Influence of inhomogeneous static magnetic field-exposure on patients with erosive gastritis: a randomized, self- and placebo-controlled, double-blind, single centre, pilot study

Márk Juha´sz1, Viktor L. Nagy1, Hajnal Székely1, Dorottya Kocsis1, Zsolt Tulassay1 and János F. László2,3

12nd Department of Internal Medicine, Semmelweis University, Budapest, Szentkirályi u. 46, 1088 Hungary
2e-Comers LLC, Csejtei u. 1-3, Budapest 1025, Hungary
3Department of Computer Science, University of Debrecen, Kassai út 26, Debrecen 4028, Hungary

This pilot study was devoted to the effect of static magnetic field (SMF)-exposure on erosive gastritis. The randomized, self- and placebo-controlled, double-blind, pilot study included 16 patients of the 2nd Department of Internal Medicine, Semmelweis University diagnosed with erosive gastritis. The instrumental analysis followed a qualitative (pre-intervention) assessment of the symptoms by the patient: lower heartburn (in the ventricle), upper heartburn (in the oesophagus), epigastric pain, regurgitation, bloating and dry cough. Medical diagnosis included a double-line upper panendoscopy followed by 30 min local inhomogeneous SMF-exposure intervention at the lower sternal region over the stomach with peak-to-peak magnetic induction of 3 mT and 30 mT m⁻¹ gradient at the target site. A qualitative (post-intervention) assessment of the same symptoms closed the examination. Sham- or SMF-exposure was used in a double-blind manner. The authors succeeded in justifying the clinically and statistically significant beneficial effect of the SMF-over sham-exposure on the symptoms of erosive gastritis, the average effect of inhibition was 56% by \( p = 0.001, n = 42 + 96 \). This pilot study was aimed to encourage gastroenterologists to test local, inhomogeneous SMF-exposure on erosive gastritis patients, so this intervention may become an evidence-based alternative or complementary method in the clinical use especially in cases when conventional therapy options are contraindicated.

1. Introduction

Gastritis is a histological definition indicating mucosal inflammation. The inflammation of the gastric mucosa is the end result of an imbalance between mucosal defensive and aggressive factors (i.e. disturbances in gastric acidity and the mucus–bicarbonate barrier). Gastritis can be classified into acute or chronic forms based upon the Sydney System [1].

Erosive gastritis is characterized by the presence of multiple gastric erosions that are defined as small superficial mucosal lesions which do not exceed the muscularis mucosae [2]. The most common cause of erosive gastritis, acute or chronic, is chemical damage: prolonged use of non-steroidal anti-inflammatory drugs (NSAID) such as aspirin and ibuprofen, steroids, oral iron supplement, potassium chloride, fluoride, anticonvulsant drugs, chemotherapeutics, taxol and its derivatives, mycophenolate, kayekxalat-, kolchicin- or bisphosphonate [3–5]. Other agents that can cause erosive gastritis include Helicobacter (H.) pylori infection, biliary reflux, alcohol, cocaine or ionizing radiation [6,7]. Traumatic injuries, critical illness, severe burns, major surgery or hypothermia can also end up in an acute erosive gastritis called stress gastritis [8]. However, it should be noted that almost one half of the diagnoses do not reveal the pathogenesis of gastritis [9].
Erosive gastritis may be asymptomatic or present with epigastric pain, dyspepsia, haematemesis or iron deficiency anaemia resulting from gastrointestinal bleeding.

Although 50% of human population is colonized by *H. pylori*, only about 10–20% of them are likely to develop mucosal injuries, and only 1–2% are at risk for either gastric cancer or mucosa-associated lymphoid tissue lymphoma [10]. *Helicobacter* negative gastritis caused by NSAID, alcohol or biliary reflux give 10% of all gastritis cases.

Conservative treatment of erosive gastritis includes the management of the underlying condition as well as antacid agents including histamine 2 blockers (such as famotidine and ranitidine) and proton pump inhibitors (such as omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole or dexlansoprazole). If gastritis is caused by the prolonged use of NSAID, it is necessary to stop taking NSAID, reduce the dose of NSAID or switch to another class of medications.

