Is Adjuvant Laser Therapy Effective for Preventing Pain, Swelling, and Trismus After Surgical Removal of Impacted Mandibular Third Molars? A Systematic Review and Meta-Analysis

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Purpose: To assess the efficacy and safety of low-level laser energy irradiation (LLEI) for decreasing pain, swelling, and trismus after surgical removal of impacted mandibular third molars (IMTMs).

Materials and Methods: MEDLINE, EMBASE, and the Central Register of Controlled Trials of the Cochrane Library were searched from their inception, and conference proceedings, cross-references, and gray literature were searched for the last 5 years for randomized and quasi-randomized controlled trials that evaluated the effects of any type of LLEI, compared with active or inactive treatments, in patients undergoing surgical removal of IMTMs. Risk of bias in included studies was assessed by 2 independent evaluators using the Cochrane Risk of Bias tool. A random-effects model meta-analysis was used to estimate the mean difference of trismus between the groups. Heterogeneity was assessed using Cochran χ^2 and I^2.

Results: Ten eligible trials were included in this systematic review. The included studies overall had a moderate risk of bias. Because of heterogeneity in the intervention and outcomes assessments, pain and swelling outcomes were only qualitatively summarized and indicated no beneficial effects of LLEI over placebo. Patients receiving LLEI had an average of 4.2 mm (95% confidence interval, 1.2 to 7.2) and 5.2 mm (95% confidence interval, 1.8 to 8.2) less trismus than patients receiving no active treatment on the second and seventh day after the surgery, respectively.

Conclusions: There was no benefit of LLEI on pain or swelling and a moderate benefit on trismus after removal of IMTMs. It is necessary to standardize the intervention and outcomes assessment and to conduct adequately powered, well-designed trials to evaluate the efficacy of LLEI.

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Surgical removal of impacted mandibular third molars (IMTMs) is one of the most common outpatient surgical procedures. It is also the most commonly performed procedure in oral and maxillofacial surgery around the world.[1,2] Nearly all patients undergoing IMTM surgical removal develop some degree of pain, swelling, and trismus after the surgery, and there seems to be no consensus on the best perioperative treatment to minimize these complications.[3-10]

The use of laser as a therapy was first described by Mester et al[11] in 1971, who concluded that low-level laser energy irradiation (LLEI) stimulates wound regeneration. Since then, laser therapy has been used for treating different syndromes and diseases, including dentin hypersensitivity,[12-16] temporomandibular joint disorders,[17-19] oral mucositis,[20,21] injury to the inferior alveolar nerve,[22] and sagittal ramus osteotomy.[23] LLEI has a reported analgesic effect. Because it induces a more stable conformation of the lipid bilayers, there is a stabilization of nerve cell membranes.[24] In addition, LLEI would enhance the redox systems of the cells and would increase adenosine triphosphate production, leading to restoration of neuronal membranes and decreasing pain transmission.[25] Moreover, LLEI has been described to increase the production of collagen by fibroblasts, the blood circulation within regenerating tissue, and the mitotic activity in HeLa cells, and suppress immune reactions.[26-28] The photochemical, photoelectrical, and photoenergetic biostimulations (primary biostimulation) and the effect on lymph vessels, with no adverse effects, also have claimed to be effects of LLEI.[29-32] Therefore, some investigators have stated that LLEI decreases pain and swelling after surgery, and that it would contribute to a faster recovery of the patients.[33] The effect of LLEI on the most common complications after IMTM removal also has been studied,[33-40] and the results have been variable. The lack of agreement among surgeons about the postoperative indications to minimize pain, swelling, and trismus after IMTM surgical removal is evident in the literature and in clinical practice, which results in different perioperative actions that range from premedication to different surgical techniques. The effectiveness of corticosteroids[5] and nonsteroidal anti-inflammatory drugs[3,10,41] have been reviewed; however, despite several trials assessing the effects of LLEI on postoperative complications after IMTM removal, the results have not been systematically summarized. The aim of this study was to systematically review and meta-analyze the efficacy and safety of LLEI for decreasing postoperative complications in patients undergoing surgical removal of IMTMs.

Materials and Methods

This systematic review was performed in accordance with a previously developed protocol.

CRITERIA FOR INCLUDING STUDIES IN THIS REVIEW

Randomized clinical trials and quasi-randomized clinical trials comparing the efficacy of LLEI with placebo for decreasing the severity of complications after IMTM surgical removal, with a minimum follow-up period of 3 days, were included. The intervention of interest was the application of any regimen of LLEI after IMTM surgical removal. LLEI was defined as an irradiation intensity low enough that its effects were due to direct irradiation and not the result of heating.[42] Trials reporting the results of any of the outcomes (pain, swelling, trismus, and adverse effects) of interest were included. There were no restrictions for patients' characteristics, type or regimen of LLEI administration, and methods of outcome measurement.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

A search strategy was developed for MEDLINE (from 1966 through July 25, 2011), EMBASE (from 1980 through July 25, 2011), and the Controlled Clinical Trials Register of the Cochrane Collaboration (Appendix). Free text terms were used to search the National Institutes of Health Clinical Trials Registry and the International Clinical Trials Registry. In addition, the online databases of the *Journal of Oral and Maxillofacial Surgery*, *International Journal of Oral and Maxillofacial Surgery*, *British Journal of Oral and Maxillofacial Surgery*, *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, *Journal of the American Dental Association*, *Journal of Dental Research*, and *Acta Odontologica Scandinavica* were searched. All these searches were performed from the inception of databases through July 20, 2011. Reference lists of relevant articles were examined to look for other pertinent articles. Online abstract indexes of the conference proceedings of the American Association of Oral and Maxillofacial Surgeons and the International Association for Dental Research annual meetings of the past 5 years were also searched. The first 300 hits of a free-term searching strategy in Google Scholar were reviewed to identify gray literature (e.g. literature that cannot be found using search strategies in the databases mentioned). No language restrictions were applied.

