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Low level laser therapy (Classes I, II and III) for treating rheumatoid arthritis (Review)

Brosseau L, Welch V, Wells GA, de Bie R, Gam A, Harman K, Morin M, Shea B, Tugwell P

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 3
METHODS 3
RESULTS 4
DISCUSSION 6
AUTHORS' CONCLUSIONS 7
ACKNOWLEDGEMENTS 7
REFERENCES 8
CHARACTERISTICS OF STUDIES 10
DATA AND ANALYSES 16
Analysis 1.1. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 1 Pain (Visual Analogue Scale 10 cm). 17
Analysis 1.2. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 2 Pain (0-12 scale). 17
Analysis 1.3. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 3 McGill Pain questionnaire. 18
Analysis 1.4. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 4 Ritchie Index. 18
Analysis 1.5. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 5 Health Assessment Questionnaire (HAQ). 18
Analysis 1.6. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 6 MCP ROM (degrees). 19
Analysis 1.7. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 7 PIP ROM (degrees). 19
Analysis 1.8. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 8 Knee ROM. 19
Analysis 1.9. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 9 Ankle ROM. 20
Analysis 1.10. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 10 Flexibility- tip to palm distance (cm). 20
Analysis 1.11. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 11 Morning stiffness duration (min). 20
Analysis 1.12. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 12 Morning stiffness not improved. 21
Analysis 1.13. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 13 Rheumatoid factor positive. 21
Analysis 1.14. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 14 Grip strength. 21
Analysis 1.15. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 15 Suprapatellar swelling - right knee (cm). 22
Analysis 1.16. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 16 Suprapatellar swelling- left knee (cm). 22
Analysis 1.17. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 17 MCP swelling (cm). 22
Analysis 1.18. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 18 PIP swelling (cm). 22
Analysis 1.19. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 19 Walking speed (sec). 23
Analysis 1.20. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 20 Fibrinogen. 23
Analysis 1.21. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 21 Leukocytes. 23
Analysis 1.22. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 22 Lymphocytes. 23
Analysis 1.23. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 23 ESR (mm/hr). 24
Analysis 1.24. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 24 CRP (g/mL). 24
Analysis 1.25. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 25 Hemoglobin. 24
Analysis 1.26. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 26 Platelets. 24
Analysis 2.1. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 1 Pain. 26
Analysis 2.2. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 2 McGill Pain questionnaire. 26
Analysis 2.3. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 3 Health Assessment Questionnaire (HAQ). 27
Analysis 2.4. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 4 Ritchie Index. 27
Analysis 2.5. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 5 PIP ROM (degrees). 27
Analysis 2.6. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 6 Knee ROM. 27
Analysis 2.7. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 7 Ankle ROM. 28
Analysis 2.8. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 8 MCP ROM (degrees). 28
Analysis 2.9. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 9 Morning stiffness duration (min). .. 29

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Analysis 2.10. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 10 Walking speed (sec). 29
Analysis 2.11. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 11 Grip strength. 29
Analysis 2.12. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 12 Suprapatellar swelling- left knee (cm). 30
Analysis 2.13. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 13 Suprapatellar swelling - right knee (cm). 30
Analysis 2.14. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 14 MCP swelling (cm). 30
Analysis 2.15. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 15 PIP swelling (cm). 30
Analysis 2.16. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 16 Thermographic index. 31
Analysis 2.17. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 17 Rheumatoid factor positive. 31
Analysis 2.18. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 18 ESR (mm/hr). 31
Analysis 2.19. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 19 CRP (g/mL). 31
Analysis 2.20. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 20 Hemoglobin. 32
Analysis 2.21. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 21 Platelets. 32
Analysis 3.1. Comparison 3 Treatment length- subgroup analysis for end of treatment results, Outcome 1 Pain (10 cm VAS or 0-12 scale). 32
Analysis 4.1. Comparison 4 Treatment length- subgroup analysis for end of follow up results, Outcome 1 Pain (10 cm VAS or 0-12 scale). 33
Analysis 5.1. Comparison 5 Methodologic quality: low (<3) vs high (=> 3), Outcome 1 Pain at end of treatment. 34
Analysis 6.1. Comparison 6 Laser vs Placebo - Joint vs Nerve - end of treatment, Outcome 1 Pain (10 cm VAS or 0-12 scale). 35
Analysis 7.1. Comparison 7 Laser vs Placebo - Joint vs Nerve - end of follow up, Outcome 1 Pain (10 cm VAS or 0-12 scale). 35
Analysis 8.1. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 1 Pain. 41
Analysis 8.2. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 2 McGill Pain questionnaire. .. 41
Analysis 8.3. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 3 Ritchie Index. 42
Analysis 8.4. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 4 Health Assessment Questionnaire (HAQ). 42
Analysis 8.5. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 5 MCP ROM (degrees). 43
Analysis 8.6. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 6 PIP ROM (degrees). 43
Analysis 8.7. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 7 Left knee Range of motion. .. 44
Analysis 8.8. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 8 Right knee ROM. 44
Analysis 8.9. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 9 Left ankle ROM. 45
Analysis 8.10. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 10 Right ankle ROM. 45
Analysis 8.11. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 11 Flexibility- tip to palm distance (cm). 46
Analysis 8.12. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 12 Morning stiffness duration (min). 46
Analysis 8.13. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 13 Morning stiffness not improved. 47
Analysis 8.14. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 14 Rheumatoid factor positive. 47
Analysis 8.15. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 15 Grip strength (mmHg, KPa, kg). 48
Analysis 8.16. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 16 Suprapatellar swelling - right knee (cm). 48
Analysis 8.17. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 17 Suprapatellar swelling- left knee (cm). 49
Analysis 8.18. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 18 MCP swelling (cm). 49
Analysis 8.19. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 19 PIP swelling (cm). 50
Analysis 8.20. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 20 Walking speed (sec). 50
Analysis 8.21. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 21 Fibrinogen. 51
Analysis 8.22. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 22 Leukocytes. 51
Analysis 8.23. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 23 Lymphocytes. 52
Analysis 8.24. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 24 ESR (mm/hr). 52
Analysis 8.25. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 25 CRP (g/mL). 53

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Analysis 8.26. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 26 Hemoglobin. 53
Analysis 8.27. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 27 Platelets. 54
Analysis 9.1. Comparison 9 Subgroup Dosage Analysis, Outcome 1 Pain VAS <= 3 J/cm2. 55
Analysis 9.2. Comparison 9 Subgroup Dosage Analysis, Outcome 2 Pain VAS > 3 J/cm2. 55
Analysis 9.3. Comparison 9 Subgroup Dosage Analysis, Outcome 3 ESR low dose. 56
Analysis 9.4. Comparison 9 Subgroup Dosage Analysis, Outcome 4 ESR high dose. 56
Analysis 9.5. Comparison 9 Subgroup Dosage Analysis, Outcome 5 CRP low dose. 56
Analysis 9.6. Comparison 9 Subgroup Dosage Analysis, Outcome 6 CRP high dose. 56
Analysis 9.7. Comparison 9 Subgroup Dosage Analysis, Outcome 7 HAQ high dose. 57
Analysis 9.8. Comparison 9 Subgroup Dosage Analysis, Outcome 8 Hemoglobin high dose. 57
Analysis 9.9. Comparison 9 Subgroup Dosage Analysis, Outcome 9 Morning stiffness (hours) high dose. 57
Analysis 9.10. Comparison 9 Subgroup Dosage Analysis, Outcome 10 Grip strength (kg) low. 57
Analysis 9.11. Comparison 9 Subgroup Dosage Analysis, Outcome 11 Grip strength (kg) high. 58
Analysis 9.12. Comparison 9 Subgroup Dosage Analysis, Outcome 12 MCP swelling (cm) low. 58
Analysis 9.13. Comparison 9 Subgroup Dosage Analysis, Outcome 13 Flexibility tip to palm (cm) low. 58
Analysis 9.14. Comparison 9 Subgroup Dosage Analysis, Outcome 14 Flexibility tip to palm high dose. 58
Analysis 10.1. Comparison 10 Laser vs Placebo- contralateral control (End of treatment), Outcome 1 Number of patients improved in pain relief. 59
Analysis 10.2. Comparison 10 Laser vs Placebo- contralateral control (End of treatment), Outcome 2 Number of patients improved in morning stiffness. 59
APPENDICES 59
WHAT'S NEW 60
CONTRIBUTIONS OF AUTHORS 60
DECLARATIONS OF INTEREST 60
SOURCES OF SUPPORT 60
INDEX TERMS 61

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[Intervention Review]

Low level laser therapy (Classes I, II and III) for treating rheumatoid arthritis

Lucie Brosseau[1], Vivian Welch[2], George A Wells[3], Rob de Bie[4], Arne Gam[5], Katherine Harman[6], Michelle Morin[7], Beverley Shea[8], Peter Tugwell[9]

[1]School of Rehabilitation Sciences, Faculty of Health Sciences, University of Ottawa, Ottawa, Canada. [2]Centre for Global Health, Institute of Population Health, University of Ottawa, Ottawa, Canada. [3]Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, Canada. [4]Department of Epidemiology, Maastricht University, Maastricht, Netherlands. [5]Vanlose, Denmark. [6]Psychology, Neuroscience, Dalhousie University, Halifax, Canada. [7]School of Rehabilitation Sciences, University of Ottawa, Ottawa, Canada. [8]Institute of Population Health, University of Ottawa, Ottawa, Canada. [9]Centre for Global Health, Institute of Population Health, Department of Medicine, Ottawa Hospital, Ottawa, Canada

Contact: Lucie Brosseau, School of Rehabilitation Sciences, Faculty of Health Sciences, University of Ottawa, 451 Smyth Road, Ottawa, Ontario, K1H 8M5, Canada. Lucie.Brosseau@uottawa.ca.

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ABSTRACT

Background

Rheumatoid arthritis (RA) affects a large proportion of the population. Low Level Laser Therapy (LLLT) was introduced as an alternative non-invasive treatment for RA about ten years ago. LLLT is a light source that generates extremely pure light, of a single wavelength. The effect is not thermal, but rather related to photochemical reactions in the cells. The effectiveness of LLLT for rheumatoid arthritis is still controversial. This review is an update of the original review published in October 1998.

Objectives

To assess the effectiveness of LLLT in the treatment of RA.

Search methods

We initially searched MEDLINE, EMBASE (from 1998), the registries of the Cochrane Musculoskeletal Group and the field of Rehabilitation and Related Therapies as well as the Cochrane Central Register of Controlled Trials (CENTRAL) up to June 2001. This search has now been updated to include articles published up to June 2005.

Selection criteria

Following an a priori protocol, only randomized controlled trials of LLLT for the treatment of patients with a clinical diagnosis of RA were eligible. Abstracts were excluded unless further data could be obtained from the authors.

Data collection and analysis

Two reviewers independently selected trials for inclusion, then extracted data and assessed quality using predetermined forms. Heterogeneity was tested using chi-squared. A fixed effects model was used throughout for continuous variables, except where heterogeneity existed, in which case, a random effects model was used. Results were analyzed as weighted mean differences (WMD) with 95% confidence intervals (CI), where the difference between the treated and control groups was weighted by the inverse of the variance. Dichotomous outcomes were analyzed with relative risks.

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Main results

A total of 222 patients were included in the five placebo-controlled trials, with 130 randomized to laser therapy. Relative to a separate control group, LLLT reduced pain by 1.10 points (95% CI: 1.82, 0.39) on visual analogue scale relative to placebo, reduced morning stiffness duration by 27.5 minutes (95%CI: 2.9 to 52 minutes) and increased tip to palm flexibility by 1.3 cm (95% CI: 0.8 to 1.7). Other outcomes such as functional assessment, range of motion and local swelling did not differ between groups. There were no significant differences between subgroups based on LLLT dosage, wavelength, site of application or treatment length. For RA, relative to a control group using the opposite hand, there was no difference observed between the control and treatment hand for morning stiffness duration, and also no significant improvement in pain relief RR 13.00 (95% CI: 0.79 to 214.06). However, only one study was included as using the contralateral limb as control. .

Authors' conclusions

LLLT could be considered for short-term treatment for relief of pain and morning stiffness for RA patients, particularly since it has few side-effects. Clinicians and researchers should consistently report the characteristics of the LLLT device and the application techniques used. New trials on LLLT should make use of standardized, validated outcomes. Despite some positive findings, this meta-analysis lacked data on how LLLT effectiveness is affected by four important factors: wavelength, treatment duration of LLLT, dosage and site of application over nerves instead of joints. There is clearly a need to investigate the effects of these factors on LLLT effectiveness for RA in randomized controlled clinical trials.

PLAIN LANGUAGE SUMMARY

Low level laser therapy for rheumatoid arthritis

Does low level laser therapy work for treating rheumatoid arthritis?
Six studies of medium quality were reviewed and provide the best evidence we have today. Collectively, these studies tested over 220 people with rheumatoid arthritis. The studies compared how well people did while receiving either laser therapy or a 'placebo' (fake) laser therapy. Laser therapy was given mostly on the hands and generally for two to three times a week for four weeks. There were also many different wavelengths and dosages given.

What is rheumatoid arthritis and low level laser therapy?
Rheumatoid arthritis (RA) is a disease in which the body's immune system attacks its own healthy tissues. The attack happens mostly in the joints of the hands and feet and causes redness, pain, swelling and heat around the joints. Drug and non-drug treatments are used to relieve pain and/or swelling. Low level laser therapy, is a non-drug treatment used to decrease swelling and pain. Without producing heat, the laser emits very pure light that causes light and chemical reactions in cells where it is targeted.

What did the studies show?
Studies showed that laser therapy decreased pain and morning stiffness more than 'placebo' laser therapy. Laser therapy also increased hand flexibility more than placebo therapy.
Pain decreased by 1.10 points on a scale of 1-10. The length of time for morning stiffness decreased by 28 minutes.

Studies also showed that laser therapy worked just as well as 'placebo' laser therapy to improve range of motion, function, swelling and grip strength.
Only two of the studies measured the effect of laser therapy three months after the end of treatment. The results from these studies indicated that laser therapy worked just as well as 'placebo' therapy after three months times.

Dose, length of laser administration time and wavelength of the laser therapies did not appear to make a significant difference, though there was some evidence indicating that longer administration times and shorter wavelengths produced better effects.

Were there any side effects?
No side effects were reported in the studies.

What is the bottom line?
There is 'silver' level evidence that low level laser therapy in people with rheumatoid arthritis for up to four weeks does decrease pain and morning stiffness. It does not appear, however, to have long-lasting effects.
Most of the studies tested laser therapy on the hand, so it is not clear whether laser therapy would affect other joints of the body the same way.

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BACKGROUND

Rheumatoid arthritis (RA) affects a large proportion of the population. The prevalence of RA is increasing with the aging population in industrial countries, especially with the baby boomers phenomenon (Walker 1996). Indeed, the number of Americans who will be diagnosed with arthritis will reach 59.4 million in 2020 compared to the 38 million diagnosed in 1990. This represents an increase of more than 59%. Thus, 18.2% of the population will be affected by arthritis: a proportion of one in five persons (Walker 1996). RA is recognized as an important source of disability and handicap which leads to considerable socioeconomic costs due to medical treatments, surgical interventions and frequent absences from work (Badley 1994).

A large number of pharmacological treatments are available for RA, ranging from analgesics to disease modifying anti-rheumatic drugs (DMARDs). The effectiveness and severity of adverse side effects of these interventions varies.

A new non invasive therapy was introduced ten years ago to existing physical agents used in medicine and physiotherapy in the treatment of RA: Low Level Laser Therapy (LLLT), Classes I, II and III (Brosseau 1994). Low Level Laser Therapy (LLLT) is a light source that generates extremely pure light, of a single wavelength. The effect is not thermal, but rather related to photochemical reactions in the cells. The effectiveness of laser therapy is still unclear (Beckerman 1992) and needs to be examined more rigorously.

In recent years, there has been increasing recognition that LLLT may have physiologic effects mediated by photochemical actions at the cellular level in animal and human tissues. Bassler et al. concluded that LLLT also has cartilage stimulatory properties in human beings (Bassler 1985). Some studies suggest that LLLT has a beneficial anti-inflammatory and pain attenuation effect in human beings (Ceccherelli 1989, King 1990, Tsurko 1983). Some studies in animals, conducted to elucidate the possible mechanism of action of LLLT irradiation, suggest also the alteration of nerve tissue (Kudoh 1989).

A meta-analysis on the effect of LLLT on musculoskeletal pain showed that LLLT has no effect on musculoskeletal pain syndromes (Gam 1993). However, this meta-analysis did not examine rheumatoid arthritis specifically. Additionally, trials which used the contralateral limb as a control were combined with those with a separate control group.

OBJECTIVES

The aim is to assess the effectiveness of Low Level Laser Therapy (LLLT) in the treatment of rheumatoid arthritis (RA).

A secondary purpose is to determine the most effective method of administering LLLT for RA, including the optimal:
-wavelength
-dosage
-application techniques
-length of treatment

METHODS

Criteria for considering studies for this review

Types of studies

Following an a priori protocol, studies were eligible if they were Randomized Controlled Trials (RCTs).

Types of participants

Only trials with subjects aged 18 years and over, with clinical or radiological confirmation of the diagnosis of RA were included. Trials published in languages other than French and English were not analyzed because of the time and cost involved in translation. Abstracts were excluded unless further data could be obtained from the authors.

Types of interventions

All types of LLLT (Classes I, II, and III) including all wavelengths from 632nm to 1064nm, were included in this review. Trials which compared one intervention group using LLLT with one standard treatment were included. Trials which were placebo-controlled were also included.

Trials which used the opposite limb as a control were analyzed separately since laser may have systemic effects (Prwemstay 1987, Young 1988).

Types of outcome measures

The primary endpoints for measurement of effectiveness were the outcome measures recommended by the conference on Outcome Measures for Rheumatoid Arthritis Clinical Trials 1993 (OMERACT 1993) .

These measures include:
a) Number of tender joints
b) Number of swollen joints
c) Pain
d) Physician global assessment
e) Patient global assessment
f) Functional status (for example, measured by the Activities of Daily Living Scale)
g) Acute phase reactants
h) Radiological damage

In addition to these outcomes, one of the authors (LB) developed a theoretical framework of important physiotherapy outcomes for the study of LLLT for the treatment of RA (Brosseau 1998). These outcomes were assessed as secondary endpoints and include:

1) Articular mobility
2) Muscular testing
3) Systemic components
4) Medication usage
5) Adverse side effects

Search methods for identification of studies

We initially searched MEDLINE up to December, 2001, EMBASE from 1988 to December 2001 and the Cochrane Central Register of Controlled Trials Register (CENTRAL), Issue 4, 1998. Details of the search strategy are given in the appendix. The electronic search was complemented by the following hand searches: 1)

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Bibliographic references; 2) Current Contents up to December 2001 (to identify articles not yet indexed in MEDLINE); 3) Abstracts published in special issues of specialized journals or in Conference Proceedings; 4) Coordinating offices of the trials registries of the Cochrane Field of Physical and Related Therapies and the Cochrane Musculoskeletal Group were also contacted. This exact search has now been updated to include articles published up until June 2005.

Reference lists were hand-searched for further identification of published work, presentations at scientific meetings and personal communications. Content experts were contacted for additional studies and unpublished data. If data could not be obtained, abstracts were not used.
The search strategy used is in Appendix 1.

Data collection and analysis

The trials retrieved by the above search strategy were assessed independently by two reviewers (LB, RD) according to the selection criteria. Differences were resolved by consensus.

From each included trial, we collected information regarding the trial design, patient characteristics, dosages and treatment periods, and baseline and end of study outcomes. Data concerning details of the study population, intervention and outcomes were extracted independently by two reviewers (LB, VR). Differences in data extraction were resolved by referring back to the original article and establishing consensus. A third reviewer (BS) was consulted to help resolve differences.

Data on the outcomes from each trial were pooled to arrive at an overall estimate of the effectiveness of laser therapy. Where possible, the analyses were based on intention-to-treat data from the individual clinical trials.

Since laser is thought to have systemic effects, we decided a priori to analyze trials separately depending on whether the control group consisted of a separate group of patients or whether the control group consisted of the patients treated with active laser on one side and sham laser on the other side (contralateral control trials).

Subgroup analyses were attempted to determine the effects of the method of LLLT administration, methodological quality and length of treatment on outcomes.

For continuous data, results are presented as a weighted mean difference [WMD]. For dichotomous data, a relative risk (RR) was calculated (Mantel 1959). A test for heterogeneity was calculated using a Chi square test, with a significance level of $p<.05$. Fixed effects models were used throughout unless heterogeneity was significant, in which case, a random effects model was used. Publication bias was not assessed due to the small number of included studies.

RESULTS

Description of studies

The initial literature search retrieved 191 articles. Of these, six trials met the inclusion criteria (Bliddal 1987, Goats 1996, Hall 1994, Johannsen 1994, Palmgren 1989, Walker 1987). Five were randomized controlled trials of laser therapy versus a placebo laser apparatus with a separate control group (Goats 1996, Hall 1994, Johannsen 1994, Palmgren 1989, Walker 1987). One used the contralateral joint as the control (Bliddal 1987). Five studies were excluded in the initial search: one study was an early abstract of one of the included studies (Walker 1983), another lacked a control group(Asada K 1989), two had insufficient statistical data (Goldman 1980; Heussler 1993) while the last one was not randomized as indicated by the title of the article (Oyamada 1988).

The updated search to June 2005 identified an additional six potential articles which had to be excluded for the following reasons: three studies were literature reviews (Ammer K 2003, Day R 1999, De Bie 1998), two articles were only available in Russian (Sidorov VD 1999; Sidorov VD 2000), and the final article included patients with juvenile RA (Fulga C 1998). Moreover, in the initial review, there were also several studies waiting assessment due to a lack of information - either because they were abstracts (Agambar 1992, Matulis 1983), or because they were published in German or Japanese (Barabas 1988, Miyagi 1989, Taghawinejad 1985). Letters were sent out at that time to the respective authors to obtain further information. However, the authors did not respond, preventing any further updated assessment by the authors of this review.

Of the included trials, several reported outcomes as graphs. The mean scores and standard deviations were estimated from the graphs. One study presented the logarithm of pain measured on a 10 cm VAS (Walker 1987). We assumed the logarithm involved the natural exponent and translated these by performing an antilog operation. Another study reported pain on a VAS scale, but then transformed these results to report only 3 categories: laser better than placebo, laser worse than placebo and no difference (Bliddal 1987). One study reported end of study scores corrected and uncorrected for disease activity (Johannsen 1994). Because randomization is assumed to control for disease activity and other variables, the uncorrected values were used for this meta-analysis.

A total of 204 patients were included in the five placebo-controlled trials, with 112 randomized to laser therapy. For the trial which used the opposite limb as a control, 18 patients were included in the analysis. The mean age ranged from 53 to 67 years and baseline morning stiffness ranged from 60 to 90 minutes. The schedule of treatment was 2-3 sessions per week for 3-4 weeks for all trials except Walker et al 1987 which treated patients for 10 weeks, 3 times per week. All trials included patients with RA of the hands or thumb except Walker et al 1987, which included patients with a diagnosis of RA, but did not specify which joints were affected. The outcomes measured in the included studies were as follows: pain was reported by six trials, functional status by two, range of motion by four, swelling by three, grip strength by three, and morning stiffness by four.

Risk of bias in included studies

The quality of the included studies was assessed using a validated scale (Jadad 1996), which includes the appropriateness of randomization, appropriateness of blinding and description of dropouts and withdrawals. Quality was assessed independently by two reviewers (LB, VR). Differences were resolved by consensus. A third reviewer (BS) was consulted when necessary.

The median methodological quality was 3, with a range from 1-5 (Table 1). The individual components of the Jadad score of randomization, blinding and withdrawals are shown in Table 1.

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Only one trial scored full points for randomization. Five trials scored full points for double-blinding and four trials did not report withdrawals and dropouts. A subgroup analysis was conducted to determine whether the methodological quality influenced the effect of laser by dividing the studies into low and high quality at the median score.

To rank the strength of scientific evidence we used the grading system adopted by the Cochrane Musculoskeletal Group (Tugwell 2004). This grading system is based on four levels: Platinum, Gold, Silver and Bronze.

Platinum: A published systematic review that has at least two individual controlled trials each satisfying the following :
·Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
·Blinding of patients and assessors for outcomes.
·Handling of withdrawals >80% follow up (imputations based on methods such as Last Observation Carried Forward (LOCF) are acceptable).
·Concealment of treatment allocation.

Gold: At least one randomised clinical trial meeting all of the following criteria for the major outcome(s) as reported:
·Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
·Blinding of patients and assessors for outcomes.
·Handling of withdrawals > 80% follow up (imputations based on methods such as LOCF are acceptable).
·Concealment of treatment allocation.

