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Laser therapy reduces swelling, but not pain or trismus: a systematic review and meta-analysis

--Manuscript Draft--

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Abstract:	Surgical removal of wisdom teeth carries morbidity and significantly affects patients quality of life. This study aims to investigate whether administration of low-level laser therapy (LLLT) is effective in reducing post-operative morbidity in patients undergoing surgical removal of mandibular third molars (MTM) compared to placebo.Material & Methods: A systematic review and meta-analysis involving a comprehensive search strategy implemented across five electronic databases. This was supplemented by hand searching, contacting international experts and grey literature. Titles, abstracts and full articles were scrutinised for studies meeting the inclusion criteria. All randomised controlled trials (RCT) comparing treatment group of LLLT to a placebo control group were eligible for inclusion. The outcomes variables were post-operative pain, swelling and trismus. Risk of bias and methodological quality assessment was carried out. We pooled data statistically and meta-analyses were carried out using a random-effects model.Results;Seventeen RCTs were included in this systematic review, all of which were considered to have a low risk of bias. Participants, aged 13-70, and 35% female, totalled 1064. Meta-analyses found significant reductions in standardised mean differences (SMD) in swelling at day 2 and day 7 postoperatively (SMD -0.611, 95% CI -0.968, -0.234; SMD -0.532, 95% CI -0.795, -0.269). There were non-significant reductions in SMD in pain and trismus at day 2 and day 7 postoperatively. Conclusion;LLLT significantly reduces swelling after extraction of MTM compared to placebo. LLLT has not shown to reduce post-operative pain and trismus. LLLT does not cause adverse effects. There is currently insufficient evidence available, to promote the investment in LLLT versus the net clinical benefit. RCTs with larger sample size and standardised study design and outcome measures are required, to make definitive recommendations to clinicians on its use on patients.

Dear Dr Hupp,

Please can you consider this review article titled: 'The use of laser therapy to reduce postoperative morbidity following third molar surgery. A systematic review and meta-analysis' for publication in the Journal of Oral and Maxillofacial Surgery.

This original article has not been published in another journal nor has it been currently submitted or accepted for publication elsewhere. This systematic review and meta-analysis has been registered on the website of the International Prospective Register of Systematic Reviews; PROSPERO. (PROSPERO 2018 CRD42018112018. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018112018)

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The authors understand that the editor reserves the right to edit manuscripts to fit the space available and to ensure conciseness, clarity, and stylistic consistency.

I remain at your disposal, please do not hesitate to get in contact.

Kind regards,

Farya Domah

REVISION COVER LETTER
(Ms. Ref. No.: YJOMS-D-20-00976R1)

Dear Dr Hupp,
Thank you for your comments on the revised manuscript titled "Laser therapy reduces swelling, but not pain or trismus: a systematic review and meta-analysis."

I have made all changes as requested. I have itemised these below:

(1) *Please cite all references in numerical order in the text of the manuscript (Reference #15 does not appear to be cited and references 23, 45, and 46 appear to be out of order)*

The references have been adjusted. #15 error has been removed. Reference 23 has been moved to #31. References 46 and 46 have been changed to cite the 2009 publication before the 2010 publication.

I have uploaded this revision cover letter along with the revised manuscript via the relevant platform.

Thank you for your patience with my hand-written references as I am experiencing difficulties with my referencing software.
I look forward to hearing from you regarding consideration for acceptance for publication.

Kind regards

Farya Domah

Title page

Title

The use of laser therapy to reduce postoperative morbidity following third molar surgery. A systematic review and meta-analysis.

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"Laser therapy reduces swelling, but not pain or trismus: a systematic review and meta-analysis"

Abstract

Purpose

Surgical removal of third molars carries morbidity and significantly affects patients' quality-of-life. This study aims to investigate whether administration of low-level laser therapy (LLLT) is effective in reducing post-operative morbidity in patients undergoing surgical removal of mandibular third molars (MTM) compared to placebo.

Material & Methods

A systematic review and meta-analysis involving a comprehensive search strategy implemented across five electronic databases. This was supplemented by hand searching, contacting international experts and grey literature. Titles, abstracts and full articles were scrutinised for studies meeting the inclusion criteria. All randomised controlled trials (RCT) comparing treatment group of LLLT to a placebo control group were eligible for inclusion. The outcomes variables were post-operative pain, swelling and trismus. Risk of bias and methodological quality assessment was carried out. We pooled data statistically and meta-analyses were carried out using a random-effects model.

Results

Seventeen RCTs were included in this systematic review, all of which were considered to have a low risk of bias. Participants, aged 13-70, and 35% female, totalled 1064. Meta-analyses found significant reductions in standardised mean differences (SMD) in swelling at day 2 and day 7 postoperatively (SMD -0.611, 95% CI -0.968, -0.234; SMD -0.532, 95% CI -0.795, -0.269). There were non-significant reductions in SMD in pain and trismus at day 2 and day 7 postoperatively.

Conclusion

LLLT significantly reduces swelling after extraction of MTM compared to placebo. LLLT has not shown to reduce post-operative pain and trismus. LLLT does not cause adverse effects. There is currently insufficient evidence available, to promote the investment in LLLT versus the net clinical benefit. RCTs with larger sample size and standardised study design and outcome measures are required, to make definitive recommendations to clinicians on its use on patients.

Keywords: laser, third molar, pain, swelling, trismus, morbidity

INTRODUCTION

Description of the condition

An average of 25% of third molars are impacted and these teeth may require surgical removal[1]. The removal of third molars is not without complications. The general public is well aware of the common risks of third molar removal including pain, swelling and trismus. There are numerous other potential complications associated with removal of third molars; these include temporary or permanent damage to the inferior alveolar nerve, infection, bruising, damage to adjacent teeth, alveolar osteitis and in rare cases - fracture of the mandible[2].

Scale of the problem

Patients experience significant disturbances in their quality-of-life (QoL) in the five days following third molar surgery[3]. One of the main reasons for patients being unhappy with their surgical treatment is the experience of pain. Also, patients do not respond well to treatment that, albeit temporary, causes them facial deformity in the form of facial swelling. Pain, swelling and trismus arise as a result of an inflammation cascade set off by the surgical procedure[4]. Traditional methods for minimising the sequelae of post-operative pain, swelling and trismus include the use of analgesia, corticosteroids and cryotherapy. However, these modes all have varying degrees of side effects. Alternative efficacious methods have been welcomed; such as low-level laser therapy (LLLT). The beneficial effects of lasers on human tissue were recognized in the 1960s and introduced in the medical field[5].

A high number of in-vitro studies found that low level lasers are capable of influencing pain levels by a sequence of events; downregulation of biochemical proteins such as prostaglandins (PGE2), interleukins (IL-1), tumor necrosis factor, inhibition of cyclo-oxygenase-2 and influencing redox reactions at a cellular level[6]. Also, by decreasing vessel size and permeability, the influx of pro-inflammatory cytokines is controlled and thus the inflammatory phase is less acute[1]. Another effect of

laser is that it alters the central uptake and release of serotonin and acetylcholine and stimulates the production of endorphins while inhibiting bradykinin and C-fibers, thereby altering pain perception[7].

Other in-vitro studies have seen an increase in fibroblasts levels with LLLT and other studies have found lasers to have an angiogenic effect[8]. It is thought that the organelle, mitochondria, is the first to absorb the light energy from the laser. The charged mitochondria will increase its production of adenosine-triphosphate, which will in turn, increase cellular turnover including proliferation of fibroblasts, growth factors and tissue oxygenation[9]. In terms of clinical application, this suggests that areas affected by injury where an acidic medium prevails resulting in poor cellular proliferation can be treated by laser therapy[5].

The current evidence on LLLT

Examination of the evidence base revealed a systematic review and meta-analysis performed in 2012 and updated in 2017[7,10]. Conclusions drawn stated that LLLT did not show net benefits but bore no adverse effects. Since publication of these reviews, new randomised controlled trials (RCTs) have been published.

Study question

A study question was formulated as such: Do individuals undergoing surgical removal of impacted mandibular third molars have less post-operative pain, swelling and trismus with administration of low-level laser therapy compared to placebo?

Hypotheses

The investigators hypothesised that LLLT is effective in reducing pain, swelling and trismus after third molar surgery. The null hypothesis is that administration of low-level laser therapy has no effect on post-operative pain, swelling and trismus following surgical removal of impacted mandibular third molars.

Study aims

The specific aims of this study were to systematically review and meta-analyse the evidence on whether administration of low-level laser therapy is effective in reducing post-operative pain, swelling and trismus in patients undergoing surgical removal of lower third molars compared to placebo.

MATERIALS AND METHODS

Study design

To address the research purpose, the investigators designed and implemented a systematic review modelled after the Cochrane Collaboration recommendations for systematic reviews, in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)' guidelines[11].

The study population was composed of all publications on the topic of LLLT and surgical MTM removal up to May 2020. To be included in the sample, publications had to satisfy the following criteria: RCTs comparing efficacy of LLLT compared to placebo after surgical removal of third molars, LLLT operating at a wavelength between 600-1000nm of any regimen and reporting outcomes of pain, swelling or trismus. No restrictions were placed on subject characteristics. No language barriers were placed, and non-English texts were translated.

Publications were excluded from the analyses if they did not have a placebo arm or were non-human studies.

Due to the retrospective nature of this study, it was granted an exemption from formal ethical approval in writing by the University of Central Lancashire Institutional Review Board. This study has been registered on the website of the International Prospective Register of Systematic Reviews; PROSPERO; CRD42018112018[12].

Variables

Treatment group

The treatment groups included subjects having received LLLT after surgical removal of MTMs. LLLT, known as biostimulation, causes a photochemical effect that can upregulate metabolism resulting in wound healing and reduce inflammatory processes. All lasers defined as low-level with a wavelength of 600-1000nm were included. All laser types such as diode lasers, infrared lasers, helium-neon and gallium-aluminium-arsenic lasers were included. The power generated by these respective lasers was between 10-500mW. The duration of application were between 15 and 180 seconds with an energy output between 3-12J/cm^2. Laser emission was either continuous or intermittent. The timing of laser therapy was either pre-operative, immediate post-operative or delayed post-operative, in either single or multiple applications. The laser was applied either intra or extraorally or both. The authors were not comparing efficacy of different laser types, wavelengths, power, energy output and duration; therefore, outcomes involving these variables were pooled by calculating their weighted average across the treatment arms. Subgroup analyses were performed for intraoral and extraoral laser application.