DATA COLLECTION

In a first screening, the title and the abstract of all potentially relevant articles were listed and evaluated using a pre-established selection criteria form. This

process was performed in duplicate and independently by 2 reviewers (I.A., N.Y.). All articles selected for full-text screening by at least 1 of the reviewers underwent this screening. In a second phase, the full text of all articles that potentially met the eligibility criteria based on the first screening results were assessed in duplicate and independently by 2 reviewers (I.A., N.Y.). Disagreements were resolved by consensus, and when no consensus was reached, a third investigator (P.S.) acted as an arbiter. Two evaluators extracted the data from all the selected studies independently and in duplicate (R.B., A.C.) using a custom-designed form created for this purpose. Discrepancies between the data were reviewed by the 2 data extractors, and when needed, a third investigator acted as an arbiter. The risks of bias in the included studies were evaluated using the Cochrane Risk of Bias tool.[43] The evaluation was performed by 2 reviewers independently (R.B., A.C.). Any disagreement between the evaluators was discussed and a consensus was reached to classify the domains as having low, moderate, or unclear risk of bias. If there were not enough data of interest in any of the trials, the authors were contacted to obtain the information. Each trial was analyzed with respect to its missing data, and if the missing data were judged to be missing at random and/or not having an association with the intervention, only available data were used.

ASSESSMENT OF HETEROGENEITY

Clinical heterogeneity was assessed qualitatively, considering patients, setting, and intervention characteristics. Methodologic heterogeneity was evaluated using the domains of the Risk of Bias tool.[43] Efforts were made to detect reporting biases, if possible, in accordance with the recommendations of the Cochrane Collaboration.[44] The χ^2 test was used to determine the presence of statistical heterogeneity, using a level of significance of 0.1. Quantification of inconsistency across the studies was done using the I^2 statistic, and its interpretation was based on the Cochrane Collaboration recommendations.[45] If statistical heterogeneity was detected, its reasons were explored.

DATA ANALYSIS

The meta-analyses were performed using Review Manager 5.1 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark, 2011). The planned analysis of the pooled effect of LLEI was to use the mean difference for continuous variables and risk ratio for categorical variables with 95% confidence intervals (CIs) between the interventions under comparison. Because significant variability was expected in the regimen of administration of LLEI, it was assumed that the studies were showing different, but related, intervention effects. Therefore, the DerSimonian random effects method was used for pooling the results.[45] When the standard deviation of the difference in any outcome between 2 time points was not available, a moderate correlation coefficient of 0.4 was assumed to calculate the standard deviation of change. A sensitivity analysis (using weak and strong correlation coefficients of 0.2 and 0.8, respectively) was performed to assess the robustness of the overall findings. If there was a need for an imputation of a correlation coefficient in split-mouth trials, a sensitivity analysis was undertaken, using a lower and a higher correlation coefficient, to determine whether the overall treatment effect was modified. However, because there was only 1 split-mouth trial included in the meta-analyses and because in all the trials it was necessary to impute a correlation coefficient to calculate a standard deviation of the change, no correlation coefficient was imputed in the split-mouth trial. Thus, this trial was treated as if it were a parallel trial, with a correlation coefficient equal to 0, producing the most conservative estimate of the treatment effect.

Results

DESCRIPTION OF STUDIES

The initial search retrieved 581 records. After removing the duplicates and after the 2 stages of screening, 452 articles were excluded. The results of the search and screening process are shown with details in Figure 1. Fourteen studies were excluded after the full-text screening process. The flow chart (Fig 1) shows the reasons for the exclusion of these trials. Eleven reports were eligible for this systematic review. However, it was noted that 2 trials by 1 author reported the same data for the control group, so after contacting this author to clarify this aspect, it was learned that the data came from only 1 trial that had been reported in 2 different articles.[34,36] Therefore, 10 trials were included in this systematic review. The trial publication dates ranged from 1990[46,47] through 2011.[48] Among the included studies, there was a clinical trial published on a Web site, with no information about the authors' affiliation, year of publication, and author contact; nevertheless, it met the eligibility criteria.[49] Two studies were described as pilot trials,[48,50] and 1 of these reported results for only 1 patient per group.[50] A description of the general characteristics of the included studies is presented in Table 1.

