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Original Research Article

A comparative evaluation of placebo effect on pain perception parameters in open-label versus double-blind groups: a prospective randomized pilot study in healthy volunteers

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ABSTRACT

Background: Considerable placebo response rate is commonly observed in placebo-controlled trials involving analgesics. However, there is paucity of evidence with regard to comparison of effect of open-label placebo versus double-blind placebo on pain perception.
Methods: In this study, cold water maintained at 4±1°C was used to induce experimental pain. Enrolled subjects were randomized to receive either 2% lignocaine gel as active drug or K-Y jelly as placebo as per the groups in open-label (two groups) and double-blind (two groups) study. Pain perception was evaluated using pain threshold time and pain tolerance time after immersion of subject's hand in the cold water. Pain intensity was assessed using visual analogue scale (VAS).
Results: Sixty-nine subjects were randomized into 4 study groups namely open-label lignocaine (OLL; N=17), open-label placebo (OLP; N=18), double-blind lignocaine (DBL; N=17) and double-blind placebo (DBP; N=17). OLP application increased pain intensity on VAS from 67 (47, 84) to 72 (39, 88) mm (p=0.018). OLL application reduced pain perception pain threshold time from 20.4 (4.0, 45.1) to 24.1 (6.3, 124.2) seconds (p=0.049) and pain tolerance time from 32.7 (6.8, 110.2) to 40.0 (7.7, 156.7) seconds (p=0.019). The change in pain parameters (before and after application of study intervention) was comparable without any significant difference among the four study groups (p=0.257 for pain threshold time, p=0.165 for pain tolerance time and p=0.563 for pain intensity score).
Conclusions: Lignocaine and placebo gel application showed comparable change in pain perception irrespective of blinding.

Key words: Open-label placebo, Double-blind placebo, Pain perception

INTRODUCTION

Placebos are inert inactive interventions which are used in clinical trials as a comparator to ascertain the efficacy of test interventions. Conventionally, the placebos are used in double-blind fashion wherein both the subjects and investigator are masked from identity of intervention so as to avoid any bias. In conditions like pain disorders and irritable bowel syndrome (IBS), considerable placebo response rate has been observed in several clinical trials.[1] The response rate with placebo in different pain conditions has been shown to vary considerably, for example, it ranged from 7-50% in different studies carried out in migraine, 19% in fibromyalgia and 20-30% in neuropathic pain.[2-4] Several studies where open-label placebo (OLP) was used, have shown a good response rate in comparison

to no treatment control (NTC).[5,6] One such example is the study related to IBS where majority of patients in OLP group have shown relief from the symptoms in comparison to NTC group.[1] Similar findings were also observed in studies carried out in patients with chronic low back pain and with acute episodic migraine.[5,7] A recent study carried out in IBS patients, however, has shown comparable results between OLP and double-blind placebo (DBP) groups.[8] Pain perception varies in individuals depending upon the nature and strength of stimuli and/or extent of tissue damage. A commonly used experimental set up involves the use of cold-water stress test that induces acute pain for the evaluation of analgesic effect of drugs.[9,10] In this test, pain perception is evaluated by measuring parameters like pain threshold time and pain tolerance time. In clinical research, pain intensity is commonly assessed using visual analogue scale.[9] In view of considerable response rate observed in placebo groups of various studies, the present study was designed to compare pain perception in OLP and DBP groups using cold water stress test performed in healthy volunteers.

METHODS

Study design

This randomized controlled parallel-arms pilot **s**tudy was conducted on adult healthy volunteers in a tertiary care hospital in Delhi (India) between February 2019 and March 2021.

Inclusion/exclusion criteria

This study included healthy adults of either gender in the range of 20-45 years who did not have any kind of pain at the time of study and were willing to give written informed consent. Individuals with any known cardiovascular disease like hypertension, coronary artery disease and peripheral vascular disease or having history of any acute or chronic pain disorder like migraine or arthritis were excluded from the study. In addition, individuals with history of any allergic reaction to topical lignocaine application or history of drug intake for any disease within last 1 week were also not enrolled. Females who were pregnant or nursing were also excluded from the study.

