

# Pulsed Electromagnetic Fields Reduce Postoperative Interleukin-1 $\beta$ , Pain, and Inflammation: A Double-Blind, Placebo-Controlled Study in TRAM Flap Breast Reconstruction Patients

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**Background:** Pulsed electromagnetic fields have been shown to reduce postoperative pain, inflammation, and narcotic requirements after breast reduction and augmentation surgical procedures. This study examined whether pulsed electromagnetic field therapy could produce similar results in patients undergoing unilateral transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction, a significantly more complex and painful surgical procedure.

**Methods:** In this double-blind, placebo-controlled, randomized study, 32 patients undergoing unilateral TRAM flap breast reconstruction received active or sham pulsed electromagnetic field therapy. Pain levels were measured by using a visual analogue scale; narcotic use and wound exudate volume were recorded starting 1 hour postoperatively. Wound exudates were analyzed for interleukin-1 $\beta$ .

**Results:** Mean visual analogue scale pain scores were 2-fold higher in the sham cohort at 5 hours and 4-fold higher at 72 hours ( $p < 0.01$ ), along with a concomitant 2-fold increase in narcotic use in sham patients ( $p < 0.01$ ). Wound exudate volume was 2-fold higher in the sham cohort at 24 hours ( $p < 0.01$ ), and mean interleukin-1 $\beta$  concentration in wound exudates of sham patients was 5-fold higher at 24 hours ( $p < 0.001$ ).

**Conclusions:** Pulsed electromagnetic field therapy significantly reduced postoperative pain, inflammation, and narcotic use following TRAM flap breast reconstruction, paralleling its effect in breast reduction patients. Both studies also report a significant reduction of interleukin-1 $\beta$  in the wound exudate, supporting a mechanism involving a pulsed electromagnetic field effect on nitric oxide/cyclic guanosine monophosphate signaling, which modulates the body's antiinflammatory pathways. Adjunctive pulsed electromagnetic field therapy could impact the speed and quality of wound repair in many surgical procedures. (*Plast. Reconstr. Surg.* 135: 808e, 2015.)

**CLINICAL QUESTION/ LEVEL OF EVIDENCE:** Therapeutic, I.

**N**oninvasive nonthermal pulsed electromagnetic fields have been used successfully as adjunctive therapy to accelerate the repair

of delayed and nonunion fractures and chronic wounds, and the reduction of pain and inflammation.<sup>1-5</sup> Recent double-blind, randomized clinical

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This study is registered under the name "Use of Pulsed Electromagnetic Fields (PEMF) After Breast Reconstruction Surgery," ClinicalTrials.gov identification number NCT01262599 (<http://clinicaltrials.gov/show/NCT01262599>).

Preliminary results from this study were presented at the American Society of Plastic Surgeons Annual Meeting, in New Orleans, Copyright © 2015 by the American Society of Plastic Surgeons

DOI: 10.1097/PRS.0000000000001152

Louisiana, October 26 through 30, 2012; and the 31st Annual Meeting of the Northeastern Society of Plastic Surgeons, in Providence, Rhode Island, September 12 through 14, 2014.

**Disclosure:** Dr. Rohde received a research grant from Ivivi Health Sciences, LLC, for this study. Dr. Pilla receives compensation as a senior scientific advisor to Ivivi Health Sciences and had no contact with patients in this study. Drs. Taylor and Ascherman and Ms. Alonso and Ms. Hardy have no financial interest with Ivivi Health Sciences and no financial interests or sources of support to disclose.

studies have reported that disposable pulsed electromagnetic field devices, applied immediately postoperatively, significantly accelerated pain reduction and reduced postoperative narcotic requirements after breast augmentation<sup>6,7</sup> and reduction.<sup>8</sup> We demonstrated in the latter study that pulsed electromagnetic fields also significantly decreased the levels of interleukin-1 $\beta$  (a principal inflammatory cytokine involved in pain hypersensitivity) in wound exudates, and wound exudate volume, in the first 24 hours postoperatively.<sup>8,9</sup> Since these clinical reports, basic studies have continued to demonstrate that pulsed electromagnetic fields can modulate calmodulin-dependent nitric oxide/cyclic guanosine monophosphate signaling,<sup>10,11</sup> a primary antiinflammatory and repair pathway.<sup>12–15</sup> It has been shown that the effect of pulsed electromagnetic fields on nitric oxide/cyclic guanosine monophosphate signaling decreases the rate of release of proinflammatory cytokines (e.g., interleukin-1 $\beta$ ) and augments the release of antiinflammatory cytokines (e.g., interleukin-6 and interleukin-10<sup>16–19</sup>) and growth factors (e.g., fibroblast growth factor-2<sup>20–22</sup>) in challenged cells and tissues. Considered together, this body of results supports the concept that adjunctive pulsed electromagnetic fields is an important tool for the surgeon to accelerate the reduction of postsurgical pain and inflammation, decrease patient morbidity, and enhance surgical outcomes.

