 lower to 0.48 higher)	⊕⊕⊖⊖ LOW

Table 1. Combined GRADE and summary of findings table. SMD–standard mean difference, RR–relative risk Rated down primarily due to incomplete outcome data (attrition bias) and selective reporting (reporting bias). [1]Rated down primarily due to incomplete outcome data (attrition bias). [2]Unexplained heterogeneity, $I^2 = 81\%$. [3]95% CI includes values below and above the minimal important difference (MID). [4]Surrogate outcome.

Meta-Analysis Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Akai *et al.*[13]	X	X	X	X	X	X	X	X	X	X	X											
Mollon *et al.*[16]	X			X	X			X				X		X								
Griffin *et al.*[15]	X			X				X						X								
Ebrahim *et al.*[14]	X			X				X						X			X	X	X	X		
Hannemann *et al.*[51,60]																	X	X	X			
Aleem *et al.*	X		X	X	X			X			X		X	X	X	X	X	X	X	X	X	X

Table 2. Trials included in previous meta-analyses and the present study. Barker *et al.*[48], (2) Kane *et al.* (1988), (3) Mooney *et al.*[55], (4) Sharrard *et al.*[57], (5) Mammi *et al.*[53], (6) Kennedy *et al.* (1993), (7) Traina *et al.*[53], (8) Scott *et al.*[56], (9) Capanna *et al.* (1994), (10) Rogozinski *et al.* (1996), (11) Goodwin *et al.*[49], (12) Betti *et al.*[43], (13) Linovitz *et al.*[52], (14) Simonis *et al.*[59], (15) Andersen *et al.* (Part 1)[46], (16) Andersen *et al.* (Part 2)[45], (17) Faldini *et al.*[44], (18) Adie *et al.*[47], (19) Hannemann *et al.*[50], (20) Shi *et al.*[58], (21) Hannemann *et al.*[51,60], (22) Martinez-Rondanelli[54].

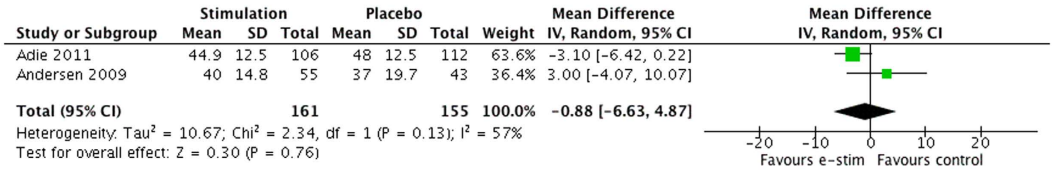

Figure 5. Pooled functional outcome data (mean difference).

LIPUS and electrical stimulation, however, were pooled together and not reported separately. In 2013, Tian *et al.* conducted a meta-analysis looking at the efficacy of various types of electrical stimulation on spinal fusion[18]. Randomized trials and observational trials were, however, combined to provide a pooled estimate and no assessment of methodological quality or risk of bias was performed.

A previous review performed by our group in 2008[16] specifically assessed long-bone fracture healing and failed to show a significant impact of electrical stimulation on radiographic healing, and inconsistent results for pain relief. In 2014[14], we performed a systematic review and network meta-analysis to indirectly comparing low-intensity pulsed ultrasonography (LIPUS) and electrical stimulation. Results were pooled separately by 3, 6 and 12-month time points and a borderline significant effect in improving union rates in nonunions or delayed unions at 3 months with electrical stimulation but not at 6 or 12 months was seen. Two trials included in that review, however, were found to have used the same patient groups on contact with the authors[43,44]. The present review's results differ given that our interpretation of the evidence is based upon the addition of 6 recent trials (424 patients) relating to fresh fractures, nonunions/delayed unions and osteotomies[44,47,50,51,54,58] (Table 2). Moreover, we restricted eligible trials to only sham-controlled randomized trials and assessed both patient-important and radiographic outcomes. Finally, we broadened our eligibility criteria to include bone healing in spinal fusions and tested the assumption regarding similarity of treatment effect using a formal test of

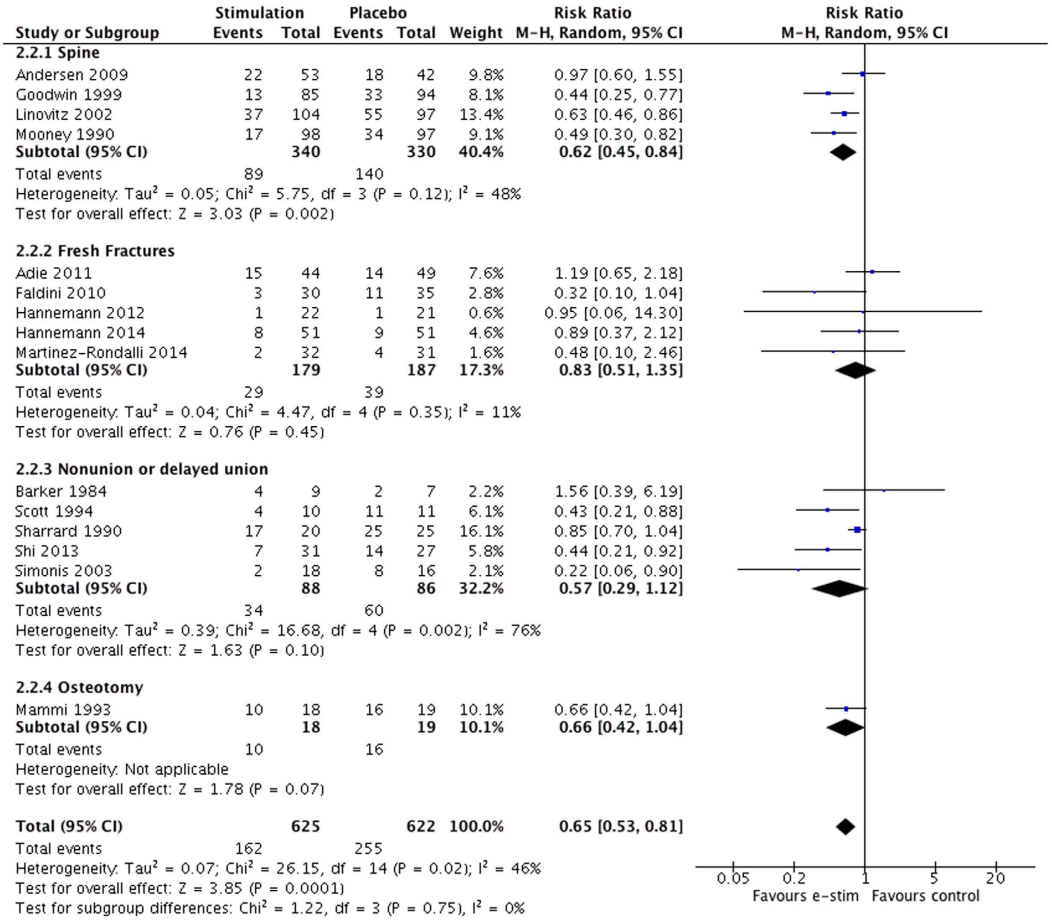

Figure 6. Radiographic nonunion at last reported follow-up to 12 months with subgroups by indication.

interaction. The addition of this information suggests that electrical stimulation for bone healing may improve rates of radiographic union and produce modest but clinically significant improvements in pain relief.

Implications for clinical practice and research. A survey of 450 Canadian trauma surgeons in 2008 (response rate 79%) demonstrated that 23% of surgeons used electrical bone stimulators to accelerate bone healing[68]. Our findings support electrical stimulation as an adjunctive modality for radiographic bone healing and reduction in pain. Large trials of high methodological quality focusing on patient important outcomes are needed to establish the effectiveness of electrical stimulation on functional outcomes[69].

Conclusions

This systematic review and meta-analysis found that patients treated with electrical stimulation as an adjunct for bone healing have significantly less pain and experience lower rates of radiographic nonunion or persistent nonunion. No difference was seen with regards to functional outcomes in a limited number of trials. Future trials focusing on functional outcomes to identify appropriate indications and ideal patient selection are warranted.

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Author Contributions

I.S.A. and M.B. were involved in the study design and concept. I.S.A., I.A., N.E. and A.A. collected the data. I.S.A., I.A., N.E., J.W.B. and M.B. analyzed and interpreted the data. I.S.A., I.A., N.E. and M.B. drafted the initial manuscript. All authors made critical revisions of the manuscript for important intellectual content and approved the final version. I.S.A. is the guarantor.

Additional Information

Supplementary information accompanies this paper at http://www.nature.com/srep

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The Use of Combined Magnetic Field Treatment for Fracture Nonunions: A Prospective Observational Study

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ABSTRACT: This study evaluated the effectiveness and safety of bone growth stimulation using combined magnetic field (CMF) for the treatment of fracture nonunions. In this prospective multicenter study, patients were assessed monthly for 9 mo, or until they demonstrated a healed nonunion, and were assessed at a final follow-up 3 mo after treatment completion. The primary outcome was the presence or absence of fracture healing at the nonunion site, determined by clinical and radiographic assessment. Enrolled in this study were 112 patients with 116 fracture nonunions. Fifty-two (44.8%) patients demonstrated a healed nonunion between treatment initiation and 12-mo–posttreatment initiation (9 mo of treatment plus 3 mo posttreatment follow-up). Tibial nonunions had a higher percentage of healed fractures compared to other fracture types (78% vs. 46.5%, respectively; $p = 0.004$). This study demonstrated that noninvasive CMF technology healed 78% of tibial fracture nonunions and 45% of all fracture nonunions ($p = 0.004$). Additionally, pain at rest, with stress, and on weight bearing all decreased following treatment with CMF, with no adverse events reported. These results indicate that CMF is a beneficial noninvasive treatment modality for nonunions.

KEY WORDS: fracture healing, bone growth stimulation, combined magnetic field, fracture nonunion

I. INTRODUCTION

In the United States, it is estimated that of the 5.6 to 7.9 million fractures occurring annually, 5% to 10% of fracture patients experience a delayed or nonunion of their fracture.[1–3] Patients treated for a fracture are often unable to carry out daily activities, demonstrating a loss of productivity and reduced quality of life.[4] Nonunions are responsible for a large economic burden on society, and morbidity associated with nonunions is substantial. A number of factors are commonly associated with fractures that develop into a nonunion, including inadequate immobilization, comminution and bone defects, concomitant soft tissue damage/high-energy injury, poor vascularity of the fracture site and surrounding soft tissues, and development of local infection at the fracture site.[5] In addition, metabolic factors have been suggested to contribute to the development of a nonunion, including calcium deficiencies, vitamins C and D deficiencies, and smoking.[4,6]

Nonunions are challenging to treat, often requiring surgical revision procedures and prolonged hospital stays. Depending on the fracture location, a nonunion may be treated with external fixation or operatively with plates and screws, intramedullary nails, bone grafting, artificial bone substitutes, or iliac-crest aspirated bone marrow.[7] Surgical intervention for nonunion carries a number of associated risks to consider, including soft tissue injury, long recovery periods, and the potential costs and impacts after subsequent revisions. Additionally, some patients may not be eligible for surgical intervention due to associated risk factors or comorbidities.[8,9] The use of noninvasive bone growth stimulators has been demonstrated to be an effective treatment modality for nonunions, forgoing the need for further surgical intervention and

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associated surgical complications.[1,4] Presently, there are a number of bone growth stimulation methods, including low-intensity pulsed ultrasound (LIPUS) and electrical stimulators (ESTIM), such as direct current, capacitive coupling, or electromagnetic field (EMF) treatments. EMF treatments include both pulsed EMF (PEMF) and combined magnetic field (CMF) treatments.[6,10,11]

LIPUS treatments have been shown to stimulate molecular and cellular responses associated with healing at the fracture site. The ultrasonic waves create micromechanical stresses at the fracture site, which is thought to be the initiator of this healing stimulation.[6,12] ESTIM treatment modalities have demonstrated the capacity to affect growth factors, proteoglycan, cytokine, and collagen synthesis. EMF treatment has been shown to affect membrane receptors and osteoblast stimulation, which releases bone growth factors such as bone morphogenic proteins 2 and 4 and TGF-β.[13,14] This stimulation has also been shown to activate voltage-gated calcium channels, providing a mechanism for fracture healing.[15,16] These effects are seen to ultimately accelerate fracture healing by creating low-energy electromagnetic waves that are thought to mimic the physiologic bone healing response.[6,17–19] Identifying therapies with limited invasiveness and proven efficacy is paramount in the treatment of nonunions. The purpose of this clinical investigation was to evaluate the effectiveness and safety of CMF for the treatment of fracture nonunions.

II. METHODS

A. Study Design

Patients with fracture nonunions were eligible for inclusion in this prospective study (Fig. 1). Fracture

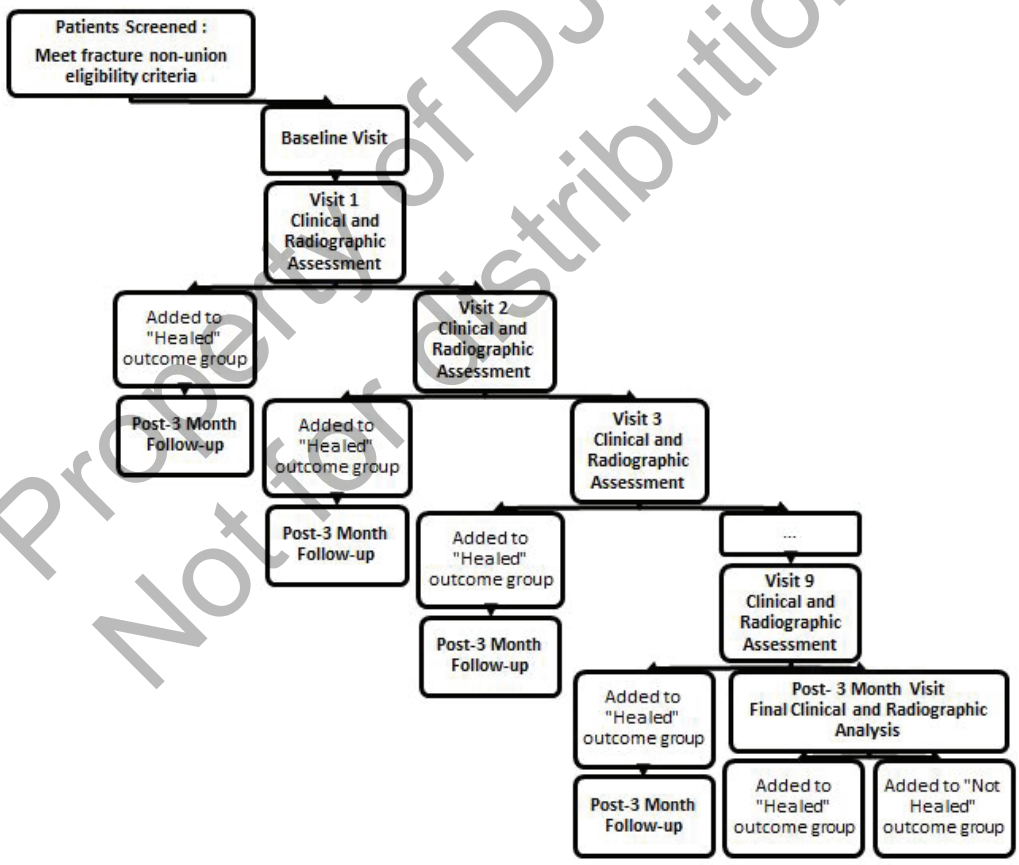

FIG. 1: Study design

nonunion was defined as 9 mo (rounded to the closest month) since injury and before enrollment. No progression to healing on a set of X-rays separated by 3 months was noted. After providing informed consent, eligible patients were treated with CMF for 30 min/d until healed or up to a maximum of 9 mo.

