Sham surgery as a control in randomized controlled trials is justified, safe and ethical to conduct: A systematic review

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Background: Sham control randomized controlled trials (RCT) are studies in which the control group includes invasive placebo procedure without the perceived active component of surgery. The sham group does not include the actual intervention but aims to mimic its invasive nature. There has been much ethical and methodological debate regarding the necessity and ethics of such studies.

Methods: Pairing of RCT studies with the same active treatment but different control groups, RCT's with sham control and RCT's with conservative control groups was performed. The final conclusion from each study was recorded and evaluated.

Results: Ten surgical interventions in sixty-eight studies that met inclusion criteria where evaluated. 32(47.05%) sham and 36(52.95%) conservative control RCTs. In 4 out of 10(40%) surgical intervention sham control RCT had different treatment recommendations than conservatives RCT's. In subjective patient reported outcome scores the placebo effect was measured to be 31% of overall treatment effect (p value=0.029). No major complication was recorded in the sham control group. The minor complications rate difference between sham and conservative control group was 0.03 per patient., Meaning that for every 33 patients in the sham group one additional minor complication is noted in the sham group compared to the conservative group.

Conclusion: Sham control RCTs are effective and safe and have a role in evaluating the efficacy of new surgical treatments. The placebo effect in surgical subjective measured outcome is 31%, comparable to previous reports in the literature.

Key Words: *Sham surgery; Perceived treatment; Vertebroplasty*

INTRODUCTION

Randomized controlled trials (RCT) are the gold standard of medical research. It has been shown that blinded comparison between two treatment options (or more) is the most objective way to neutralize the placebo effect. However, RCT are not bias proof. The planning, methodology, execution and analysis of RCTs require high proficiency and multidisciplinary cooperation [1].

The placebo effect is defined as "any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties" [2]. This definition has been extended to include the effect of surgical treatment [3]. McRae et al. reported on the quality of life of participants in a double-blind sham surgery-controlled trial designed to determine the effectiveness of transplantation of human embryonic dopamine neurons into the brains of persons with advanced Parkinson's disease. The authors showed the importance of placebo effect based on "perceived treatment" in the transplant and sham surgery groups [4].

This is supported by earlier studies showing the psychological effect and benefit of "perceived treatment" [5]. However, the actual quantification of the placebo effect is not straight forward. In a meta-analysis by Hrobjartsson et al., the authors concluded that placebos had no significant effects on objective or binary outcomes, and may have some benefits when evaluating continuous subjective outcomes such as pain [6]. This can be attributed to placebo induced changes demonstrated in brain functional MRI [7].

The aforementioned benefits and pitfalls of a blinded RCT are even more complex considering surgical interventions [3].

Despite that double blind RCT's are the gold standard when evaluating new treatments, they are not commonly used in surgery. There is no placebo control group in the majority of clinical studies. Several authors attempted to solve the problem of blinding surgical treatment by incorporating sham surgeries as a control arm in the study. Sham surgeries are procedures in which an actual invasive procedure is performed – cystoscopy, arthroscopy or spinal injection, However, the actual intervention under study is performed only in the active treatment group while in the control group the invasive procedure does not include the actual intervention.

This methodology raises an ethical dilemma. Whether performing sham surgery control RCT is justified? In many cases, a conservative treatment option exists, i.e., medication, physiotherapy. Does placebo ("sham surgery") have a role in surgery? If we use Sham surgery as a control group will this change study results? Do sham procedures hold similar risks and complications as the actual procedures? is the risk justified [8-14]?

The aim of this study is to compare the conclusions drawn from sham control RCTs to the conclusions drawn from "conservative" non-sham control RCTs. Also, comparison of complication types and rates between the study types, and measurement of the placebo effect in Sham surgery control RCTs.

METHOD

A comprehensive search was performed in Medline (PubMed), the Cochrane Library, SCOPUS, Embase and Scholar google for the terms: "Sham surgery" OR "Sham procedure" with and without the term "randomized control trial".

