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Pharmacological Control of Complications Following to Third Molar Removal: Evidence Based on A Meta-Analysis

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ABSTRACT

Aims The purpose of this meta-analysis was to evaluate the clinical efficacy of non-steroidal anti-inflammatory drugs and dexamethasone on the trismus, postsurgical pain, facial swelling, as well as the analgesic consumption after third molar surgery.

Material and Methods The reports were identified in the most important medical databases. Those studies that met the requirements were fully assessed according to the inclusion and exclusion criteria. The quality of each report was evaluated with the Oxford Quality Scale and using the Cochrane Collaboration's risk of bias tool. Each meta-analysis was done using the technique of mean difference and 95 % confidence intervals employing a random effects model with the Review Manager 5.3., from the Cochrane Library. Significant statistical difference was accepted when the p value was less than 0.05 on the test of overall effect (Z value).

Results Qualitative evaluation was done using the data of 330 patients extracted from seven articles and the quantitative assessment with data of 200 patients from three reports. It was not observed difference among non-steroidal anti-inflammatory drugs and dexamethasone in any of the clinical effectiveness indicators.

Conclusion The outcomes of our meta-analysis indicate that non-steroidal anti-inflammatory drugs and dexamethasone have good therapeutic effect for the management of inflammatory complications following to third molar surgery.

Introduction

All patients undergoing extraction of third molars present postsurgical complications despite receiving pharmacological treatment which directly affect the quality of life [1, 2]. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are the two kind of drugs mainly used to control these postsurgical signs and symptoms [2]. NSAIDs are the most used drugs to treat the complications after mandibular third molar surgical extraction showing different grades of clinical effectiveness [3]. Moreover, the corticosteroids are used with the same purpose [4, 5]. Dexamethasone is the most used corticosteroids for control of postsurgical pain, swelling, and limitation of the mouth opening which has demonstrated good clinical efficacy when compared with placebo according to some systemic reviews and meta-analysis [2]. However, the comparison between dexamethasone and placebo provides limited information on the clinical efficacy of this drug in oral surgery due to inactivity of placebo and the wide variety of treatments available.

There are several clinical reports comparing the clinical effectiveness of NSAIDs and dexamethasone after third molar surgery [5–12]. With the purpose of support to the general dentists as well as to oral and maxillofacial surgeons for the election of one or another treatment the efficacy of NSAIDs and dexamethasone could be evaluated. For this reason, the aim of this systematic review and meta-analysis was to assess the clinical effectiveness of NSAIDs and dexamethasone for the control of pain, facial swelling, and trismus in third molar surgery.

Material and Methods

This systematic review and meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [13]. Trials comparing NSAIDs and dexamethasone were searched from most important medical databases worldwide. The words utilized were: "Non-steroidal anti-inflammatory drugs", "NSAIDs", "dexamethasone", "third molar surgery", "oral surgery", and "dental surgery". Reports published up to August 2017 were eligible. The ▶ **Fig. 1** shows the flow chart of the study.

Inclusion criteria: 1). Randomized, double-blind, clinical trials; 2). Clinical test comparing a NSAID with dexamethasone in third molar surgery; 3). Study assessing any of the following variables: rescue analgesic medication, mouth opening among the upper and lower dental incisors, postoperative pain using the Visual Analogous Scale, facial edema measured through anatomical points, and adverse effects; and 4). Article in English. Exclusion criteria: 1). Loss of follow-up greater than 20 % of those entered. Two clinical researchers evaluated each full text article and any difference or disagreement in the information obtained by both researchers was resolved by consensus with the participation of a third research.

Oxford Quality Scale and Cochrane Collaboration's risk of bias tool were used to evaluate each study [14], like previously was made [15–17]. The differences or disagreements were resolved as was explained above. The studies meeting all the inclusion criteria without any exclusion point and an Oxford Quality Score ≥ 3 were included in our qualitative and quantitative analysis.