Many regimens of LLEI administration were observed in the included studies. These regimens differed mainly by the type of LLEI used, the schedule and duration of the administration, and the power of the LLEI. Table 2 presents the characteristics of the

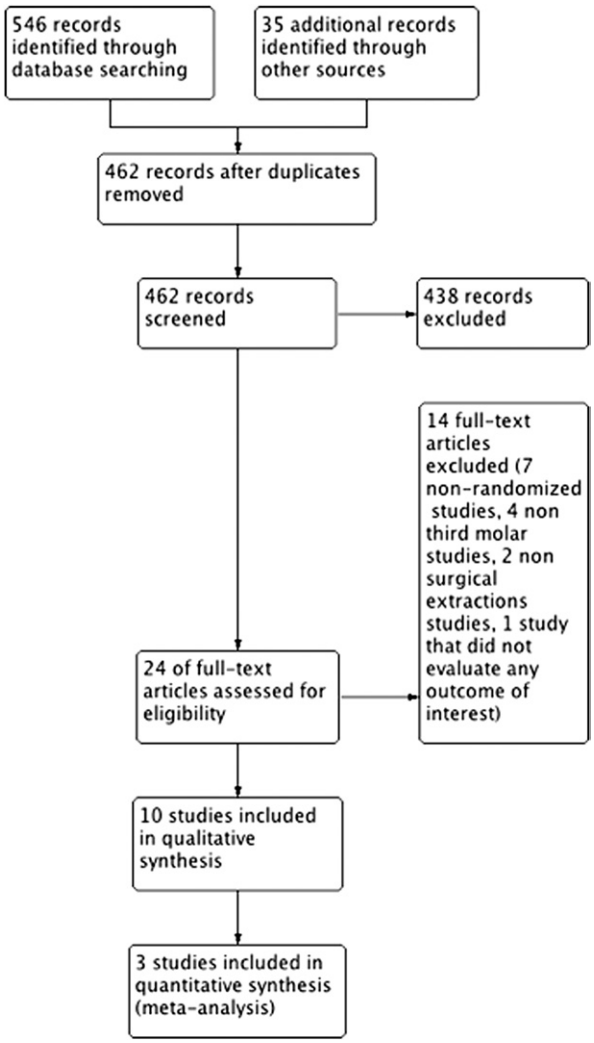

FIGURE 1. Study flowchart.

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regimen of intervention in each study. Several cointerventions were identified in the included studies. In 8 trials patients received analgesics postoperatively,[34-36,39,47,48,51,52] in 6 trials patients received postoperative antibiotics,[34-36,39,47,48] and in 1 trial patients received preoperative corticosteroids.[35] However, these cointerventions were administered to all patients in the study, and thus the differences between the intervention and control groups can be attributed to the effects of the LLEI.

RISK OF BIAS OF INCLUDED STUDIES

The main challenge to judge the risk of bias of the included studies was the low quality of their reporting. Most articles focused on a description of the details of the intervention with regard to its clinical features; however, information about the methodology of the trial and efforts to avoid bias was scarce. In consequence, many domains were judged as unclear owing to a lack of information. In cases in which the authors could be contacted and responded to questions about the methodology, their answers were used to determine the risk of bias of the trial. The risk of bias in each of the domains of interest per study is shown in Figure 2. The domain with the lower risk of bias was blinding, whereas the domain with the higher risk of bias was selective reporting, mainly because of the reporting of the results in graphs and with no measurements of dispersion. No protocol of any of the included studies was found to evaluate other potential sources of bias or differences between the protocol and the final report.

EFFICACY OF LLEI

Because of the clinical heterogeneity among the included studies, it was possible to undertake a meta-analysis for the outcome trismus only at 2 and 7 days after the surgery. The other outcomes of interest are presented qualitatively in Tables 3 and 4.

PAIN

Nine trials reported results for the outcome pain[35,39,46-52]; however, all of these trials differed in the scale used for measuring pain, the times in which the measurements were performed, the summary statistics presented, and the design of the trial. In consequence, the reviewers decided not to undertake a meta-analysis to combine them. Table 3 lists the characteristics of each of these variables. The results of 1 trial are not reported because the trial authors failed to describe when the measurement was performed.[49]

Only 1 study reported statistically significant differences in pain between the groups the first 2 days after the surgery,[35] which favored LLEI over placebo. In all other trials, neither statistically nor clinically significant differences were reported; nevertheless, it should be noted that the study showing differences was the study with the lowest risk of bias of the included studies in this systematic review. An author of the only trial that did not report pain[34,36] was contacted and that author reported that this outcome was measured in the clinical trial; however, it had not been reported because of a lack of statistical significance.

TRISMUS

Six trials evaluated the effects of LLEI on trismus. Three studies provided data that were eligible for meta-analyses.[35,36,48] The results of these meta-analyses are shown in Figures 3 and 4. It was necessary to impute a correlation coefficient to determine the standard deviation of change for trismus in each group. A total of 82 patients contributed to the results of this outcome. At the second day after the surgery, patients who received adjuvant LLEI had an average of 4.2 mm

