The effect of needle penetration on experimental pain in healthy subjects:

A double-blind (practitioner-patient masking) placebo-controlled study

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Competing interests

NT and Hanada College possess the US patent 6575992B1, the Canadian patent CA 2339223, the Korean patent 0478177, the Taiwan patent 150135 and the Chinese patent ZL00800894.9 (Title: Safe needle, placebo needle, and needle set for double blind) of the needles described in the manuscript. NT is a salaried employee of Hanada College and has received research funding from the college.

Authors' Contributions

NT designed the double-blind needles and the study, collected the data, performed the analysis, and wrote the manuscript. HY participated in the designing of the study, data collection and analysis, and preparation of the manuscript. NT is the guarantor.

Abstract

Background

Double-blind (practitioner-patient masking) evaluation of acupuncture treatment has not been reported. To investigate whether needle penetration has an analgesic advantage over skin pressure under double-blind placebo controlled study which has been impossible to implement.

Methods

We used a newly designed pair of double-blind non-penetrating placebo and matched penetrating needles to examine the analgesic effect of acupuncture in a crossover method with non-penetrating placebo needle, matched penetrating needle, and no-acupuncture control groups. Pain elicited by electrical stimulation applied to the posterior forearm of 56 healthy volunteers was measured on a visual analog scale (VAS) before needle application at the Large Intestine 4 point, during the 20 min needle application, and after needle removal. Skin penetration pain and the deep dull pain (*de qi*) associated with the application of the needle were measured on a VAS.

Results

Significant analgesic effects were observed immediately after the needle application in both the penetrating (p = 0.001) and non-penetrating needle (p = 0.006) groups compared to the no-acupuncture control group. The significant analgesia induced by the penetrating needle (10 min after needle removal, p = 0.026) lasted slightly longer than the non-penetrating needle (immediately after needle removal, p = 0.024). The largest mean difference in the pain intensities between the penetrating needle and no-acupuncture control groups was -8.64 (95% confidence interval [CI], -13.93 to -3.34; p < 0.001) and that between the non-penetrating needle and no-acupuncture control groups was -8.68 (95% CI, -13.97 to -3.39; p < 0.001), at just before needle removal. No significant differences were observed in analgesia between the penetrating and non-penetrating groups throughout the study. No significant correlation was found between analgesic effect and *de qi* that is considered essential in achieving successful acupuncture analgesia.

Conclusion

Needle penetration *per se* did not have any specific analgesic advantage over skin pressure.

Introduction

The practice of acupuncture and the recognition of its role as an alternative medicine therapy in pain management are both increasing steadily. However, the strongest evidence supporting the efficacy of acupuncture has been obtained using single-blind methods [1, 2]. The single-blind trials using placebo or sham needles play a significant role in this field [3-5], but they fail to meet the methodological standards for blinding studies in current medical practice [6-9]. As a result, the efficacy of acupuncture has remained controversial, even though studies of the highest possible design level have been published in leading medical journals [9]. The reason for this is that the patients might be biased towards the unmasked practitioners in single-blind trials [6-14].

Before the recent development of double-blind placebo needles (practitioner-patient masking) [15, 16], there were no procedures or placebo needles that could mask practitioners because such needles aimed at masking practitioners had been considered largely unfeasible [8, 9, 14] due to which double-blind acupuncture studies were not conducted to assess its efficacy. In this study,

therefore, we investigated acupuncture analgesia using the double-blind non-penetrating placebo and matched needles [15, 16]. The aim of this study was to obtain a plausible amount of pain relief using single needle penetration under double-blind placebo-controlled conditions.

Methods

To gather fundamental information about the analgesic effects of needle penetration and to test the practicality of the double-blind needles prior to a clinical trial, we recruited highly experienced, licensed acupuncturists and 56 eligible healthy volunteers as experimental subjects who were familiar with acupuncture treatment (mean age: 32.1 ± 9.9 years, 31 males, 25 females), from Hanada College. Resources limited the size of the sample we could use. The study was conducted in the Department of Acupuncture, Moxibustion, and Physiotherapy, Hanada College. Before the study began, the purpose and format of the study were explained and the subjects provided written informed consent. The Showa University Ethics Committee gave their approval.

