Introduction

Two of the greatest problems encountered in acupuncture research relate to difficulties choosing appropriate controls, and uncertainties about the stimulation strength of different acupuncture techniques. ‘Sham’ points or minimally invasive techniques are often used as controls in randomised controlled trials (RCTs), yet it is accepted that both suffer inherent problems, not the least of which being the assumption that they have no, or at least minimal, effect. It is recognised that sham points may have a physiological effect, may induce subjective needling sensation (de qi), and may produce an overt clinical outcome. Araujo concludes that ‘sham’ acupuncture appears almost as active as ‘real’ acupuncture.

Methods

Sixty nine healthy subjects (age range 18-56 years, mean 29.9; 48 females) completed the study, which employed a counterbalanced experimental design with two stimulation sessions of LI4 approximately one week apart. One half of the participants received point injection first, and the other half received traditional acupuncture first. Baseline physiological data were recorded, then measurements were made before, during and after stimulation; each subject also reported needle sensation (de qi). The measures were heart rate, derived pressure rate product and mean arterial pressure.

Results

Although stronger sensations of de qi were reported with point injection, no significant differences were found for mean heart rate (HR), pressure rate product (PRP) and mean arterial pressure (MAP) before and after stimulation by the two techniques. No subject gender or age bias was encountered and previous exposure to acupuncture had no effect on outcome. Power spectral analysis of heart rate variability (HRV) made on data from a small subset (n=10) of this cohort also showed no significant differences in autonomic response.

Conclusion

Point injection and traditional acupuncture seem to provoke similar physiological responses, although the greater needle sensation seen with point injection might indicate it could have more powerful clinical effects. Further studies of repeated point injection are necessary to indicate whether this technique may provide a method of increased strength of point stimulation, as an alternative to traditional needling in acupuncture research.

Keywords

Acupuncture, point injection, physiology, heart rate, mean arterial pressure, de qi.
effects. Vincent concludes that the results of RCTs using sham points as controls only show the difference between sham and real acupuncture, not the real effect of acupuncture. In light of this, the conclusion reached by Ryan that acupuncture researchers should cease using sham acupuncture as a control in trials seems valid. Even the newer Streitberger placebo needle has been demonstrated to have shortcomings. Minimal acupuncture is designed to produce just that - minimal effect. Yet, this method may also produce distinct subjective and objective effects, as noted by White et al. Marcus postulates that the effect of acupuncture is the result of several factors that are operative during, and very shortly after, the initial skin penetration: 1) manipulation for longer than five seconds does not appear to increase stimulus strength since the initial tissue damage caused by skin penetration leads to the release of inflammatory mediators that sensitize local nerve endings; 2) the acupuncture effect is a direct result of a cone of tissue damage proportional to the depth of needling and the diameter of the needle, this damage regulating the dose of inflammatory mediators released; 3) the needle may also cause direct nerve and muscle stimulation. Skin penetration also induces microcurrents that may have a local effect. These latter two mechanisms occur during the initial penetration and settle quickly thereafter.

Acupuncture point injection (PI) of a small amount of a drug, vitamin, saline, or plant extract is a recent innovation of traditional acupuncture that aims to enhance and prolong the effect of stimulation of acupuncture points. One suggested advantage of this technique is that it offers the opportunity to standardise and replicate treatment, which is difficult to achieve with classic acupuncture. PI is well documented, and many standard texts contain references to the use of PI. A PubMed search of ‘acupuncture AND point injection’ produced more than 100 references, the earliest reporting the treatment of acute appendicitis by distilled water injection to an acupuncture point having been published in Chinese in 1960. Belitskaya et al concluded that the clinical response to PI was due to the specificity of acupuncture stimulation by the introduction of fluid, and not the composition of the fluid itself. Yang and colleagues demonstrated that PI to PC6 (Neiguan) controlled post surgical vomiting, and thus lent support to the suggestion that PI is simple, convenient, timesaving and effective. We suggest that PI offers the opportunity to titrate the dose of saline injected into an acupuncture point, thus increasing the stimulus in a controlled and measurable manner. Identifying a dose response curve for acupuncture could be an alternative strategy to comparing acupuncture with ‘placebo’ in the demonstration of biological effects of acupuncture. One aim of this study, therefore, was to explore the effects of titrated injections.

