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Original Research

Pulsed electromagnetic fields improve pain management and clinical outcomes after medial unicompartmental knee arthroplasty: A prospective randomised controlled trial

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ABSTRACT

Background: To assess pain relief and clinical outcomes in patients undergoing unicompartmental knee arthroplasty (UKA) stimulated with pulsed electromagnetic fields (PEMFs) compared to a control group.
Methods: A prospective randomised controlled trial (RCT) was performed in which 72 patients undergoing medial UKA were randomised into a control group or an experimental PEMFs group. The patients allocated to the experimental group were instructed to use PEMFs for 4 h per day for 60 days. They were evaluated before a surgery and then during the time points corresponding to 1 month, 2 months, 6 months, 12 months, and 36 months after the surgery. No placebo group was included in the RCT. Clinical assessment included the Visual Analogue Scale (VAS) for pain, Oxford Knee Score (OKS), the Short Form 36 (SF-36) health survey questionnaire, and joint swelling. During each follow-up visit, the consumption of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) was recorded.
Results: The VAS decreased on follow-up visits in both the groups; a statistically significant difference between the groups was observed during the 6 ($p = 0.0297$), 12 ($p = 0.0003$), and 36 months ($p = 0.0333$) follow-ups in favour of the PEMFs group. One month after UKA, the percentages of patients using NSAIDs in the PEMFs and control group were 71% and 92%, respectively ($p = 0.0320$). At the 2 months point, 15% of the patients in the PEMFs group used NSAIDs compared to 39% in the control group ($p = 0.0317$). The objective knee girth evaluation showed a statistically significant difference at 6 ($p = 0.0204$), 12 ($p = 0.0005$), and 36 ($p = 0.0005$) months with improved values observed in the PEMFs group. The subjective assessment of the swelling demonstrated a statistically significant difference at 2 ($p = 0.0073$), 6 ($p = 0.0006$), 12 ($p = 0.0001$), and 36 ($p = 0.0011$) months with better values noted in the PEMFs group. Last, the OKS result was significant higher in the experimental group during all the follow-ups (1mth: $p = 0.0295$; 2mths: $p = 0.0012$; 6mths: $p = 0.0001$; 12mths: $p < 0.0001$; 36mths: $p = 0.0061$).
Conclusions: The use of PEMFs leads to significant pain relief, better clinical improvement, and lower NSAIDs consumption after medial UKA when compared to the control group.
Level of evidence: II.

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What are the new findings

- Pulsed electromagnetic fields lead to significant pain relief after medial UKA compared to the standard protocol
- Pulsed electromagnetic fields lead to a higher percentage of patients who achieve the highest degree of satisfaction after medial UKA compared to the standard protocol
- Pulsed electromagnetic fields should be considered a completion of the surgery procedure

Introduction

The success behind a prosthetic surgery depends on surgical (type, design, and material of the implant, surgeon's ability, and rehabilitation plan) and biological factors (inflammatory reaction, pain, tissues and bone oedema, and patients' characteristics) [1–6]. The post-operative course of knee arthroplasty is often associated with a severe local inflammatory reaction caused by the previous osteoarthritis and, especially, the surgical insult. Post-operative inflammatory response is the physiological basis for the healing process. However, if it is not controlled, then it leads to fibrotic permanent tissue damage, thereby resulting in chronic pain, local joint swelling, and joint stiffness [7].

Biophysical stimulation using pulsed electromagnetic fields (PEMFs) performs an anti-inflammatory action on the whole joint. This decreases the release of catabolic factors and increases the production of anabolic factors, thereby stimulating the synthesis of the cartilage matrix, exercising a chondroprotective effect and trophic action on the subchondral bone, preventing sclerosis, and facilitating bone oedema reabsorption [8]. The production of catabolic and pro-inflammatory mediators such as cytokines, nitric oxide, prostaglandin E2, and neuropeptides in the inflamed synovium is directly responsible for cartilage matrix degeneration and clinical symptoms. In particular, a significant inverse correlation was found between the intra-articular concentration of interleukin-6 (IL-6) measured in the patient's joint after total knee arthroplasty (TKA) and the patient's post-operative functional recovery during the first--month follow-up [9]. The local inflammatory response is more important than the systemic response for the purpose of early post-operative functional recovery. Synovium-targeted therapy after surgery could help alleviate the symptoms of the disease and perhaps prevent the structural progression of the osteoarthritis (OA) joint [8,10]. The synovial membrane is a promising target in terms of novel strategies to prevent structural alterations and treat clinical symptoms.

PEMFs act as modulators of adenosine and can increase the functionality of the endogenous agonist. An interesting observation is that in human osteoarthritic synovial fibroblasts, PEMFs inhibit the release of prostaglandin E2 (PGE2) and the proinflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8), while it stimulates the release of interleukin-10 (IL-10), an anti-inflammatory cytokine; these effects are mediated by the PEMF-induced upregulation of adenosine A_{2A} and A_3adenosine receptors [11]. Moreover, PEMFs counteract the interleukin-1β (IL-1β) effect, thus increasing the synthesis of proteoglycans and proliferation of chondrocytes acting in concert with insulin-like growth factor-1 (IGF-1) present in both synovial fluid and articular cartilage; it plays a key role among the anabolic growth factors that control articular joint metabolism [12].

During the last few years, various studies have been conducted on the use of PEMFs after joint surgery such as chondral abrasion and/or perforations, matrix-assisted autologous chondrocyte implantation, bone marrow-derived cells seeded on a collagen scaffold, anterior cruciate ligament reconstruction, and total knee arthroplasty, showing that PEMFs led to a significantly greater and more rapid reduction in post-operative pain symptoms (measured with Visual Analogue Scale for Pain) as early as the first month after surgery, and resulting in a significant difference compared to the control group during the long term follow-up [13–16].