Author; design study (parallel or crossover groups); treatment groups; size sample; dose and administration route; period of evaluation; analgesic ingestion; trismus; postoperative pain; facial swelling; and adverse effects were extracted of each clinical report.

The means, standard deviations (SDs), and the number of participants (n) of postoperative analgesic consumption were analyzed in a meta-analysis using a random effects model employing the technique of mean difference and 95 % confidence intervals with the Review Manager 5.3., from the Cochrane Library. The heterogeneity of the meta-analysis was assessed with the I^2 statistic. An I^2 value between 0 and 40 % was considered as no heterogeneity, among 40 and 70 % was deliberated like acceptable, and major to 70 % was considerable or significant. Funnel plot was used to detect important differences between studies [18]. Significant statistical difference was accepted when the p value was less than 0.05 on the test of overall effect (Z value).

Results

A total of 8 articles comparing NSAIDs and dexamethasone were identified. Only one was excluded because did not meet the points of the Oxford Quality Scale (▶ **Table 1**). Thus, the data of 330 patients from seven clinical reports contributed for the qualitative synthesis. On the other hand, the quantitative analysis was carried out using 3 studies only (▶ **Fig. 1**). The Cochrane Collaboration's risk of bias tool showed a low level of bias. The green color represented more than 50 % in all cases; the yellow color between 14.28 and 42.85 % (11 yellow points of a total of 49 points); and the red 14.28 % (2 red points of a total of 49 points) (▶ **Fig. 2**).

Six of seven clinical trials reported the analgesic intake. The qualitative analysis shows four clinical studies reporting similar postoperative analgesic consumption, one in favor to NSAIDs and other for dexamethasone (▶ **Table 2**). The funnel plot showed no important difference among the studies because all points are within of two lines (▶ **Fig. 3a**). The pooled assessment was made with the data of 200 patients extracted from three clinical studies. This meta-analysis showed an acceptable heterogeneity without statistical difference regard to the analgesic intake (▶ **Fig. 3b**).

Five of seven documents evaluated the trismus. The qualitative evaluation shows that three clinical documents informed a superior anti-trismus activity of dexamethasone when compared to NSAIDs, two clinical reports a similar effect, and the rest of the studies did not evaluate the mouth opening (▶ **Table 2**).

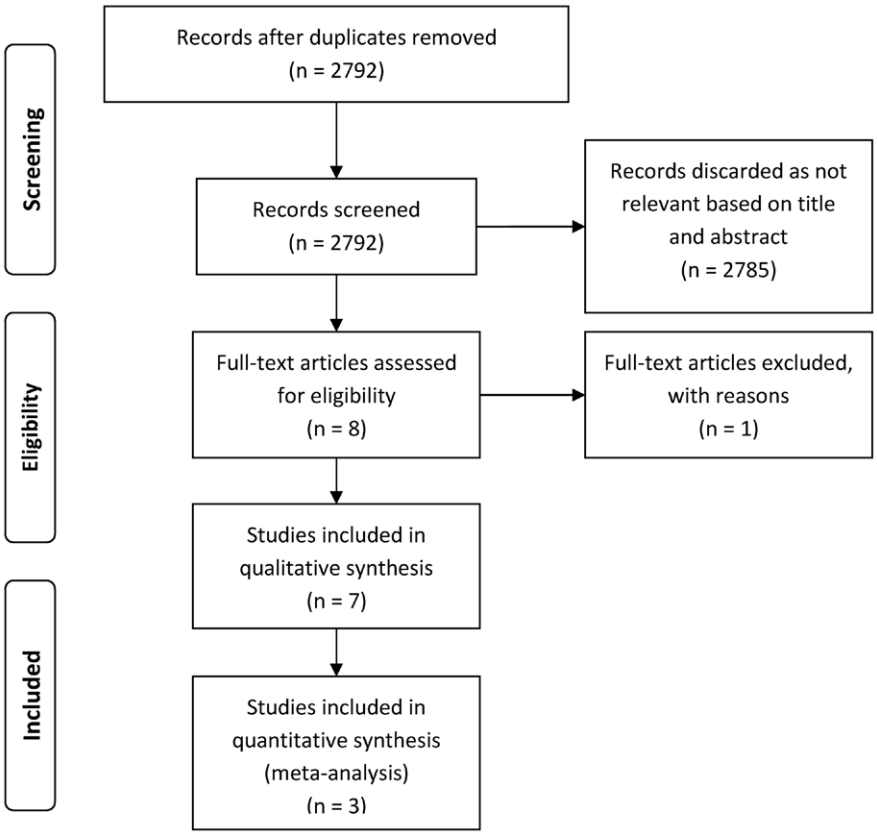
All clinical trials included for the qualitative analysis evaluated the postoperative pain. One article was in favor to NSAIDs, two for dexamethasone, and four obtained similar pain scores (▶ **Table 2**).