To date, the physiological effects of PI have not been compared with those of traditional acupuncture (TA). A comparison of the effects of two methods applied at the same acupuncture point is a first step in investigating PI and validating the technique for clinical use. Previous studies of the physiological response to acupuncture have used, in part, heart rate (HR) and non-invasive (measurement of) blood pressure (NIBP).

Others have used invasive measures such as microelectrode implant in muscle or repeated blood sampling. Ballegaard also used the derived pressure rate product (PRP) as an outcome measure of cardiac workload, which Wright et al had demonstrated to be a sensitive assessment for even small cardiac workloads. The main aim of this study, therefore, was to compare the physiological responses to PI and TA, using non-invasive measures (HR, MAP, and PRP) along with self reported sensation of de qi, to facilitate a comparison with published data.

Methods

Volunteers

An initial sample size calculation determined that we would need a minimum of 63 subjects (assuming a 50% difference between groups, with a power of 0.8, and 95% confidence level). With the approval of the Human Research Ethics Committees of the University of Queensland (UQ) and Australian College of Natural Medicine (ACNM), 75 healthy subjects were initially recruited. Healthy subjects were chosen, as this was a laboratory study and not a clinical trial. All gave written informed consent. None had a history of psychiatric or neurological disorders or head trauma with loss of consciousness. Sixty nine (48 female) aged between 18 and 56 (mean 29.9) completed the study. Of these, 59 had experienced acupuncture previously (they were either
students or faculty in acupuncture school) and 10 were naïve to acupuncture.

**Procedure**

A counterbalanced experimental design was employed to avoid order effects. Volunteers were randomly assigned to one of two groups, the first group received TA in the first session and PI in the second, this being reversed for the second group. Sessions were scheduled one week apart to allow for washout of any effects. Prior to enrolment in the study, personal details were collected. Physiologic data (resting HR, NIBP, and respiration rate) were obtained before entering the laboratory. These parameters, as well as peripheral oxygen saturation (SpO2) were then measured 10 minutes before and 10 minutes after point stimulation. During the intervention, these parameters were measured continuously at 2.5 second intervals. After each session, volunteers scored their experience of the stimulation (pain on insertion, pain at needle site, *de qi*, and any unpleasant feeling) on an 11-point numerical scale, where 0 signified no noticeable sensation and 10 signified maximum tolerable sensation. *De qi* was defined as any one of numbness, heaviness, distension, soreness at the point, spreading away from the point with time, or other sensation that the subject may have related to the acupuncture point stimulation.

The laboratory was controlled for temperature and humidity and each session was conducted at approximately the same time of day and week for each volunteer. During each session, the volunteer rested comfortably on a standard treatment couch facing away from the investigator and monitoring apparatus.

**Stimulation**

The acupuncture point LI4 (*Hegu*), situated on the dorsum of the left hand between the first and second metacarpals at the midpoint of the second metacarpal bone close to its radial border, was chosen for this study. Being easy to identify and having only pregnancy or possible pregnancy as its only described traditional contraindication, it is one of the most commonly studied points. As this study was intended to compare two methods of acupuncture point stimulation, it was appropriate to use only one acupuncture point and not use a control point. An acupuncturist with 30 years’ experience in traditional needling techniques and four years’ experience in PI (MWS) performed all stimulations. The selected needle – either a solid 0.35 x 13mm sterile, single use needle (Cathay Herbal Laboratories, Sydney, 2010, Australia) for TA or a hollow 0.50 x 16mm sterile, single use hypodermic needle (Terumo Corp, Elkton, MD, 21921, USA) for PI – was inserted to a depth of 13mm.

