Pulsed Electromagnetic Fields for Post-appendectomy Pain Management: A Randomized, Placebo-controlled Trial

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Abstract

BACKGROUND

Pulsed electromagnetic fields (PEMF) has been shown to improve post-caesarean section pain previously. This study evaluated the efficacy of PEMF in postoperative pain reduction among patients undergoing urgent appendectomy.

METHODS

This is a double-blinded, randomized trial. Adults with a clinical diagnosis of acute appendicitis were enrolled. Patients were allocated randomly to receive an active-PEMF device or an inactive device after the surgery in addition to the standard post-operative pain management. The primary endpoint was 12-hour postoperative pain score measured using the Visual Analogue Scale. The primary analysis in this trial compared the two study groups for the median pain score using the Wilcoxon rank sum test.

FINDINGS:

118 subjects were randomized, 58 were allocated to the active-PEMF group and 60 to the inactive control group. Median pain score of both intervention groups reduced in a similar fashion over the course of 12 post-operative hours. Median pain score at rest and on movement did not differ significantly 12 hours after the procedure. ($W = 1161$, p -value 0.3542 for resting pain score; $W = 1437.5$, p -value 0.3183 for pain on movement).

DISCUSSION

PEMF was not superior to placebo as an adjunct pain management for up to 12 hours post-appendectomy. Previously reported effect of PEMF on post-operative pain intensity and analgesia uses in similar surgical settings cannot be verified.

Clinical trial registration:

National Medical Research Register Malaysia (NMRR-15-670-25805) & Thai Clinical Trials Registry (retrospectively registered at November 01, 2019, Study ID - TCTR20191102002)

Introduction

Acute appendicitis is one of the most common indication for surgery in patients admitted to hospital for acute abdominal pain.[1, 2] Urgent appendectomy is still the recommended treatment for acute

uncomplicated appendicitis.[3, 4] Although emergency appendicectomy is usually well tolerated by most patients, post-operative pain is nevertheless an important postoperative morbidity.

Postoperative pain prolonged hospital stay, increases healthcare cost and results in higher risks of various long term adverse outcomes.[5] Current available methods of postoperative pain management have undesirable adverse effects. Moreover, their effectiveness vary across individual.[6, 7] Epidural analgesia, a highly effective postoperative pain control approach, requires technical expertise that might not be readily available, especially in setting of limited resources. It also has a number of contraindications and can potentially result in complications.[8] Opioids use are also similarly associated with various side effects.[9] Thus, a safer and effective post-appendicectomy pain management approach is still highly sought after.

Pulsed electromagnetic field (PEMF) therapy has been learned to have the properties to increase anti-inflammatory cytokines, endogenous analgesic agents, and endogenous opioid precursor proteins.[10, 11] In addition, PEMF also has been shown to decrease pro-inflammatory cytokines and endogenous hyperalgesia agents. Several recent studies have shown suggestive results for its use in the pain management of some plastic and oral surgeries.[12–15] Furthermore, the use of PEMF devices for the promotion of soft tissue healing, and the improvement of circulation has also been approved by the US Food and Drug Administration.

Given these results of PEMF therapy and the growing body evidence on its safety, analgesia, anti-inflammatory, and tissue-healing effects, we intend to further explore the potential use of PEMF therapy in the management of post-operative pain in appendicectomy. This study aimed to evaluate the efficacy of PEMF therapy in reducing post-operative pain and intravenous (IV) analgesic use in post-appendicectomy patients. We hypothesized that, if PEMF therapy does improve post-operative pain in appendicectomy, IV fentanyl use via PCA is expected to reduce while the perceived post-operative pain will at least remain (if not reduce concurrently). The logical framework of the study hypothesis is provided as supplementary material (1).

Materials And Methods

Patients

We undertook a prospective, randomized, double-blinded, placebo-controlled trial. The study took place in the Hospital Tengku Ampuan Rahimah, Klang (a tertiary referral centre) Malaysia. The study protocol was reviewed by and registered with the National Medical Research Register, Malaysia (NMRR-15-670-25805) prior to the enrolment of the first subject. Additional registration of the study protocol to the Thai Clinical Trials Registry was also performed retrospectively (Study ID: TCTR20191102002). All patients provided signed, informed consent.