The main purpose of this prospective randomised controlled trial (RCT) was to clinically assess pain relief in patients undergoing medial mobile-bearing unicompartmental knee arthroplasty (UKA) stimulated with PEMFs as compared to a control group. The secondary objective was to evaluate the functional and clinical improvement in the knee joints during the 1 month, 2 months, 6 months, 12 months, and 36 months follow-ups. It was hypothesised that the patients treated with pulsed magnetic fields endured less pain during the follow-ups than the patients present in the control group.

Material and methods

Study design and selection criteria

All the procedures involving human participants in this study were performed in accordance with the ethical standards of the institutional and/or national research committee, as well as with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was conducted following the CONSORT checklist for RCT and has been registered in the International Standard Randomized Controlled Trial Number (ISCRCTN) registry [17]. In addition to the informed consent gained from all the participants in the study, appropriate ethical approval was also obtained.

In order to have two groups with no statistical differences at baseline, patients were randomised into a control or experimental group stimulated with PEMFs, using a web-based computer program (www.randomization.com/) that was stratified by the following parameters: sex (F/M), age (50–75 years; 75–85 years), and smoking status (yes/no). All the patients signed their informed consents for recruitment (the first patient enrolled on 3rd November 2014; the last patient enrolled on 11th April 2017).

The inclusion criteria included ages between 60 and 85 years, chronic and debilitating knee pain, medial compartment osteoarthritis with varus or valgus deformity not exceeding 3°, a range of motion greater than 100° with less than 10° of flexion contracture, the integrity of the anterior and posterior cruciate ligaments, and intact lateral meniscus. The exclusion criteria comprised previous knee infection, total hip arthroplasties, bone marrow oedema of the medial knee compartment, rheumatoid arthritis, autoimmune and systemic diseases, tumours, severe malalignments and body mass index (BMI) greater than 30 kg/m^2, revision surgery, and previous surgery of the affected knee (except arthroscopy for meniscectomy).

Biophysical stimulation

Patients allocated to the experimental group were instructed to use PEMFs (I-ONE® - IGEA SpA Carpi (Modena), Italy) for 4 h per day, although not necessarily consecutively, for a duration of 60 days. The treatment started within 3–7 days after the surgery and was managed at home or during the rehabilitation period. The PEMF device consisted of a signal generator system, which produced a pulsed signal of 1.5 mT peak magnetic field intensity and a frequency of 75 Hz, and a coil was placed on the operated knee. The patients could wear the battery operated device day or night and were instructed to interrupt the treatment in case of adverse events such as skin irritation or a burning sensation. The device included a clock to record the patients' compliance.

Surgical procedure and rehabilitation

All the operations were carried out by a senior surgeon experienced in knee replacement surgery with the use of a minimally invasive surgical technique on all the patients. The Oxford® Partial Knee with Microplasty Instrumentation (Oxford, Zimmer Biomet, Warsaw, Indiana, USA) was

implanted in all the patients [18]. This procedure employed a medial parapatellar approach without the dislocation of the patella. Both patient groups followed the same rehabilitation protocol, which involved passive mobilisation from Day 1 after the surgery and active progressive mobilisation of the joint and assisted walking with two crutches starting Day 2. Gradually, as per each patient, an increase in load during walking was recommended, which was followed by isometric muscle-toning exercises until the walking aids were completely abandoned.

Clinical evaluation

The clinical follow-up was performed by two independent clinicians who were not involved in the index surgery. The patients were evaluated before a surgery and then during the time points corresponding to 1 month, 2 months, 6 months, 12 months, and 36 months (+/− 5 days) after surgery. Clinical assessment included the Visual Analogue Scale (VAS) for pain, Oxford Knee Score (OKS), and the Short Form 36 (SF-36) health survey questionnaire [19–21]. Joint swelling was determined by measuring the circumference of the knee at midpatellar height in the supine position using an ordinary tape measure and evaluated in accordance with Soderberg et al. [22] using the following scores: 40 – no difference in knee girth; 30 – <0.5 cm; 20 – between 0.5 and 1 cm; 10 – between 1 and 1.5 cm; 0 – >1.5 cm. For the subjective assessment of swelling, questions from section number 2 of the Cincinnati Rating System Questionnaire pertaining to joint swelling were used; the score ranges from 0 (Severe problem all the time, with simple walking activities) to 10 (No swelling) in steps of 2 [23]. The consumption of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed by the physician post-surgery was recorded during each follow-up visit. Finally, during the third-year follow-up, surveys were conducted to investigate each patient's persistence of pain, limitation of daily activities, and use of NSAIDs; the complications for each patient were recorded. All physicians in charge of assessing clinical outcomes were blinded to patient treatment.

Satisfaction percentage

To assess whether the use of biophysical stimulation was able to increase the percentage of patients achieving maximal satisfaction after an already well-established surgical treatment such as UKA, we considered the percentage of patients for each clinical evaluation in the experimental and control groups who achieved a predefined value of each score at 6 months and 12 months.

For objective girth score: maximum satisfaction = 40 cm; for subjective assessment of the swelling: maximum satisfaction = 10; for Oxford score: maximum satisfaction score ≥45; for VAS: maximum satisfaction value at 6 months <1, at 12 months <0.5 [24].

Statistical analysis

The power analysis was conducted on the primary outcome of the study, i.e., pain expressed as VAS, given the presence in the literature of several studies on the effects of electromagnetic fields on pain. Starting from two homogeneous groups with similar VAS values at the baseline, we hypothesised a difference of 40% in the VAS reductions between groups [13]: that is, we assumed a reduction of VAS of 43% in the control group and 83% in the active group. Group sample sizes of 33 in Group 1 and 33 in Group 2 achieved 91% power to detect a difference between the group proportions of 40% when the percentage reduction in Group 1 (the treatment group) was assumed to be 43% under the null hypothesis and 83% under the alternative hypothesis. The test statistic used was the two-sided Fisher's exact test. The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design was 0.0338. The descriptive analysis of the quantitative variables was performed by calculating the mean value and standard deviation in each treatment group; categorical variables were reported as frequency and percentage. The normality distribution of the two samples was tested by the Kolmogorov–Smirnov test, and all the quantitative variables indicated no evidence of a non-normal distribution. The two groups were compared at the baseline and at all the follow-ups using the two-tailed heteroscedastic student's t-test. The analysis of the variations of the quantitative variables in each group for the individual subject with respect to the baseline values was performed by a paired two-tailed student's t-test with multiple tests Bonferroni correction. The comparison of categorical variables between groups was performed using contingency tables and a chi-square test. The statistical analyses were conducted with NCSS (NCSS 9. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com/).