Patients were clinically assessed monthly until clinical healing or study termination at 9 mo. A nonunion was considered healed if no motion was seen clinically at the fracture site, three or more cortices bridged the fracture gap by radiographic assessment, and no pain was associated with the nonunion. Pain was assessed at rest, with the application of stress, and with weight bearing when applicable.

Patients served as their own controls in this pretest/posttest observational study design. This study methodology was used due to the questionable practicality of conducting a randomized controlled trial (RCT) for nonunion treatment, because it is considered unethical to use a placebo or sham device in patients who suffer from a nonunion.

B. Patient Screening

Patients presenting to 17 participating sites in North America (United States: 15 sites; Canada: two sites) with a fracture nonunion were screened for participation in this prospective study by the site investigator. Patients were included based on the following criteria: (1) development of a nonunion following a high- or low-energy trauma; (2) no clinical evidence of union present at least 9 mo after injury; (3) no surgical intervention received within 3 mo before enrollment; (4) no radiographic evidence of healing on two sets of X-rays separated by 3 mo before enrollment; and (5) radiographic evidence of skeletal maturity or at least 18 yr old.

Patients were excluded from participation in this study if (1) written informed consent was not provided; (2) a fracture gap greater than half the diameter of the bone existed; (3) the fracture involved a vertebrae, flat bone (cranial, pelvic, sternal, or rib cage fractures), or pathological fracture; (4) congenital or true synovial pseudoarthrosis existed at the fracture site; (5) nonunion was due to a failed fusion of spine, skull, or joint; (6) pregnancy or became pregnant while enrolled in the study; and (7) a demand-type pacemaker was implanted in proximity to the treatment site.

C. Intervention

The OrthoLogic 1000™ is a CMF bone growth stimulator device that is used as a treatment for fractures that have been deemed nonunion. The OrthoLogic 1000 is portable, battery-powered, noninvasive, and avoids the need for direct skin contact. The device provides local magnetic field treatment through very-low-energy combined static and dynamic magnetic fields, and treatment compliance requires 30 min/d of treatment. The static magnetic field is maintained at a gauss strength of 20 μT, whereas the dynamic magnetic field represents a sine wave, with a frequency of 76.6 Hz, and an amplitude of 40 μT. The OrthoLogic device is capable of recording compliance through documentation of timing and duration of use.

D. Data Collection

After meeting eligibility criteria, baseline demographics were recorded and assessed for each subject. Baseline demographics included gender, age, weight, height, time since injury, medical history, fracture location, and fracture characteristics. Treatments with CMF were provided daily for a maximum 9-mo interval, and patients were clinically and radiographically assessed monthly. Patients underwent a final follow-up 3 mo after their last treatment, during which final outcome data were recorded. The primary outcome was the presence or absence of fracture healing at the nonunion site, as determined by our aforementioned healing criteria. Secondary outcomes included pain at rest, pain on stress, pain on weight bearing, and cortices bridged as seen on X-ray. If the attending surgeon believed that the evaluation would cause pain or harm to the patient due to the precarious nature of the injury, the clinical evaluation was not performed.

E. Data Analysis

The data were pooled across all investigational sites. Descriptive statistics comprised of frequencies for dichotomous data and means, standard deviations,

and ranges for continuous variables were calculated to describe demographic statistics of the patient population. Analyses used in this study included chi-squared analysis of variance and *t*-tests. Statistical significance was determined using calculated significance (*p*) values for 95% or 99% confidence intervals. Data are presented for the total population and for each of three outcome groups: patients who healed, patients who did not heal, and discontinued cases. Patients who demonstrated a healed nonunion at any follow-up stage of the study were analyzed post hoc, apart from patients who did not demonstrate a healed nonunion during the course of the study. The statistical analysis performed looked for similarities and differences among these groups, with respect to demographic and outcomes data.

III. RESULTS

A. Patient Characteristics

Enrolled in this study were 112 patients with 116 fracture nonunions. In four patients, two distinct nonunion sites were treated concurrently. Eleven nonunion fracture sites were seen in this study: tibia (n = 52), femur (n = 19), scaphoid (n = 17), humerus (n = 9), ulna (n = 7), fibula (n = 6), ankle (n = 2), radius (n = 1), metacarpal (n = 1), capitate (n = 1), and metatarsal (n = 1). Fracture characteristics are reported in Table 1. Thirty-two cases were discontinued from active participation during the treatment phase of this study. Sixteen of these (50.0%) cases voluntarily withdrew from the study. In five cases (15.6%), the patients were discontinued by their attending surgeons due to noncompliance with the prescribed use of the study device. Eight of the 32 (25.0%) cases discontinued due to other study-protocol violations. Of these eight deviations, two were a result of uncovering a failed fusion, two were due to the nonunion gap being unstable and exceeding the protocol gap limit, and one discontinuation, respectively, was due to the presence of a pathological fracture, the diagnosis of pseudoarthrosis at the nonunion site, an unreported screw removal surgery by a nonparticipating surgeon, and interference of magnetic waves due to previous total-hip-arthroplasty implant materials. The remaining three cases (9.4%) were unable to continue their treatment due to circumstances that were unanticipated at the time of enrollment. With regard to these three cases, one case was hospitalized for a preexisting medical condition, one case was incarcerated, and one was discontinued due to geographic relocation.

Within the sample, 85 of 116 (73.3%) cases were male, mean age was 38.2 ± 13.1 yr, mean weight was 175.5 ± 40.1 lbs, and mean height was 68.5 ± 3.8 in. The mean time since initial injury for the total population was 29.3 ± 35.6 mo, with an absolute range of 8.5 to 252.9 mo (21.08 yr). Patient demographics and preenrollment medical history are summarized in Table 2.

B. Fracture Healing

During the course of the study, 52 (44.8%) cases demonstrated a healed nonunion, 32 (27.6%) cases did not heal, and 32 (27.6%) cases were discontinued from the study. Nonunion healing occurred at a mean of 6 mo after study enrollment, occurring earliest at 3-mo after study enrollment. Excluding those cases that were discontinued before completing treatment requirements, 52 of 84 (61.9%) cases had a healed nonunion at their final visit.

Cortical bridging was evaluated at each follow-up visit (Fig. 2). For the group that went on to heal, 94.1% (48 of 51) of the cases had none or one bridged cortice at baseline, whereas 100% (32 of 32) of cases within the group that did not heal had no visible cortice bridged on X-ray at baseline. At the 3-mo–posttreatment follow-up visit, 60% (24 of 40) evaluable cases in the healed group had reached four cortices bridged, whereas the remaining 40% (16 of 40) of cases had three cortices bridged. At the 3-mo–posttreatment follow-up visit, 58.3% of cases had no cortical bridging in the nonhealed group (Fig. 2).

C. Pain at the Fracture Site

Only 7.3% (three of the 41 evaluable cases) of healed patients had resting pain at 3 mo posttreatment, compared to 25% (six of the 24 evaluable cases) of patients who did not heal (Fig. 3). Twelve and a half percent (five of 40) of evaluable cases reported

TABLE 1: Fracture characteristics

	Total *n* = 116		Healed *n* = 52		Not Healed *n* = 32		Discontinued *n* = 32	
Fracture characteristic	**Frequency**	**%**	**Frequency**	**%**	**Frequency**	**%**	**Frequency**	**%**
Tibia*	52	44.8	32	61.5	9	28.1	11	34.4
Femur	19	16.3	5	9.6	8	25.0	6	18.8
Scaphoid	17	14.6	4	7.7	8	25.0	5	15.6
Humerus	9	7.8	2	3.9	2	6.3	5	15.6
Ulna	7	6.0	4	7.7	1	3.1	2	6.3
Fibula	6	5.2	1	1.9	3	9.4	2	6.3
Ankle	2	1.7	1	1.9	0	0.0	1	3.1
Radius	1	0.9	0	0.0	1	3.1	0	0.0
Metacarpal	1	0.9	1	1.9	0	0.0	0	0.0
Capitate	1	0.9	1	1.9	0	0.0	0	0.0
Metatarsal	1	0.9	1	1.9	0	0.0	0	0.0
Open fracture	48	41.4	25	48.1	9	28.1	14	43.7
Closed fracture	8	58.6	27	51.9	23	71.9	18	56.3
Low-energy trauma	47	40.9	20	38.5	14	43.8	13	41.9
High-energy trauma	68	59.1	32	61.5	18	56.2	18	58.1
Unknown trauma	1	—	0	—	0	—	1	—
Proximal fracture	18	15.5	6	11.5	7	21.9	5	15.6
Mid fracture	47	40.5	20	38.5	10	31.3	17	53.1
Distal fracture	44	37.9	23	44.2	14	43.8	7	21.9
Intra-articular fracture	6	5.2	2	3.9	2	6.3	2	6.3
Diaphyseal fracture	35	30.2	21	40.4	9	28.1	5	15.6
Metaphyseal fracture	10	8.6	5	9.6	1	3.1	4	12.5
Transverse fracture	51	44.0	17	32.7	16	50.0	18	56.2
Oblique fracture	34	29.3	18	34.6	9	28.1	7	21.9
Spiral fracture	7	6.0	2	3.8	2	6.3	3	9.4
Comminuted fracture	22	19.0	15	28.9	3	9.4	4	12.5
Other fracture	2	1.7	0	0.0	2	6.2	0	0.0
Displaced fracture	53	45.7	26	50.0	19	59.4	8	25.0
Nondisplaced fracture	63	54.3	26	50.0	13	40.6	24	75.0

*When compared to all other fracture sites, tibial fractures contributed a statistically significant amount of healed patients versus nonhealed or discontinued patients.

TABLE 2: Patient demographics

	Total *n* = 116		Healed *n* = 52		Not Healed *n* = 32		Discontinued *n* = 32	
Characteristic	**Mean**	**Range**	**Mean**	**Range**	**Mean**	**Range**	**Mean**	**Range**
Age	38.2 ± 13.1	17.1 – 77.9	37.6 ± 13.0	18.0 – 77.9	37.8 ± 11.4	17.1 – 69.7	39.6 ± 14.9	17.8 – 73.4
Weight (lbs)	175.5 ± 40.1	99.0 – 315.0	173.3 ± 34.8	99.0 – 265.0	172.1 ± 39.1	120.0 – 295.0	182.4 ± 48.7	120.0 – 315.0
Height (in)	68.5 ± 3.8	58.0 – 77.0	68.9 ± 4.3	58.0 – 77.0	68.0 ± 3.2	60.0 – 74.0	68.5 ± 3.4	62.0 – 74.0
Time since injury (mo)**	29.3 ± 35.6	8.5 – 256.0	18.8 ± 13.4	8.9 – 78.6	44.1 ± 55.1	8.5 – 252.9	31.7 ± 30.7	9.1 – 178.7
% Male	73.3		76.9		71.9		68.7	
Medical history	**Frequency**	**%**	**Frequency**	**%**	**Frequency**	**%**	**Frequency**	**%**
Cancer	2	1.7	1	1.9	1	3.1	0	0.0
Cardiovascular disease	4	3.4	2	3.8	0	0.0	2	6.3
Endocrine disorder	2	1.7	1	1.9	1	3.1	0	0.0
Hypertension*	18	15.5	3	5.8	6	18.8	9	28.1
Psychiatric disorder	5	4.3	4	7.7	1	3.1	0	0.0
Pulmonary disorder*	5	4.3	0	0.0	4	12.5	1	1.3
Smoking	65	56.0	29	55.8	16	50.0	20	62.5
Substance abuse	16	13.8	9	17.3	1	3.1	6	18.8

*Statistically significant differences were seen between the healed group and the other outcome groups (both nonhealed and discontinued).

**Statistically significant difference was seen between the healed and not healed groups.

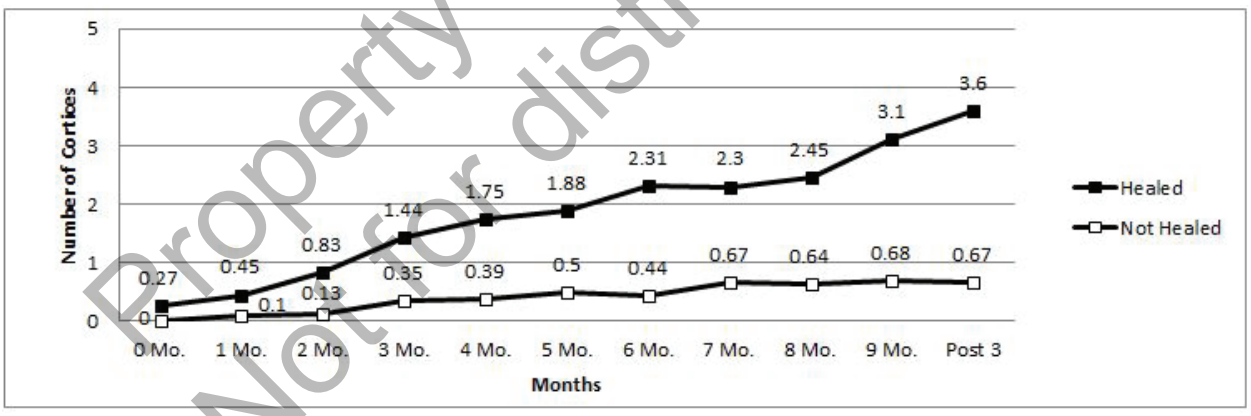

FIG. 2: Average number of cortices bridged

pain with stress at the nonunion fracture site at the 3-mo–posttreatment visit, whereas 62.5% (15 of the 24 evaluable cases) in the nonhealed group still had pain on stress at the 3-mo–posttreatment follow-up (Fig. 4). For the group that went on to heal, 34.4% (11 of 32) patients reporting pain on weight bearing at the 3-mo–posttreatment visit, whereas 58.3% (seven of 12 cases) in the nonhealed group still reported weight-bearing pain (Fig. 5).