Table 1. CHARACTERISTICS OF INCLUDED STUDIES

Study	Design	Age (yrs)	Gender	Participants (n)	
				Intervention	Comparison
Carrillo et al,[46] 1990	Parallel	Mean 27	67% women	34	66
Taube et al,[47] 1990	Split-mouth	Range 19-31	71% women	17	17
Clokie et al,[51] 1991	Split-mouth	Mean 22.3, range 16-25	67% women	15	15
Fernando et al,[39] 1993	Split-mouth	Range 18-50	NR	64	64
Braams et al,[52] 1994	Split-mouth	Mean 23, range 17-35	56% women	43	43
Fikackova et al,[50] 2003	Unclear	NR	NR	1	1
Aras and Güngörmüş,[34] 2009*	Parallel	Range 18-27	66% women	16	16
Aras and Güngörmüş,[36] 2010*	Parallel	Range 18-27	71% women	32	16
Amarillas-Escobar et al,[35] 2010	Parallel	Mean 21.5	63% women	15	15
López-Ramírez et al,[48] 2011	Split-mouth	Mean 23.4, range 18-37	55% women	20	20
Neckel and Kukiz[49]	Parallel	NR	52% women	105	105

Abbreviation: NR, not reported.

*Randomized controlled trial reported in 2 different articles. The author confirmed conducting a trial with 4 arms. The placebo group is the same in the 2 reports.

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(95% CI, 1.2 to 7.2 mm; $\chi^2 = 0.87$; $P = .65$; $I^2 = 0\%$) fewer millimeters of trismus compared with patients receiving placebo. A comparison of parallel with split-mouth trials produced similar results. Carrillo et al[46] reported that the larger mean percentage of trismus occurred on the second day after the surgery, which was 38.61% (standard error, 3.43%) in patients in LLEI group versus 48.52% (standard error, 3.21%) in patients in the placebo group. Fikackova et al[50] reported that 1 patient in the LLEI group had a severe mouth-opening limitation at the first and third days after the surgery, whereas 1 patient in placebo group did not.

On the seventh day after the surgery, the results were very similar to those observed on the second day (Fig 4). There was an average of 5.0 mm (95% CI, 1.8 to 8.2 mm; $\chi^2 = 1.92$; $P = .38$; $I^2 = 0\%$) less trismus in patients in the LLEI arm. At this time point, however, there were differences in the effect estimate between the parallel and split-mouth trials. Parallel trials showed that patients in LLEI arm had a trismus of 6.6 mm (95% CI, 2.7 to 10.5 mm) less than patients in the placebo arm, whereas split-mouth trials showed that this difference in trismus was only 1.8 mm (95% CI, −3.9 to 7.4 mm; test for subgroup differences, $P = .17$; $I^2 = 47\%$). There were 3 other studies that reported the differences in trismus at 7 days after the surgery. Carrillo et al[46] reported that the mean percentage of trismus was 22.94% (standard error, 2.78%) in patients receiving LLEI, whereas it was 31.22% (standard error, 3.38%) in patients receiving placebo. Braams et al[52] reported a difference in trismus of 0.5 mm between groups. Fikackova et al[50] observed no differences between patients receiving LLEI and those receiving placebo.

Sensitivity analyses were performed to test the robustness of the results, using a low ($r = .2$) and a high ($r = .8$) correlation coefficient. The change in the effect estimate was minimum (<0.7 mm when using a low coefficient and >0.7 mm when using a high coefficient) on the second day after the surgery, but the 95% CI was narrower when using a high coefficient and wider when using a low coefficient. The same was observed at 7 days after the surgery.

SWELLING

Eight trials described that this outcome was measured; nevertheless, only 7 reported the results of the analysis.[35,36,39,47,48,50,51] Carrillo et al[46] described in the results section that no significant differences in the percentages of facial swelling were observed and did not report the data on this outcome. Although the time point at which facial swelling was measured was similar among the studies, all studies used different methods to measure this outcome. In addition, different statistics were used to summarize the results in each of these trials. In consequence, the reviewers decided not to conduct a meta-analysis to pool the results. Table 4 presents a description of the scales used, times of measurement, statistics used, and results of facial swelling in the trials. Only 2 trials[35,48] reported a statistical comparison of LLEI versus pla-

Table 2. REGIMEN OF THE INTERVENTION

Study	Laser Regimen of Administration								Comparison
	Type	Wavelength	Power	Energy	Site	Duration (s)	Mode	Timing	
Carrillo et al,[46] 1990	He-Ne	632.8 nm	0.3 W/cm^2	10 J/cm^2	Intraoral in 6 points	NR	NR	NR	Placebo
Taube et al,[47] 1990	He-Ne	632.8 nm	8 mW	NR	Intraoral	120	NR	Before suturing wound and 1 day after surgery	Placebo
Clokie et al,[51] 1991	He-Ne	632.8 nm	10 mW	NR	Intraoral, 2 mm from wound	180	Continuous	After surgery	Placebo ibuprofen
Fernando et al,[39] 1993	Ga-Al-As	830 nm	30 mW	4 J/cm^2	Intraoral, inserted into socket	132	Intermittent	After surgery	Placebo
Braams et al,[52] 1994	Ga-Al-As	829 nm	30 mW	NR	Intraoral	66	NR	NR	Placebo
Fikackova et al,[50] 2003	Ga-Al-As	830 nm	200 mW/cm^2	12 J	Intraoral	108	Intermittent	10 min, 1 and 3 days after surgery	Placebo
Aras and and Güngörmüş, 2009,[34] 2010[36]	Ga-Al-As	NR	100 mW	4 J/cm^2	Intraoral, 1 cm from wound and extraoral in contact with masseter muscle, factorial design	120	NR	Intra- and extraoral after surgery	Placebo
Amarillas-Escobar et al,[35] 2010	Nd-YAG	810 nm	100 mW	4 J/cm^2	Intraoral, 1 cm from wound and extraoral in 6 zones	NR	Continuous	Intraoral after surgery, extraoral at 24, 48, and 72 h after surgery	No treatment
López-Ramírez et al,[48] 2011	Ga-Al-As	810 nm	0.5 W	4 J/cm^2	Intraoral, 1 cm from wound	32	Continuous	NR	Placebo
Neckel and Kukiz[49]	Ga-Al-As	810 nm	36 mW	11.3 J/cm^2	Intraoral	150	NR	After surgery	Placebo