Results

Seventy-two consecutive patients (36 from PEMFs group, 36 from control group) with an indication for UKA were assessed for eligibility. Of the 36 patients included in the PEMFs group, two dropped out during the one-month follow-up due to personal reasons. Of the 36 patients in the control group, two were no longer included during the 36 months follow-up; one patient died, and the other had a prosthetic surgical revision due to a traumatic event. At the baseline, the two groups were homogeneous for the following patient characteristics: age (p = 0.4637), sex (p = 0.5), weight (p = 0.4032), height (p = 0.4071), smoking status (p = 0.7985), VAS (p = 0.2074), Objective Knee Girth (p = 0.4703), Subjective assessment of the swelling (p = 0.2179), Oxford Knee Score (p = 0.3238). The only statistical difference between the two groups involved the SF-36 Global Health Survey score, which was higher in the treatment group (p = 0.0114). The patients in the PEMFs group used the PEMF device for a mean of 155 ± 109 h. The detailed results are reported in Table 1.

VAS

The pre-operative pain was high in both the groups (PEMFs group: 7.2 ± 1.8, control group: 7.6 ± 1.8, p = 0.2074). As shown in Table 2, the VAS value decreased with follow-up visits in case of both the groups and a statistically significant difference between the groups was observed during the 6 months (0.8 ± 0.4 vs 0.6 ± 0.4, p = 0.0297), 12 months (0.6 ± 0.4 vs 0.3 ± 0.3, p = 0.0003), and 36 month s(0.6 ± 0.4 vs 0.5 ± 0.3, p = 0.0333) follow-ups in favour of the PEMFs group.

Use of NSAIDs

One month after UKA, the percentages of patients using NSAIDs in the PEMFs and control groups were 71% and 92%, respectively (p < 0.05) (Fig. 1). At 2 months of follow-up, a considerable reduction in the requirement of drugs was also observed: 15% of patients in the PEMFs group used NSAIDs compared to 39% in the control group (p < 0.05). After 6, 12, and 36 months, no patient from either group needed to consume NSAIDs.

Table 1
Characteristics of the patient study population.

Number of Patients	CONTROL	PEMFs	p value
	N = 36	N = 36	
Gender	14M/22F	15M/21F	0.5000
	Mean ± std	**Mean ± std**	
Age (years)	69 ± 9	69 ± 8	0.4637
Weight (kg)	74 ± 13	75 ± 15	0.4032
Height (cm)	166 ± 8	166 ± 9	0.4071
Smoking status (yes/no)	12/24	10/26	0.7985
VAS	7.6 ± 1.8	7.2 ± 1.8	0.2074
Objective Knee Girth	21.7 ± 7.4	21.5 ± 8.4	0.4703
Subjective assessment of the swelling	2.1 ± 3.1	2.7 ± 3.6	0.2179
Oxford Knee Score	20.3 ± 6.7	21.0 ± 6.7	0.3238
SF-36	48.6 ± 13.4	55.5 ± 11.8	**0.0114**

Bold indicates statistical significant value (p < 0.05).

Table 2
Mean VAS, objective and subjective swelling scores at different time points.

VAS			
TIME (months)	CONTROL	PEMFs	p value
0	7.6 ± 1.8	7.2 ± 1.8	0.2074
1	3.7 ± 1.5	3.3 ± 1.7	0.1589
2	1.7 ± 0.9	1.7 ± 0.9	0.3679
6	0.8 ± 0.4	0.6 ± 0.4	**0.0297**
12	0.6 ± 0.4	0.3 ± 0.3	**0.0003**
36	0.6 ± 0.4	0.5 ± 0.3	**0.0333**
OBJECTIVE KNEE GIRTH SCORE			
TIME (months)	**CONTROL**	**PEMFs**	**p value**
0	21.7 ± 7.4	21.5 ± 8.4	0.4703
1	25.3 ± 7.4	25.3 ± 7.5	0.4963
2	29.2 ± 5.5	30.3 ± 8.0	0.2485
6	32.8 ± 5.7	35.6 ± 5.6	**0.0204**
12	34.2 ± 5.0	37.9 ± 4.1	**0.0005**
36	34.1 ± 5.0	37.9 ± 4.1	**0.0005**
SUBJECTIVE ASSESSMENT OF SWELLING SCORE			
TIME (months)	**CONTROL**	**PEMFs**	**p value**
0	2.1 ± 3.1	2.7 ± 3.6	0.2180
1	1.3 ± 2.1	2.2 ± 3.0	0.0770
2	4.0 ± 2.9	5.6 ± 2.6	**0.0073**
6	7.1 ± 1.9	8.4 ± 1.3	**0.0006**
12	8.2 ± 1.0	9.2 ± 1.1	**0.0001**
36	8.6 ± 1.4	9.5 ± 0.9	**0.0011**

Bold indicates statistical significant value ($p < 0.05$).

Swelling

The objective knee girth evaluation, evaluated in accordance with Soderberg et al. [22], showed a statistically significant difference after 6 (32.8 ± 5.7 vs 35.6 ± 5.6, $p = 0.0204$), 12 (34.2 ± 5.0 vs 37.9 ± 4.1, $p = 0.0005$), and 36 (34.1 ± 5.0 vs 37.9 ± 4.1, $p = 0.0005$) months with higher values and consequently minor swelling in the PEMFs group ($p < 0.05$).

The subjective assessment of the swelling showed a statistically significant difference after 2 (4.0 ± 2.9 vs 5.6 ± 2.6, $p = 0.0073$), 6 (7.1 ± 1.9 vs 8.4 ± 1.3, $p = 0.0006$), 12 (8.2 ± 1.0 vs 9.2 ± 1.1, $p = 0.0001$), and 36 (8.6 ± 1.4 vs 9.5 ± 0.9, $p = 0.0011$) months with higher and consequently better values in the PEMFs group ($p = 0.05$). The detailed results are reported in Table 2.