At 30 seconds after needle insertion, LI4 was stimulated for one second by needle rotation at 3Hz (TA intervention) or by infusion of 0.5ml normal physiological saline (PI intervention) repeated at 30 second intervals for five stimulation periods, a total intervention time of 180 seconds (see Figure 1). A purpose built, computer controlled syringe driver (Figure 2) was used to perform precise saline infusion; the fluid delivery line was connected by 3 way tap to a Baxter Uniflow pressure transducer (Baxter Healthcare Corp, Irvine, CA) allowing measurement and recording of intra acupuncture point pressure at 2.5 second intervals, simultaneously with the HR and SpO2 recordings. The instrumentation has been previously reported.

**Heart rate variability (HRV)**

Towards the end of the study, a recording electrocardiograph (PowerLab 5, ADInstruments Pty Ltd) became available. During both intervention sessions, a subset (n=10) of the enrolled cohort underwent continuous electrocardiograph (ECG) recording from limb leads (I, II, or III) for later analysis of HRV, with the aim of monitoring any modulation of the autonomic nervous system (ANS) activity resulting from acupuncture stimulation.

**Statistical analysis**

Data were analysed with SPSS (Macintosh Version 11.0.4, SPSS Inc). Using paired samples *t* tests at a significance level of 0.05 to determine any significant differences between the baseline and endpoint of the experiment, comparative analyses were made of self reported *de qi* sensation, MAP, HR, and derived PRP, all measured before and after stimulation. Repeated measures ANOVA of peak pressure recordings was made to determine any differences in acupuncture point pressure from injection to injection. ECG recordings were analysed in Chart 5 with HRV extension (ADInstruments Pty Ltd) and the computed
low frequency (LF) and high frequency (HF) components (expressed in normalised units) and LF/HF ratio were imported to SPSS for analysis of any differences of the mean by paired samples t test.

Results
Of the original 75 volunteers enrolled, five were unable to complete the second session within the one week timeframe and a sixth experienced anxiety during the first session and withdrew, leaving 69 to complete the study. Separate analysis of the acupuncture naïve group demonstrated no differences when compared with the group that had prior acupuncture experience. In addition, there were no significant differences between the male and female subjects, nor were there any age related differences. Therefore data from all participants were analysed together. Data are presented as means and standard deviations, and P values of the paired samples t tests are reported, where appropriate.

Table 1 presents the results of self reported subjective data. In general, there were significant differences in the in situ needle sensation (P<0.001), de qi (P<0.001) and unpleasantness during experiment (P<0.001) with subjects reporting that TA provided a lower intensity in all three sensations.

Figure 1 The trial protocol is shown: baseline measurements were taken 20 minutes before needle insertion, with the subject settled comfortably on couch. Endpoint measurements were taken 10 minutes after removal of needle and before the participant left the laboratory.

Figure 2 This is a schematic view of the basic layout of the saline delivery system: the trigger can be provided by any mechanism delivering a 1V peak to peak signal. For this study, manual triggering was used with activation of the system occurring 30 seconds after needle insertion.
Table 1  Difference in sensation reported after TA and PI (n=69)

<table>
<thead>
<tr>
<th>Sensation</th>
<th>TA</th>
<th>PI</th>
<th>t*</th>
<th>P (two tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on needle insertion</td>
<td>3.22</td>
<td>3.49</td>
<td>0.89</td>
<td>0.38</td>
</tr>
<tr>
<td>Pain at needle site during the scan</td>
<td>3.13</td>
<td>5.13</td>
<td>5.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>De qi (numbness, heaviness, distension, soreness, spreading away)</td>
<td>3.39</td>
<td>5.58</td>
<td>5.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unpleasantness</td>
<td>2.10</td>
<td>3.77</td>
<td>4.96</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD) scores on a 0-10 numerical scale; TA – traditional acupuncture; PI – point injection
*Paired t test