The study was a crossover design to eliminate much of the between-individual variation [17] with three groups: the penetrating needle group; the non-penetrating placebo needle group; and, the no-acupuncture control group. The subjects were randomly assigned to a penetrating or a non-penetrating needle group then they received the other needle. For the no-acupuncture control group,

we measured pain intensity similarly and over the same time course but without applying the needle before the abovementioned acupuncture trials.

Pain-eliciting electrical stimulation was applied using a constant-voltage isolation unit (SEN-3301, SS-104 J; Nihon Kohden Corp. Tokyo, Japan), to the midpoint of the posterior surface of the right forearm through surface electrodes [18-22]. The strength of the painful stimulation (square wave pulse: duration, 1 ms; interval, 1 s) that produced a clear pain sensation (voltage, pain threshold × 1.1–1.2) in the individual subjects was determined prior to each experiment. The mean intensities for each of the groups were not significantly different from each other (no-acupuncture control 69.2 ± 20.4 V, penetrating needle 69.9 ± 22.0 V, and non-penetrating needle groups 70.0 ± 22.8 V) (Wilcoxon test, $p = 0.937$). Pain thresholds remained stable over time for individual subjects.

Subjects reclined on a bed in the supine position with the right hand resting by the side of the body, and the thumb and index finger uppermost. Throughout the trial, the subjects were blindfolded except when pain intensity, skin penetration pain, or *de qi* were being recorded. Each experiment was performed at about the

same time on different days. We measured pain intensity using visual analog scale (VAS) according to a previous placebo study [23].

Five minutes before needle insertion, a well-trained assistant who had little knowledge of acupuncture, delivered painful electrical stimulation (square wave pulse: duration, 1 ms; interval, 5 s) using a constant-voltage isolation unit for 1 min to give a baseline reading of pain. Immediately after the painful stimulation, the assistant showed the subject a VAS sheet, the scale ranging from 0-150, where 0 indicated no pain, and the baseline pain intensity was arbitrarily assigned 100 on the VAS. The subjects received a painful electrical stimulation for 1 min immediately following and 10 min after needle insertion, and 1 min before, immediately after, and 10-, 20-, 30-, and 40 min after needle removal. After completion of each episode of painful stimulation, the subjects rated the subjective pain intensity on the VAS, comparing it with the baseline pain intensity (100) prior to the needle being applied.

We used double-blind (practitioner-patient masking) non-penetrating placebo needles, the tip of which presses against the skin but cannot penetrate it, and

matched penetrating needles with a specified insertion depth to be used in acupuncture studies [15, 16]. The appearance and feel of the penetrating and non-penetrating needles are indistinguishable from one another (Figure 1).

Each of 56 sterilized penetrating needles (10 mm insertion depth [24]) and 56 sterilized non-penetrating needles was sealed in a small-sterilized opaque container. Containers with a penetrating needle and a non-penetrating needle were paired and each pair of containers was sealed in an opaque envelope.

The acupuncturist randomly took a container containing a penetrating or a non-penetrating needle from the envelope and applied that needle to the right LI-4 point which is the most important analgesic point [18, 19, 24] using the alternating twirling technique. After inserting the needle, the practitioner recorded whether he judged the needle to be ‘penetrating’, ‘non-penetrating’, or ‘unidentifiable.’ The subjects rated the skin penetration pain and *de qi* (the deep dull pain sensation) that has been claimed to be essential for a successful acupuncture treatment [24] on a VAS ranging from 0 (no skin penetration pain or *de qi*) to10 (the most intense skin penetration pain or *de qi*) [3]. The needle was left in place for 20

min.