Our initial double-blind randomized pulsed electromagnetic field study showed significant reductions in pain, narcotic use, and interleukin-1 $\beta$  in breast reduction surgery. This study investigates whether the same adjunctive pulsed electromagnetic field therapy can accelerate pain and edema reduction, and decrease narcotic use and interleukin-1 $\beta$  after transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction, a significantly more complex and painful surgical procedure.

### PATIENTS AND METHODS

This study was approved by the Institutional Review Board at Columbia University Medical Center. Before the start of this study, a sample size analysis, assuming a clinically meaningful 50  $\pm$  40 percent (mean  $\pm$  SD) decrease in pain scores from pulsed electromagnetic field treatment,<sup>23</sup> suggested that a minimum of 11 patients per group were needed. Patients requiring unilateral unipedicled TRAM flap breast reconstruction surgery following mastectomy, either immediate or delayed, were candidates for this study. Patients

undergoing bilateral breast reconstruction or free flap breast reconstruction were excluded. Thirty-two consecutive TRAM flap patients, aged 34 to 72 years, were enrolled in this double-blind, placebo-controlled, randomized study. All enrolled patients gave written informed consent. Randomization was performed by the blinded assignment of pulsed electromagnetic field devices from a list of their serial numbers. Breast reconstructions were performed by two surgeons (C.H.R. and J.A.A.) who have similar TRAM flap surgical techniques. The surgeon decided whether to use ipsilateral or contralateral pedicles and used a fascia-sparing technique. In all cases, the abdominal donor-site fascia was closed primarily, with an additional onlay of polypropylene mesh. Use of pulsed electromagnetic field was the only addition to the current standard of care. Jackson-Pratt drains (10 mm) were placed into the breast and abdominal donor sites and brought out through separate stab incisions. These drains were left in place while the patient remained in the hospital. This permitted the collection of wound exudates in the immediate postoperative stages of healing. Exudates were collected into 15-ml polypropylene tubes, starting 1 hour postoperatively and at regular intervals, and total volume was recorded. Tubes were stored at  $-80^{\circ}\text{C}$  for subsequent analysis.

Patients were randomly assigned two disposable pulsed electromagnetic field devices placed within the surgical dressings on the breast flap and abdominal donor sites (Fig. 1). Pulsed electromagnetic field therapy was identical for both sites and was delivered by means of disposable 18-cm-diameter coils (Ivivi Health Sciences, San



**Fig. 1.** Pulsed electromagnetic field devices placed over the breast flap and abdominal donor site as shown. Both devices were activated immediately postoperatively while the patient was on the recovery stretcher.

Francisco, Calif.) that were programmed to apply pulsed electromagnetic fields for 15 minutes every 2 hours. Devices were activated on transfer to the recovery stretcher and remained in place to continuously deliver the pulsed electromagnetic field program while the patient was in the hospital. The pulsed electromagnetic field signal consisted of a 2-msec burst of 27.12-MHz radiofrequency sinusoidal waves repeating at 2 bursts/second.<sup>3</sup> Peak magnetic field was 0.05 G, which induced an average electric field of  $4 \pm 1$  V/m in each target site. The 18-cm coil produced a therapeutically useful signal up to 10 cm above and below the plane of the coil. This ensured adequate depth of signal penetration (dose) for abdominal/chest wall, subcutaneous, and skin suture line pain. Sham devices appeared identical to and were used in exactly the same manner as active devices but produced no electromagnetic field in tissue. Both sham and active devices had indicator lights that blinked during pulsed electromagnetic field application. These pulsed electromagnetic field devices do not produce heat, per se, or cause any sensation. The average in situ magnetic field induced by the pulsed electromagnetic field signal is at least 1000-fold below the earth's magnetic field and is not detectable using standard Gauss meters. Therefore, only measurements with specialized laboratory equipment, not normally available in the recovery or hospital room, could determine whether a device was active. Physicians, health professionals, and patients could not determine whether a device was active or a placebo throughout the study.