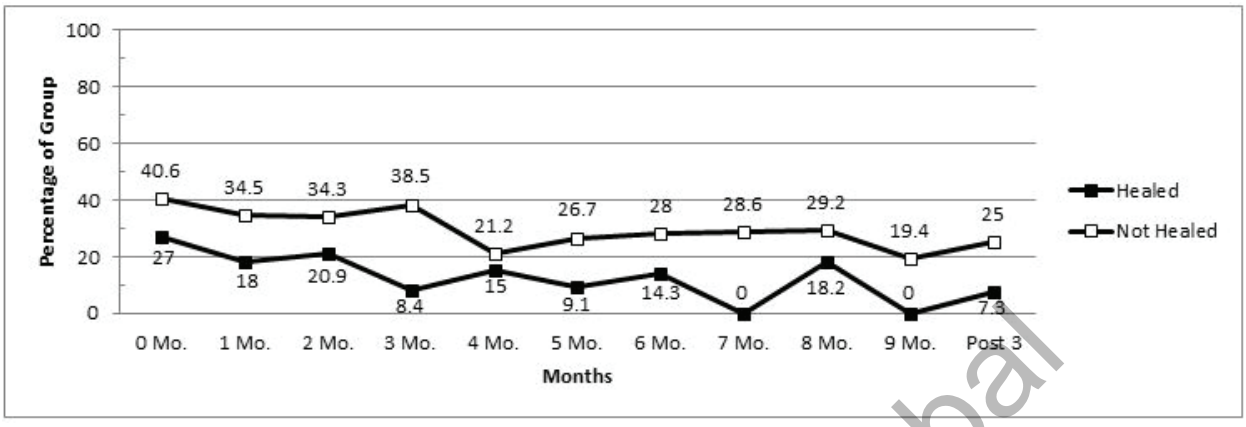

FIG. 3: Presence of pain at rest

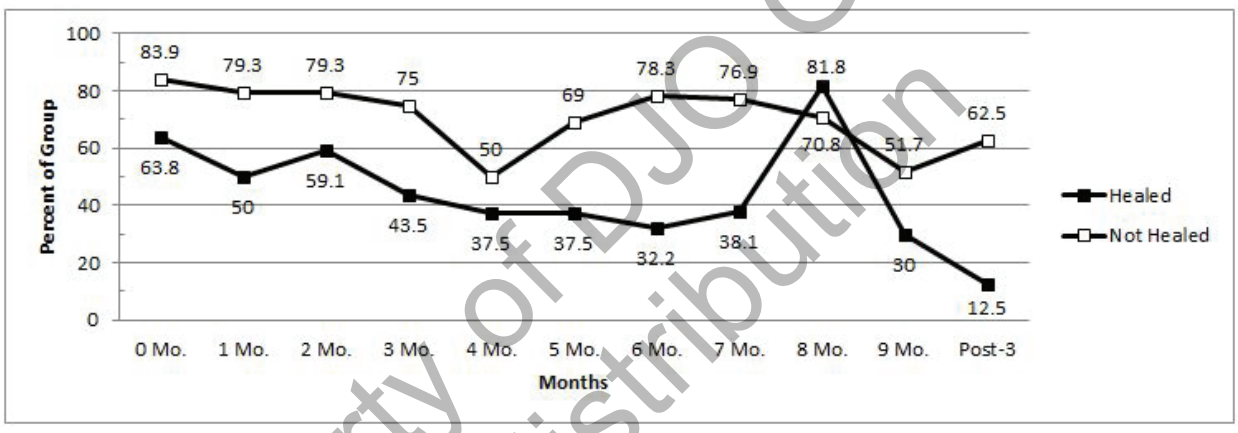

FIG. 4: Presence of pain on stress

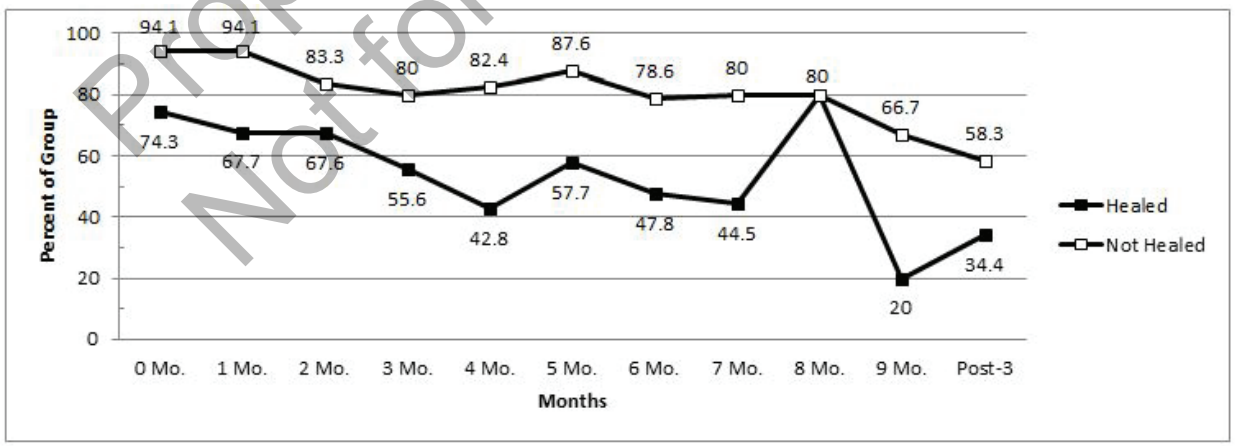

FIG. 5: Presence of pain on weight bearing

D. Prognostic Factors

The nonhealed group demonstrated a significantly longer mean time interval since injury relative to the healed group ($p < 0.001$). There were four patients with >10 yr between their injury and study enrollment in the nonhealed group. If these four cases are omitted from analysis, the nonhealed and healed groups have similar mean times between injury and study enrollment.

Gender, age, weight, and height distribution between the healed and nonhealed group were comparable. There was no significant correlation between successful healing of nonunion and previous history of cancer, cardiovascular disease, endocrine disorder, psychiatric disorder, smoking, or substance abuse. There was a significantly smaller proportion of patients with either hypertension or pulmonary disease within the healed group, when compared to both the nonhealed and discontinued group ($p = 0.019$ and 0.022, respectively).

Tibial fractures demonstrated a significantly greater tendency to heal than other fracture sites: 61.5% of all healed fractures were tibial fractures. In comparison, 28.1% of all nonhealed fractures were tibial fractures. These differences between percentages of tibial nonunion cases that healed compared to those that did not heal or were discontinued were statistically significant ($p = 0.004$). Of the 41 tibial fracture nonunions that made it to study completion, 78.05% (32 of 41) demonstrated a healed nonunion, whereas 46.5% (20 of 43) of nonunions that were not tibial healed (78.05% vs. 46.5%; $p = 0.004$). There were no significant differences between outcome groups with respect to open versus closed fractures, low- versus high-energy trauma, fracture location on bone, or fracture configuration. A significantly greater portion of nondisplaced fractures appeared within the discontinued group, when compared to both the healed and nonhealed groups. This was significant at the 0.05 level ($p = 0.016$).

E. Safety

No adverse events or medical complications related to the use of the OrthoLogic 1000 device were reported during this clinical investigation. Patients reported minor complaints including skin irritation and sensations of burning, tingling, numbness, and discomfort during this study. These symptoms were present at baseline and were related to the condition of the soft and hard tissue at the nonunion site as well as the presence of casts, braces, splints, and fixation devices. In general, complaints reported during the study resolved following diagnosis and correction of the underlying cause.

F. Compliance

The mean compliance for the total population was 73.5 ± 21.3%. The compliance for the healed group was 79.6 ± 17.7%, whereas compliance for the nonhealed and discontinued group was 76.8 ± 17.4% and 60.4 ± 24.9%, respectively. No statistically significant difference in compliance was seen between the healed and nonhealed groups ($p = 0.481$), but the discontinued group demonstrated a statistically significant difference from both the healed ($p < 0.001$) and the nonhealed ($p = 0.003$) groups.

IV. DISCUSSION

This clinical investigation demonstrated the efficacy of CMF bone growth stimulation in the treatment of nonunions; 61.9% of patients who completed the study demonstrated a healed nonunion. All patients demonstrated significant improvement with respect to cortical bridging as well as pain at rest, on stress at the fracture site, and on weight bearing. Patients with a history of hypertension or pulmonary disease may not benefit from CMF bone stimulation treatment to the same extent as other patients. Additionally, patients with an excessively long interval between injury and treatment (10 yr or more) did not respond to CMF treatment.

Tibial fracture nonunions demonstrated a significantly higher proportion of healing than other fracture sites. We found that 78.05% of subjects with tibial fractures who completed the study demonstrated a healed nonunion. In comparison, the next three were the most prevalent fracture sites: 38.5% of femur, 33.3% of scaphoid, and 50% of humerus fractures healed within this study. This is of importance, because tibial shaft fracture nonunions

are typically the most frequent form of long bone nonunion.[20–22] Other studies on the use of EMF treatment demonstrate similar results. A study by Ito and Shirai[23] showed an 83.3% rate of tibial nonunion healing using PEMF treatment. Additionally, PEMF treatment successfully led to a healed tibial nonunion in 77.3% of cases in a study by Assiotis et al.[24]

The rate of femur nonunion healing was lower than that in other studies investigating EMF treatment; a study by Marcer et al.[25] reported successful femoral nonunion healing in 81% of cases using PEMF. The difference is likely due to the small number of femur nonunions included in the current analysis and not to the treatment modality. A literature review suggested that the approximate healing rate of LIPUS treatment for femur nonunion is 82%.[26] Marcer et al.[25] reported that 38.5% of humerus nonunions healed after PEMF treatment, less than the 50% seen in this study. The healing rate of LIPUS treatment for humerus nonunion was reported to be ~67% in an additional literature review.[26]

The results outlined above are difficult to compare to the present study, due to the variability in measurements used to define a nonunion as well as the criteria used to define a healed nonunion. Clearly defined and validated criteria for the definition of a fracture nonunion, as well as for a healed nonunion, are required to be more consistent to provide meaningful comparison among bone growth stimulation options.

The efficacy of CMF bone stimulation treatment in healing unions provides a noninvasive alternative treatment modality, because it forgoes the risk of surgically related complications.[27] Surgical interventions may be successful; however, any surgical procedure is associated with potential medical and fracture-related complications and can be a substantial economic burden to the health care system. Because nonsurgical treatment of nonunions has a lower rate of adverse events, as well as a lower cost to the health care system, noninvasive nonunion fracture treatment should be considered before proceeding with surgery. It is also of note that healing rates in smokers were similar to nonsmokers with use of CMF, despite smoking having a known correlation to impaired fracture healing.[28]

This clinical investigation is strengthened by its detailed reporting and analysis of demographics, medical history, and fracture characteristic data as potential prognostic factors for nonunion treatment with CMF bone stimulation. The study is limited by its pretest/posttest design, because it is not as optimal as an RCT. However, this study design is deemed to be an appropriate choice for a study investigating nonunion treatment, when factoring in the major ethical and administrative issues when conducting an RCT. An RCT would result in 50% of patients, who are already 9 mo postfracture treatment, to undergo another 9 mo of placebo treatment. This is inappropriate due to the extended burden placed on the patient, which can also create a lack of appeal for patients deciding to enroll in this hypothetical RCT. It is for these reasons that a pretest/posttest study was undertaken, to ensure that all patients would receive an active treatment modality for their fracture nonunion. This study is also limited by its lack of patient metabolic status data with respect to serum calcium and vitamin D levels, which may also impact on healing outcomes.

The results of this study demonstrate the effectiveness and safety of using CMF bone stimulation as a treatment modality for fracture nonunions. Specifically, the positive results with respect to tibial fracture nonunion treatment warrants futher investigation of CMF bone stimulation for tibial fracture nonunions using a high-quality large-scale study.

V. CONCLUSION

Fracture nonunions create a significant burden on patients and the health care system, due to the need for surgeries, prolonged hospital stays, and a decrease in patient quality of life. CMF demonstrated substantial healing of established nonunions, especially for individuals with a tibial fracture. This study demonstrated that noninvasive CMF technology healed 78% of tibial fracture nonunions and 45% of all fracture nonunions. There were no complications seen following CMF treatment, demonstrating that it is a safe and effective method of nonoperative treatment for fracture nonunion.

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ORIGINAL RESEARCH

Economic burden of illness among US patients experiencing fracture nonunion

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Objectives: To compare economic outcomes in a real-world study of patients with fracture nonunion receiving non-invasive electrical bone growth stimulation (EBGS), low-intensity pulsed ultrasound stimulation (LIPUS), or other non-stimulation fracture management interventions (No-stim).

Methods: Medical and pharmacy claims from a US commercially-insured population were analyzed to select adult patients newly diagnosed with a fracture nonunion between July 2006 and September 2009. The date of initial nonunion diagnosis was set as the index date. Three cohorts were constructed based on the first treatment prescribed post index date: EBGS, LIPUS, or No-stim. Baseline demographics, clinical characteristics, and health care costs 9 months before and 1 year after the index date were assessed. Multivariate regression analyses were performed to compare health care costs between cohorts in the post index period.

Results: 11,628 patients (mean age 45.4 years; 45.7% males) with a fracture nonunion were identified within the three treatment groups (EBGS: 29.5%, LIPUS: 12.3%, and No-stim: 58.2%). In the post-index period, EBGS patients were significantly less likely to receive fracture-related treatments when compared to the LIPUS (33.6% vs 42.2%, $P < 0.01$) and the No-stim (33.6% vs 60.3%, $P < 0.01$) cohorts. Additionally, after adjusting for demographic and clinical characteristics, the EBGS cohort had significantly lower predicted health care-associated costs 1 year post index date when compared to the LIPUS (mean: $21,632 vs $23,964, $P < 0.01$) and the No-stim (mean: $21,632 vs $23,843, $P < 0.01$) cohorts. Furthermore, the predicted fracture-related costs (FRC) of EBGS patients were also significantly lower than the FRC of the LIPUS (mean: $9100 vs $10,255, $P < 0.01$) and the No-stim (mean: $9100 vs $10,354, $P < 0.01$) patients.

