The effect of electroacupuncture and tramadol on experimental tourniquet pain

Frauke Musial,1,2 Kyung-Eun Choi,1 Tim Gabriel,1 Rainer Lüdtke,3 Thomas Rampp,1 Andreas Michalsen,4 Gustav Dobos1

ABSTRACT
Objectives The hypoalgesic effect of electroacupuncture (EA) was directly compared with the analgesic effect of pharmacological interventions using the submaximum effort tourniquet technique (SETT).

Methods 125 healthy subjects (mean age 24.44 ± 4.46 years; 62.4% female, 37.6% male) performed SETT at baseline and under one of five experimental conditions (n = 25 per group): EA (2 Hz with burst pulses in alternating one-phase-square wave pulses; burst length 180 µs, burst frequency 80 Hz, stimulation time/pulse width 3 s), tramadol (50 mg), ibuprofen (400 mg), placebo pill or non-treatment control. EA was performed at LI4 and LI10 contralaterally with stimulation beginning 20 min before SETT and lasting throughout SETT. The pharmacological interventions were given in a double-blind design 1 h before the SETT assessment.

Results Subjects showed a hypoalgesic effect of the opiates and of the EA for subjective pain rating (EA p = 0.0051; tramadol p = 0.0299), and pain tolerance index (time/rating) (EA p = 0.043; tramadol p = 0.047) analysed using analysis of covariance. More subjects reached the strict time limit of 30 min (analysed by logistic regression and adjusted OR as a post-hoc analysis) under EA compared with most other experimental conditions. Only EA and tramadol were not significantly different (95% Wald confidence limits: non-treatment control vs EA 0.011 to 0.542; placebo pill vs EA 0.009 to 0.438; ibuprofen vs EA 0.021 to 0.766; tramadol vs EA 0.065 to 1.436).

Conclusion In a laboratory setting, an EA procedure was as effective as a single dose of an orally administered opiate in reducing experimentally induced ischaemic pain.

The two large German acupuncture trials, acupuncture randomised trials and German acupuncture trials, yielded convincing evidence for the clinical effectiveness of acupuncture but also raised many new questions, as the so-called sham or minimal acupuncture was in general superior to waiting list control or even as effective as ‘verum’ acupuncture. However, the concept of sham acupuncture or minimal acupuncture as a valid control for acupuncture has been criticised, not only by clinicians, but also by physiologists. The fact that ‘sham’ acupuncture or ‘minimal’ acupuncture was in many cases as effective as ‘verum’ acupuncture, has fostered a discussion, whether acupuncture may simply represent a particularly effective placebo. In particular, a recent ‘white paper’ by Langevin et al discusses this problem extensively as ‘paradox 1’.

The individual placebo response has been extensively investigated by Benedetti and colleagues. In the experimental pain tolerance setting utilised it was shown that both conditioning and expectation processes play a role in placebo analgesia. The expectation-induced placebo response was completely blocked by the opiate antagonist naloxone, and is assumed to be mediated by the endogenous opiate system. Acupuncture analgesia is similar to the expectation-dependent placebo effect in that it can also be blocked by naloxone, ie, it is also opiate dependent (for an overview, see Mayer). Expectation-dependent placebo analgesia may thus utilise the same mechanisms as at least some aspects of the acupuncture effect.

While there is an ongoing discussion about the mechanisms of acupuncture hypoalgesia, there is a lack of information about the effectiveness of acupuncture in direct comparison with well-established analgesic interventions such as pharmacological agents. Furthermore, well-established experimental pain models for the investigation of the possible analgesic effects of acupuncture in a standardised, non-clinical, experimental laboratory setting are rare in humans (but common in animal models). Therefore, the aim of this study was to establish the standard procedure of experimental placebo research as an experimental pain model for acupuncture. If acupuncture has a strong placebo component, then the submaximum effort tourniquet technique (SETT) should be a sensitive and valid tool for the evaluation of hypoalgesic acupuncture effects.

Moreover, acupuncture was directly compared with the ‘gold standard’, the opiate tramadol as a pharmacological analgesic agent. In order to test possible peripheral analgesic effects of acupuncture, a non-steroidal analgesic agent...
was also included. All conditions were tested against a placebo pill and a non-treatment control group. The rationale was not to test acupuncture against a different acupuncture condition (sham, minimal, etc.), but to test acupuncture against known and established analgesic treatments in an experimental, laboratory setting. Furthermore, healthy young pain-free probands rather than chronic pain patients participated in the study, in order to avoid possible acupuncture or other treatment effects, which are due to the chronic manifestation of clinical pain. If acupuncture is an effective treatment, then it was assumed that it would be as effective as the non-steroidal analgesic or the opiate.