Control group

All subjects in control groups had placebo therapy. The placebo involved mimicking application of laser therapy with absence of photon energy transfer.

Predictor variables

The primary predictor variables were postoperative pain, swelling and trismus and were reported for day 2 and day 7 postoperatively. For studies that did not include outcomes on these days, data obtained from the closest time point was considered.

Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. This outcome was assessed using the visual analogue scale (VAS). This patient

reported outcome measure is an instrument that aims at measuring pain intensity and ranges across a continuum of values between 0 and 10. Mean postoperative pain values were used for meta-analyses.

Swelling or oedema is the result of fluid accumulation in the soft tissues. Measurement of swelling is challenging as it can present in different tissue planes and can be localised or diffuse. As such, measurements of swelling are rarely standardized. Subgroup analyses were conducted for the most used methods of swelling assessment; distance between tragus and commissure; distance between gonion and canthus and Amin & Laskin method (measured as distance between commissure and lower part of auricular lobe & distance between canthus and angle of mandible)[13].

Trismus describes the state of reduced mouth opening and is usually secondary to pain, swelling and pathology. It is measured in millimetres as the distance from the maxillary incisal edge to the mandibular incisal edge. Studies not using this method of assessment were not included in the meta-analyses.

Other variables

Intrinsic variables such as age, sex and pain sensitivity are well recognized modifiers of pain, swelling and trismus. Extrinsic variables in the form of co-interventions such as antibiotics, analgesics, steroids and mouthwashes can confound the findings by amplifying the effect of LLLT.

Search methods

A comprehensive search strategy was used and several databases were searched for published studies from inception of these respective databases to May 2020: Medline, Embase, Dentistry and Oral Sciences Source, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Academic Search Complete, Cochrane Library. Ongoing and unpublished trials were searched on: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Internet-based databases were also searched: www.ClinicalTrials.gov, www.controlledtrials.com, www.scholar.google.co.uk. References from eligible published studies were scrutinised by hand searching: Journal of American Dental Association, International Journal of Oral and Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery. Grey literature search was performed on 'OpenGrey'. Experts in the field were contacted if further information was required. Search was performed from conception of electronic databases. No search restrictions were placed at this stage. Search criteria can be found in Appendix A.

Data collection method

The results obtained from each of the 5 respective electronic databases were transferred to the referencing software Refworks©. Duplicate results were then eliminated. The title and abstracts of the remaining studies were then screened for eligibility and any non-relevant articles were excluded. Potential salient trials were assessed in full text format and cross-referenced against inclusion and exclusion criteria. Trials not meeting the inclusion criteria were eliminated.

This process was performed in duplicate by two independent reviewers. Disagreements were resolved by consensus and when no consensus could be reached, a third investigator acted as an arbitrator.

The final studies were evaluated by two investigators independently and in duplicate. Distillation of information was expediated using custom designed data extractions tables. The risk of bias in the included studies were evaluated using the Cochrane Risk of Bias Tool. Again, this was performed by

two reviewers independently to reach a mutual consensus. Risk was classified as low, high or unclear. If data was missing, the authors were contacted to obtain information.

Data analyses

We pooled data statistically and conducted meta-analyses on available outcomes using a random-effects model. All analyses were undertaken, and forest plots created using Comprehensive Meta-Analysis software (version 3). Results were expressed as standardised mean differences (SMD) with 95% confidence intervals (CI) for dichotomous outcomes. We performed statistical tests for heterogeneity based on I^2 statistic. Relevant heterogeneity will be tested for using the I^2 statistic and significant heterogeneity assumed if I^2 is greater than 40% (i.e. more than 40% of the variability in outcome between trials could not be explained by sampling variation). We assessed for evidence of publication bias graphically using Funnel plots and statistically using Egger's test[14].

In the analysis of swelling, models were selected based on the methods of assessing swelling: method 1 – distance between tragus and commissure; method 2- Amin & Laskin method; method 3 – distance between gonion and canthus.

RESULTS

Description of studies

Four hundred and sixty-two results were obtained from the five databases searched. Hand searching produced 5 additional papers making a total of 467 papers. Eighteen studies were excluded at the full text screening stage with justification[7,10,15-30]. Seventeen studies met the inclusion criteria[1,31-46]. The flow of information is illustrated in a PRIMSA diagram, see Figure 1.

All 17 studies were randomised controlled trials. However, the study designs varied. Nine studies had a split-mouth design[33-37,40-42,46]. The rest of the studies had parallel designs[1,31,32,38,39,43-45]. All 17 studies followed study subjects for at least 7 days.

A total of 1064 study subjects participated across the 17 studies. Two studies did not record participant gender and age[31,43]. The study subjects were aged between 16- 70 years and there were 370 recorded female subjects. All studies took place in a hospital setting. The general characteristics of included studies is presented in Table 1.

All 1064 study subjects in the studies had surgical removal of their lower third molars followed by either laser therapy or placebo. However, the LLLT regimens varied in the type of LLLT used, the approach, power, site and duration of application. Table 2 presents the LLLT regimen employed within each study. Several co-interventions were also employed within the studies. Subjects had prophylactic antibiotic in nine studies[1,32,34-37,42,44-46]. Seven studies provided oral acetaminophen to be taken post-operatively[27,32,35,40,41,44,45]. Six studies prescribed non-steroidal anti-inflammatory (NSAID) post-operative medication [1,34,36,37,42,46]. All 17 studies had used placebo as a comparator[1,31-46].

Risk of bias of included studies

Using the 'Cochrane Risk of Bias Assessment Toolkit', seven studies had adequate randomization processes[33-36,38,39,46]. Ten studies stated that their study subjects were randomized but did not specify their method of randomization[1,31,32,37,40-45]. One study discussed allocation concealment[33]. Three studies mentioned that subjects were randomized only after the surgery was performed[1,38,40]. By randomizing after the surgery, both the surgeon and patient would be unaware of future treatment allocation. Surgeons were blinded in five studies[33,34,37,38,42]. Three studies used different surgeons to perform the surgery and administer the laser, but it was unclear as to whether the surgeons were blinded[31,32,35]. All study subjects in the 17 studies were blinded to the intervention they received[1,31-46]. Three studies had made available their study protocol[31,33,38]. In 16 studies, the prespecified outcomes set out in the aims have been reported on and discussed[1,31,32-38,40-46]. One study carried out a sample

size calculation[33]. Treatment and follow-up protocols were the same for both treatment and control groups across the studies. Seven studies declared no interests[1,31,32,34-36] and three studies declared funding[43,44,46]. After consideration of each domain, calculation of an overall risk of bias for each study found that all 17 studies had a lower overall risk of bias[1,31-46]. Figure 2 illustrates a traffic light system to categorise the risk of bias for each respective domain for each study.

Efficacy of LLLT

Pain

Fifteen studies, with a total of 66 subjects, measured pain[1,31,32-43,46]. Ten studies found that LLLT reduces pain in subjects post-operatively[1,32,35-38,40,41,46]. Five of these studies reported that the pain reduction was statistically significant[32,34,37,38]. Three studies found no clinical nor statistical difference in pain levels between the treatment and control group[31,33,43]. In one study, LLLT showed higher pain scores compared to placebo in the four hours after surgery[39]. The included trials had a degree of variation in the times at which measurements were performed; the statistical analysis and the study designs. Saber et al., in addition to pain intensity, also measured pain duration. Laser group participants had shorted duration of pain compared to control groups in that study[38].

Five out of 15 studies that reported pain, demonstrated homogeneity and were included in meta-analyses. The results showed not significant reductions in standardised mean differences (SMD) for pain on day 2 and day 7 in the intervention group compared to the control group(SMD -0.502, 95% CI -1.038, 0.034; SMD -0.244, 95% CI -0.542, 0.053, respectively). See Figures 3 & 4. The funnel plot suggests there is potential publication bias based on asymmetry; however, the Eggers regression intercept suggests publication bias[14]. It is important to note however that this must be interpreted with caution as it has been suggested the use of this test with less than 10 studies reduces its power[47]. See Figure 5.

Swelling

Eleven studies, with a total of 380 subjects, looked at swelling as an outcome measure[1,32,33,36,37,40,42-46.] The measurement of swelling differed across the studies. Most swelling measurements were taken as the distance between two facial points. Facial landmarks used were: tragus, commissure of mouth, gonion, canthus and auricular lobe. Two studies used the Amin and Laskin method[44,45]. Two studies used observed values[42,43]. One study used a 3-dimensional photogrammetric system to measure volumetric postoperative swelling[32]. Seven of these studies found clinically important reduction in facial swelling among the laser groups compared to the placebo groups[1,32,36,37,42,43,44]. Only 2 studies showed statistically significant reduction in swelling between laser and control group[44,46].

Five out of 11 studies demonstrated homogeneity and were included in the meta-analyses. The overall analysis of these five studies demonstrated significant reductions in swelling with either intraoral or extraoral application of LLLT on day two in the models with swelling assessment method (SMD -0.557, 95%CI -0.925, -0.189 and SMD -0.611, 95%CI -0.988, -0.234, respectively). See Figures 6 & 7.

The overall analysis of the five studies also found significant reductions in swelling with both intra-oral and extra-oral application of LLLT in Aras et al. 2010 and with swelling coefficient as the method of swelling assessment in Eshghpour et al. 2016 on day 7 (SMD -0.513, 95%CI -0776, -0.250 and SMD -0.532, 95%CI -0.795, -0.269, respectively). See figures 8 and 9.

Analysis of three studies that used tragus to commissure as the method of swelling assessment found a not significant reduction in swelling on day two (SMD -0.448, 95%CI -0.968, 0.071) and a statistically significant reduction on day seven (SMD -0.443, 95%CI -0.786, -0.101) in the LLLT group compared to the control group. See Figures 10 & 11.

Analysis of two studies that used Amin & Laskin method as their method of swelling assessment found significant reductions in swelling in either intraoral and extraoral LLLT groups compared to controls

on day two (SMD -0.760, 95%CI -1.326, -0.195 and SMD -0.931, 95%CI -1.448, -0.415, respectively) and day seven (SMD -0.667, 95%CI -1.172, -0.163 and SMD -0.740, 95%CI -1.247, 0.233, respectively). See Figures 12, 13, 14 & 15.

Analysis of two studies that used distance between gonion and canthus as their method of swelling assessment found a significant reduction with LLLT on day two (SMD -0.603, 95%CI -1.112, -0.094) but not on day seven (SMD -0.441, 95%CI -1.740, 0.858, respectively). See Figures 16 & 17.