All adults examined in the emergency department and suspected to have an acute appendicitis were assessed for possible inclusion to the study. Patients were excluded if one of the following criteria were

present: age less than 19 years or more than 50; pregnancy or a positive pregnancy test; having underlying chronic pain or history of long term opioid use; appendicectomy lasted more than three hours; or inability to understand information about the protocol or to sign the informed consent form. The on-duty medical officers from the anaesthesiology department enrolled the eligible patients. Patients eligible for inclusion to the study were informed of the protocol and invited to participate.

Randomization and masking

After informed consent was obtained, patients were individually and randomly assigned to either the active PEMF group or the control group (inactive PEMF) according to the randomization schedule prepared prior to the trial initiation. A simple randomization with a 1:1 allocation ratio in this study. The on-call medical officer taking care of the post-operative recovery room opened a consecutively numbered envelope that contained the random allocation code and performed the placement of the trial device onto the enrolled subjects after the operation. Opaque, sealed, identical and sequentially numbered envelopes were used.

The randomization schedule (with the allocation codes) was generated by a trial researcher not involved in the care of the trial subjects prior to the trial start. The same researcher also prepared the numbered envelopes according to the computer-generated schedule. A free, web-based randomization schedule generator from www.graphpad.com/quickcalcs/randomize1/ was used.

Procedures

Immediately after the appendicectomy, either an active or an inactive PEMF device was placed on the surgical wound on top of the dressing for 12 hours (see Picture). Patients were admitted to the hospital after the operation irrespective of the trial intervention received.

The PEMF devices used in this study (RecoveryRx, BioElectronics Corp.) is a battery powered 12 cm elliptical coil radiofrequency energy generator (frequency = 27.1 MHz, pulse rate = 1000 per second, pulse duration = 100 ms). The surface of the device was cleaned and disinfected using 70% isopropyl alcohol wipes prior to application. All visible soil (if any) were first removed via the first wipe. A second wipe was then performed to disinfect the device surface area. The wipe contacted the whole device surface for at least 3 seconds during the disinfection process.

Appendicectomy was performed according to surgeons' standard practice (via a McBurney incision). All patients also received general anaesthesia according to the standard protocol. Anaesthesia was induced with IV fentanyl (1-1.5 µg/kg to a maximum of 100 µg) and propofol (2-3 mg/kg), followed by a muscle relaxant of the anaesthesiologists' choice. All patients then receive IV morphine 0.05 mg/kg intraoperatively. Surgery was commenced after the patient was successfully anesthetized. No local infiltration of any anaesthetic agents was performed on the incised skin. All patients were supplemented with patient-controlled analgesia (PCA) with IV fentanyl post-operatively for 12 hours.

Assessments and endpoints

The primary outcome of our study was the postoperative pain intensity measured using the visual analogue scale (VAS). Secondary outcome was the total amount of IV fentanyl used (in mg/dL) via PCA over the first 12 postoperative hours. Participants were asked to report their pain intensity based on the VAS. Pain intensity was evaluated at 0, 4, 8, and 12 hours after surgery. The requirement for PCA IV fentanyl post-operatively were recorded by a research assistance.

The VAS is an unidimensional measure of pain intensity.[16] It is a continuous scale comprised of a horizontal line of 10 cm in length. The scale ranges from 0 (representing no pain) to 10 (representing worst imaginable pain). Patients were educated on how to use and report their pain with the VAS. They were also asked to place a crossline on the unmarked horizontal scale at the required times interval.

PCA is a pain control system which allow a patient to self-administer a predetermined dose of analgesic medication for pain relief.[17] Fentanyl is a mu opioid receptor agonist with strong analgesic effects, rapid onset of action and a low risk of adverse effect.[18] IV-PCA using fentanyl has been widely adopted globally for postoperative pain management. We used the [CADD Legacy PCA, model 6300; Smiths Medical International, Kent, UK] PCA system in this study. The PCA system was programmed as follow: bolus, 1 mL; lockout time, 5 minutes; maximum dose, 6 mL/h; no background infusion. Infusion solutions containing 1.0 mg of fentanyl adjusted to 100 mL by dilution with saline (concentration of fentanyl, 10 µg/mL). The amount of IV fentanyl used (in mg/dL) via the PCA system was recorded over the first 12 hours after the operation. It is expected that, if the PEMF therapy is effective in reducing post-operative pain, lower amount of IV fentanyl would have been used via the PCA.

The patients and the surgeons, nurses and other healthcare workers including the acute pain service (APS) team involved with direct patient care were blinded to allocation group. The APS team provided all pain-related clinical management to all studies subjects. The research assistant who collected the PCA data was also blinded to the allocation. The identification of treatment was concealed by using an identical yet inactive device.