Inclusion criteria included randomized clinical trial in which both study and control groups were invasive procedures. Exclusion criteria were studies of alternative medicine (e.g., acupuncture) or studies in which the study and/or control procedures were not invasive.

Forty-three randomized clinical trials were found in which sham procedures were used in RCTs that met both inclusion and exclusion criteria. Further search was performed to match between RCTs studies in which non-surgical treatment and sham procedures were the control groups, and the active

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procedure group was similar. Sham control trials that had no conservative RCT matching were further excluded from the study.

For example, RCT's comparing vertebroplasty with pain medication and physiotherapy matched with RCT's comparing vertebroplasty with sham procedure.

The following data were extracted from each included study: publication year, medical/surgical discipline, surgical procedure, control type (sham procedure or conservative treatment), number of patients in study and control groups, follow-up time (months), publication journal impact factor, number of citations of each study, statistically significant primary end-point, final study conclusion; whether the active treatment (active group) was superior or no difference was found. The improvement rate was also documented for both the active and control groups.

The improvement was calculated as the difference in percent between the initial and final scores for each group. For this calculation, the initial reported score was considered as 100%. This method of calculation enabled the comparison of different studies (evaluating different surgical procedures and utilizing different scores or end-points).

The treatment effect was calculated for each study as the difference between improvements in the active *vs.* control groups. In order to evaluate the placebo effect of sham surgical procedures, we compared the treatment effect in sham control RCT to the treatment effect in conservative control RCT. In this comparison, a smaller treatment effect means a smaller difference between the study and control groups.

Statistical analysis was performed by an experienced biostatistician (A.H.). Continuous variables are presented as mean (± standard deviation). Categorical variables are presented as count (percent). Comparisons between study types – sham control *vs* conservative control RCTs was done with the rank sum Wilcoxon-Mann-Whitney test or Chi-Square tests for continuous or categorical data, respectively.

To compare treatment effect two-way analysis of variance (ANOVA) was used with treatment effect as the dependent covariate. Independent (explanatory) covariates in the model were: control type (sham *vs* conservative), surgical procedure studied and their interaction. All p values reported are two-sided. P value less than 0.05 is considered statistically significant.

RESULTS

A total of 68 RCT's were included in the study. There were 32 (47.05%) Sham control RCT's and 36 (52.94%) conservative control RCT's. Overall 10,917 patients were included. Sham control RCTs included 3,193 (29.2%) and conservative control RCT included 7,724 (70.8%) patients. The studies encompass five different medical disciplines: Cardiology (4 studies, 5.9%), Neurosurgery (4 studies, 5.9%), Orthopaedics (46 studies, 67.6%), Urology (7 studies, 10.3%) and Gynecology (7 studies, 10.3%). The medical interventions (i.e., treatments) included in the study were: Vertebroplasty [15-25], Arthroscopy for knee osteoarthritis [26-30], Menisectomy for degenerative meniscal tears [31-37], Intradiscalelectrotheramal therapy [38-43], Radiofrequency for facet or dorsal root denervation [44-53], arthroscopic shoulder subacromial decompression [54-60], Transurethral thermo-ablation [61-67], Gastric cardia plication for GERD [68-71], Endometriosis laparoscopic excision [72-78], percutaneous coronary intervention [79-82].

Mean Journal impact factor for the published manuscripts was 11.4 (± 16.22). Mean citation number was 302.5 (± 571.28). There was no statistically significant difference, in published journal or citations between sham control and conservative control RCTs (Table 1).

TABLE 1: Characteristics of the studies.