Trismus

Eleven studies, with a total number of 398 study subjects, measured trismus[1,32-34,36,39,41,43-46]. Two of them found statistically significant reduction in trismus with laser group compared to placebo[39,44]. The most popular method of measurement was distance from upper central incisors to lower central incisors. One study measured percentage trismus[39] and one study used observed values[43].

Six out 11 studies, demonstrated homogeneity and were included in the meta-analyses. The results showed no difference between LLLT and control groups, regardless of site of laser in Aras et al 2009, 2010 and day of assessment in Farhadi et al. 2017 were included in the models. Figures 18 & 19 present respective results for day two (SDM 0.002, 95%CI -1.159, 1.163 and SDM 0.075, 95%CI -1.187, 1.036) and Figures 20 and 21 for day seven (SDM 0.068, 95%CI -0.469, 0.605 and SDM 0.143, 95%CI -0.471, 0.758).

DISCUSSION

The purpose of this study was to investigate the benefits of LLLT in post-operative healing after surgical exodontia. The authors hypothesized that LLLT was effective in reducing post-operative sequelae after oral surgery. The null hypothesis was that administration of LLLT had no effect on post-operative healing. The specific aims of this study were to systematically review and meta-analyse the evidence on whether administration of low-level laser therapy was effective in reducing post-operative pain, swelling and trismus in patients undergoing surgical removal of lower third molars compared to placebo.

Seventeen RCTs were included in the review[1,31-46]. Data was statistically pooled to achieve meta-analyses for each overall outcome.

The results of this study show statistically significant reduction in post-operative swelling with the use of LLLT compared to placebo after dental surgery. LLLT does not significantly reduce pain or trismus after surgery as compared to placebo.

While statistical significance indicates the reliability of the study results, clinical significance reflects its impact on clinical practice. Many studies included in this review generalised statements on clinically important differences and statistical significance as related to the outcome variables. However, no studies, described clear parameters on what they considered to be clinically significant.

Ten out of seventeen studies reported clinically important positive differences in pain levels with the laser group compared to the placebo group[1,32,35-38,40,42,46]. However, only five of these respective studies showed statistically significant improvement[32,34,35,37,38].

Seven studies demonstrated clinical reduction in swelling in the LLLT over the control group[1,32,36,42-44]. However, only two of these demonstrated this reduction in swelling with LLLT over placebo to be statistically significant[37,44]. Investigators across the studies used different facial landmarks or observed values to measure swelling. This heterogeneity may account for the lack of consistency in the effectiveness of LLLT on swelling reduction.

From the eleven studies that reported on trismus as an outcome measure, two of them demonstrated statistically significant reduction in trismus in LLLT group compared to control[39,44]. Four of them found LLLT to have no net benefit in reducing trismus following third molar surgery[1,32,33,36].

With regards to extrinsic variables in the form of co-interventions, post-operative medication was given in most of the studies[1,32-37,40-46]. The medications included antibiotics, analgesia and mouthwashes. Co-interventions along with LLLT can certainly confound the findings. Due to the fact that co-interventions were the same in treatment and control groups, any size of treatment effect would be attributed to the laser alone. The lack of standardization in both intrinsic and extrinsic variables across the studies did not allow pooling of data and effect measurement.

All studies lasted at least seven days[1,31-46]. A seven day follow up period is appropriate as the sequelae of IMTM surgery is short lived[36]. Pain, swelling and trismus are at their highest in the first 2 to 3 days after surgery and mostly subsides by the seventh day.

Three studies received funding[43,45,46] and 7 studies declared no conflict of interests[31,32,34-36,43,44]. Three studies specifically stated that LLLT bore no negative outcomes[33,35,36]. Thus, it appears that application of LLLT is safe as there is no evidence to suggest otherwise.

This systematic review and meta-analysis updated the evidence presented by Brignardello et al. and Dawdy et al on the use of low-level laser therapy in reducing the post-operative complications of pain, swelling, trismus following surgical removal of impacted third mandibular molars[7,10].

Brignardello et al. reported that LLLT was not effective in reducing pain and swelling, but effective in reducing trismus after removal of IMTMs compare to placebo[7]. Dawdy reported negligible benefits from LLLT[10]. This is not mirrored by the findings of this review which concluded a significant reduction in swelling but pain or trismus following surgery.

The recommendations stated by Brignardello et al. on the need for more well-reported RCTs with standardized methods and timings of evaluating the outcomes of interest appears to have been

followed[7]. The new studies had low overall risk of bias, they administered laser therapy at the same time, most of them used the VAS for pain measurement and trismus measurements were standardised.

This review had several strengths. First, the searches were conducted with high methodological rigour involving comprehensive searches and including all available sources from five electronic international databases. Characteristics of all search terms including MeSH and free keywords for this topic were carefully identified and scrutinised. In addition, we contacted an international panel of experts. A comprehensive search strategy would ensure that no relevant studies would be inadvertently excluded.

Second, this review included 17 studies, totalling 1064 study subjects compared to Brignardello et al. who reported on 10 studies involving 740 subjects[7]. Our significant sample size increases the study power.

Third, all included studies were high quality randomized controlled trials with low risk of bias. On the pyramid of hierarchy of evidence, this is Level 1b evidence, which is the most robust type of empirical evidence when assessing the outcome of an intervention.

Fourth, all the subjects across the studies were treated in a hospital setting. This is in line with the fact that surgical removal of MTMs require specialist intervention. Presumably, the level of competence of the surgeons would be similar across the trials; which further standardizes the surgery. This ensures that any difference in outcome assessment is down to the intervention (i.e LLLT) alone.

All recruits across the studies required surgical removal of MTMs. This strict inclusion criteria ensured that the outcome assessments were not confounded by differences in baseline characteristics. The 17 included studies were performed in several countries across the world. The results of this study are therefore generalizable internationally as the study populations came from both economically developed and less economically developed countries [1,31-46].

The main limitations of this systematic review stem from the heterogeneity; both clinical and methodological of included populations, diversity of measuring outcomes and their definitions. The results of both split mouth and parallel trials were pooled together. The significance of the heterogeneity in study design is not known; however, despite differences in study approach, the designs were of high quality and low risk of bias, minimizing risk of spurious findings.

The non-significant data on pain and trismus does not mean that there is no efficacy of the intervention compared with controls. Several factors may play a role, including small sample size issues in our meta-analyses. Due to the heterogeneity of included studies, the conducted meta-analyses need to be interpreted with caution.

Despite the postulated benefits of LLLT after surgery, there are still barriers to its use and implementation in oral and maxillofacial clinics. Implementation of laser treatment requires capital investment in the form of equipment, training and clinical time. Furthermore, implementation of any novel therapy has a significant learning curve. None of the studies have discussed the cost implications and effectiveness of laser provision compared to pharmaceutical management. On the surface, pharmaceutical management after removal of third molars appears to be a cost-effective option that does not require additional investment. Estimates on the cost of a helium-neon laser is from $14,000. Additional training costs make this a high initial investment therapy. So far, there is insufficient evidence to recommend this investment as a standard of practice for oral surgery.

Furthermore, no studies have completed an oral health related quality of life (OHRQoL) assessment on the use of LLLT following surgical removal of MTMs. The authors are therefore unable to comment on the impact of LLLT on quality of life (QoL) following oral surgical procedures. As such, this would be an area of interest for future research.

In conclusion, adults undergoing surgical removal of impacted mandibular third molars have significantly less postoperative swelling with administration of low-level laser therapy compared to placebo. Adults undergoing surgical removal of impacted mandibular third molars do not appear to

have less postoperative pain and trismus with administration of low-level laser therapy compared to placebo.

Few studies have investigated the use of low-level laser therapy after surgical removal of impacted mandibular third molars; therefore, this study makes a significant contribution to the evidence base. There is, however, not yet enough evidence to promote the investment involved with the routine use of laser therapy after third molar surgery.

Future, high quality RCTs with standardization of study designs, outcome measures and LLLT regimen, together with an investigation into its cost-effectiveness would serve to better advise patients, doctors and policy makers about the use of low-level laser therapy in patients undergoing removal of impacted mandibular third molars.

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Table 1. Characteristics of included studies.

Study	Design	Age	Gender	Intervention participants	Placebo participants
Carillo et al., 1990	Parallel	Mean 27	67F 33M	34	34
Clokie et al., 1991	Split-mouth	Range 16-25	10F 5M	15	15
Fernando et al., 1993	Split-mouth	Range 18-50	Not recorded	64	64
Braams et al., 1993	Split-mouth	Range 17-35	24F 19M	43	43
Fikackova et al., 2003	Parallel	Not recorded	Not recorded	1	1
Aras et al., 2009	Parallel	Range 18-27	21F 11M	16	16
Aras et al., 2010	Parallel	Range 18-27	34F 14M	32	16
Lopez-Ramirez et al., 2017	Split mouth	Range 18-37	11F 9M	20	20
Saber et al., 2012	Parallel	Range 18-70	50F 50M	50	50
Sierra et al., 2015	Parallel	Range 13-60	Not recorded	40	20
Eroglu et al., 2016	Split-mouth	Range 18-40	15F 20M	35	35
Eshghpour et al., 2016	Split-mouth	Range 18-35	24F 20M	44	44
Kahraman et al., 2017	Split-mouth	Range 16-35	36F 24M	60	60
Farhadi et al., 2017	Parallel	Range 18-35	24F 24M	24	24
Hamid et al., 2017	Split-mouth	Range 19-29	16F 14M	30	30
Sampaio et al., 2018	Split-mouth	Range 18-28	13F 29M	42	42
Asutay et al., 2018	Parallel	Range17-29	25F 20M	15	15

