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Pulsed electromagnetic fields dosing impacts postoperative pain in breast reduction patients

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ABSTRACT

Background: Pulsed electromagnetic fields (PEMF) reduce postoperative pain and narcotic requirements in breast augmentation, reduction, and reconstruction patients. PEMF enhances both calmodulin-dependent nitric oxide and/or cyclic guanosine monophosphate signaling and phosphodiesterase activity, which blocks cyclic guanosine monophosphate. The clinical effect of these competing responses on PEMF dosing is not known.

Methods: Two prospective, nonrandomized, active cohorts of breast reduction patients, with 15 min PEMF per 2 h; "Q2 (active)", and 5 min PEMF per 20 min; "5/20 (active)", dosing regimens were added to a previously reported double-blind clinical study wherein 20 min PEMF per 4 h, "Q4 (active)", dosing significantly accelerated postoperative pain reduction compared with Q4 shams. Postoperative visual analog scale pain scores and narcotic use were compared with results from the previous study.

Results: Visual analog scale scores at 24 h were 43% and 35% of pain at 1 h in the Q4 (active) and Q2 (active) cohorts, respectively ($P < 0.01$). Pain at 24 h in the 5/20 (active) cohort was 87% of pain at 1 h, compared with 74% in the Q4 (sham) cohort ($P = 0.451$). Concomitantly, narcotic usage in the 5/20 (active) and Q4 (sham) cohorts was not different ($P = 0.478$), and 2-fold higher than the Q4 (active) and Q2 (active) cohorts ($P < 0.02$).

Conclusions: This prospective study shows Q4/Q2, but not 5/20 PEMF dosing, accelerated postoperative pain reduction compared with historical shams. The 5/20 (active) regimen increases NO 4-fold faster than the Q4 (active) regimen, possibly accelerating phosphodiesterase inhibition of cyclic guanosine monophosphate sufficiently to block the PEMF effect. This study helps define the dosing limits of clinically useful PEMF signals.

1. Introduction

Acute postoperative pain is a significant medical problem. Postoperative pain must be managed effectively to optimize surgical outcomes, reduce morbidity, shorten the duration of hospital stay, and control ever-increasing health-care costs [1]. For the vast majority of surgical procedures, pain mechanisms involve increased sensitivity of nociceptors due to increased presence of proinflammatory cytokines in the wound milieu [2]. Narcotics are most commonly used to treat postoperative pain; however, narcotics do not reduce nociceptor sensitivity and cause undesirable side effects and

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potential addiction. Alternative approaches to decrease postoperative pain involve slowing the appearance of proinflammatory agents at the surgical site [2].

To this end, a new modality, nonthermal, nonpharmacologic radio frequency pulsed electromagnetic field (PEMF) therapy has been reported to instantaneously enhance calmodulin (CaM)-dependent nitric oxide (NO) release in challenged cells and tissues. This, in turn, enhances the body's primary anti-inflammatory pathway, CaM-dependent nitric oxide/cyclic guanosine monophosphate (NO/cGMP) signaling [3–7]. In the surgical context, NO/cGMP signaling decreases the rate of release of proinflammatory cytokines, such as interleukin-1 beta (IL [interleukin]-1β) [8], and increases the release of growth factors, such as fibroblast growth factor-2 (FGF-2) [9], in the wound milieu. This mechanism is schematically represented in Figure 1. PEMF modulation of angiogenesis via effects on FGF-2 has been reported [10–15]. In some studies, the PEMF effect could be blocked with an FGF-2 inhibitor, consistent with a PEMF effect on NO/cGMP signaling [12,13].

In the clinical setting, PEMF has been reported to accelerate postoperative pain decrease, with a concomitant reduction in narcotic requirements, in double-blinded, randomized clinical studies on breast reduction (BR) [16], breast augmentation [17,18], and autologous flap breast reconstruction [19]. The BR study also showed that PEMF reduced inflammation by reducing IL-1 beta more than two-fold in the wound exudate, which correlated with the higher rate of pain reduction from PEMF [16]. PEMF can and has been used throughout the body, including after abdominoplasties, major intra-abdominal surgery, extremity procedures, and facial fat grafting [20,21].