METHODS

Study participants

One hundred and twenty-five healthy young probands (mean age ±SD; 24.44±4.46 years; 62.4% female and 37.6% male) were recruited (table 1). Study participants were pain free and naive to both the experimental procedure and acupuncture. Before participating in the study, all volunteers were screened for exclusion criteria: peripheral vascular abnormalities, hypotension, chronic pain syndromes, peripheral neuropathy, current medication and alcohol/drug abuse. After a full explanation of the experimental procedure, each proband signed a standardised consent form. It was stressed that the probands could withdraw from the study at any point without necessarily giving a reason. The data of one participant, randomly assigned to the tramadol group, had to be excluded because he felt nauseated after the ingestion of the pill.

Study design

All test persons participated in two sessions. On the first attendance a pain induction procedure (SETT) without further intervention was conducted in order to provide baseline data. Probands were requested to attend a second session at least 48 h after the first attendance. They were randomly assigned to one of five experimental groups: electroacupuncture (EA), an opiate (tramadol 50 mg), a non-steroidal analgesic (ibuprofen 400 mg), a placebo pill or non-treatment control. Pills were administered in a double-blind fashion, 1 h before the beginning of the session. In addition to the pain ratings during SETT, which were performed every 3 min on a numerical rating scale (NRS) from 0 to 10, all study participants were asked before the start of the second (treatment) session about their expectations concerning the treatment effects in this session. For this purpose, two NRS ranging from −5 to +5, with 0 referring to the baseline SETT session, were used. The reason for the different scaling for measuring expectation was that the participants rated their expected SETT duration as well as the expected pain intensity for this particular session in comparison with the duration and the pain intensity of the baseline SETT session.

Pain induction

SETT was performed according to the standard procedure in placebo research,7 12–14 which allows the study participants to end SETT at the point of unbearable pain. Subjects were asked to relax 20 min on a bed in a comfortable, supine position. Then they were asked to expose their non-dominant arm to above the bulk of the biceps/triceps. A standard blood pressure cuff was applied, with its distal margin approximately 5 cm above the elbow crease, the arm was elevated straight to the ceiling for 30 s and the cuff was then rapidly inflated to 250 mm Hg. Immediately after inflating subjects lowered their arms and performed 12 gripping exercises with their hand using maximal grip strength. The exercises were performed in a standardised manner, maintaining the grip for 2 s and then relaxing it for 2 s.

Subjects were prompted every 3 min to rate their pain on a NRS from 0 (no pain) to 10 (unbearable pain). The first rating was obtained after relocating the arm back in the horizontal position. Compared with most SETT studies, a rather short time limit of 30 min was used. SETT ended at 30 min or when a pain rating of 10 was reached. At the end of SETT the cuff was deflated slowly over a 2-min period. Upon completion of the procedure the cuff was carefully removed and the skin examined for evidence of trauma. No side effects of SETT occurred throughout the study.

Acupuncture procedure

The acupuncture procedure described in the following paragraph was the result of extensive pretesting before the study in order to develop the most efficient acupuncture intervention for SETT. Acupuncture was carried out as EA at LI4 and LI10 on the arm contralaterally to SETT application. Needle insertion was performed with 0.25×25 mm stainless steel needles. All needles were inserted perpendicularly, with approximately 1–2 cm depth. Needle insertion was performed in a manner to elicit de qi feeling by rotating the needle clockwise and counterclockwise with a 180–360° amplitude for each rotation and for approximately 5–10 s of total stimulation. Stimulation stopped when subjects indicated they achieved de qi feeling. Subjects were told that de qi is a dull, maybe hot or slightly sore sensation as a result of the needle stimulation. Stimulation intensity was increased to tolerance, but subnoxious, and the electrostimulation of these acupuncture points was performed starting 20 min before the application of SETT and throughout the session. The stimulation was conducted with a frequency of 2 Hz, with burst pulses (burst length

| Table 1 | Mean ages (±SD) of study participants and ratio of female to male participants |
|----------------|-----------------|-------|-------|------|
| Treatment      | n   | Mean age | SD   | Ratio f/m |
| Non-treatment control | 25 | 27.4      | 5.2  | 15:10 |
| Placebo pill   | 25  | 25.0      | 3.8  | 16:9  |
| Ibuprofen      | 25  | 24.4      | 4.0  | 17:8  |
| Tramadol       | 24  | 26.2      | 4.6  | 16:8  |
| EA             | 25  | 24.3      | 4.2  | 14:11 |

EA, electroacupuncture; f, female; m, male.
180 μs, burst frequency 80 Hz, stimulation time/pulse width 3 s) in alternating one-phase-square wave pulses. The acupuncture was carried out by a licensed acupuncturist who was not involved in data collection or analysis.