Oxford Knee Score

The Oxford Knee Score showed significantly higher results in the PEMFs group during all the follow-ups with respect to the control group, indicating a better condition in the first group (Fig. 2). After 1 month from surgery, the mean Oxford Knee Score was 20.9 ± 4.0 in the PEMFs group and 19.0 ± 4.1 in the control group ($p = 0.0295$); after 2 months, it was 34.3 ± 4.4 vs 30.8 ± 4.9 respectively ($p = 0.0012$); after 6 months it was 43.5 ± 2.7 vs 40.3 ± 3.8 respectively ($p = 0.0002$); at 12 months the score was 45.9 ± 2.0 in PEMFs group and 43.3 ± 2.9 in the control group (0.0001); finally, at 36 months the mean Oxford Knee Score was 46.2 ± 1.6 in the PEMFs group and 44.3 ± 3.8 in the control group, with a p value of 0.0122.

SF-36 health survey, body pain, and role physical score

The statistical differences between the two groups were recorded at the baseline ($p = 0.0114$), which resulted in a significantly higher score in the case of the PEMFs group during each follow-up ($p = 0.003$). Due to this reason, the two specified items of the SF-36 health survey were analysed separately: body pain and physical role. The detailed results are shown in Table 3.

Body pain exhibited higher results, showing a significant ($p < 0.05$) improvement in the PEMFs group during each post-operative follow-up, thus confirming the results of the VAS score evaluation, except at two months after surgery ($p = 0.131$), and the physical score was statistically superior in the PEMFs group during each post-operative follow-up ($p < 0.05$).

Percentage of satisfaction

The statistically significant differences between the two groups were recorded during the 6 months and 36 months follow-ups, with a higher percentage in the case of the PEMFs group ($p < 0.05$). The detailed results are provided in Table 4.

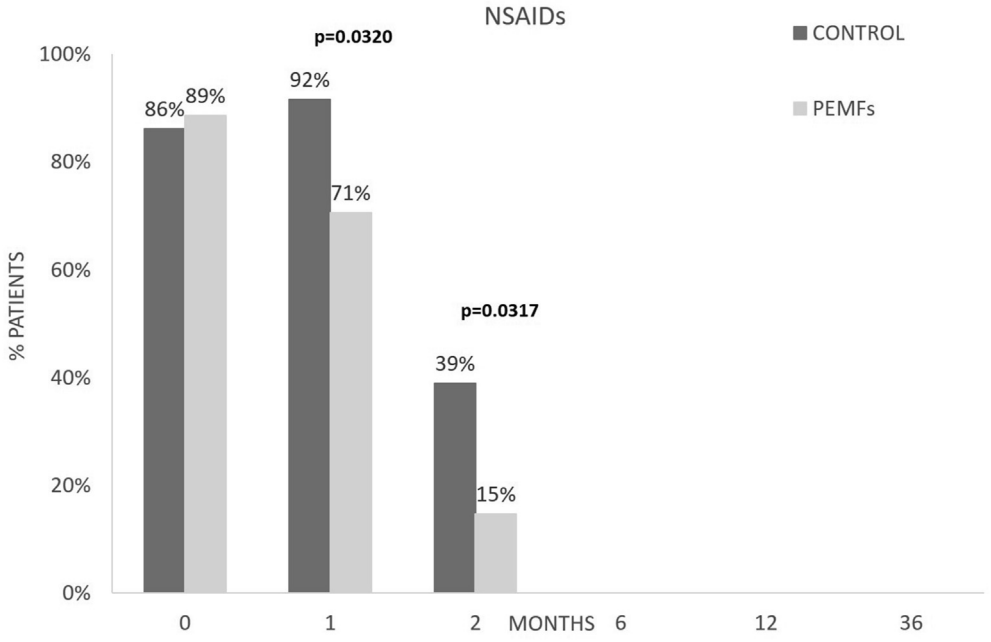

Fig. 1. The graph shows the percentage of NSAIDs used in the two different groups, which reports a statistically significant difference by chi-square test during the first and second post-operative months in favour of the treatment group.

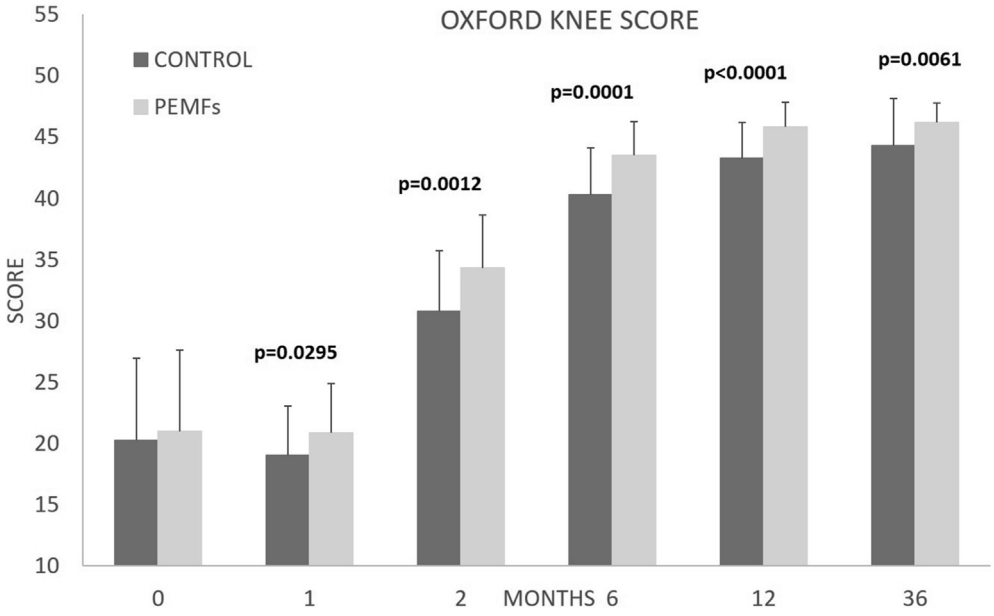

Fig. 2. The graph shows the Oxford Knee Score during the study period, which reports a higher clinical score during each follow-up in favour of the treatment group. Vertical bars represent the standard deviation. P values correspond to uncoupled 2-tailed student t-test for comparison between groups with correction for multiple testing.