Pulsed electromagnetic field signal amplitude and configuration were verified for each device by a third party, who had no contact with patients, with a calibrated shielded loop probe 1 cm in diameter (model 100A; Beehive Electronics, Sebastopol, Calif.) connected to a calibrated 100-MHz oscilloscope (model 2012B; Tektronix, Beaverton, Ore.). Measurement of the pulsed electromagnetic field signal distribution in a validated saline tissue phantom<sup>24</sup> revealed that pulsed electromagnetic field amplitude in tissue from active devices was uniform to within  $\pm 25$  percent. An additional measure in the tissue phantom showed that the specific absorption rate, a measure of peak radiofrequency power in tissue, was 1 mW/kg,<sup>25,26</sup> which is well below the level at which temperature could rise above background thermal fluctuations.<sup>26</sup>

The primary outcome measure in this study was the rate of decrease of postsurgical pain. Secondary outcomes were interleukin-1 $\beta$  concentration

dynamics in the wound bed, wound exudate volume, and postoperative narcotic requirements. Pain levels were assessed by self-evaluation with a visual analogue scale, previously validated for postsurgical pain.<sup>27,28</sup> Visual analogue scale data were obtained at intervals starting at 1 hour postoperatively and at specified intervals thereafter until hospital discharge. Use of narcotic pain medication (oxycodone/acetaminophen) over the hospital course was assessed by comparing pill counts for each group. All patients received patient-controlled analgesia for initial pain control, and then oxycodone/acetaminophen (Percocet; Endo Pharmaceuticals, Inc., Malvern, Pa.) as soon as they were able to tolerate oral intake, usually by postoperative day 1 or 2. Because oxycodone/acetaminophen was the most common narcotic pain medication taken postoperatively, an equianalgesic table was used to convert other narcotics (i.e., morphine, hydromorphone, fentanyl, codeine, and hydrocodone) given in the immediate postoperative period into Percocet equivalents.<sup>29</sup> This conversion enabled a comparison of pain medication use between active and sham groups.

Wound exudate was collected hourly starting at 1 hour postoperatively for the first 6 hours and at 6- to 12-hour intervals thereafter. All exudate fluid at each time point was completely removed, so that samples only contained fluid drained since the prior fluid collection, allowing volume at each time point to be recorded. For determination of interleukin-1 $\beta$ , exudates were thawed, cellular debris was pelleted by centrifugation, and resulting supernatants were divided into smaller aliquots and frozen at  $-80^{\circ}\text{C}$  until analysis. Interleukin-1 $\beta$  was quantified using enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn.).

Data were analyzed using one-way analysis of variance, one-way repeated measures analysis of variance, *t* test, or Mann-Whitney rank sum test, as appropriate. The Pearson product-moment correlation was used to test for possible relations between patient variables, such as age and body mass index, and the primary outcome measure (SigmaStat 3.5; Systat Software, Inc., San Jose, Calif.). Intention-to-treat using last value carried forward was used for missing data.<sup>30</sup> Significance was accepted at  $p \leq 0.05$ .

## RESULTS

The portable and disposable pulsed electromagnetic field devices were well tolerated. Possible adverse events attributable to pulsed

**Table 1. Patient Demographics**

Index	Active	Sham	<i>p</i>
Age, yr	51.1 ± 2.4	53.5 ± 2.3	0.481
BMI	24.5 ± 0.84	25.1 ± 0.78	0.623