Table 2. Low level laser therapy regimen employed across the included studies

Study	Type	Wavelength	Power	Energy	Site	Duration	Mode	Timing	Comparison
Carillo et al., 1990	He-Ne	632.8nm	0.3W/cm²	10J/cm²	Intraoral	Not recorded	Not recorded	Postoperatively	Placebo
Clokie et al., 1991	He-Ne	632.8nm	10mW	Not recorded	Intraoral	180s	Continuous	Postoperatively	Placebo
Fernando et al., 1993	Ga-Al-As	830nm	30mW	4J/cm²	Intraoral	132s	Intermittent	Postoperatively	Placebo
Braams et al., 1994	Ga-Al-As	829mn	30mW	NR	Intraoral	66s	Not recorded	Not recorded	Placebo
Fikackova et al., 2003	Ga-Al-As	830nm	200mW/cm²	12J	Intraoral	108s	Intermittent	10min, 1& 3 days after surgery	Placebo
Aras et al., 2009	Ga-Al-As	808nm	100mW	12J/cm²	Intraoral Extraoral	120s	Not recorded	Postoperatively	Placebo
Aras et al., 2009	Ga-Al-As	808nm	100mW	12J	Intraoral Extraoral	120s	Continuous	Postoperatively	Placebo
Lopez-Ramirez et al., 2001	Ga-Al-As	810nm	500mW	4j/cm²	Intraoral	32s	Continuous	Postoperatively	Placebo
Saber et al., 2012	Diode laser	810nm	100mW	5J/cm²	Intraoral	Not recorded	Continuous	Postoperatively	Placebo
Sierra et al., 2015	Red diode laser Infrared laser	652nm 808nm	100mW	106J	Intraoral Extraoral	120s 120s	Continuous	Not recorded	Placebo
Eroglu et al., 2016	Diode laser	940nm	275mW	50J	Extraoral	Time to reach 50J	Continuous	Postoperatively	Placebo
Eshghpour et al., 2016	Diode laser GA-Al-As	660nm 810nm	200mW	6J/cm²	Intraoral Extraoral	120s 90s	Continuous	Not recorded	Placebo
Kahraman et al., 2017	GA-Al-As	830nm	100mW	3J/cm²	Intraoral Extraoral	15s	Continuous	Preoperatively Postoperatively	Placebo

Farhadi et al., 2017	Diode laser	550nm	100mW	5J/cm²	Intraoral	25s	Continuous	Postoperatively	Placebo
Hamid et al., 2017	Ga-Al-As	810nm	100mW	9J	Intraoral	90s	Continuous	Postoperatively	Placebo
Sampaio, 2018	Red diode laser	660nm	100mW	6J	Extraoral	60s	Not recorded	Immediately, 24hr, 48hr postoperatively	Placebo
Asutay, 2018	Ga-Al-As	810nm	300mW	12J	Extraoral	40s	Continuous	Postoperatively	Placebo

APPENDIX A

#	Query
1	MH molar third
2	MH tooth impacted
3	MH tooth extraction
4	Exodontia
5	lower third molar
6	third molar
7	third molar surgery
8	t??th extract*
9	dental extraction
10	wisdom t??th
11	impact* t??th
12	mandibular t??th
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	MH low-level light therapy
15	MH laser therapy
16	MH lasers
17	laser*
18	laser irradiation
19	LLLT
20	laser therapy
21	low level light therapy
22	low level laser therapy
23	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24	MH pain
25	MH pain measurement
26	MH pain postoperative
27	pain
28	discomfort
29	postoperative pain
30	#24 OR #25 OR #26 OR #27 OR #28 OR #29
31	MH edema
32	edema
33	oedema
34	swelling
35	#31 OR #32 OR #33 OR #34
36	MH trismus
37	trismus
38	mouth opening
39	lock* jaw
40	#36 OR #37 OR #38 OR #39
41	treatment outcomes
42	wound healing
43	#34 OR #35

44	#30 OR #35 OR #40 OR #43
45	**#13 AND #23 AND #44**

Figure 1. PRISMA diagram illustrating flow of information from search strategy to final included studies.

Figure 2: Risk of bias analysis of the included studies

Figure 3. Forest plot showing standardised mean differences and 95% CI for changes in pain reduction on day 2 after LLLT vs controls following third molar surgery (random-effects model).

Figure 4. Forest plot showing standardised mean differences and 95% CI for changes in pain reduction on day 7 after LLLT vs controls following third molar surgery (random-effects model).

Figure 5. Funnel plot showing SMD of pain reduction following LLLT intervention vs controls.

Figure 6 (overall). Forest plot showing standardized mean differences and 95% CI for swelling on day 2 after LLLT vs control following third molar surgery (random-effects model) [Aras Intra-oral laser]

Figure 7 (overall). Forest plot showing standardized mean differences and 95% CI for swelling on day 2 after LLLT vs control following third molar surgery (random-effects model) [Aras extra-oral laser]

Figure 8 (overall). Forest plot showing standardized mean differences and 95% CI for Swelling on day 7 after LLLT vs control following third molar surgery (random-effects model) [Eshghpour 2016 a = Distance between tragus and commissure (swelling coefficient) - Aras 2010 Intra-oral laser]

Figure 9 (overall). Forest plot showing standardized mean differences and 95% CI for Swelling on day 7 after LLLT vs placebo following third molar surgery (random-effects model) [Eshghpour 2016 a = Distance between tragus and commissure (swelling coefficient) - Aras 2010 Extra-oral laser]

Figure 10. Forest plot showing standardized mean differences and 95% CI for Swelling (tragus to commissure) measurement on day 2 after LLLT vs placebo following third molar surgery (random-effects model)

Figure 11. Forest plot showing standardized mean differences and 95% CI for Swelling (tragus to commissure) on day 7 after LLLT vs placebo following third molar surgery (random-effects model).

Figure 12. Forest plot showing standardized mean differences and 95% CI for swelling (Amin & Laskin method) on day 2 after LLLT (intra-oral laser) vs control following third molar surgery (random-effects model)

Figure 13. Forest plot showing standardized mean differences and 95% CI for swelling (Amin & Laskin method) on day 2 after LLLT (extra-oral laser) vs control following third molar surgery (random-effects model)

Figure 14. Forest plot showing standardized mean differences and 95% CI for swelling (Amin & Laskin method) on day 7 after LLLT (intra-oral laser) vs control following third molar surgery (random-effects model)

Figure 15. Forest plot showing standardized mean differences and 95% CI for swelling (Amin & Laskin method) on day 7 after LLLT (extra-oral laser) vs control following third molar surgery (random-effects model)

Figure 16. Forest plot showing standardized mean differences and 95% CI for swelling (gonion & canthus) on day 2 after LLLT vs control following third molar surgery (random-effects model)

Figure 17. Forest plot showing standardized mean differences and 95% CI for swelling (gonion & canthus) on day 7 after LLLT vs control following third molar surgery (random-effects model)

Figure 18. Forest plot showing standardized mean differences and 95% CI for trismus on day 2 after LLLT vs control following third molar surgery (random-effects model) [For Aras 2010 extra-oral laser data used - Farhadi 2017 day 1]

Figure 19. Forest plot showing standardized mean differences and 95% CI for trismus on day 2 after LLLT vs control following third molar surgery (random-effects model) – [For Aras 2010 intra-oral laser data used - Farhadi 2017 day 1]

*Figure 20. Forest plot showing standardized mean differences and 95% CI for trismus on day 7 after LLLT vs control following third molar surgery (random-*effects model) [For Aras 2010 intra-oral laser data used*]*

Figure 21. Forest plot showing standardized mean differences and 95% CI for trismus on day 7 after LLLT vs control following third molar surgery (random-effects model) [For Aras 2010 extra-oral laser data used]