Statistical Analysis

This study was based on the notion that PEMF therapy would reduce post-operative pain and analgesia use in appendicectomy. We estimated the required sample size based on the Wilcoxon rank sum test using the Monte-Carlo simulation technique. In our simulation, we assumed that the mean pain score in the control group vs. the intervention was 1.0 and 2.0 respectively. The expected difference of VAS pain score was 1.0. [16] A common standard deviation of 1.5 (for the pain score) for both groups were used. [19] The sample size was then varied by simulation until the proportion of significant (0.05) reaches the desired power of 0.80. Thereafter, an additional 10% drop out rate was added to the target sample size. The simulation was performed using the MKpower package (<https://cran.r-project.org/package=MKpower>).

Based on our simulation, we found that a sample size of 80 patients (in the ratio of 1:1 for intervention and control group) would give an 80% power to establish whether PEMF treatment was superior to

placebo in relation to post-operative pain reduction. With the additional consideration of potential drop out (10%) and rounding to the nearest full number, we determined that the target sample size should be 100 (50:50 for control and intervention).

Study outcomes were assessed for all randomised participants who have completed the study process. The primary analysis in this trial compared the two study groups for their median pain score and average IV fentanyl use via PCA. The comparisons were made using the Wilcoxon rank sum test with continuity correction. All reported p values are two-sided and were not adjusted for multiple testing. We used R version 3.3.2 for all the analyses.

Results

A total of 118 subjects were enrolled and randomized. 58 were assigned to the active-PEMF group and 60 to the inactive PEMF (control) group. 11 subjects from the intervention group and 5 subjects from the control group were excluded after assignment because of the following reasons: accidental device off, PCA not initiated due to patient factor, data collection/documentation error, accidental add-on analgesia exposure, PCA machine malfunction, and allergic to IV fentanyl. Ultimately, 47 subjects from the intervention group and 55 subjects from the control group completed the study; their data were used for the subsequent analyses. (Fig. 1) The trial started its recruitment from 1st August 2015 and ended in December 31st, 2015 for accomplishing the intended sample size.

Table 1 shows the baseline characteristics of the trial participants and the comparison of these characteristics between the intervention and placebo groups. Overall, these characteristics appear balance between the intervention group and the placebo group.

Table 1
Demographics and Baseline Characteristics of Participants

	Overall	Control	PEMF	P-value
Number of patients	102	55	47	
Age (mean (SD))	27.82 (7.37)	27.53 (6.91)	28.16 (7.94)	0.672
Sex = Male (%)	69 (67.6)	38 (69.1)	31 (66.0)	0.901
BMI (mean (SD))	22.96 (4.49)	23.01 (4.84)	22.91 (4.09)	0.918
Ethnicity (%)				0.137
Indian	15 (14.7)	5 (9.1)	10 (21.3)	
Malay	57 (55.9)	32 (58.2)	25 (53.2)	
Non-citizen	20 (19.6)	10 (18.2)	10 (21.3)	
Others	10 (9.8)	8 (14.5)	2 (4.3)	
Perforated Appendicitis (%)	12 (11.8)	9 (16.4)	3 (6.4)	0.211
Baseline Readings				
Systolic BP (mean (SD))	124.30 (12.45)	122.91 (12.70)	125.94 (12.07)	0.223
Pulse Rate (mean (SD))	73.82 (12.48)	74.02 (12.51)	73.60 (12.58)	0.866
Respiratory Rate (mean (SD))	16.67 (3.01)	16.49 (3.04)	16.87 (3.00)	0.526
Post-operative resting pain score (mean (SD))	2.36 (1.11)	2.33 (1.04)	2.40 (1.19)	0.728
Post-operative pain score on movement (mean (SD))	3.48 (1.16)	3.51 (1.17)	3.45 (1.16)	0.788

Median pain score of both intervention groups reduced in a similar fashion over the course of 12 post-operative hours. (Fig. 2) The pattern appears similar for both the resting pain score and pain score on movement. Median pain score at rest and on movement did not differed significantly 12 hours after the procedure. (W = 1161, p-value 0.3542 for resting pain score comparison; W = 1437.5, p-value 0.3183 for movement pain score comparison). There were no missing for all the endpoint data. Data of all the included participants who have completed the study were used in these analyses. The analyses were performed by their original assigned groups.