Conclusion: In a real-world setting, EBGS is a more cost-effective fracture nonunion treatment across a variety of fracture locations when compared to LIPUS or No-stim. Fracture nonunion patients receiving EBGS had lower total health care resource use and overall costs as compared to LIPUS or No-stim.

Keywords: electrical bone growth stimulation, low-intensity pulsed ultrasound stimulation, nonunion, fracture, health care utilization, economic burden

Introduction

Approximately 7.9 million patients sustain fractures in the United States annually, and up to 10% go on to have impaired bone healing resulting in a delayed union or a nonunion.[1] The distinction between a delayed union and a nonunion has been redefined over the years. A delayed union is currently defined as a fracture that has slower than expected bone healing.[2] Prior to 1998, the Food and Drug Administration (FDA) defined a nonunion as a fracture 9 months post-injury that shows no visibly

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progressive signs of healing for a minimum of 3 months.[3–5] In 1998, the FDA's Orthopedics and Rehabilitation Device Advisory Panel revised the definition of a nonunion to be a fracture that shows no visibly progressive signs of healing.[3,6] This new definition has no timeframe restrictions associated with the determination of a nonunion.

Not all fractures are alike, and fracture healing has been shown to vary substantially depending on the fracture location. Non-operatively treated clavicular fractures have a reported nonunion rate of 6.2%, but that rate differs by the fracture site: 8.3% for medial end fractures, 4.5% for diaphyseal fractures, and 11.5% for lateral end fractures.[7] Scaphoid fractures have an approximate nonunion rate of 10%, but the risk of nonunion can be as high as 55% when the fracture is displaced.[8] Moreover, depending on the specific fracture characteristics and the initial fracture management, 7%–28% of fractures of the proximal fifth metatarsal result in nonunion.[9] Differences in vascularity at the fracture site, fracture severity, and patient comorbidities affect the ability of different fractures to heal, resulting in the different reported nonunion rates.[10–14] Consequently, individualized fracture management is required to promote fracture healing.

Common methods for treating fracture nonunions include surgical repair, allografts, synthetic bone grafts, autogenous bone grafts, recombinant bone morphogenetic proteins, and amputation when other treatment options have failed to induce healing.[15–18] Non-invasive therapies, including electrical bone growth stimulation (EBGS) and low-intensity pulsed ultrasound stimulation (LIPUS), are FDA regulated Class III medical devices approved for the treatment of fracture nonunions.[14,16,19–23] The first EBGS device received approval for the treatment of fracture nonunions in 1979; since then three additional competitive non-invasive EBGS device systems and one LIPUS device have also received approval for the treatment of fracture nonunions.[19–25] With over 30 years of clinical use, EBGS has proven to be a safe and effective treatment for the management of fracture nonunions.[26–39]

In today's health care environment, understanding the economic evaluation of different treatment options is important. In 2006, bone growth stimulation represented a $500 million market in the US for fracture management as a result of the significant economic burden associated with fracture nonunions.[40] An economic review conducted by Kanakaris and Giannoudis reported that the average direct costs for treating humeral, femoral, and tibial fracture nonunions were £15,566, £17,200, and £16,330, respectively, in the United Kingdom in 2007. Converted to US dollars, these costs are equivalent to $31,132, $34,400, and $32,660, respectively.[41] While existing clinical literature supports the efficacy and safety of non-invasive EBGS therapy in the treatment of fracture nonunions,[26–39] the economic data supporting its use in the US is sparse. Therefore, the objective of this study was to evaluate the real-world cost-effectiveness of EBGS in the treatment of fracture nonunions. This study compares the demographic differences, clinical characteristics, and treatment patterns of patients receiving EBGS, LIPUS, or no stimulation (No-stim) treatment for the management of their fracture nonunions and the health care resource use and costs associated with these different treatment options.

Methods

Data source and sample selection

This retrospective study utilized administrative claims data from the Truven Health Analytics MarketScan Commercial Insurance Databases[42] from October 2005 through September 2010. Patients were included in the study if they had at least one medical claim with associated diagnosis suggesting fracture nonunion (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 733.82) between July 2006 and September 2009. Patients may have had multiple medical claims with associated diagnosis codes suggesting fracture nonunion for the initial diagnosis, subsequent treatment, and follow-up visits; therefore, the date of the first such medical claim was set as the index date. Patients were required to have at least one medical claim related to the diagnosis of their fracture in the 9 months prior to the index date. Only patients with claims for fractures of the appendicular system were included. Additional inclusion criteria required patients to be between 18–64 years old on the index date (this age range represents a commercially insured patient population; patients 65 years old or older were excluded as these patients are typically insured by Medicare and Medicaid), and have a minimum of 9 months of insurance eligibility prior to and 12 months following the index date. Patients were excluded if they had claims suggesting cancer metastasis (ICD-9-CM: 198.5), malignant tumor of bone (ICD-9-CM: 170.xx), fracture nonunion, use of EBGS or LIPUS, or fractures in multiple locations during the 9 months before the index date (Figure 1).

Three cohorts were created based on the first treatment that patients received within the 12 months following the index date: EBGS, LIPUS, and No-stim. The use of EBGS was identified if a medical claim had an associated Current Procedural Terminology (CPT) code of 20974 or Healthcare

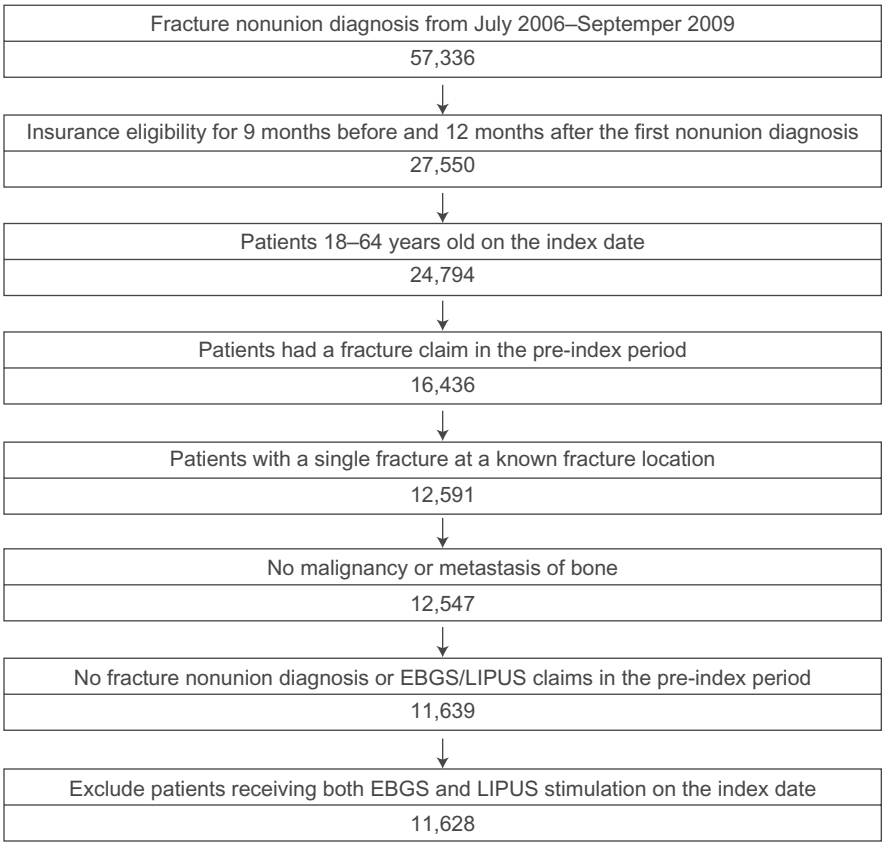


Figure 1 Selection flow chart for patient eligibility.
Abbreviations: EBGS, electrical bone growth stimulation; LIPUS, low-intensity pulsed ultrasound stimulation.

Common Procedure Coding System (HCPCS) code of E0747. Use of LIPUS was identified if a claim had an associated CPT code of 20979 or HCPCS code of E0760. The No-stim cohort included those patients with fracture nonunion diagnosis that did not receive EBGS or LIPUS after the index date.

Study measures

Demographic parameters including age, gender, geographic region of US residence (Northeast, North Central, South, West, and unknown), and insurance plan type (health maintenance organization, preferred provider organization, comprehensive, point of service, exclusive provider organization, and consumer-directed health plans) are listed in Table 1. Comorbidities and risk factors for fracture nonunion were assessed based on medical and pharmacy claims in the 9 months before the index date. The burden of chronic diseases was measured by the Charlson Comorbidity Index (CCI).[43,44] Fracture characteristics including open vs closed, fracture location, and the time between initial fracture and nonunion diagnosis were also reported. Clinical outcomes were neither reported nor available from the database for analysis.

Health care costs for the 9 months before and the 12 months after the index date were evaluated. Total health care costs included the costs associated with inpatient care, outpatient care, and medication use. Fracture-related costs included all claims associated with services required to diagnose and treat the patient's fracture. Pharmacy-related costs were excluded from the fracture-related costs as there are no specific medications designated for the treatment of a fracture. All costs were adjusted for inflation using the Consumer Price Index and standardized to 2011 US dollars so that cost measures from different years would be comparable.[45]

Statistical analysis

Descriptive statistics for demographics, comorbidities, treatment patterns, fracture locations, and post-index health care and fracture-related costs were compared among the three different treatment cohorts. Percentages were reported for categorical variables, while the mean and standard deviation were reported for continuous variables. A Student's *t*-test was used to detect differences in age and days between initial fracture and nonunion diagnosis; a χ^2 test was used to detect

Table 1 Demographics and comorbidities of the three treatment cohorts: EBGS, LIPUS and No-stim

	Treatment cohorts						*P*-values		
	EBGS (N = 3,430)		LIPUS (N = 1,434)		No-stim (N = 6,764)		EBGS vs LIPUS	EBGS vs No-stim	LIPUS vs No-stim
	N	(%)	N	(%)	N	(%)			
Age (years)							0.51	<0.01	<0.01
18–24	345	(10.1)	133	(9.3)	978	(14.5)			
25–34	316	(9.2)	118	(8.2)	708	(10.5)			
35–44	597	(17.4)	242	(16.9)	1,137	(16.8)			
45–54	1,084	(31.6)	456	(31.8)	1,888	(27.9)			
55–64	1,088	(31.7)	485	(33.8)	2,053	(30.4)			
Gender							0.77	<0.01	<0.01
Male	1,379	(40.2)	583	(40.7)	3,350	(49.5)			
Female	2,051	(59.8)	851	(59.3)	3,414	(50.5)			
Insurance plan type							0.06	0.08	<0.01
Comprehensive	104	(3.0)	31	(22)	265	(3.9)			
EPO	16	(0.5)	8	(0.6)	30	(0.4)			
HMO	503	(14.7)	192	(13.4)	1,003	(14.8)			
POS	339	(9.9)	143	(10.0)	584	(8.6)			
PPO	2,254	(65.7)	995	(69.4)	4,542	(67.1)			
POS w/capitation[a]	25	(0.7)	3	(0.2)	42	(0.6)			
CDHP	86	(2.5)	28	(2.0)	146	(2.2)			
Missing/unknown	103	(3.0)	34	(2.4)	152	(2.2)			
Region							<0.01	<0.01	<0.01
Northeast	481	(14.0)	131	(9.1)	640	(9.5)			
North Central	769	(22.4)	304	(21.2)	1,944	(28.7)			
South	1,481	(43.2)	739	(51.5)	2,744	(40.6)			
West	625	(18.2)	223	(15.6)	1,309	(19.4)			
Unknown	74	(2.2)	37	(2.6)	127	(1.9)			
Charlson Comorbidity Index							0.47	<0.01	0.01
CCI = 0	2,394	(69.8)	1,012	(70.6)	5,029	(74.3)			
CCI = 1	344	(10.0)	154	(10.7)	567	(8.4)			
CCI = 2	443	(12.9)	163	(11.4)	685	(10.1)			
CCI > 3	249	(7.3)	105	(7.3)	483	(7.1)			
Comorbidities of fracture nonunion									
Diabetes	479	(14.0)	183	(12.8)	742	(11.0)	0.26	<0.01	0.05
Osteoporosis	173	(5.0)	66	(4.6)	271	(4.0)	0.52	0.02	0.30
Malnutrition	3	(0.1)	4	(0.3)	20	(0.3)	0.11	0.04	0.92
Anemia	234	(6.8)	121	(8.4)	498	(7.4)	0.05	0.32	0.16
Risk factors of fracture nonunion									
Smoking	7	(0.2)	5	(0.3)	23	(0.3)	0.35	0.23	0.96
Excessive alcohol drinking	27	(0.8)	5	(0.3)	57	(0.8)	0.09	0.77	0.05
Received chemotherapy	79	(2.3)	43	(3.0)	142	(2.1)	0.16	0.50	0.04
Received steroid	651	(19.0)	308	(21.5)	1,254	(18.5)	0.05	0.59	0.01
Received NSAIDs	940	(27.4)	370	(25.8)	1,563	(23.1)	0.25	<0.01	0.03

Note: [a]Capitation pays a physician or group of physicians a set amount for each enrolled person assigned to them, per period of time, whether or not that person seeks care.
Abbreviations: CCI, Charlson Comorbidity Index; CDHP, consumer-directed health plan; EBGS, electrical bone growth stimulation; EPO, exclusive provider organization; HMO, health maintenance organization; LIPUS, low-intensity pulsed ultrasound stimulation; No-stim, other non-stimulation fracture management interventions; NSAIDs, non-steroidal anti-inflammatory drugs; POS, point of service; PPO, preferred provider organization.

differences for categorical variables; and a non-parametric Wilcoxon test was used to detect differences for CCI scores and health care and fracture-related costs. A generalized linear regression model (GLM) assuming gamma distribution and log link function was utilized to compare the total and fracture-related health care costs between treatment cohorts while controlling for between-cohort differences in patient demographics and baseline clinical characteristics. Because it is difficult to interpret the log-transformed regression coefficients from the GLM, predicted health care costs and the marginal effect of treatment were estimated. Specifically, the predicted costs for EBGS were estimated by applying the regression coefficients derived from the GLM to the covariates included in the model, and setting

EBGS to 1 and LIPUS to 0 while other covariates remained constant. Similarly, the predicted costs for LIPUS treatment were estimated by setting EBGS to 0 and LIPUS to 1, while the predicted costs for No-stim treatment were estimated by setting both EBGS and LIPUS to 0. An analysis of the marginal effects of treatment demonstrated how total and fracture-related health care costs are predicted to change as treatment changes from No-stim to EBGS to LIPUS.

