Effects of electroacupuncture on the BIS and anxiety in anxious volunteers:
a prospective, randomized, blinded study

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ABSTRACT

Introduction Acupuncture is a low-risk intervention that is increasingly used. Some studies examined the potential clinical effects of acupuncture on anxiety and the bispectral index of the EEG (BIS), used as an objective and indirect measure of anxiolysis. Those studies used the same acupuncture point and achieved conflicting results.

Methods Anxious subjects were recruited for a prospective, controlled and crossover study with random group allocation. Acupuncture was performed on different sessions at the experimental point He7 (Heart 7) and at a control point Lu 9 (Lung 9). Participants were asked to fill an anxiety visual analog scale (VAS) before and after the acupuncture procedure. BIS was evaluated at 3 different stages, (1) rest state (10 min.) (2) during electro-acupuncture (20min.) (3) post acupuncture (5 min.).

Results Acupuncture significantly decreased self-assessed anxiety levels both on the control and the experimental group (p=0.002 and p=0.001); however, there was no difference between the groups. Acupuncture on He7 did not show a significant decrease in BIS values compared to the rest state (89.7 ± 5.0 to 86.5 ± 7.2; p>0.05). However, acupuncture on He7 was related to a significant decrease in BIS values as compared to acupuncture on Lu9 (means: 90.7 ± 4.3 to 86.5 ± 7.2; p=0.009. Minimum BIS was also significantly lower for He7 (80.6 ± 9.6 to 71.9 ± 12.3; p=0.011).

Discussion and Conclusions Acupuncture on He7 was superior over acupuncture on Lu9 to decrease BIS values in anxious volunteers but it didn’t show to decrease BIS compared to the rest state, possibly due to a high standard deviation. Self-perceived anxiety decreased with acupuncture on both acupuncture points. However acupuncture on He7 was not superior to acupuncture on Lu9 in decreasing anxiety VAS scores. Our study found that He7 is another possible point for assessing acupuncture effects on anxiety.

KEYWORDS: acupuncture, bispectral index of the EEG, electro-acupuncture, anxiety

INTRODUCTION

Acupuncture is increasingly used in western countries. In France 21% of the population experienced acupuncture (Fisher, et al., 1994) (Barnes, et al., 2004) and 20% of medical doctors in United States and United Kingdom recommended acupuncture to their patients (White, et al., 1997).

Acupuncture can be defined as the insertion of one or more needles on specific points on the body’s surface with therapeutic means and originally a part of Traditional Chinese Medicine (TCM) (Nasir, 2002). Acupuncture points can be stimulated by electrical current, heat, pressure, laser light (Whittaker, 2004) and shockwaves (Everke, 2005). Acupuncture has the advantages of safety and low side effects. Severe side effects occur rarely and are associated with traumatic injury of internal organs (pneumo-
rach and cardiac tamponade) and hepatitis C virus and HIV infection (Ernst, et al., 1997). Several large prospective studies have shown that such severe side effects are extremely rare (White, et al., 2001). It was also demonstrated that mild and transient side effects such as pain secondary to needle insertion and bleeding occurred in 7-11% of all cases (Birch, et al., 2004).

In 1997, the USA National Institute of Health, declared that acupuncture had proven benefits for several medical conditions (NIH Consensus Statement Online, 1997) and a review by the World Health Organization in 2003 concluded that acupuncture is efficient in 28 medical conditions (World Health Organization, 2003). This document has been criticised as being too optimistic and not sufficiently supported by scientific evidence. Some authors claim that acupuncture is effective in a myriad of medical conditions while others claim the opposite. According to Ernst, the evidence from systematic reviews invalidates both perspectives (Ernst, 2006) as none of them takes in account the totality of scientific knowledge. Moreover there still is a complex issue: the difficulty in implementing an efficient double-blinded method to perform well designed controlled studies.

The EEG is used to assess cerebral function, namely in relation to central nervous system physiologic alterations (sleep) and disease. It is also used to assess the effect of drugs on the brain. Due to the complexity of the EEG signal, processed indexes derived from the EEG have been introduced in order to allow clinicians an easier evaluation of cortical electrical activity. The Bispectral Index of the EEG (BIS) is the most widely used of such indexes. In 2004, the FDA approved the BIS for reducing the incidence of intra-operative awareness during general surgery (Joahansen, 2000). Bispectral analysis employs statistical equations to study phenomena with nonlinear character, representing a different description of the EEG, and it predominantly quantifies the coherence of different frequencies in the EEG (Joahansen, 2000).