Twenty minutes after the insertion of the needle, the needle body of the penetrating or the non-penetrating needle was returned to the starting position in the opaque guide tube and then the entire needle assembly was taken away from the skin and sealed in an opaque envelope by a second acupuncturist. The second acupuncturist reconfirmed the accuracy of the needle location at the LI-4 point. All possible precautions were taken to ensure that the authenticity of a needle was not revealed to the practitioner, subjects, or investigators.

The primary outcome was the pain elicited by when electrical stimulation was applied to the posterior forearm. The skin penetration pain and *de qi* associated with needle application were the secondary outcome measures.

The practitioner was asked to guess the authenticity of the needle after each needle removal. We asked each subject to state verbally anything that they noticed, however trivial, regarding the needle application after each treatment. To minimize bias, we did not inform the subjects of the possibility that non-penetrating

needles might be used [6]. The true identity of the test needles was revealed only after the results had been tabulated.

Statistics

The chi-squared (goodness-of-fit) test determined whether or not the number of correctly and incorrectly identified needles fitted a probability of 0.5. Statistical comparisons of the two groups (penetrating needle and non-penetrating needle) in relation to the VAS scores for skin penetration pain and *de qi* were made using the Wilcoxon test. Statistical comparisons were performed on the three groups (penetrating needle, non-penetrating needle, and no-acupuncture control) in relation to the VAS scores of pain intensity using a two-way repeated-measures ANOVA with 'time' and 'group' as the within-subject factors. There were significant differences among the groups (Greenhouse-Geisser correction, $F_{(1.846, 101.510)} = 6.332$; $p = 0.003$) but not for time (Greenhouse-Geisser correction , $F_{(1.763, 96.955)} = 0.386$; $p = 0.654$), with no interaction between the two factors (Greenhouse-Geisser correction $F_{(5.141, 282.753)} = 1.070$, $p = 0.378$). Then we compared the three groups at each time interval at which measurements were taken using Scheffé's test to identify pair wise group differences. Pearson's correlation coefficient was used to indicate a relationship between pain intensity and *de qi*. To check for

an order/carry-over effect we performed statistical comparisons for the VAS scores for pain intensity between the penetrating needle-first group (n = 35) and the non-penetrating needle-first group (n = 21) for the penetrating needles and non-penetrating needles, respectively, using two-way repeated ANOVA with ‘order’ as the between-subject factor and ‘time’ as the within-subject factor.

Further, for the VAS scores for pain intensity we performed statistical comparisons of all combinations between the 34 non-penetrating needles with skin penetration pain, 22 non-penetrating needles with no skin penetration pain, 44 penetrating needles with skin penetration pain, and the 12 penetrating needles with no skin penetration pain using the two-way repeated-measures ANOVA with ‘group’ as the between-subject factor and ‘time’ as the within-subject factor. In addition, we performed statistical comparisons of all of the combinations between the 23 non-penetrating needles with *de qi*, 33 non-penetrating needles with no *de qi*, 33 penetrating needles with *de qi*, and 23 penetrating needles with no *de qi* using the two-way repeated-measures ANOVA with ‘group’ as the between-subject factor and

‘time’ as the within-subject factor for the VAS scores for pain intensity. All analyses were performed using SPSS, version 15.0J (SPSS Inc, Chicago, IL).

Results

Participant flow is shown in Figure 2. Twenty-one subjects received the penetrating needle first and 35 subjects received the non-penetrating needle first. All 56 subjects completed the study.

Significant analgesia was observed immediately after needle application for both the penetrating and non-penetrating needle groups (penetrating *vs.* control; difference, -7.04; 95% CI, -11.45 to -2.62; $p = 0.001$) (non-penetrating *vs.* control; difference, -5.84; 95% CI, -10.26 to -1.42; $p = 0.006$) when compared with the no-acupuncture control group. The analgesia remained until 10 min after the removal of the penetrating needle (penetrating *vs.* control; difference, -6.57; 95% CI, -12.51 to -0.63; $p = 0.026$) and remained until immediately after the removal of the non-penetrating needle (non-penetrating *vs.* control; difference, -5.84; 95% CI, -11.06 to -0.62; $p = 0.024$) (Table 1). No significant difference in analgesia was found between the penetrating and non-penetrating needles at all of the time points measured (Table 1).