Results

Among the commercially insured individuals in the dataset, 57,336 patients had at least one claim for fracture nonunion from July 2006 to September 2009. After applying the inclusion/exclusion criteria, 11,628 patients were selected for further study analysis (Figure 1): 3430 patients (29.5%) were in the EBGS cohort, 1434 patients (12.3%) were in the LIPUS cohort, and 6764 patients (58.2%) were in the No-stim cohort.

Basic patient demographics found that the average patient age was 45.4 years old (standard deviation: 13.4), 45.7% were males, 67.0% were enrolled in preferred provider organization plans, and 42.7% resided in the southern United States. Overall, the EBGS and LIPUS cohorts were similar in the distribution of age, gender, and type of patient insurance plan. However, both stimulation cohorts had more female patients and a higher average age than the No-stim cohort (Table 1).

Patients within the different treatment groups were also evaluated for fracture risk factors and comorbidities as these factors have been previously shown to have a negative impact on the success of bone healing.[10–14] Diabetes was the most common condition among the comorbidities associated with increased risk of fracture nonunion (Table 1). The proportion of patients with diabetes was significantly higher in the EBGS cohort when compared to the No-stim cohort (14.0% vs 11.0%, $P < 0.01$), but was not significantly different between the EBGS and LIPUS cohorts (14.0% vs 12.8%, $P = 0.26$). The proportion of patients receiving non-steroidal anti-inflammatory drugs was significantly higher in the EBGS cohort (27.4% vs 23.1%, $P < 0.01$) and the LIPUS cohort (25.8% vs 23.1%, $P = 0.03$) when compared to the No-stim cohort. In addition, both the EBGS (CCI = 0: 69.8% vs 74.3%, $P < 0.01$) and the LIPUS (CCI = 0: 70.6% vs 74.3%, $P = 0.01$) cohorts were less likely to have low CCI scores when compared to the No-stim cohort.

Basic fracture characteristics found that tarsal and metatarsal fractures were the most common nonunion fractures treated; the average time between initial fracture and nonunion diagnosis was 130–136 days; and 3.6% of the initial fractures were open fractures. The No-stim cohort had a significantly higher proportion of patients with open fractures than the EBGS (4.4% vs 2.7%, $P < 0.01$) and the LIPUS (4.4% vs 1.8%, $P < 0.01$) cohorts (Table 2). Additionally, although the EBGS and LIPUS cohorts had a comparable distribution of fractures treated by bone location ($P = 0.17$), the distribution was significantly different when compared to the No-stim cohort (both $P < 0.01$).

In the 9 months prior to the index date, the EBGS and LIPUS cohorts had a similar number of fracture-related interventions (60.1% vs 57.5%, $P = 0.10$). The No-stim cohort, however, had significantly fewer fracture-related interventions compared to either the EBGS (60.1% vs 48.0%, $P < 0.01$) or the LIPUS (57.5% vs 48.0%, $P < 0.01$) cohorts (Table 2). The most common fracture-related treatment was the application of a cast/splint. The EBGS and LIPUS cohorts had significantly more patients receiving a cast/splint to manage their fractures than the No-stim cohort (EBGS vs No-stim: 32.3% vs 24.3%, $P < 0.01$; LIPUS vs No-stim: 31.0% vs 24.3%, $P < 0.01$). Open reduction with internal fixation was the most common invasive treatment. The EBGS and LIPUS cohorts had a similar proportion of open reduction procedures (20.8% vs 19.1%, $P = 0.19$). However, both had a significantly higher proportion of open reduction procedures compared to the No-stim cohort (EBGS vs No-stim: 20.8% vs 14.5%, $P < 0.01$; LIPUS vs No-stim: 19.1% vs 14.5%, $P < 0.01$).

During the 12-month post-index period, the proportion of fracture-related procedures was significantly less in the EBGS cohort than in the No-stim (33.6% vs 60.3%, $P < 0.01$) and LIPUS (33.6% vs 42.2%, $P < 0.01$) cohorts. Additionally, the LIPUS cohort also had significantly fewer fracture-related interventions when compared to the No-stim cohort (42.2% vs 60.3%, $P < 0.01$) (Table 2). Bone grafting was the most common fracture-related treatment in the post-index period. The proportion of patients that underwent bone grafting procedures was significantly lower in the EBGS cohort than in the LIPUS (16.2% vs 22.2%, $P < 0.01$) or the No-stim (16.2% vs 31.8%, $P < 0.01$) cohorts. Similarly, the LIPUS cohort had significantly fewer patients treated by bone grafting procedures when compared to the No-stim cohort (22.2% vs 31.8%, $P < 0.01$). The other documented non-stimulation fracture management interventions included cast/splint, application of external fixation device, closed reduction with and without internal fixation, open reduction with and without internal fixation, and arthroscopy.

The total health care costs in the 9 months prior to the index date were significantly higher in the EBGS

Table 2 Characteristics of fracture-related treatments in the different treatment cohorts

	Treatment cohorts			*P*-values		
	EBGS (N = 3,430)	LIPUS (N = 1,434)	No-stim (N = 6,764)	EBGS vs LIPUS	EBGS vs No-stim	LIPUS vs No-stim
Days between first fracture claim and nonunion, mean (SD)	135 (75)	136 (78)	130 (88)	0.50	<0.01	<0.01
Open fracture, N (%)	93 (2.7)	26 (1.8)	299 (4.4)	0.06	<0.01	<0.01
Fracture location, N (%)				0.17	<0.01	<0.01
Clavicle	207 (6.0)	96 (6.7)	565 (8.4)			
Humerus	180 (5.2)	65 (4.5)	431 (6.4)			
Radius and ulna	210 (6.1)	97 (6.8)	688 (10.2)			
Carpal	261 (7.6)	107 (7.5)	993 (14.7)			
Metacarpal	47 (1.4)	8 (0.6)	146 (2.2)			
Phalanges of hand	29 (0.8)	11 (0.8)	363 (5.4)			
Neck of femur	35 (1.0)	13 (0.9)	213 (3.1)			
Other parts of femur	78 (2.3)	47 (3.3)	163 (2.4)			
Tibia and fibula	332 (9.7)	160 (11.2)	374 (5.5)			
Ankle	275 (8.0)	133 (9.3)	690 (10.2)			
Tarsal and metatarsal bones	1,661 (48.4)	645 (45.0)	1,609 (23.8)			
Phalanges of foot	76 (2.2)	33 (2.3)	263 (3.9)			
Other	39 (1.1)	19 (1.3)	266 (3.9)			
Treatment in 9 months before index date						
Any fracture-related treatment, N (%)[a]	2,061 (60.1)	825 (57.5)	3,244 (48.0)	0.10	<0.01	<0.01
Cast/splint	1,107 (32.3)	444 (31.0)	1,645 (24.3)	0.37	<0.01	<0.01
Application of external fixation device	107 (3.1)	64 (4.5)	188 (2.8)	0.02	0.33	<0.01
Closed reduction without internal fixation	152 (4.4)	69 (4.8)	290 (4.3)	0.56	0.74	0.38
Closed reduction with internal fixation	58 (1.7)	31 (2.2)	213 (3.1)	0.26	<0.01	0.05
Open reduction without internal fixation	421 (12.3)	148 (10.3)	590 (8.7)	0.05	<0.01	0.05
Open reduction with internal fixation	712 (20.8)	274 (19.1)	982 (14.5)	0.19	<0.01	<0.01
Bone graft	80 (2.3)	39 (2.7)	103 (1.5)	0.43	<0.01	<0.01
Arthroscopy	83 (2.4)	45 (3.1)	144 (2.1)	0.15	0.35	0.02
Treatment in 12 months after index date						
Any fracture-related treatment, N (%)[a]	1,151 (33.6)	605 (42.2)	4,077 (60.3)	<0.01	<0.01	<0.01
Cast/splint	582 (17)	275 (19.2)	1,635 (24.2)	0.07	<0.01	<0.01
Application of external fixation device	48 (1.4)	21 (1.5)	152 (2.2)	0.86	<0.01	0.06
Closed reduction without internal fixation	46 (1.3)	21 (1.5)	87 (1.3)	0.74	0.82	0.59
Closed reduction with internal fixation	4 (0.1)	3 (0.2)	25 (0.4)	0.44	0.02	0.34
Open reduction without internal fixation	204 (5.9)	95 (6.6)	1,043 (15.4)	0.37	<0.01	<0.01
Open reduction with internal fixation	362 (10.6)	199 (13.9)	1,640 (24.2)	<0.01	<0.01	<0.01
Bone graft	555 (16.2)	319 (22.2)	2,148 (31.8)	<0.01	<0.01	<0.01
Arthroscopy	107 (3.1)	53 (3.7)	377 (5.6)	0.30	<0.01	<0.01

Notes: [a]Overall values indicate the total number of patients receiving some fracture-related treatment. The treatment groups detail the incidence of the individual treatments. Some patients may have received more than one treatment.

Abbreviations: EBGS, electrical bone growth stimulation; LIPUS, low-intensity pulsed ultrasound stimulation; No-stim, other non-stimulation fracture management interventions; SD, standard deviation.

(mean: $16,749; median: $7824) and LIPUS (mean: $19,441; median $8574) cohorts than in the No-stim cohort (mean: $16,360; median: $5548) (both $P < 0.01$). However, total health care costs were not significantly different between the EBGS and LIPUS cohorts ($P = 0.12$) (Table 3). Outpatient care, the biggest component of the total health care costs, was significantly higher in the EBGS (mean: $9146; median: $5417) and LIPUS (mean: $9789; median: $5586) cohorts than in the No-stim cohort (mean: $8159; median: $3967) (both $P < 0.01$).

Fracture-related health care costs in the pre-index period were the highest in the LIPUS cohort (mean: $8749; median: $1089) followed by the EBGS (mean: $7392; median: $1223) and No-stim (mean: $7129; median: $893) cohorts (all pair-wise comparisons: $P < 0.01$) (Table 3). Inpatient stays were the highest portion of the fracture-related health care costs in the pre-index period. Pre-index fracture-related inpatient costs were significantly higher in the LIPUS cohort (mean: $6258; median: $0) than in the EBGS (mean: $4726; median: $0) ($P = 0.02$) and No-stim

Table 3 Health care costs before and after the index date for patients in the different treatment cohorts[a]

	Treatment cohorts									*P*-values		
	EBGS (N = 3,430)			LIPUS (N = 1,434)			No-stim (N = 6,764)			EBGS vs LIPUS	EBGS vs No-stim	LIPUS vs No-stim
	Mean	Standard error	Median	Mean	Standard error	Median	Mean	Standard error	Median			
Costs in 9 months before index date ($)												
Total health care costs	16,749	716	7,824	19,441	1,048	8,574	16,360	473	5,548	0.12	<0.01	<0.01
Cost of inpatient admissions	6,051	639	0	8,168	754	0	6,801	348	0	<0.01	0.80	<0.01
Cost of outpatient services	9,146	209	5,417	9,789	492	5,586	8,159	229	3,967	0.56	<0.01	<0.01
Cost of medications	1,551	57	277	1,484	161	223	1,401	45	139	0.03	<0.01	0.26
Fracture-related health care costs	7,392	639	1,223	8,749	737	1,089	7,129	320	893	<0.01	<0.01	<0.01
Cost of inpatient admissions	4,726	625	0	6,258	693	0	4,974	304	0	0.02	0.71	<0.01
Cost of outpatient services	2,666	77	1,072	2,491	149	919	2,155	52	799	<0.01	<0.01	<0.01
Costs in 12 months after index date ($)												
Total health care costs	20,743	601	11,233	23,271	929	12,456	24,315	553	12,255	<0.01	0.81	<0.01
Cost of inpatient admissions	4,746	432	0	6,526	643	0	9,182	385	0	<0.01	<0.01	<0.01
Cost of outpatient services	13,790	300	8,876	14,584	428	9,608	13,198	279	8,642	<0.01	<0.01	<0.01
Cost of medications	2,207	82	379	2,161	208	331	1,934	62	243	<0.01	<0.01	<0.01
Fracture-related health care costs	8,103	226	4,075	9,777	365	4,309	10,984	290	4,769	<0.01	<0.01	<0.01
Cost of inpatient admissions	2,150	191	0	3,168	312	0	5,896	277	0	<0.01	<0.01	<0.01
Cost of inpatient services	5,952	102	4,027	6,609	167	4,141	5,088	84	2,937	<0.01	<0.01	<0.01

Note: [a]All costs presented are in US dollars and represent raw, unadjusted costs observed in the medical claims dataset.

Abbreviations: EBGS, electrical bone growth stimulation; LIPUS, low-intensity pulsed ultrasound stimulation; No-stim, other non-stimulation fracture management interventions.

(mean: $4974; median: $0) ($P < 0.01$) cohorts. Additionally, the costs for fracture-related outpatient services were significantly higher in the EBGS (mean: $2666; median: $1072) and LIPUS (mean: $2491; median: $919) cohorts when compared to the No-stim (mean: $2155; median: $799) cohort (both $P < 0.01$).

During the year following the first nonunion diagnosis, the total health care costs for the EBGS cohort (mean: $20,743; median: $11,233) were significantly lower than the costs for the LIPUS cohort (mean: $23,271; median: $12,456) ($P < 0.01$), but not significantly different from that of the No-stim cohort (mean: $24,315; median: $12,255) ($P = 0.81$) (Table 3). The inpatient costs were the lowest in the EBGS cohort (mean: $4746; median: $0), followed by the LIPUS (mean: $6526; median: $0) and then the No-stim (mean: $9182; median: $0) cohorts (all pair-wise comparisons: $P < 0.01$).

The fracture-related costs in the 12 months after the index date were the lowest in the EBGS cohort (mean: $8103; median: $4075), followed by the LIPUS (mean: $9777; median: $4309) and the No-stim (mean: $10,984; median: $4769) cohorts (all pair-wise comparisons: $P < 0.01$). Similarly, the fracture-related inpatient costs were the lowest in the EBGS cohort (mean: $2150; median: $0), followed by the LIPUS (mean: $3168; median: $0) and then the No-stim (mean: $5896; median: $0) cohorts (all pair-wise comparisons: $P < 0.01$). Conversely, the fracture-related outpatient costs (which includes device associated costs) were the lowest in the No-stim cohort (mean: $5088; median: $2937), followed by the EBGS (mean: $5952; median: $4027) and LIPUS (mean: $6609; median: $4141) cohorts (all pair-wise comparisons: $P < 0.01$).