The BIS algorithm uses a complex formula that combines several EEG variables into a single index of hypnotic level with advanced artefact rejection techniques to define a dimensionless BIS value from 0 (isoelectric EEG) to 100 (alert and oriented) that is relatively independent of hypnotic agent (Joahansen, 2000). BIS monitoring is moving out of the operating room and ICU into hands of practitioners using conscious sedation in a variety of locations (Morse, et al., 2002) (Overly, et al., 2005) (Miner, et al., 2003) (Bell, et al., 2004) (Motas, et al., 2004) (Matsuzaki, et al., 2004) (Coimbra, et al., 2003).

Our aim was to evaluate acupuncture point He7 (Heart 7) commonly used for treating anxiety and its possible impact in decreasing subjective anxiety and the Bispectral Index (BIS) in anxious volunteers, compared to Lu9 (Lung 9), a neutral point, normally not used for anxiety. Almost all previ-
ous studies focused on extra-1 acupuncture point over subjective anxiety and BIS values but no published experiment had ever tested He7 acupuncture point isolated, although many practitioners use this point frequently in their practice to treat anxiety. A recent animal experiment showed that acupuncture on He7 but not on S36 (Stomach 36) decreased anxious behaviour in anxious rats (Park, 2005).

In the current experiment we hypothesized that electro-acupuncture on H7 could decrease subjective anxiety and BIS values comparatively to acupuncture on L9 in anxious subjects.

MATERIAL AND METHODS

Subjects
Participants were recruited among students present in the premises of the University by mid afternoon. Potential participants were asked to fill a questionnaire to assess whether they were in a state of anxiety. Inclusion criteria were: age between 18 and 40; being in a state of anxiety. Anxiety was assessed by a version of Zung Anxiety Rating Scale gauged for the Portuguese population (Serra, et al., 1982) and defined as a score above 37 (strong suspicion of being anxious).

All the participants gave their written informed consent. Exclusion criteria were: cardiac, respiratory, neurological or psychiatric disease; pregnancy or lactancy; anticoagulant medication, psychopharmaceuticals or regular use of dietetic supplements; smoking more than 10 cigarettes/day; having had a meal or coffee less than 1 hour previously; having ever been acupunctured and having needles’ phobia.

Before the experimental procedure, selected subjects filled in a questionnaire to assess biometric parameters and their expectations about acupuncture.

Study Design

Nineteen subjects were enrolled in this prospective, crossover experiment. The procedure was briefly outlined and a four-lead BIS sensor (X4 sensor from ASPECT Medical provided by the manufacturer for this study) was placed on the forehead. Blood pressure and heart rate were also evaluated. Headphones were placed and nonmonotonous solo instrument music was played along the procedure so that environmental sounds would be smoothed but sleep was not facilitated. From then on any contact with the participants was made via a microphone connected to the headphones. Subjects were asked to answer (yes or no) to any question made during the procedure by moving the head. They were asked to keep their eyes closed and to lie still.

The experimental procedure was composed of 3 parts: (1) the stabilization period, corresponding to the first 10 minutes, so that a baseline could be established for posterior comparisons; (2) the acupuncture period, when a needle was inserted in the control or the experimental point and stimulated by electrical current during 20 minutes (3) the
post-acupuncture period, when the electrical current was switched off and the recordings continued for 5 minutes more.

Subjects were assessed their level of anxiety by means of a visual analog scale (VAS) with maximum serenity on one extreme and maximum anxiety on the other (corresponding to a 0 and 10 score, respectively); this evaluation was performed twice: right before the experimental procedure and at the end. After the acupuncture session, participants filled a questionnaire about biometric parameters, and stated their perception of whether the control or experimental point was used and also if he/she had fall asleep. At least 1 week later, the subjects returned to repeat the procedure but this time on the experimental point or on the control acupuncture point, whether acupuncture was applied on the control or on the experimental point in the previous session. In order to ensure participants commitment for the 2 sessions a monetary incentive was offered.