Silver: A systematic review or randomised trial that does not meet the above criteria. Silver ranking would also include evidence from at least one study of non-randomised cohorts that did and did not receive the therapy, or evidence from at least one high quality case-control study. A randomised trial with a 'head-to-head' comparison of agents would be considered silver level ranking unless a reference were provided to a comparison of one of the agents to placebo showing at least a 20% relative difference.

Bronze: The bronze ranking is given to evidence if at least one high quality case series without controls (including simple before/after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

For all the outcomes included in this review, a silver level of evidence has been given, mostly because of the small samples size.

Effects of interventions

Analysis of Trials with a Separate Control Group
There was no significant heterogeneity for any comparisons, indicating that the difference between treated and control groups was consistent across trials. Each following recommendation has been graded as level silver. Since pain was measured by the visual analogue scale in three trials (Goats 1996, Hall 1994, Walker 1987), we used weighted mean differences to pool the end study results and found a statistically significant improvement in pain with a WMD -1.10, (95% CI: -1.82, -0.39). Johannsen 1994 also demonstrated an improvement in pain relief measured this time with a 0-12 scale (Johannsen 1994). This improvement was proved by a decrease of 1.00 point (95% CI: 0.23, 1.77) for the laser group relative to the placebo group. We found a clinical relevance of 28%, 25%, 19% and 22% of efficacy respectively for each of these trials. However, Goats 1996 did not find any significant difference in pain relief measured with the McGill pain questionnaire (Goats 1996). Statistically significant improvements were also found for tip to palm flexibility with a difference of 1.3 cm, (95% CI: 0.9 to 1.7 cm) (Johannsen 1994, Palmgren 1989) and morning stiffness duration with an improvement of 27 minutes, (95% CI: 3 to 52 minutes) (Goats 1996,Hall 1994,Palmgren 1989). For flexibility, we found a clinical relevance of 76% calculated with Johannsen 1994 results and 157% measured by Palmgren 1989 results. Results extracted from Goats 1996, Hall 1994 and Palmgren 1989 trials demonstrated a clinical relevance of 93%, -19% and -78% respectively. Morning stiffness assessed in one trial had an unusually large variance (Goats 1996). Excluding this trial, the effect of laser on morning stiffness was still significant and similar in magnitude (difference of 30 minutes, 95% CI: 5.6 to 55 minutes). Also, another trial measured the morning stiffness duration by number of patients who did not improved but did not find a significant relative risk: 0.25 (95% CI: 0.03, 2.09) (Johannsen 1994) favouring the laser group relative to the placebo group.

There is conflicting evidence about range of motion. Goats 1996 found a positive effect of laser on knee range of motion after the treatment of this joint supported by a WMD of 31.80 (95% CI: 4.27, 31.80), but no significant difference at the ankle was noted with the same treatment (Goats 1996).

No other outcomes for RA were significantly affected by LLLT. These included functional status, swelling, range of motion (for metacarpal phalangeal, proximal interphalangeal and ankle joints), grip strength, and walking speed.

Only two trials (Goats 1996, Hall 1994) followed patients after the LLLT was discontinued. Both measured outcomes three months after the end of treatment. These RCTs found no significant differences between LLLT and placebo in any outcome measure at this time point.

For the subgroup analysis regarding methodologic quality, there was no difference between low (<3) and high (=>3) quality for pain reduction at the end of treatment.

For the subgroup analysis regarding joint versus nerve application, only one study applied LLLT to the nerves (Walker 1987). There was a trend towards greater pain reduction with joint/nerve application compared to joint application, but the confidence intervals for joint application (pain SMD:-0.8 (95% CI: -1.5, -0.2)) overlap those for nerve application (SMD: -1.5 (95% CI: -2.5, -0.6)).

For the subgroup analysis concerning treatment duration, only one trial treated patients for more than 4 weeks (Walker 1987). The results of this analysis did not demonstrate a significant statistical difference with the longer treatment with an SMD for pain at 4 weeks of -0.4 (-0.8, +0.1) and an SMD pain at 10 weeks of -0.7 (-1.2, -0.3).

For the subgroup analysis concerning wavelength, the only outcome with data available for different wavelength comparisons was pain. There were no statistical difference between wavelengths. However, there was a trend for improved outcome

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with the 632 nm compared to 820 nm for pain although the confidence limits overlap [SMD 632 nm: -0.7 (95% CI: -1.2, -0.3) vs SMD 820 nm: -0.4 (95% CI: -0.8, 0.1)].

For the subgroup analysis concerning dosage, studies using a dosage of less than 3 Joules/cm2 were considered low doses. This subgroup analysis was possible for VAS pain, grip strength and flexibility (tip to palm distance in cm). For pain (VAS), the low dose was significantly better than placebo (SMD: -0.8, 95% CI: -1.2, -0.4). In contrast, high dose studies found no difference between laser and placebo for pain (VAS). There was no dose effect on grip strength and flexibility (tip to palm).

Analysis of Contralateral Control Trials

The trial which used the opposite limb of the same individual as a control did not find any improvement in laser treated hands. There was no significant difference between laser and placebo for pain relief (RR 13.00, 95% CI: 0.79, 214.06). Less than half of the subjects found the lasered hand improved compared to the placebo treated hand. Relative to baseline, most patients reported similar or no changes in both laser and placebo treated hands. Specifically, the number of patients who reported this result were 11 out of 17 patients (Bliddal 1987). There was no difference in morning stiffness, mobility joint neither in laboratory tests.

DISCUSSION

In RA, this meta-analysis suggests that LLLT is effective at reducing pain relative to placebo and reducing morning stiffness. However, according to Lineker et al. 1999, duration of morning stiffness has a poor sensitivity to be considered as an outcome measure of morning stiffness (Lineker 1999). Being as morning stiffness is related to various other conditions, such as OA, it is not possible to make the difference between two conditions by comparing the duration. Definition of morning stiffness should be more specific to RA. The results show no statistical improvements for any of the following: localized swelling, muscle strength, functional status, joint tenderness or global assessments with laser treatment.

The major limitation of this meta-analysis is the heterogeneity of clinical application, including different dosages, wavelengths and types of LLLT. In addition, the results are subject to publication bias, if negative trials are not published. Furthermore, the treated joints in all but one of the RA trials were hand joints, and these results may not be generalized to other treatment sites due to different penetrations and dosages.

The possible systemic effects of laser use may be the key to understanding the improvement on pain scales. Although much of the source of inflammatory pain is peripheral (i.e., joint capsule, ligament, muscle and skin), it is within the central nervous system (CNS) that perception and interpretation of pain occurs, and particularly long-standing pain for RA (Coderre 1993). Perhaps laser irradiation positively modifies the sensory input to the CNS and provides an improvement in the perception of pain localized to the area of treatment. It has been well demonstrated that a painful stimulus in one extremity has a contralateral effect (Coderre 1993). The improved pain scores contralaterally in the studied trial provide clinical evidence of CNS involvement. Although there is not a sufficient number of studies to support this idea, the trend towards greater pain reduction when nerves as well as joints were irradiated in the study by Walker 1987, suggests that this treatment strategy should be explored to support CNS input theory.

The results suggest that improvement in overall pain relative to controls followed LLLT applied at local sites including the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and knee joints. Other work on the histologic evaluation of rheumatoid synovial membrane has shown that inflammatory changes present in the damaged synovial membrane can be reversed. Exposure to LLLT has been shown to result in: 1) anti-inflammatory and analgesic effects (Barabas 1988, Matulis 1983, Nishida 1990); 2) increased protein synthesis of rheumatoid synovial cells (Goldman 1980) , 3) normalization of the permeability of the synovial membrane (Tsurko 1983) and 4) enhancement of regional microcirculation (Matulis 1983). According to Goldman 1980, the laser energy irradiates inflamed synovial cells and modifies the level of antigen-antibody complexes and helps stabilize the membranes in RA subjects(Goldman 1980). These processes support the hypothesis that LLLT has systemic effects (Prwemstay 1987, Young 1988). Several investigators have recently called for further investigation to establish that key histologic changes can be captured with our clinical measurements (Anderson 1993).

The results in this meta-analysis suggest that LLLT does not have long-lasting effects. In this review, only one trial (Walker 1987) had a treatment duration greater than four weeks. Support for a time-related effect of LLLT comes from animal model studies. Schultz and collaborators noted, in a pig in vitro cartilage model, that only after the fourth week of LLLT irradiation, a joint regeneration process began which they hypothesized to be a reactivation of the mitotic control mechanism (Schultz 1985). Furthermore, the healing of the joint surface lesion was not complete until the end of 6 weeks of application.

The subgroup analyses for dosage, wavelength and site of application indicated no significant effects of these factors on the effectiveness of LLLT in RA. However, these subgroup analyses indicated trends towards improved outcomes with longer dose duration, nerve application and shorter wavelengths. Even though there is more evidence that wavelengths not only determine penetration depth, but also specific tissue interactions (Bolagni 1985, Karu 1987). Our results do not appear to support this hypothesis. According to Seichert 1991, the wavelength effect of the two most commonly used lasers, HeNe and GaAlAs lasers, is negligible. Furthermore, ''the laser light loses its coherency completely after only a few tenths of millimeters in depth'' (Seichert 1991).

A subgroup analysis of the dosages in these RCTs did not reveal a relationship between the dosage and the outcomes of interest. The dosages were calculated by hand since they were not consistently reported in the articles. As previously stated, this situation shows that uniformity in reporting the dosages used is imperative (Morin 1996). The large variability in methodological quality reflects the need for standardization of conducting and reporting clinical trials in physiotherapy. In this meta-analysis, we were only able to pool certain outcomes, such as pain, morning stiffness and range of motion. The use of validated clinical measurements sensitive enough to detect changes is also needed (Anderson 1993). There is an urgent need for further well designed RCTs evaluating different durations of treatment, nerve versus joint application, different wavelengths and different dosages. Further clinical hypothesis could be investigated for each of these aspects.

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The development and use of a theoretical framework to rationalize LLLT and also to report LLLT application in clinical settings and in scientific reports is imperative (Calderhead 1991, Rothstein 1991) There is also a need for evaluation of standardized OMERACT outcomes, including joint count and physician and patient global assessment with laser treatment for RA. These outcomes are recognized as responsive to changes in RA status.

Several authors recommend further studies to elucidate the effectiveness of LLLT for RA (Beckerman 1992,King 1990,Quirion-DeGirardi 94). These studies are needed to contribute to evidence-based practice.

In summary, LLLT for RA is beneficial as a minimum of a four-week treatment with reductions in pain and morning stiffness. On the one hand, this meta-analysis found that pooled data gave some evidence of a clinical effect, but the outcomes were in conflict, and it must therefore be concluded that firm documentation of the application of LLLT in RA is not possible. Conversely, a possible clinical benefit in certain subgroups cannot be ruled out from the present meta-analysis and further large-scale studies are recommended with special attention to the findings in this meta-analysis (e.g. low versus high dose, wavelength, nerve versus joint application and treatment duration).

AUTHORS' CONCLUSIONS

Implications for practice

According to this meta-analysis, there is ''silver'' level of evidence that low level laser therapy decreases pain and morning stiffness in patients with rheumatoid arthritis if applied for at least 4 weeks. No side effects were reported. However, we conclude that there is insufficient data to draw firm conclusions.

Implications for research

There is a need for further RCTs evaluating different lengths of treatment, nerve vs joint application, different wavelengths and different dosages.

There is a need for evaluation of other OMERACT outcomes including joint count and physician and patient global assessment with laser treatment for RA. These outcomes are recognized as responsive to changes in RA status.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bliddal 1987

Methods	Randomized Double-blind Placebo Sample size at entry 17 Patients being their own control Study duration: 3 weeks and follow-up at 4 weeks

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Bliddal 1987 *(Continued)*

Participants	Patients with active RA and symmetrical involvement of the metacarpophalangeal joint of the index. No change in other therapy was accepted during the study. F/M: 16/2 Median age: 57 years Median duration of RA: 10 years Class II: 11 Class III: 7
Interventions	Patients were randomized to therapy on the MP joint of the right and left index with laser or placebo. Therapy was given on 3 alternate days a week for 3 consecutive weeks followed by an observation time of 4 weeks. Laser: He-Ne Wavelength: 633nm Output power: 10mW Spot size : 0.5cm^2 Dosage:6J/cm^2 Irradiation time: 5 min Placebo: Placebo apparatus containing a red 12 V, 10 W bulb and a relflecting mirror giving as far as possible the same red light through an identical optic fibre and pen
Outcomes	Pain (VAS) Morning stiffness
Notes	Quality Jadad's 4/5

Goats 1996

Methods	Randomized Double blind (partial) Placebo controlled Sample size at entry: LAser: 25; placebo: 10 Study duration: 6 months
Participants	Patients with RA affecting 2 or more of tibio-femoral, talocrural, subtalar, midtarsal or MCP joints No steroids, immunosuppressants or intra-articular injections in the last 2 months Mean age (yrs): Laser 57 yrs, placebo 64 yrs Sex % F: Laser 80%; placebo: 80% Disease duration (mean): Laser 7.54 yrs, Placebo: 9.80 yrs
Interventions	Gr1: Laser: Ga-As-Al Class: 3B Wavelength: 850 nm Output power: 940 mW Power density: Frequency: 5 Hz Duty cycle: 80% Spot size : 0.125 cm^2 Divergence: Dosage: 8.1 J/cm^2 to each aspect of the joint (24.3 J/cm^2 for each right and left tibiofemoral joint, 16.2 J/cm^2 for each right and left MTP) Area treated: Tibiofemoral, talocrural, subtalar, midtarsal and metatarsophalangeal joints Irradiation time: 4 minutes per joint Schedule: 2 times/week for 4 weeks Total sessions: 8 Calibrated: no Placebo: Dummy laser probe, subjects wore eye protection that dimmed visible radiation Measurements: 0, 1, 3, and 6 months after start of treatment

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Goats 1996 *(Continued)*

	Gr2:Gr 2 : Placebo (identical in external appearance but having no output).
Outcomes	Pain (VAS 10 cm) McGill Pain questionnaire ESR CRP HAQ Hemoglobin Platelets Knee ROM Ankle ROM Suprapatellar swelling (cm) Morning stiffness duration (hours) Walking speed (sec) Ritchie index Rheumatoid factor
Notes	Quality Jadad's: 2/5

Hall 1994

Methods	Randomized Triple blind Sample size at entry: Laser 20; placebo : 20 Study duration: 6 months
Participants	Patients with RA, Steinbrocker functional class II or III, and active synovitis of some or all of the MCP and PIP joints No changes to NSAIDs in last 30 days, DMARDS last 3 months, joints incapable of response for mechanical reasons Setting: outpatient clinics Mean age (yrs): Laser: 67.1; Placebo: 60.9 Sex % F: Laser 85%; Placebo 85% Disease duration: Laser: 146.4 months, Placebo: 111.6 months Duration of hand symptoms: Laser 52.5 months; placebo: 54.5 months
Interventions	Laser: Ga-As-Al Wavelength: 820 nm Output power: Actual 40 mW (Rated 50 mW) Power density: Frequency: 5 Hz Duty cycle: 80% Spot size : 0.1 cm^2 Divergence: 6 degrees Dosage:3.6 J/cm^2 per radiant exposure for each joints Area treated: 90 seconds per joint on the radial, ulnar, dorsal, ventral aspects of 1st to 5th MCP and PIP joints of the most affected hand Irradiation time: 18 minutes per treatment Schedule: 4 weeks Total sessions: 12 Calibrated:no Placebo: Dummy laser probe (identical apparatus)
Outcomes	Pain (10 cm VAS) Health Assessment Questionnaire (HAQ) Grip strength (mmHg) Hemoglobin (g/dL) CRP (g/mL)

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Hall 1994 *(Continued)*

	Ritchie Index Platelets (x10/L) Duration of morning stiffness (minutes) MCP swelling (cm) PIP swelling (cm) MCP ROM (degrees) PIP ROM (degrees) Thermographic index
Notes	Quality Jadad's: 3/5

Johannsen 1994

Methods	Randomized Double-blind Placebo controlled Sample size at entry: Laser: 10 Placebo: 12 Study duration 4 weeks
Participants	Participants with RA, Steinbrocker functional class I or II With no changes to steroids, NSAID or analgesics in last month and no changes to DMARDs within the last 3 months Median age : Laser 59 yrs, Placebo 62 yrs Sex % F: Laser: 90; placebo: 83 Disease duration not measured
Interventions	Laser: GaAsAl Wavelength: 830 nm Output power: 21 mW Power density: NA Frequency: NA Duty cycle: NA Spot size: 0.07 cm2 spot size Divergence: NA Dosage: 23.2 J per treatment with 2.9J on 4 points on 2 joints Area treated: 2 most painful metacarpal phalangeal joints (MCP) on worst affected hand Schedule: 3 times/week for 4 weeks Total sessions: 12 Calibration: yes Placebo: Same apparatus giving red visible light
Outcomes	Joint tenderness Pain (range 0 to 12) Erythrocyte sedimentation rate (ESR) C Reactive Protein (CRP) Pinch strength Flexibility- tip to palm distance (cm) Grip strength (kg) Improvement in morning stiffness
Notes	Quality Jadad's: 5/5

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Palmgren 1989

Methods	Randomized Double-blind Placebo controlled Sample size at entry: Laser : 19; placebo : 16 Study duration: 4 weeks
Participants	Patients with classic RA, Steinbrocker functional class between I and III No changes to basic medication during study Patients with unstable disease excluded Mean age (yrs) : Laser, M: 66.0, Laser, F: 61.1; Placebo M: 68.0, Placebo F: 57.5 Sex % F: Laser 74%; Placebo: 88% Disease duration: Laser: 13.4 yrs; Placebo: 15.5 yrs
Interventions	Laser: GaAlAs Wavelength: 820 nm Output power: 15 mW Power density: NA Frequency: NA Duty cycle: NA Spot size: 0.1256 cm2 Divergence: 6 degrees Dosage: 5.5 J/cm2 Irradiation time: 60 s on each lateral side of each joint Area treated: 2nd to 5th MCP and proximal interphalangeal (PIP) joints of the most affected hand Schedule: 3 times/week for 4 weeks Total sessions: 12 Placebo: Similar but disconnected diode
Outcomes	Joint swelling ESR Fibrinogen (mmol/L) Leukocytes (10^9/L) Lymphocytes (%) Hemoglobin (mmol/L) Grip strength Flexibility - tip to palm distance (mm) Duration morning stiffness (hrs)
Notes	Quality Jadad's: 3/5

Walker 1987

Methods	Partially blinded Placebo controlled Sample size at entry: Laser : 38; Placebo : 34 Study duration 10 weeks
Participants	Participants with RA, defined by the American Rheumatism Association (ARA) Median age: Laser 61.5 yrs, Placebo 60.0 yrs Sex % F: Laser 60%, Placebo 79% Disease duration (median yrs): Laser 6 yrs, Placebo 11 yrs
Interventions	Laser: He-Ne Class: I Wavelength: 632.5 nm Output power: 1 mW Power density: 47.7 per cm^2

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Walker 1987 *(Continued)*

	Frequency: 20 Hz Duty cycle: 50% Spot size: 4 mm^2 Divergence: 30 degrees Dosage: 3.6 mJ/cm^2 Area treated: Radial, median, saphenous nerves for 20 s bilaterally and painful joints for 3 x 10 s along the circumference Schedule: 3 times/week for 10 weeks Total sessions: 30 Placebo: Sham apparatus with no light, subjects closed eyes
Outcomes	Pain (10 cm visual analogue scale)
Notes	Quality Jadad's: 1/5

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agambar 1992	Only abstract available
Ammer K 2003	Literature Review
Asada K 1989	No control group
Barabas 1989	Foreign language
Day R 1999	Literature Review
De Bie 1998	Literature Review
Fulga C 1998	Patients with juvenile RA; no control group
Goldman 1980	Insufficient statistical data
Heussler 1993	Insufficient statistical data
Matulis 1983	No control group
Miyagi 1989	Foreign language
Oyamada 1988	Although reported as double-blind in the abstract, a reply from the authors indicated that this trial was not randomized
Sidorov VD 1999	Abstract only available in English; Article was in Russian
Sidorov VD 2000	Abstract only available in English; Article was in Russian
Taghawinejad 1985	Foreign language
Tsurko 1983	Insufficient statistical data
Walker 1983	Duplicate of Walker 1987

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DATA AND ANALYSES

Comparison 1. Laser vs Placebo- End of treatment (approx 10 wks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (Visual Analogue Scale 10 cm)	3	147	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-1.82, -0.39]
2 Pain (0-12 scale)	1	22	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.77, -0.23]
3 McGill Pain questionnaire	1	35	Mean Difference (IV, Fixed, 95% CI)	1.5 [-1.22, 4.22]
4 Ritchie Index	1	40	Mean Difference (IV, Fixed, 95% CI)	2.60 [-4.50, 9.70]
5 Health Assessment Questionnaire (HAQ)	2	75	Mean Difference (IV, Fixed, 95% CI)	0.93 [-2.01, 3.87]
6 MCP ROM (degrees)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-15.99, 14.99]
7 PIP ROM (degrees)	1	40	Mean Difference (IV, Fixed, 95% CI)	4.0 [-6.60, 14.60]
8 Knee ROM	1	70	Mean Difference (IV, Fixed, 95% CI)	-18.03 [-31.80, -4.27]
8.1 Right knee ROM	1	35	Mean Difference (IV, Fixed, 95% CI)	-12.90 [-31.98, 6.18]
8.2 Left knee ROM	1	35	Mean Difference (IV, Fixed, 95% CI)	-23.60 [-43.47, -3.73]
9 Ankle ROM	1	70	Mean Difference (IV, Fixed, 95% CI)	4.60 [-0.33, 9.53]
9.1 Right ankle ROM	1	35	Mean Difference (IV, Fixed, 95% CI)	5.90 [-1.21, 13.01]
9.2 Left ankle ROM	1	35	Mean Difference (IV, Fixed, 95% CI)	3.40 [-3.43, 10.23]
10 Flexibility- tip to palm distance (cm)	2	57	Mean Difference (IV, Fixed, 95% CI)	-1.28 [-1.72, -0.85]
11 Morning stiffness duration (min)	3	110	Mean Difference (IV, Fixed, 95% CI)	-27.45 [-51.95, -2.95]
12 Morning stiffness not improved	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.49, 1.19]
13 Rheumatoid factor positive	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.61, 1.34]
14 Grip strength	3	97	Mean Difference (IV, Fixed, 95% CI)	0.62 [-0.36, 1.60]
14.1 Grip strength (mmHg)	2	75	Mean Difference (IV, Fixed, 95% CI)	7.71 [0.15, 15.27]
14.2 Grip strength (kg)	1	22	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.49, 1.49]

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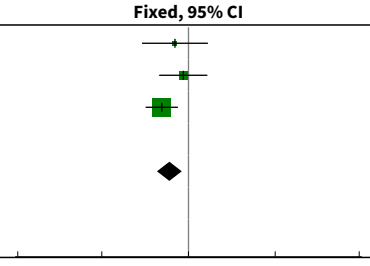
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Suprapatellar swelling - right knee (cm)	1	35	Mean Difference (IV, Fixed, 95% CI)	-2.94 [-6.31, 0.43]
16 Suprapatellar swelling- left knee (cm)	1	35	Mean Difference (IV, Fixed, 95% CI)	-2.69 [-6.33, 0.95]
17 MCP swelling (cm)	1	40	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.78, 1.18]
18 PIP swelling (cm)	2	75	Mean Difference (IV, Fixed, 95% CI)	0.53 [-1.12, 2.18]
19 Walking speed (sec)	1	35	Mean Difference (IV, Fixed, 95% CI)	-1.87 [-7.08, 3.34]
20 Fibrinogen	1	35	Mean Difference (IV, Fixed, 95% CI)	1.5 [-0.00, 3.00]
21 Leukocytes	1	35	Mean Difference (IV, Fixed, 95% CI)	1.60 [0.62, 2.58]
22 Lymphocytes	1	35	Mean Difference (IV, Fixed, 95% CI)	3.0 [-6.57, 12.57]
23 ESR (mm/hr)	3	92	Mean Difference (IV, Fixed, 95% CI)	-10.09 [-15.04, -5.15]
24 CRP (g/mL)	2	57	Mean Difference (IV, Fixed, 95% CI)	2.55 [-14.11, 19.21]
25 Hemoglobin	2	70	Mean Difference (IV, Fixed, 95% CI)	0.47 [0.01, 0.93]
26 Platelets	1	35	Mean Difference (IV, Fixed, 95% CI)	20.35 [-64.36, 105.06]