After controlling for demographics, CCI score, and fracture characteristics (open vs closed, treatments in the pre-index period, and fracture location), the EBGS cohort had significantly lower total health care (estimated regression coefficient = –0.097, $P < 0.01$) and fracture-related (estimated regression coefficient = –0.129, $P < 0.01$) costs in the 12 months following nonunion diagnosis when compared to the No-stim cohort; whereas patients in the LIPUS cohort had similar total health care (estimated regression coefficient = 0.005, $P = 0.86$) and fracture-related (estimated regression coefficient = –0.013, $P = 0.71$) costs to patients in the No-stim cohort (Table 4). Older age and higher CCI scores were associated with significantly higher total health care costs. Other factors associated with significantly higher total health care costs included living in the West region as compared to the South (estimated regression coefficient = 0.129, $P < 0.01$), receiving a cast/splint vs no cast/splint before nonunion diagnosis (estimated regression coefficient = 0.056, $P = 0.01$), receiving open reduction vs no open reduction (estimated regression coefficient = 0.095, $P < 0.01$), receiving other invasive treatments including bone graft, bone marrow aspiration, arthroscopy, amputation, or implant of recombinant bone morphogenetic protein vs not (estimated regression coefficient = 0.375, $P < 0.01$), and having a fracture in the arm (estimated regression coefficient = 0.170, $P < 0.01$) or the leg (estimated regression coefficient = 0.653, $P < 0.01$) vs in the foot. Similar patterns were found for fracture-related costs (Table 4).

Predicted total and fracture-related health care costs were generated based on the GLM and the regression coefficients generated in Table 4. The predicted total health care costs in the 12 months following nonunion diagnosis for the EBGS cohort ($21,632) were significantly lower than the No-stim ($23,843, marginal difference: –$2211, $P < 0.01$) and the LIPUS ($23,964, marginal difference: –$2332, $P < 0.01$) cohorts (Figure 2). Meanwhile, the marginal difference between the predicted total health care costs of the LIPUS and the No-stim cohorts was not significant ($121, $P = 0.86$). The predicted fracture-related health care costs in the 12-month post-index period for the EBGS cohort ($9100) were also significantly lower than the No-stim ($10,354, marginal difference: –$1253, $P < 0.01$) and the LIPUS ($10,225, marginal difference: –$1125, $P < 0.01$) cohorts. Alternatively, the predicted fracture-related costs for the LIPUS and the No-stim cohorts were not significantly different ($129, $P = 0.71$).

Discussion

In a commercially insured US population, the majority of the patients diagnosed with a fracture nonunion received No-stim treatment, despite the presence of clinical evidence supporting the efficacy and safety of EBGS and LIPUS.[17,26–39] Preclinical studies have demonstrated that EBGS increases cellular proliferation and the expression of naturally occurring growth factors including bone morphogenetic proteins to help with the bone repair process.[46–53] However, due to the device cost and the limited economic evidence to compare their cost-effectiveness to other fracture management practices, bone growth stimulators have often had insurance coverage limited to a subset of the approved indications within medical policy guidelines. Over the years, the Centers for Medicare and Medicaid Services (CMS) have revised the reimbursement policy for bone growth stimulators multiple times and recently, the Agency for Healthcare Research and Quality concluded that further evaluation with randomized

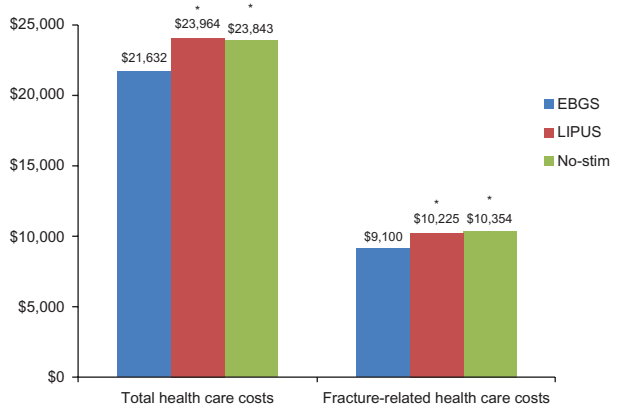
Table 4 Comparison of the total health care and fracture-related costs in the year following nonunion diagnosis[a]

	Total health care costs			Fracture-related health care costs		
	Estimated regression coefficient[b]	Standard error	*P*-value	Estimated regression coefficient[b]	Standard error	*P*-value
Treatment cohort (ref: No-stim)						
EBGS cohort	–0.097	0.021	<0.01	–0.129	0.025	<0.01
LIPUS cohort	0.005	0.028	0.86	–0.013	0.034	0.71
Gender (ref: female)						
Male	–0.071	0.019	<0.01	0.083	0.023	<0.01
Age (ref: 18–24)						
Age 25–34	0.012	0.039	0.76	–0.140	0.046	<0.01
Age 35–44	0.137	0.035	<0.01	–0.095	0.042	0.02
Age 45–54	0.322	0.033	<0.01	–0.033	0.040	0.40
Age 55–64	0.381	0.034	<0.01	–0.008	0.041	0.85
Region (ref: South)						
Northeast	0.016	0.031	0.61	–0.001	0.036	0.98
North Central	0.034	0.022	0.13	0.014	0.027	0.59
West	0.129	0.025	<0.01	0.090	0.030	<0.01
Unknown	–0.127	0.064	0.05	–0.170	0.076	0.02
Insurance plan type (ref: PPO)						
Comprehensive	0.057	0.050	0.25	0.010	0.059	0.86
EPO	–0.085	0.131	0.52	0.046	0.156	0.77
HMO	0.011	0.026	0.67	–0.024	0.031	0.45
POS[c]	0.027	0.032	0.39	–0.045	0.037	0.23
CDHP	0.056	0.061	0.36	0.063	0.072	0.38
Missing/unknown	0.088	0.058	0.13	0.032	0.068	0.64
Charlson Comorbidity Index (CCI) (ref: CCI = 0)						
CCI = 1	0.421	0.032	<0.01	0.197	0.038	<0.01
CCI = 2	0.432	0.029	<0.01	0.234	0.035	<0.01
CCI = 3 or higher	1.057	0.036	<0.01	0.487	0.043	<0.01
Open fracture (ref: closed fracture)	0.037	0.049	0.45	0.083	0.058	0.15
Treatment received in pre-index period						
Cast/splint (ref: no cast/splint)	0.056	0.021	0.01	–0.037	0.025	0.13
Other invasive treatment[d] (ref: no other invasive treatment)	0.375	0.036	<0.01	0.459	0.043	<0.01
Close reduction (ref: no close reduction)	–0.025	0.021	0.24	–0.016	0.025	0.53
Open reduction (ref: no open reduction)	0.095	0.026	<0.01	0.215	0.031	<0.01
Location of fracture (ref: foot)						
Hand	–0.118	0.029	<0.01	0.092	0.035	0.01
Arm	0.170	0.024	<0.01	0.534	0.028	<0.01
Leg	0.653	0.029	<0.01	1.010	0.034	<0.01

Notes: [a]The data presented in this table were used to generate the predicted health care costs presented in Figure 2; [b]the estimated regression coefficient is used as a measurement for how similar the group of interest is to the reference group. The closer to zero, the more similar the two groups are. Positive values indicate that the associated costs for the group of interest are greater than the reference group; negative values indicate that the associated costs for the group of interest are less than the reference group; [c]category combines POS with and without capitation due to small sample sizes; [d]other invasive treatments include bone graft, bone marrow aspiration, arthroscopy, amputation, or implant of recombinant bone morphogenetic protein.

Abbreviations: CCI, Charlson Comorbidity Index; CDHP, consumer-directed health plan; EBGS, electrical bone growth stimulation; EPO, exclusive provider organization; HMO, health maintenance organization; LIPUS, low-intensity pulsed ultrasound stimulation; No-stim, other non-stimulation fracture management interventions; NSAIDs, non-steroidal anti-inflammatory drugs; POS, point of service; PPO, preferred provider organization.

controlled clinical trials is needed, particularly for patients aged 65 years old or older.[25] CMS's insurance coverage policy is often used as a guideline for commercial payers establishing their individual coverage policies and therefore is important to consider even for patients insured by commercial health care plans. Interestingly, while additional studies may further elucidate the benefits of bone growth stimulation, EBGS, unlike LIPUS, has existing randomized, placebo controlled nonunion studies demonstrating significantly improved healing of fracture nonunions with either capacitive coupling stimulation[35] or pulsed electromagnetic field stimulation.[36] Studies that compare EBGS to standard treatment practices may be helpful in supporting more extensive device coverage. Today, most commercial



Comparison	Total health care costs		Fracture-related health care costs	
	Marginal effect	*P*-value	Marginal effect	*P*-value
EBGS vs LIPUS	–$2332	<0.01	–$1125	<0.01
EBGS vs No-stim	–$2211	<0.01	–$1253	<0.01
LIPUS vs No-stim	$121	0.86	–$129	0.71

Figure 2 Comparison of total and fracture-related health care costs between the three different treatment cohorts.[a]

Notes: [a]Controlled for age, gender, region of residence, type of insurance, CCI score, open fracture, fracture location, and treatments received during the pre-index period, which include cast or splint use, open reduction, close reduction, and invasive treatment. *Predicted costs were significantly higher when compared to the EBGS cohort at $P < 0.01$.

Abbreviations: CCI, Charlson Comorbidity Index; EBGS, electrical bone growth stimulation; LIPUS, low-intensity pulsed ultrasound stimulation; No-stim, other non-stimulation fracture management interventions.

insurance plans offer coverage for EBGS devices to treat fracture nonunions. However, the coverage is often limited to certain bones and requires an elapsed timeframe before the device can be prescribed.[54] Notably, this study is the first to compare actual health care utilization between EBGS, LIPUS, and No-stim treatment for fracture nonunions. Study results found that EBGS can offer significant cost-savings in the treatment of fracture nonunions when compared to both LIPUS and No-stim treatment.

Interestingly, in this study, prior to nonunion diagnosis (pre-index period), both the EBGS and LIPUS cohorts were more likely to receive fracture-related treatment, including application of external fixation devices, open reduction, or bone grafting, than the No-stim cohort, which suggests that the fractures in the stimulation cohorts were more severe and difficult to heal. In the 12 months following nonunion diagnosis, the pattern reversed, and the costs for the EBGS and the LIPUS cohorts were less than for the No-stim cohort, suggesting that stimulation treatment may be effective in managing nonunion fractures without the need for more invasive procedures. These differences in fracture management may explain the observed differences in health care costs between the different treatment cohorts. Specifically, the EBGS cohort had the lowest fracture-related costs in the 12 months following nonunion diagnosis and also the lowest costs due to inpatient admissions. The cost savings of EBGS were mainly driven by the higher savings associated with inpatient services. Notably, the fracture-related outpatient costs in the 12 months after nonunion diagnosis were significantly higher in both the EBGS and LIPUS groups when compared to the No-stim cohort. The costs of the stimulation devices, which averaged around $3000 (EBGS: mean: $2719, median: $2800; LIPUS: mean: $2626, median: $2765), were responsible for the higher outpatient costs. Interestingly, the cost savings in the outpatient services for the No-stim group were less than that required to cover the device cost, suggesting that the No-stim patients may have also required more non-device related outpatient care than the stimulation cohorts. Despite the initial cost of the stimulation device, this study shows that patients receiving bone growth stimulators actually incur less overall treatment costs by avoiding more expensive and invasive treatments.

Due to the differences in the pre-index fracture management practices between the different treatment cohorts, a sensitivity analysis was conducted to verify that the differences in pre-index fracture management did not have an effect on required post-index fracture management. For this analysis, patients were stratified by the presence of fracture-related inpatient stays in the pre-index period and compared for differences in post-index period health care costs. Among those patients without fracture-related inpatient stays in the pre-index period, LIPUS had significantly higher costs in the 1-year post-index period when compared to the EBGS cohort, although the costs between the No-stim and the EBGS cohorts were similar. Alternatively, among those patients with fracture-related inpatient stays in the pre-index period, No-stim incurred significantly higher costs than the EBGS cohort during the 1-year post-index period, while the costs between the LIPUS and the EBGS cohorts were comparable. This sensitivity analysis confirms that differences in pre-index fracture management did not impact the observed cost savings for EBGS in the post-index period as compared to the other treatment cohorts.

Previous research has shown through economic modeling that LIPUS used in combination with conservative treatment resulted in a cost savings of over $15,000 for patients with tibial fresh fractures.[55,56] Cost savings in this model were mainly attributed to the avoidance of subsequent surgery and a reduction in workers' compensation costs. Additionally,

part of the cost savings in the LIPUS study was attributed to a decrease in the rate of delayed unions. Alternatively, in this recent study of actual administrative claims, EBGS demonstrated an 11%–12% reduction in fracture-related costs compared to both LIPUS and No-stim treatment. The observed cost savings were likely due to less frequent invasive treatments required by patients in the EBGS cohort when compared to the LIPUS and No-stim cohorts. The cost savings reported in this study were not as substantial as those reported by Heckman et al[56] because indirect medical costs, such as workers' compensation and disability costs, which are not available in administrative claims, were not taken into account. Notably, this study included a broad range of nonunion fractures from different anatomical locations, and used administrative claims to more accurately reflect the real-world cost savings of EBGS for health care payers and provide a direct economic comparison of the different treatment techniques.

Study limitations

In administrative claims, nonunion diagnosis is not accompanied by the diagnosis of the specific fracture. To assess the characteristics of the initial fracture, we limited our analysis to patients with fractures at a single location. In addition, we were unable to identify the fracture severity using administrative claims. Alternatively, we used the post-initial fracture management data as an indicator for fracture severity. The incidence of soft tissue damage to nearby blood vessels and nerves, the development of post-traumatic wound infection, and the presence of traumatic compartment syndrome were also assessed. The prevalence of these conditions was generally very low (<1%) and comparable between the different treatment cohorts. For this study, the calculated fracture-related costs were based on claims for imaging procedures of bones and claims with diagnosis/treatment codes suggesting fracture, fracture nonunion, or malunion. It is possible that these claims may relate to diagnosis or treatment of other conditions. However, it is important to note that the identified limitations apply to all treatment cohorts and therefore would not create any bias toward a specific cohort that could impact the validity of the data analysis. Notably, this study measured actual health care resource utilization and did not assess healing time or the loss of work productivity in determining health care cost savings.

Conclusion

This is the first real-world study comparing the costs associated with the treatment of fracture nonunions between EBGS, LIPUS, and other fracture management practices (No-stim). Patients receiving EBGS for the treatment of fracture nonunions were less likely to undergo invasive procedures resulting in less health care resource use and cost savings to payers and patients. Patients receiving EGBS also had significantly less total and fracture-related costs in the year following nonunion diagnosis than patients receiving LIPUS or No-stim treatment. These study outcomes suggest that EBGS is a more cost-effective treatment for fracture nonunions when compared to both LIPUS and No-stim treatment.