Taken together, preclinical and clinical results support an anti-inflammatory mechanism for PEMF based on modulation of CaM-dependent NO/cGMP signaling. However, the NO/cGMP cascade is dynamic [22] and regulated, in part, by phosphodiesterase (PDE) inhibition of cyclic guanosine monophosphate (cGMP) [23]. This inhibition is particularly important for PEMF therapy because PDE isoenzymes are also CaM-dependent, meaning the timing of PDE activity is modulated by the same PEMF signal that modulates NO/cGMP signaling [24]. Thus, although the dynamics of NO/cGMP signaling in challenged tissue can be modulated by PEMF, the effect of PEMF dosing on the competing dynamics of CaM-dependent NO/cGMP signaling and PDE inhibition of cGMP on pain outcome is not understood. Although PEMF has been shown to significantly accelerate postsurgical pain decrease, the optimal dosage of PEMF in this clinical setting is not known. Therefore, this prospective study, building on our previous double-blind randomized PEMF study on BR patients [16], assessed the effect of PEMF regimen by adding two active cohorts in which the rate of expected NO release was varied up to four-fold, with the hypothesis that more frequent PEMF dosing could further enhance its effect on postoperative pain relief.

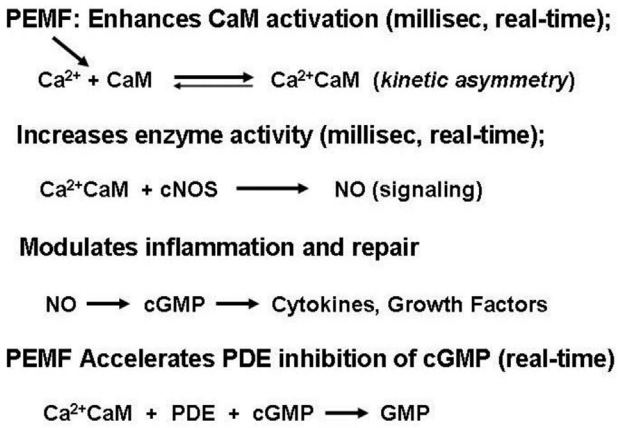

Fig. 1 – Schematic summary of the body's primary anti-inflammatory cascade and the proposed manner by which PEMF may accelerate postoperative pain relief. Surgical injury increases cytosolic Ca^{2+}, which activates CaM. PEMF accelerates CaM activation thereby enhancing NO/cGMP anti-inflammatory signaling. PEMF also enhances CaM-dependent PDE activation, which accelerates cGMP inhibition. This study suggests that PEMF dosing must take into account the competing dynamics of NO/cGMP signaling and PDE inhibition of cGMP.

2. Materials and methods

This prospective study, which adds two active (nonrandomized) cohorts to our previous randomized, double-blind, placebo–controlled study on BR was approved by the Institutional Review Board at Columbia University Medical Center. The study intent was to determine whether more frequent PEMF dosing could further enhance postoperative pain reduction over every 4 h dosing or placebo from our previous study. The sample size analysis, as used in our previous BR study [16], which assumed a clinically meaningful 50% (±40% standard deviation) decrease in pain scores from PEMF treatment [25], indicated that a minimum of 11 patients per additional cohort were needed. Thus, 26 healthy women, aged 21–59 y, who were candidates for BR for symptomatic macromastia, were consecutively enrolled in this prospective study. All patients undergoing BR surgery were asked to participate, and all enrolled patients gave informed consent. Patients were assigned to be treated using the 5/20 (active) or Q2 (active) regimen. BRs were performed by the same surgeon (C.H.R.) who performed the surgery in the original BR study using Wise pattern and vertical pattern superomedial pedicle reduction techniques [26–28]. As a routine practice of this surgeon, 10-mm Jackson–Pratt drains were placed in each breast and removed on the first postoperative morning before discharge. As in the initial study, use of PEMF coils was the only addition to the current standard of care.

Patients were assigned an active disposable dual coil PEMF device (SofPulse Duo, donated by Ivivi Health Sciences, LLC, San Francisco, CA). This device is cleared by the Food and Drug Administration for pain and edema relief and is reimbursed by Medicare for chronic wound repair [24]. The PEMF device, which commercially costs approximately $200, consists of a soft dual coil applicator (Fig. 2) that is noninvasive, nonpharmacologic, with no known adverse side effects. The device was placed over dressings and within the postsurgical support bra normally used for all patients, as described elsewhere [16,17]. Devices were activated on transfer to the recovery stretcher. Once activated, pilot lights blinked at the