Treating *H. pylori* infections is important, even if the patient is not experiencing symptoms due to the infection. Untreated *H. pylori* gastritis may lead to cancer or the development of ulcers in the stomach or small intestine. The regimen most commonly recommended for first line treatment of *H. pylori* is triple therapy with a proton pump inhibitor (lansoprazole, omeprazole, pantoprazole, rabeprazole or esomeprazole), amoxicillin or clarithromycin. Treatment may also include bismuth subsalicylate, quadruple therapy, to help eliminate the bacteria [11]. Only a few references can be found in the literature in connection with alternative treatments of erosive gastritis; the effects of probiotics and phytotherapy are controversial [12]. Although no physical agent has ever been evidenced to reduce the symptoms of erosive gastritis, some relevant cases can be found in the literature for the use of static magnetic field (SMF)-exposure. SMF-exposure has been found beneficial in different situations including inflammatory conditions. Relevant *in vitro*, *in vivo* experimental and human studies are detailed to some extent in the Discussion.

On the basis of previous experiences of one of the present authors (J.F.L.) with SMF on the mechanism of antinociception and analgesia [13,14], the authors decided to collect further evidence in a clinical trial. They attempted to show whether 30 min local exposure to external inhomogeneous SMF would significantly contribute to the subjective healing process of erosive gastritis as assessed by the symptoms associated with erosive gastritis by the patients themselves.

Local SMF-exposure would offer a safe, drug-free, durable and non-invasive alternative therapy option for reducing symptoms of erosive gastritis, maybe even contributing to healing with the help of inexpensive devices. SMF-therapy is classified as self-healing that can be applied comfortably at home without requiring special skills. It may also come handy in clinical situations, when other therapy options are contraindicated by allergy, cardiovascular overdose, other reasons or by multiple combined challenges.

2. Material and methods

2.1. Participants, recruitment, groups and ethics

The single-centre study was performed between January and June 2013 at the 2nd Department of Internal Medicine of Semmelweis University in Budapest, Hungary (2DIM). Sixteen patients of 2DIM covering an age range between 20 and 78 years (55.6 ± 4.7 years, mean ± s.e.m.) participated in the study. An unbalanced gender ratio was produced by 11 women (59.2 ± 5.8 year) and five men (47.8 ± 7.7 year). The age distribution of participants can be seen in table 1. Subjects were identified according to their medical history and were recruited exclusively at 2DIM. However, no distinction was made between acute and chronic cases of erosive gastritis in the hope that SMF-exposure would be effective in either as experienced in animal models (e.g. [14,15]). The sample size may seem to be low for even a pilot test. We conservatively (for normally distributed data) estimated 0% placebo effect based on an earlier study including a skin prick test for allergy on healthy volunteers applying a 15 min local exposure with an identical SMF generator [16] as in the present trial and 75% SMF effect based on an *in vivo* animal experimental series of alcohol-induced ulcer in mice that has not yet been published, so we could keep 80% statistical power by *α* = 5% and *n* = 7/group.

Inclusion criteria were as follows:

- ability to provide informed consent,
- willingness to participate in the test and undersign the written informed consent,
- age above or equal to 18 years, and
- absence of exclusion criteria.

It was considered an advantage, if the patient was drug-naive. Exclusion criteria were as follows:

- past or present taking of an NSAID or other medicament that has a known side effect profile of potentially causing erosive gastritis,
- any types of cardiovascular disease, arrhythmia or pacemaker,
- tumour,
- illness of the haematological system,
- purulent skin condition over the stomach,
- fever due to any reason including pancreatitis,
- neurological or neuromuscular illness,
- any kind of mental disorder including depression,
- hints of addiction or
capability or restricted capability.

Patients were distributed randomly into one of the following two groups: Group 1 sham-exposed (placebo control): seven patients or Group 2 SMF-exposed: nine patients. Two types of

| Table 1. Age distribution of participants. |
|-----------------|---------|---------|
| age (year)      | women   | men     |
| <20             | 1       | 0       |
| 21–25           | 0       | 0       |
| 26–30           | 1       | 1       |
| 31–35           | 0       | 0       |
| 36–40           | 0       | 1       |
| 41–45           | 1       | 0       |
| 46–50           | 1       | 0       |
| 50–55           | 1       | 0       |
| 56–60           | 0       | 0       |
| 60–65           | 1       | 1       |
| 66–70           | 2       | 1       |
| 71–75           | 3       | 0       |
| 76–80           | 1       | 0       |
| all             | 11      | 5       |
subgroups were defined for each group: (i) man or woman, (ii) age below 55.6 years or over 55.6 years. Immature cessation of trial: two persons in Group 2, both under the age of 55.6 years, one man and one woman. In these cases the subjects filled in the first evaluation sheet (pre-SMF-intervention data), but failed to do so with the second evaluation sheet (post-SMF-intervention). All their data were excluded from the analysis. In two post-SMF-exposure sheets we found one missing symptom mark, each. With the confidence that no mark denotes no complain, we substituted 0 for each of these missing marks. Figure 1 shows the CONSORT flow diagram of the trial.