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Disclosure

Ning Wu, Yuan-chi Lee, Teresa Wilcox, and Luke Boulanger are employees of United BioSource Corporation, which provides consulting and other research services to pharmaceutical, device, government, and non-government organizations. In their salaried positions, they work with a variety of companies and organizations, and were precluded from receiving payment or honoraria directly from these organizations for services rendered during the preparation of this manuscript. Daniel Segina is employed by Health First Physician Group and is a paid physician consultant by Biomet Spine and Bone Healing Technologies. Hallie Murray is an employee of Biomet Spine and Bone Healing Technologies, the study sponsor. The authors report no other conflicts of interest in this work.

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An early cost analysis of magnetic bone growth stimulation in England

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ORIGINAL RESEARCH

An early cost analysis of magnetic bone growth stimulation in England

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ABSTRACT

Background: Fracture nonunions impact on morbidity and health care costs and are associated with substantial pain, reduced mobility, prolonged morbidity, and a lower quality of life. CMF OrthoLogic 1000 (OL1000) is a bone growth stimulator used to promote fracture healing potentially reducing the need for surgical intervention. A cost analysis comparing CMF OL1000 versus surgical care for patients with nonunion tibial fractures was conducted.

Methods: A Markov model was developed to compare the difference in costs between CMF OL1000 versus surgical care within the English National Health Service over a 2-year time horizon. The effectiveness of CMF OL1000 was based on recently published registry data. Cost data were derived from published sources and national cost databases. Sensitivity and scenario analyses were conducted.

Results: The use of CMF OL1000 is estimated to lead to cost-savings of £1,104 per patient, a reduction in average healing time of 2.1 months and a relative risk of infection of 0.19 compared to immediate surgical intervention (standard of care). The results of the model are robust to most changes in input parameters and scenarios considered.

Conclusions: This early analysis shows cost-savings for CMF OL1000 compared with surgical intervention for individuals with nonunion tibial fractures.

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CMF orthologic 1000; cost analysis; economic analysis; magnetic bone growth stimulation; nonunion; tibia fracture

1. Introduction

Fracture nonunions, although representative of a smaller proportion of fracture care outcomes, have devastating impacts on morbidity and health care costs. The National Institute of Health and Care Excellence (NICE) defines fracture nonunion as fractures that have not reached bony union within 6 to 9 months after the initial fracture treatment [1]. Rates of nonunion vary by the bone fractured. A population-based study estimated the incidence of nonunion to be 13 per 1,000 per annum for pelvis and femur fractures, 30 per 1000 per annum for the humerus fractures, and 55 per 1000 per annum for the tibia and fibula fractures [2]. Tibia fractures are at higher risk of nonunion given the lack of soft tissue envelope and resulting limitation of blood supply.

Fracture nonunions are associated with substantial pain, reduced mobility, prolonged morbidity, and a lower quality of life [3]. Fracture nonunions often require surgical intervention to promote fracture healing. Types of procedures used to promote fracture healing include internal fixation or external fixation and bone grafting. Additional surgeries are burdensome for fracture patients as they often lead to prolonged disability and an increased loss of function and productivity. In addition, there is a high cost to the health care system due to the need for surgical intervention and extended patient care and follow-up.

To reduce the need for surgical intervention, noninvasive bone healing devices known as bone growth stimulators may be used to treat fracture nonunions. EXOGEN, a device that uses low-intensity pulsed ultrasound (LIPUS) at the fracture nonunion site, has demonstrated cost-savings when compared with invasive nonunion surgery for tibial fractures [4]. While EXOGEN uses LIPUS to facilitate fracture healing, other bone growth stimulators use electrical currents or magnetic stimulation to achieve this outcome. For example, the CMF OrthoLogic 1000 (OL1000) device is a portable, battery-powered medical device that provides local magnetic field treatment through very low-energy combined static and dynamic magnetic fields. Broad uptake in bone growth stimulators has been slow due to compliance factors, including i) issues caused by the requisite use of a gel medium for device signals to transmit, and ii) long durations of wear time (up to 2 hours). Due to the slow uptake of bone growth stimulators, surgical intervention represents standard of care (and the relevant comparator) within the health system. CMF OL1000 does not require a gel medium for the device to work and requires a comparatively shorter wear time (30 minutes). Broad uptake in bone growth stimulators has been slow due to compliance factors [5,6]. These include i) issues caused by the requisite use of a gel medium for device signals to transmit, and ii) long durations of wear time (20 minutes to beyond 2 hours) [4,7]. Due to the slow uptake of bone growth stimulators, surgical intervention represents standard of care

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Supplemental data for this article can be accessed here.

(and the relevant comparator) within the health system [8]. CMF OL1000 does not require a gel medium for the device to work and requires a comparatively shorter wear time (30 minutes).

Treatment with CMF OL1000 can either result in the fracture healing, or a fracture that does not heal and requires surgery to promote fracture healing. Following surgical intervention, patients may experience fracture healing or continued nonunion. They may also develop an infection. Additionally, patients may require multiple surgeries to treat their nonunion and/or infection [9].

Evidence for the cost-effectiveness of devices using electrical currents or magnetic stimulation to achieve bony union is understood to be limited. To address this gap in the literature, a cost analysis comparing CMF OL1000 versus surgical intervention (standard of care) as treatment options for patients suffering from a nonunion following a tibial shaft fracture was conducted.

2. Methods

2.1. Model overview

An economic Markov state transition model was developed to compare the difference in costs between CMF OL1000 versus surgical care in patients with tibial shaft nonunions.

2.2. Clinical outcomes

In the absence of comparative data for CMF OL1000 and surgical care, clinical effectiveness data for both groups were obtained from separate sources. The tibial shaft fracture healing data for outcomes following treatment with CMF OL1000 were obtained from registry data published in 2016 [9]. The reported registry data included rates of fracture healing and time to healing for tibial fracture nonunions in monthly increments from the date of the initial fracture [9]. Following the NICE definition of nonunion, fracture healing times between 6 to 9 months from the initial fracture were aggregated to estimate an average time to healing for nonunion tibial fractures. These rates were then converted into a transition probability of successful treatment of the tibial shaft nonunion. For the surgical care group, the transition probability of successful treatment was extracted from published literature [10]. Since the baseline characteristics of patients were not available from the registry data, statistical matching of the treatment and comparator groups was not possible. Table 1 summarizes the clinical estimations that were used in this analysis.

2.2.1. Determination of costs

NHS reference costs and Personal Social Services Research Unit costs (Supplementary Material A) were primarily used to estimate the total NHS cost implications for both treatments (Table 2). The perspective of the model was the payer (English NHS). Costs and effects in the model were discounted at 3.5% per annum in line with the NICE reference case [11]. A time horizon of two years was used to capture the expected benefits of CMF OL1000 and surgical intervention as it was assumed based on clinician input that all patients would achieve fracture union by two years. Costs were valued in 2018/19 prices.

2.3. Markov modeling

A Markov model with 1,000 simulated patients was developed to estimate the expected changes in costs and to capture movements between health states over time for both treatment groups. Model cycles were monthly to capture the granularity in the registry data for CMF OL1000 and the potential time for movement between health states. The structure of the model is presented in Figure 1. The primary outcome of the model was the incremental total cost per patient. This was determined by calculating the total costs (device and health state costs) associated with CMF OL1000 and standard of care and calculating the difference. The model therefore used a total of 24 cycles, for a total time horizon of 2 years.

All patients enter the model in the *unhealed: not infected (1)* health state.

Following treatment with CMF OL1000, the health states a patient may enter are:

- The fracture heals: *Healed*
- The fracture does not heal and requires surgery to promote fracture healing: *Surgery*
- Following surgical intervention, the fracture heals: *Healed*
- Following surgical intervention there is continued nonunion: *Unhealed, not infected 2*
- Following surgical intervention there is continued nonunion and an infection: *Unhealed, infected*
- Patients may require multiple surgeries to treat their nonunion and/or infection: *Unhealed, not infected 2*

These health states can be either progressive or regressive, with potential movements in and out of surgery.

Table 1. Clinical estimations.

Parameter	Value	Source
Percentage that heal within 6–9 months of treatment post injury[a]	72.1%[a]	Phillips, M. et al. 2016.[5]
Weighted time to healing[a]	6.83 months[a]	Phillips, M. et al. 2016. [5]
Transition success probability[a]	16.82%[a]	Calculated from data in Phillips, M. et al. 2016. [5]
Surgery success probability	86.0%	Gebauer et al. 2005.[6]
Infection risk	1.4%	Exogen report[1]
Monthly probability of unhealed fracture healing without intervention	0.2%	Assumption based on clinical input
Monthly probability of having surgery for an unhealed fracture	50.0%	Assumption based on clinical input

[a]Used solely in the CMF OL1000 arm of the model.

Table 2. Cost inputs.

Parameter	Value	Source
Cost of CMF OL1000 (one-off cost per person)	£2,500	Price charged by DJO Global
Unhealed: Not infected (monthly cost)	£220	National schedule of reference costs 2019[8], NICE EAC review report[a] 2019[9], PSSRU 2019[10], Portsmouth CCG spending[a] 2013[11], Exogen report[1].
Surgery (one-off cost)	£4,175	NICE EAC review report[a] 2019[6], HES 2019[9], NICE CG124[a10], National schedule of reference costs 2019[5], NICE EAC review report[a] 2019[9], PSSRU 2019[10], Exogen report[1]
Unhealed: infected (one-off cost)	£15,203	National schedule of reference costs 2019[5], NICE EAC review report[a] 2019[9], PSSRU 2019[10], Exogen report[1] (resource use).
Healed (monthly cost in first month only)	£29	Portsmouth CCG spending[a] 2013[11].

[a]Inflated using PSSRU to 2018/19 prices

NICE EAC – National Institute for Health and Care Excellence, external assessment center. PSSRU – Personal Social Services Research Unit. HES – Hospital Episode Statistics. NICE CG – National Institute for Health and Care Excellence, clinical guidelines.

The first health state: *unhealed: not infected (1)* represents individuals who have a nonunion fracture that does not have a diagnosed deep infection. A proportion of these individuals do, however, have an unexpected (or undiagnosed) deep infection. Such deep infections are not diagnosed until patients undergo surgery at which point the infection is treated. Superficial infections do not prevent treatment with CMF OL1000, and outcomes associated with superficial infections are not included in the model.

The cost of this additional surgical treatment to remove a deep infection, as reported in Table 2, was applied to 5% of the initial cohort of patients in both arms of the model [12]. All individuals begin in this health state, as this state represents all people eligible for treatment with CMF OL1000. Each cycle, individuals either heal from CMF OL1000 or standard of care (transition to healed) or remain in *unhealed: not infected (1)* for up to 9 cycles (maximum continuous use of CMF OL1000 is 270 days as per the instructions for use of the device). After a maximum of 9 cycles within *unhealed: not infected (1)*, patients transition to *surgery* and CMF OL1000 can no longer be administered. This is applied within the model using time-dependent transition probabilities as presented in Figure 1.

Patients may undergo *surgery* to promote fracture healing. Patients cannot remain in this health state in a subsequent cycle and must transition to a healed or unhealed health state. In order to capture the delay to healing post-surgery (reported to be 7.2 months from surgery in aseptic nonunion tibia fractures [13]) a delay of 7 months occurred in the model before the patients transition into the *healed* health state. This is applied using tunnel health states which are not pictured on Figure 1 for simplicity.

When surgery fails but the patient did not contract a deep infection, and are in a health state of watchful waiting before a subsequent surgery (*unhealed: not infected (2)*), patients can experience spontaneous fracture healing (assumed probability of 0.2%), transition back to surgery (assumed probability of 50%), or remain in this health state.

The *unhealed: infected* health state includes patients whose fracture has not healed following surgery, and who have developed a deep infection at the nonunion site following surgery. It was assumed that individuals in this health state would require additional surgery to treat the infection which was assumed successful 100% of the time. This would move them to the *unhealed (not infected)* health state. Individuals in the *unhealed (infected)* health state cannot remain in this state in a subsequent cycle.

The final health state is *healed*, in which patients' fractures are healed from successful treatment from CMF OL1000 or standard of care. This is an absorbing health state; for individuals in this health state there are no subsequent transitions.

2.4. Sensitivity and scenario analyses

The robustness of the assumptions used and their impact on the model's results were investigated using sensitivity analyses (deterministic and probabilistic) and scenario analyses.

Deterministic sensitivity analysis (DSA) is a method to investigate the sensitivity of the model results to variations in a specific input parameter or set of parameters. Deterministic, univariate sensitivity analyses were conducted around the model inputs, whereby inputs were varied independently between an upper and lower limit to determine the impact of different parameter values on the model results.

Probabilistic sensitivity analysis (PSA) is a technique used in economic modeling to determine the level of confidence in the outputs of a model based on uncertainty in the model inputs. PSA allows for the combined model parameter uncertainty to be explored; each model input has an associated distribution for which the value of the input can be drawn from. Each time the model is run using PSA, that iteration of the model results is recorded, with the results reflecting the values of each of the inputs from their random draws. This process is repeated over many iterations, with model results recorded in each iteration, until stability in mean results of the model is achieved. The PSA was conducted using 1,000 iterations, which is typically deemed to achieve stability in results. Within the PSA, upper and lower values for the distributions were determined using the upper and lower limits of the respective standard error for inputs, or ±25% of the base case value when a standard error was not available. Probabilities in the model had a beta distribution applied, and costs had a gamma distribution applied.