Analysis 1.1. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 1 Pain (Visual Analogue Scale 10 cm).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	5.2 (3)	10	5.9 (2.4)		14.2%	-0.78[-2.68,1.12]
Hall 1994	20	4 (2.2)	20	4.3 (2.2)		26.57%	-0.3[-1.69,1.09]
Walker 1987	38	3.7 (2.2)	34	5.2 (1.8)		59.23%	-1.54[-2.47,-0.61]
Total ***	**83**		**64**			**100%**	**-1.1[-1.82,-0.39]**
Heterogeneity: Tau^2=0; Chi^2=2.24, df=2(P=0.33); I^2=10.9%							
Test for overall effect: Z=3.02(P=0)							



Analysis 1.2. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 2 Pain (0-12 scale).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Johannsen 1994	10	4.5 (0.6)	12	5.5 (1.2)		100%	-1[-1.77,-0.23]
Total ***	**10**		**12**			**100%**	**-1[-1.77,-0.23]**

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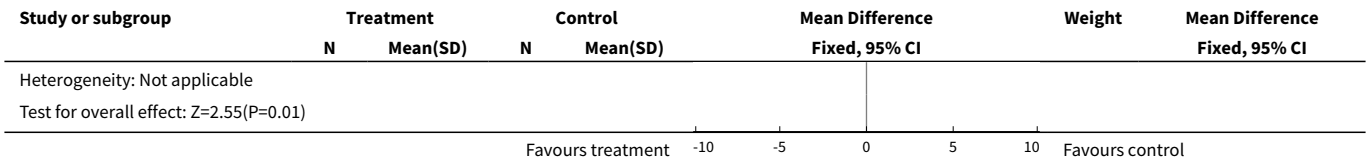
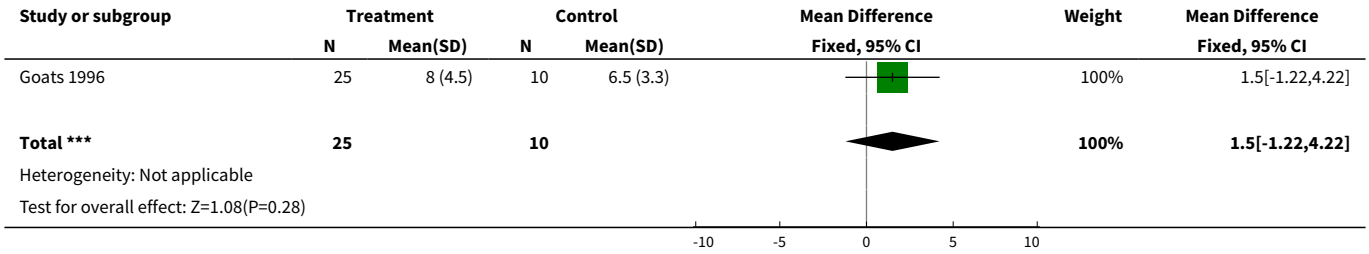
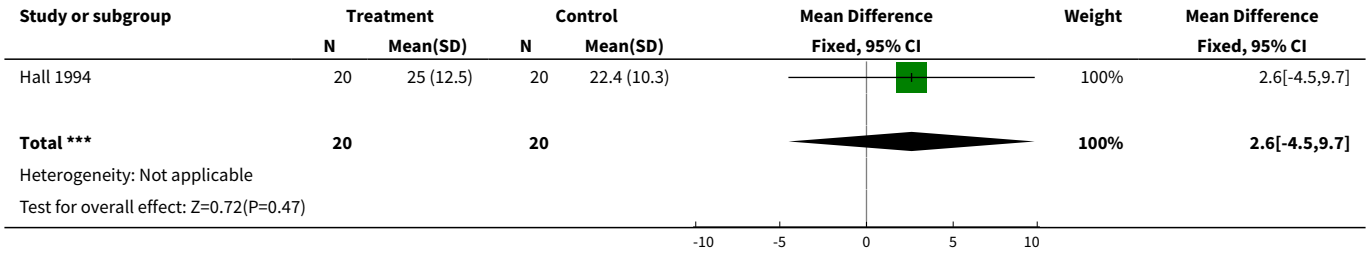


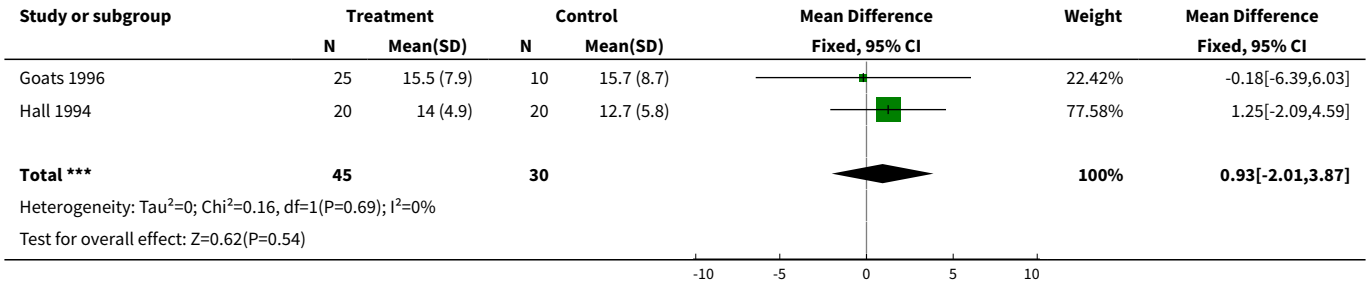
Analysis 1.3. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 3 McGill Pain questionnaire.



Analysis 1.4. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 4 Ritchie Index.



Analysis 1.5. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 5 Health Assessment Questionnaire (HAQ).



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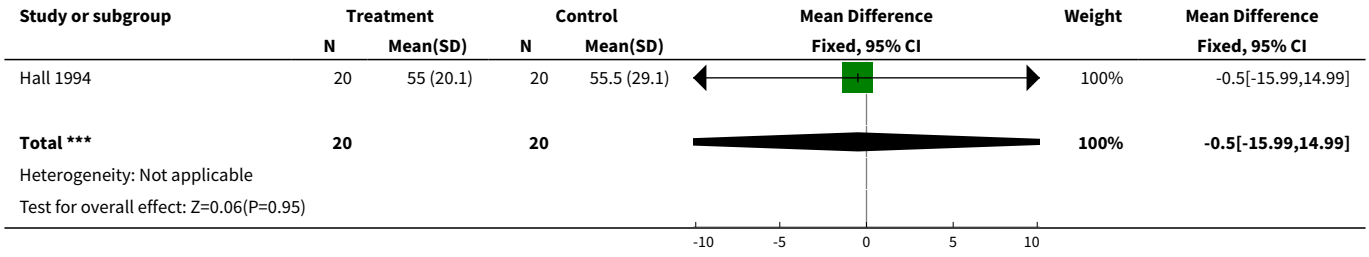
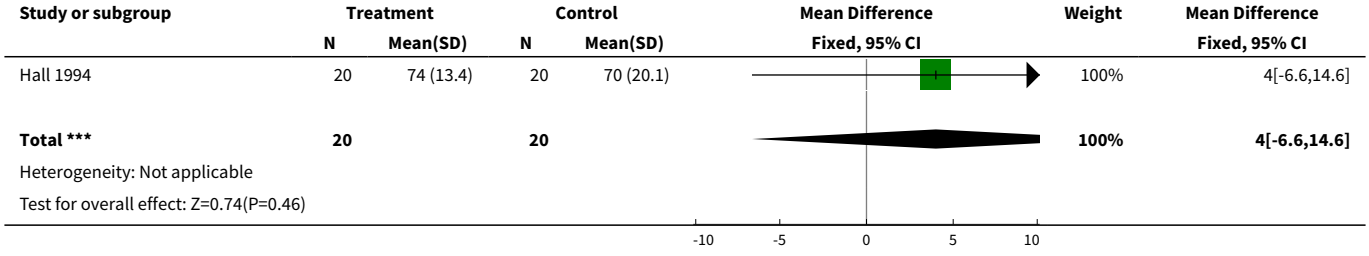
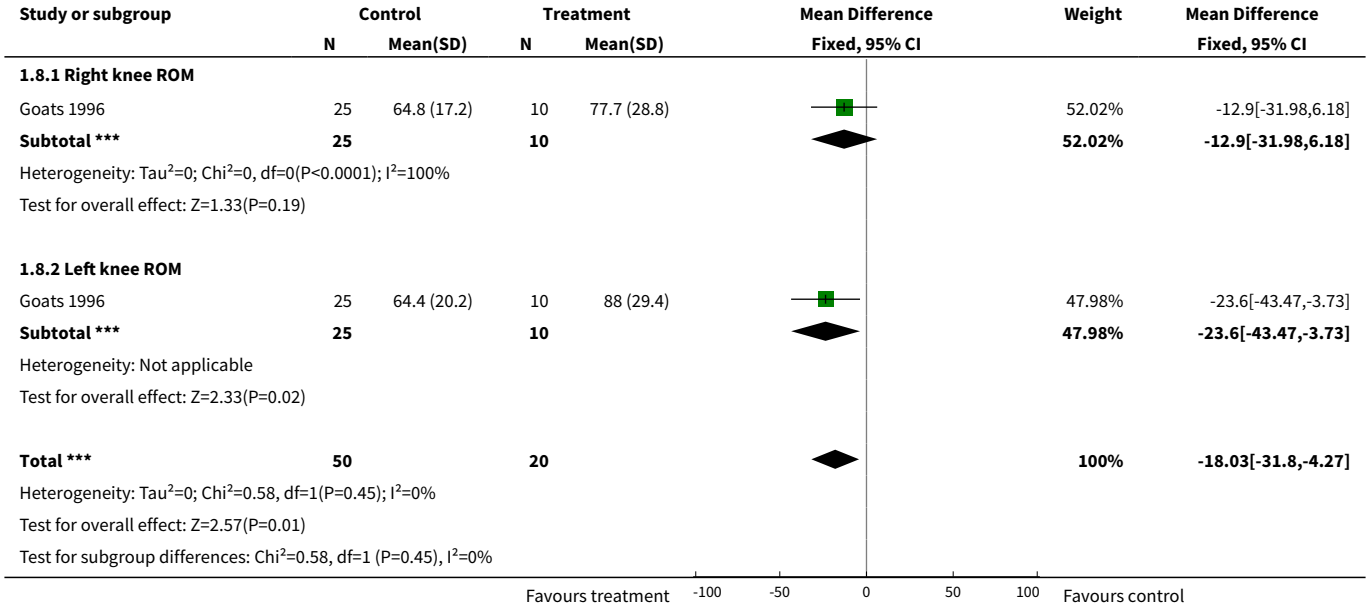
Analysis 1.6. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 6 MCP ROM (degrees).



Analysis 1.7. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 7 PIP ROM (degrees).



Analysis 1.8. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 8 Knee ROM.



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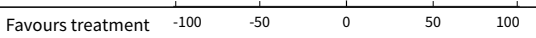
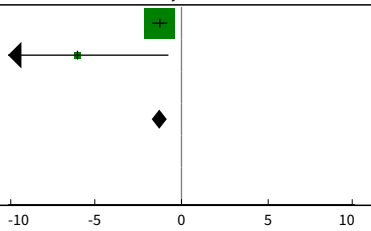
Analysis 1.9. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 9 Ankle ROM.

Study or subgroup	Control N	Control Mean(SD)	Treatment N	Treatment Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.9.1 Right ankle ROM							
Goats 1996	25	43.5 (14)	10	37.6 (7.3)		48.01%	5.9[-1.21,13.01]
Subtotal ***	**25**		**10**			**48.01%**	**5.9[-1.21,13.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.63(P=0.1)							
1.9.2 Left ankle ROM							
Goats 1996	25	43.2 (13.6)	10	39.8 (6.9)		51.99%	3.4[-3.43,10.23]
Subtotal ***	**25**		**10**			**51.99%**	**3.4[-3.43,10.23]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.98(P=0.33)							
Total ***	**50**		**20**			**100%**	**4.6[-0.33,9.53]**
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%							
Test for overall effect: Z=1.83(P=0.07)							
Test for subgroup differences: Chi^2=0.25, df=1 (P=0.62), I^2=0%							



Analysis 1.10. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 10 Flexibility- tip to palm distance (cm).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Johannsen 1994	10	0 (0.2)	12	1.3 (0.8)		99.32%	-1.25[-1.68,-0.82]
Palmgren 1989	19	0 (6)	16	6 (9.2)		0.68%	-6[-11.25,-0.75]
Total ***	**29**		**28**			**100%**	**-1.28[-1.72,-0.85]**
Heterogeneity: Tau^2=0; Chi^2=3.13, df=1(P=0.08); I^2=68.04%							
Test for overall effect: Z=5.81(P<0.0001)							



Analysis 1.11. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 11 Morning stiffness duration (min).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	104.4 (275.4)	10	63.6 (67.8)		4.47%	40.8[-75.05,156.65]
Hall 1994	20	57.8 (65.3)	20	72 (85)		27.22%	-14.2[-61.16,32.76]
Palmgren 1989	19	30.6 (43.7)	16	67.8 (45.3)		68.31%	-37.2[-66.84,-7.56]
Total ***	**64**		**46**			**100%**	**-27.45[-51.95,-2.95]**
Heterogeneity: Tau^2=0; Chi^2=2.05, df=2(P=0.36); I^2=2.66%							
Test for overall effect: Z=2.2(P=0.03)							

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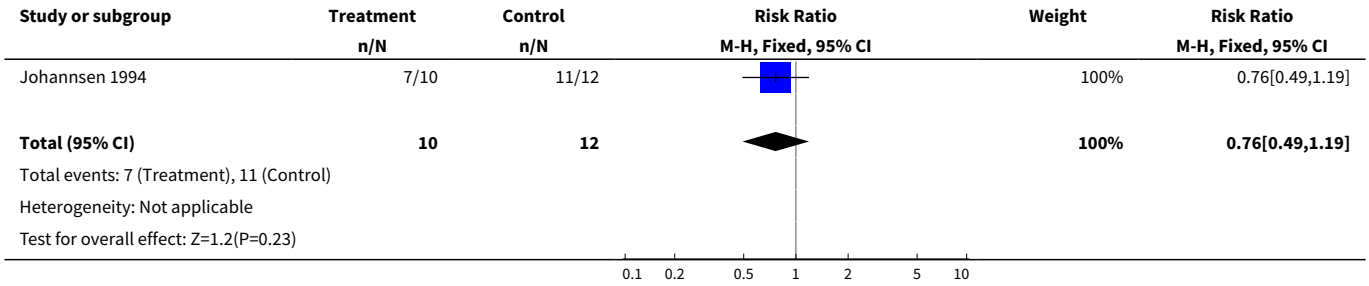
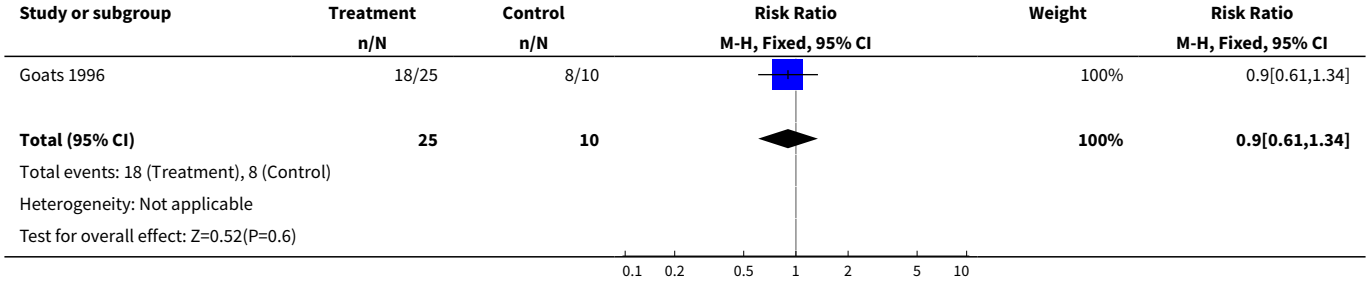
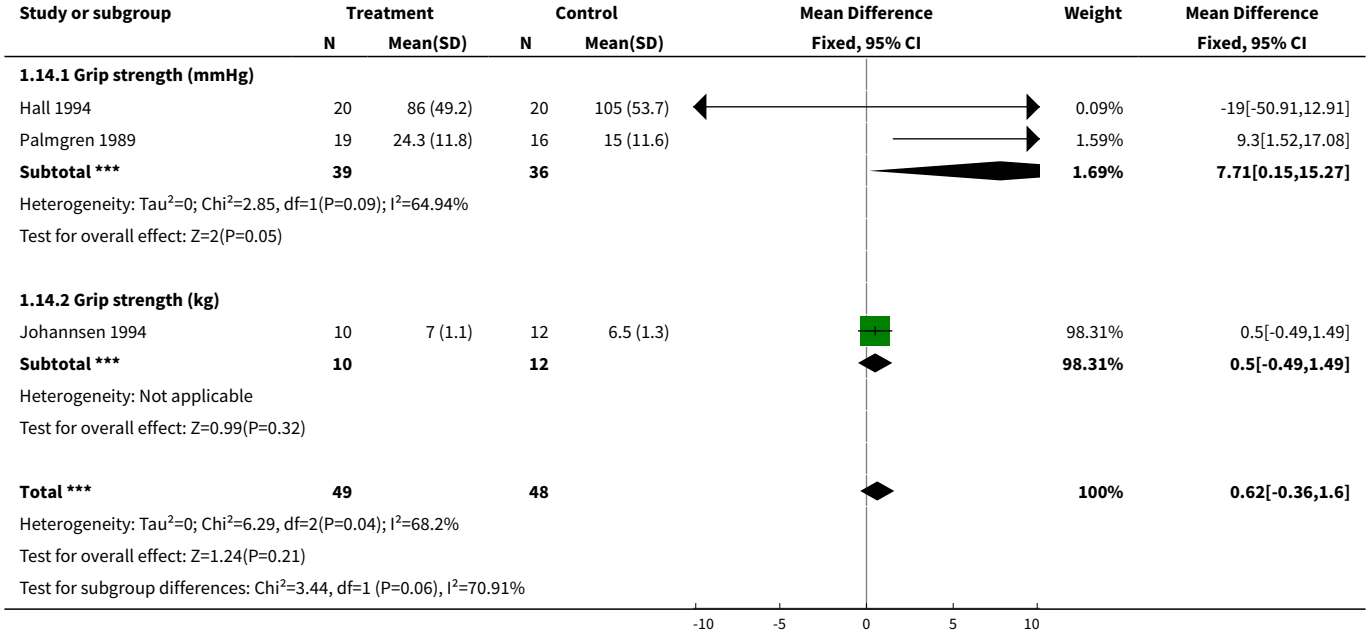
Analysis 1.12. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 12 Morning stiffness not improved.



Analysis 1.13. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 13 Rheumatoid factor positive.



Analysis 1.14. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 14 Grip strength.



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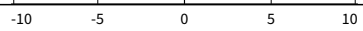
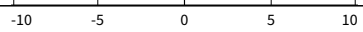
Analysis 1.15. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 15 Suprapatellar swelling - right knee (cm).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	37.6 (3.3)	10	40.5 (5)		100%	-2.94[-6.31,0.43]
Total ***	**25**		**10**			**100%**	**-2.94[-6.31,0.43]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.71(P=0.09)							



Analysis 1.16. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 16 Suprapatellar swelling- left knee (cm).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	37.6 (3.4)	10	40.3 (5.5)		100%	-2.69[-6.33,0.95]
Total ***	**25**		**10**			**100%**	**-2.69[-6.33,0.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.45(P=0.15)							



Analysis 1.17. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 17 MCP swelling (cm).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hall 1994	20	20 (1.8)	20	19.8 (1.3)		100%	0.2[-0.78,1.18]
Total ***	**20**		**20**			**100%**	**0.2[-0.78,1.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.4(P=0.69)							

Analysis 1.18. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 18 PIP swelling (cm).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hall 1994	20	62.8 (5.8)	20	60.3 (4.5)		26.45%	2.5[-0.71,5.71]
Palmgren 1989	19	8.3 (1.2)	16	8.5 (3.8)		73.55%	-0.18[-2.11,1.75]
Total ***	**39**		**36**			**100%**	**0.53[-1.12,2.18]**
Heterogeneity: Tau^2=0; Chi^2=1.97, df=1(P=0.16); I^2=49.14%							
Test for overall effect: Z=0.63(P=0.53)							

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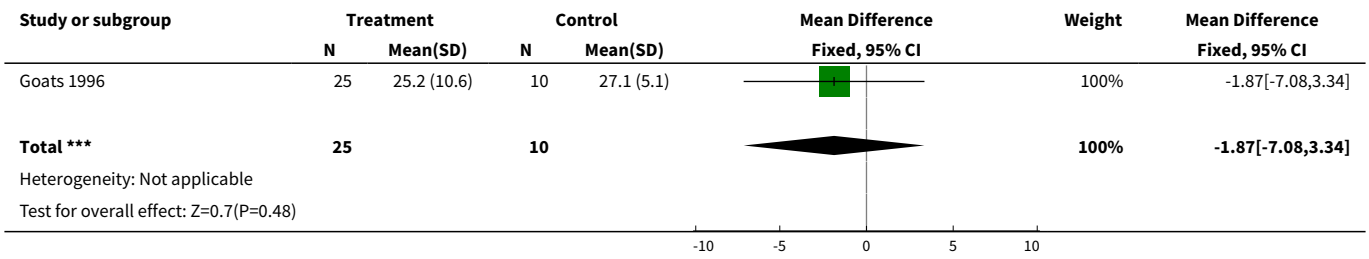
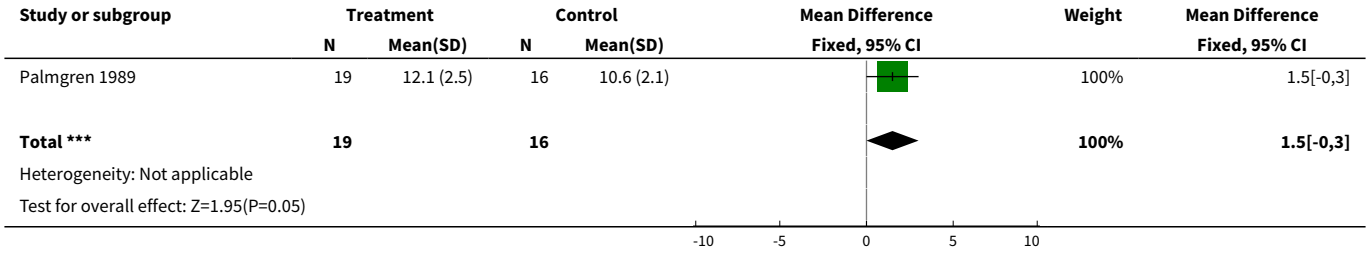
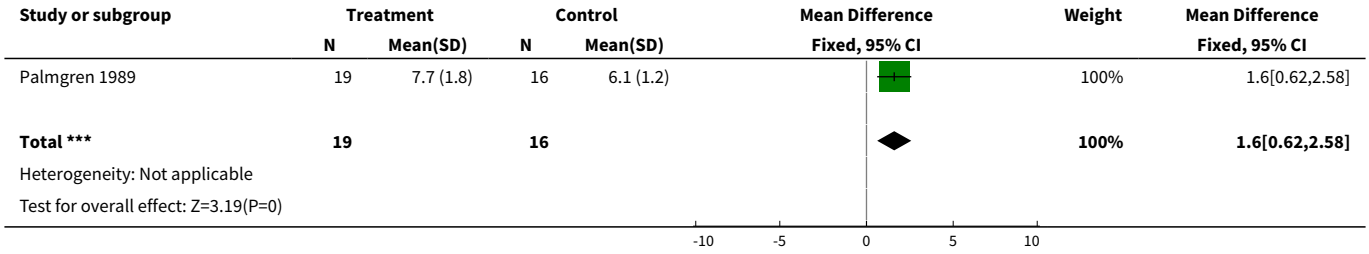
Analysis 1.19. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 19 Walking speed (sec).



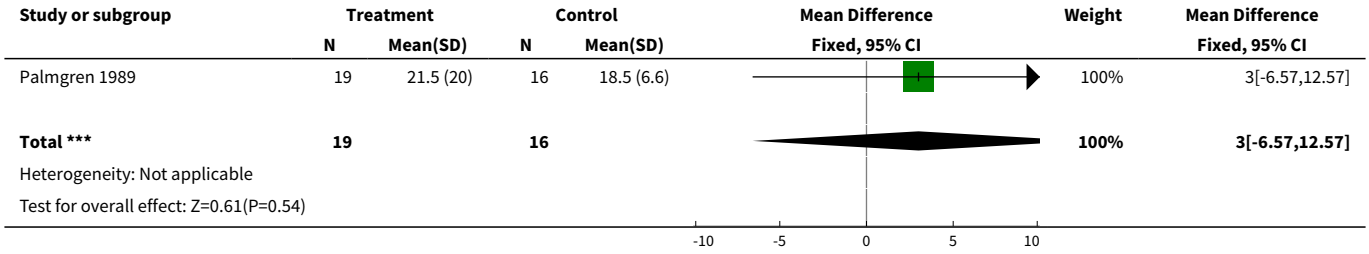
Analysis 1.20. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 20 Fibrinogen.