Significant differences in the pain intensity were not apparent between the

penetrating needle-first and non-penetrating needle-first groups for both the penetrating needle (p = 0.956) and non-penetrating needle (p = 0.519), respectively. There was no carry-over or order effect revealed.

The mean skin penetration pain and *de qi* upon application of the penetrating needle was significantly larger (p = 0.001) than that experienced upon application of the non-penetrating needle. However, the mean pain intensity in the subjects who perceived needle sensations was not significantly less than that in the subjects who did not perceive needle sensations for both types of needles at all of the time points measured (Figure 3).

At all time points measured no significant correlation was found between the pain intensity versus the skin penetration pain and between the pain intensity versus the *de qi* for both the penetrating and non-penetrating needles.

The practitioner identified 33 needles correctly, 31 incorrectly, and was unable to identify 48 needles (‘unidentifiable’). The 33 correct and 31 incorrect identifications fitted a probability of 1/2 (χ^2 = 0.063, p = 0.803), excluding the 48 ‘unidentifiable’ needles. None of the subjects commented that they had received a

non-penetrating needle.

Neither serious adverse events nor apparent minor adverse events were reported in this study.

Discussion

In this first double-blind (practitioner-patient) placebo-controlled study on acupuncture, we found that the penetrating needle and the non-penetrating needle, respectively, produced statistically significant analgesia when compared with the no-acupuncture control group. Pain relief using needle penetration was relatively delicate and less persistent when compared with previous studies on acupuncture analgesia that were conducted without effective double-blind controls [18, 19]. Furthermore, the needle penetration that is the distinctive feature of acupuncture did not exceed the skin pressure in pain relief.

The small sample size in this study gave an inadequate statistical power when the significance of the differences in the pain intensities between the penetrating needle and non-penetrating needle groups is considered. However, the differences between the groups were so small that they were probably not clinically significant [25] even if we were able to detect statistical significance with an adequately large sample size. Since the effect produced by skin pressure when using a blunt-tipped needle, which we believe to be nothing more than a healing

ritual, is recognized as the placebo [26], the significant analgesia produced with needle penetration can only be seen as placebogenic. However, it cannot be totally refuted that the possibility of a non-placebogenic analgesia produced by skin pressure from the non-penetrating needle that might stimulate high-threshold skin mechanoceptors [27] is similar to that seen with acupressure [28]. To draw final conclusions about whether the significant analgesia produced by the non-penetrating needle is truly placebogenic, double-blind studies using appropriate controls are necessary.

No significant correlation was observed between pain intensity and *de qi*, which is considered to be important in the production of acupuncture analgesia [24], when either type of needle was used. Furthermore, the mean pain intensity in the subjects who perceived *de qi* with the application of the penetrating and non-penetrating needles was not significantly less than it was for the subjects who did not have such a perception. Taking into account the fact that the needle was designed to provide uniform direction and depth of needle insertion to ensure homogeneity of stimulation across the subjects, this result casts doubts on the

precondition of ensuring *de qi* to induce acupuncture analgesia.

The practitioners failed to identify either the penetrating or the non-penetrating needles regardless of their level of experience in practice. The needles caused a lot of deliberation among well-experienced practitioners about the true identity of each needle. The fact that the practitioners identified approximately 50% of the needles incorrectly shows that these needles have potential in practitioner-patient masking. We believe that skin penetration and further insertion by the needles were masked from the acupuncturists in this study.