For secondary endpoints, the average use of IV fentanyl via PCA over 12-hour post-operatively also did not differ between the two intervention groups (W = 1296.5, p-value = 0.9812); the pattern of its use appears similar (Fig. 3).

Discussion

This randomized controlled study involving 102 post-appendicectomy patients indicates no significant effect PEMF has on both the patient-reported pain intensity measures (i.e. sitting and moving) over the initial 12 hours post procedure. Similarly, the secondary endpoint – post-operative use of IV fentanyl via PCA – also did not show any difference in between the intervention arm vs. the placebo arm. Hence, previously reported effect of PEMF on post-operative pain intensity and analgesia use in other surgical settings cannot be verified.

The reason of our negative findings is not immediately obvious. We proposed the following for further deliberation. Firstly, acute post-operative pain occurs as a result of tissue trauma or direct nerve injury.[20] Tissue trauma releases local inflammatory mediators which cause increased sensitivity to stimuli in the area surrounding an injury (i.e. hyperalgesia) or misperception of pain to non-noxious stimuli (allodynia). Additionally, the sensitization of the peripheral pain receptors and increased excitability of central nervous system neurons also contribute to hyperalgesia and allodynia.[20] Different surgical conditions and related procedures might bring about a different mixed of these pain aetiologies, thereby affecting the effect of PEMF on cellular mechanisms that induces pain during the acute post-operative period. Hence the possibility of differing PEMF efficacy in different surgical conditions and procedures should be considered.

Next, it is increasingly known that genetic factors play a significant role in influencing one's responses to pain and analgesia.[21, 22] For example, our production of opioid metabolizing enzymes and expression of various pain receptors and signal transduction elements are affected by various genetic factors. It also interacts with other physio-pathological, psychological as well as environmental factors that give rise to various pain-related outcomes.[23] These differences are known to give rise to the large variability in terms of pain perception and post-operative pain management needs. Our study was conducted on a sample of south-east Asian who may pose very different genetic make-ups compared to the Caucasian population, where most of the earlier studies was focused on.[19, 24, 25]

Furthermore, existing evidence on post-operative use of PEMF therapy have not been very consistent. Heden and Pilla (2008) reported a controlled trial of PEMF use among 42 females with post breast augmentation surgery.[12] The study indicated a large and significant effect (more than 3 times different) PEMF had on postoperative pain and pain medication use observable from the 3rd day after the procedure. In another setting, Adravanti et al. (2014) assessed the use of PEMF among 33 subjects with total knee arthroplasty. [25] The therapy was administered for four hours a day for a duration of 60 days. The main difference in this study is that the therapy was initiated only after one week of the operative procedure. Subjects were then assessed at one, two- and six-months post-procedure. The study reported that pain score (measured using the VAS) were consistently lower among those applied with PEMF. The differences were consistent across the three postoperative follow-ups. More recently, the interest of PEMF has been extended further to other surgical discipline. A randomized, double-blind, placebo-controlled evaluation of PEMF by Khooshideh et al. (2017) on postoperative pain, analgesia use and wound healing

in patients undergoing caesarean section has been reported.[19] This study was motivated by the lack of data on PEMF efficacy for deep organ surgery. Seventy-two women were investigated for their pain intensity (assessed using a VAS) at regular interval starting from 2 hours to 7 days post procedure. Analgesia use were also examined. The data shows that pain score and analgesia use were significantly lower among those assigned to the intervention vs. the placebo control. The effect was again largely consistent across the entire observational period (from 2nd hour post procedure to the 7th day).

Despite these positive results, there are also a significant body of reports with negative findings. For instance, Stocchero's study in 2014 represented an important piece of evidence with negative findings. [15] In Stocchero's study, 120 patients undergoing unilateral mandibular third molar extraction were randomly assigned into three study groups (enabled PEMF, disable PEMF and no device) after the procedure. Pain score and analgesia use were assessed for a week. This study, similar to our evaluation, found no significant difference in between those applied with placebo or without device and those with PEMF during the seven days post procedure. Similar negative results have also been reported in a number of PEMF studies: post blepharoplasty [26], breast augmentation [24] and dental implantation procedure [14].