Complications

No adverse effects due to the use of PEMFs therapy were recorded in the follow-up visits.

Discussion

The main purpose of the RCT was to evaluate the pain relief in patients undergoing medial mobile-bearing UKA and stimulated with PEMFs as compared to a non-stimulated control group. During all the follow-ups, the PEMFs group showed lower pain, lower usage of NSAIDs, and higher clinical and satisfaction scores (objective and subjective swelling, SF-36, and OKS).

In the case of the current study, the use of PEMFs after UKA has revealed that it is possible to further improve outcomes after such surgeries; in fact, despite the newer advancements over the past decades and proven advantages of minimally invasive UKA, surgeons are still reluctant to use this procedure in spite of its indication. This is most likely due to concerns regarding survivability, patient selection, ideal bearing design, and the judicious use of advanced technology, among many others [25].

As reported by Mathis regarding total knee arthroplasty (TKA), if the causes of the post-UKA complaints are known, a decision for therapy can be made reliably and sustainably at an early stage before the pain becomes chronic [26]. According to this statement, PEMFs therapy may represent an important adjunct to post-operative to avoid chronic pain onset by preventing the detrimental effect of inflammation induced by UKA on joint tissues, thereby resulting in short and long-term benefits for patients. As reported by another author [14], PEMFs can be considered as a part of the surgical and post-operative treatment.

After analysing various reports by studies reporting survivorship with >500 medial UKAs, 10-year survivorship percentages of 93–98% have been reported with good to excellent subjective scores [27–29]. However, these satisfying results are greater than that supported by the recent global and national registries, with 10-year survivorship percentages between 81% and 88% [28].

Recently, Barker demonstrated that knee pain is more commonly a reason for revision after unicompartmental arthroplasty than it is after total knee arthroplasty, but the reasons behind this finding remain unclear [29]. Since the other modes of failure are at the same level in the cohort and registry-based studies, a possible explanation is that some patients with unexplained pain show (early) progression of OA. Park discovered that in several patients with unexplained pain, the OA progression in the other compartments was not visible using radiographs but was always visible using magnetic resonance imaging (MRI), of which 82% even had grade 3 of 4 OA, thereby suggesting that in some cases, unexplained pain may be caused by OA progression, which is, therefore, underreported [30].

In our study, we demonstrated a significant reduction in VAS pain score after using PEMFs over the follow-up period, thereby reducing the risk of failure due to pain and increasing the percentage of patients achieving maximal satisfaction after an already well-established surgical treatment.

To our knowledge, this is the first RCT that analyses and reports results concerning the use of PEMFs after a medial mobile-bearing UKA, although several reports have already confirmed the efficacy of this treatment after orthopaedic surgery [13,14,31].

In particular, in 2014, Adravanti et al., compared the clinical outcomes of 33 patients undergoing TKA randomly assigned to the control

Table 3
Mean SF-36 Body Pain and Physical role scores at different time points.

SF-36 BODY PAIN ITEM SCORE			
TIME (months)	CONTROL	PEMFs	p value
0	37 ± 11	42 ± 14	0.0548
1	44 ± 10	50 ± 10	**0.0088**
2	56 ± 10	59 ± 11	0.1310
6	73 ± 11	78 ± 10	**0.0326**
12	81 ± 13	91 ± 11	**0.0008**
36	78 ± 13	87 ± 12	**0.0026**
SF-36 ROLE PHYSICAL ITEM SCORE			
TIME (months)	**CONTROL**	**PEMFs**	**p value**
0	17 ± 27	25 ± 33	0.1244
1	3 ± 8	13 ± 29	**0.0320**
2	18 ± 23	33 ± 38	**0.0250**
6	61 ± 26	80 ± 24	**0.0012**
12	76 ± 26	94 ± 14	**0.0002**
36	77 ± 31	88 ± 20	**0.0471**

Bold indicates statistical significant value ($p < 0.05$).

Table 4
Percentage of satisfaction in the two cohorts of patients.

Percentage of satisfaction						
	CONTROL	PEMFs	p value	CONTROL	PEMFs	p value
	6 months			36 months		
Joint swelling objective (score=40)	33%	59%	0.0324	41%	79%	0.0013
Subjective assessment of the swelling (score=10)	6%	32%	0.004	41%	76%	0.0031
Oxford Knee Score (score≥45)	11%	44%	0.0028	65%	88%	0.0222
VAS (score < 1.0)	47%	74%	0.0247			
	12 months					
VAS (score < 0.5)	33%	89%	<0.0001			

group or the PEMFs group. PEMFs therapy was administered post-operatively 4 h per day for 60 days. The patients were assessed before surgery and then during the time points corresponding to 1 month, 2 months, and 6 months post-operatively using international scores [14]. At 1 month after TKA, the VAS pain score and knee swelling were evaluated considering differences between knees girths in accordance with Soderberg et al. [22], and functional scores of Knee Society Score (KSS) were significantly better in the case of the PEMFs group as compared to the control group.

Pain reduction was statistically significant for both groups with respect to preoperative level 1 month after TKA, although it was more evident in the treated group (−61%, $p < 0.001$ and −26% $p < 0.05$ for treated and control groups, respectively). Indeed, a significant difference between groups was observed at the one-month follow-up in favour of the treated group ($p < 0.05$). The pain was significantly lower in the PEMFs group at 6 months follow-up ($p < 0.05$), with a 90% pain reduction from baseline in the treated group. Moreover, three years after surgery, severe pain and occasional walking limitations were reported in a significantly lower number of patients in the case of the PEMFs group as compared to the control group [14].