Notwithstanding that skin penetration pain and *de qi* were less common and stronger for the non-penetrating needles than they were for the penetrating needles, none of the subjects suspected that they had received a non-penetrating placebo needle. This could be due in part to the facts that pain does not necessarily accompany needle insertion or removal, and that the subjects had previously experienced the very faint sensation elicited by the insertion of a fine needle. In fact, about 20% of the penetrating needle applications in this study elicited neither skin penetration pain nor *de qi*. This suggests that the small

proportion of study participants who had no sensation of needle penetration when penetrating needles were used might have guessed that a non-penetrating needle was being used if they had been previously informed of the possible use of the non-penetrating needles. We believe the subjects were unaware of the fact that we used non-penetrating needles as in the skin pressure by the blunt tip of the single-blind needle [3-5]. However, the subjects were unlikely to report that they had received the non-penetrating needle even if they had suspected it, because we did not ask the subjects whether they thought they had received the penetrating or non-penetrating needles. Thus, the successful subject masking observed in this study might contain some favorable bias towards our expectation. However, the pain relief felt by the subjects who received the non-penetrating needle and perceived needle sensations was not significantly greater than the pain relief felt by the subjects who did not perceive needle sensations and who might have noticed that the needle received was non-penetrating if they had been informed of the possible use of non-penetrating needles. If they had noticed that they had received a non-penetrating needle but did not report it, the result could have been different.

In future clinical studies we will have to validate the masking capability of the double-blind needle on study participants when they have been informed of the possible use of non-penetrating needles, and perform an assessment of a subject's speculation of the type of needle used.

The double-blind procedure is an indispensable tool in medical science [6, 7]. Validated single-blind studies where placebo needles are used [29-31] overcome the inadequacies of previous control procedures and provide stronger evidence in acupuncture studies [9, 14]. However, results from single-blind studies can still show bias due to the practitioner being unmasked [6-14]. In this study we have contributed fundamentally to improvements in acupuncture science, thereby enabling acupuncture to go some way towards fulfilling the scientific standards of conventional medicine. Although the findings from the current study must be cautiously extrapolated due to the abovementioned limitations, they tell us the future direction of perceptions towards double blind approaches in acupuncture research. Further double-blind investigations are warranted to demonstrate the genuine effectiveness of needle penetration in acupuncture.

Conclusion

Needle penetration *per se* did not have any specific analgesic advantage over skin pressure under double-blind (practitioner-patient masking) placebo-controlled conditions.

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Tables

Table 1: **The mean pain intensity for 56 subjects during and after application of the penetrating needle, non-penetrating needle application and the control group**

					Non-penetrating needles *vs* Control		Penetrating needles *vs* Control		Non-penetrating needles *vs* Penetrating needles	
	Time	Control (mean ± SD)	Non-penetrating needles (mean ± SD)	Penetrating needles (mean ± SD)	Difference (95% confidence interval)	P value	Difference (95% confidence interval)	P value	Difference (95% confidence interval)	P value
During acupuncture	0 min	101.93 ± 9.20	96.09 ± 11.28	94.89 ± 11.64	-5.84 (-10.26 to -1.42)	0.006	-7.04 (-11.45 to -2.62)	0.001	1.20 (-3.22 to 5.61)	0.798
	10 min	102.30 ± 11.54	95.71 ± 12.75	94.24 ± 11.48	-6.59 (-11.03 to -2.15)	0.002	-8.06 (-12.51 to -3.62)	< 0.001	1.47 (-2.97 to 5.92)	0.714
	20 min	102.11 ± 14.84	93.43 ± 13.95	93.47 ± 13.36	-8.68 (-13.97 to -3.39)	< 0.001	-8.64 (-13.93 to -3.34)	< 0.001	-0.04 (-5.34 to 5.25)	> 0.999
After acupuncture	0 min	101.45 ± 15.47	95.61 ± 13.84	95.71 ± 13.31	-5.84 (-11.06 to -0.62)	0.024	-5.74 (-10.96 to -0.52)	0.027	-0.10 (-5.31 to 5.12)	0.999
	10 min	101.21 ± 19.69	97.04 ± 14.31	94.64 ± 14.66	-4.17 (-10.12 to 1.76)	0.222	-6.57 (-12.51 to -0.63)	0.026	2.40 (-3.55 to 8.33)	0.608
	20 min	101.52 ± 20.53	95.80 ± 17.38	95.25 ± 16.02	-5.72 (-12.29 to 0.86)	0.103	-6.27 (-12.84 to 0.31)	0.065	0.55 (-6.02 to 7.13)	0.978
	30 min	100.46 ± 23.23	96.54 ± 17.99	95.07 ± 17.25	-3.92 (-10.92 to 3.09)	0.385	-5.39 (-12.39 to 1.62)	0.167	1.47 (-5.54 to 8.47)	0.874
	40 min	100.89 ± 23.83	96.93 ± 17.37	96.43 ± 17.51	-3.96 (-10.41 to 2.48)	0.316	-4.46 (-10.91 to 1.98)	0.233	0.50 (-5.95 to 6.95)	0.982