A notable feature among the existing evidence on PEMF and its effect on postoperative pain is their small sample sizes in general. Besides the study reported by Stocchero et al. (2014) [15], the study sizes of those described above ranges from 11–72 with the median study size being 36. The problem with a small sample size in clinical research is of two edges. A small study may risk not being able to detect a clinically significant difference due to the lack of statistical power, hence committing a type II error.[27] This is a well-known limitation when a study with small sample size is reported, particularly when the finding is negative. An equally important but less well appreciated problem with small study size is related to a phenomenon known as the "small study effect".[28] It has been found that, trials with small number of patients are more likely to report larger and significant treatment effects compared to their larger counterparts.[29, 30] One of the possible reason, as illustrated by Kjaergard and colleagues [31] is the lower study quality often associated with small studies. The lack of adequate sequence generating, allocation concealment and blinding can significantly exaggerate the intervention effect compared to large trials. Furthermore, trials with subjective outcomes, such as pain score in this context, also has been reported to have the potential of exaggerated effect sizes when there was inadequate concealment or blinding.[32] This is in contrast to trials with objective outcomes such as mortality, as there was little evidence that inadequate concealment and lack of blinding would distort the estimated effect sizes. Furthermore, the difference in the subjective experience of pain may cause great variations in reported VAS pain scores and need of pain medication. As reported by Svaerdborg and colleagues [24] in their study, patients reported VAS scores of 9 to 10 during the first postoperative day and yet other patients reported VAS scores of only 1. As a result, the risk of registering an underlying difference in pain threshold in the different groups by chance can be potentially large (hence, biased) given a small study size.

Findings from this study should be interpreted with the following limitations. First, different PEMF devices may have slightly different settings. The differences may affect the efficacy and contribute to the

inconsistent findings. The potential effect of the different device setting on effectiveness has been previously demonstrated.[13] Our study used a device closely resemble that used previous studies [19, 33] which has obtained a significant positive outcome. Next, our study only collected data that spanned over the 12 hours observation period during the immediate post-operative phase. There is possibility that the effect of PEMF will require longer observation to be noticed. Thus, our conclusion of the lack of effect can only be interpreted within the time limit of our data. It is however worth noting that previously reported positive studies [19] have hinted to a significant effect visible as early as 4 hours post operation. Thirdly, in order to balance between the generalizability of our study conclusion and the study efficiency (and safety), we have excluded the younger as well as the older age patients (i.e. < 19 and > 50 years old) despite their significant representation of the population with appendicitis and appendicectomy. Furthermore, we have also excluded those with complicated appendicectomy (which their operative time has exceeded three hours) and those with potentially altered pain perception (i.e. with underlying chronic pain or long-term use of opioid). These exclusions from the study population has limited the external validity of our study findings and conclusion. Interpretation of our study should therefore take into account of this limited generalizability. Lastly, we excluded some randomized subjects prior to the completion of the data collection because of the various reasons described above. If the dropouts are systematically related to both the treatment assignment and study outcomes, a confounded effect is possible. We lack the data to further analyse these excluded subgroups, hence were unable to inform about the risk of a confounded effect.

In conclusion, this study has not been able to verify the effect of PEMF on postoperative pain previously reported. Given the currently available evidence, a recommendation to using PEMF as a routine part of post-operative pain management is not warranted especially for pain management during the immediate post-operative period and of use for short durations. Future larger scale study may be required to provide more convincing evidence regarding the effect of these devices. A high-quality systematic analysis of the currently available evidence might be required to clarify the current evidence gap in order to better inform future study design and focus.

Declarations

Ethics approval and consent to participate The study protocol was reviewed and approved by the National Medical Research Register, Malaysia (NMRR Study Registration: 15-670-25805). All patients provided signed, informed consent.

Consent for publication Not applicable

Availability of data and materials Datasets analysed for the study are available from the corresponding author on reasonable request.

Competing interest The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. CYF is a employee of IQVIA Asia Pacific, Real World Insights – a research consulting organization.

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Authors' contributions MP, AIAL, MPS, and MRZA conceptualize and designed the study. EN, PF and TSW supported the study operation and management. CYF analysed the study data and drafted the manuscript. All authors contributed to the review and revision of the manuscript and approved the final manuscript.

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Figures

Figure 1

PEMF device placed on the surgical wound on top of the dressing for 12 hours

Figure 2

Consort diagram

Figure 3

Changes of Pain Score Post-appendectomy – PEMF vs Control

Figure 4

Changes of PCA Fentanyl Use Post-appendectomy – PEMF vs Control

Supplementary Files

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- [Supplementarymaterial1.pdf](#)
- [CONSORT2010Checklist.docx](#)