Previously, Moretti et al. aimed to evaluate whether PEMFs therapy can be used to limit the pain and enhance patient recovery after TKA [13]. Pre-operatively, no differences were observed between the groups in terms of age, sex, weight, height, knee score, VAS, SF-36, and joint swelling, with the exception of the functional score. In case of the PEMFs group, the Functional Score of The Knee Society Score was significantly higher during the 12 months follow-up as compared to the control group: at 2 months (66.0 ± 28.7 vs. 40.4 ± 17.5, $p < 0.0001$), 6 months (80.0 ± 19.4 vs. 51.0 ± 18.2, $p < 0.0001$) and 12 months (87.3 ± 16.8 vs. 55.0 ± 33.2, $p < 0.005$). Significant differences between groups were observed also for SF-36 health survey evaluation, higher values in PEMFs group: 2 months (65.8 ± 15.2 vs. 32.5 ± 9.2, $p < 0.0001$), 6 months (75.1 ± 9.6 vs. 49.5 ± 17.2, $p < 0.0001$) and 12 months (76.3 ± 8.7 vs. 59.7 ± 19.6, $p < 0.05$). Moreover, VAS values were significantly lower in the experimental than the control group at all follow-up visits: 1 month (2.4 ± 1.6 vs. 4.9 ± 1.8, $p < 0.0001$), 2 months (1.1 ± 1.0 vs. 4.6 ± 1.8, $p < 0.0001$), 6 months (1.5 ± 2.8 vs. 5.6 ± 2.9, $p < 0.001$) and 12 months (0.5 ± 1.3 vs. 3.6 ± 3.9, $p < 0.05$). In the PEMFs group, NSAIDs use was reduced, and the joint swelling resolution was more rapid than in the control group. The effect of PEMFs therapy was maintained after the use of the device was discontinued [13].

The study confirmed that PEMFs therapy should be considered after TKA to prevent the inflammatory reaction caused by surgery in order to ensure pain relief and speedy functional recovery.

In 2019, La Verde et al. conducted a randomised prospective controlled study on the effects of PEMFs in reverse total shoulder arthroplasty, thereby discovering a better Constant Shoulder Score (CSS) and lower VAS pain score during the first (CSS: 70 vs 61, $p < 0.05$; VAS:1.8 vs 2.9, $p < 0.05$), second (CSS: 76 vs 63, $p < 0.05$; VAS:1.6 vs 2.6, $p < 0.05$), and third (CSS: 78 vs 67, $p < 0.05$; VAS:1.5 vs 2.2, $p < 0.05$) months after surgery in the PEMFs therapy treated group versus the control group ($p < 0.05$). During the 6 months follow-up, no significant differences were found between the groups [32].

Considering that one of the main reasons behind UKA failure is the progression of OA in the other compartment, the use of PEMFs therapy after UKA is not only related to relief of pain but also to contrast the contralateral OA degeneration due to the presence of a joint inflammatory microenvironment. A recent systematic review of 15 studies demonstrates results that align with this study showed that PEMFs therapy had a beneficial effect on pain, stiffness, and physical function in patients with OA when compared to placebo [33]. Similar results were confirmed by Viganò et al. whose analysis of 13 studies comprising 914 unique patients evaluated the effect of electromagnetic field treatment on the symptoms of knee OA using the VAS and/or Western Ontario McMaster Universities Osteoarthritis Index (WOMAC). An overall reduction in the pain score was observed after treatment [34].

To better understand the clinical effectiveness of PEMFs after joint replacement, it is important to analyse their function in a joint microenvironment, particularly bone and cartilage. In the case of cartilage, PEMFs exposure enhances mesenchymal stem cells (MSCs) chondrogenic differentiation through direct activation of chondrogenic signalling pathways and indirect paracrine mechanism, which is mediated by MSC secretome. In this way, PEMFs can be applied as adjuvant therapy to increase cartilage-specific gene expression and chondrogenic differentiation of the MSCs to overcome the obstacles of using growth factors in vivo [11]. Second, PEMFs stimulation can also act as a chemotactic signal for MSCs and chondrocytes, thus favouring cell migration to the site of injury to promote tissue repair. Third, PEMFs exert a strong anti-inflammatory effect and a chondroprotective effect on cartilage tissue degenerated by the catabolic activity of pro-inflammatory cytokines [11].

The positive effects on bone growth may be the result of both the primary effect of PEMFs on the bone and an induced one due to the increased vascular growth, secondary to the release of angiogenetic factors such as IL-8, basic fibroblast growth factor (bFGF), Vascular-Endothelial Growth Factor (VEGF), and nitric oxide synthases. Additionally, PEMFs were effective in increasing the amount of new bone around hydroxyapatite porous implants in the proximal tibia of rabbits, although somewhat insignificant effects were detected in tricalcium phosphate ones, which were probably due to the different pore sizes (the greater the diameter, the greater the effectiveness of the stimulation) [11,35].

The final findings of our study concern the significantly reduced consumption of drugs with PEMFs therapy, particularly NSAIDs. Analysing this data is necessary to evaluate the socioeconomic implications related to the lower consumption of drugs; in fact, the prevalence of chronic postoperative pain after knee arthroplasty varies among studies and affects roughly 15–20% of patients for 1–7 years after surgery [36–38]. Using qualitative semi-structured interviews, Woolhead et al. reported that a high proportion of patients complained of pain in the post-operative period, although 90% were satisfied with the surgical results [39].

Limitations

Future studies should analyse whether PEMFs could be the solution to reducing and improving CPP to reduce the consumption of drugs, favour

fast recovery and, most importantly, eliminate the side effects of NSAIDs from prolonged uses. The lack of a placebo group is a limitation of this study. However, it must be acknowledged that all clinical evaluations were carried out by physicians unaware of whether the patient belonged to the control or experimental group. Furthermore, the limited number of patients may explain the difference in the SF-36 health survey observed at the baseline between the two groups. Patients' compliance was a concern because the use of I-ONE for 4 h per day for 60 days required significant commitment. Finally, another limitation of the study is the use of a modified Cincinnati Rating System Questionnaire to assess patient satisfaction that is a not validated scale.