Randomization and allocation

Healthy volunteers were screened for their eligibility to participate in the study and were enrolled after written informed consent. Baseline blood pressure and anthropometric parameters (height, weight and body mass index using body composition analyser; TBF-410, Tanita Corporation, Japan) of all the study participants were assessed and recorded to ascertain the general health status of the participants. The enrolled participants were randomized into four study groups namely open-label lignocaine (OLL), OLP, double blind lignocaine (DBL) and DBP by block randomization with a block size of 4 using a computer-generated random sequence. Allocation concealment was followed using sequentially numbered sealed opaque envelopes by a third person who was not involved in the study. In this study, commercially available K-Y jelly was used as placebo and 2% lignocaine gel was used as treatment (an active comparator) and their packaging were changed to mask identification. Participants in the open-label groups were informed about the intervention they received while the investigator and participants in the double-blind groups were blinded to the intervention. A post-study unblinding was carried out for data analysis.

Cold water stress test procedure

Cold water stress test was performed as per the standard operating procedure prepared in accordance with previously published studies.[10-13] Before initiating cold stress test, procedure was well explained to the participants. Participants were checked for adequate sleep over previous night and had light breakfast 2 hours before performing the test in the morning. During screening, participants were told to avoid taking caffeinated drink, alcohol, energy drinks or smoking at least 2 hours before the experiment.

Participants were told to relax for a period of 10-15 minutes in quiet environment. All the participants underwent an initial session (baseline) of cold-water stress test without any topical application during screening. Participants who reported any discomfort or change in cardiovascular parameters (systolic blood pressure >250 mm Hg and/or diastolic blood pressure >130 mmHg) during cold stress test were excluded from the study. Likewise, participants showing delayed response after the cut off limit of 4 minutes were also excluded from the test session of cold stress test which was done on the next day after application of interventions under similar conditions. During the test session, participants immersed their non-dominant hand till wrist joint in a bucket of water maintained at temperature 35 ± 1 °C for 2 minutes (to equalize the baseline temperature for all subjects). OLP and OLL groups were explained about the allocated intervention and then placebo labelled K-Y jelly and labelled 2% lignocaine gel was applied respectively in the two groups. DBP and DBL groups received either 2% lignocaine gel or K-Y jelly without any labelled information. One fingertip unit (approx. 0.5 gm) of the gel/placebo was applied topically on hand (both dorsal and ventral aspects till wrist joint) of the study participants 5 minutes before the cold-water stress test. The cold-water stress test apparatus consisted of a chamber half-filled with ice (kept in a mesh), and remaining with water to a level deep enough to cover participant's hand. The water temperature in the chamber was maintained at 4 ± 1 °C by adding/removing cold water to adjust temperature. The participants immersed their non-dominant hand in the cold-water chamber with dorsum surface facing upwards and without touching the walls or surface of the chamber. The SOP was also kept by the side of the test setup. The test began at the time the participant immersed his/her

hand (till wrist joint) in the water and stop watch was started. They were instructed to inform immediately when they would first feel the pain, and the time difference between the beginning of the test and the first report of pain was recorded as "pain threshold". Participants were instructed to voluntarily withdraw their hand at the point at which the pain became unbearable, the time between the beginning of the test and this voluntary withdrawal was recorded as "pain tolerance".

After voluntary withdrawal of hand from the chamber, participants were asked to rate their pain on a visual analogue scale (VAS) for perceived "pain intensity" on a scale of 0 to 100 where 0 represented no pain and 100 represented maximum pain. Immediately after the end of test procedure, participants were told to immerse their hand in the normal water bucket to normalize hand temperature. All participants were blinded to the actual cut-off time limit for the experiment but for safety reasons, the test was terminated after 4 min if the participant had not already removed their hand. The test time limit of 4 min was selected to minimize the risk of tissue injury in accordance with previous studies.[13,14] The entire cold water stress test procedure was repeated three times with 10-15 minutes interval between the tests and pain threshold time, pain tolerance time and pain intensity scores were recorded. The mean of three such readings was considered for analysis.