Analysis 1.21. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 21 Leukocytes.



Analysis 1.22. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 22 Lymphocytes.



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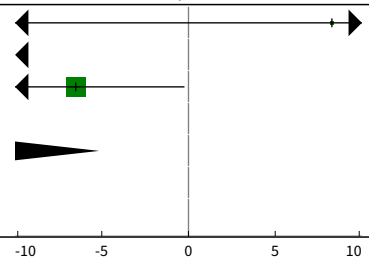
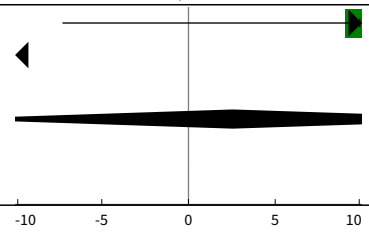
Analysis 1.23. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 23 ESR (mm/hr).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	46.8 (36.1)	10	38.6 (26)		5.32%	8.27[-13.18,29.72]
Johannsen 1994	10	12 (6.7)	12	32 (13.5)		32.42%	-20[-28.69,-11.31]
Palmgren 1989	19	19 (5.6)	16	25.5 (11.7)		62.26%	-6.5[-12.77,-0.23]
Total ***	**54**		**38**			**100%**	**-10.09[-15.04,-5.15]**
Heterogeneity: Tau²=0; Chi²=9.08, df=2(P=0.01); I²=77.96%							
Test for overall effect: Z=4(P<0.0001)							



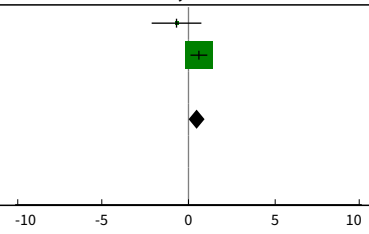
Analysis 1.24. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 24 CRP (g/mL).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	32.3 (27.7)	10	22.4 (21.4)		94.36%	9.88[-7.27,27.03]
Johannsen 1994	10	96 (100)	12	216 (58)		5.64%	-120[-190.13,-49.87]
Total ***	**35**		**22**			**100%**	**2.55[-14.11,19.21]**
Heterogeneity: Tau²=0; Chi²=12.43, df=1(P=0); I²=91.96%							
Test for overall effect: Z=0.3(P=0.76)							



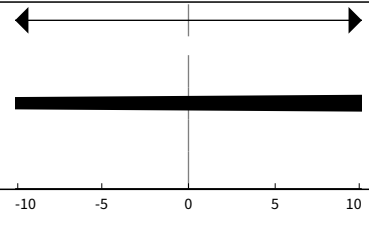
Analysis 1.25. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 25 Hemoglobin.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	12.2 (2.8)	10	12.9 (1.5)		10.28%	-0.69[-2.12,0.74]
Palmgren 1989	19	8.1 (0.9)	16	7.5 (0.6)		89.72%	0.6[0.11,1.09]
Total ***	**44**		**26**			**100%**	**0.47[0.01,0.93]**
Heterogeneity: Tau²=0; Chi²=2.79, df=1(P=0.09); I²=64.17%							
Test for overall effect: Z=1.99(P=0.05)							



Analysis 1.26. Comparison 1 Laser vs Placebo- End of treatment (approx 10 wks), Outcome 26 Platelets.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	377.8 (130.8)	10	357.4 (108.8)		100%	20.35[-64.36,105.06]
Total ***	**25**		**10**			**100%**	**20.35[-64.36,105.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.47(P=0.64)							



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Comparison 2. Laser vs Placebo- End of follow-up (approx 20 wks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	2	54	Mean Difference (IV, Fixed, 95% CI)	0.06 [-1.24, 1.36]
1.1 Pain (10 cm visual analogue scale)	2	54	Mean Difference (IV, Fixed, 95% CI)	0.06 [-1.24, 1.36]
2 McGill Pain questionnaire	1	28	Mean Difference (IV, Fixed, 95% CI)	1.39 [-2.23, 5.01]
3 Health Assessment Questionnaire (HAQ)	2	54	Mean Difference (IV, Fixed, 95% CI)	1.10 [-2.80, 4.99]
4 Ritchie Index	1	26	Mean Difference (IV, Fixed, 95% CI)	3.30 [-5.74, 12.34]
5 PIP ROM (degrees)	1	26	Mean Difference (IV, Fixed, 95% CI)	2.0 [-16.30, 20.30]
6 Knee ROM	1	56	Mean Difference (IV, Fixed, 95% CI)	-11.47 [-31.26, 8.31]
6.1 Right knee ROM	1	28	Mean Difference (IV, Fixed, 95% CI)	-13.60 [-41.44, 14.24]
6.2 Left knee ROM	1	28	Mean Difference (IV, Fixed, 95% CI)	-9.30 [-37.43, 18.83]
7 Ankle ROM	1	56	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-11.69, 9.28]
7.1 Right ankle ROM	1	28	Mean Difference (IV, Fixed, 95% CI)	1.80 [-12.59, 16.19]
7.2 Left ankle ROM	1	28	Mean Difference (IV, Fixed, 95% CI)	-4.60 [-19.91, 10.71]
8 MCP ROM (degrees)	1	26	Mean Difference (IV, Fixed, 95% CI)	10.0 [-6.86, 26.86]
9 Morning stiffness duration (min)	2	54	Mean Difference (IV, Fixed, 95% CI)	12.16 [-31.00, 55.31]
10 Walking speed (sec)	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.91 [-12.60, 8.78]
11 Grip strength	1	26	Mean Difference (IV, Fixed, 95% CI)	-29.0 [-61.44, 3.44]
11.1 Grip strength (mmHg)	1	26	Mean Difference (IV, Fixed, 95% CI)	-29.0 [-61.44, 3.44]
11.2 Grip strength (kg)	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Suprapatellar swelling- left knee (cm)	1	28	Mean Difference (IV, Fixed, 95% CI)	-2.89 [-14.38, 8.60]
13 Suprapatellar swelling - right knee (cm)	1	28	Mean Difference (IV, Fixed, 95% CI)	-3.29 [-14.66, 8.08]
14 MCP swelling (cm)	1	26	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.23, 0.43]
15 PIP swelling (cm)	1	26	Mean Difference (IV, Fixed, 95% CI)	0.90 [-1.88, 3.68]

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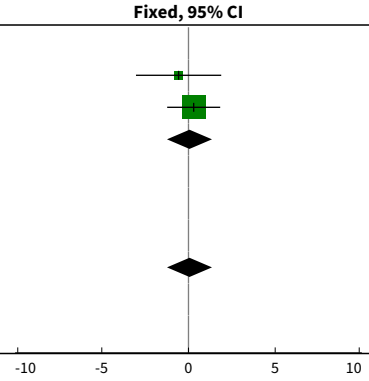
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Thermographic index	1	26	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.11, 1.31]
17 Rheumatoid factor positive	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.60, 1.68]
18 ESR (mm/hr)	1	28	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-26.94, 22.94]
19 CRP (g/mL)	2	54	Mean Difference (IV, Fixed, 95% CI)	-4.21 [-20.25, 11.83]
20 Hemoglobin	2	54	Mean Difference (IV, Fixed, 95% CI)	0.98 [-0.21, 2.16]
21 Platelets	2	54	Mean Difference (IV, Fixed, 95% CI)	32.68 [-37.76, 103.11]

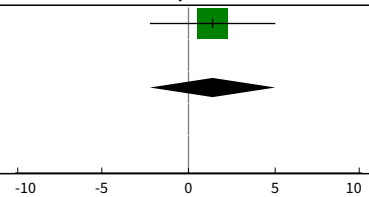
Analysis 2.1. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 1 Pain.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Pain (10 cm visual analogue scale)							
Goats 1996	20	5.3 (3.6)	8	5.9 (2.7)		27.89%	-0.57[-3.03,1.89]
Hall 1994	13	3.1 (2.2)	13	2.8 (1.8)		72.11%	0.3[-1.23,1.83]
Subtotal ***	**33**		**21**			**100%**	**0.06[-1.24,1.36]**
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.56); I^2=0%							
Test for overall effect: Z=0.09(P=0.93)							
Total ***	**33**		**21**			**100%**	**0.06[-1.24,1.36]**
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.56); I^2=0%							
Test for overall effect: Z=0.09(P=0.93)							



Analysis 2.2. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 2 McGill Pain questionnaire.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	20	8.5 (6.3)	8	7.1 (3.4)		100%	1.39[-2.23,5.01]
Total ***	**20**		**8**			**100%**	**1.39[-2.23,5.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.75(P=0.45)							



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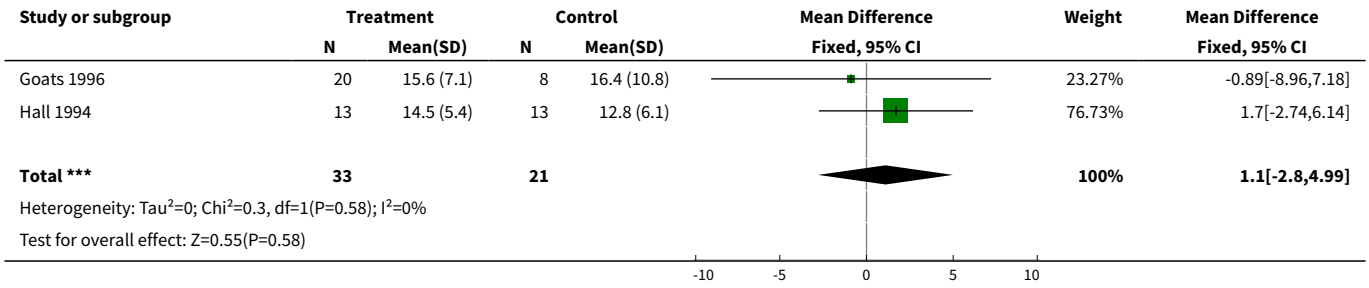
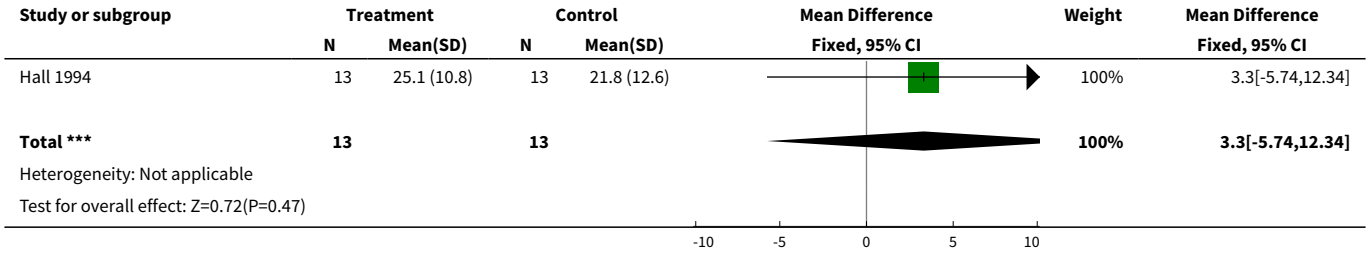
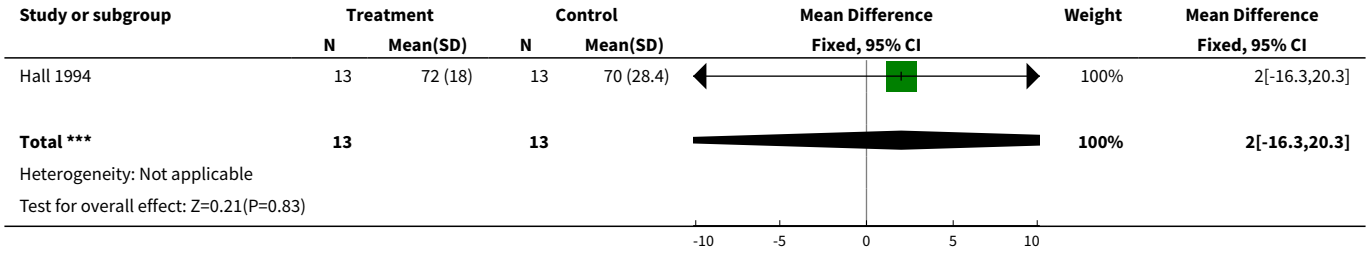
Analysis 2.3. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 3 Health Assessment Questionnaire (HAQ).



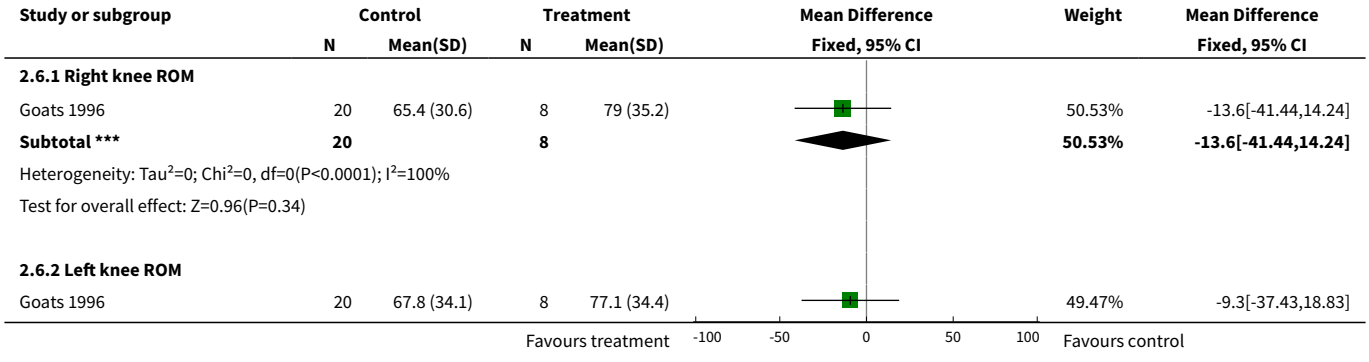
Analysis 2.4. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 4 Ritchie Index.



Analysis 2.5. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 5 PIP ROM (degrees).



Analysis 2.6. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 6 Knee ROM.



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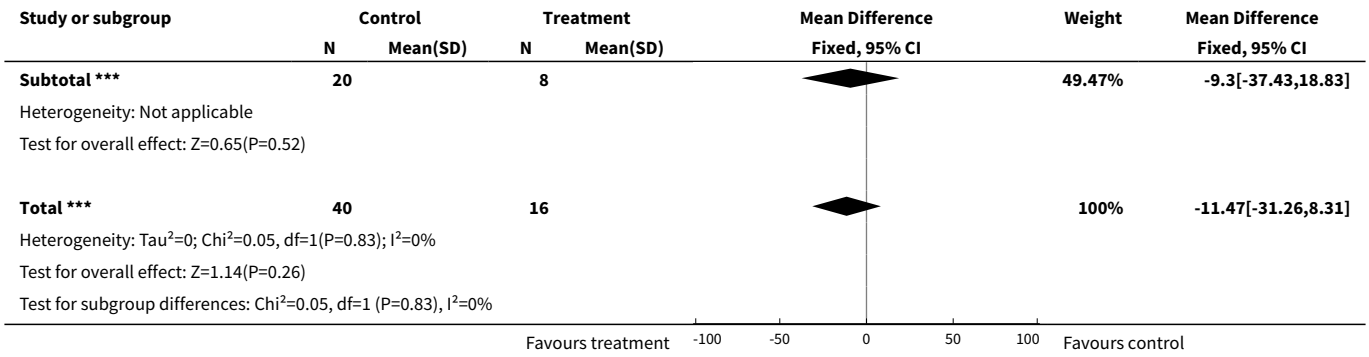
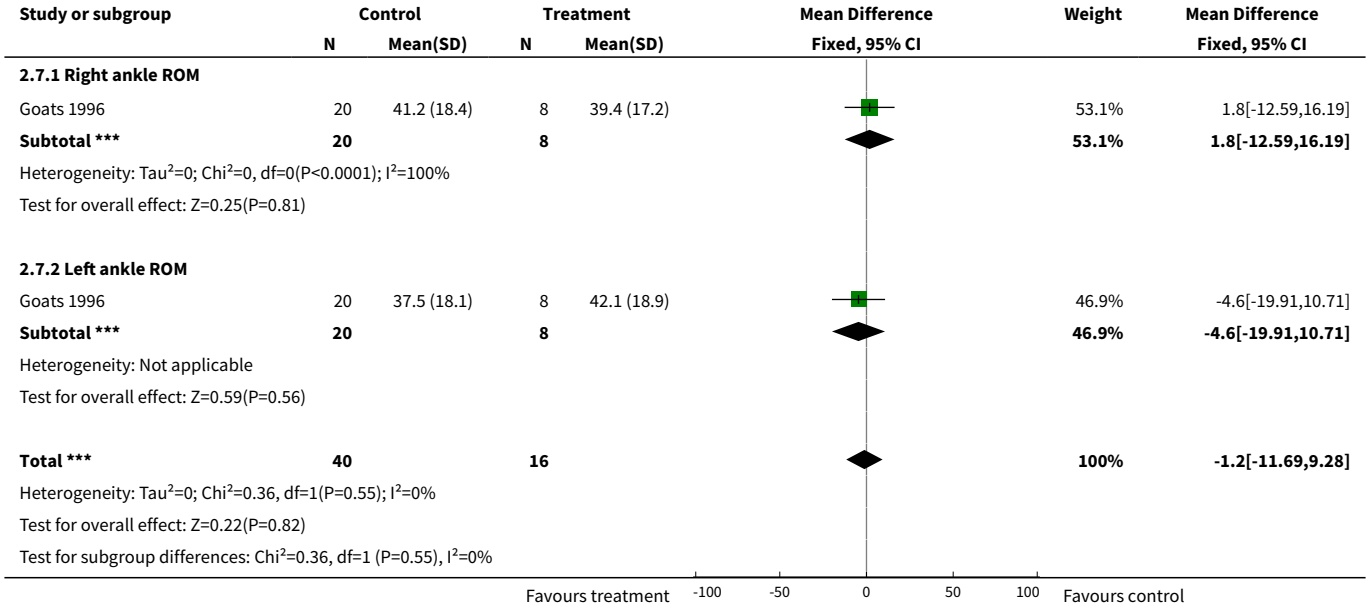
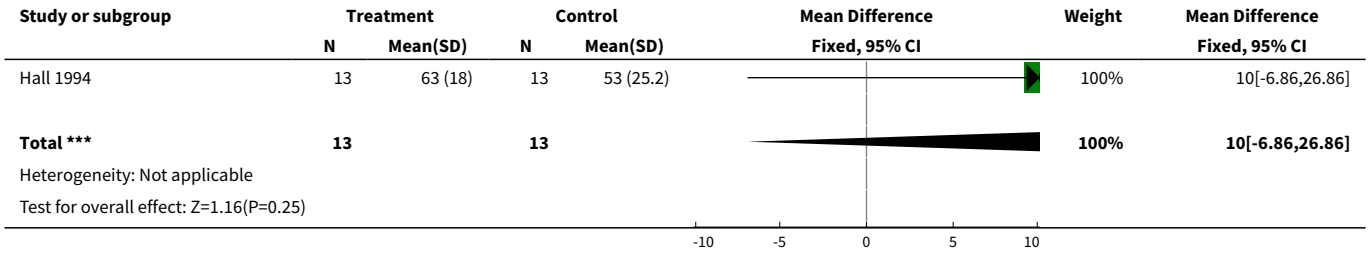


Analysis 2.7. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 7 Ankle ROM.



Analysis 2.8. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 8 MCP ROM (degrees).



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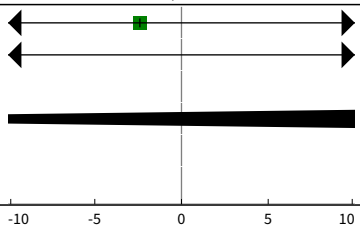
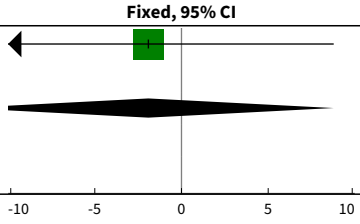
Analysis 2.9. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 9 Morning stiffness duration (min).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	20	75.6 (75.6)	8	78 (84.6)		41.07%	-2.4[-69.74,64.94]
Hall 1994	13	70 (98.4)	13	47.7 (31.7)		58.93%	22.3[-33.92,78.52]
Total ***	**33**		**21**			**100%**	**12.16[-31,55.31]**
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.58); I^2=0%							
Test for overall effect: Z=0.55(P=0.58)							



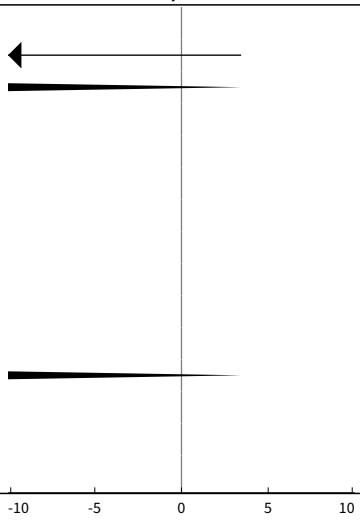
Analysis 2.10. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 10 Walking speed (sec).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	20	26.5 (13.2)	8	28.4 (13)		100%	-1.91[-12.6,8.78]
Total ***	**20**		**8**			**100%**	**-1.91[-12.6,8.78]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.35(P=0.73)							



Analysis 2.11. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 11 Grip strength.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.11.1 Grip strength (mmHg)							
Hall 1994	13	70 (25.2)	13	99 (54.1)		100%	-29[-61.44,3.44]
Subtotal ***	**13**		**13**			**100%**	**-29[-61.44,3.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.75(P=0.08)							
2.11.2 Grip strength (kg)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**13**		**13**			**100%**	**-29[-61.44,3.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.75(P=0.08)							
Test for subgroup differences: Not applicable							



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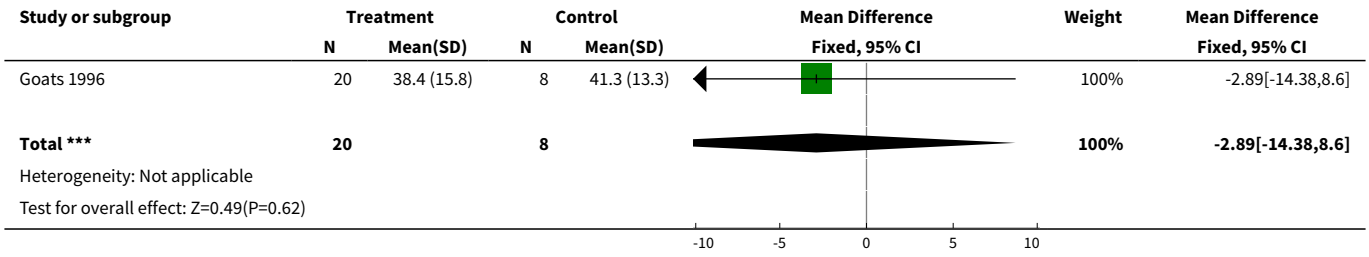
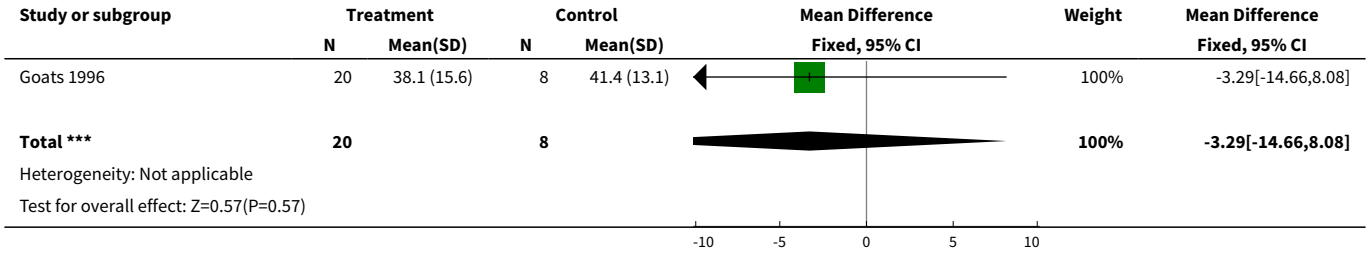
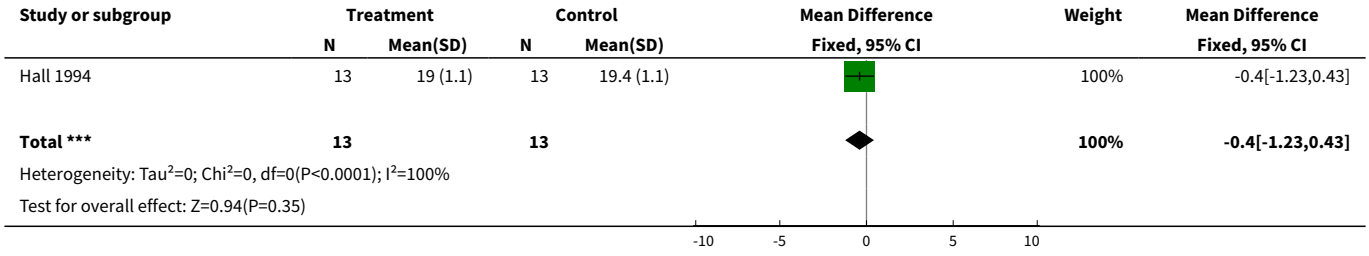
Analysis 2.12. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 12 Suprapatellar swelling- left knee (cm).