Figure 1

Click here to access/download;Figure;Figure 1 - PRISMA diagram.tif

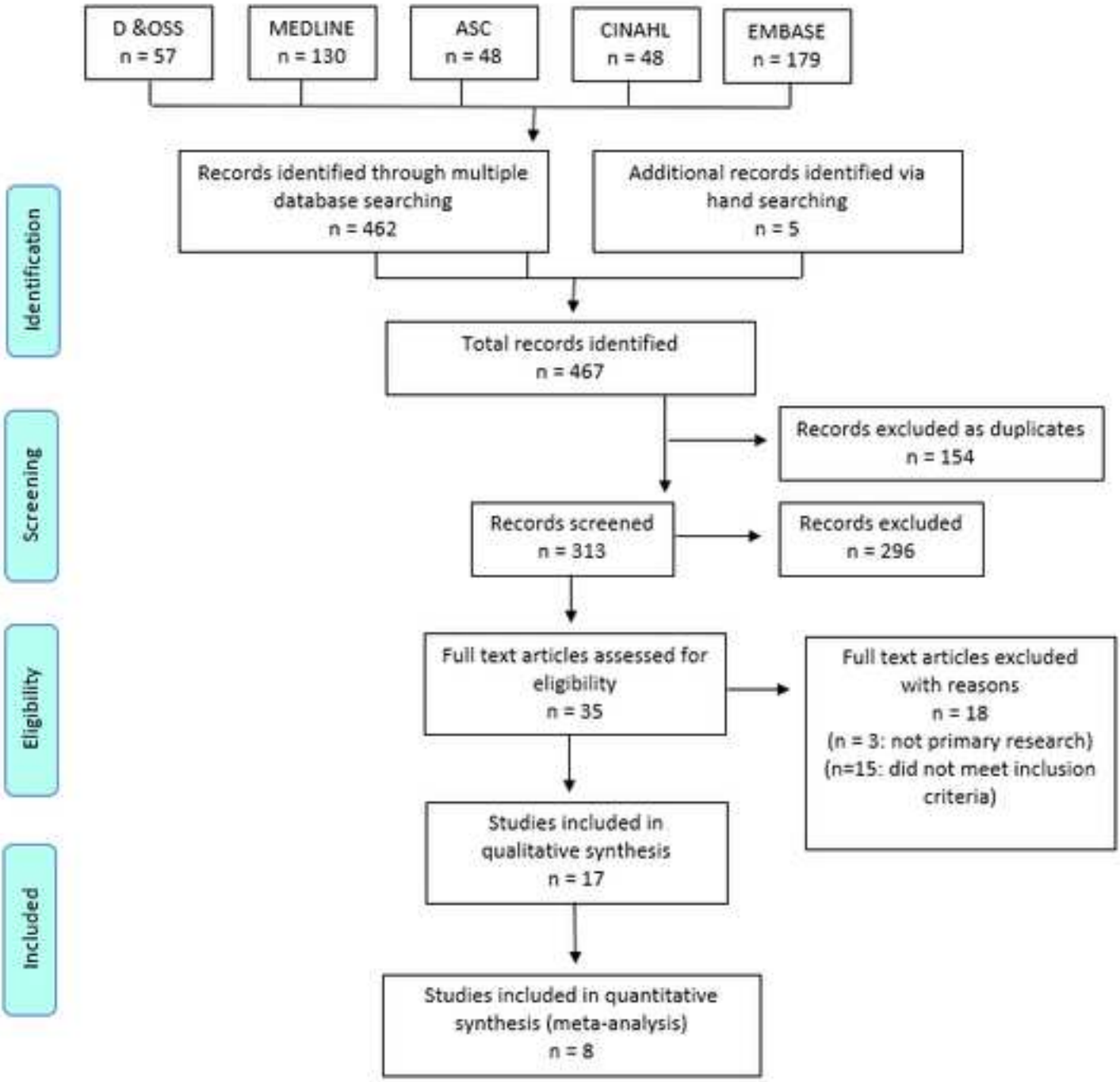


Figure 2

Click here to access/download;Figure;Figure 2 - Risk of bias analysis.tif

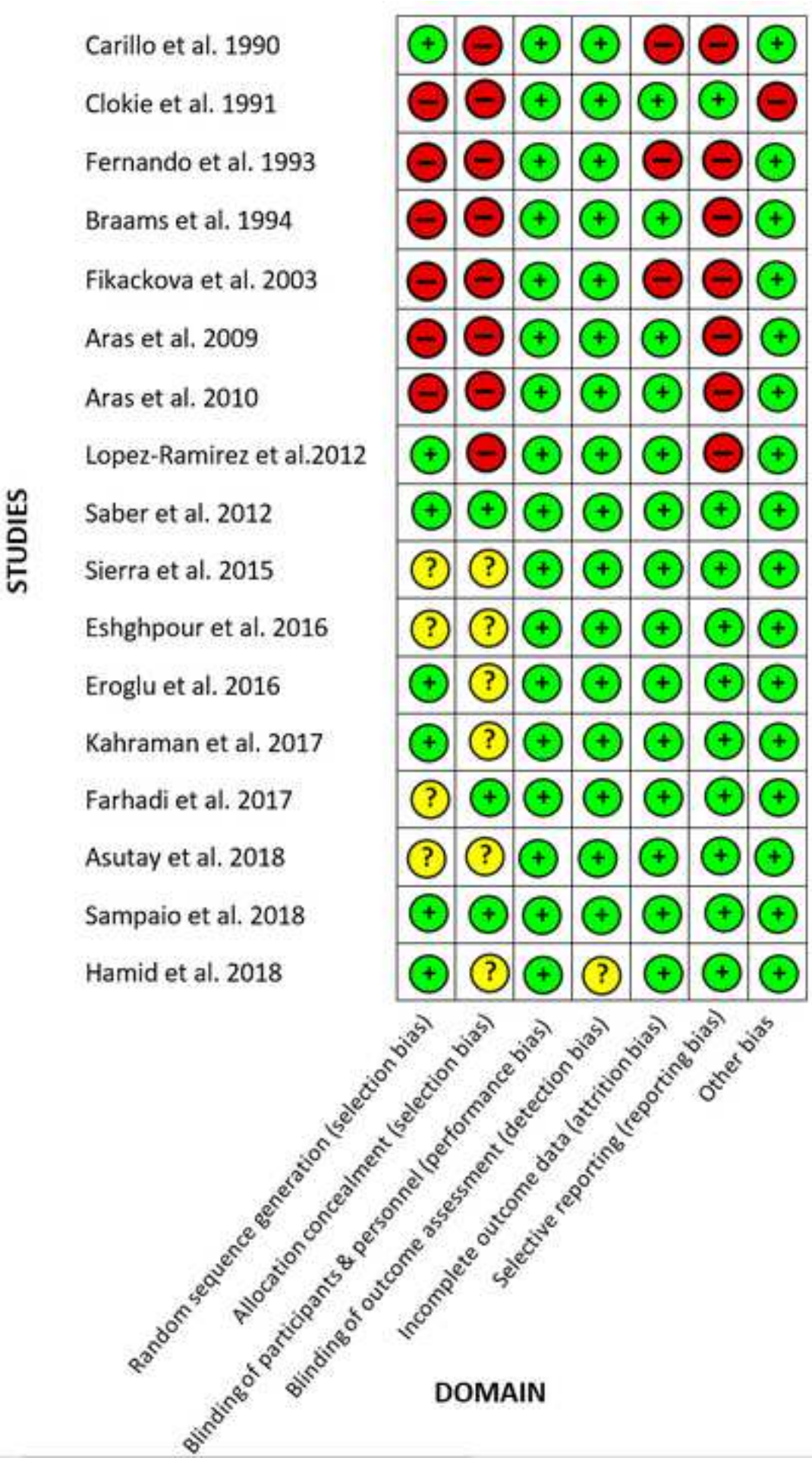
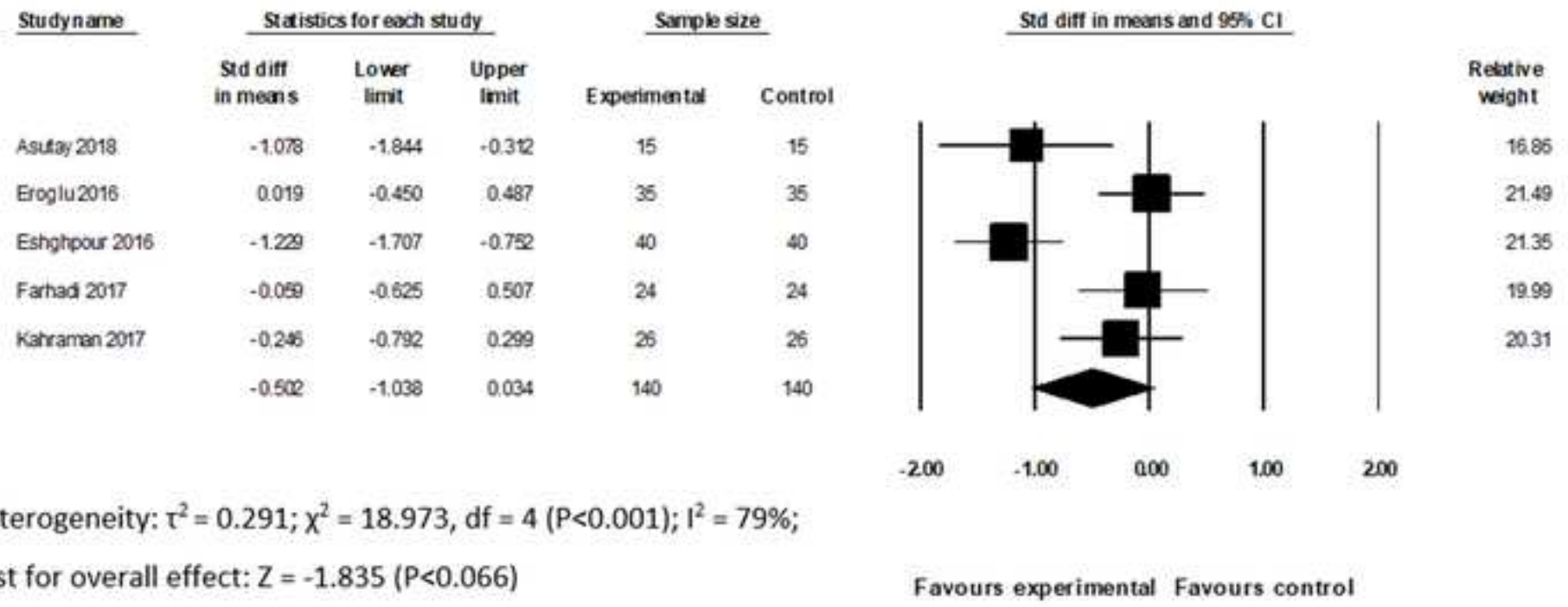


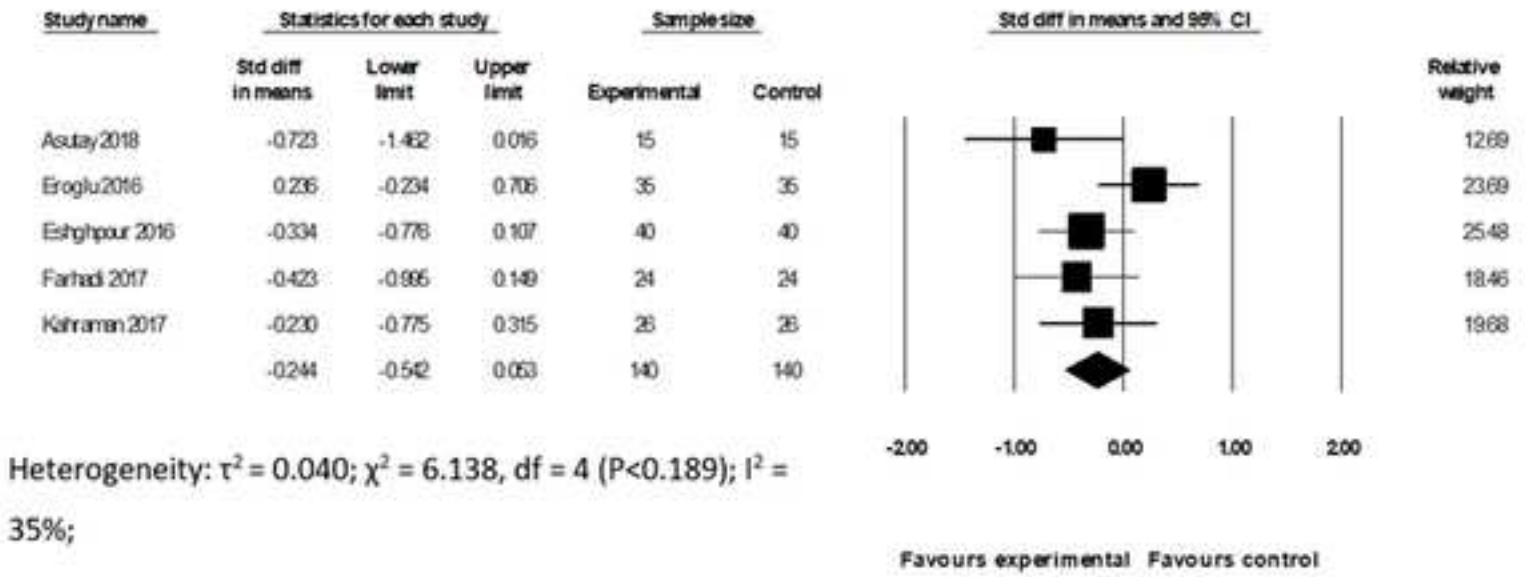
Figure 3



Heterogeneity: $\tau^2 = 0.291$; $\chi^2 = 18.973$, df = 4 ($P<0.001$); $I^2 = 79\%$;