Statistical analysis

Data for study parameters were entered in Microsoft-excel and analysis was done using 'IBM SPSS statistics (version 23.0)'. The data was checked for normal distribution using Shapiro Wilk test. Descriptive statistics using mean and standard deviations (SD) for continuous variables or frequency and percentage for categorical variables were employed for describing the socio-demographic characteristics of the study participants. Data which was found to be non-normally distributed was expressed as median and range (minimum, maximum). The per-protocol data analysis was done. Baseline socio-demographic characteristics between the four study groups were compared by Kruskal-Wallis test.

The data on pain threshold and pain tolerance values was recorded in seconds and presented as median (minimum, maximum). The score of pain threshold, pain tolerance and VAS was compared in the open label treatment, open label placebo, double-blind treatment and double-blind placebo groups. Wilcoxon Signed Rank test was used for analysis of paired data (before and after changes in the study groups) and ANOVA/Kruskal-Wallis test was used for analysis of unpaired data (comparison of changes in study groups). Correlation analysis between each of the pain perception parameters (pain threshold time, pain tolerance time and pain intensity score on VAS) were done by Kendall's tau-b correlation coefficients (τb), p value <0.05 was considered as statistically significant.

RESULTS

Healthy volunteers from the hospital and community (N=71) were screened for eligibility to participate in the study while conducting the cold-water stress test to obtain the baseline values of pain perception parameters and of these, 2 were excluded. Sixty-nine participants enrolled in the study were randomized into four study groups and they all completed the study. In view of this, a per-protocol analysis was done in this study (Figure 1).

Demographic characteristics of participants

Demographic and other baseline characteristics of study participants are shown in (Table 1). The mean (SD) age of participants in OLL, OLP, DBL and DBP groups were 29.0 (4.3), 28.4 (3.4), 28.9 (5.0) and 29.3 (3.2) years, respectively (p=0.925). Majority of participants in each of the four study groups were males. The mean BMI of participants in OLL, OLP, DBL and DBP groups were 25.7 vs 25.8 vs 25.8 vs 25.6 kg/m^2, respectively (p=0.997). All the demographic characteristics of the participants among the four study groups were comparable.

Baseline study parameters of enrolled participants

Initial session of cold stress test was done at the time of screening before application of study interventions (i.e., placebo or lignocaine) and the observed pain parameters were recorded as the baseline values. All the pain perception related parameters namely, pain threshold time, pain tolerance time and pain intensity recorded during the cold stress test were found to be similar in the four study groups (Table 2).

Effect of intervention on pain perception parameters

Initial session (baseline) of cold-water stress test performed at the time of screening, was followed by same test performed next day after application of the study interventions (lignocaine/placebo). In the open-label lignocaine (OLL) group, a significant increase in pain threshold time and pain tolerance time was observed (p<0.05 for both the parameters). In the open-label placebo (OLP) group, no significant change in pain threshold time and pain tolerance time was observed. However, pain intensity on VAS scale was found to be significantly increased in the OLP group after application of placebo gel (p=0.018). Also, one of the study participants could tolerate cold stress test up till pre-defined cut-off of 4 minutes after application of placebo gel. In the DBL and DBP groups, no change in any of the pain perception parameters (pain threshold, pain tolerance and pain intensity) was observed after application of respective intervention in double blinded fashion. Further, the analysis of data revealed that all the four study groups were comparable with regard to the change in the values of all the pain perception parameters from the baseline values (Table 3).

Table 1: Demographic characteristics of participants included in the study.

Parameters		OLL (N=17)	OLP (N=18)	DBL (N=17)	DBP (N=17)	P value
Age (years)		29.0 (4.3)	28.4 (3.4)	28.9 (5.0)	29.3 (3.2)	0.925
Gender N (%)	Male	10 (58.8)	9 (52.9)	10 (58.8)	12 (70.6)	0.672
	Female	7 (41.2)	9 (47.1)	7 (41.2)	5 (29.4)	
BMI (kg/m^2)		25.7 (3.2)	25.8 (4.4)	25.8 (3.3)	25.6 (3.5)	0.997

Age and BMI data are expressed as Mean (SD). #One way ANOVA; OLL: Open-Label Lignocaine; OLP: Open-Label Placebo; DBL: Double-Blind Lignocaine; DBP: Double-Blind Placebo; BMI: Body Mass Index.