Four of seven studies assessed the facial inflammation. The qualitative analysis demonstrated that one clinical trial was in favor to dexamethasone and three found a similar effect (▶ **Table 2**).

Three of seven clinical trials evaluated the adverse reactions. One clinical trial reported nausea and headache in all groups. Non adverse event was reported by the use of these drugs in two studies (▶ **Table 2**).

Discussion

To our knowledge this is the first time that NSAIDs and dexamethasone are compared in a systematic review and meta-analysis to determinate the clinical efficacy of these drugs in the management of postoperative complications after third molar surgery. The pooled analysis on the analgesic intake demonstrated similar drug



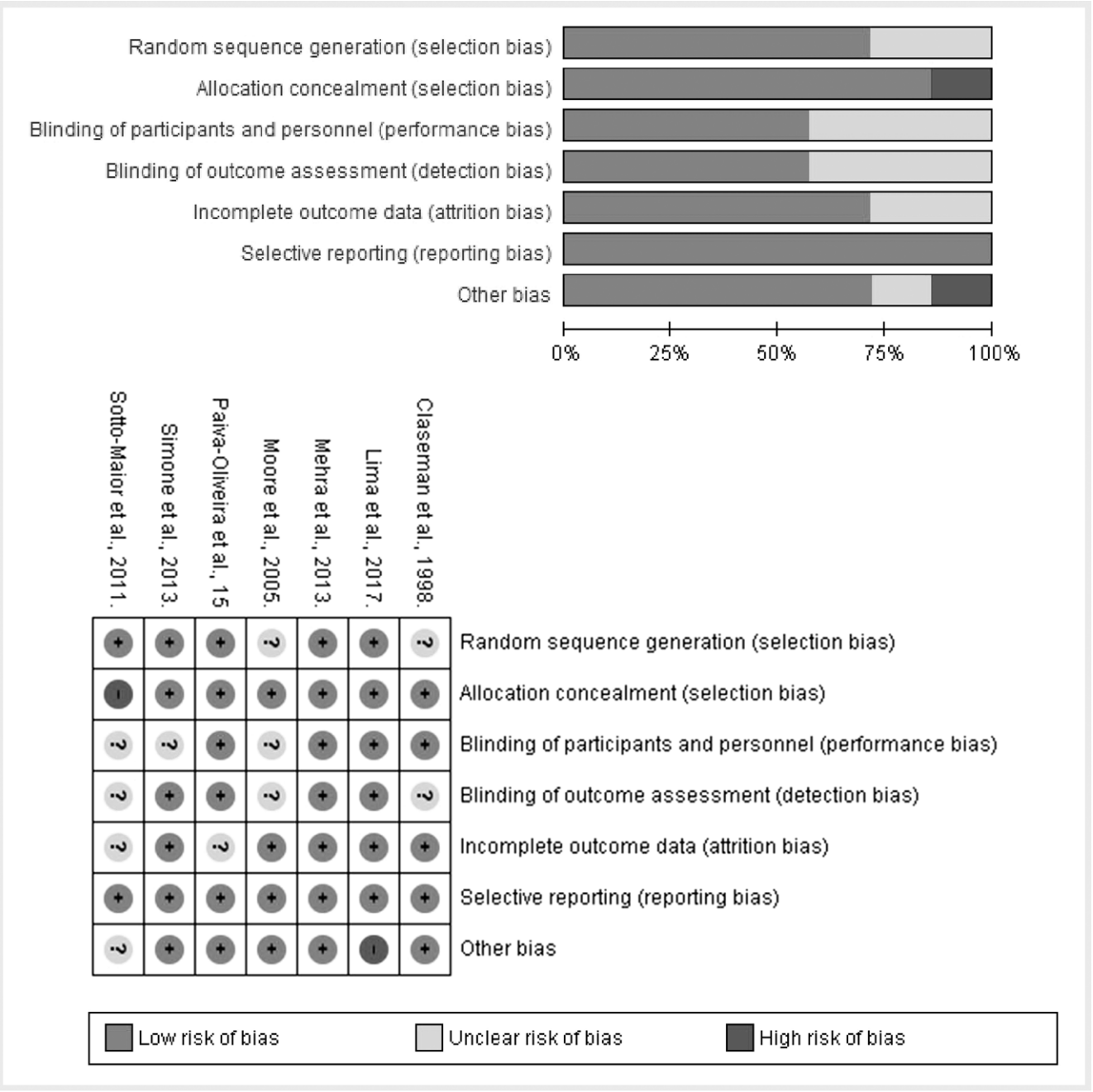
▶ **Fig. 1** Study flow diagram.