Table 2  Physiological variables before and after TA and PI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-stimulation TA</th>
<th>Post-stimulation TA</th>
<th>Pre-stimulation PI</th>
<th>Post-stimulation PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>110.04 (10.91)</td>
<td>112.28 (10.26)</td>
<td>110.61 (10.43)</td>
<td>112.58 (11.00)</td>
</tr>
<tr>
<td>DBP</td>
<td>63.75 (7.67)</td>
<td>67.49 (8.91)</td>
<td>63.51 (7.62)</td>
<td>65.81 (7.66)</td>
</tr>
<tr>
<td>MAP</td>
<td>79.25 (7.62)</td>
<td>82.49 (7.95)</td>
<td>79.25 (7.65)</td>
<td>81.42 (7.95)</td>
</tr>
<tr>
<td>HR</td>
<td>67.62 (10.75)</td>
<td>67.57 (10.33)</td>
<td>68.20 (11.24)</td>
<td>67.57 (9.66)</td>
</tr>
<tr>
<td>PRP</td>
<td>7.48 (1.59)</td>
<td>7.63 (1.61)</td>
<td>7.56 (1.57)</td>
<td>7.62 (1.43)</td>
</tr>
<tr>
<td>SpO2</td>
<td>97.67 (1.64)</td>
<td>97.94 (1.47)</td>
<td>97.29 (1.76)</td>
<td>97.75 (1.61)</td>
</tr>
</tbody>
</table>

All values are means (SD); SBP – systolic blood pressure (mmHg); DBP – diastolic blood pressure (mmHg); MAP – mean arterial pressure (mmHg); HR – heart rate (beats per minute); PRP – pressure rate product; SpO2 – peripheral oxygen saturation (%)

Table 3  Comparison of pre- and post-stimulation HR and PRP

<table>
<thead>
<tr>
<th>Visit</th>
<th>Pre-stimulation</th>
<th>Post-stimulation</th>
<th>Paired difference</th>
<th>t*</th>
<th>DF</th>
<th>P (two tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>1</td>
<td>72.36 (12.42)</td>
<td>67.91 (11.48)</td>
<td>4.45</td>
<td>68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>73.16 (11.49)</td>
<td>67.56 (8.78)</td>
<td>5.61</td>
<td>68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRP</td>
<td>1</td>
<td>8.09 (1.76)</td>
<td>7.64 (1.71)</td>
<td>0.14</td>
<td>68</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8.28 (1.62)</td>
<td>7.55 (1.36)</td>
<td>0.729</td>
<td>68</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All values are means (SD); HR – heart rate (beats per minute); PRP – pressure rate product; Visit 1 = traditional acupuncture (TA); Visit 2 = point injection (PI)
*Paired samples t test

Table 4  Analysis of HRV components before and after TA and PI

<table>
<thead>
<tr>
<th>n</th>
<th>LF Before</th>
<th>TA After</th>
<th>LF Before</th>
<th>TA After</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>60.13 (14.26)</td>
<td>68.01 (13.78)</td>
<td>63.97 (16.03)</td>
<td>65.27 (16.31)</td>
</tr>
<tr>
<td>10</td>
<td>47.01 (35.05)</td>
<td>29.72 (13.11)</td>
<td>32.70 (8.66)</td>
<td>31.91 (15.11)</td>
</tr>
<tr>
<td>10</td>
<td>2.52 (2.97)</td>
<td>3.09 (2.30)</td>
<td>2.46 (1.48)</td>
<td>2.88 (2.72)</td>
</tr>
</tbody>
</table>

Values are mean (SD) normalised units (ms²); HRV – heart rate variability; TA – traditional acupuncture; PI – point injection; LF – Low frequency (0.04-0.15Hz); HF – High frequency (0.15-0.4Hz)
Note: normal values (in normalised units) for the LF and HF spectral components of HRV are given as: LF 54±4 ms², HF 29±3 ms²; LF being seen as a measure of sympathetic tone while HF reflects parasympathetic tone and fluctuations caused by spontaneous respiration. The LF/HF ratio (normal range 1.5-2.0) is used to indicate balance between sympathetic and parasympathetic tone, 25 with a decrease in the score being a possible indication of either an increase in parasympathetic or decrease in sympathetic tone.
There was no significant difference between TA and PI (P=0.38) for the sensation associated with needle insertion.