Before the beginning of the trial protocol on the first day a detailed clarification of the test was presented to the patient upon which he/she signed a written informed consent. Human studies were carried out according to the guidance and spirit of the Helsinki Declaration (1964) modified in Tokyo (1975), in Venice (1983), in Hong Kong (1989) and in Somerset West (1996).

2.2. Trial design, interventions and safety

The trial was a self- and placebo-controlled, double-blind, randomized, 1:1 parallel-group, single centre, clinical trial complying with the recommendations of the CONSORT (Consolidated Standards of Reporting Trials) Group for RCT-NPT (Randomized, Controlled Trial extended to Non-pharmacological Treatments) [17]. Our study was not a crossover study; no other treatments have been applied before or after the local exposure to SMF- or sham-field related to the study. Those patients, who were not drug-naive took their medicines normally. Patients were instructed to avoid smoking and maintain a diet that was low on coffee, carbonated beverages, alcohol, spicy, fried and/or fatty foods. Unfortunately, we could not check whether these dietary requirements were fulfilled between days 1 and 2. Instrumental analysis was carried out by a double-line upper panendoscope. Schedule for the first day: checkup of inclusion criteria, briefing, signing informed consent, upper panendoscopy, ECG and diagnosis. If the existence of erosive gastritis was verified by the panendoscopy, appointment for the second day: 30 min treatment with either sham or SMF device. ECG and diagnosis followed the identification of patient and method of treatment. No follow-up beyond day 2 was included in the trial.

The SMF was generated with an exposure system elaborated originally for experimental testing [13]. The exposure system used was identical to the one described by Mészáros et al. [18]. In brief, it contained a single ferrous matrix of 196 individual cylindrical NdFeB grade N35 magnets (remnant magnetic induction $B_r = 1.2$ T) of size $L \times 2R = 10 \times 10$ mm. The individual magnets were close-packedy = 10 mm apart (distance between axes) in the laterally plane matrix. Neighbouring magnets sat in the matrix with alternating polarity. The arrangement was one-sided. Dosimetric values of the magnetic induction perpendicular to the magnets’ surface and their lateral gradient: $192 \pm 0.1$ mT peak-to-peak magnetic induction, $19.2$ T m$^{-1}$ lateral gradient at $z = 3$ mm from the surface of the magnets, $10 \pm 0.1$ mT peak-to-peak magnetic induction, $1.0$ T m$^{-1}$ lateral gradient at $z = 10$ mm (estimated minimum SMF-exposure depth in the target), $3 \pm 0.1$ mT peak-to-peak magnetic induction, $0.3$ T m$^{-1}$ lateral gradient at $z = 15$ mm. SMF was analysed by a calibrated 5 V Hall probe with 12.3 mV T$^{-1}$ sensitivity (Model UGN3503, Allegro Microsystems, Worcester, MA, USA). These measurements were performed well before the gastroenterology trial as described by model #3 in [13]. Line scans were taken in parallel planes at $3, 10$ and $15$ mm from the surface of magnets with a lateral increment of 1 mm. At $z = 40$ mm (estimated maximum SMF-exposure depth in the target) the applied SMF was no more distinguishable from the geomagnetic field background. The value of the magnetic induction at $40$ mm was $2.77 \mu$T as estimated with an analytical calculation: for $z \geq 0$ with $x$ and $y$ lateral dimensions, modelling the magnetic induction along the axis of a magnet in the isocentre of the arrangement. This estimate of the target depth depends strongly on individual skin thickness and anatomical distances. Colbert et al. [19] proposed a standardization of the description of clinical study reports including SMF. Table 2 contains our corresponding data.