**Acupuncture**

Acupuncture was performed by post-graduates in Traditional Chinese Medicine at the Biomedical Sciences Institute Abel Salazar – University of Porto (ICBAS-UP), Portugal. They all had an education session about He7 and Lu9 location and needle insertion technique with Henry J. Greten, M.D., DGTCM Chairman (Deutsche Gesellschaft für Traditionelle Chinesische Medizin) and the TCM Post-graduation Chairman at ICBAS-UP.

He7 was the experimental point and is located on the wrist crease, in the medial side, in a small depression just lateral to the pisiform bone. Lu9, the control point, thought to have a neutral action on anxiety, is located also in the wrist crease, laterally to the radial artery. The EA was applied unilaterally.

Acupuncture stimulation was performed with electrical current (electro-acupuncture). Electro-acupuncture (EA) was chosen for 3 reasons mainly: first, it is measurable and reproducible; second, it has been shown to produce a stronger effect than manual acupuncture although for other purposes (Ulett, et al., 1998); also, it allows a continuous and stable stimulation for any period of time.

The decision on what point to acupuncture first, the control point or the experimental point, was randomly made by the acupuncturist by coin flip. The selected point was then registered using an alphabetical code, so that all other investigators who analyzed the data did not know to which group (control or experimental) it corresponded. Only after the end of the entire study did the acupuncturists reveal the codification key. The acupuncturist and the researcher controlling data capture were separated by a screen, so that the acupuncturist could not see the BIS values and the staff person collecting the data could not see which point was being acupunctured.

A device was created to effectively apply the stimulation only to the point being ana-
lyzed (Fig. I). Once the device was in place, EA with continuous waves, 2Hz and 10-50mA was started and the subject was asked to tell when an electrical sensation was felt. From then on, each 5 minutes, the acupuncturist increased the current slightly. Stainless needles were used, 0,25mmx25mm and the EA device was the Multi-Purpose Health Device, KWD-808. Electrical current frequency and intensity were calibrated with a multimeter Meterman 37XR(True RMS).

Data collection
BIS values were assessed using a Model A-2000™ (Aspect Medical Systems, Inc., Natick, MA) 4.0 software version. BIS data was captured and synchronized each 5 seconds through ASYS (Bressan, et al., 2008) (Anesthesia Synchronization Software) and automatically registered in an Excel file.

Blood pressure was assessed twice, one 5 minutes after the start of the experiment and the other at the end of the Pos-Acupuncture period. Heart rate was assessed each 2 minutes. Both heart rate and blood pressure were manually registered.

Statistical Analysis
Data are presented as mean ± standard deviation. Intra-session and inter-session group comparisons were done with the Wilcoxon signed-rank test. P<0,05 was assumed as significant.

RESULTS
For BIS analysis, 3 time frames were considered. First, the basal status was defined as the 5 minutes that preceded acupuncture; second, acupuncture period corresponded to the total electro-acupuncture time less the 2 initial minutes (18 minutes) as needle insertion distorts the BIS pattern; third, the 5 minutes measurements after electrical-current was switched off was considered to be the post-acupuncture period. Nineteen subjects were recruited for the study but 4 were eliminated due to BIS data acquisition abnormalities. From the 15 subjects under analysis, 10 were female and 5 were male; mean BMI was 21,1 ± 2,1, mean age was 21,6 ± 2,4 and mean Zung’s Anxiety Rating Scale score was 41 ± 4,7; all were Caucasian.

We did not find significant correlation between acupuncture expectations, Zung’s scale score and self-perceived group allocation compared to BIS variables. Also, blood pressure and heart rate changes had
no correlation with self-perceived anxiety or BIS values.

BIS missing values were replaced using a linear interpolation method.

For the effects of acupuncture on the BIS and anxiety VAS, the within analysis refers to comparisons between the acupuncture period and the rest state; the between analysis refers to comparisons of acupuncture period on the experimental point over acupuncture period on the control point, so that we could compare if there was a significant difference of acupuncture on He7 over acupuncture on Lu9. Basically, within analysis refers to an intra-session analysis and between to an inter-session analysis.

Anxiety VAS scores were significantly lower in both groups after acupuncture (table 1). However, no significant difference was found between acupuncture on He7 and Lu9, represented as the percent decrease in VAS scores after acupuncture compared to VAS before acupuncture between groups.

For BIS, the within analysis showed no significant differences, comparing the acupuncture with the rest state on both the experimental and the control group. Also, there was no significant relation when comparing BIS in the post acupuncture period and the rest state (table 2).