Results for the physiological variables are presented in Table 2. No significant differences that could be related to the method of acupuncture stimulation were demonstrated. Although SpO\textsubscript{2} was measured throughout, there was no change from measurement to measurement.

Repeated measures ANOVA was conducted comparing the peak pressures recorded at LI4 from each of the five injections, and the results are shown in Table 3 as mean and standard deviation. Data were also plotted, as shown in Figure 3. Although the mean peak pressure steadily increases with each injection, statistical analysis does not show any significant differences.

For the subset of 10 volunteers in which HRV analysis could be undertaken, the low frequency (LF) and high frequency (HF) components of power spectral analysis (PSA) are presented in Table 4 as in normalised units, along with the ratio of LF/HF. Comparative analyses using paired samples \textit{t} tests at a significance level of 0.05 demonstrate no significant difference in autonomic response after stimulation either within or between methods.

\textbf{Discussion}

As suggested by Marcus and by Pomeranz, it seems reasonable to postulate that one main acupuncture effect is brought about by the initial skin penetration.\textsuperscript{8,9}

This causes both local tissue damage leading to release of inflammatory mediators and also may initiate a microcurrent that causes changes to cell membrane function and set off afferent impulses from local nerve endings. The initial effect is likely to be proportional to both the needle diameter and the depth of penetration, and further manual stimulation beyond this seems unlikely to produce greater effects.

A number of functional imaging studies have demonstrated the effects of acupuncture in the CNS, but the reports do not mention whether these effects are the result of the initial stimulation or are a cumulative effect of repeated stimulations.\textsuperscript{2,26-30} Using acupuncture point injection, once the initial needle response has subsided, incremental stimulation should produce parallel response differentials. Therefore, simply changing the research technique may address many of the current concerns surrounding controls for acupuncture research. Additionally, comparing the physiological effects of PI against TA would be a first step in investigating the mode of action of PI and its validation as a clinical tool.
Papers

For this correlational study of differing acupuncture methods, a single point (LI4, Hegu) was chosen for several reasons: 1) point location is easy and reproducible; 2) Hegu has an excellent research track record; and 3) it is relatively safe to use. Healthy subjects were chosen in line with previously reported research protocols.

Although there were some differences between needles used – Terumo hypodermic needles having a low friction coating not obtainable with similarly sized acupuncture needles – we considered this might have little effect on de qi. As no difference in skin erythema was observed between sessions, our conclusion appeared to be supported. However, the needles were also of slightly differing diameters (Terumo: 0.5mm, Cathay: 0.35mm), since needles of comparable size were not commercially available.

Therefore the decision was taken to examine subjective reports of any differences in needling sensations as part of the study. It was noted that sensations of de qi and unpleasantness were greater with the hypodermic needle, an outcome that might be related to the larger diameter or the cutting edge. To test this relationship further would require the manufacture of 0.5mm diameter acupuncture needles at a cost beyond the scope of this study.

HR and NIBP are two of the most commonly used physiological markers of acupuncture effect; although we considered derived PRP a more sensitive measure of physiological response. A comparison of these data provided no significant differences that could be related to the differing methods of acupuncture stimulation. Examining changes in autonomic response with power spectral analysis of HRV or non-linear measures (such as Poincaré plots) may improve the statistical value of the physiologic data. Although apparatus for measuring HRV only became available towards the end of the data collecting period, we used HRV to examine whether this would provide further data to address our hypotheses. Analysis of HRV in a small cohort of volunteers likewise provided no demonstrable difference in autonomic response, although this must be interpreted with considerable caution as the sample size was small and the time between final stimulation and final ECG recording was only 10 minutes. Interestingly, the stress induced increase in ANS activity that may have been anticipated was not noted. A previous study has considered the usefulness and limitations of HRV analysis in neuroimaging using PI as the method of acupuncture point stimulation.