▶ **Table 1** Assessment of relevant studies.

Study	Criteria		Oxford Quality Scale	Included
	Inclusion	Exclusion		
Campbell and Kendrick, 1991.	1-4	0	2	No
Claseman et al., 1998.	1-4	0	3	Yes
Lima et al., 2017.	1-4	0	3	Yes
Mehra et al., 2013.	1-4	0	5	Yes
Moore et al., 2005.	1-4	0	4	Yes
Paiva-Oliveira et al., 2015.	1-4	0	5	Yes
Simone et al., 2013.	1-4	0	5	Yes
Sotto-Maior et al., 2011.	1-4	0	3	Yes

consumption for both treatments (▶ **Fig. 3b**). The quantitative analysis of trismus was not possible due to the diversity of anatomical points evaluated and the data statistical management. In case of postsurgical pain only one document allowed us to obtain the means and standard deviations and six studies reported the results through graphs. For this reason, it was not possible to extract the data for the statistical analysis.

Currently, a systematic review and meta-analysis carried out with 10 studies demonstrated that the use of dexamethasone added to the common treatment for sore throat produce better pain relief when compared to placebo. Sadeghirad et al., 2017 evaluated the adverse reactions to corticosteroids and placebo in a meta-analysis where found that this king of drugs produces mild adverse effects [19]. NSAIDs have a large number of adverse effects which mainly affect the gastrointestinal tract, kidneys, and cardiovascular systems [20]. Patients taking therapeutic doses of NSAIDs and for a short period of time usually tolerate them well [21, 22]. In this sense, in our review the statistical analysis was not done because only three of seven studies evaluated adverse events –two studies not reported about them and another informed a similar distribution between treatment groups–. Unfortunately, none report presented results on adverse reactions (number of events) which would have been crucial to recommend one of the evaluated treatments because there is not difference in the clinical assessments on the control of complications in third molar surgical removal according to the quantitative analysis.



▶ **Fig. 2** Evaluation of risk of bias.