The matrix was covered with a thin, soft tissue and was applied on the skin surface closest to the location of the accompanying pain sensation (if existed), typically at the lower sternal region over the stomach. The matrix was applied on the patient lying on his back for 30 min. A ‘sham’ device was identical to the SMF producing generator, but the magnetic...
Table 2. Ten essential dosing parameters for this study as suggested in [19].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>target tissue</td>
<td>skin, viscera</td>
</tr>
<tr>
<td>site of magnet application</td>
<td>lower sternal region, typically over the stomach</td>
</tr>
<tr>
<td>distance of magnet surface from target tissue(s)</td>
<td>10–40 mm strongly depending on the skin thickness at the lower sternal region and variations in the anatomy</td>
</tr>
<tr>
<td>magnetic field induction</td>
<td>1.2 T remanent induction, 192 mT, 10 mT and 3 mT (peak-to-peak magnetic induction, averaged for all neighbours) by 19.2, 1.0 and 0.3 T m⁻¹ (lateral magnetic induction gradient of the main induction component, averaged for all neighbours) at 3, 10 and 15 mm from a cylindrical magnet in the isocentre of the matrix along its axis, respectively. At 40 mm no artificial SMF can be measured.</td>
</tr>
<tr>
<td>material composition of permanent magnet</td>
<td>N35 grade neodymium – iron – boron (NdFeB)</td>
</tr>
<tr>
<td>magnet dimensions</td>
<td>rectangular matrix (120 × 140 mm) containing 12 × 14 pieces of 10 × 10 mm close-packed cylindrical magnets</td>
</tr>
<tr>
<td>magnet polar configuration</td>
<td>neighbouring magnets are placed with alternating poles (checkerboard configuration)</td>
</tr>
<tr>
<td>magnet support device</td>
<td>ferrous plate beneath the magnets, plastic framing around and soft coverage on the contact site</td>
</tr>
<tr>
<td>frequency of magnet application</td>
<td>single session</td>
</tr>
<tr>
<td>duration of magnet application</td>
<td>30 min continuous</td>
</tr>
</tbody>
</table>

2.3. Objectives and symptoms

Our basic null-hypothesis was that SMF-exposure would have a significant inhibitory effect on all six symptoms under investigation: (0 = LHB, lower heartburn (in the ventricle); 1 = UHB, upper heartburn (in the oesophagus); 2 = EP, epigastric pain; 3 = RG, regurgitation; 4 = BL, bloating; 5 = DC, dry cough) compared to baseline scores. The symptoms were selected as suggested in [22]. These symptoms of dyspepsia lead to a marked reduction in health-related quality of life and result in a substantial burden on society [23]. Additionally, we also supposed that post-sham-exposure scores would not be significantly different from baseline scores.

2.4. Implementation, blinding, randomization sequence and allocation concealment

All personal data were handwritten on paper by either J.M. or H.S., and the papers were locked in a file cabinet at 2DIM. Only Z.T. was authorized to see and handle these data later. They were not opened by or shown to any third person. We first informed the care providers in writing and also orally that the subjective pain perception the patients would describe following the interventions would not be directly correlated with the magnetic induction of the device the patients had over their skin. We emphasized that the sham device would also be able to increase the patients’ subjective pain tolerance threshold. We also advised patients in advance in writing and orally about this. Care providers as well as patients were asked to remove any magnetically anisotropic objects from their reach during the 30 min time period of the exposure.

Two of the present authors (J.M. and H.S.) provided the care; they enrolled and assigned patients to different groups according to diagnosis. V.L.N. generated the allocation sequence; he was responsible for selecting the appropriate intervention device for the selected patients. Altogether one SMF and one sham generator were used, only V.L.N. knew, which was SMF and which was sham.

One of the present authors (V.L.N.) was in charge of the randomization and control of the double-blind manner: Both participants and care providers were blinded to intervention. Within groups a series of random binary numbers was generated and assigned to the patient number list in the given group. If number 0 was allocated to a patient, he/she received sham-exposure, if number 1, then SMF-exposure. The numbered patient list together with the assigned binary numbers remained concealed from patients and care providers. A table with patients numbers, age, gender, medication taken, number of exposure device (identifying sham or SMF), and two tables with scores per patient were provided to J.F.L., who assessed the results, executed the statistical analysis. He was the only person to whom these data were revealed, but he did not receive the corresponding list of patient names.