The first scenario analysis (Scenario 1) was conducted using costing data from the NICE External Assessment Center review report for the X-ray and physiotherapy cost inputs [14]. This was conducted because the costs of these two inputs were much higher than the costs used in the base case. In the base case an X-ray is costed at £29.00 compared with £87.29 in the EAC report after inflation, and

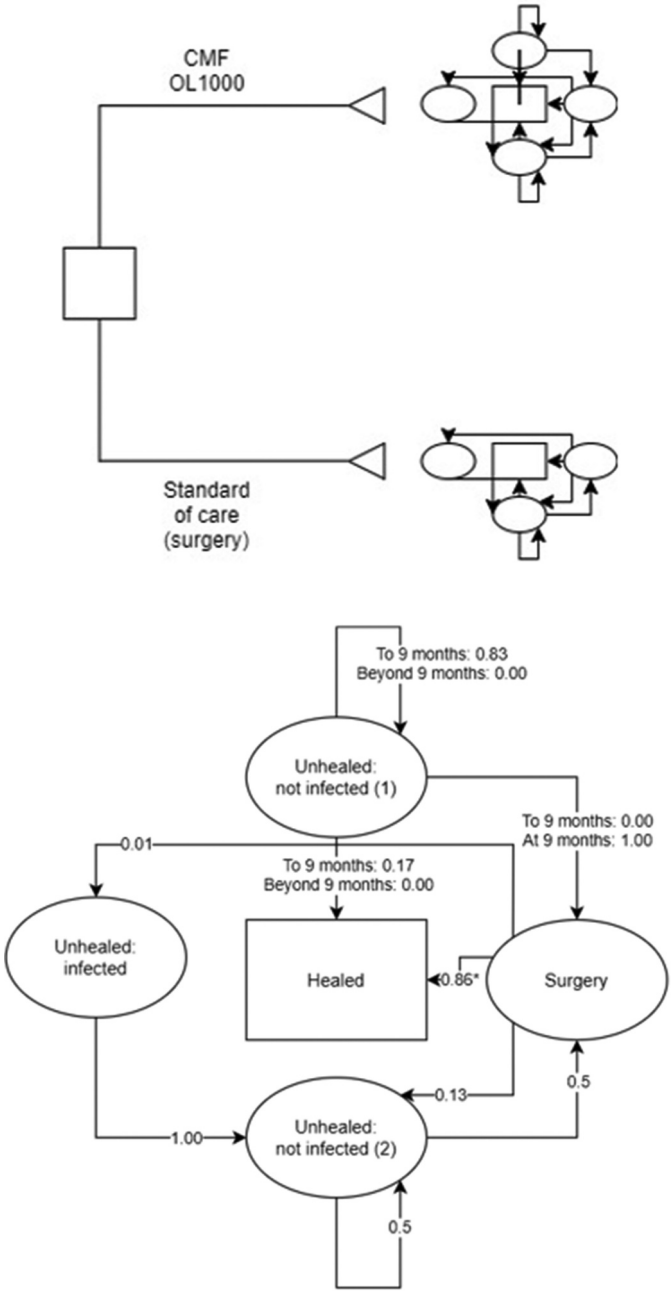

Figure 1. Markov model of all health states associated with tibial fracture nonunion.

This figure shows the model structure whereby patients either enter the Markov model using CMF OL1000 or standard care (surgery). The Markov model structure is similar in both treatment arms. Numbers on arrows represent the transition probabilities. Patients using CMF OL1000 enter the model in the 'unhealed: not infected (1)' health state, whilst patients using standard care enter directly in the 'surgery' health state. After 9 cycles in 'unhealed: not infected (1)' patients who do not experience healing must transition to surgery. Infection refers to deep bone infection.* Note that this transition occurs after a delay of 6 months for healing (not pictured for simplicity).

physiotherapy in the base case is costed at £58.00 compared with £286.98 in the EAC report. Both costs in the EAC report were inflated to 2018/19 pricing using PSSRU data [15]. Whilst recognizing the merits of the EAC review report, these costs were not used in the base case because alternatives were identified that were judged to better reflect the current cost of these parameters. Specifically, the model results were generated using alternative cost data from the EAC review report [14] for an X-ray and physiotherapy appointment.

An additional scenario analysis (Scenario 2) was undertaken using the data from the Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT). In this, currently unpublished data, 38 participants with either a closed or Type 1 open fracture had a nonunion surgery or a surgery to promote fracture healing. The results of this study show that 5/38 participants (13.2%) were diagnosed with an infection after surgery. In Scenario 2 the base-case infection risk value of 1.4% is replaced with 13.2%.

3. Results

3.1. Base case analysis

The use of CMF OL1000 is cost saving when compared with surgical intervention in people with nonunion tibial fractures in the English NHS over a two-year time horizon (Table 3). Furthermore, the clinical outcomes are also presented in Table 3 and show a breakdown in the absolute and relative differences of clinical events between CMF OL1000 and surgical care.

3.2. Deterministic sensitivity analysis

The results are shown in a 'tornado chart'; a summary (stack) of bar graphs representing univariate sensitivity analyses for a wide range of input values, ordered according to the spread of variation of the resulting model output value (with the widest variation on top). The tornado chart for this model identified that both the monthly healing probability of CMF OL1000 (a model input) and the cost of surgery had sufficient power to change the direction of the base-case results from cost saving to cost incurring (see Figure 2).

The monthly healing probability of CMF OL1000 was calculated to be 16.8%. The device was estimated to be cost saving provided that the monthly healing probability with CMF OL1000 was above 11.1% per month. The cost of surgery was identified as £4,174 and was also a key driver of the model results. The higher the cost of surgery, the greater the cost savings estimated with CMF OL1000 because people using CMF OL1000 require relatively fewer operations than patients who receive operative treatment of the tibial nonunion. Provided surgery costs were over £2,950, CMF OL1000 was estimated to be cost saving.

3.3. Probabilistic sensitivity analysis

When all of the input parameters for CMF OL1000 and standard of care were varied simultaneously, using 1,000 iterations of the simulated data, CMF OL1000 was cost saving compared with standard of care in 76% of the 1,000 simulations. The average incremental cost saving for CMF OL1000 compared with surgery was £870 per person.

3.4. Scenario analyses

In Scenario 1 (Supplementary Material B, Table B.2) the source for the cost inputs for an X-ray and physiotherapy is the NICE

Table 3. Cost per patient breakdown and clinical outcomes.

Outcomes	CMF OL1000	Surgical Care	Difference Between Groups (Surgical Care as Reference)	Percentage Change Between Groups
Cost outcomes (per patient)				
Unhealed: Not infected	£3,561	£71	£3,490	+4933.0%
Surgery	£1,002	£5,395	-£4,393	−81.4%
Unhealed: infected	£46	£246	-£201	−81.3%
Healed	£28	£28	£0	0%
Total	**£4,637**	**£5,741**	**-£1,104**	**−19%**
Clinical outcomes (per patient)				
Total surgical procedures	0.22	1.16	−0.95	−81.0%
Total number of deep infections	0.00	0.02	−0.01	−99.9%
Average time to fracture healing (months) from entry to the model	6.43	8.49	−2.1	−24.0%

External Assessment Center review report [14]. The results show the cost outcomes per patient increased in both arms of the model, but particularly for time spent in the *unhealed: not infected* health state in the CMF OL1000 arm. However, CMF OL1000 remained cost saving by £543 per patient. There was no impact on the clinical outcomes.

In Scenario 2 (Supplementary Material B, Table B.2) unpublished SPRINT data was used for the rate of infection input. The increased risk of infection in this scenario resulted in CMF OL1000 remaining cost saving. The impact on the cost outcomes is primarily shown in the increased cost per patient in the *unhealed: infected* health state, where the cost increased for both interventions. The cost increase was caused by the increased need for infection treatment compared to the base case (3 infections compared with 29 infections for CMF1000, and 16 infections compared with 153 infections for standard of care). As a result, the total cost saving per-patient increased from £1,104 to £2,792 with CMF OL1000. In addition, the difference in average time to fracture healing increased from 6.43 to 6.45 months with CMF1000, and increased from 8.49 to 8.62 with standard of care.

4. Discussion

The current model found that the management of tibial fracture nonunions with CMF OL1000 costs less than immediate surgical intervention. The differences in costs were driven by several factors including: the difference in treatment costs between CMF OL1000 compared with immediate surgical management (£2,500 compared with £4,174); a shorter time to healing of the nonunion for patients treated with CMF OL1000 compared with surgical intervention (6.4 months compared with 8.49 months); fewer patients requiring surgical management when treated with CMF OL1000 (221 compared with 1,162; 81% reduction); and a lower rate of infection in patients treated with CMF OL1000 (3 infections compared with 16, a relative risk of 0.19).

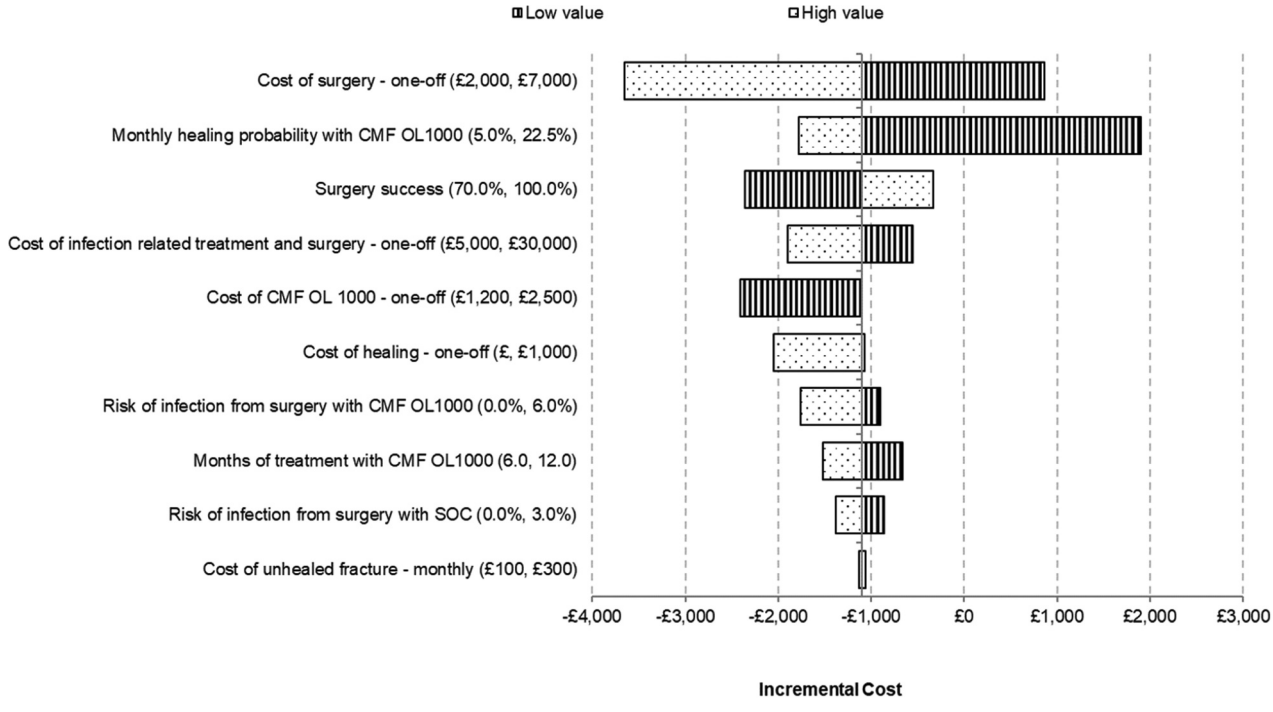

Figure 2. Tornado diagram presenting deterministic sensitivity analysis.

The tornado diagram presents the impact of varying each model input univariately on the results of the model.

Other benefits of CMF OL1000 include an expected improvement in patient compliance and convenience compared to other bone growth stimulators and surgical intervention. Compliance with CMF OL1000 was not be modeled because effectiveness data for CMF OL1000 is from observational (registry) data; compliance implicitly modifies the average clinical effectiveness of CMF OL1000 and should not be double counted.

By using CMF OL1000, patients reduce their risk of infection incurred from surgery as they are likely to be healed using CMF OL1000 before surgery is required. The estimated cost of treating one deep infection in the English NHS is £15,202. This includes the cost of medical treatment of the infection as well as additional surgery required for the nonunion fracture. The unhealed and infected health state is therefore the most expensive health state within the Markov model, and one which is often avoided if a patient begins treatment using CMF OL1000.

The results of this study provide similar results to previous investigations on the cost-analyses of bone growth stimulator use for fracture nonunion management. A Markov model comparing EXOGEN's base-case analyses found EXOGEN (LIPUS) ultrasound device to be cost saving for both delayed union (cost saving of £684 relative to control) and for nonunion (cost saving of £2,310 relative to surgery) [4]. While other options have demonstrated similar findings, the short daily application period of CMF OL1000 may improve compliance rates and convenience for patients.

The analysis is strengthened by our use of Markov modeling with multiple sensitivity analyses conducted. Additionally, this model used the available literature to incorporate all potential associated costs from fracture nonunion management.

As with any model, multiple assumptions were made. It was assumed that all individuals in the standard of care arm received surgical treatment rather than watchful waiting. This assumption is conservative for the incremental clinical benefit of CMF OL1000, as the success rate for surgery is much higher than the success rate for watchful waiting. The use of surgery as standard of care is also a logical assumption that has been clinically validated. We also assumed that patients in both treatment groups would have a 5% rate of undiagnosed infection on entry to the model, which was based on trial data [12]. The cost of surgery has been extracted from a previous single technology appraisal in the area of nonunion tibial fractures [1]. This cost has been accepted by NICE and validated by the External Assessment Center. We do not consider it likely that the cost of surgery will be significantly less than the cost which was previously presented. Finally, several parameters from published literature [9] were considered when calculating the monthly healing probability for CMF OL1000 of 16.8%. To reduce the monthly healing probability of CMF OL1000 to 7.5%, at which point the direction of the results change from cost saving to cost incurring, would be a substantial underestimation of the current observational study literature surrounding the efficacy of CMF OL1000.

There are two limitations that we consider particularly important. The first is that the registry data used to populate the economic model are from American patients [9]. The generalizability of the results to the English NHS are therefore uncertain as the clinical care pathways and baseline characteristics of American and English patients may differ. However, the sensitivity analysis that we have conducted has quantified the impact of some of this uncertainty and clinical input has suggested that the patients included within the registry are likely to be similar to those receiving treatment in the English NHS. Secondly, the results of the economic model represent a naïve comparison. A systematic review of the clinical evidence was not undertaken to populate the economic model with the most relevant evidence for both arms, and both arms of the model are unmatched on patient characteristics. Because potential confounding factors between study participants in the treatment and control arm were not identified or controlled for via randomization, the magnitude of the cost savings and clinical success rate for CMF OL1000 may be biased. However, clinical input recommends that the patients informing the data on CMF OL1000 and surgery are likely to be similar. Additionally, the cost data were obtained from UK sources and may not be generalizable to other jurisdictions with different health care and reimbursement systems.

5. Conclusion

The results of this study indicate a £1,104 cost saving per person when using CMF OL1000 compared with undergoing surgical intervention for individuals with nonunion tibial fractures (that are not deeply infected). A reduction in costs is caused by a lower incremental treatment cost for CMF OL1000, fewer patients requiring surgery, shorter average incremental time to healing and an incremental reduction in the incidence of deep infections arising from surgical intervention. The results of the model are robust to most changes in input parameters and scenarios considered.

Author contributions

Joel Russell and Michelle Green designed and built the model with input from all other authors. All authors contributed to the drafting of the paper which was reviewed and signed off by Mohit Bhandari.

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Declaration of interest

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