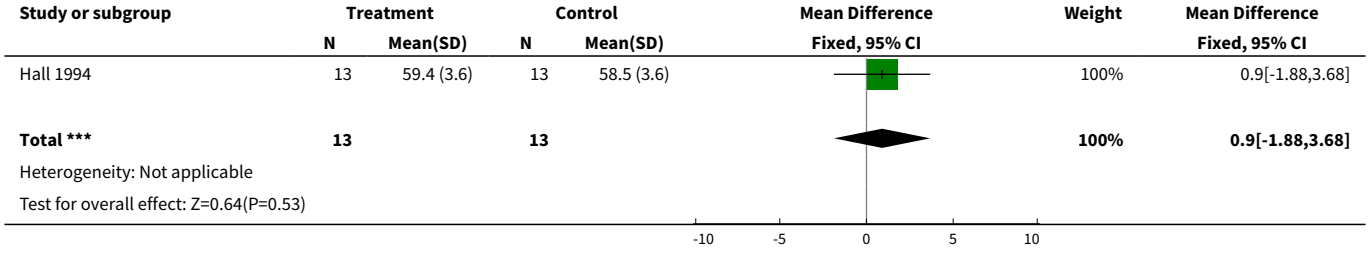
Analysis 2.13. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 13 Suprapatellar swelling - right knee (cm).



Analysis 2.14. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 14 MCP swelling (cm).



Analysis 2.15. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 15 PIP swelling (cm).



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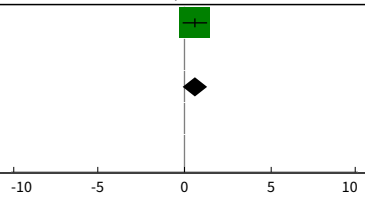
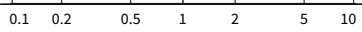
Analysis 2.16. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 16 Thermographic index.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hall 1994	13	3.8 (0.7)	13	3.2 (1.1)		100%	0.6[-0.11,1.31]
Total ***	**13**		**13**			**100%**	**0.6[-0.11,1.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.67(P=0.1)							



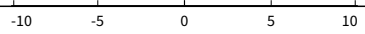
Analysis 2.17. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 17 Rheumatoid factor positive.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goats 1996	9/12	6/8		100%	1[0.6,1.68]
Total (95% CI)	**12**	**8**		**100%**	**1[0.6,1.68]**
Total events: 9 (Treatment), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



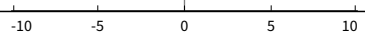
Analysis 2.18. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 18 ESR (mm/hr).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	20	44.9 (32.1)	8	46.9 (29.7)		100%	-2[-26.94,22.94]
Total ***	**20**		**8**			**100%**	**-2[-26.94,22.94]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.16(P=0.88)							



Analysis 2.19. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 19 CRP (g/mL).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	20	22.1 (17.6)	8	27.2 (25.4)		69.72%	-5.17[-24.38,14.04]
Hall 1994	13	27 (36.1)	13	29 (39.7)		30.28%	-2[-31.15,27.15]
Total ***	**33**		**21**			**100%**	**-4.21[-20.25,11.83]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%							
Test for overall effect: Z=0.51(P=0.61)							



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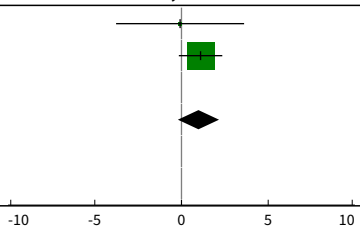
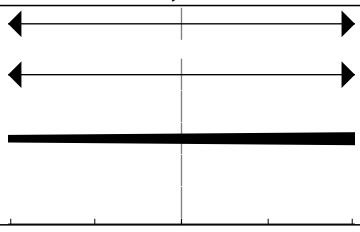
Analysis 2.20. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 20 Hemoglobin.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	20	12.5 (5.5)	8	12.6 (4.1)		10.33%	-0.08[-3.77,3.61]
Hall 1994	13	12.5 (1.8)	13	11.4 (1.4)		89.67%	1.1[-0.15,2.35]
Total ***	**33**		**21**			**100%**	**0.98[-0.21,2.16]**
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.55); I^2=0%							
Test for overall effect: Z=1.62(P=0.11)							



Analysis 2.21. Comparison 2 Laser vs Placebo- End of follow-up (approx 20 wks), Outcome 21 Platelets.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	20	335.1 (159.8)	8	306.7 (137.7)		35.43%	28.44[-89.89,146.77]
Hall 1994	13	340 (144.2)	13	305 (72.1)		64.57%	35[-52.65,122.65]
Total ***	**33**		**21**			**100%**	**32.68[-37.76,103.11]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%							
Test for overall effect: Z=0.91(P=0.36)							

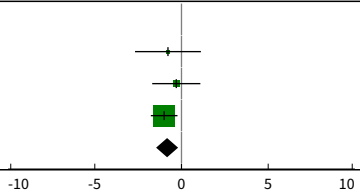


Comparison 3. Treatment length- subgroup analysis for end of treatment results

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (10 cm VAS or 0-12 scale)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Treatment for 4 weeks	3	97	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-1.46, -0.20]
1.2 Treatment for 10 weeks	1	72	Mean Difference (IV, Fixed, 95% CI)	-1.54 [-2.47, -0.61]

Analysis 3.1. Comparison 3 Treatment length- subgroup analysis for end of treatment results, Outcome 1 Pain (10 cm VAS or 0-12 scale).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.1.1 Treatment for 4 weeks							
Goats 1996	25	5.2 (3)	10	5.9 (2.4)		11.14%	-0.78[-2.68,1.12]
Hall 1994	20	4 (2.2)	20	4.3 (2.2)		20.83%	-0.3[-1.69,1.09]
Johannsen 1994	10	4.5 (0.6)	12	5.5 (1.2)		68.03%	-1[-1.77,-0.23]
Subtotal ***	**55**		**42**			**100%**	**-0.83[-1.46,-0.2]**



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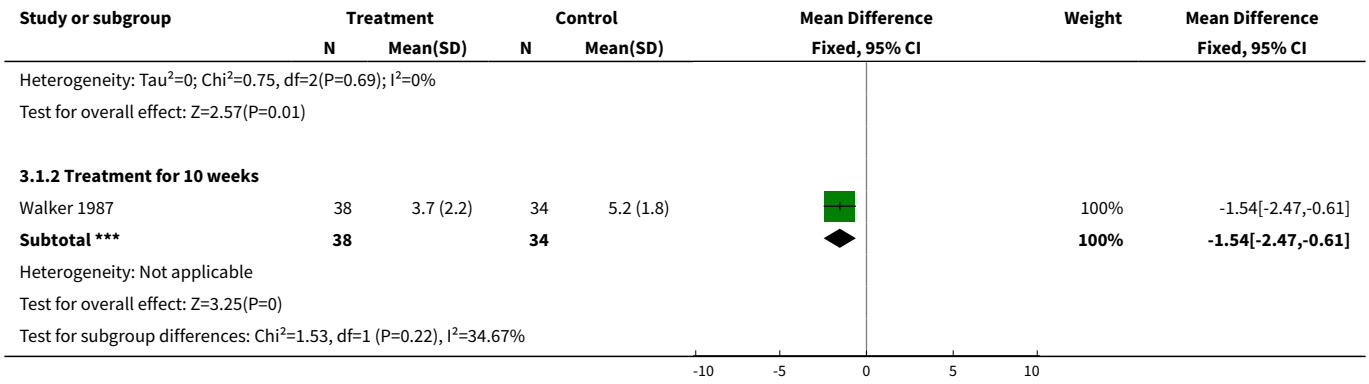
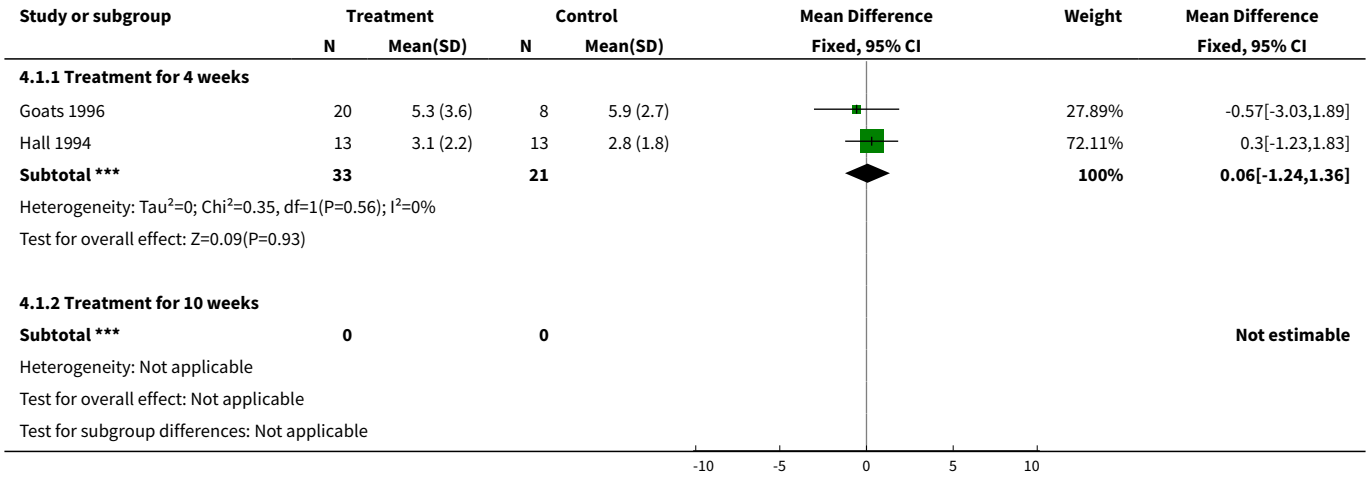


Comparison 4. Treatment length- subgroup analysis for end of follow up results

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (10 cm VAS or 0-12 scale)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Treatment for 4 weeks	2	54	Mean Difference (IV, Fixed, 95% CI)	0.06 [-1.24, 1.36]
1.2 Treatment for 10 weeks	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Treatment length- subgroup analysis for end of follow up results, Outcome 1 Pain (10 cm VAS or 0-12 scale).



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Comparison 5. Methodologic quality: low (<3) vs high (=> 3)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at end of treatment	4	169	Mean Difference (IV, Fixed, 95% CI)	-1.05 [-1.58, -0.53]
1.1 Low quality (<3)	2	107	Mean Difference (IV, Fixed, 95% CI)	-1.39 [-2.23, -0.56]
1.2 High quality (=> 3)	2	62	Mean Difference (IV, Fixed, 95% CI)	-0.84 [-1.51, -0.16]

Analysis 5.1. Comparison 5 Methodologic quality: low (<3) vs high (=> 3), Outcome 1 Pain at end of treatment.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.1.1 Low quality (<3)							
Goats 1996	25	5.2 (3)	10	5.9 (2.4)		7.61%	-0.78[-2.68,1.12]
Walker 1987	38	3.7 (2.2)	34	5.2 (1.8)		31.71%	-1.54[-2.47,-0.61]
Subtotal ***	**63**		**44**			**39.31%**	**-1.39[-2.23,-0.56]**
Heterogeneity: Tau^2=0; Chi^2=0.5, df=1(P=0.48); I^2=0%							
Test for overall effect: Z=3.27(P=0)							
5.1.2 High quality (=> 3)							
Hall 1994	20	4 (2.2)	20	4.3 (2.2)		14.23%	-0.3[-1.69,1.09]
Johannsen 1994	10	4.5 (0.6)	12	5.5 (1.2)		46.46%	-1[-1.77,-0.23]
Subtotal ***	**30**		**32**			**60.69%**	**-0.84[-1.51,-0.16]**
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%							
Test for overall effect: Z=2.44(P=0.01)							
Total ***	**93**		**76**			**100%**	**-1.05[-1.58,-0.53]**
Heterogeneity: Tau^2=0; Chi^2=2.28, df=3(P=0.52); I^2=0%							
Test for overall effect: Z=3.95(P<0.0001)							
Test for subgroup differences: Chi^2=1.04, df=1 (P=0.31), I^2=3.59%							

Comparison 6. Laser vs Placebo - Joint vs Nerve - end of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (10 cm VAS or 0-12 scale)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Joint application	3	97	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-1.46, -0.20]
1.2 Nerve application	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Joint and nerve application	1	72	Mean Difference (IV, Fixed, 95% CI)	-1.54 [-2.47, -0.61]

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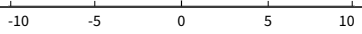
Analysis 6.1. Comparison 6 Laser vs Placebo - Joint vs Nerve - end of treatment, Outcome 1 Pain (10 cm VAS or 0-12 scale).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.1.1 Joint application							
Goats 1996	25	5.2 (3)	10	5.9 (2.4)		11.14%	-0.78[-2.68,1.12]
Hall 1994	20	4 (2.2)	20	4.3 (2.2)		20.83%	-0.3[-1.69,1.09]
Johannsen 1994	10	4.5 (0.6)	12	5.5 (1.2)		68.03%	-1[-1.77,-0.23]
Subtotal ***	**55**		**42**			**100%**	**-0.83[-1.46,-0.2]**
Heterogeneity: Tau²=0; Chi²=0.75, df=2(P=0.69); I²=0%							
Test for overall effect: Z=2.57(P=0.01)							
6.1.2 Nerve application							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.1.3 Joint and nerve application							
Walker 1987	38	3.7 (2.2)	34	5.2 (1.8)		100%	-1.54[-2.47,-0.61]
Subtotal ***	**38**		**34**			**100%**	**-1.54[-2.47,-0.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.25(P=0)							
Test for subgroup differences: Chi²=1.53, df=1 (P=0.22), I²=34.67%							



Comparison 7. Laser vs Placebo - Joint vs Nerve - end of follow up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (10 cm VAS or 0-12 scale)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Joint application	2	54	Mean Difference (IV, Fixed, 95% CI)	0.06 [-1.24, 1.36]
1.2 Nerve application	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Joint and nerve application	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 Laser vs Placebo - Joint vs Nerve - end of follow up, Outcome 1 Pain (10 cm VAS or 0-12 scale).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
7.1.1 Joint application							
Goats 1996	20	5.3 (3.6)	8	5.9 (2.7)		27.89%	-0.57[-3.03,1.89]
Hall 1994	13	3.1 (2.2)	13	2.8 (1.8)		72.11%	0.3[-1.23,1.83]

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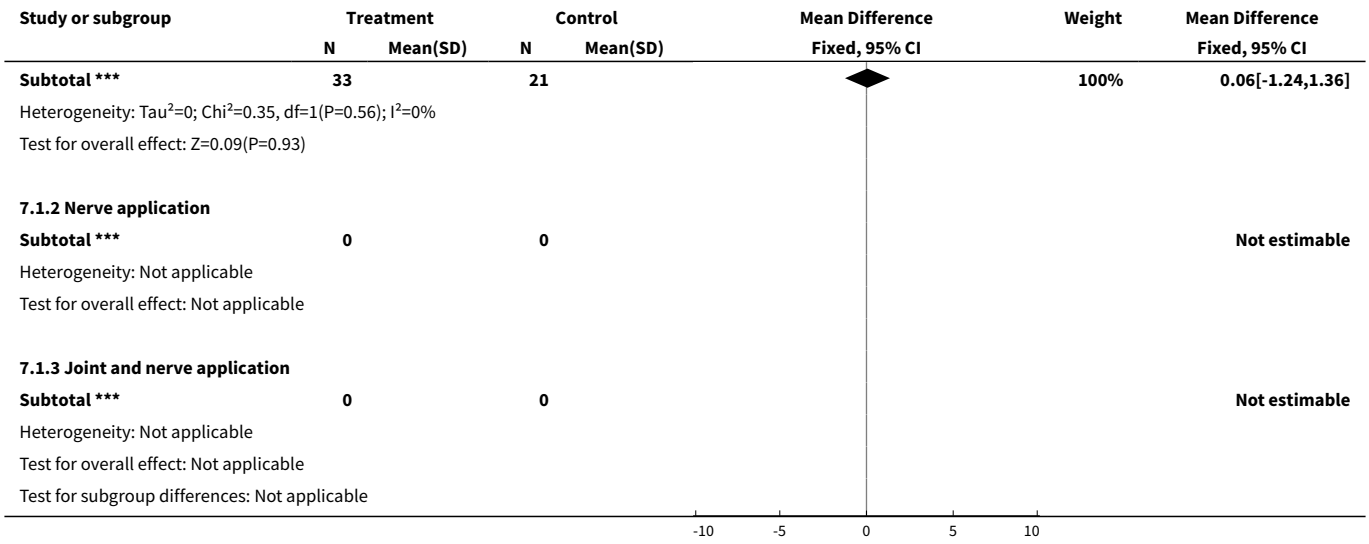

Comparison 8. Laser vs Placebo- Wavelength analysis - End of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Wavelength < 660 nm	1	72	Mean Difference (IV, Fixed, 95% CI)	-1.54 [-2.47, -0.61]
1.2 Wavelength 820, 830 nm	2	62	Mean Difference (IV, Fixed, 95% CI)	-0.84 [-1.51, -0.16]
1.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-2.68, 1.12]
2 McGill Pain questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	1.5 [-1.22, 4.22]
3 Ritchie Index	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Wavelength 820, 830 nm	1	40	Mean Difference (IV, Fixed, 95% CI)	2.60 [-4.50, 9.70]
3.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Health Assessment Questionnaire (HAQ)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Wavelength 820, 830 nm	1	40	Mean Difference (IV, Fixed, 95% CI)	1.25 [-2.09, 4.59]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-6.39, 6.03]
5 MCP ROM (degrees)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Wavelength 820, 830 nm	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-15.99, 14.99]
5.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 PIP ROM (degrees)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Wavelength 820, 830 nm	1	40	Mean Difference (IV, Fixed, 95% CI)	4.0 [-6.60, 14.60]
6.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Left knee Range of motion	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	-23.60 [-43.47, -3.73]
8 Right knee ROM	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	-12.90 [-31.98, 6.18]
9 Left ankle ROM	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	3.40 [-3.43, 10.23]
10 Right ankle ROM	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	7.90 [0.79, 15.01]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Flexibility- tip to palm distance (cm)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Wavelength 820, 830 nm	2	57	Mean Difference (IV, Fixed, 95% CI)	-1.28 [-1.72, -0.85]
11.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Morning stiffness duration (min)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Wavelength 820, 830 nm	2	75	Mean Difference (IV, Fixed, 95% CI)	-30.65 [-55.71, -5.58]
12.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	40.80 [-75.05, 156.65]
13 Morning stiffness not improved	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Wavelength < 660 nm	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Wavelength 820, 830 nm	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.49, 1.19]
13.3 Wavelength 650-950 nm	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Rheumatoid factor positive	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Wavelength < 660 nm	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Wavelength 820, 830 nm	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Wavelength 650-950 nm	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.61, 1.34]
15 Grip strength (mmHg, KPa, kg)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Wavelength 820, 830 nm	3	97	Mean Difference (IV, Fixed, 95% CI)	0.62 [-0.36, 1.60]
15.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Suprapatellar swelling - right knee (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	-2.94 [-6.31, 0.43]
17 Suprapatellar swelling- left knee (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	-2.69 [-6.33, 0.95]
18 MCP swelling (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Wavelength 820, 830 nm	1	40	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.78, 1.18]
18.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 PIP swelling (cm)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Wavelength 820, 830 nm	2	75	Mean Difference (IV, Fixed, 95% CI)	0.53 [-1.12, 2.18]
19.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Walking speed (sec)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	-1.87 [-7.08, 3.34]
21 Fibrinogen	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.2 Wavelength 820, 830 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	1.5 [-0.00, 3.00]
21.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Leukocytes	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
22.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Wavelength 820, 830 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	1.60 [0.62, 2.58]
22.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Lymphocytes	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
23.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 Wavelength 820, 830 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	3.0 [-6.57, 12.57]
23.3 Wavelength 650-950 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 ESR (mm/hr)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
24.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Wavelength 820, 830 nm	2	57	Mean Difference (IV, Fixed, 95% CI)	-11.12 [-16.21, -6.04]
24.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	8.27 [-13.18, 29.72]
25 CRP (g/mL)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
25.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.2 Wavelength 820, 830 nm	1	22	Mean Difference (IV, Fixed, 95% CI)	-120.0 [-190.13, -49.87]
25.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	9.88 [-7.27, 27.03]
26 Hemoglobin	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
26.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Wavelength 820, 830 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	0.60 [0.11, 1.09]
26.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-2.12, 0.74]

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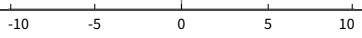
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27 Platelets	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
27.1 Wavelength < 660 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.2 Wavelength 820, 830 nm	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.3 Wavelength 650-950 nm	1	35	Mean Difference (IV, Fixed, 95% CI)	20.35 [-64.36, 105.06]

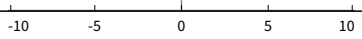
Analysis 8.1. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 1 Pain.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.1.1 Wavelength < 660 nm							
Walker 1987	38	3.7 (2.2)	34	5.2 (1.8)		100%	-1.54[-2.47,-0.61]
Subtotal ***	**38**		**34**			**100%**	**-1.54[-2.47,-0.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.25(P=0)							
8.1.2 Wavelength 820, 830 nm							
Hall 1994	20	4 (2.2)	20	4.3 (2.2)		23.44%	-0.3[-1.69,1.09]
Johannsen 1994	10	4.5 (0.6)	12	5.5 (1.2)		76.56%	-1[-1.77,-0.23]
Subtotal ***	**30**		**32**			**100%**	**-0.84[-1.51,-0.16]**
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%							
Test for overall effect: Z=2.44(P=0.01)							
8.1.3 Wavelength 650-950 nm							
Goats 1996	25	5.2 (3)	10	5.9 (2.4)		100%	-0.78[-2.68,1.12]
Subtotal ***	**25**		**10**			**100%**	**-0.78[-2.68,1.12]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.81(P=0.42)							
Test for subgroup differences: Chi^2=1.53, df=1 (P=0.46), I^2=0%							



Analysis 8.2. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 2 McGill Pain questionnaire.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.2.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.2.2 Wavelength 820, 830 nm							