Figure legend

Figure 1: **Double-blind placebo and matched needle**
Design of the double-blind acupuncture needles. Each needle assembly comprises an opaque guide tube (1) and upper stuffing (2) to provide resistance to the needle body during its passage through the guide tube. The body of the penetrating needle (3) is longer than the guide tube by an amount equal to the insertion depth, but the body of the non-penetrating needle (4) is long enough to allow its blunt tip to press against the skin when the needle body is made to advance to its limit. The non-penetrating needle contains lower stuffing (5) to give a sensation similar to that of skin puncture and tissue penetration. Both needles have a stopper (6) that prevents the needle handle (7) from advancing further when the sharp tip of the penetrating needle (8) or the blunt tip of the non-penetrating needle (9) reaches the specified position. The pedestal (10) on each needle is adhesive, allowing it to adhere firmly to the skin surface. The diameter of the needles in this study was 0.16 mm.

Figure 2: **Flow of study participants**

Figure 3: **Relationships between needle sensation and acupuncture analgesia**
Comparison of mean pain intensities between all the groups consisting of subjects who felt needle sensation (SPP or *"de qi"*) with the non-penetrating needle, subjects who felt no needle sensation (SPP or *"de qi"*) with the non-penetrating needle, subjects who felt needle sensation (SPP or *"de qi"*) with the penetrating needle, subjects who felt no needle sensation (SPP or *"de qi"*) with the penetrating needle.