2.5. Outcome measures and statistical considerations

The primary outcome measure of the trial was the individual raw subjective score, a five-dimensional binary quantity:

\[ x(i, j, k, l, m) = \begin{cases} 0 & \text{where } i = 0, 1, 2, \ldots, 5 \text{ are the monitored} \\ 1 & \text{monitor} \end{cases} \]
symptoms LHB, UHB, EP, BL, DC, respectively, $j = 0, 1, 2, \ldots, n_i$, the number of the patient, $n_i$ the total number of patients with regard to a symptom, $k = 0, 1, 2, \ldots, 5$ the possible grades of score, $l = 0$ or 1 denoting whether the score results from a pre- (0) or post-intervention (1) evaluation, and $m = 0$ or 1 showing whether the intervention was sham- (0) or SMF-exposure (1).

The evaluation sheet the patient had to fill in before (pre) and after (post) the intervention contained a table with the six symptoms ($i$) in rows and the six integer scores from 0 to 5 ($k$) in columns. He/she had to put a cross in the cell, which most accurately described his/her subjective feeling. Patients were required to enter a cross for each symptom. The only scores representing SMF-exposure were the post-SMF-exposure $x(i,j,k,1,1)$ scores and these were compared to the scores of all other (sham or placebo) situations: Pre-intervention scores for both interventions $x(i,j,k,0,1)$ and $x(i,j,k,0,0)$, and post-sham-exposure $x(i,j,k,0,1)$ scores.

In this notation, the four-dimensional frequency of a specific score $k$ for the $i$ symptom as a secondary outcome measure appears as $f(i, k, 1, 1) = \sum_{j=0}^{n_i} x(i,j,k,1,1)$ for SMF-exposure and similarly $f(i,k,0,1)$, $f(i,k,0,0)$, and $f(i,k,1,0)$ for sham- and pre-SMF-exposure.

A derived tertiary outcome measure was introduced as the three-dimensional sum of complex scores $c(i,1,1) = \sum_{j=0}^{n_i} k \times f(i,k,1,1)$ for SMF-exposure and similarly $c(i,0,0)$, $c(i,0,1)$, and $c(i,1,0)$ for sham- and pre-SMF-exposure.

Since none of the raw individual subjective scores ($x$), frequencies ($f$) or complex scores ($c$) were normally distributed, non-parametric statistical analysis methods had to be used. When examining paired data, pre-intervention against post-intervention complex scores, the Wilcoxon signed-rank test was used, otherwise (for comparing post-SMF-exposure scores to all other scores) the Mann–Whitney test. According to the null-hypothesis pre- and post-SMF-intervention scores were compared with left-tailed, pre- and post-sham-intervention scores with two-tailed calculations. The two missing scores were taken as zero.

$\mu_{i,j}$ denotes the median of scores. The effect or merit of post- over pre-intervention scores for example for symptom $i$ and for intervention $l$ in per cent was defined as $M_l = 100 \times [1 - c(i,l,1)/c(i,l,0)]$. The merit can be negative and can exceed 100% in absolute value.

Although the population numbers for the test did not allow detailed analyses, we carried out two sets of ancillary analysis: on the gender-selected and on the age-selected subsets of participants.

### 3. Results

#### 3.1. Participant flow and baseline data

There was no significant difference in the average age between female (59 ± 6 years) and male patients (48 ± 8 years): $p = 0.278$ as assessed by single factor ANOVA. There was no significant difference in the baseline scores between $x(i,j,k,0,0)$ and $x(i,j,k,1,0)$, the minimum probability of significance for the $i$ symptoms was $\min(p_i) = 0.469$, $i = 0, 1, 2, \ldots, 5$ (Mann–Whitney tests). Accordingly, no baseline correction of the raw subjective scores was necessary.

#### 3.2. Numbers analysed, outcomes and estimates

The distribution of raw complex scores $f(i,k,l,m)$ can be seen in figure 2a–f for the six different symptoms ($i$) measured. Shaded triangles and solid lines for the median denote $f(i,k,1,1)$ (SMF-exposure), open circles and dashed lines for the median denote $f(i,k,l,m)$, where $l + m \neq 2$ (sham-exposure).

The trend of SMF-exposure causing lower medians $\mu_{i,j,1}$ than sham-exposure $\mu_{i,j,0}$ was revealed for all symptoms other than upper heartburn (figure 2). The unpaired comparison between post-SMF-exposed $c(i,j,1)$ and all other scores $c(i,j,m)$, where $l + m \neq 2$ complex scores for all symptoms resulted in a significant difference, an overall effect of $M = 56\%$, $p = 0.001$ for the $n = 42 + 96$ scores.