	Sham surgery control (N=32)	Placebo control (N=36)	p value
Publication year	2005 (± 7.35)	2008 (± 7.61)	0.06
Medical discipline			
Cardiology	1 (3.1%)	3 (8.3%)	
Gastroenterology	3 (9.4%)	1 (2.8%)	
Orthopedics	20 (62.5%)	26 (72.2%)	
Urology	5 (15.6%)	2 (5.6%)	
Gynecology	3 (9.4%)	4 (11.1%)	0.407
Journal impact factor	13.11 (± 17.17)	9.95 (± 15.45)	0.6
Citation number	316.34 (± 453.26)	289.88 (± 667.72)	0.47
Number of patients in active treatment group	53.83 (± 40.50)	107.55 (± 189.25)	0.021
Number of Patient in control group	45.90 (± 34.38)	107.00 (± 188.25)	0.005
Follow-up time (months)	6.89 (± 5.70)	22.34 (± 22.38)	<0.001
Intension to treat analysis			
No	21 (65.6%)	18 (50.0%)	
Yes	18 (50.0%)	18 (50.0%)	0.193
Complication per patient in active group	0.21 (± 0.36)	0.49 (± 0.11)	0.015
Complication per patient in control group	0.11 (± 0.19)	0.08 (± 0.21)	0.016

Mean ± standard deviation. Statistical hypothesis testing was done with the Chi-square test and WMW rank sum test.

Mean number of patients in the active and control groups was 82.29 (± 142.58) and 78.25 (± 141.43), respectively. RCTs with sham control procedures had lower sample sizes in both active and control arms, compared with conservative control RCTs. These differences were statistically significant (Table 1). The overall mean follow up time was 15.07 (± 18.36) months. RCTs with sham control had lower follow up time than RCTs with conservative control (p<0.001, Table 1).

TABLE 2: Conclusion by procedure type.

	Sham control RCT		Conservative control RCT		
	Favors Active group	**No difference**	**Favors Active group**	**No difference**	**Different results**
Vertebroplasty	0 (0%)	2 (100%)	8 (88.9%)	1 (11.1%)	1
Knee Arthroscopy for Osteoarthritis	0 (0%)	3 (100%)	1 (50%)	1 (50%)	1
Transurethral thermoablation for BPH	5 (100%)	0 (0%)	2 (100%)	0 (0%)	0
Degenerative meniscus Meniscetomy	0 (0%)	1 (100%)	1 (16.7%)	5 (83.3%)	0
Gastric Cardia Plication	3 (100%)	0 (0%)	1 (100%)	0 (0%)	0
IntradiscalElectrothermal therapy	2 (40%)	3 (60%)	1 (100%)	0 (0%)	1
RF Facet denervation	3 (42.9%)	4 (57.1%)	1 (33.3%)	2 (66.7%)	0
Subacromial decompression	0 (0%)	2 (100%)	1 (20.0%)	4 (80.0%)	0
Endometriosis laparoscopic lysis/excision	3 (100%)	0 (0%)	1 (25%)	3 (75%)	1
Percutaneous coronary intervention	0	1 (100%)	0	3 (100%)	0

RCT: Randomized Controlled Study

No major complications were reported in the sham control groups of all RCTs included in the study. Minor complications were more common in the active treatment arms in both Sham and conservative control studies. Sham control arms had a slightly higher mean complication rate per patient 0.11 (± 0.19) compared to conservative control 0.08 (± 0.21), this difference was found to be statistically significant (p value=0.016).

TABLE 3: Study treatment effect by procedure type, in studies with subjective measure outcomes.