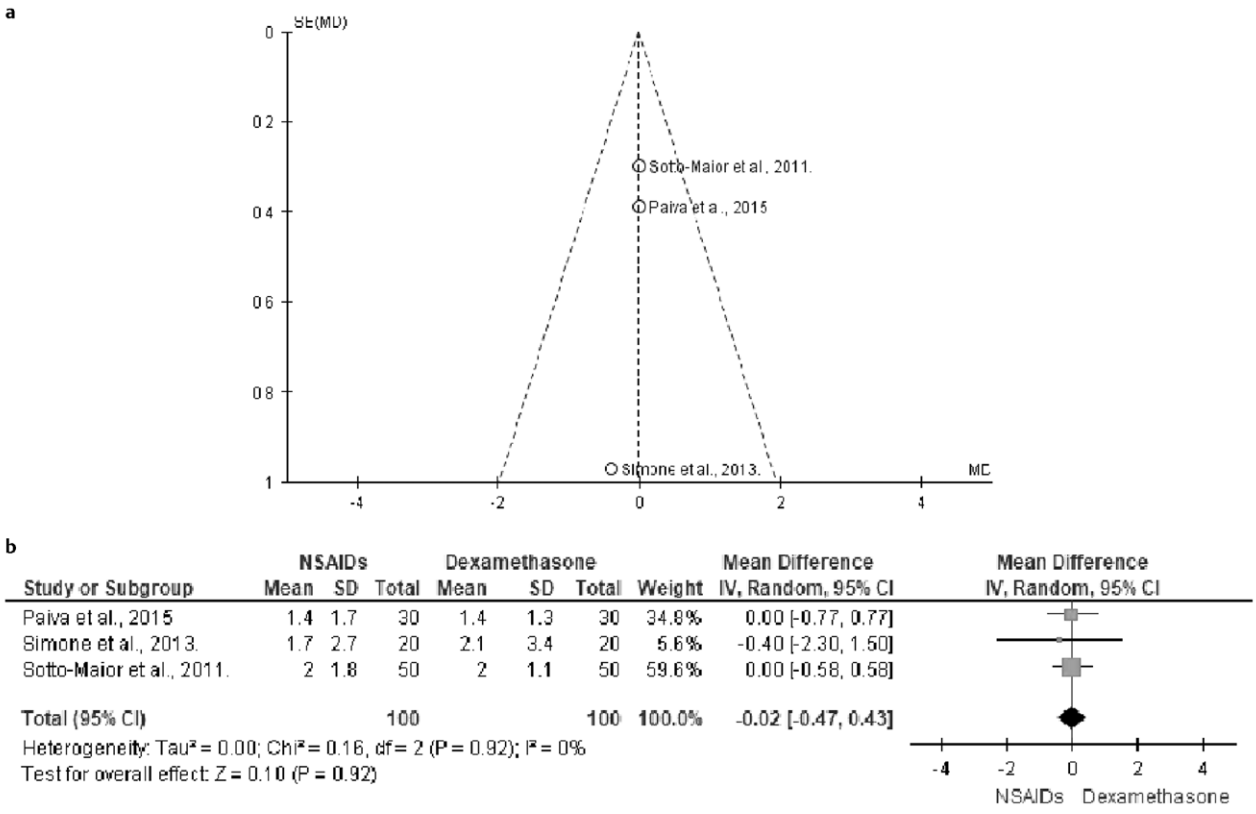
Randomized clinical trials are considered the gold research method for the assessment of health treatments or interventions [23]. In this regard, a systematic review by Loguercio et al. demonstrated that only few clinical studies published are quality reports according to international quality guidelines, e. g.: Consolidate Standard Of Randomized Trials (CONSORT) Statement [24]. The CONSORT guideline tries to standardize the writing and publication of clinical trials through the description of specific items in this kind of reports. CONSORT statement has been actualized in 2001 [25] and 2010 [26, 27].

Strengths of our review include the use of eligibility criteria, bibliographic search in the most import medical databases, elimination of duplicated reports, evaluation of quality and risk of bias of all articles included, data extraction considering the most important clinical results and adverse effects, and a correct statistical analysis. The limitations of our report were the little number of studies included in the qualitative and quantitative analyses, a pooled analysis using different NSAIDs in comparison with dexamethasone as well as the great difference in the moments of post-surgical evaluation.

In summary, the results of this systematic review and meta-analysis show that both NSAIDs and dexamethasone produce similar therapeutic effect on the trismus as well as comparable analgesic intake following third molar extraction.

▶ **Table 2** Details of studies included.