In the case of SMF-exposure, the merit of post- versus pre-intervention scores is always higher than 35% with the only exception of epigastric pain (figure 3) and for three out of six symptoms this merit is significant: $p = 0.039$ for LHB, $p = 0.039$ also for RG, $p = 0.015$ for BL by $n = 14$ for all. Meanwhile, in the case of sham-exposure no significant difference occurs but for all symptoms altogether and
all merits are below the SMF-exposed merits with the only exception of regurgitation. The significance ($p = 0.012$, $n = 84$) between post- and pre-sham-exposure for the total of symptoms is caused by regurgitation alone, without RG: $p = 0.056$, $n = 70$. This effect however, is probably not significant in a clinical sense speaking of an effect of 21%. The effect size of SMF- and sham-exposure more or less (disregarding RG) verifies the moderate sample size.

### 3.3. Ancillary analyses

The unpaired comparison between post-SMF-exposed $c(i,1,1)$ and all other scores $c(i,l,m)$, where $l + m \neq 2$ complex scores for all symptoms resulted in a significant difference for both men and women, an effect of $M = 89\%$, $p = 0.002$ for $n = 12 + 30$ and $M = 42\%$, $p = 0.027$ for $n = 28 + 66$, respectively. As for the age subgroups: below 55.6 years, $M = 52\%$, $p = 0.077$ non-significant for $n = 12 + 42$ and over 55.6 years, $M = 58\%$, $p = 0.001$ for $n = 30 + 54$ was achieved.

The paired comparisons between pre- and post-intervention data for all symptoms were significantly different for the SMF-exposed subgroups: $M = 94\%$, $p = 0.003$, $n = 24$ for men, $M = 34\%$, $p = 0.005$, $n = 60$ for women, $M = 26\%$, $p = 0.053$ non-significant, $n = 24$ for the age group below 55.6 years and $M = 44\%$, $p < 0.001$, $n = 60$ for the age group over 55.6 years.

In the sham-exposed subgroup of men post- and pre-intervention scores differed significantly, $M = 65\%$, $p = 0.004$, $n = 24$; this effect occurred also in the age subgroup below 55.6 years: $M = 41\%$, $p = 0.025$, $n = 30$. Meanwhile, $M = 20\%$, $p = 0.081$, $n = 60$ was obtained for women, and $M = 7\%$, $p = 0.150$, $n = 48$ for the group with higher average age.

Sample size allowed detailed paired analysis between pre- and post-SMF-exposed women. Table 3 contains the data for all six symptoms. The SMF-exposed age group over 55.6 years could also be analysed in detail (table 4).

### 3.4. Adverse events

No adverse effects were recorded in either group that could have been attributed to the applied sham- or SMF-exposure. The 30 min long intervention was never interrupted or discontinued for any reason.

### 4. Discussion

#### 4.1. Generalizability, limitations and strengths

This pilot study did not aim to provide details about the background mechanism of action. Preceding studies of one of the present authors (J.F.L.) in mouse models made it...
probable that SMF-exposure could have a beneficial effect on symptoms induced by an inflammatory background and also wound healing beyond that of placebo. No laboratory or other devices were used for the analysis in the present study. Accordingly, the present authors can only hypothesize why SMF-exposure had a significant beneficial effect on most of the symptoms of erosive gastritis.

A further limitation is that the gender distribution in the two groups was unbalanced. Our study enrolled only Caucasian patients, so generalizability may be limited. Furthermore, generalizability is also somewhat hindered by the low number of participants. No other exposure duration than 30 min was tested.

The individual variation of skin thickness over the sternum and anatomical distances determined the 10–40 mm depth which the applied external SMF-exposure should have covered. Meanwhile at 10 mm the magnetic induction of the applied SMF is three orders of magnitude beyond that of the geomagnetic field, at 40 mm the external SMF decays in the magnetic background of the Earth. The results achieved by SMF-exposure in symptom release probably strongly depend on the actual penetration depth of SMF for a given patient.

A strength of the trial was that there was no baseline difference in the raw individual scores that may have influenced the changes observed throughout the study. Also the two groups were balanced in age. While the size of the study was small, results allow for the conclusion on the main outcome measures of our study thus providing evidence that local exposure with inhomogeneous SMF did not cause any adverse effects. They also support that SMF-exposure beneficially affects the symptoms of erosive gastritis. A further advantage of our study is that our primary and ancillary analyses (with a full set of data and those allocated to age and gender subgroups) gave corresponding results.