	RCT with Sham procedure control			RCT with conservative control		
	Imprv % Active	**Imprv % Control (Sham)**	**Effect size %**	**Imprv % Active**	**Imprv % Control**	**Effect Size**
Vertebroplasty	23.99% (± 5.26%)	27.64% (± 2.73%)	-3.65% (± 7.99%)	59.78% (± 22.64%)	37.16% (± 23.44%)	22.62% (± 11.97%)
Knee Arthroscopy for osteoarthritis	23.1% (± 14.55%)	15.53% (± 7.84%)	7.57% (± 7.33%)	26.36% (± 0%)	13.99% (± 0%)	12.37% (± 0%)
Meniscetomy	36.04% (± 0%)	38.76% (± 0%)	-2.72% (± 0%)	49.83% (± 10.34%)	41.31% (± 16.52%)	8.52% (± 10.34%)
Intradiscal Electrothermal therapy	18.4% (± 16.17%)	9.8% (± 8.44%)	8.59% (± 16.09%)	62.5% (± 0%)	6.25% (± 0%)	56.25% (± 0%)
RF Facet denervation	32.05% (± 15.94%)	18.1% (± 9.42%)	13.95% (± 23.16%)	43.43% (± 22.32%)	31.28% (± 8.74%)	12.15% (± 16.25%)
subacromial decompression	54.38% (± 34.81%)	47.34% (± 27.23%)	7.04% (± 7.58%)	42.49% (± 17.00%)	37.89% (± 24.99%)	4.59% (± 11.63%)
endometriosis laparoscopic lysis/ excision	25.82% (± 10.99%)	9.06% (± 8.53%)	16.76% (± 14.6%)	56.86% (± 18.77%)	50.12% (± 10.75%)	6.74% (± 12.73%)
Total	28.51% (± 17.34%)	19.05% (± 14.68%)	9.46% (± 16.13%)	49.51% (18.08%)	35.86% (± 19.53%)	13.64% (± 14.59%)

From the ten interventional procedures included in this study, in 4 procedures (40%) the conclusion drawn from sham *vs.* conservative RCTs studies was different (Table 2). For surgical procedures such as vertebroplasty, osteoarthritic knee arthroscopy, and intradiscalelectrothermal therapy, the sham control studies showed there was no difference between active procedure and sham procedures. Conversely, conservative control RCT studies showed active treatment superiority. Evaluating laparoscopic excision of endometriosis, the conservative control RCT showed that there was no difference while sham control studies showed that active treatment is superior to sham control (Table 2).

The treatment effect was defined as the difference between improvements (percent) in the active group minus improvement (percent) in the control group. The mean treatment effects for all sham control studies was 14.07% (± 16, .94%) and for all conservative control studies 14.12% (± 15.06%).

This difference is clinically insignificant. In studies utilizing subjective outcome measures (i.e pain, function, quality of life etc.) the total treatment

effect was 9.46% (± 16.13%) in sham control RCT's compared to 13.64% (± 14.59%) in conservative control RCTs (Table 3).

The ratio between treatment effects (9.46/13.64) is 0.69, meaning that sham procedure effect constitutes 31% of the treatment effect. This is the placebo effect of sham surgery. This was found to be statistically significant (p value=0.029).

DISCUSSION

Using sham control group changed the conclusion drawn in 4 out of 10 (40%) surgical interventions evaluated in this study. It is the first study to investigate pairs of sham control RCT *vs* conservative control RCTs. This enables to estimate the placebo effect, safety and efficacy of sham control RCTs. In subjective patients reported outcome (e.g., pain) the sham placebo effect was estimated 31%. This means that in subjective outcome, 31% of overall treatment effect can be attributed to the placebo effect.

The study included comparable number of sham control RCTs [32] and conservative treatment control RCTs [36], from varied medical fields. No differences of journal impact factor or citation numbers were found, reflecting the fact that sham control RCTs enjoy the same readership exposure as conservative controls RCTs. Also, this attests to the methodological quality of the included studies. Future investigators may favorably take this into consideration when devising a study methodology [8,10,14].

In all included sham control RCTs in this study, no major complications were reported. Minor complications were reported in the active groups of both sham and conservative control studies. However, the difference between complications rate in sham control studies (0.11 per pt.) and conservative control studies (0.08 per pt.) is only 0.03 complications per patient. This small difference means that 33 sham treated patients are required in order to produce one additional minor complication. Therefore, sham control RCT's should be regarded as safe.

The safety of sham surgery has been evaluated by other authors [8,14]. Probst et al. conducted a meta-analysis on sham control RCT's attempting to evaluate whether placebo intervention can serve as a safe comparator [14]. The authors found no statistically significant difference between the active and placebo groups for major complications (serious adverse events). Also, there were significantly more minor complications in the active groups than placebo controls.