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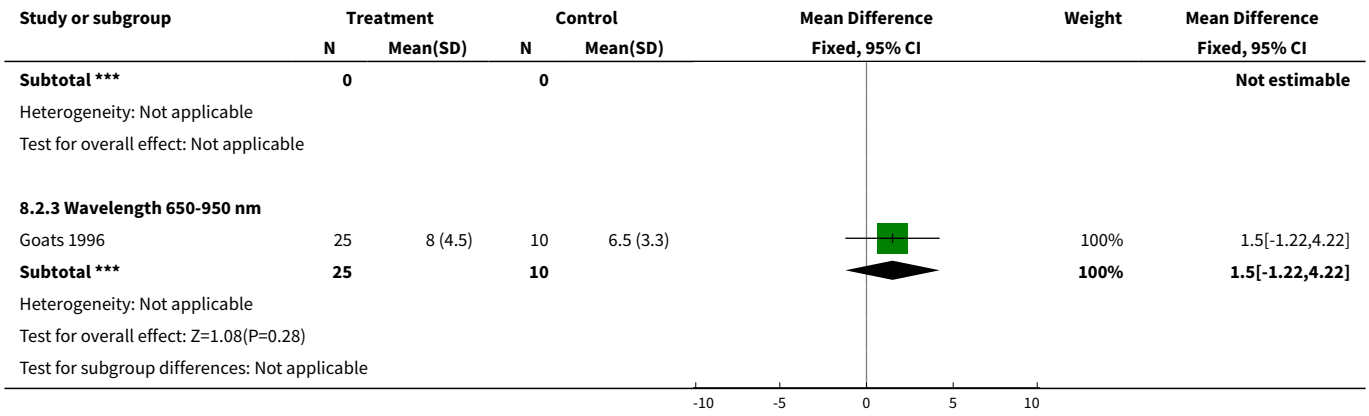
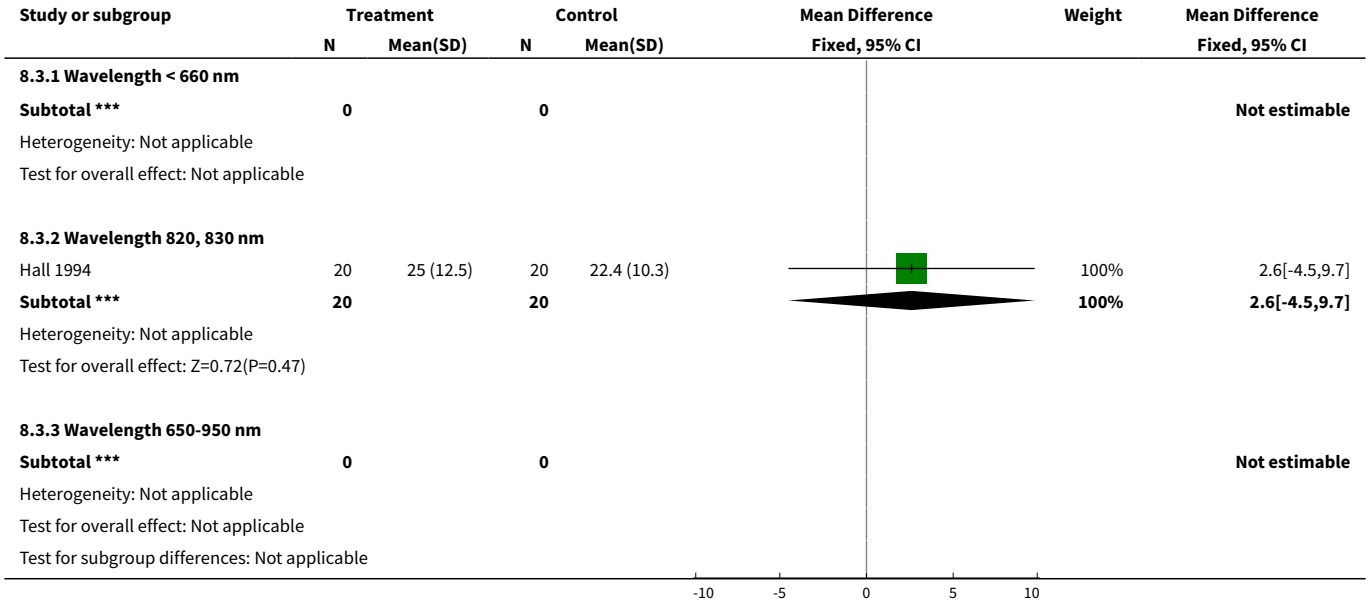
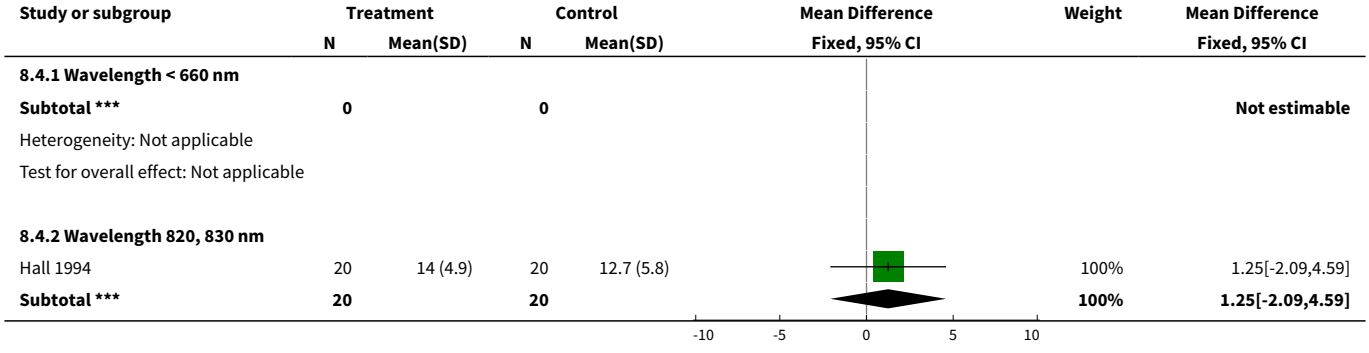


Analysis 8.3. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 3 Ritchie Index.



Analysis 8.4. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 4 Health Assessment Questionnaire (HAQ).



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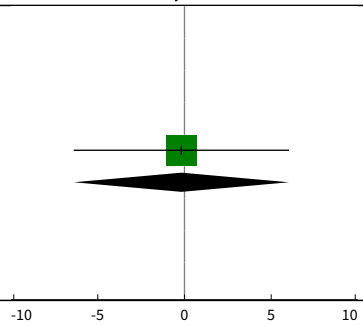
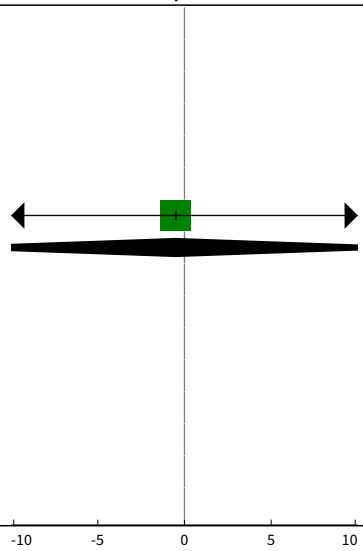
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.46)							
8.4.3 Wavelength 650-950 nm							
Goats 1996	25	15.5 (7.9)	10	15.7 (8.7)		100%	-0.18[-6.39,6.03]
Subtotal ***	**25**		**10**			**100%**	**-0.18[-6.39,6.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%							



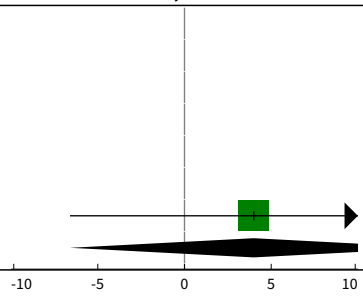
Analysis 8.5. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 5 MCP ROM (degrees).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.5.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.5.2 Wavelength 820, 830 nm							
Hall 1994	20	55 (20.1)	20	55.5 (29.1)		100%	-0.5[-15.99,14.99]
Subtotal ***	**20**		**20**			**100%**	**-0.5[-15.99,14.99]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							
8.5.3 Wavelength 650-950 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Analysis 8.6. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 6 PIP ROM (degrees).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.6.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.6.2 Wavelength 820, 830 nm							
Hall 1994	20	74 (13.4)	20	70 (20.1)		100%	4[-6.6,14.6]
Subtotal ***	**20**		**20**			**100%**	**4[-6.6,14.6]**



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Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							
8.6.3 Wavelength 650-950 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

-10 -5 0 5 10

Analysis 8.7. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 7 Left knee Range of motion.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.7.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.7.2 Wavelength 820, 830 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.7.3 Wavelength 650-950 nm							
Goats 1996	25	64.4 (20.2)	10	88 (29.4)		100%	-23.6[-43.47,-3.73]
Subtotal ***	**25**		**10**			**100%**	**-23.6[-43.47,-3.73]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.33(P=0.02)							
Test for subgroup differences: Not applicable							

-10 -5 0 5 10

Analysis 8.8. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 8 Right knee ROM.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.8.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.8.2 Wavelength 820, 830 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

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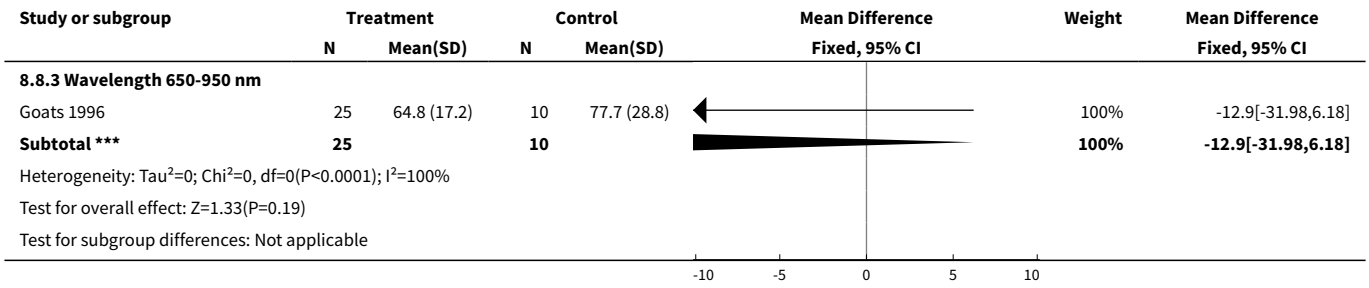
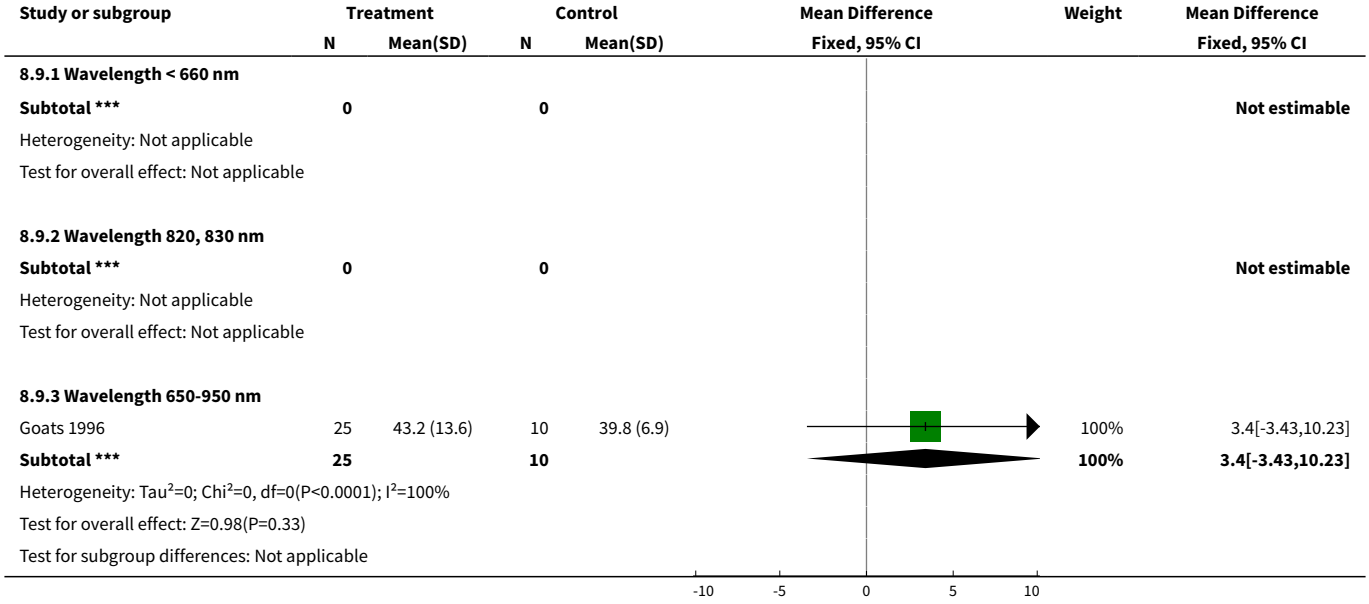
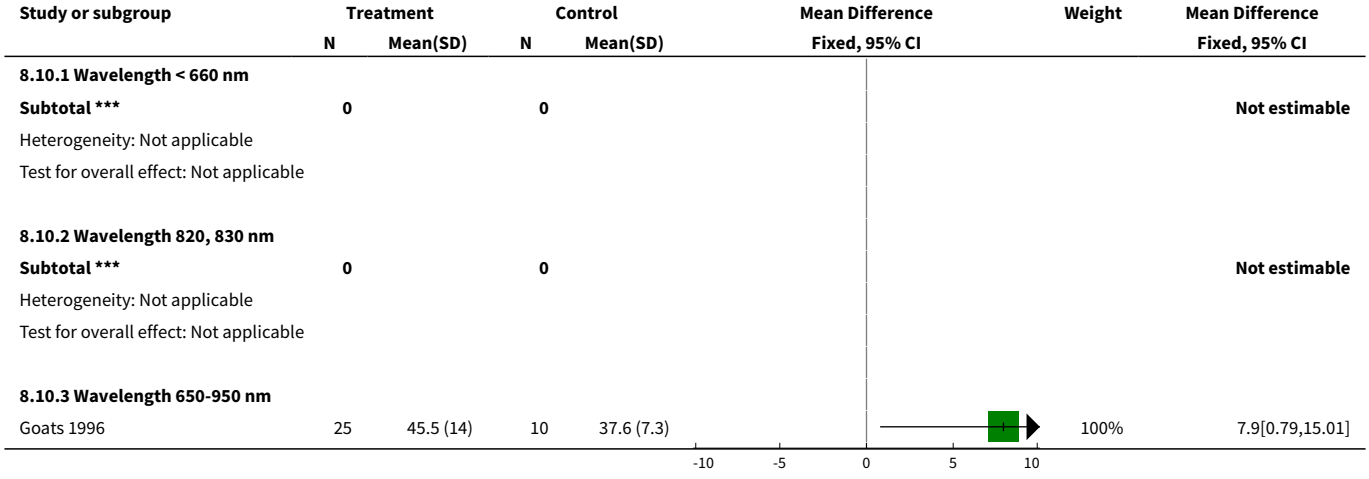


Analysis 8.9. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 9 Left ankle ROM.



Analysis 8.10. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 10 Right ankle ROM.



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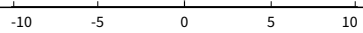
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Subtotal ***	**25**		**10**			**100%**	**7.9[0.79,15.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.18(P=0.03)							
Test for subgroup differences: Not applicable							



Analysis 8.11. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 11 Flexibility- tip to palm distance (cm).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.11.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.11.2 Wavelength 820, 830 nm							
Johannsen 1994	10	0 (0.2)	12	1.3 (0.8)		99.32%	-1.25[-1.68,-0.82]
Palmgren 1989	19	0 (6)	16	6 (9.2)		0.68%	-6[-11.25,-0.75]
Subtotal ***	**29**		**28**			**100%**	**-1.28[-1.72,-0.85]**
Heterogeneity: Tau^2=0; Chi^2=3.13, df=1(P=0.08); I^2=68.04%							
Test for overall effect: Z=5.81(P<0.0001)							
8.11.3 Wavelength 650-950 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Analysis 8.12. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 12 Morning stiffness duration (min).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.12.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.12.2 Wavelength 820, 830 nm							
Hall 1994	20	57.8 (65.3)	20	72 (85)		28.49%	-14.2[-61.16,32.76]
Palmgren 1989	19	30.6 (43.7)	16	67.8 (45.3)		71.51%	-37.2[-66.84,-7.56]
Subtotal ***	**39**		**36**			**100%**	**-30.65[-55.71,-5.58]**
Heterogeneity: Tau^2=0; Chi^2=0.66, df=1(P=0.42); I^2=0%							
Test for overall effect: Z=2.4(P=0.02)							

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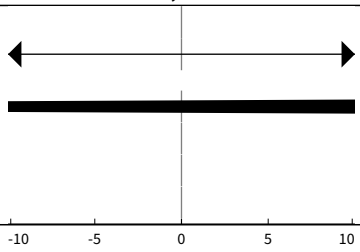
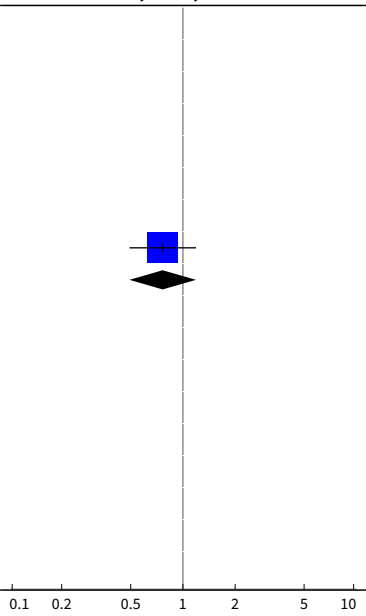
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.12.3 Wavelength 650-950 nm							
Goats 1996	25	104.4 (275.4)	10	63.6 (67.8)		100%	40.8[-75.05,156.65]
Subtotal ***	**25**		**10**			**100%**	**40.8[-75.05,156.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.69(P=0.49)							
Test for subgroup differences: Chi^2=1.4, df=1 (P=0.24), I^2=28.36%							



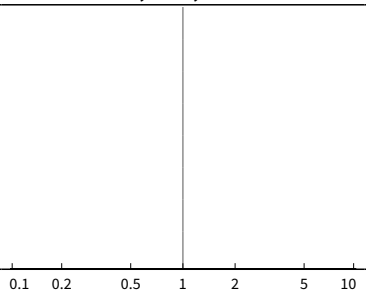
Analysis 8.13. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 13 Morning stiffness not improved.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.13.1 Wavelength < 660 nm					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
8.13.2 Wavelength 820, 830 nm					
Johannsen 1994	7/10	11/12		100%	0.76[0.49,1.19]
Subtotal (95% CI)	**10**	**12**		**100%**	**0.76[0.49,1.19]**
Total events: 7 (Treatment), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					
8.13.3 Wavelength 650-950 nm					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 8.14. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 14 Rheumatoid factor positive.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.14.1 Wavelength < 660 nm					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
8.14.2 Wavelength 820, 830 nm					
Subtotal (95% CI)	**0**	**0**			**Not estimable**



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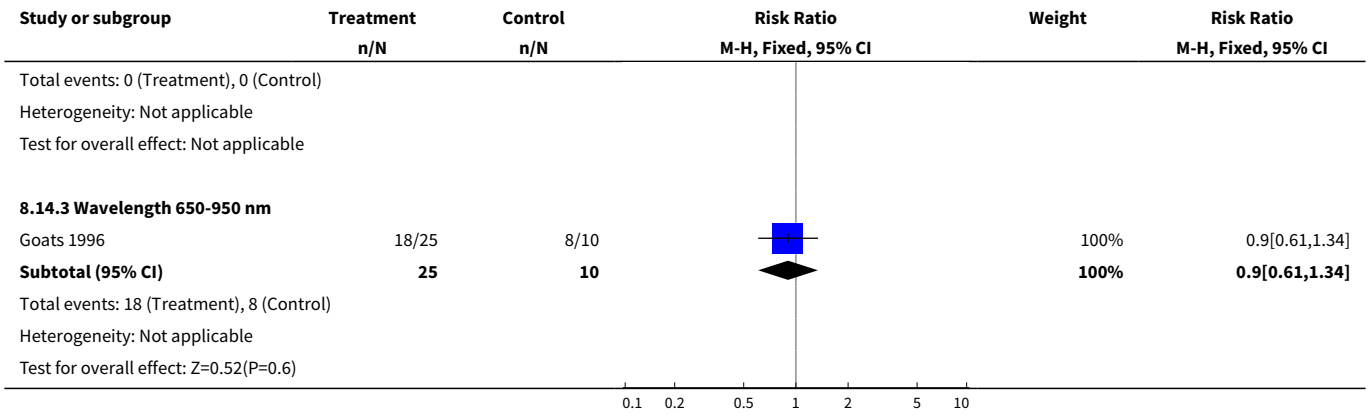
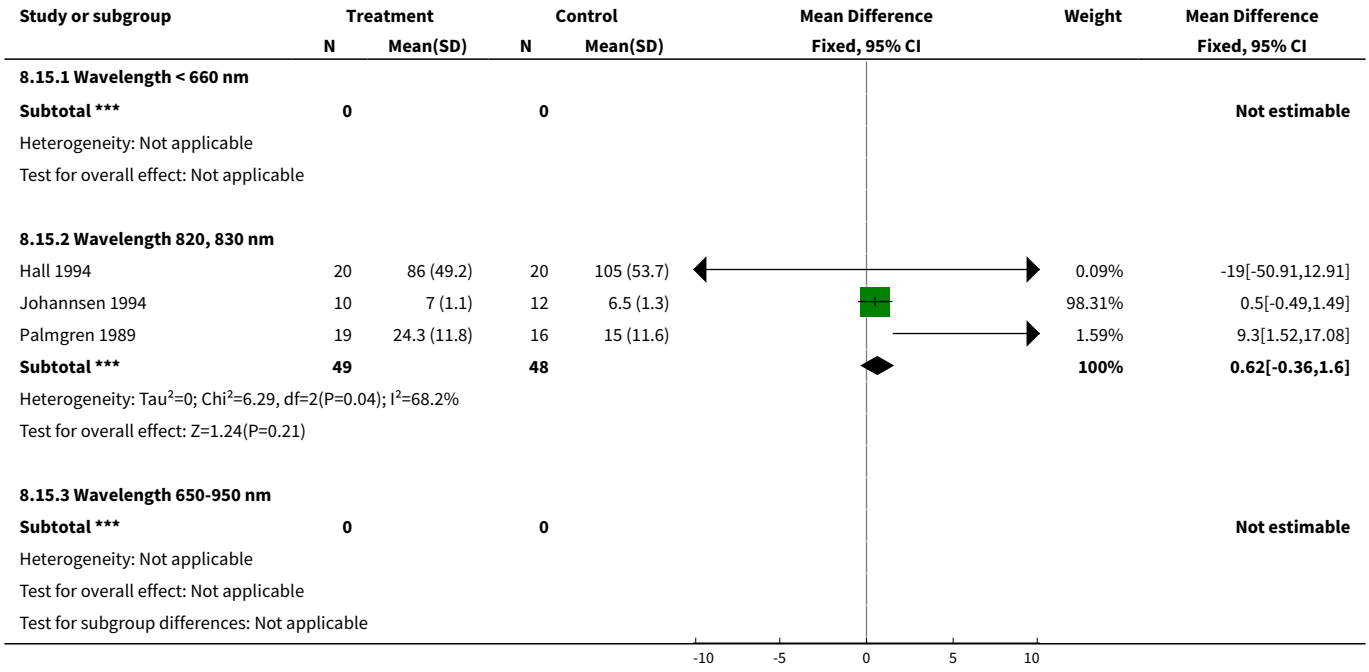
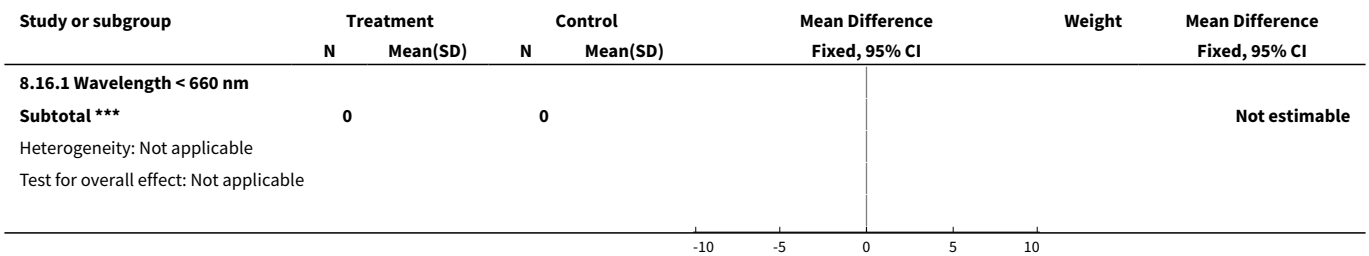


Analysis 8.15. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 15 Grip strength (mmHg, KPa, kg).



Analysis 8.16. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 16 Suprapatellar swelling - right knee (cm).