4.2. Comparison with other studies

Evidence has been collected since 1987 supporting the idea that SMF-exposure has an impact on inflammatory conditions in humans, in experimental animals, and the effect can be proved in vitro as well.

4.2.1. Human trials

Myshkin et al. [24] compared anastomoses in clinical practice in six patients with and without the use of permanent magnets in 1987. Lud & Demeckiy [25] observed the stimulation of the central and peripheral blood flow, the prevention of hypercoagulation and the reduction of oedema and inflammation in their patients for reconstructive surgery, where the main arteries were operated using venous grafts. Alekseenko et al. [26–29] carried out experiments on patients with trophic ulcer and found ‘wound surface has completely cleaned from necrotic tissues, surrounding inflammatory changes eliminated, epithelization of the wounds began’. Man et al. [30] watched for changes in wound healing from the aspect of plastic surgery and in a placebo-controlled study found that the treated group had significant reductions in pain, in oedema, and in discoloration when compared with the control group. Szor & Holewinski [31] found convincing evidence that SMF-exposure can significantly help wound healing. Eccles & Hollinworth [32] also executed a double-blind study on leg ulcer healing by SMF-exposure and found positive effects. In a direct study of pain sensation under inflammatory conditions of the temporomandibular joint exposed to local, inhomogeneous SMF László et al. [33] observed a significantly beneficial effect beyond placebo.

4.2.2. Animal experiments

Nursal et al. [34] studied the effect of SMF-exposure on wound healing in 50 rats. They could not identify any effect. An experimental model on induced preterm birth in mice suggested on the other hand, that 30 min d⁻¹ repetitive SMF-exposure prolonged the time of birth by about 20% [35]. Henry et al. [36] reviewed the literature on SMF-assisted wound healing in 2008. Forty-eight diabetic rats under 180 mT SMF-exposure proved that the exposure significantly increased the healing rate and reduced the gross healing time [37]. When SMF is oriented perpendicular to the wound on rats, increased wound healing occurs [38]. Studies with acute peripheral [39], visceral [14] inflammation or even chronic neuropathy [15] showed that SMF-exposure contributes to the machinery of the mammalian body to recover from inflammation. Mice with induced disseminated intravascular coagulation showed lower mortality rate if exposed to SMF [40].

4.2.3. In vitro studies

SMF of 120 μT increased human umbilical vein cell proliferation by 40% over a period of 2 days [41]. Endothelial cell functionality increased after SMF treatment which upregulated endothelial nitric oxide synthase expression. The authors concluded that SMF-exposure has a significant rejuvenation effect on endothelial cells. SMF-exposure inhibited IL-6 secretion in another study [42]. A recent experiment [43] provided evidence that the secretion of pro-inflammatory cytokines as IL-6, IL-8 and TNF-α from macrophages and lymphocytes was inhibited, meanwhile that of the anti-inflammatory cytokine IL-10 was promoted. SMF-exposure was found to significantly decrease IL-6 expression in BV-2 cells during the LPS-induced inflammatory response [44].

Evidence also supports that SMF-exposure affects vascular resistance, blood flow, capillary circulation [45–47], it
influences the generation of vasoactive agents, such as prostaglandins and nitric oxide [48–50].

4.3. Interpretation

Throughout the present trial no invasive intervention was possible, no biochemical analysis could be made. In the absence of such data, the possible background mechanism cannot be determined.