**Side effects**

Except for one participant in the tramadol group who felt nauseous after the ingestion of the pill, none of the participants reported adverse side effects. All participants in the tramadol group were instructed not to drive a car or handle difficult machinery for the rest of the day. This instruction was given after the session was over and the pharmacological condition was revealed to the study participants.

**Statistics**

All outcome criteria were analysed with analyses of covariance (ANCOVA), taking the post-treatment measurement (T2) as a dependent, treatment as the between-subject factor, and the respective baseline value as a covariate. For post-hoc testing α-adjusted Tukey–Kramer tests were used. Expectation was initially included as a covariate in all ANCOVA, but never reached statistical significance. Therefore, final analyses were calculated without expectation as a covariate.

As it turned out that the dependent measure ‘time to unbearable pain’ was blurred by a strong ceiling effect due to the time limit of 30 min, resulting in a high number of zero differences, the originally intended ANCOVA seemed to be inappropriate. Therefore, the data were post-hoc dichotomised and analysed by a logistical regression analysis. The Wald test was used in order to estimate whether an independent measure adds a significant effect to a generalised regression model.

As regression analysis revealed that time to unbearable pain was a relevant variable, we defined a new variable, ‘pain tolerance index’, which represents the ratio of SETT duration divided by the NRS pain rating at break-off. Theoretically, this ratio can vary between 3 (a pain rating of 10) and 30 (a pain rating of 1) and has no units. A high value represents a high pain tolerance.

**RESULTS**

There were no baseline differences (one-way ANCOVA) between the groups for any of the measures (table 2).

**Table 2** Mean±SD for baseline and treatment conditions for SETT duration, mean NRS ratings for pain and pain tolerance index

<table>
<thead>
<tr>
<th>SETT duration (min)</th>
<th>Mean NRS rating</th>
<th>Pain tolerance index (SETT duration/NRS rating at break-off)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
</tr>
<tr>
<td>Non-treatment control (n=25)</td>
<td>19.44±6.5</td>
<td>20.32±6.2</td>
</tr>
<tr>
<td>Placebo pill (=25)</td>
<td>20.76±9.1</td>
<td>22.16±7.8</td>
</tr>
<tr>
<td>Ibuprofen (n=25)</td>
<td>21.56±8.0</td>
<td>23.68±6.8</td>
</tr>
<tr>
<td>Tramadol (n=24)</td>
<td>19.17±8.0</td>
<td>23.25±6.8</td>
</tr>
<tr>
<td>EA (n=25)</td>
<td>19.68±8.0</td>
<td>22.96±8.1</td>
</tr>
</tbody>
</table>

EA, electroacupuncture; NRS, numerical rating scale; SETT, submaximum effort tourniquet technique.

**Mean pain ratings**

EA and tramadol showed the strongest decrease in mean pain rating. One-way ANCOVA showed a significant difference between groups (F=4.588, df=4.123, p=0.002) and post-hoc testing revealed that the EA group (p=0.0051) as well as the tramadol group (p=0.0299) differed significantly from the non-treatment control group. There was no significant difference between the tramadol and EA groups (figure 1).

**Time to unbearable pain**

Due to the rather strict time limit of 30 min, a total of 31 probands reached the limit during baseline measurement, leading to a high number of zero values when calculating the differences between baseline and treatment (table 3). As this strong ceiling effect blurred the actual treatment effect, we dichotomised all time data into whether or not the proband reached the time limit and fitted a logistical regression model as a post-hoc analysis instead of an ANCOVA. The baseline data were included as a an additional (binary) predictor.

In this model, two independent variables (predictors) were defined: one was ‘baseline’, meaning the proband tolerated SETT until the 30 min time criterion during the baseline measurements. Consequently, the variable
baseline consisted of two levels (yes/no). The other independent variable was ‘treatment’ with the five different treatments as levels. The dependent measure was the number of subjects tolerating SETT until the time limit of 30 min was reached.