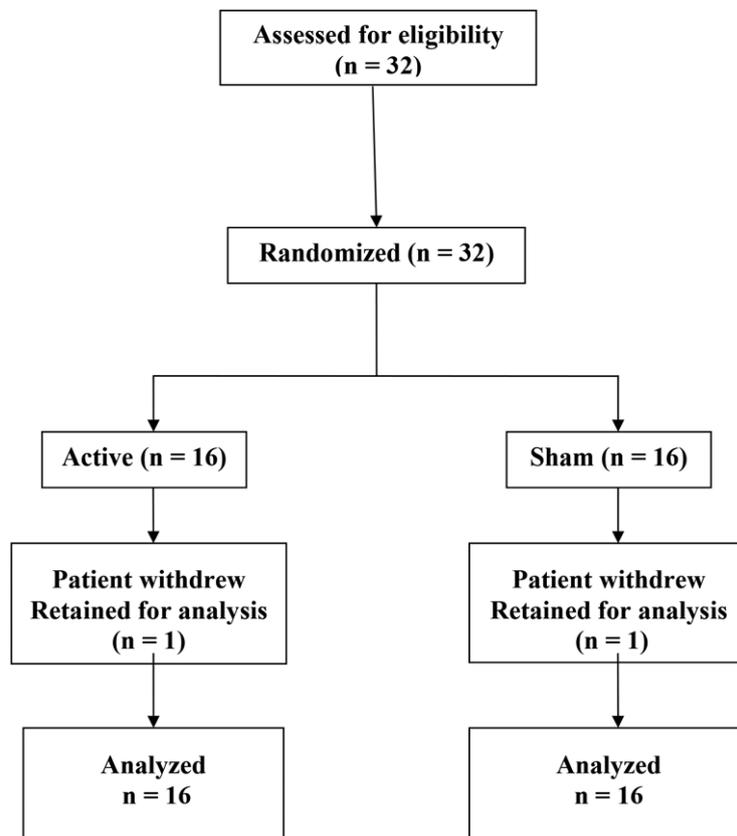
BMI, body mass index.

electromagnetic field therapy were monitored, and no adverse events were reported. Thirty-two consecutive unilateral, unipedicled TRAM flap patients agreed to participate in the study, resulting in data from 16 active and 16 sham patients available for analyses. There were no significant differences in sham versus active groups with respect to age or body mass index (Table 1).

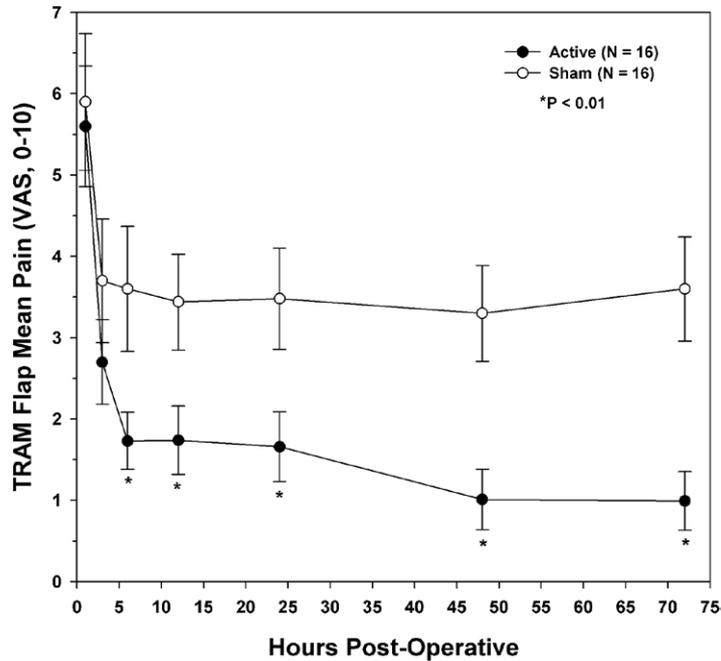
Nonetheless, to be certain there was no relation between age or body mass index and the primary outcome measure, the Pearson product-moment correlation for each cohort at each time point was evaluated. The results showed there was no significant relation between age or body mass index and postoperative pain at any time point ( $p > 0.05$ ). Two patients withdrew early during the study: one active patient because of an

unrelated skin reaction to a chemotherapeutic agent, and one sham patient because she had discomfort from the dressings and device and asked that everything be removed. These patients were retained for analyses using intention-to-treat (last value carried forward). Patient flow is shown in Figure 2.

Mean visual analogue scale scores over the 72-hour postsurgical period were compared both within and between cohorts. The results show that visual analogue scale pain scores in the sham cohort were approximately 2-fold higher than visual analogue scale scores in the active cohort at 5 hours postoperatively and approximately 4-fold higher in shams versus the active cohort at 72 hours ( $p < 0.01$ ). The overall rate of pain decrease in the active cohort over 72 hours was nearly 4-fold faster than that in the sham cohort (active-to-sham slope ratio, 3.8;  $p < 0.001$ ). In addition, visual analogue scale pain score in the active group was significantly lower by 3 hours compared with its value at 1 hour ( $p = 0.025$ ); by 72 hours, it was only 17 percent of starting pain ( $p < 0.001$ ). In contrast, the visual analogue scale



**Fig. 2.** Patient flow chart for randomized clinical trial on pulsed electromagnetic field effect on postoperative pain and inflammation in patients undergoing TRAM flap breast reconstruction.