Conclusions

This is the first study that analyses PEMFs therapy after medial UKA and demonstrates that PEMFs treatment has been well-tolerated and includes no negative side effects. Furthermore, the use of PEMFs leads to significant clinical improvements, such as pain reduction, lower NSAIDs consumption, less swelling, and a higher percentage of patients, with respect to control, who achieve the maximal degree of satisfaction after an already well-established surgical treatment such as UKA.

Ethical approval

Appropriate ethical approval was obtained from the Ospedale San Raffaele Ethical Committee (CE 86/2014 – Milan, 17/7/2014).

Study registration

https://www.isrctn.com/ISRCTN67242974 - www.isrctn.com.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

All authors consent to the publication of the manuscript.

Authors contributions

R.D. writing, revision, data analysis; C.U. writing, data collection; S.S revision, statistics, data analysis; M.S. data collection; N.U. surgery, final revision.

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Availability of data and materials

All the materials are available on request to s.setti@igeamedical.com.

Declaration of competing interest

None.

References

[1] Canovas F, Dagneaux L. Quality of life after total knee arthroplasty. Orthop Traumatol Surg Res 2018;104(1S):S41–6. https://doi.org/10.1016/j.otsr.2017.04.017.
[2] Tyagi V, Farooq M. Unicompartmental knee arthroplasty: indications, outcomes, and complications. Conn Med 2017;81(2):87–90. pmid:29738151.
[3] D'Ambrosi R, Anghilieri FM, Corona K, Mariani I, Valli F, Ursino N, et al. Similar rates of return to sports and BMI reduction regardless of age, gender and preoperative BMI as seen in matched cohort of hypoallergenic and standard Cobalt Chromium medial unicompartmental knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2022 Mar;30(3):890–8. https://doi.org/10.1007/s00167-021-06467-1.
[4] Arirachakaran A, Choowit P, Putananon C, Muangsiri S, Kongtharvonskul J. Is unicompartmental knee arthroplasty (UKA) superior to total knee arthroplasty (TKA)? A systematic review and meta-analysis of randomized controlled trial. Eur J Orthop Surg Traumatol 2015;25(5):799–806. https://doi.org/10.1007/s00590-015-1610-9.
[5] Mittal A, Meshram P, Kim WH, Kim TK. Unicompartmental knee arthroplasty, an enigma, and the ten enigmas of medial UKA. J Orthop Traumatol 2020;21(1):15. https://doi.org/10.1186/s10195-020-00551-x.
[6] Postler A, Lützner C, Beyer F, Tille E, Lützner J. Analysis of total knee arthroplasty revision causes. BMC Musculoskelet Disord 2018;19(1):55. https://doi.org/10.1186/s12891-018-1977-y.
[7] Langkilde A, Jakobsen TL, Bandholm TQ, Eugen-Olaen J, Blauenfeldt T, Petersen J, et al. Inflammation and post-operative recovery in patients undergoing total knee arthroplasty-secondary analysis of a randomized controlled trial. Osteoarthritis Cartilage 2017;25(8):1265–73. https://doi.org/10.1016/j.joca.2017.03.008.
[8] Paish HL, Baldock TE, Gillespie CS, Del Carpio Pons A, Mann DA, Deehan DJ, et al. Chronic, active inflammation in patients with failed total knee replacements undergoing revision surgery. J Orthop Res 2019;37(11):2316–24. https://doi.org/10.1002/jor.24398.
[9] Prince N, Penatzer JA, Dietz MJ, Boyd JW. Localized cytokine responses to total knee arthroplasty and total knee revision complications. J Transl Med 2020;8(1):330. https://doi.org/10.1186/s12967-020-02510-w.
[10] Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010;6(11):625–35. https://doi.org/10.1038/nrrheum.2010.159.
[11] Varani K, Vincenzi F, Ravani A, Pasquini S, Merighi S, Gessi S, et al. Adenosine receptors as a biological pathway for the anti-inflammatory and beneficial effects of low frequency low energy pulsed electromagnetic fields. Mediators Inflamm 2017;2017:2740963. https://doi.org/10.1155/2017/2740963.
[12] De Mattei M, Pellati A, Pasello M, Ongaro A, Setti S, Massari L, et al. Effects of physical stimulation with electromagnetic field and insulin growth factor-I treatment on proteoglycan synthesis of bovine articular cartilage. Osteoarthritis Cartilage 2004;12(10):793–800. https://doi.org/10.1016/j.joca.2004.06.012.
[13] Moretti B, Notarnicola A, Moretti L, Setti S, De Terlizzi F, Pesce V, et al. I-ONE therapy in patients undergoing total knee arthroplasty: a prospective, randomized and controlled study. BMC Musculoskelet Disord 2012;13:88. https://doi.org/10.1186/1471-2474-13-88.
[14] Adravanti P, Nicoletti S, Setti S, Ampollini A, de Girolamo L. Effect of pulsed electromagnetic field therapy in patients undergoing total knee arthroplasty: a randomised controlled trial. Int Orthop 2014;38(2):397–403. https://doi.org/10.1007/s00264-013-2216-7.
[15] Collarile M, Sambri A, Lullini G, Cadossi M, Zorzi C. Biophysical stimulation improves clinical results of matrix-assisted autologous chondrocyte implantation in the treatment of chondral lesions of the knee. Knee Surg Sports Traumatol Arthrosc 2018;26(4):1223–9. https://doi.org/10.1007/s00167-017-4605-8.
[16] Benazzo F, Zanon G, Pederzini L, Modonesi F, Cardile C, Falez F, et al. Effects of biophysical stimulation in patients undergoing arthroscopic reconstruction of anterior cruciate ligament: prospective, randomized and double blind study. Knee Surg Sports Traumatol Arthrosc 2008;16(6):595–601. https://doi.org/10.1007/s00167-008-0519-9.
[17] Cuschieri S. The CONSORT statement. Saudi J Anaesth 2019;13(Suppl 1):S27–30. https://doi.org/10.4103/sja.SJA_559_18.
[18] Zhang Q, Zhang Q, Guo W, Liu Z, Cheng L, Yue D, et al. The learning curve for minimally invasive Oxford phase 3 unicompartmental knee arthroplasty: cumulative summation test for learning curve (LC-CUSUM). J Orthop Surg Res 2014;9:81. https://doi.org/10.1186/s13018-014-0081-8.
[19] Heller GZ, Manuguerra M, Chow R. How to analyze the visual Analogue scale: myths, truths and clinical relevance. Scand J Pain 2016;13:67–75. https://doi.org/10.1016/j.sjpain.2016.06.012.
[20] Padua R, Zanoli G, Ceccarelli E, Romanini E, Bondì R, Campi A. The Italian version of the Oxford 12-item Knee Questionnaire-cross-cultural adaptation and validation. Int Orthop 2003;27(4):214–6. https://doi.org/10.1007/s00264-003-0453-x.
[21] Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. J Clin Epidemiol 1998;51(11):1025–36. https://doi.org/10.1016/s0895-4356(98)00094-8.
[22] Soderberg GL, Ballantyne BT, Kestel LL. Reliability of lower extremity girth measurements after anterior cruciate ligament reconstruction. Physiother Res Int 1996;1(1):7–16. https://doi.org/10.1002/pri.43.
[23] Agel J, LaPrade RF. Assessment of differences between the modified Cincinnati and International Knee Documentation Committee patient outcome scores: a prospective study. Am J Sports Med 2009;37(11):2151–7. https://doi.org/10.1177/0363546509337698.
[24] Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis 1978;37(4):378–81.
[25] Johal S, Nakano N, Baxter M, Hujazi I, Pandit H, Khanduja V. Unicompartmental knee arthroplasty: the past, current controversies, and future perspectives. J Knee Surg 2018;31(10):992–8. https://doi.org/10.1055/s-0038-1625961.
[26] Mathis DT, Hauser A, Iordache E, Amsler F, Hirschmann MT. Typical pain patterns in unhappy patients after total knee arthroplasty. J Arthroplasty 2021;36(6):1947–57. https://doi.org/10.1016/j.arth.2021.01.040.
[27] Jennings JM, Kleeman-Forsthuber LT, Bolognesi MP. Medial unicompartmental arthroplasty of the knee. J Am Acad Orthop Surg 2019;27(5):166–76. https://doi.org/10.5435/JAAOS-D-17-00690.