Figures

Figure 1

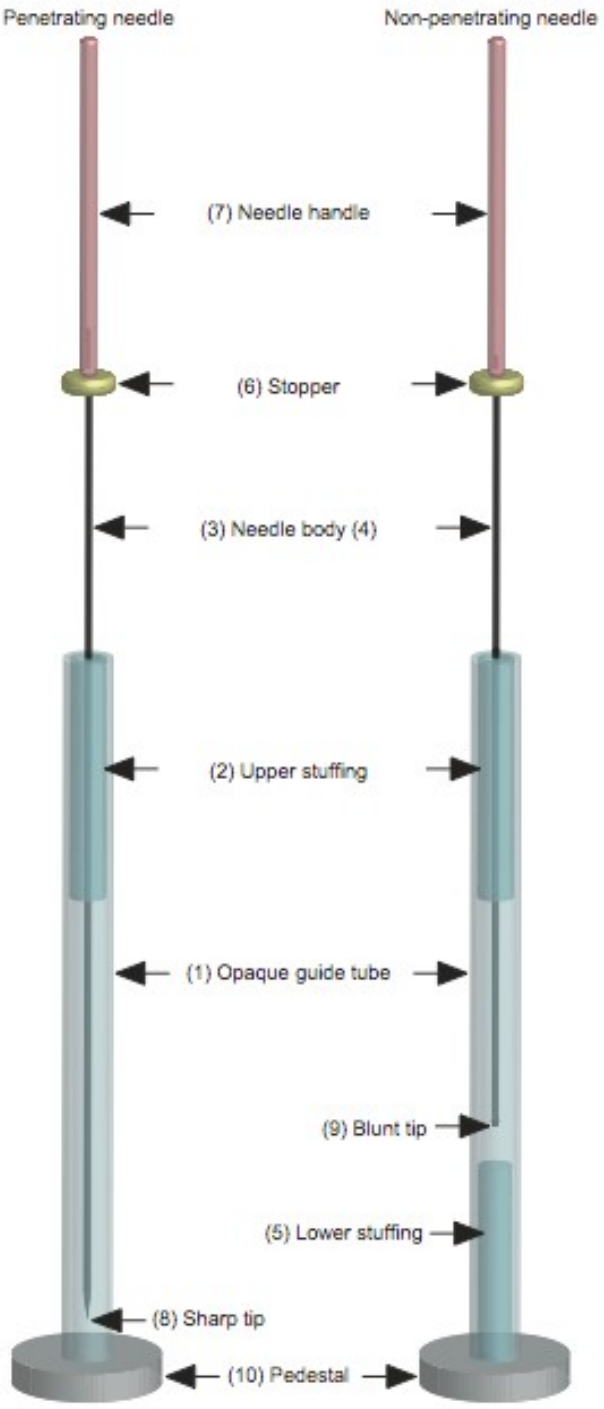

Penetrating needle
Non-penetrating needle
(7) Needle handle
(6) Stopper
(3) Needle body (4)
(2) Upper stuffing
(1) Opaque guide tube
(9) Blunt tip
(5) Lower stuffing
(8) Sharp tip
(10) Pedestal