**Fig. 3.** Effect of pulsed electromagnetic field therapy on postoperative pain. Mean visual analogue scale (VAS) pain score in the sham cohort was approximately 2-fold higher than that in the active cohort at 5 hours and approximately 4-fold higher at 48 hours. Visual analogue scale pain score decreased nearly 2.5-fold faster in the active cohort in the first 5 hours postoperatively.

pain score in the sham group was not significantly different at 3 hours compared to its value at 1 hour ( $p = 0.196$ ) and, by 72 hours, had only decreased to 63 percent of its value at 1 hour ( $p = 0.017$ ), confirming that pulsed electromagnetic field therapy accelerated the rate of postoperative pain decrease by nearly 4-fold. These results are summarized in Figure 3.

Intercohort comparisons for postoperative pain are shown in Table 2. As may be seen, mean visual analogue scale score in the sham cohort is 2-fold higher than that in the active cohort at 5 hours postoperatively and nearly 4-fold higher at

72 hours postoperatively. These results confirm those obtained from the intracohort analyses.

The effect of pulsed electromagnetic fields on postoperative narcotic use is summarized in Figure 4. Sham patients required more than 2-fold more narcotic medication (Percocet equivalents) compared with the sham group by 3 hours postoperatively ( $p < 0.01$ ). It is also of significance that patients in the sham group required approximately 6-fold more narcotics than the active group between 48 and 72 hours. Thus, the active cohort required a mean of  $2.2 \pm 0.4$  Percocet equivalents over this time range, compared with a mean of  $12.6 \pm 1.4$  Percocet equivalents in the sham cohort over the same time range ( $p < 0.02$ ).

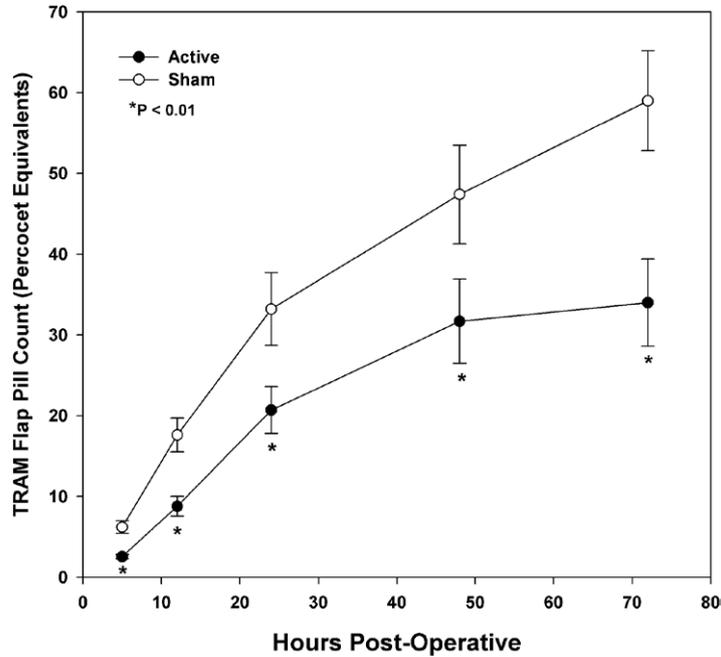
The effect of pulsed electromagnetic fields on the dynamics of wound exudate volume is summarized in Figure 5. Total wound exudate volume from both the breast flap and abdominal donor site in the sham cohort was more than 2-fold higher in the sham cohort from 6 to 24 hours postoperatively compared with that in the active cohort over the same time range ( $p < 0.01$ ). The pulsed electromagnetic field effect on wound exudate volume was similar for both the abdominal donor and the breast reconstruction sites. Total exudate volume from the breast reconstruction site at 24 hours was