Table 2: Baseline values of pain perception parameters in study groups.

Parameters	OLL (N=17)	OLP (N=18)	DBL (N=17)	DBP (N=17)	P value
Pain threshold (seconds)	20.4 (4.0, 45.1)	18.2 (9.6, 26.1)	12.9 (9.0, 45.0)	19.0 (5.5, 34.4)	0.266
Pain tolerance (seconds)	32.7 (6.8, 110.2)	38.4 (17.3, 240.0)	29.3 (11.8, 112.7)	30.7 (18.0, 76.0)	0.151
Pain intensity rating (VAS)	73.0 (28.0, 90.0)	67.0 (47.0, 84.0)	75.0 (45.0, 90.0)	72.0 (15.0, 91.0)	0.231

Data expressed as median (minimum, maximum), Kruskal-Wallis test; OLL: Open-Label Lignocaine; OLP: Open-Label Placebo; DBL: Double-Blind Lignocaine; DBP: Double-Blind Placebo; VAS: Visual Analogue Scale

Comparison of effect of interventions in open-label and double-blind study groups

In present study, both open-label and double-blind study groups were included to evaluate the effect of intervention on pain perception parameters. Our results show that change in pain threshold time, pain tolerance time and pain intensity was not significantly different (p=0.409, p=0.947 and p=0.373 respectively) when the effect of open-label placebo was compared with double-blind placebo (Figure 2). Similar to placebo groups, the change in respective pain perception parameters was not significantly different between the OLL and DBL groups (p=0.361, p=0.091, and p=0.448).

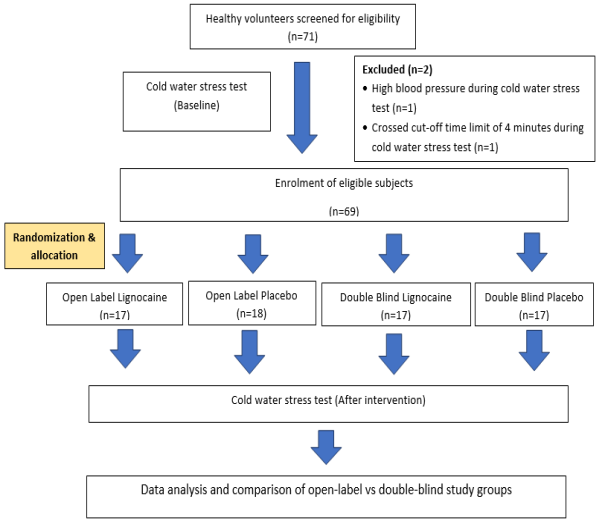

Figure 1: Consort chart showing screening, enrolment and randomization of participants.

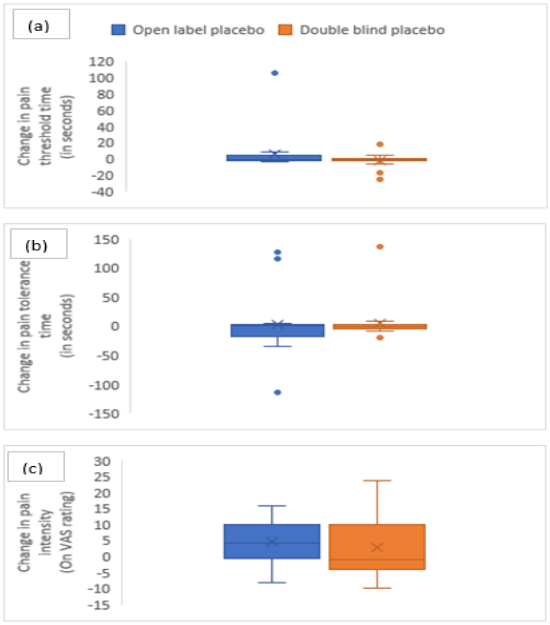

Figure 2: Comparison of placebo effect in open label placebo (OLP) vs. double blind placebo (DBP) groups for change in pain perception parameters. Box and whisker plots showing comparison of change in (a) pain threshold time, (b) pain tolerance time and (c) pain intensity (with respect to baseline) in OLP versus DBP groups.