First author and study design	Interventions (n)	Rescue analgesia	Trismus	Postoperative pain	Facial edema	Adverse Effects
Claseman et al., 1998. Randomized, double-blind, parallel, clinical trial.	Group A: Ketorolac 30 mg was intravenously administered (n = 9). Group B: Dexamethasone 8 mg was intravenously administered (n = 7). All treatments were preoperatively administered.	The intake of rescue analgesics was similar for both groups.	Not evaluated	No difference was observed between groups.	Not evaluated	None side effect was reported.
Lima et al., 2017. Randomized, double-blind, split-mouth (crossover), clinical trial.	Group A: Oral diclofenac 50 mg every 8 h for 3 days (n = 30). Group B: Oral dexamethasone 4 mg every 8 h for 3 days (n = 30).	The consumption of dipyrone 500 mg was lower in patients receiving dexamethasone when compared with whom receiving diclofenac.	Dexamethasone was more effective than diclofenac for the control of trismus.	Dexamethasone was more effective than diclofenac for the control of pain.	Dexamethasone was more effective than diclofenac for the control of swelling.	Not evaluated
Mehra et al., 2013. Randomized, double-blind, parallel, clinical trial.	Group A: Preoperative ibuprofen 600 mg every 6 h for a week (intraoperative saline) (n = 20). Group B: Single intravenous dose of dexamethasone 8 mg intraoperatively plus preoperative and postoperative placebo tablets (n = 20).	Consumption of codeine 30 mg was superior in the dexamethasone group when compared to ibuprofen group.	No differences were found in the management of trismus.	Ibuprofen was more effective than dexamethasone for the control of postoperative pain.	The anti-inflammatory effect was similar for both groups.	Not evaluated
Moore et al., 2005. Randomized, double-blind, parallel, clinical trial.	Group A: Preoperative rofecoxib 50 mg was orally administered 30 min before surgery and placebo intraoperatively (n = 5). Group B: Preoperative placebo 30 min prior the surgery and dexamethasone 10 mg IV intraoperatively after star the surgery (n = 9).	Not evaluated.	No difference was found in the management of trismus.	Similar postoperative pain scores were observed.	Not evaluated.	Nausea and headache were reported in all treatment groups.
Paiva-Oliveira et al., 2015. Randomized, double-blind, split-mouth (crossover), clinical trial.	Group A: One capsule of ketorolac tromethamine 10 mg before surgery and every 8 h for 2 days after surgical removal (n = 30). Group B: One capsule of dexamethasone 8 mg preoperatively and placebo capsules every 8 h for 2 days (n = 30).	No difference was reported on the consumption of metamizol 500 mg in the postoperative period.	Dexamethasone was more effective than ketorolac for control of trismus in the 7 postoperative days.	Both experimental groups presented similar postoperative pain scores.	There was no statistically significant difference between the ketorolac and dexamethasone groups.	None reported.
Simone et al., 2013. Randomized, double-blind, parallel, clinical trial.	Group A: Single oral dose of 50 mg of diclofenac (n = 20). Group B: Single oral doses of 8 mg of dexamethasone (n = 20).	Intake of paracetamol 1000 mg was similar for both treatments.	No evaluated.	Dexamethasone was more effective than diclofenac for management of postoperative pain.	Not evaluated.	Not evaluated.
Sotto-Maior et al., 2011. Randomized, double-blind, crossover, clinical trial.	Group A: Single dose of 120 mg of etoricoxib (n = 50). Group B: Single dose of dexamethasone 4 mg (n = 50). The administration route was not described.	The consumption of paracetamol 750 mg was similar in both treatment groups.	The anti-trismus effect was similar between the two groups.	No differences were observed regarding pain.	Similar effect on the swelling in both therapeutic approaches was observed.	Not evaluated.



▶ **Fig. 3** Funnel plot (**a**) and forest plot (**b**) of the analgesic consumption.

Ethics statement/confirmation of patients' permission
Not necessary.

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Conflict of Interest

No conflict of interest has been declared by the author(s).

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