**Table 2. Intercohort Comparisons of Mean Visual Analogue Scale Pain Scores**

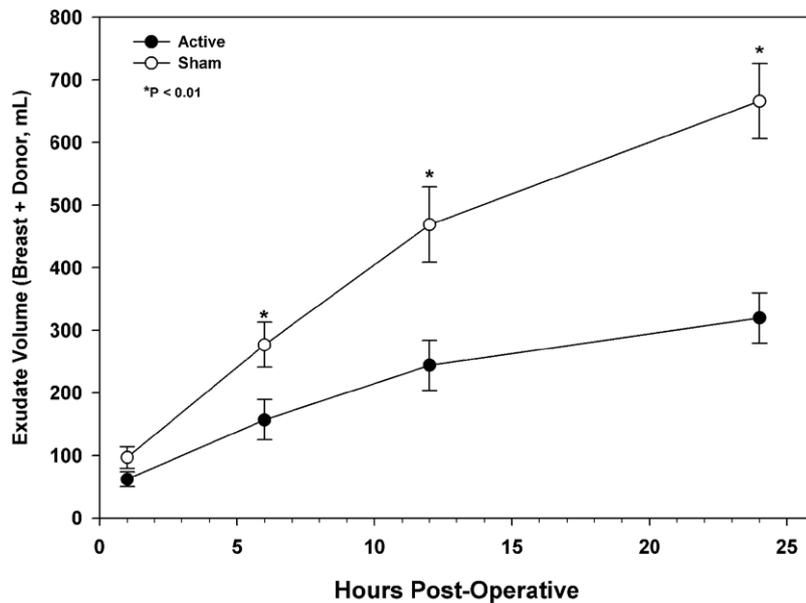
Hours Postoperatively	Mean VAS Score		<i>p</i>
	Active	Sham	
1	5.60 ± 0.75	5.91 ± 0.85	0.911
3	2.69 ± 0.52	3.77 ± 0.75	0.273
6	1.71 ± 0.35	3.61 ± 0.78	0.036*
12	1.74 ± 0.41	3.44 ± 0.59	0.024*
24	1.67 ± 0.43	3.48 ± 0.61	0.023*
48	1.01 ± 0.37	3.30 ± 0.59	0.003*
72	0.99 ± 0.37	3.56 ± 0.64	0.002*

VAS, visual analogue scale.

\*Statistically significant.



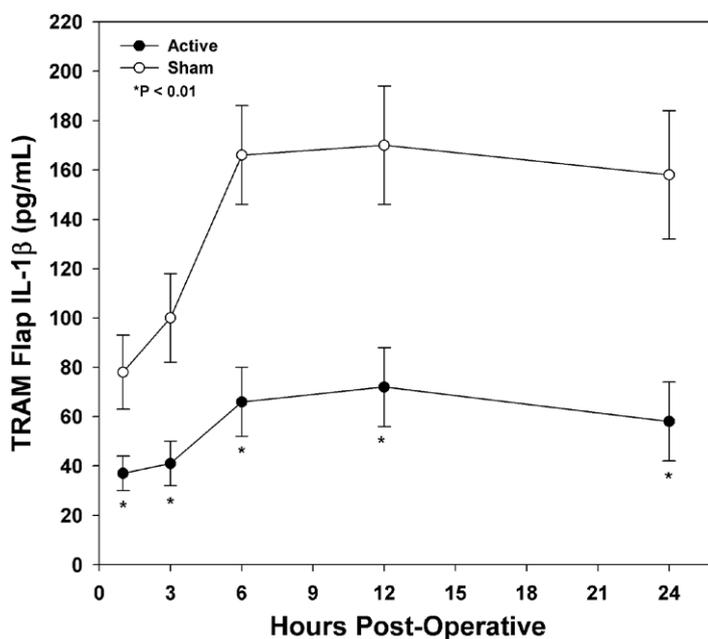
**Fig. 4.** Effect of pulsed electromagnetic fields on postoperative narcotic requirements. Sham patients used more than 2-fold more narcotics by 3 hours postoperatively ( $p < 0.01$ ). In addition, sham narcotic use was 6-fold higher than active use between 48 and 72 hours postoperatively.



**Fig. 5.** Effect of pulsed electromagnetic fields on wound exudate volume. Total volume from both the breast flap and the abdominal donor sites is approximately 2-fold higher 6 to 24 hours postoperatively in the sham cohort compared with that in the active cohort.

168 ± 17 ml in the active cohort and 320 ± 36 ml in the sham cohort ( $p < 0.01$ ). Similarly, total exudate volume from the abdominal donor site at 24 hours was 164 ± 20 ml in the active cohort compared to 346 ± 46 ml in the sham cohort ( $p < 0.01$ ).