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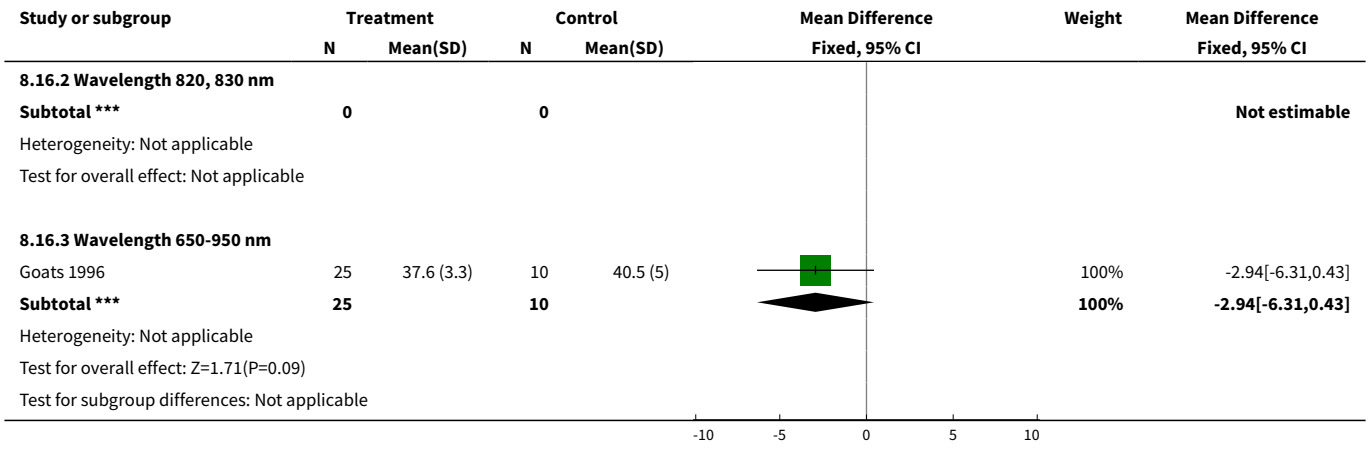
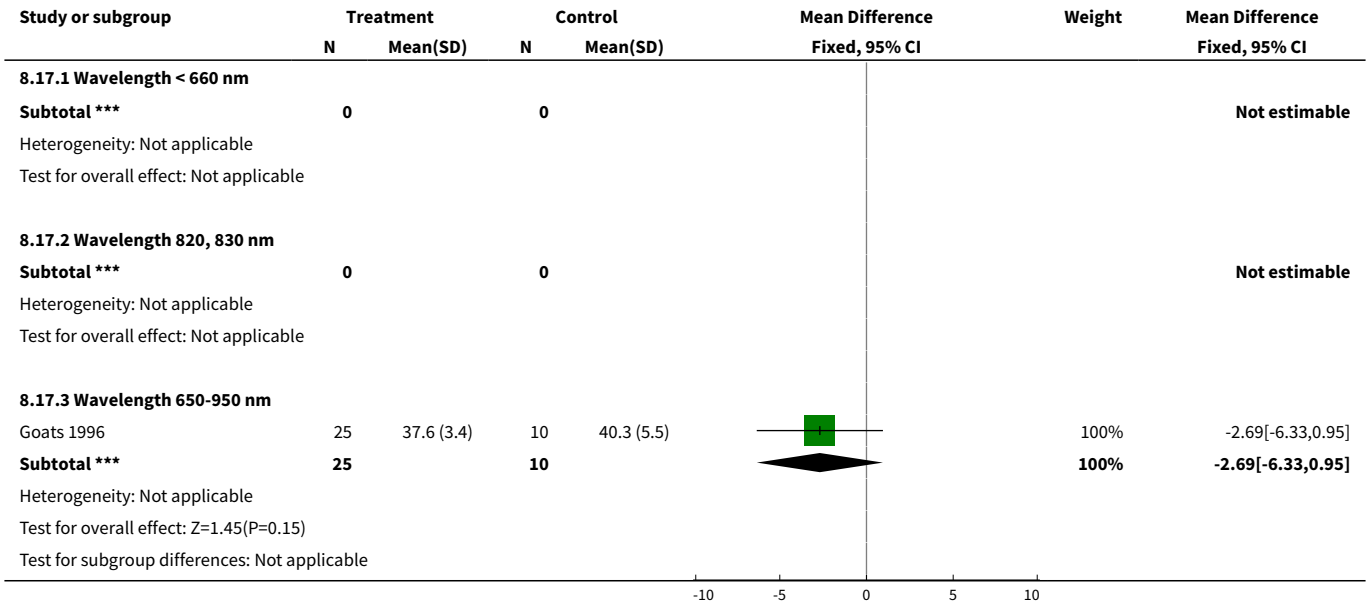
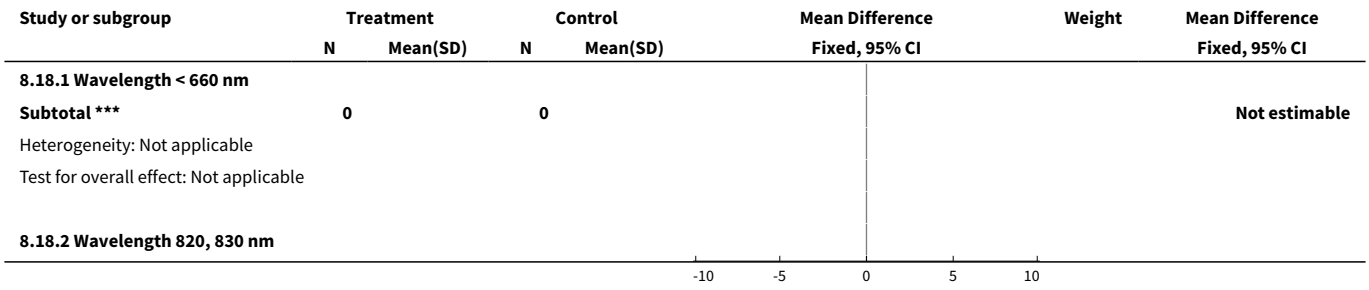


Analysis 8.17. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 17 Suprapatellar swelling- left knee (cm).



Analysis 8.18. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 18 MCP swelling (cm).



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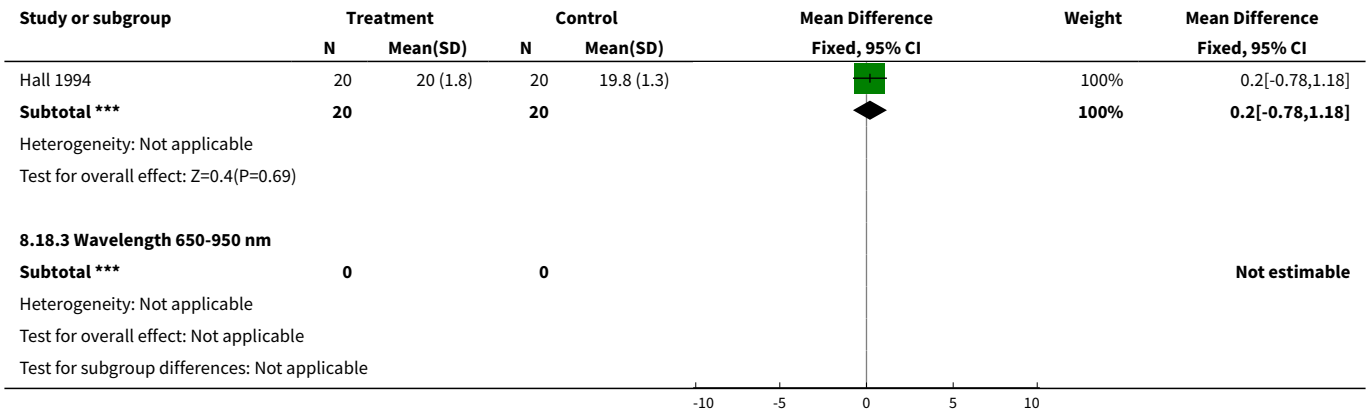
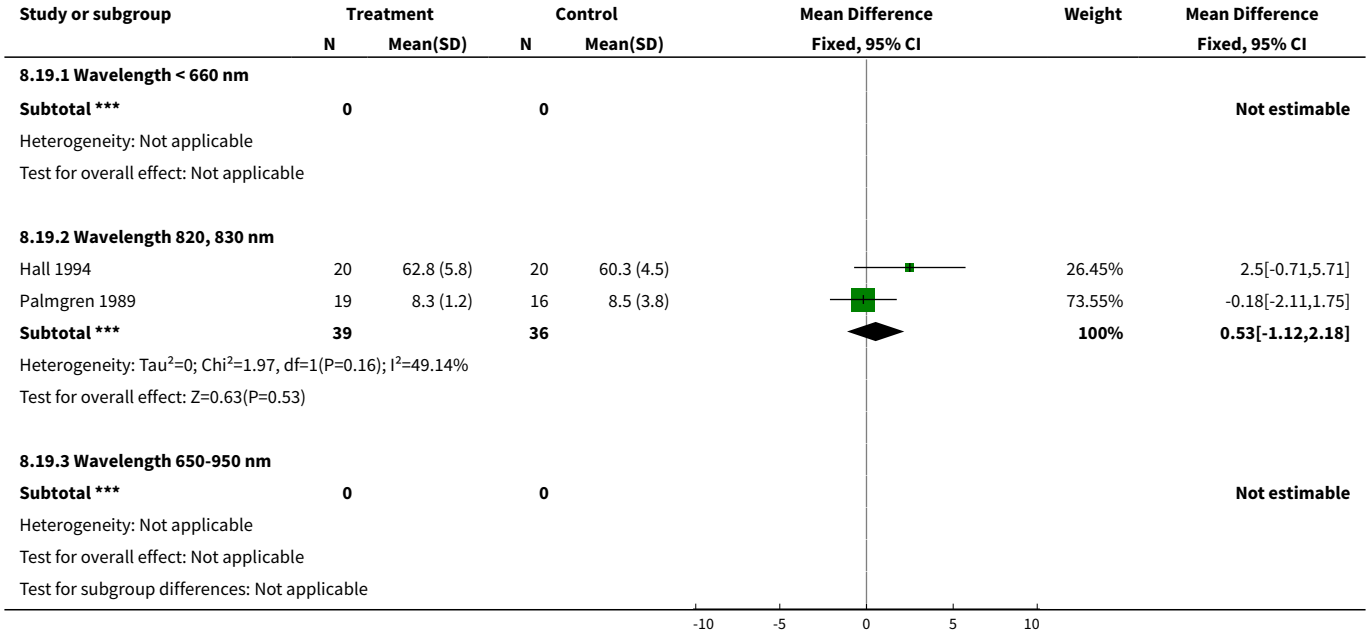
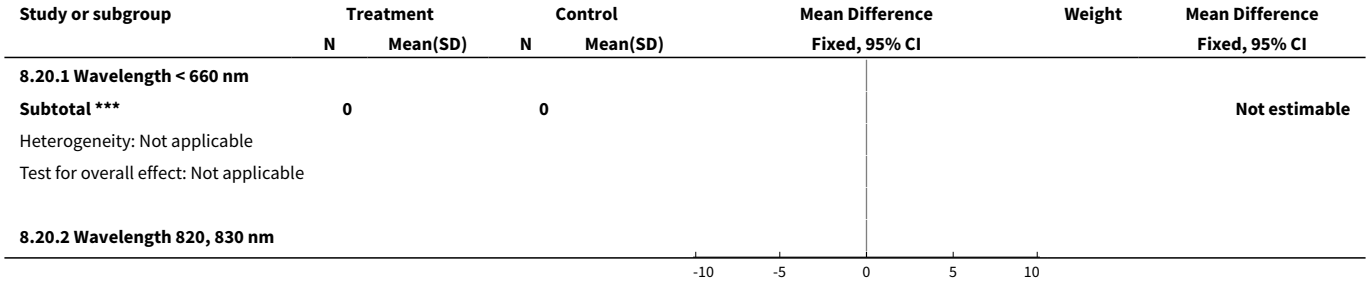


Analysis 8.19. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 19 PIP swelling (cm).



Analysis 8.20. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 20 Walking speed (sec).



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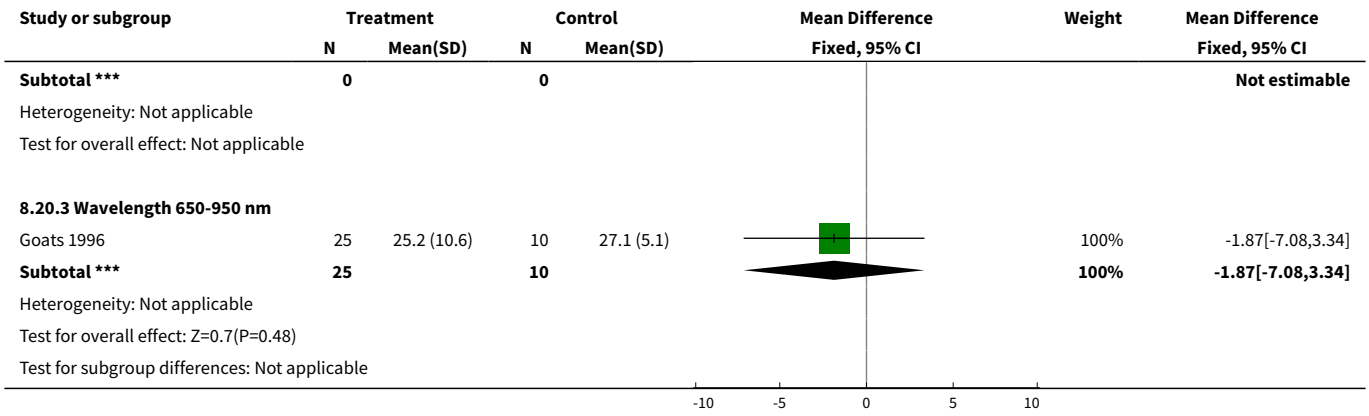
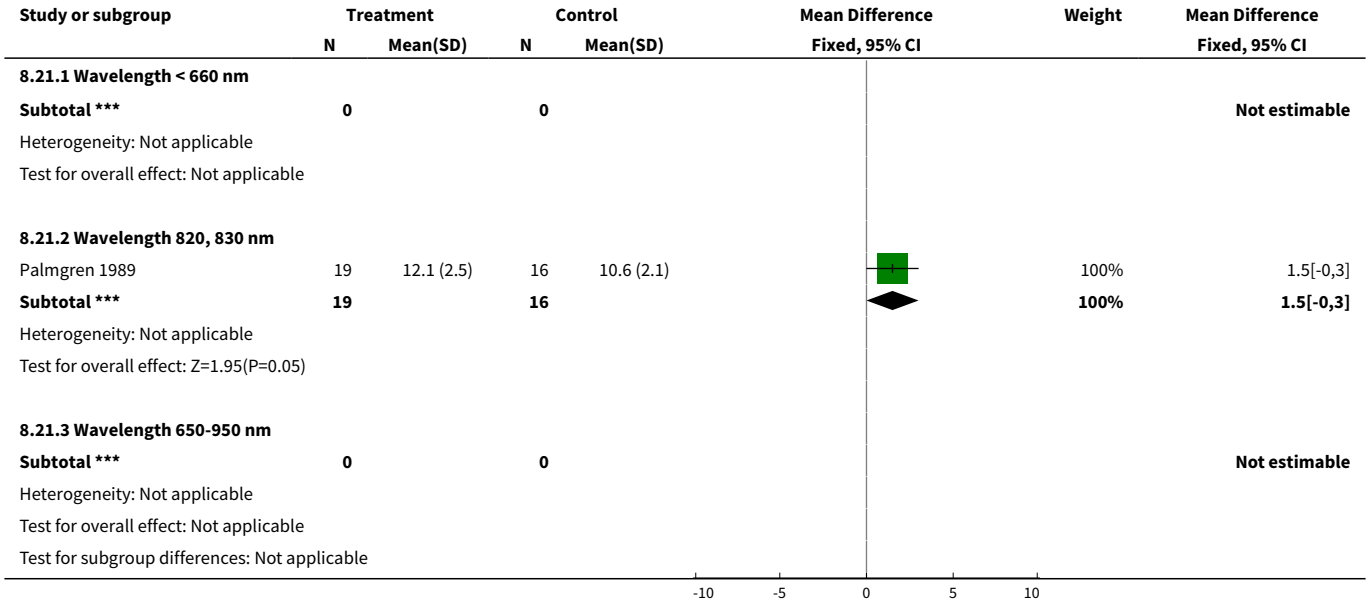
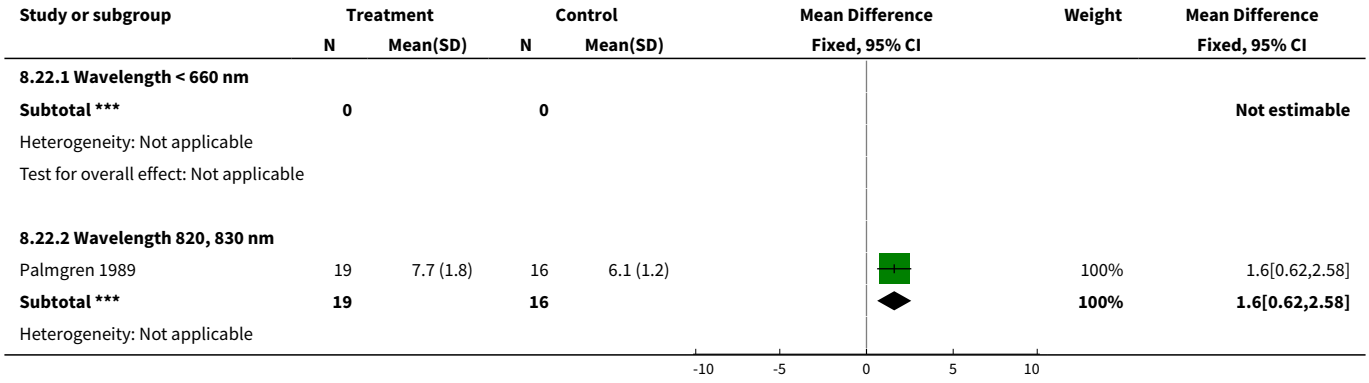


Analysis 8.21. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 21 Fibrinogen.



Analysis 8.22. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 22 Leukocytes.



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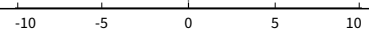
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=3.19(P=0)							
8.22.3 Wavelength 650-950 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Analysis 8.23. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 23 Lymphocytes.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.23.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.23.2 Wavelength 820, 830 nm							
Palmgren 1989	19	21.5 (20)	16	18.5 (6.6)		100%	3[-6.57,12.57]
Subtotal ***	**19**		**16**			**100%**	**3[-6.57,12.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.61(P=0.54)							
8.23.3 Wavelength 650-950 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Analysis 8.24. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 24 ESR (mm/hr).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.24.1 Wavelength < 660 nm							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.24.2 Wavelength 820, 830 nm							
Johannsen 1994	10	12 (6.7)	12	32 (13.5)		34.25%	-20[-28.69,-11.31]
Palmgren 1989	19	19 (5.6)	16	25.5 (11.7)		65.75%	-6.5[-12.77,-0.23]
Subtotal ***	**29**		**28**			**100%**	**-11.12[-16.21,-6.04]**
Heterogeneity: Tau²=0; Chi²=6.1, df=1(P=0.01); I²=83.61%							
Test for overall effect: Z=4.29(P<0.0001)							

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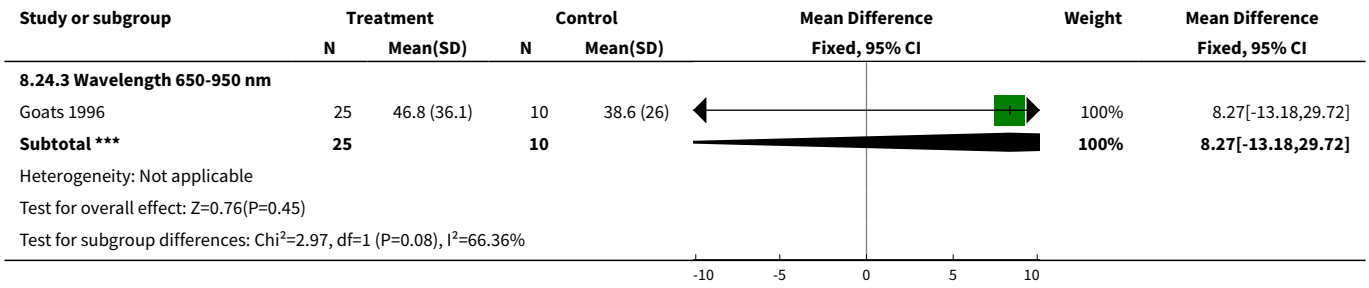
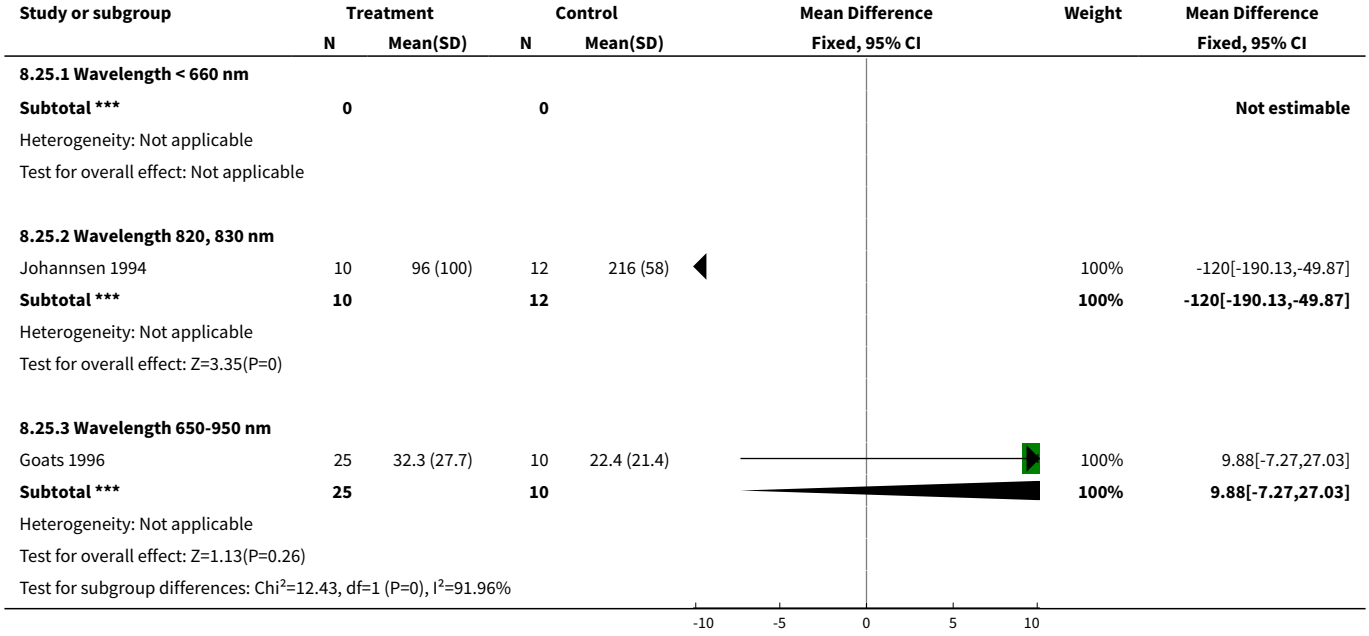
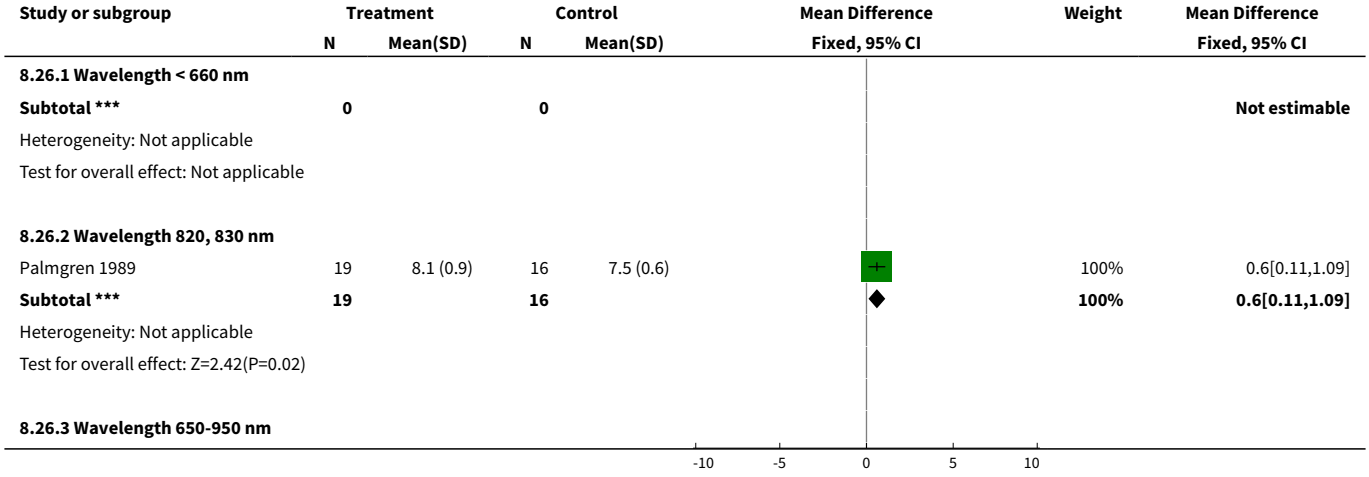


Analysis 8.25. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 25 CRP (g/mL).