Abbreviation: NR, not reported.

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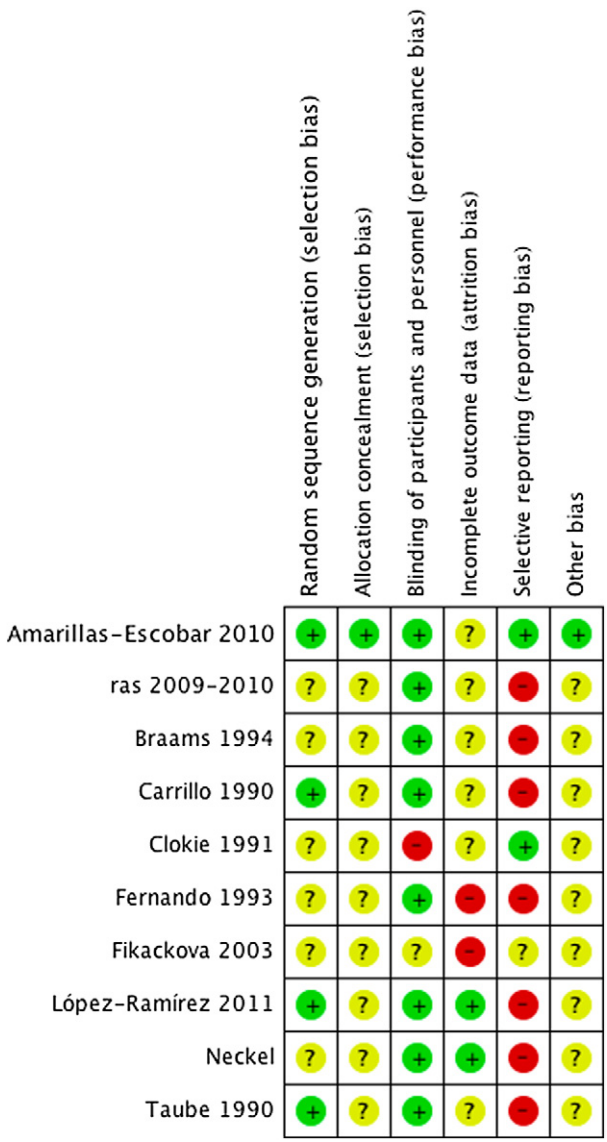

FIGURE 2. Summary of low (*green*), unclear (*yellow*), and high (*red*) risk of bias according to the reviewers' judgments about each risk-of-bias item for each included study.

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cebo and reported no statistically significant differences in facial swelling between groups.

SAFETY OF LLEI

Half the trials failed to report the presence or absence of adverse effects. Two studies reported that no adverse effects were observed,[34,47] 1 reported that there were no infectious complications attributable to LLEI,[48] 1 described that there were 4 patients in whom the wound healing was impaired but that these were equally distributed between the groups,[52] and 1 reported that the infection rate was lower in patients receiving LLEI than in patients receiving placebo.[49]

PUBLICATION BIAS

Unfortunately, because of the small number of trials included in the meta-analysis, publication bias could not be assessed.

Discussion

The purpose of this study was to assess the efficacy and safety of LLEI for decreasing postoperative complications in patients undergoing surgical removal of an IMTM. The present results suggest that the postoperative use of LLEI is not effective at minimizing pain and swelling, but may be beneficial for minimizing mouth-opening reduction compared with placebo. The safety of LLEI was not investigated in most of these trials.

The impact of LLEI on pain was evaluated in several clinical trials; however, all but 1 reported no benefit. The mechanism for the analgesic effects of LLEI has been reported to be multifactorial.[33] Because it induces a more stable conformation of the lipid bilayers, there is a stabilization of nerve cell membranes.[24] In addition, LLEI has been shown to enhance the redox systems of the cells and increase adenosine triphosphate production, leading to a restoration of neuronal membranes and decreasing pain transmission.[25] Moreover, LLEI has been described to increase the production of collagen by fibroblasts, improve the blood circulation within regenerating tissue and the mitotic activity in HeLa cells, and suppress immune reactions.[26-28] In 2006, a systematic review reported that there is strong evidence that LLEI has local anti-inflammatory, microcirculatory, and angiogenetic effects, probably because of a modulation of inflammatory markers, an increase in growth factors, and a formation of collateral vessels.[53] This modulation of inflammatory process was proposed to be responsible for acute pain relief. LLEI may have impact on pain; however, further studies are needed with careful design and standardized pain assessment.

