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LITERATURE REVIEW

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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.

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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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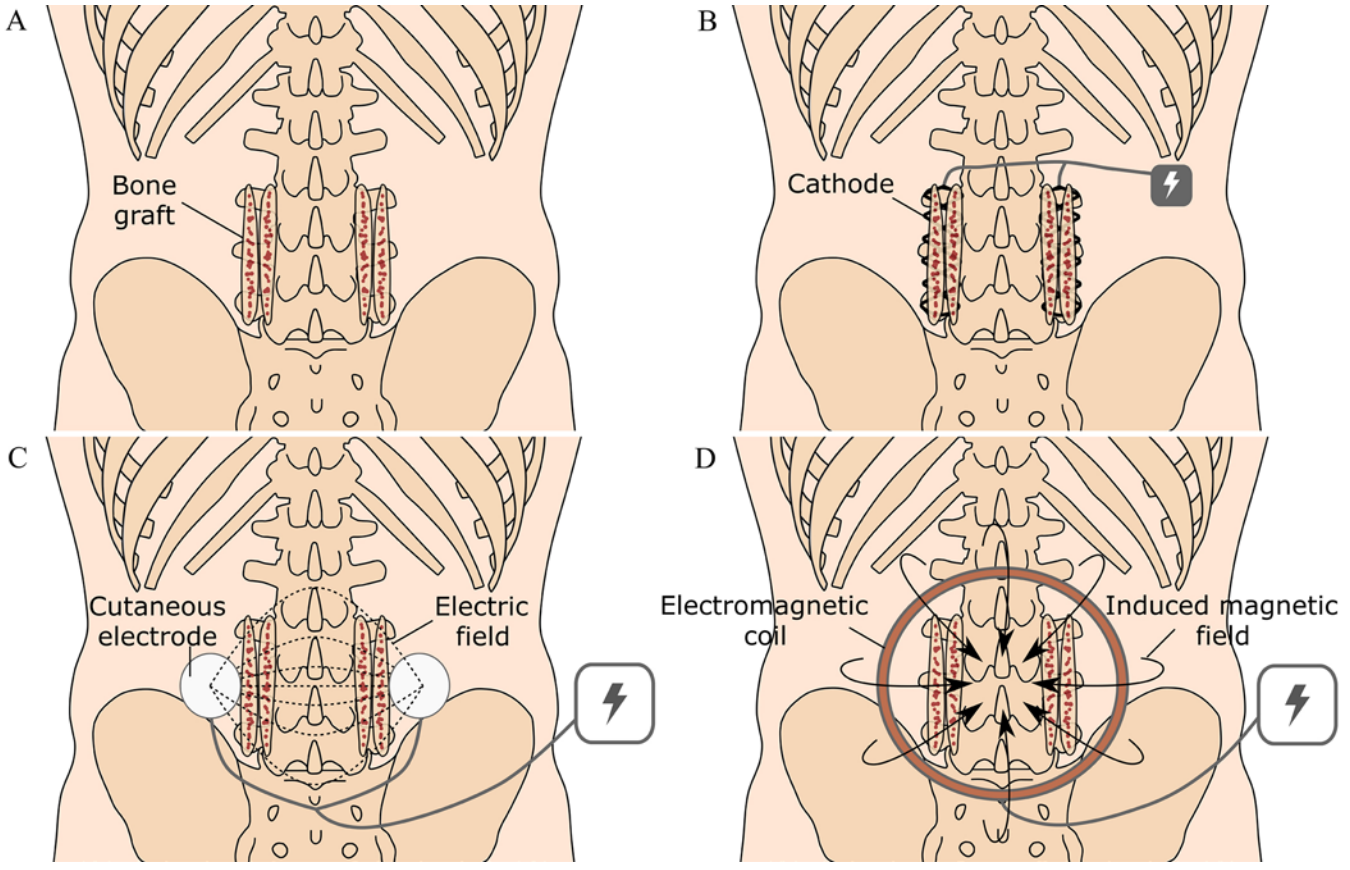

FIG. 1. Conceptual illustrations of the 3 types of electrical stimulation therapies used in spinal fusion. **A:** Posterolateral L3–5 inter–transverse process spinal fusion using bone graft, without electrical stimulation. **B–D:** Same procedure illustrating postoperative adjuvant therapy with DCS (B), 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.