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**Table 1 - VAS Comparison within groups**

<table>
<thead>
<tr>
<th>Before A vs After A</th>
<th>Before B vs After B</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.83 ± 2.01</td>
<td>3.60 ± 1.89</td>
</tr>
<tr>
<td>2.32 ± 1.62</td>
<td>1.79 ± 1.37</td>
</tr>
<tr>
<td><strong>p=0.002</strong></td>
<td><strong>p=0.001</strong></td>
</tr>
</tbody>
</table>

**VAS between groups B and A**

| -39.9% ± 27.5 | -40.5% ± 59.8 |
| **p=0.05**    |              |

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**Table 2 – BIS Comparison within group**

<table>
<thead>
<tr>
<th>Rest A vs Acup A</th>
<th>Rest B vs Acup B</th>
<th>Rest B vs PosAcup B</th>
</tr>
</thead>
<tbody>
<tr>
<td>89.3 ± 5.6</td>
<td>90.7 ± 4.3</td>
<td>89.7 ± 5.0</td>
</tr>
<tr>
<td><strong>p=0.05</strong></td>
<td><strong>p=0.05</strong></td>
<td><strong>p=0.005</strong></td>
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</table>

Between analysis showed a significant decrease of BIS values during acupuncture on the experimental point (He7) compared to the control point (Lu9), but this difference was lost during the 5 minutes after current was switched off (post-acupuncture period). A corrected between analysis was performed so that before BIS averages were compared between control and experimental groups, corrected to the respective rest state. The corrected between analysis also showed a significant decrease upon acupuncture on He7 compared to acupuncture on Lu9, (table 3). BIS minimum values were identified and compared between the experimental and the control groups: significantly lower BIS minimum values were found with acupuncture on He7 in comparison to acupuncture on Lu9 (table3).

**Table 3 – BIS Comparison between group**

<table>
<thead>
<tr>
<th>Acup A vs Acup B</th>
<th>Acup A - PreAcup A vs Acup B - PreAcup B*</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.7 ± 4.3</td>
<td>86.5 ± 7.2</td>
</tr>
<tr>
<td><strong>p=0.009</strong></td>
<td><strong>p=0.011</strong></td>
</tr>
<tr>
<td>80.6 ± 9.59*</td>
<td>71.9 ± 12.3*</td>
</tr>
<tr>
<td><strong>p=0.011</strong></td>
<td></td>
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*Minimum BIS values means

The average BIS and the minimum BIS for each subject for acupuncture on He7 and Lu9 were evaluated. Although there was a significant decrease in overall average BIS,
when comparing for the same subject acupuncture in the control point and the experimental point, this effect was not consistent in all subjects as in 10 acupuncture on He7 lowered BIS comparatively to Lu9, in 4 it was similar and in 1 case the opposite occurred; as for minimum BIS for each subject something similar happened, as in 10 acupuncture on He7 caused lower minimum BIS, in 3 it was similar and in 2 the opposite occurred (Figures II and III).

Figure II – Individual BIS means for the control (lozenges) and acupuncture group (squares). The x axis represents the subject’s code number and the y axis the BIS.

Graph III – Individual BIS minimums for the control (lozenges) and acupuncture group (squares). The x axis represents the subject’s code number and the y axis the BIS.

The DISCUSSION

Our study focused on anxious subjects in order to assess a clinically relevant population.

After a careful analysis of the studies on acupuncture, BIS and anxiety we tried to improve some methodological issues in terms of objectivity and reproducibility.

Since manual acupuncture and acupressure are difficult in terms of standardization of frequency and pressure amount during a period of time we chose to use electro-acupuncture, which can be applied with a certain frequency and current intensity that can be easily reproduced by others and minimizes acupuncturists possible bias. In order to be able to precisely apply the current to the desired acupuncture point we built and used a simple device in which a copper ring is placed around the needle and electrodes were connected to both, inducing current flow in the direction of the acupunctur...
ture point. Previous studies used manual recording of BIS; since BIS is updated every second and variability is present, we performed BIS data acquisition and synchronization from the BIS monitor using a new software (ASYS) that we helped develop, which allowed automatic recording of BIS values every 5 seconds during the entire procedure.

A crossover design was implemented to eliminate inter-individual variability when comparing control point versus the experimental point, also representing a methodological improvement in comparison to previous studies.