Statistically significant difference was not observed for any of the three pain perception parameters between the two groups. Horizontal line inside the box depicts median, upper and lower boundaries of the box denotes inter-quartile range. The lower and upper horizontal lines outside the box (whiskers) denote minimum and maximum value (range). Dots denote outlier values.

Table 3: A comparison of baseline and after-intervention values of pain perception parameters in study groups.

OLL (N=17)			OLP (N=18)			DBL (N=17)			DBP (N=17)			Change in OLL vs. OLP vs. DBL vs. DBP groups
Baseline	**After intervention**	**P value***	**Baseline**	**After intervention**	**P value***	**Baseline**	**After intervention**	**P value***	**Baseline**	**After intervention**	**P value***	**P value^**
Pain threshold (seconds)												
20.4 (4.0, 45.1)	24.1 (6.3, 124.2)	0.049	18.2 (9.6, 26.1)	18.0 (8.1, 132.0)	0.316	12.9 (9.0, 45.0)	14.3 (7.5, 34.3)	0.554	19.0 (5.5, 34.4)	13.3 (5.4, 52.7)	0.552	0.257
Pain tolerance (seconds)												
32.7 (6.8, 110.2)	40.0 (7.7, 156.7)	0.019	38.4 (17.3, 124.1)	34.7 (19.1, 240)	0.777	29.3 (11.8, 112.7)	28.7 (8.8, 116.1)	0.943	30.7 (18.0, 76.0)	28.5 (14.3, 213.4)	0.463	0.165
Pain intensity (VAS)												
73.0 (28.0, 90.0)	76.0 (51.0, 84.0)	0.836	67.0 (47.0, 84.0)	72.0 (39.0, 88.0)	0.018	75.0 (45.0, 90.0)	79.0 (51.0, 95.0)	0.177	72.0 (15.0, 91.0)	74.0 (31.0, 87.0)	0.368	0.563

Data expressed as median (minimum, maximum). *Wilcoxon Signed Rank test; ^Kruskal-Wallis test; OLL: Open-Label Lignocaine; OLP: Open-Label Placebo; DBL: Double-Blind Lignocaine; DBP: Double-Blind Placebo; VAS: Visual Analogue Scale

Table 4: Correlation matrix showing Kendall's tau-b correlation coefficients (τb) between study parameters at baseline in the study participants (n=69).

Parameters		Pain threshold	Pain tolerance	Pain intensity
Pain threshold	τb	1.000	0.489	-0.178
	P value	-	<0.001	0.032
Pain tolerance	τb	0.489	1.000	-0.198
	P value	<0.001	-	0.017
Pain intensity	τb	-0.178	-0.198	1.000
	P value	0.032	0.017	-

Correlation among pain perception parameters

The study also evaluated the correlation among the pain perception parameters (Table 4). There was a positive and statistically significant correlation between pain threshold time and pain tolerance time (τb=0.489, p<0.001). Pain threshold time and pain tolerance time also showed weakly negative but statistically significant correlation with VAS pain intensity score. Also, after application of study intervention, change in pain threshold time (not shown in table) also showed significant correlation with change in pain tolerance time (τb=0.382, p<0.001).

Safety assessment

None of the study subjects reported any serious adverse event. One subject had excessive increase in blood pressure during screening (which got stabilized after some time) and hence was excluded from the main study.