Analysis 8.26. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 26 Hemoglobin.



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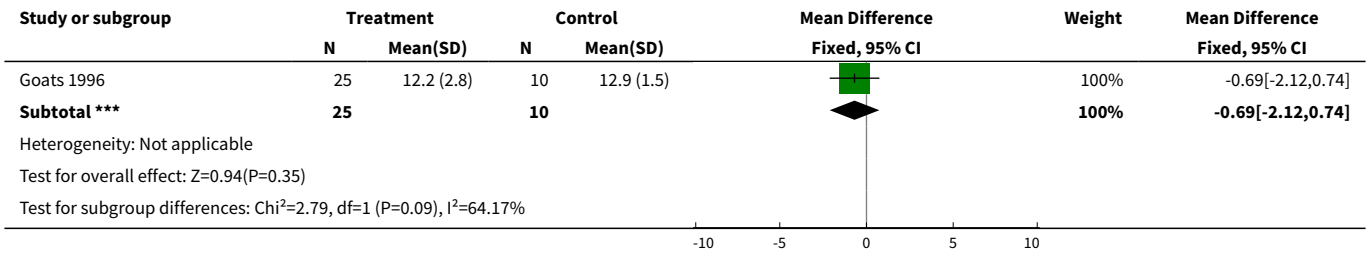
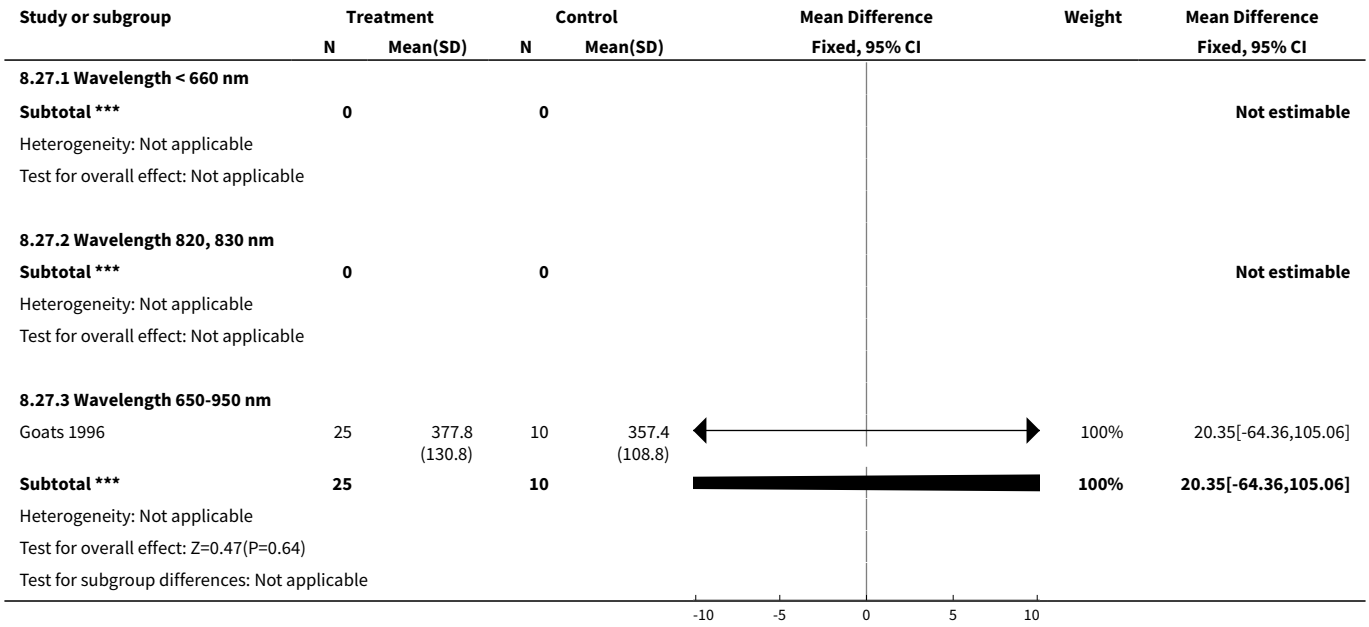


Analysis 8.27. Comparison 8 Laser vs Placebo- Wavelength analysis - End of treatment, Outcome 27 Platelets.



Comparison 9. Subgroup Dosage Analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS <= 3 J/cm2	2	94	Mean Difference (IV, Fixed, 95% CI)	-1.22 [-1.81, -0.63]
2 Pain VAS > 3 J/cm2	2	75	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-1.59, 0.65]
3 ESR low dose	1	22	Mean Difference (IV, Fixed, 95% CI)	-20.0 [-28.69, -11.31]
4 ESR high dose	2	70	Mean Difference (IV, Fixed, 95% CI)	-5.34 [-11.35, 0.68]
5 CRP low dose	1	22	Mean Difference (IV, Fixed, 95% CI)	-120.0 [-190.13, -49.87]
6 CRP high dose	1	35	Mean Difference (IV, Fixed, 95% CI)	9.88 [-7.27, 27.03]
7 HAQ high dose	2	75	Mean Difference (IV, Fixed, 95% CI)	0.93 [-2.01, 3.87]

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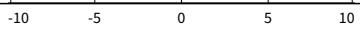
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Hemoglobin high dose	2	70	Mean Difference (IV, Fixed, 95% CI)	0.47 [0.01, 0.93]
9 Morning stiffness (hours) high dose	3	110	Mean Difference (IV, Fixed, 95% CI)	-27.45 [-51.95, -2.95]
10 Grip strength (kg) low	1	22	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.49, 1.49]
11 Grip strength (kg) high	2	75	Mean Difference (IV, Fixed, 95% CI)	7.71 [0.15, 15.27]
12 MCP swelling (cm) low	2	75	Mean Difference (IV, Fixed, 95% CI)	0.53 [-1.12, 2.18]
13 Flexibility tip to palm (cm) low	1	22	Mean Difference (IV, Fixed, 95% CI)	-1.25 [-1.68, -0.82]
14 Flexibility tip to palm high dose	1	35	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-11.25, -0.75]

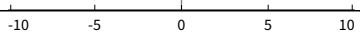
Analysis 9.1. Comparison 9 Subgroup Dosage Analysis, Outcome 1 Pain VAS <= 3 J/cm2.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Johannsen 1994	10	4.5 (0.6)	12	5.5 (1.2)		59.43%	-1[-1.77,-0.23]
Walker 1987	38	3.7 (2.2)	34	5.2 (1.8)		40.57%	-1.54[-2.47,-0.61]
Total ***	**48**		**46**			**100%**	**-1.22[-1.81,-0.63]**
Heterogeneity: Tau²=0; Chi²=0.77, df=1(P=0.38); I²=0%							
Test for overall effect: Z=4.03(P<0.0001)							



Analysis 9.2. Comparison 9 Subgroup Dosage Analysis, Outcome 2 Pain VAS > 3 J/cm2.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	5.2 (3)	10	5.9 (2.4)		34.84%	-0.78[-2.68,1.12]
Hall 1994	20	4 (2.2)	20	4.3 (2.2)		65.16%	-0.3[-1.69,1.09]
Total ***	**45**		**30**			**100%**	**-0.47[-1.59,0.65]**
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%							
Test for overall effect: Z=0.82(P=0.41)							



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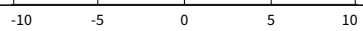
Analysis 9.3. Comparison 9 Subgroup Dosage Analysis, Outcome 3 ESR low dose.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Johannsen 1994	10	12 (6.7)	12	32 (13.5)		100%	-20[-28.69,-11.31]
Total ***	**10**		**12**			**100%**	**-20[-28.69,-11.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.51(P<0.0001)							

Analysis 9.4. Comparison 9 Subgroup Dosage Analysis, Outcome 4 ESR high dose.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	46.8 (36.1)	10	38.6 (26)		7.87%	8.27[-13.18,29.72]
Palmgren 1989	19	19 (5.6)	16	25.5 (11.7)		92.13%	-6.5[-12.77,-0.23]
Total ***	**44**		**26**			**100%**	**-5.34[-11.35,0.68]**
Heterogeneity: Tau^2=0; Chi^2=1.68, df=1(P=0.2); I^2=40.41%							
Test for overall effect: Z=1.74(P=0.08)							



Analysis 9.5. Comparison 9 Subgroup Dosage Analysis, Outcome 5 CRP low dose.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Johannsen 1994	10	96 (100)	12	216 (58)		100%	-120[-190.13,-49.87]
Total ***	**10**		**12**			**100%**	**-120[-190.13,-49.87]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.35(P=0)							

Analysis 9.6. Comparison 9 Subgroup Dosage Analysis, Outcome 6 CRP high dose.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goats 1996	25	32.3 (27.7)	10	22.4 (21.4)		100%	9.88[-7.27,27.03]
Total ***	**25**		**10**			**100%**	**9.88[-7.27,27.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							

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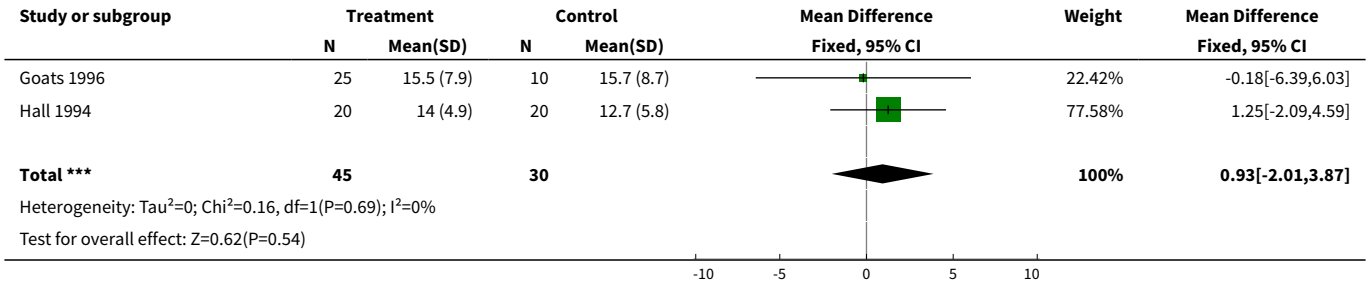
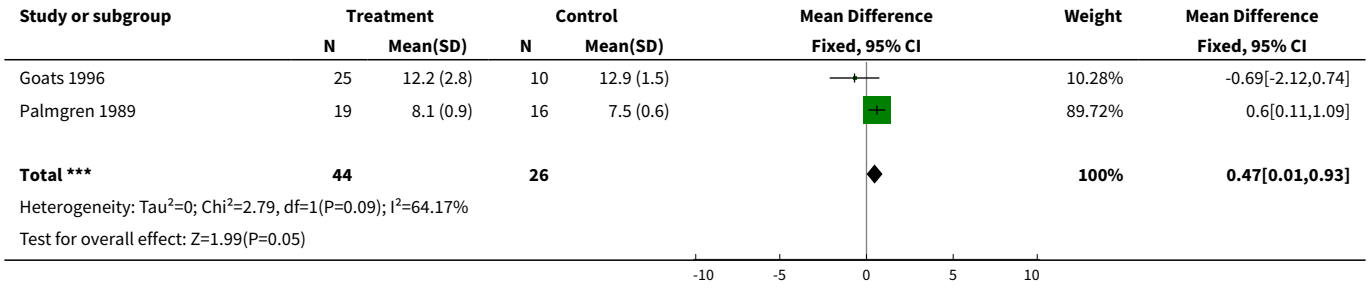
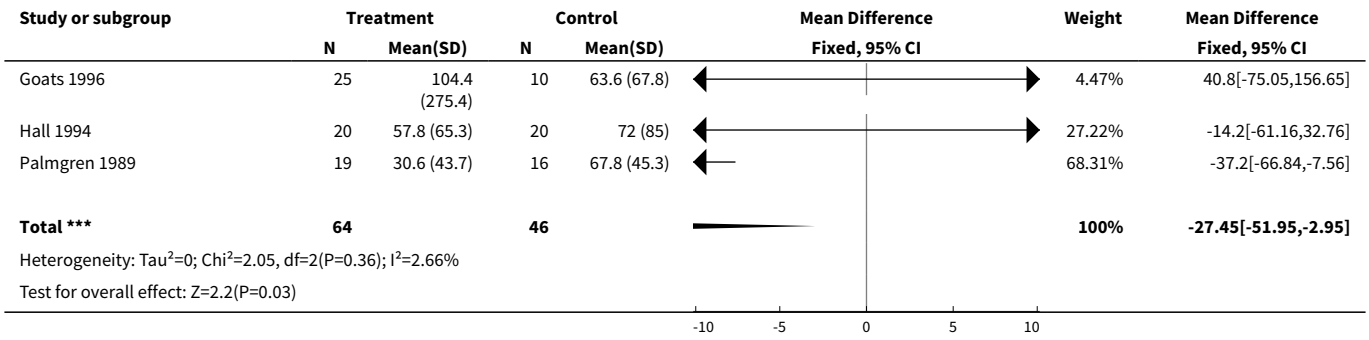
Analysis 9.7. Comparison 9 Subgroup Dosage Analysis, Outcome 7 HAQ high dose.



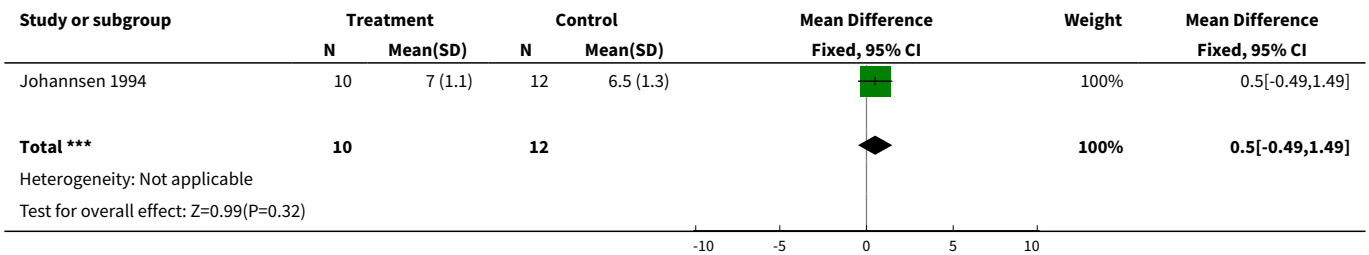
Analysis 9.8. Comparison 9 Subgroup Dosage Analysis, Outcome 8 Hemoglobin high dose.



Analysis 9.9. Comparison 9 Subgroup Dosage Analysis, Outcome 9 Morning stiffness (hours) high dose.



Analysis 9.10. Comparison 9 Subgroup Dosage Analysis, Outcome 10 Grip strength (kg) low.



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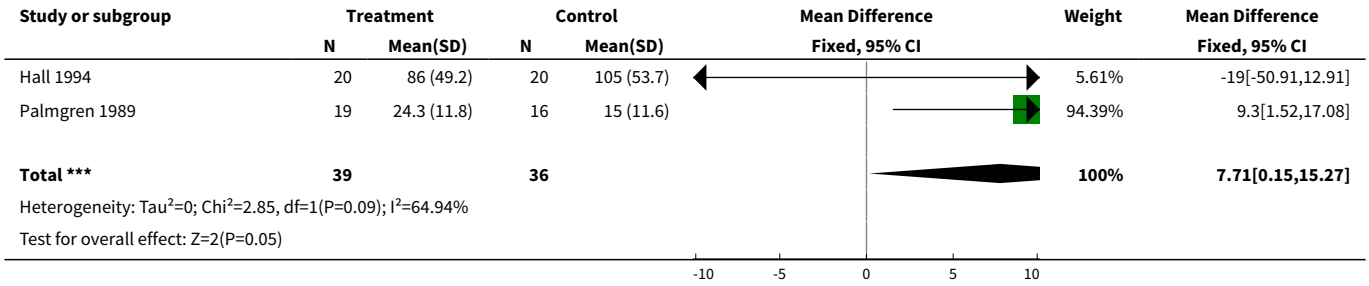
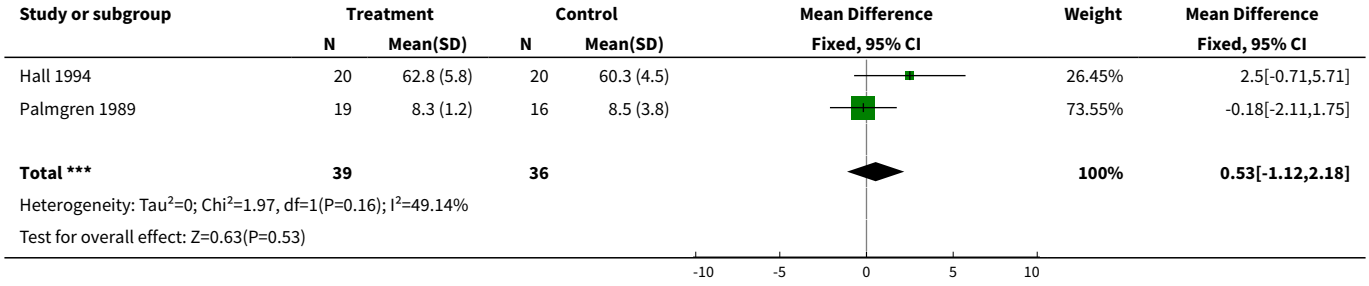
Analysis 9.11. Comparison 9 Subgroup Dosage Analysis, Outcome 11 Grip strength (kg) high.



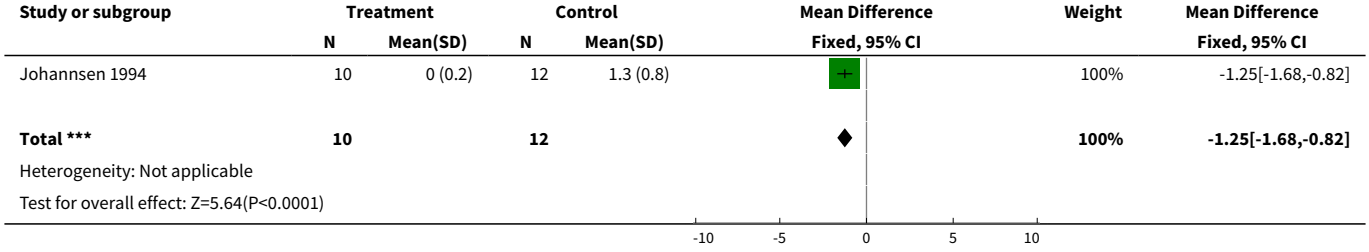
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hall 1994	20	86 (49.2)	20	105 (53.7)		5.61%	-19[-50.91,12.91]
Palmgren 1989	19	24.3 (11.8)	16	15 (11.6)		94.39%	9.3[1.52,17.08]
Total ***	**39**		**36**			**100%**	**7.71[0.15,15.27]**
Heterogeneity: Tau^2=0; Chi^2=2.85, df=1(P=0.09); I^2=64.94%							
Test for overall effect: Z=2(P=0.05)							

Analysis 9.12. Comparison 9 Subgroup Dosage Analysis, Outcome 12 MCP swelling (cm) low.



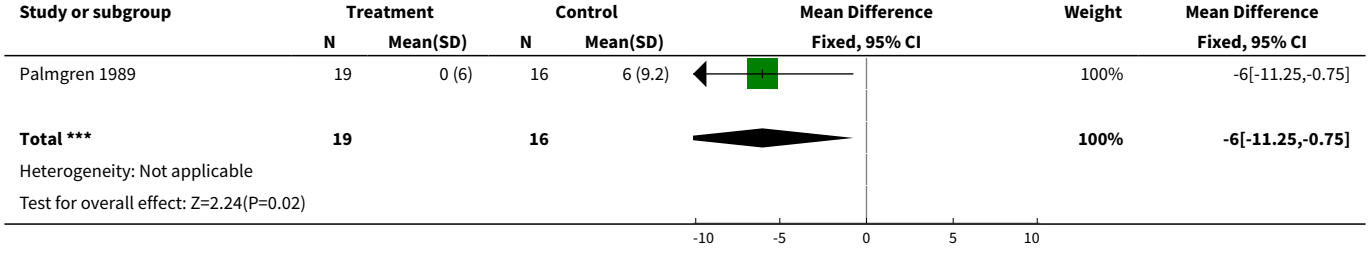
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hall 1994	20	62.8 (5.8)	20	60.3 (4.5)		26.45%	2.5[-0.71,5.71]
Palmgren 1989	19	8.3 (1.2)	16	8.5 (3.8)		73.55%	-0.18[-2.11,1.75]
Total ***	**39**		**36**			**100%**	**0.53[-1.12,2.18]**
Heterogeneity: Tau^2=0; Chi^2=1.97, df=1(P=0.16); I^2=49.14%							
Test for overall effect: Z=0.63(P=0.53)							

Analysis 9.13. Comparison 9 Subgroup Dosage Analysis, Outcome 13 Flexibility tip to palm (cm) low.



Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Johannsen 1994	10	0 (0.2)	12	1.3 (0.8)		100%	-1.25[-1.68,-0.82]
Total ***	**10**		**12**			**100%**	**-1.25[-1.68,-0.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.64(P<0.0001)							

Analysis 9.14. Comparison 9 Subgroup Dosage Analysis, Outcome 14 Flexibility tip to palm high dose.



Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Palmgren 1989	19	0 (6)	16	6 (9.2)		100%	-6[-11.25,-0.75]
Total ***	**19**		**16**			**100%**	**-6[-11.25,-0.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.24(P=0.02)							

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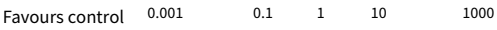
Comparison 10. Laser vs Placebo- contralateral control (End of treatment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients improved in pain relief	1	34	Risk Ratio (M-H, Fixed, 95% CI)	13.0 [0.79, 214.05]
2 Number of patients improved in morning stiffness	1	34	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.50, 32.20]

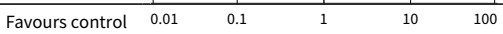
Analysis 10.1. Comparison 10 Laser vs Placebo- contralateral control (End of treatment), Outcome 1 Number of patients improved in pain relief.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bliddal 1987	6/17	0/17		100%	13[0.79,214.05]
Total (95% CI)	**17**	**17**		**100%**	**13[0.79,214.05]**
Total events: 6 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.79(P=0.07)					



Analysis 10.2. Comparison 10 Laser vs Placebo- contralateral control (End of treatment), Outcome 2 Number of patients improved in morning stiffness.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bliddal 1987	4/17	1/17		100%	4[0.5,32.2]
Total (95% CI)	**17**	**17**		**100%**	**4[0.5,32.2]**
Total events: 4 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					



APPENDICES

Appendix 1. Full search strategy

1 degenerative arthritis.tw.
2 exp arthritis, rheumatoid/
3 rheumatoid arthritis.tw.
4 rheumatism.tw.
5 arthritis, juvenile rheumatoid/
6 caplan's syndrome.tw.
7 felty's syndrome.tw.

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8 rheumatoid.tw.
9 ankylosing spondylitis.tw.
10 arthrosis.tw.
11 sjogren$.tw.
12 or/1-11
13 laser$.sh.
14 laser$.tw.
15 exp light/
16 infrared.tw.
17 ultraviolet.tw.
18 monochromatic.tw.
19 or/13-18
20 12 and 19
21 clinical trial.pt.
22 randomized controlled trial.pt.
23 tu.fs.
24 dt.fs.
25 random$.tw.
26 placebo$.tw.
27 ((sing$ or doubl$ or tripl$) adj (masked or blind$)).tw
28 sham.tw.
29 or/21-28
30 20 and 29

WHAT'S NEW

Date	Event	Description
29 September 2008	Amended	Converted to new review format. CMSG ID: C049-R

CONTRIBUTIONS OF AUTHORS

Lucie Brosseau is responsible for the content of the paper and revisions.
Vivian Robinson conducted data extraction, analyses and contributed to the manuscript.
George Wells helped interpret the data from the individual trials and the statistically pooled results.
Arne Gam and Rob de Bie contributed to the literature selection and data extraction.
Katherine Harman provided content expertise in pain control theory.
Michelle Morin contributed to the theoretical framework that was used for data extraction.
Bev Shea helped with quality assessment and editing of the manuscript.
Peter Tugwell contributed to the clinical interpretation and presentation of results.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Ottawa, Canada.

External sources

- No sources of support supplied

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INDEX TERMS

Medical Subject Headings (MeSH)

*Low-Level Light Therapy; Arthritis, Rheumatoid [*radiotherapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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