Overall evidence indicates that LLEI is not effective in minimizing swelling compared with placebo. Although all investigators measured swelling using different scales and tools and at different time points, none of the studies reported that patients receiving LLEI had less swelling than patients receiving placebo or no treatment.

LLEI seems to be effective for minimizing mouth-opening reduction compared with nonactive comparators (no treatment and placebo). However, the difference between 4 mm on the second day and 5 mm on the seventh day after the surgery has moderate clinical importance. Taking into account the fact that the patients had only a moderate mouth-opening reduction, eg, their mouth opening was 27 mm on average on the second day after the surgery, the 4-mm

Table 3. RESULTS FOR THE OUTCOME PAIN

Study	Scale	Postsurgical Times of Measurement	Results				
			Postsurgical Time	Statistic	LLEI	Control	Comparison
Carrillo et al,[46] 1990*	intensity: ordinal scale 0-4	1-4 hr	1 day	mean (SD)	1.76 (0.24)	1.88 (0.23)	NR
	supplementary analgesia (number of pills)	1, 2, 7 days					
Taube et al,[47] 1990	VAS 0-10	every hour on first day and 3 times/ day on second and third days	10 hr†	no information‡	2.4	2.6	NR
Clokie et al,[51] 1991	ordinal scale, 10 categories collapsed to 3	baseline, 1 day, 2 days	1 day	proportion of intervention with less pain	favors laser 0.6		NR
			2 days		favors laser 0.47		
Fernando et al,[39] 1993	verbal digital score 0-9	1, 3, 7 days	1 day	median‡	4	4	NR
Braams et al,[52] 1994	ordinal scale 0-5	1-6 days	1 day	mean‡	2.7	3.2	"significant differences were not observed"
			2 days		2.0	2.5	
Fikackova et al,[50] 2003	VAS 10 cm	1-7 days	1 day	mean	26	29	NR
			2 days		27	26	
Amarillas-Escobar et al,[35] 2010	VAS 10 cm	3, 6 hr, 1, 2, 7 days	1 day	mean (SD)§	4.6 (2.6)	6.4 (3.3)	
			2 days		2.9 (1.9)	4.1 (2.2)	
			1 day	median	2.3	4.6	$P < .5$
			2 days		3.9	4.4	$P < .5$
López-Ramírez et al,[48]	VAS 10 cm	2, 4, 6 hr, 1-5 days	1 day	mean‡	22	23	"nonstatistically significant differences"
			2 days		17	20	

Note: Standard deviations are not listed for studies that did not report them.

Abbreviations: LLEI, low-level laser energy irradiation; NR, not reported; SD, standard deviation; VAS, visual analog scale.

*Study that compared LLEI with placebo and ibuprofen. Only the placebo results of placebo are presented.

†Latest time point reported. It is the closest to the time point of interest.

‡Author reported data in graphs.

§Data provided by author.

Table 4. RESULTS FOR THE OUTCOME SWELLING

Study	Scale or Method	Postsurgical Time of Measurement	Results				
			Postsurgical Time	Statistic	LLEI	Control	Comparison
Taube et al,[47] 1990	Facebow technique, 5 ordinal categories	1 day	1 day	Proportion of intervention with less swelling	Same on 2 sides 0.59		NR
					Favors laser 0.24		
					Favors control 0.18		
Clokie et al,[51] 1991	Obvious differences	7 days	7 days	Proportion of patients having more swelling in 1 vs other side	Same swelling on 2 sides 46%		NR
					More swelling on LLEI side 27%		
					More swelling on control side 27%		
Fernando et al,[39] 1993	Verbal digital score 0-9	1, 3, 7 days	1 day	Median	5	5	$P = .712$
Fikackova et al,[50] 2003	VAS 0-100 mm, collapsed to 3 categories (0-1-2)*	1-7 days	1 day	Observed value	2	2	NR
			2 days	2	1		
Amarillas-Escobar et al,[35] 2010	Ustun	Baseline, 1, 2, 3, 7 days	Baseline	Median	452.6	455.9	$P > .5$
			2 days	464.8	470		
Aras and Güngörmüş,[36] 2010†	Amine-Laskin	Baseline, 2, 7 days	Baseline	Mean (SD)	101.5 (3.1)	102.6 (3.8)	NR
			2 days	107.3 (3.0)	109.1 (4.4)		
López-Ramírez et al,[48] 2011	Schultze-Mosgau modified	Baseline, 2, 7 days	Baseline	Mean (SD)	H 103.4 (5.1)	H 103.0 (6.0)	$P = .218$
					V 106.6 (5.8)	V 106.8 (6.3)	
			2 days		H 109.7 (5.0)	H 111.9 (5.5)	
					V 111.6 (8.7)	V 114.0 (7.5)	

Abbreviations: LLEI, low-level laser energy irradiation; H, horizontal measurement; NR, not reported; SD, standard deviation; V, vertical measurement; VAS, visual analog scale.
*0 = none, 1 = mild, 2 = severe.
†Article reported results for placebo and intraoral and extraoral LLEI. Only results of the intraoral LLEI are listed.