DISCUSSION

Double-blind placebo controlled randomized trial are considered to be the most appropriate study design to establish efficacy of any new intervention during clinical research. Due to ethical concerns, there has been recent interest in exploring the utility of open-labelled placebo as comparator in clinical research and trials. Double-blind placebo group is known to show very good response rate in clinical trials on disorders with subjective symptoms like pain, IBS and depression.[4,15] Several studies have shown that open-label placebo can also have better effect in comparison to no treatment control group on pain conditions like migraine, chronic low back pain, fibromyalgia etc.[5,7] Efficacy of open-label placebo in cancer related fatigue, attention deficit hyperactivity disorder, allergic rhinitis, major depression, irritable bowel syndrome and menopausal hot flushes has been shown in a recently published metanalysis as well.[16] However, evidence with regard to relative efficacy of placebo use in open label versus double blind fashion is very sparse. The present study was designed to evaluate the effect of placebo on pain perception parameters in healthy volunteers where K-Y jelly was applied locally on hand in OLP and DBP groups. The study also included a comparator group (active control) where lignocaine gel was applied instead of placebo. A simple test was carried out to evaluate the effect of these interventions on pain perception parameters using cold stress test (CST). CST has been historically used to simulate acute pain to test analgesics in experimental laboratories.[17] CST has also been used as a pain model for conditions like chronic low back pain, post-operative pain and spinal cord injuries.[18,19] In this test, pain perception is evaluated by measuring pain threshold time, pain tolerance time and pain intensity. In this study, open-label treatment group showed significant improvement in pain threshold and tolerance after application of lignocaine gel. Lignocaine is well known to decrease sensitivity to painful stimuli.[20] Topical preparations of lignocaine are routinely used for painful procedures like intubation, digital rectal examination, urethral catheterization and for temporary relief of pain caused by minor skin irritations for example, sunburn, minor burns, minor cuts and insect bites.[21] Evidence of significant analgesic effect of open-labelled lignocaine gel as active control further validates the results of this study. However, no significant improvement was observed in pain parameters after application of lignocaine in double-blind manner indicating thereby that blinding or knowledge of prospective treatment does influence pain perception.

In this study, open-label placebo group showed increased sensitivity to pain perception as indicated by increase in pain intensity. This is contradictory to other studies wherein beneficial analgesic effect of placebo was reported.[5] Increase in perceived pain intensity after OLP suggests possible role of negative expectancy when participants were made aware that they will be given inactive intervention before experimentally induced pain. Another possible explanation for this could be that cold stress test induces pain mainly via ischemia of peripheral blood vessels which is possibly not affected to large extent by placebo mechanisms.[13] This is unlike conditions such as post-operative pain, irritable bowel syndrome and migraine wherein good placebo response is frequently observed and role of central neurobiological mechanisms are relatively better established.[1,7] Statistically significant difference in change in pain parameters was also not observed on comparison of open-label lignocaine treated group with either OLP or DBP. This could have resulted due to smaller sample size and subjective nature of pain perception parameters. In the current study, change in pain perception parameters were found to be similar across the interventions (placebo or lignocaine) irrespective of blinding suggesting thereby that placebo might produce comparable analgesic effect when given in open-label fashion through some hitherto unknown neurobiological mechanisms. This is further substantiated by the findings of a randomized controlled trial on chronic low back pain patients, wherein adding open-label placebo to usual treatment relieved pain symptoms and disability.[5] In another recent study on healthy adults, it was observed that intravenous open label placebo administration resulted in reduced electrical pain sensitization.[22] The data of present study was further analyzed to draw correlation among the pain perception parameters used in this study. It is interesting to note that a significant correlation was found among these parameters using CST that validates the model as a simple and useful tool to study analgesics. Although, the results of this pilot study are limited by small sample size in each group and subjective nature of pain perception parameters being recorded by cold stress test. A significant positive analgesic response to lignocaine when applied in open-label fashion and a significant correlation observed among the pain parameters validate the results of this study. This is the first study evaluating the relative effect of placebo on pain perception parameters under blinded and open-label conditions. Further studies with larger sample size and probably

additional objective parameters may add to the clinical significance of use of open-label and double-blind placebo.

CONCLUSION

This study demonstrates that placebo did not affect pain perception in experimentally induced acute pain when applied in open-label or double-blind fashion while lignocaine gel significantly reduced pain perception after open-label intervention and not when applied in a double-blind fashion. Both the interventions, however, showed comparable change in pain perception irrespective of blinding.

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