Test for overall effect: $Z = -1.835$ ($P<0.066$)

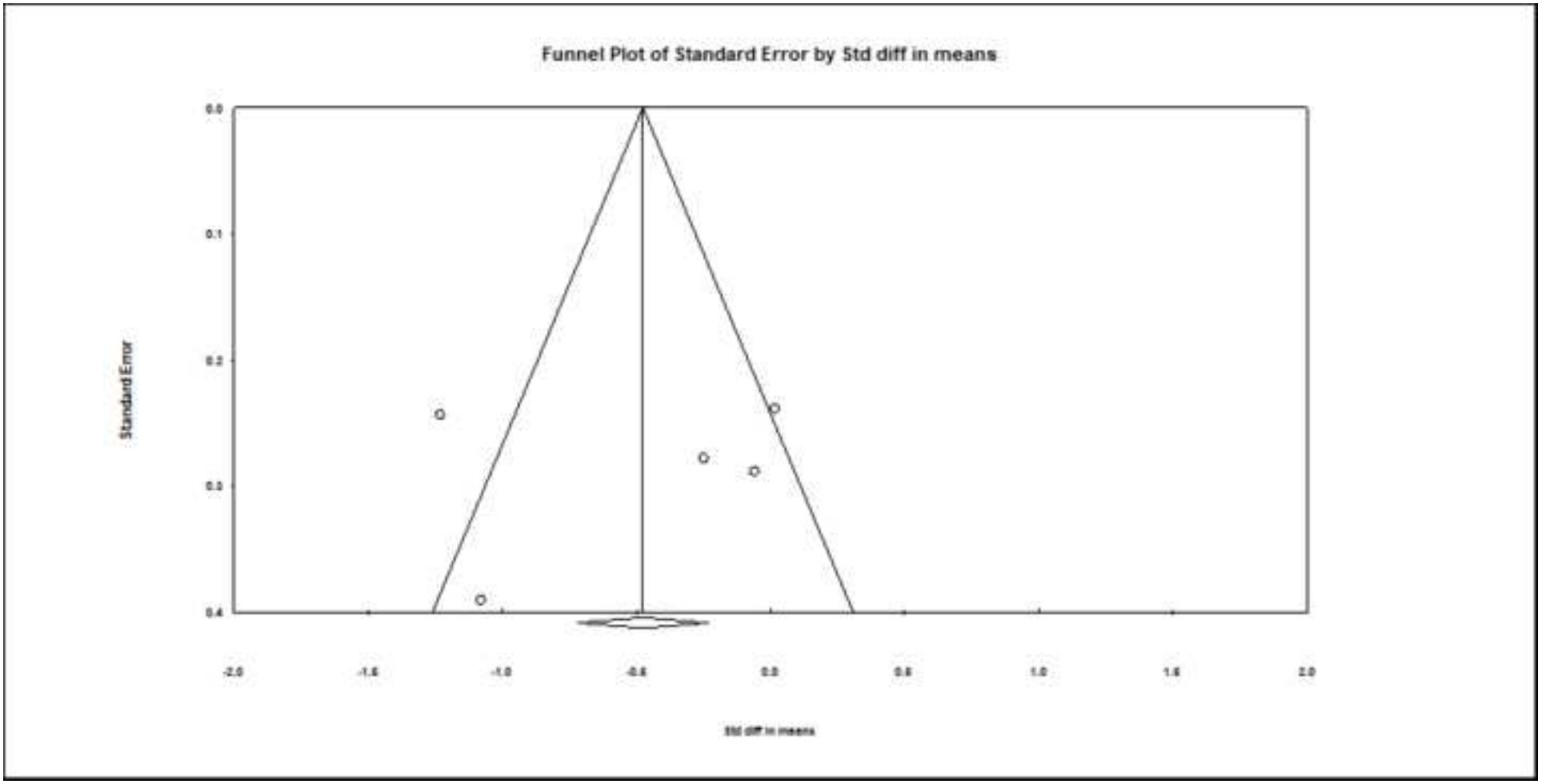
Figure 4



Heterogeneity: $\tau^2 = 0.040$; $\chi^2 = 6.138$, df = 4 ($P<0.189$); $I^2 = 35\%$;

Figure 5

Click here to access/download;Figure;Figure 5 - Funnel plot.tif



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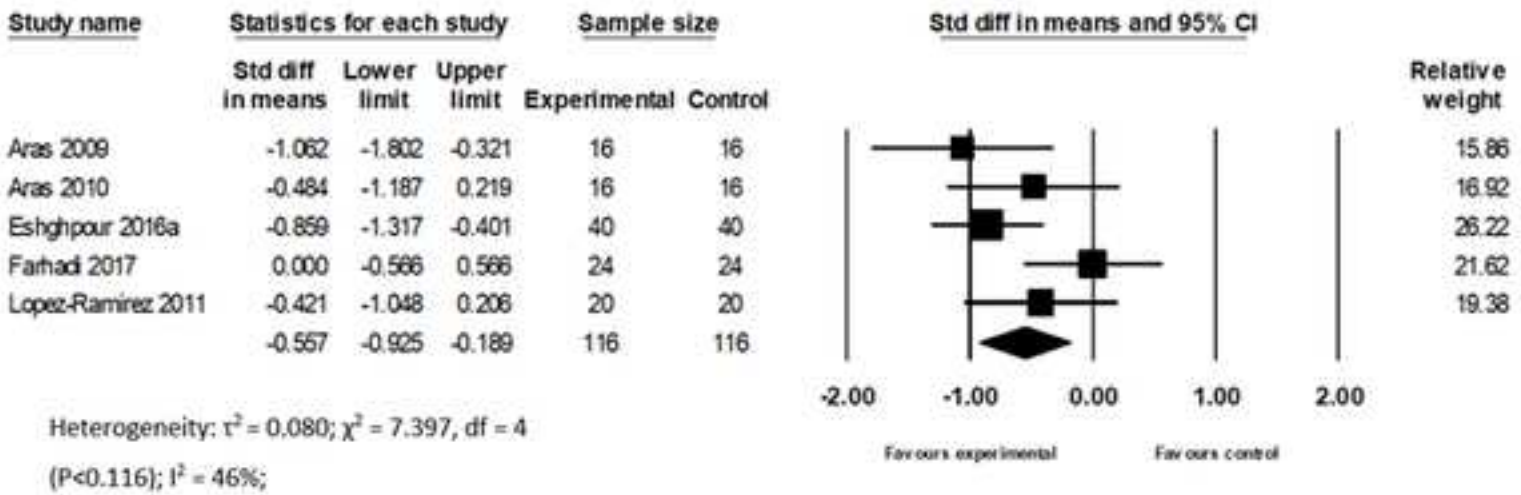

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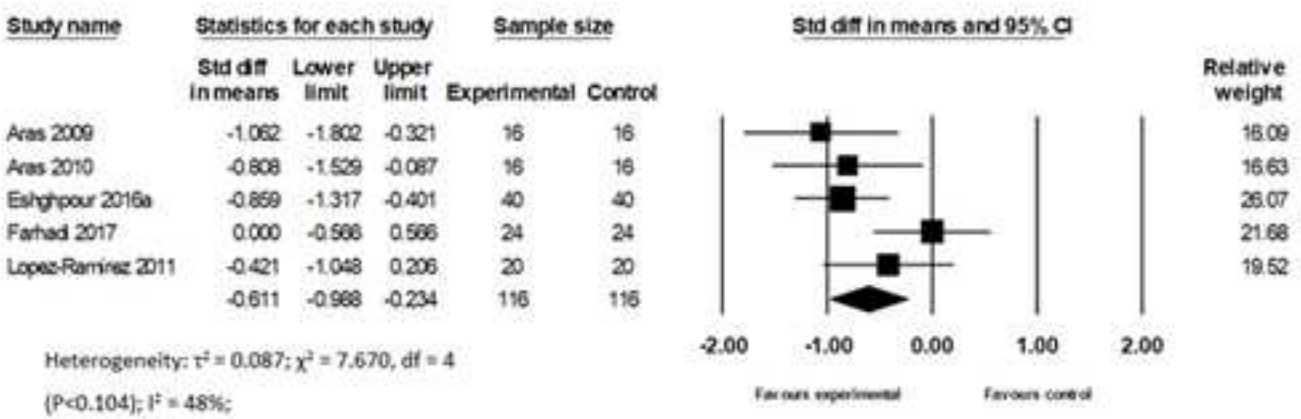

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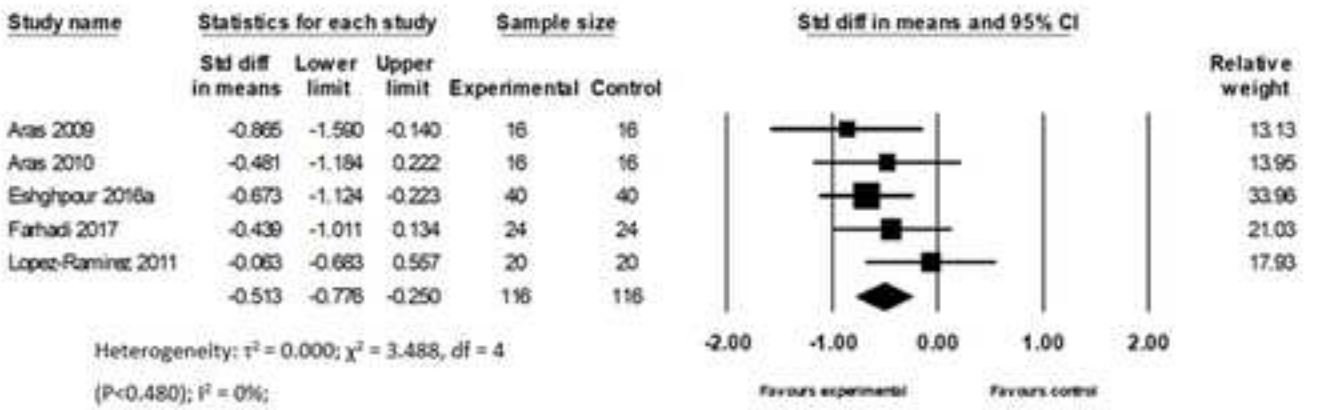