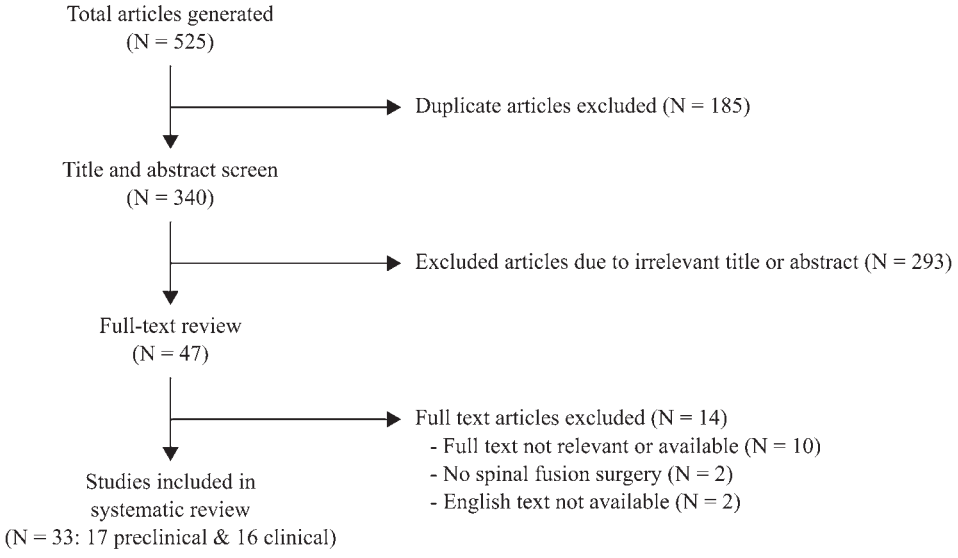

FIG. 2. Diagram of the consolidated standards of reporting trials for article selection.

[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)			

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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)		

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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
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)

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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)

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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).

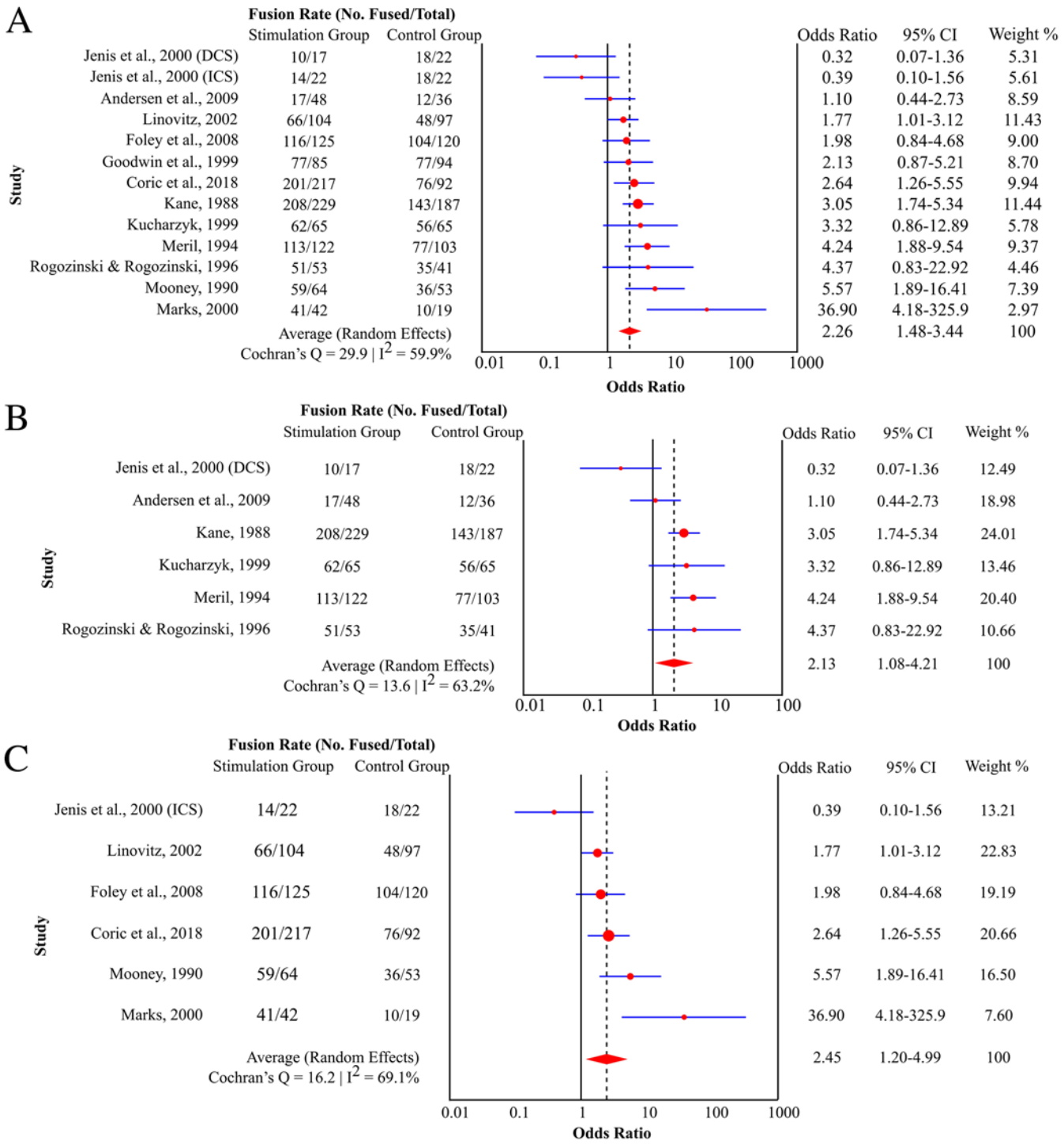

FIG. 3. Forest plots demonstrating random-effects meta-analysis of the fusion rates from all clinical studies (**A**), only clinical studies examining the effect of DCS on spinal fusion (**B**), and only clinical studies examining the effect of ICS on spinal fusion (**C**). Only studies reporting fusion 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

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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%)**		

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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**

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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

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Author Contributions

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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