[28] van der List JP, Zuiderbaan HA, Pearle AD. Why do medial unicompartmental knee arthroplasties fail today? J Arthroplasty 2016;31(5):1016–21. https://doi.org/10.1016/j.arth.2015.11.030.
[29] Baker PN, Petheram T, Avery PJ, Gregg PJ, Deehan DJ. Revision for unexplained pain following unicompartmental and total knee replacement. J Bone Joint Surg Am 2012;94(17):e126. https://doi.org/10.2106/JBJS.K.00791.
[30] Park CN, Zuiderbaan HA, Chang A, Khamaisy S, Pearle AD, Ranawat AS. Role of magnetic resonance imaging in the diagnosis of the painful unicompartmental knee arthroplasty. Knee 2015;22(4):341–6. https://doi.org/10.1016/j.knee.2015.03.007.
[31] Ongaro A, Varani K, Masieri FF, Pellati A, Massari L, Cadossi L, et al. Electromagnetic fields (EMFs) and adenosine receptors modulate prostaglandin E(2) and cytokine release in human osteoarthritic synovial fibroblasts. J Cell Physiol 2012;227(6):2461–9. https://doi.org/10.1002/jcp.22981.
[32] La Verde L, Franceschetti E, Palumbo A, Giovannetti E, Ranieri R, Sorini G, et al. Applicazione dei campi magnetici pulsati nei pazienti sottoposti a protesi inversa di spalla: valutazione clinica e funzionale. G Ital Ortop Traumatol 2019;45(1):37–46. https://doi.org/10.32050/0390-0134-116. Italian.
[33] Yang X, He H, Ye W, Perry TA, He C. Effects of pulsed electromagnetic field therapy on pain, stiffness, physical function, and quality of life in patients with osteoarthritis: a systematic review and meta-analysis of randomized placebo-controlled trials. Phys Ther 2020;100(7):1118–31. https://doi.org/10.1093/ptj/pzaa054.
[34] Viganò M, Perucca Orfei C, Ragni E, Colombini A, de Girolamo L. Pain and functional scores in patients affected by knee OA after treatment with pulsed electromagnetic and magnetic fields: a meta-analysis. Cartilage 2021;13(1_suppl):1749S–61S. https://doi.org/10.1177/1947603520931168.
[35] Massari L, Benazzo F, Falez F, Perugia D, Pietrogrande L, Setti S, et al. Biophysical stimulation of bone and cartilage: state of the art and future perspectives. Int Orthop 2019;43(3):539–51. https://doi.org/10.1007/s00264-018-4274-3.
[36] Fuzier R, Serres I, Bourrel R, Palmaro A, Montastruc JL, Lapeyre-Mestre M. Analgesic drug consumption increases after knee arthroplasty: a pharmacoepidemiological study investigating postoperative pain. Pain 2014;155(7):1339–45. https://doi.org/10.1016/j.pain.2014.04.010.
[37] Hawker G, Wright J, Coyte P, Paul J, Dittus R, Croxford R, et al. Health-related quality of life after knee replacement. J Bone Joint Surg Am 1998;80(2):163–73. https://doi.org/10.2106/00004623-199802000-00003.
[38] Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. Pain 2011;152(3):566–72. https://doi.org/10.1016/j.pain.2010.11.023.
[39] Woolhead GM, Donovan JL, Dieppe PA. Outcomes of total knee replacement: a qualitative study. Rheumatology (Oxford) 2005;44(8):1032–7. https://doi.org/10.1093/rheumatology/keh674.