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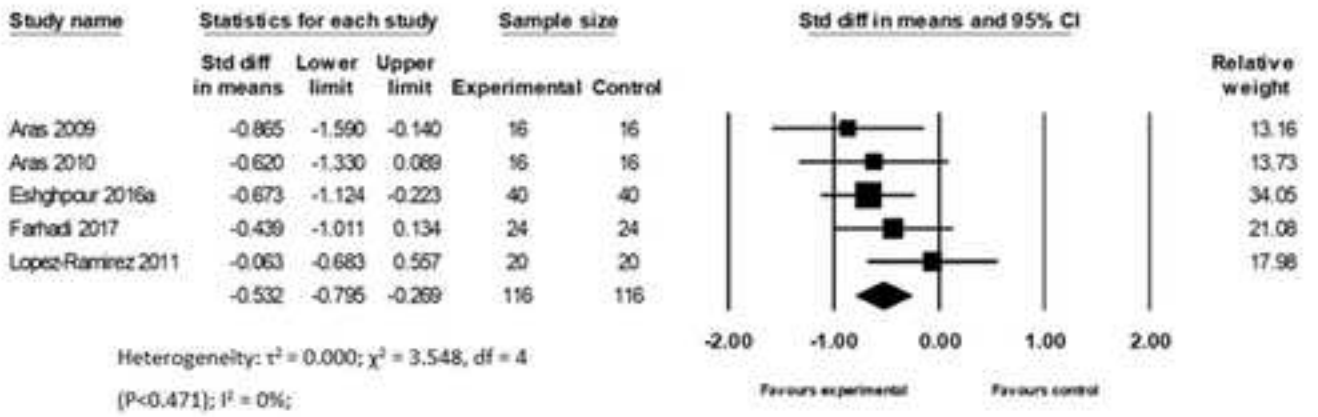

Figure 10

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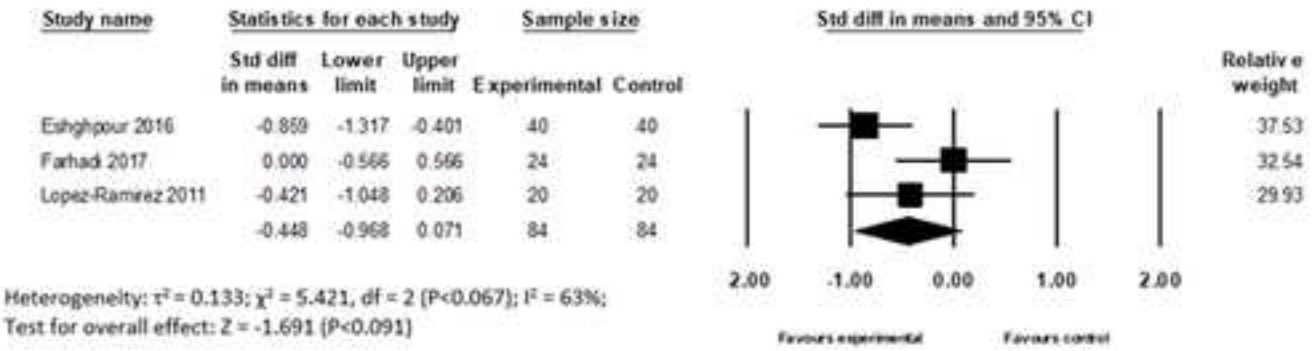

Figure 11

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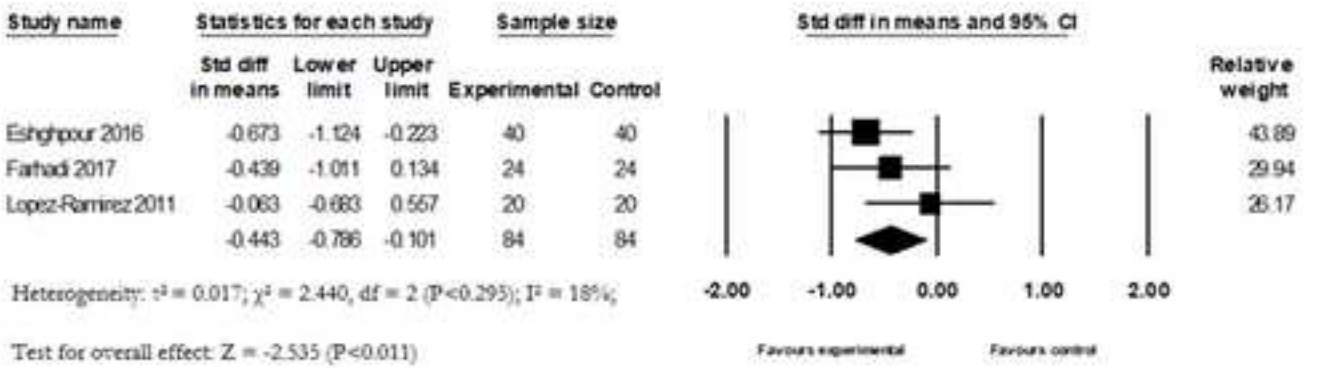

Figure 12

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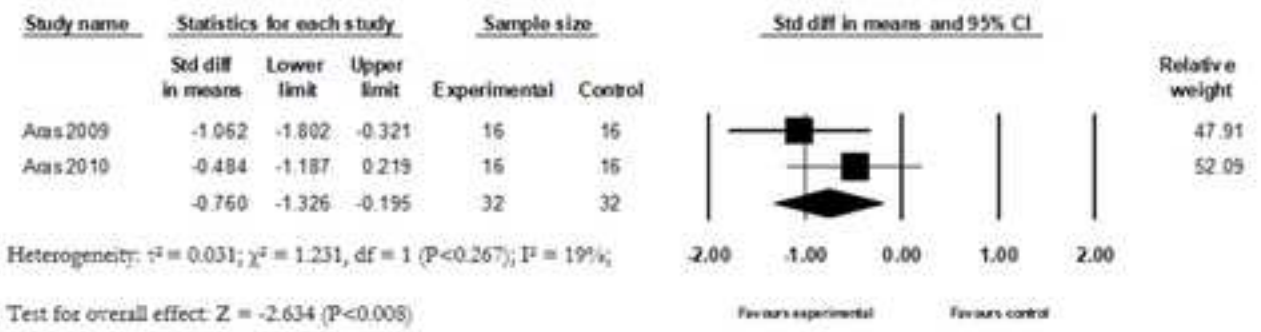

Figure 13

Click here to access/download;Figure;Figure 13.tif

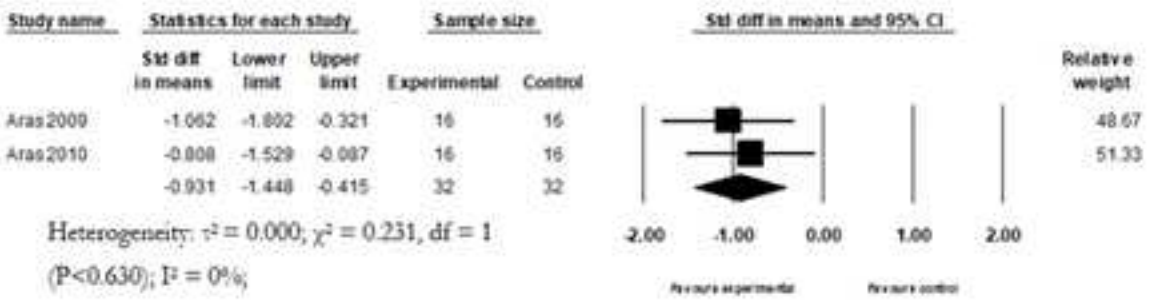

Figure 14

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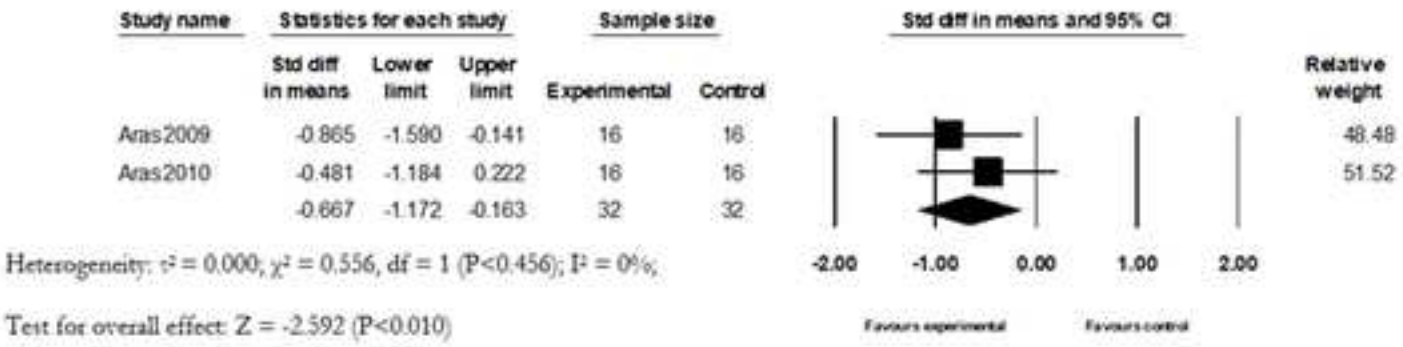

Heterogeneity: $\tau^2 = 0.000$; $\chi^2 = 0.556$, df = 1 (P<0.456); $I^2 = 0\%$;

Test for overall effect: Z = -2.592 (P<0.010)

Figure 15

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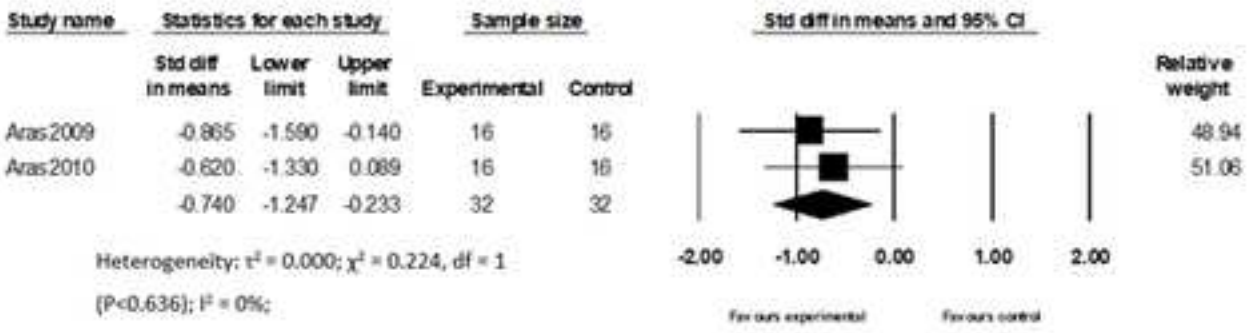