The model revealed an effect of the variable ‘baseline’, with Wald $\chi^2=33.9165$, df=1, p<0.0001 and a global treatment effect with Wald $\chi^2=10.8183$, df=4, p=0.0287. This means that the fact that a proband reached the 30 min criterion under baseline conditions was the strongest predictor of whether he or she reached the criterion on day 2. However, treatment was also a significant predictor, meaning that the fact that 10 participants more reached the 30 min criterion on day 2 under treatment conditions suggests a relevant influence of at least some of the treatments.

In order to clarify the impact of the different treatment conditions, adjusted OR were calculated (table 4). Significantly more participants reached the 30 min time limit in the EA group compared with the non-treatment control, placebo pill and ibuprofen groups. Only the comparison between tramadol and EA was not significantly different.

### Pain tolerance

Even though time was analysed by logistical regression, the rating at the time limit of 30 min is important information. Therefore, ‘pain tolerance index’ defined as SETT duration divided by the NRS rating given at the point of break-off (SETT duration/NRS rating at break-off) was calculated. Figure 2 shows the difference values between the two sessions. The EA and tramadol groups showed the strongest increase in pain tolerance index. One-way analysis of variance showed a global treatment effect (F=3.241, df=4.123, p=0.015). Post-hoc testing revealed that the EA group (p=0.043) as well as the tramadol group (p=0.047) differed significantly from the non-treatment control group. There was no difference between the tramadol and the EA groups (figure 2).

### DISCUSSION

The results of this study show that EA and the opiate tramadol, administered as a single dose, were similarly effective in increasing pain tolerance in experimental tourniquet pain. The effect was robust and was shown in all three dependent measures: subjective pain ratings, the time SETT was tolerated, and the ratio of time to rating (SETT duration/NRS rating at break-off). In conclusion, a standard paradigm of experimental placebo research, SETT, is a valid and sensitive tool for the experimental investigation of analgesic acupuncture effects, and both EA and the opiate used were effective in reducing tourniquet pain while there was no effect of the non-steroidal analgesic or the placebo pill.

There have been attempts to utilise SETT for acupuncture research before by Barlas et al.17 However, no effect of acupuncture compared with sham acupuncture was seen in that study. The study was well controlled and the results show a trend for all treatment conditions to have some analgesic effects; however, there were no significant group differences. The reason for this outcome was maybe the fact that ‘sham’ or minimal acupuncture may not be an inactive treatment.5 Control approaches in which points other than the verum points are needled assume that verum acupuncture points are specific. Point specificity means that only certain, specifically localised points, or at least a specific area, are to be needled. Inversely, it is assumed that needling non-acupuncture points will not result in the desired effect. However, as early as 1983, Lewith and Machin18 showed that needling non-acupuncture points...
will result in pain reduction in up to 50% of patients, compared with 60% of patients when acupuncture points are needlel. Therefore, the comparison of two possibly active treatments, as in the study of Barlas et al.,17 may not yield significant results. This consideration specifically applies for the German acupuncture trials.1–4 A recently updated Cochrane review supports the notion that these trials differ from other trials on pain.19 Across a wide variety of conditions, the analysis revealed no considerable placebo effect, even among trials with a low risk of bias. The effect on pain was particularly variable, and the similarly designed German acupuncture trials reported the largest effects, whereas the other trials reported no more than low effects. Performing a re-analysis of the data, Linde et al.20 concluded that effects associated with sham acupuncture interventions might, on average, be indeed larger than pharmacological and other physical placebos. Further support was adduced from a recent meta-analysis showing that sham acupuncture interventions are often associated with moderately large non-specific effects compared with inert placebo interventions.21 Under the assumption that the ‘sham’ control condition in the above-mentioned trials was active, these results can easily be explained. Furthermore, former attempts to investigate acupuncture analgesia with SETT that revealed no significant difference between true and sham acupuncture have17 have to be re-evaluated. Moreover, acceptance of the fact that the ‘sham’ control in acupuncture trials may in fact be an active control would have considerable implications for the design of future acupuncture trials.