Figure 2

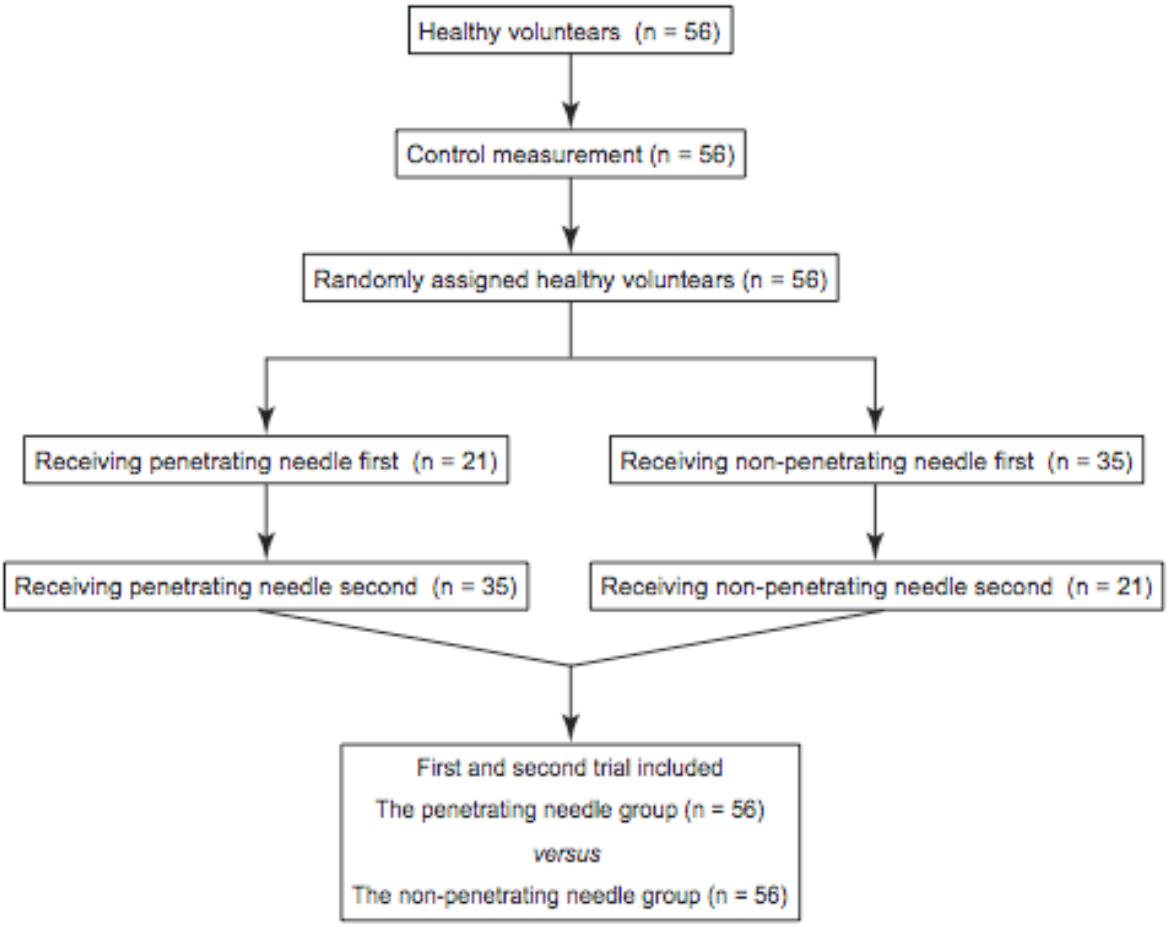
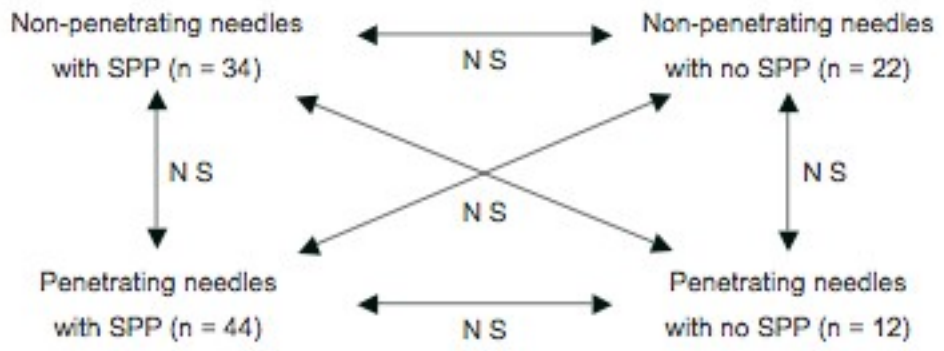
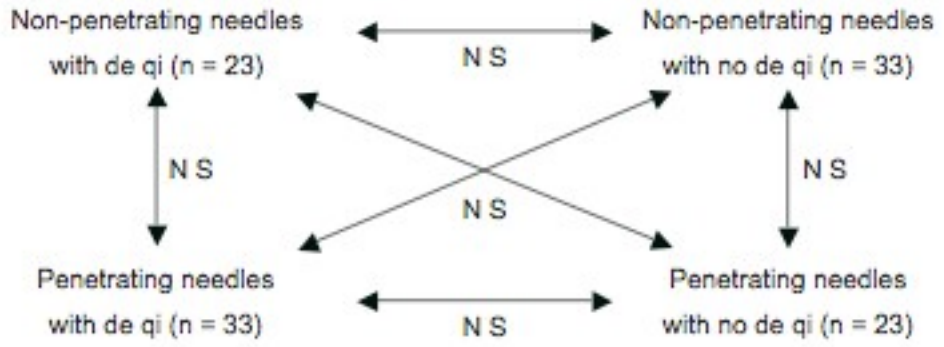

Healthy voluntears (n = 56)
Control measurement (n = 56)
Randomly assigned healthy voluntears (n = 56)
Receiving penetrating needle first (n = 21)
Receiving non-penetrating needle first (n = 35)
Receiving penetrating needle second (n = 35)
Receiving non-penetrating needle second (n = 21)
First and second trial included
The penetrating needle group (n = 56)
versus
The non-penetrating needle group (n = 56)

Figure 3





There was no significant (N S) difference between all two groups designated by arrows througout the study