Figure 16

Click here to access/download;Figure;Figure 16.tif

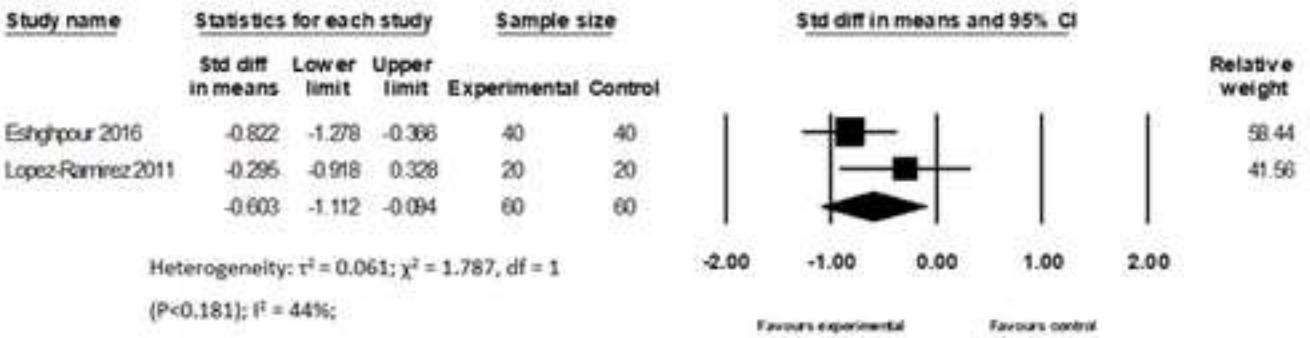

Figure 17

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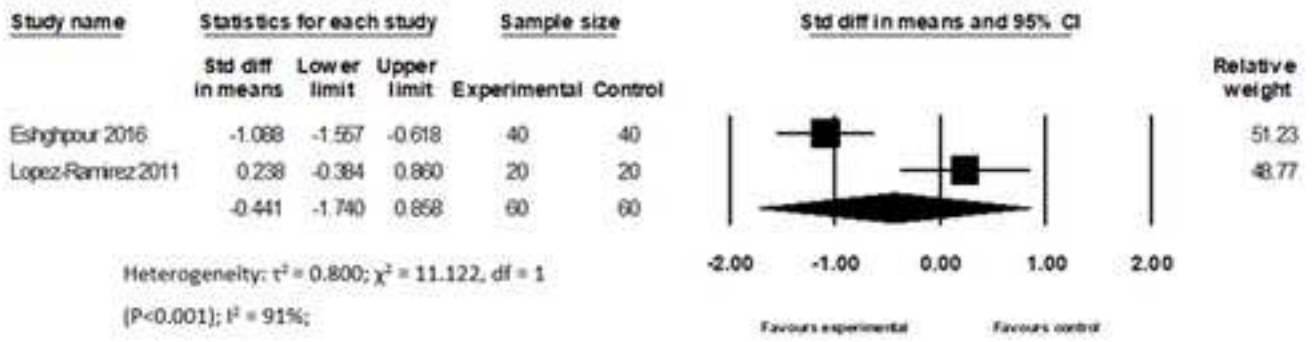


Figure 18

Click here to access/download;Figure;Figure 18.tif

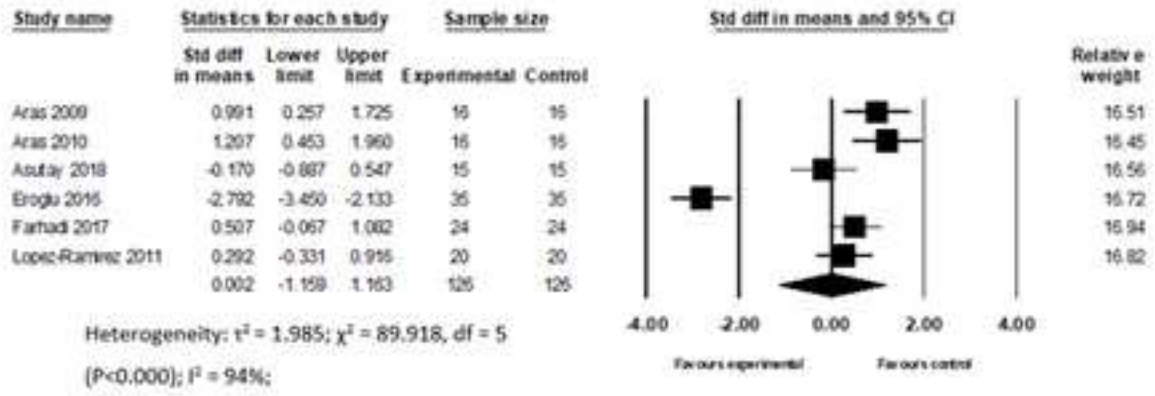


Figure 19

Click here to access/download;Figure;Figure 19.tif

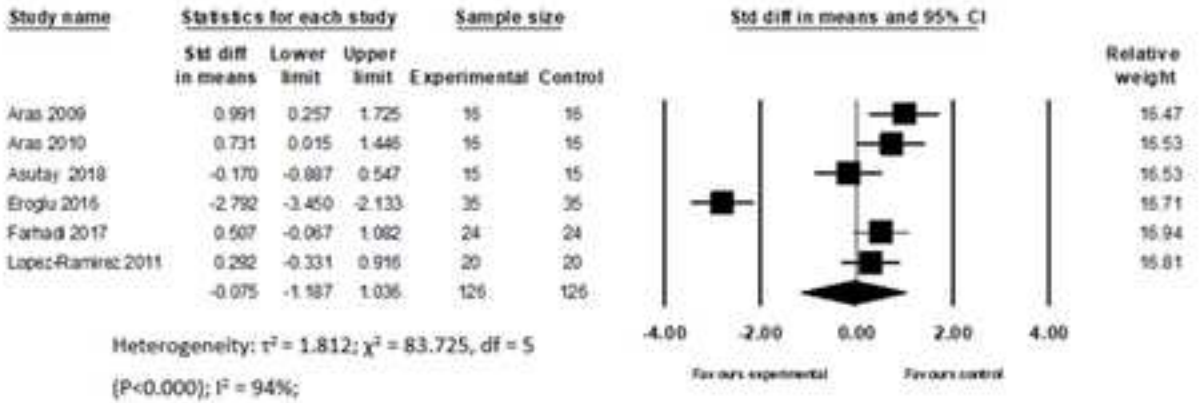


Figure 20

Click here to access/download;Figure;Figure 20.tif

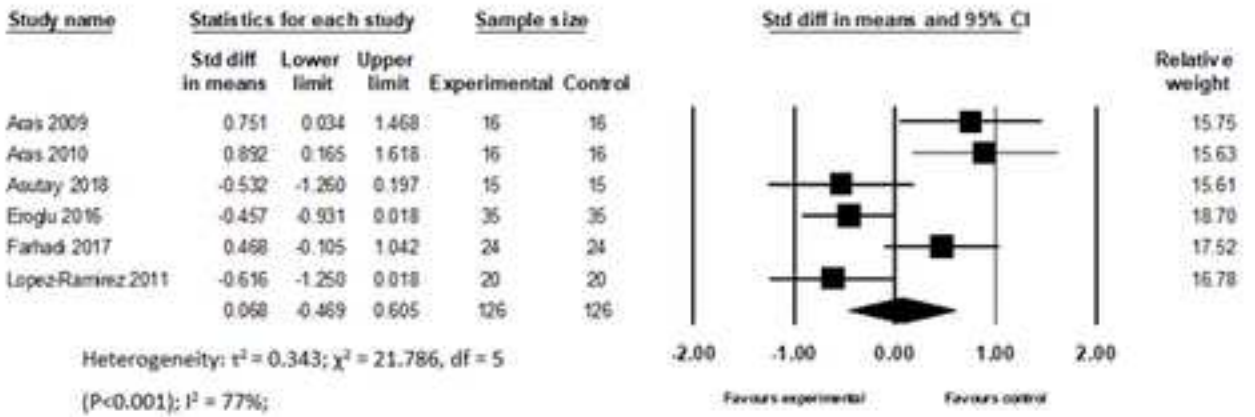
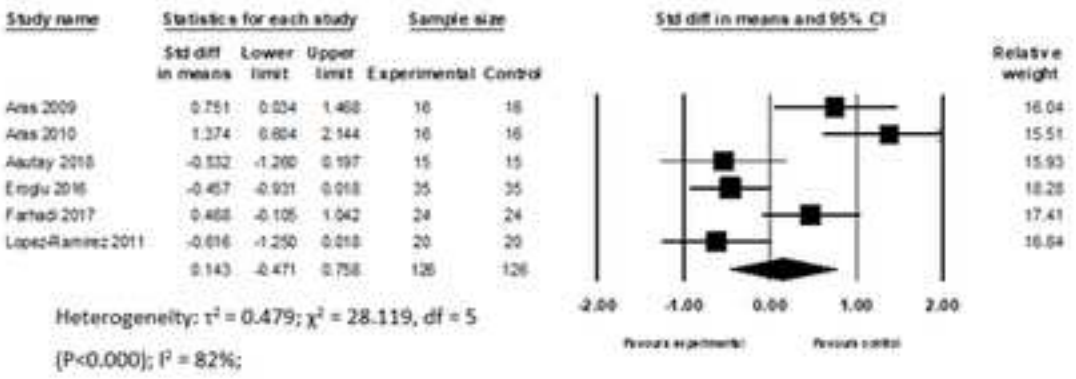


Figure 21

Click here to access/download;Figure;Figure 21.tif



Heterogeneity: $\tau^2 = 0.479$; $\chi^2 = 28.119$, df = 5

(P<0.000); $I^2 = 82\%$;

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Name: Farya Domah Date: 31.05.2020

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Corresponding author

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___ 2nd Co-Author (if applicable)

Name: Ulugbek Nurmatov

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___ 3rd Co-Author (if applicable)

Name: Nara Tagiyeva-Milne

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___ 4th Co-Author (if applicable)

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___ 6th Co-Author (if applicable)

Name: _____ _____

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