In a later study on experimental pain, Barlas et al.22 used a different pain paradigm (pressure pain) and the non-penetrating Streitberger needle as one control for acupuncture. In this even more sophisticated study the authors found a clear hypoalgesic effect of high intensity EA,20 an EA condition that is comparable to the condition utilised in our study. Therefore, the hypoalgesic effect of EA seen in our study matches the outcome of this group’s second study.22

In the present study, SETT has been shown to be a sensitive and valid instrument for experimental acupuncture research. It supports two recent studies from our own group,23 24 showing an analgesic effect of EA, as reflected by SETT, in direct comparison to the top-down mechanism of meditation. One of the reasons why SETT has proved such a suitable instrument for acupuncture effects may be its opiate sensitivity.12–14 For instance, very different types of opiate antagonists can block acupuncture-induced analgesia, and there is cross-tolerance between acupuncture analgesia and morphine analgesia (for a discussion see Stux et al.).11 Numerous other findings indicate that acupuncture analgesia is distinctly associated with the endogenous opiate system. Using EA, it has been shown that different classes of endorphins are released, depending on the frequency of electrical stimulation. Low frequencies induce the release of β-endorphins and met-enkephalin in the spinal cord and the brain, while high-frequency stimulation promotes the release of dynorphin in the spinal cord.25–27

Similarly to acupuncture, the expectation-induced placebo response is also mediated by the endogenous opiate system.7 Concerning the neurophysiological mediation of the expectancy-dependent placebo effect and the analgesic properties of acupuncture, there are obvious similarities. Moreover, in a re-analysis of data from four randomised controlled trials on acupuncture treatment of migraine, tension-type headache, chronic low back pain and osteoarthritis of the knee in 864 patients, a significant association was shown between better improvement and higher outcome expectations.28 However, that does not necessarily imply that the effects of acupuncture analgesia are generally mediated through an expectancy-induced placebo effect, but rather that both interventions utilise the same, opiate-dependent pathway. In the study presented here, there was no influence of expectation on any of the outcome measures. Furthermore, EA was similarly as effective as the opiate tramadol, which is supposed to be a pharmacological agent with a known pathway. If the hypoalgesic effect of EA in this study was a placebo, then the effect size is similar to that of tramadol.

It has to be admitted that the experimental procedure and the acupuncture procedure presented here are somewhat artificial compared with clinical pain situations and clinical acupuncture practice. Nonetheless, a change of 30–50% pain reduction in a clinical trial is considered to be in the range of clinical significance.29 Table 5 shows the average percentage change to baseline for mean rating and pain tolerance. The greatest change occurs for both measures in the acupuncture and the tramadol group. However, only the percentage change for pain tolerance is in the range of clinical significance. Furthermore, variability is considerable. Part of it is due to the time limit of 30 min and the corresponding ceiling effect inducing a high number of zero differences between tolerated SETT time during baseline and treatment day. However, with respect to pain tolerance, variability was particularly high in the placebo pill and ibuprofen groups. It is likely that both groups were heterogeneous with regard to placebo responders. Nonetheless, especially against the background that SETT is a rather unpleasant pain tolerance paradigm, tramadol and EA did indeed induce changes that can be considered clinically relevant.

In conclusion, our results confirm the results of Barlas et al.,22 reporting an analgesic effect of high-frequency, intense EA for another, standard laboratory pain paradigm, SETT. Furthermore, the effect size of acupuncture

<table>
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<th>Table 5 Average percentage (mean±SD) change from baseline</th>
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<tr>
<td>Treatment</td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
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<td>Placebo pill</td>
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<td>Tramadol</td>
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<td>Acupuncture</td>
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NRS, numerical rating scale.
was comparable to that of an orally administered opiate, tramadol. Against the background of the ongoing discussion, whether clinical acupuncture effects are mediated through a strong placebo effect, the similar effect size of EA and the gold standard, the opiate tramadol, on experimental tourniquet pain is remarkable. We stress that—even if acupuncture effects were based on mere placebo effects—the described acupuncture effects in this study were comparable to those of an established, pharmacological pain treatment.

Summary points

- Submaximal effort tourniquet technique is a reliable test of threshold for acute pain
- We compared EA with analgesic drugs in 125 volunteers
- EA and tramadol raised the threshold by a similar degree
- Implications for ‘placebo’ acupuncture are discussed

Contributors

FM conceptionalised and designed the study, and interpreted the data. RL analysed and interpreted the data. TG and KEC operationalised the study and conducted the experiment. TR developed the acupuncture procedure and was involved in the conceptualisation and design of the study. All listed authors were involved in drafting the article or revising it critically for important intellectual content. All authors approved the final version of the manuscript.

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Competing interests

None.

Ethics approval

Ethics approval was given by the institutional review board of the medical institutions of the University Duisburg-Essen, Germany (no. 07-3431).

Patient consent

Obtained.

Data sharing statement

All data compiled in this study, except individual data regarding possible exclusion and including criteria, are presented in the manuscript.

Provenance and peer review

Not commissioned; externally peer reviewed.

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