According to the study of Schenck [51], there are several possibilities of an interaction of even homogeneous SMF with the tissue: (i) magnetic forces due to tissue susceptibility differences between tissues involved, (ii) magnetic torques due to anisotropic susceptibilities, (iii) flow or motion-induced currents causing nerve or muscle stimulation, (iv) changes in chemical reaction rates, (v) magnetohydrodynamic forces and pressures and (vi) magnetic excitation of sensory receptors leading to sensations such as nausea, vertigo and magnetophoresis. Almost all human tissues are diamagnetic and have susceptibilities in a narrow range of about \( \pm 20\% \) from the susceptibility of water [51]. (i) probably does not have a significant contribution to the presently observed effects. Although certain proteins and other macromolecules can produce shape- or anisotropy-dependent rotation under external SMF-exposure, the effect in vivo has never been evidenced probably due to the enormous magnetic induction needed to influence a large enough number of molecules for detection [51]. Accordingly, (ii) fails to come into question. If an electrically charged object moves in an external SMF, its trajectory gets modified according to the Lorentz force. Owing to the redistribution of multiple moving electric charges under SMF-exposure a change occurs in the magnetic flux and accordingly, an electric current develops. This phenomenon, from the physical point of view, is identical to that when the charges do not move, but the magnetic field is time-dependent. Although in the present trial the patients during local SMF-exposure lay still, reducing the chances of developing electric currents, but electric charges moved in the exposed volume of their body. As discussed to some extent in [52] in this (iii) case, again extremely strong SMF would only be capable of producing nerve stimulation that eventually could affect the presently experienced change in symptoms. At the electron spin level, it is accepted that the action of SMF-exposure on the symptoms may be based on the modified lifetime of free radical pairs as detailed in [53]. This effect relies on the fact that an external SMF can enhance the interconversion of such pairs from singlet (S) to triplet (T) states. Radicals of the pair may react with DNA and conclusively undesirable free radical damage can occur. Related to (iv), an alternative situation is when beneficial effects arise. Regarding (v), flow-induced electric currents can only be observed at magnetic induction above 10 T [51]. No sensory effects were registered during the present investigations suggesting that (vi) did not play a role in the monitored symptom variations due to SMF-exposure. Sensory effects were first registered in MRI devices using 1.5 T magnetic induction [51].

The inhomogeneity of SMF makes the picture more complex since SMF gradients have the ability of evoking magnetic potential differences in the living matter that is fully at rest and even without fluids of electric charge carriers flowing through the exposed volume. These potentials however, are extremely difficult to model in biological systems due to the inseparability of the potential response to SMF gradients from that to the magnetic induction of SMF and/or to the electric currents induced in the system. Inhomogeneous SMF-exposure may be able to induce physiological changes in the area of (iii) in animals with self-motion [53]. Exposure to similar SMF as in the present trial was shown to have an antinociceptive effect experimentally, probably due to the enhanced release rate of \( \beta \)-endorphin and/or endorphin-2 [14]. Among the many beneficial effects, exposure to the present inhomogeneous SMF could most importantly achieve was, the present authors believe, the contribution to the restitution of the patient’s homeostasis as suggested by Gmitrov et al. [47] for rabbit microcirculation. This led to the relief of symptoms associated with erosive gastritis.

Making the decision as to whether the beneficial effect found is due to the influence of the SMF-exposure on gastric wound healing, or reinforcing the microcirculation of the gastric mucosa, or balancing of the endocrine or the nitric oxide system related to the gastric track, or a direct anti-inflammatory action, or all of these, remains a task for the future.

4.4. Overall evidence

In spite of the fact that erosive gastritis has a 1.6 times higher prevalence in men than in women [54], many more women volunteered for participation in the present trial than men at 2DIM. Our baseline data did not show significant difference between female and male raw scores in any (sub)groups. Men were much more sensitive to SMF-exposure than women, but they also showed higher impact on the placebo effect. The effect of age seemed to influence the scores in a complex manner: the age group over the average age 55.6 years was more sensitive to SMF-exposure, while the other group was more sensitive to placebo. However, neither of these observed effects for gender and age allows us to draw detailed conclusions on the main difference between SMF- and sham-exposure, because neither group was balanced in gender or in age. Further studies with more patients and balanced groups are required to estimate how the effect depends on the exposure duration (only 30 min was tested), the spatial distribution of the SMF, its magnetic induction, its lateral gradient, etc.

5. Conclusion

The overall significant merit of 56% of SMF-over sham-exposure in a clinical trial of 16 patients and six symptoms usually attributed to erosive gastritis is a clinically as well as statistically funded basis for the beneficial influence of SMF-exposure under inflammatory conditions. For future therapeutical applications as an evidence-based complementary or alternative method, further studies are needed that, among others, should clarify the dynamics of the effect.

The accredited Scientific and Research Ethics Committee of the Medical Research Council approved the examination (license code: CSM5999AHU02).

Acknowledgement. This study was initiated by a series of experiments on alcohol-induced gastric ulcer in mice. A similar SMF generator as presented was used. These experiments were carried out at Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary, under the supervision of Prof. K. Gyires. J.F.L. is grateful for fruitful discussions with Prof. L. A. Bancu at Department of Internal Medicine, University of Medicine and Pharmacy, Targu-Mures, Romania.
References