Similarly, Wartolowska et al. concluded in their review of the use of placebo controls in the evaluation of surgery, that in general placebo control arm was reported to be safer and adverse events were more serious and more common in the active group [8].

However, three critical points should be emphasized when comparing these conclusions to the one of the current study. First, the current study evaluated the use of sham surgery versus the alternative of "conservative" control arms and not sham versus active groups as the above-mentioned studies. Second, all studies (including the current study) share a common weakness. They all evaluate sham or placebo procedures as one homogenous group, while in reality, these procedures differ considerably in harm/adverse events potential. Horng et al. have described a classification system differentiating sham procedures according to their inherent potential risk to the patient [12]. Third, not all complications should be attributed to the active or sham procedure. In some instances, an adverse event can be a result of the investigated medical condition and the active or sham procedure ineffectiveness rather than harmful. Therefore, the safety of sham procedures should be evaluated specifically on case to case basis and not as a general rule.

This study offers interesting and unique insights for the clinician, on the way sham control RCTs compare with conservative treatment control RCTs to evaluate the effectiveness of active procedure. In 4 out of 10 procedures examined in this study, sham control RCTs showed active treatment to be no more effective than placebo, as opposed to conservative control RCTs, in which active treatment was superior. These findings might be explained by the placebo effect of sham surgery. In a study by Wartolowska et al. authors reported that in about three-quarters of the studies included in their meta-analysis an improvement was observed in both active and sham groups [8]. In other studies in the aforementioned meta-analysis, improvement was reported only in the active group and not in the placebo group. However, in most of these studies, outcome measures were not subjective. This is in accordance to the current study in which surgical placebo effect was shown only when subjective outcome measures were tested.

Interestingly, there is paucity of data in the medical literature evaluating and quantifying the "surgical" placebo effect.

In the current study, the placebo effect was measured to be 31% of the treatment effect.

The surgical placebo effect is thought to be comparable to other therapeutic interventions, accounting for up to 35 percent [6]. This is true only for subjective measured outcome. However, the authors of the current study are not aware to previous reported estimation of surgical placebo effect based on the comparison of conservative and sham surgery as a control for active treatment

An explanation to this result can be biologically explained in the study by Wagner et al. [7]. They have studied placebo brain effect on pain perception using functional MRI. When placebo treatment was given for pain treatment, lower activity was observed in functional MRI in brain area that is responsible for pain perception. For a better understanding of pain perception, further studies on the biological effect of pain and its treatment should be performed.

Interestingly the majority of studies included in this work were from the orthopedic discipline. This might be due to the fact that minimally invasive procedures are widely available in orthopedic surgery and the measured outcomes studied are subjective with emphasis on pain and quality of life.

Conducting research utilizing sham surgical procedures as control will always be a matter of debate from the ethical prospective. While some authors oppose [13], others are in favor or at least recognize their contribution in evaluating treatment efficacy [2,9,10]. Extensive efforts were made by different investigators to describe the circumstances for which sham surgery can be used in an ethically safe and justified way.

Additionally, using sham surgery as a control group when evaluating new surgical treatment may reveal that some surgical procedures had no additional effect over placebo effect of sham surgery and not comparing those surgeries to sham may expose patients to surgeries with questionable medical benefits.

Horng and Miller set an ethical framework for the use of sham procedures in clinical trials [12]. Their criteria for performing ethical sham control RCTs: [1] there is a valuable, clinically, relevant question; [2] the sham procedure is methodologically necessary; [3] the risk of the sham procedure has been minimized; [4] the risk of the sham control does not exceed acceptable risk; [5] the risk is justifiable; [6] the misleading of sham procedure is adequately disclosed. Based on the results presented in the current study, we support the use of sham surgery as control when conducting medical research. We propose adding additional criteria to Horng and Miller framework: [7] the outcome measures used in the study should be of a subjective nature.

CONCLUSION

To conclude, the study showed that sham control RCTs is safe to conduct and in subjective outcome it allows the researchers to study the true effect of suggested surgical treatment. Thus, Sham surgery has a role in evaluating new surgical therapies.

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