Although control and experimental points significantly decreased self-perceived anxiety, acupuncture on He7 didn’t show superior benefit over acupuncture on Lu9. This fact may be interpreted as proof that acupuncture in itself may lower anxiety levels, but that stimulation of a point specific for anxiety (He7), as a demonstrable and measurable cerebral effect. The BIS levels achieved with stimulation of He7 are the values observed when pharmacological sedation is performed.

Because of difficulties in assessing anxiety levels in individuals and due to many possible bias and confounding variables when performing anxiety tests, we evaluated the BIS as it is being increasingly used as an indirect measure of anxiety levels and sedative interventions, in which anxiolysis corresponds to a milder form of sedation. BIS absolute means and minimums means were significantly reduced by acupuncture on He7 compared to acupuncture on Lu9. In the meanwhile, none of the acupuncture groups showed a significant decrease in BIS means when comparing the acupuncture period to the rest state. However it should be noted that acupuncture on He7 was related to a relevant (but non-significant) decrease in BIS means compared to the rest state but with a high standard deviation. A larger sample could possibly have shown a statistical significant difference.

Another interesting finding was that acupuncture on He7 did not produce consistent effects on all the individuals, showing a variable response between subjects to acupuncture.

Immediately after electrical current was switched off and BIS values were recorded for 5 more minutes, the post-acupuncture period, the BIS normalized to values similar to the rest state, showing that the decrease of BIS values with acupuncture on He7 compared to acupuncture on Lu9 dissipated after the current was switched off.

Regarding possible mechanisms that underlie the effect of He7 acupuncture on anxiety and BIS, current research is very insufficient to give a satisfactory answer. Most of the research on acupuncture focused on analgesic properties and underlying mechanisms, consistently showing that endorphins play an essential role in mediating the analgesic effect of acupuncture and electro-acupuncture (Han, 2004). In the meanwhile,
previous studies showed that the effect of extra-1 point acupuncture on BIS and subjective anxiety was not related to a change in β-endorphin and melatonin plasma levels (Fassoulaki, et al., 2007). Consistent with this findings is preliminary evidence demonstrating that remifentanil, an opioid, even at large doses, produced no modification of BIS (Hans, et al., 2000) (Guignard, et al., 2000)(Koitabashi, et al., 2002). The only experiment addressing the effects of acupuncture on He7 was performed in maternally separated rats, a model for anxiety studies in rats, showed a decrease in anxious behaviour and a correspondent increase in the expression of neuropeptide Y in the basolateral amygdale, compared to acupuncture on S36 (stomach 36). Those findings suggested that acupuncture treatment might reduce anxiety-like behaviour in adult rats following maternal separation by modulating the NPY system in the amygdale (Park, 2005).

Furthermore, stimulation frequency is a determinant factor in electro-acupuncture as different frequencies correlate with different neurotransmitters and hormones secretion (Han, 2003)(Iverfeldt, 1989)(He, et al., 1990)(Racke, 1989)(Frank, 1993). In conclusion, our results demonstrate that low-frequency electro-acupuncture on He7 significantly, decreased the Bispectral Index of the EEG (BIS) when compared to acupuncture on Lu9 Acupuncture on He7 was related to a larger BIS mean variation (90.7 ± 4.3 to 86.5 ± 7.2) than did a 10mg single dose of diazepam (96.1±1.8 to 93.5±3.5) compared to control groups (Hirota, et al., 1999)

LIMITATIONS AND FUTURE PERSPECTIVES

Acupuncture on He7 can be of therapeutical usefulness in the future, constituting an alternative or complement to current anxiolytic therapies. Moreover acupuncture is a very low risk technique with minimal interactions, making it suitable to be used in almost any patient and it is a low cost intervention. In the meanwhile, further research is needed, to evaluate it’s efficacy in different and larger samples as well as to clarify the underlying mechanisms (Birch, et al., 2004). It could also be interesting to study the effects of He7 acupuncture compared to a conventional therapy like an anxiolytic drug on the BIS and subjective anxiety perception.

Acupuncturist blinding difficulties remains a major methodological concern and a possible source of significant bias. The current study, although patient blinded and researchers blinded, didn’t eliminate this factor as well as almost all other acupuncture studies in humans. Also, the sample size was small and further studies could address this issue on a bigger sample as well as assessing variable responses between individuals to acupuncture and the underlying causes.
AKNOWLEDGEMENTS

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