The effect of pulsed electromagnetic fields on the dynamics of interleukin-1 $\beta$  in wound exudates from breast flap and abdominal donor sites is summarized in Figure 6. Interleukin-1 $\beta$  in sham wound exudates was approximately 4-fold higher



**Fig. 6.** Effect of pulsed electromagnetic fields on the dynamics of interleukin (*IL*)-1 $\beta$  concentration in wound exudates. Results from breast flap and abdominal donor sites were combined. Interleukin-1 $\beta$  concentration was approximately 4-fold higher at 6 hours postoperatively and approximately 5-fold higher at 24 hours postoperatively in the sham cohort compared with the corresponding interleukin-1 $\beta$  concentration in the active cohort.

at 6 hours postoperatively and approximately 5-fold higher at 24 hours compared with that in the corresponding wound exudates in the active cohort. The concentration of interleukin-1 $\beta$  in the wound exudates collected in the study is consistent with that reported in other studies.<sup>31–35</sup> The pulsed electromagnetic field effect on the dynamics of interleukin-1 $\beta$  in wound exudates correlate well with the rapid decrease of postoperative pain in patients in the active cohort.

## DISCUSSION

This study shows that a pulsed electromagnetic field signal, known to modulate calmodulin-dependent nitric oxide signaling, significantly reduced postoperative pain and inflammation (serous exudate), use of narcotic medications, and interleukin-1 $\beta$  in both the breast flap and the abdominal donor locations following pedicled TRAM flap breast reconstruction. The effects of pulsed electromagnetic field therapy on postoperative pain and narcotic use were similar to those reported in breast augmentation<sup>6,7</sup> and reduction<sup>8</sup> studies. In addition, the pulsed electromagnetic field effect on inflammation and interleukin-1 $\beta$  was similar to that reported by our group in

a previous study on breast reductions using the same pulsed electromagnetic field signal.<sup>8,36</sup>

The mechanism of action of pulsed electromagnetic field signals is not yet completely elucidated; however, more is known than in our previous breast reduction study. Recent basic studies have shown that the radiofrequency pulsed electromagnetic field signal used in this study modulates calmodulin-dependent nitric oxide/cyclic guanosine monophosphate signaling, an important antiinflammatory pathway, in challenged cells and tissues.<sup>10,11,26,36</sup> Direct evidence of the immediate effect of pulsed electromagnetic fields on real-time nitric oxide production in a neuronal cell line challenged with lipopolysaccharide has recently been reported.<sup>11</sup> Other studies have confirmed that this pulsed electromagnetic field signal can augment calmodulin-dependent nitric oxide and cyclic guanosine monophosphate release from human umbilical vein endothelial cell and fibroblast cultures,<sup>10,11,26,36</sup> wherein the calmodulin antagonists *N*-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide hydrochloride (W-7) and trifluoperazine were able to block the pulsed electromagnetic field effect on additional nitric oxide release, supporting a pulsed electromagnetic field effect on calmodulin activation.<sup>10</sup> Furthermore,

this pulsed electromagnetic field signal has been shown to enhance microvascular perfusion<sup>37</sup> and neuronal regeneration.<sup>38</sup>

Neutrophils and macrophages, the first cellular responders in the inflammatory phase of wound repair,<sup>39</sup> produce interleukin-1 $\beta$ , which in turn can up-regulate inducible nitric oxide synthase activity, resulting in proinflammatory amounts of nitric oxide to be released into the wound bed.<sup>40</sup> The calmodulin-dependent nitric oxide/cyclic guanosine monophosphate signaling pathway modulates the down-regulation of both interleukin-1 $\beta$  and inducible nitric oxide synthase.<sup>41</sup> Use of pulsed electromagnetic fields has been reported to down-regulate inducible nitric oxide synthase at the mRNA and protein levels in monocytes.<sup>42</sup> This pulsed electromagnetic field signal has been shown to down-regulate the proinflammatory cytokine interleukin-1 $\beta$  and up-regulate the antiinflammatory cytokines interleukin-5, interleukin-6, and interleukin-10 in fibroblasts and keratinocytes.<sup>16</sup> Pulsed electromagnetic fields reduced interleukin-1 $\beta$  in cerebrospinal fluid 6 hours after posttraumatic brain injury in a rat model.<sup>19</sup> Pulsed electromagnetic fields down-regulated interleukin-1 $\beta$  and up-regulated interleukin-10 in a mouse cerebral ischemia model<sup>17</sup> and up-regulated interleukin-10 within 7 days in a chronic inflammation model in the mouse.<sup>18</sup>