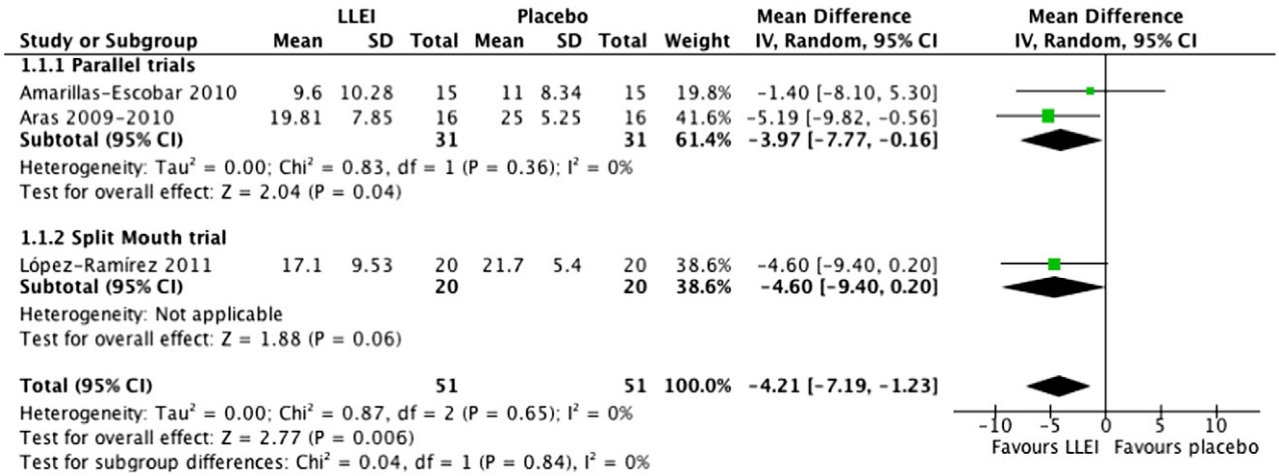

FIGURE 3. Low-level laser energy irradiation (LLEI) versus nonactive comparator for minimizing trismus 2 days after impacted mandibular third molar surgery. CI, confidence interval; SD, standard deviation.

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difference constitutes a 15% difference and could be significant from a patient's perspective.

To the reviewers' knowledge, this is the first comprehensive systematic review on this subject. However, the results of this systematic review were obtained from only 581 patients across the 10 included studies. Compared with the number of people who undergo this procedure every year, this is a very small number. In addition, not all studies reported on all outcomes. Furthermore, the sample of patients obtained was representative of most people undergoing the surgical removal of an IMTM. The cointerventions observed were the same as those found in clinical practice. All the trials included compared the effects of LLEI with placebo or no treatment, which is not the adjuvant treatment provided to patients undergoing IMTM surgical removal. The reviewers believe the present results provide the best possible synthesis on the topic and underscore the importance of the proper evaluation of newer techniques before they become routine based on anecdotal experiences. In consequence, these results are applicable to a wide range of patients.

However, the quality of the evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group criteria[54] is very low for the outcome of pain, low for swelling, and moderate for trismus. In addition, the outcomes of pain and swelling presented problems related to the imprecision of the results. Moreover, pain presented inconsistencies among the results of the trials. In consequence, it can be claimed that the evidence of the effects of LLEI regarding pain is very uncertain, that the evidence regarding swelling is likely to change, and that the estimates

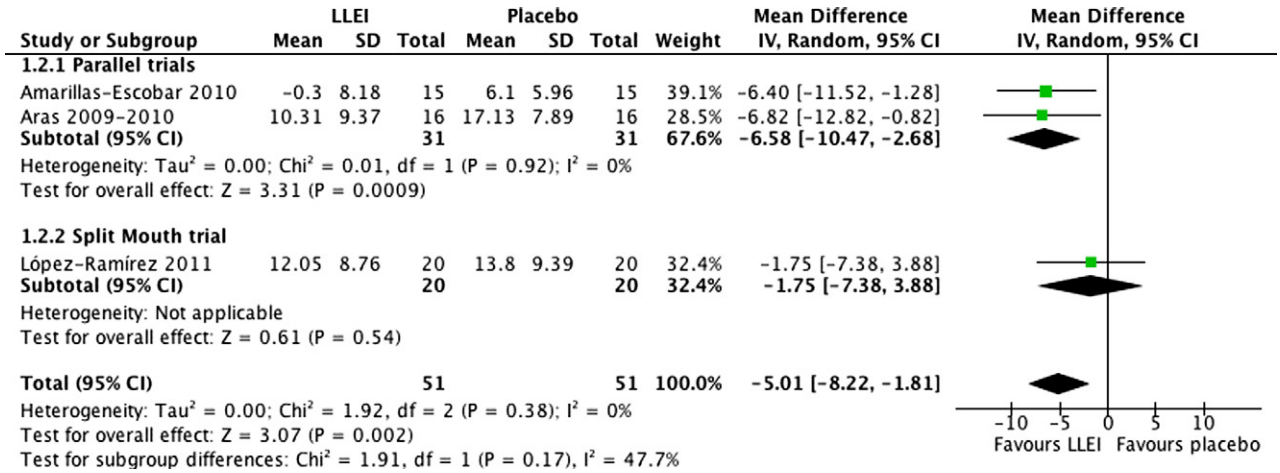

FIGURE 4. Low-level laser energy irradiation (LLEI) versus nonactive comparator for minimizing trismus 7 days after impacted mandibular third molar surgery. CI, confidence interval; SD, standard deviation.