The one significant difference between PI and TA appeared in the subjective response, de qi. De qi is typically described as a response to insertion and manipulation of a filiform acupuncture needle, although it has also been described in connection with electroacupuncture (EA). As there is a lack of consensus on whether de qi is necessary to produce clinical effects, it was deemed reasonable to accept de qi as an outcome measure of subjective response. Most subjects reported a more powerful stimulation response with PI. This may be an anticipatory response even though a counterbalanced design was used and every effort was made to provide exactly the same environment and stimulation at every encounter. Since de qi is claimed to relate to clinical outcome, these subjective differences may indicate that PI provides a more powerful clinical outcome; with stronger sensations being translated into a stronger clinical response, as outlined by Wang et al and Luo and Chen. Not all subjects adequately reported the quality of de qi experienced; therefore analysis of the qualitative results was not formally undertaken. The increased sensation of unpleasantness needs further exploration, as it was not adequately defined in this study. ‘Unpleasantness’ is a very broad term that includes responses to experiences or events that are not pleasing or a situation that is not pleasing. It was noted that a number of subjects had formed preconceptions of the needlestick experience that might have biased the results of this study.

Although the measured pressure at LI4 demonstrated a trend to increase from injection to injection, these changes were not statistically significant; therefore, this trend must be regarded as inconclusive and worthy of further investigation. Pressure measurement is mathematically one step removed from actual compliance; although pressure and volume were measurable, it does not follow that compliance has been measured. When interstitial fluid volume increases above control volume, the interstitial pressure curve levels off; above 150-200% of the control volume, the interstitial compliance is virtually infinite. Therefore it is possible that an incremental response occurred but could not be observed. This measure was still valuable as it can be used as an objective measure of stimulus delivery.
We accept that there are limitations to the study, and generalisable conclusions are difficult to make. Different needle diameters were, of necessity, employed. Although no subjective differences were noted, and there did not appear any differences in skin response on visual inspection, it may be possible that slight differences could have occurred. Next, the saline dose and rate were empirically determined for this study as there have been no previous studies using this methodology. Effects of different injectates and rates of injection need further investigation. We used only one form of TA needle manipulation, ie rotation, and might have obtained different results with other methods of needle manipulation. The manipulation for this investigation was chosen as it has been used in most of the previously reported neuroimaging studies, for which PI was being assessed as an alternative stimulatory model. Finally, the questionnaire for subjective sensations was not formally validated, although it was tested on randomly chosen subjects before the study, and each subject was also given the opportunity before and after the actual experiment to discuss his or her response prior to scoring, and any ambiguity was clarified.

**Conclusions**

This exploratory study was unable to detect any differences between the physiological responses of healthy volunteers to TA and PI. No subject gender or age effects were encountered and previous exposure to acupuncture had no effect on outcome. The subjective perception of *de qi* is greater with PI, as is the unpleasantness; PI may therefore produce a better outcome clinically, if it is acceptable to patients. Further research is justified into whether a titrated response can be seen on repeated injection into the same point, although no effect was seen in this study. Measurement of injection pressure could prove valuable as an objective measure of the actual delivery of the stimulus.

**Acknowledgements and Funding**

The technical assistance and ongoing advice of Dr SJ Wilson (School of Information Technology & Electrical Engineering, UQ) and Dr GI de Zubicaray (Centre for Magnetic Resonance, UQ) throughout this project is gratefully acknowledged.

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**Conflict of interest**

None declared.

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**Summary points**

- Point injection (PI) is well documented as a therapy
- Physiological parameters associated with PI were no different from those of traditional acupuncture needling (TA)
- Volunteers reported greater needle sensation with PI than TA
- PI might provide the opportunity to study dose response curves of stimulation

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