It follows that the pulsed electromagnetic field signal as used in this clinical study can have an antiinflammatory effect by means of modulation of calmodulin/nitric oxide/cyclic guanosine monophosphate signaling,<sup>16</sup> which could down-regulate both interleukin-1 $\beta$  and inducible nitric oxide synthase, and modulate other inflammatory cytokines. This translates directly to this and our previous<sup>8</sup> clinical study. Indeed, interleukin-1 $\beta$  levels in wound exudates, and the volume of exudate, of patients treated with active pulsed electromagnetic field coils were significantly reduced in both studies. These clinical results suggest that pulsed electromagnetic field therapy can produce endogenous changes in the dynamics of interleukin-1 $\beta$  availability in the wound bed by means of its effects on nitric oxide/cyclic guanosine monophosphate signaling, which should impact the many known subsequent inflammatory events that are mediated by this cytokine.<sup>14,43,44</sup>

It is also notable that pulsed electromagnetic field dosing is important because phosphodiesterase activity, which blocks cyclic guanosine monophosphate by converting it to guanosine monophosphate,<sup>45</sup> is modulated by this pulsed electromagnetic field signal as well. The effect of

pulsed electromagnetic field dosing on the competing dynamics of calmodulin-dependent nitric oxide/cyclic guanosine monophosphate signaling and phosphodiesterase inhibition of cyclic guanosine monophosphate on pain outcome in breast reduction patients was recently investigated.<sup>46</sup> This study compared several pulsed electromagnetic field signal configurations and showed that pain outcomes were dependent on the rate of increased nitric oxide in tissue. The results confirmed that the pulsed electromagnetic field signal used in this and our previous study provided adequate dosing to have a net positive effect on postoperative pain reduction.

The clinical implications of our findings are significant. Certain patients were noticeably more comfortable and active than others and, in retrospect, found to be in the active pulsed electromagnetic field group. The pulsed electromagnetic field devices do not increase the normal effort or time required to place a postoperative dressing. The device weighs only 2.4 ounces, fits easily in a surgical bra or dressings and, once positioned and activated, requires no further intervention. Patients are instructed to remove the device only for bathing, and to replace the device in its original position. The cost of the pulsed electromagnetic field device used in this study is approximately \$200, comparable to that of an implantable local anesthetic pain pump, which requires more intervention and use of a bulky reservoir.<sup>47</sup> It is also important to note that there are no known side effects associated with the use of pulsed electromagnetic field devices, whereas narcotic pain medications can cause side effects of nausea, vomiting, or constipation and have addictive potential. With this in mind, the cost of the pulsed electromagnetic field device is a fraction of the cost of treating side effects from narcotics. The benefits of reducing the severity and duration of the inflammatory phase of wound repair with noninvasive, nonpharmacologic pulsed electromagnetic field therapy, which can manipulate the body's endogenous orchestration of wound repair with no known side effects, could thus have a major impact on the reduction of patient morbidity and perhaps surgical recovery and overall outcomes. This, in turn, may lead to a reduction in hospital stays, with consequent reductions in the cost of health care.

## CONCLUSIONS

This study provides further evidence that non-thermal radiofrequency pulsed electromagnetic

field therapy can reduce pain levels and pain medication requirements in the immediate postoperative period, even for complex surgical procedures. The concomitant reduction of interleukin-1 $\beta$  in the wound bed is consistent with a pulsed electromagnetic field effect on nitric oxide/cyclic guanosine monophosphate signaling, suggesting that pulsed electromagnetic fields could have a profound effect on wound repair outcome. As shown elsewhere,<sup>46</sup> the pulsed electromagnetic field dosing used is known to produce a clinically significant outcome. As these results are confirmed with more clinical studies, the current availability of both economical and disposable pulsed electromagnetic field devices could easily translate to many, if not most, postsurgical situations, potentially leading to lower morbidity, enhanced surgical healing, shorter hospital stays, increased productivity, and a reduction in the cost of health care.

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#### ACKNOWLEDGMENT

*The pulsed electromagnetic field devices used in this study are cleared by the U.S. Food and Drug Administration for relief of postoperative pain and edema in superficial soft tissues and were donated by Ivivi Health Sciences, LLC (San Francisco, Calif.). This article is dedicated to the memory of Diana Casper, Ph.D., who played a pivotal role in pulsed electromagnetic field research and was first to suggest that wound exudate analysis would help elucidate the mechanism of action of pulsed electromagnetic fields in the clinical arena.*

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