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of mouth-opening reduction may change with further research.

The strengths of this review include the unbiased process, comprehensive search, meticulous data collection, obtaining information from authors, and assessment of risk of biases in the included studies. However, the limitations must be acknowledged. The included studies had marked heterogeneity in the intervention and outcome assessments, the studies were mostly underpowered, and 1 study lacked information on the authors. Unfortunately, it was not possible to perform a formal assessment of the likelihood of publication bias. However, because many of the articles included in the review failed to show statistically or clinically important differences between LLEI and no active treatment, which was disregarded by their journal of publication, it does not seem likely that publication bias could be influencing the results of this review. The most important limitation of this review is not related to the process itself, but to the quality of the evidence for the outcomes of interest. No single outcome had a high quality of evidence; moreover, the outcomes of swelling and pain, which can be considered the most important to the patient outcomes of this review, had a low and a very low quality of evidence, respectively, supporting the results. Another limitation could be that, in the split-mouth trials that were pooled together with the parallel trials, the 2 surgeries were performed at different times, making an observation of a carry-across effect of the intervention unlikely. In addition, because the results were treated using a within-patient correlation of 0, the estimates obtained are conservative.

In conclusion, there is not enough evidence to support the use of LLEI over no active treatment to minimize pain, swelling, and mouth-opening reduction after IMTM surgical removal. The beneficial effects of LLEI on mouth-opening reduction were the most consistent across studies, but had moderate clinical importance. There seems to be no adverse effects associated with the administration of LLEI; however, it has not been studied adequately. It is necessary to improve the methodologic and reporting quality of randomized clinical trials in this area. Furthermore, it is essential to standardize the methods, tools, and schedules to measure the outcomes of interest. A well-designed clinical trial should be powered to find differences between groups in the 3 outcomes of interest. In addition, if a beneficial effect of LLEI is detected, cost-effectiveness studies should be undertaken to determine whether it is advisable to use LLEI in patients undergoing IMTM surgical removal.

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Appendix:

SEARCH STRATEGIES

Medline

1. laser therapy/or laser therapy, low-level/or lasers/tu or (low adj2 level* adj3 laser*).ti,ab. (31979)
2. third molar/or (wisdom adj2 (tooth or teeth)).ti,ab. or (third adj2 molar*).ti,ab. or tooth, impacted/or ((molar* or tooth or teeth) adj2 (remov* or extract*)).ti,ab. or tooth extraction/(25918)
3. 1 and 2 (249)
4. (randomized controlled trial or controlled clinical trial or meta analysis or multicenter study).pt. or randomized controlled trials as topic/or controlled clinical trials as topic/or multicenter studies as topic/or meta analysis as topic/or randomized controlled trials/or random allocation/or double-blind method/or single-blind method/or (random* or (doubl* adj2 dummy) or ((Singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or RCT or RCTs or (control* adj5 trial*) or multicent* or placebo* or metaanalys*

or (meta adj5 analys*) or sham or effectiveness or efficacy or compar*).ti,ab. (3531960)
5. 3 and 4 (141)
6. limit 5 to humans (134)

Embase

1. laser/or diode laser/or yag laser/or low level laser therapy/or laser coagulation/or (low adj2 level* adj3 laser*).ti,ab. (59845)
2. molar tooth/or tooth extraction/or extraction/or (wisdom adj2 (tooth or teeth)).ti,ab. or (third adj2 molar*).ti,ab. or ((molar* or tooth or teeth) adj2 (remov* or extract*)).ti,ab. or (impacted adj2 (tooth or teeth or molar*)).ti,ab. (65065)
3. 1 and 2 (729)
4. limit 12 to "treatment (1 term high sensitivity)" (121)
5. ct.fs. or randomized controlled trial/or controlled clinical trial/or multicenter study/or meta analysis/or (random* or (doubl* adj2 dummy) or ((Singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or RCT or RCTs or (control* adj5 trial*) or multicent* or placebo* or metaanalys* or (meta adj5 analys*) or sham or effectiveness or efficacy or compar*).ti,ab. (4244600)
6. 3 and 5 (371)
7. 4 or 6 (372)

Controlled Clinical Trials Register of the Cochrane Collaboration

1. laser/or diode laser/or yag laser/or low level laser therapy/or laser coagulation/or (low adj2 level* adj3 laser*).ti,ab. or laser therapy/or laser therapy, low-level/or lasers/tu (2341)
2. molar tooth/or tooth extraction/or extraction/or third molar/or (wisdom adj2 (tooth or teeth)).ti,ab. or (third adj2 molar*).ti,ab. or tooth, impacted/or ((molar* or tooth or teeth) adj2 (remov* or extract*)).ti,ab. or Tooth Extraction/or (impacted adj2 (tooth or teeth or molar*)).ti,ab. (2354)
3. 1 and 2 (68)