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RESEARCH ARTICLE

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Analgesic efficacy of preoperative dexketoprofen trometamol: A systematic review and meta-analysis

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Abstract

Clinical evidence supports the use of dexketoprofen trometamol (DEX) to manage acute postoperative pain. However, controversies surround the impact of the use of this drug in preoperative analgesic protocols. The aim of the present meta-analysis was to evaluate the effectiveness of the preoperative administration of DEX under postoperative pain conditions. Electronic and manual searches were conducted through diverse electronic databases. A systematic review and meta-analysis to evaluate the analgesic efficacy of the preoperative administration of DEX was performed including Randomized Clinical Trials (RCTs) published between 2002 and 2017. Suitable individual studies were evaluated through a quality system, and the data were extracted and analyzed. Fourteen RTCs were included (12 parallel trials and 2 cross-over trials), published in the English and Turkish languages. Follow-up periods ranged from 4, 6, 8, 24, and 48 hr. All trials measured the outcome result as Acute Pain Level (APL) (VAS, NRS, VRS), time to requiring a second dose of DEX or analgesic emergency and consumption of opioids via patient-controlled analgesia. When the comparators were other drugs - paracetamol, Lornoxicam or placebo during the preoperative time, preoperative administration of DEX was superior. When the comparison comprised preoperative and postoperative DEX, both alternatives exhibited comparable analgesic effects. The analgesic efficacy of the preoperative administration of DEX when compared to placebo, lornoxicam, and paracetamol on postoperative pain was evident. Preoperative administration of DEX compared to its immediate postoperative administration showed a similar analgesic effect.

KEYWORDS

acute pain, analgesic, NSAIDs, pain management, postoperative pain

1 | INTRODUCTION

Dexketoprofen trometamol (DEX) is a Non-Steroidal Anti-Inflammatory Drug (NSAID). It is an arylpropionic acid derivative, the S (+) enantiomer of ketoprofen that is considered to be a powerful inhibitor of prostaglandin synthesis in vitro (Barbanoj, Antonijoan, & Gich, 2001). The use of a single isomer of ketoprofen simplifies the pharmacokinetics of the drug and allows a reduction of 50% in its effective dose (Burke & Bannister, 2003; Rodríguez, Arbós, & Amaro, 2008). Its maximal concentration can be reached after 30 min, showing rapid absorption, gastric protection, and an acceptable safety profile (Mauleón, Artigas, García, & Carganico, 1996; Sweetman, 2003). DEX presents effective potency at lower doses, with acceptable tolerability and without serious adverse events (Gaskell, Derry, Wiffen, & Ra, 2017).

Surgical procedures are often followed by physiological processes of acute inflammation that lead to postoperative pain. Acute postoperative pain continues to be undermanaged in different surgical scenarios

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(Gregory & McGowan, 2016; Polanco-García, García-Lopez, Fábregas, Meissner, & Puig, 2017) while effective postoperative pain management increases patient satisfaction, improves patient outcomes, and reduces care costs (Michel & Sanders, 2003). Different strategies are utilized to control postoperative acute pain (Elvir-Lazo & White, 2010; Hartrick, 2004; Ramsay, 2000). Preoperative administration of NSAID represents a "seductive alternative" (e.g., preemptive or preventive analgesia), due to its potential effect to diminish the risk of central sensitization and postoperative pain, to decrease the intake of postoperative analgesics, and to improve the local anesthetic blockade and acceptance by patients (Chavarria-Bolaños & Esparza-Villalpando, 2017).

Preclinical and clinical studies suggest that the use of different preoperative analgesic medications can be effective in inhibiting hypersensitization of nociceptors and, consequently, postoperative pain (Costa et al., 2015; Katz, Clarke, & Seltzer, 2011). However, there is still controversy regarding methodological aspects of the published clinical trials available, leading to confusion or misinterpretation (Brennan & Kehlet, 2005; Dahl & Møiniche, 2004; Møiniche, Kehlet, & Dahl, 2002; Yamaguchi & Sano, 2013). The aim of the present study was to evaluate the effectiveness of the preoperative administration of DEX under postoperative pain conditions via a systematic review and meta-analysis.

2 | METHODS

This systematic review and meta-analysis was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) principles used by Liberati et al. (2009), the Cochrane Group fundamentals, and the recommendations of Higgins and Green (2011).

2.1 | Selection criteria

Articles reporting on the clinical efficacy of the analgesic effect of preoperative (preemptive/preventive) analgesia under postoperative pain conditions were considered as eligible (including Randomized Clinical Trials [RCTs], parallel groups, or cross-over or split-mouth designs (Pandis, Walsh, Polychronopoulou, Katsaros, & Eliades, 2013). Observational prospective or retrospective studies, narrative literature reviews, case reports (or case series), in vitro or animal studies, abstracts, and unpublished data were excluded. Intervention, control, and outcome parameters were selected in accordance with the Population, Interventions, Control, and Outcome (PICO) question:

Population: Postoperative pain conditions.

Interventions: Preoperative administration of DEX

Control: Placebo/other analgesics and postoperative DEX.

Outcome: Effectiveness of pain relief (VAS, NRS, VE, and others).

2.2 | Literature-search strategy and data extraction

The electronic literature search of relevant references was made between July 2016 and June 2017 in electronic databases, without language or publication-date restrictions. MEDLINE (via PubMed), Cochrane Library, EMBASE (Elsevier Science), Google Scholar, SCOPUS, Web of Science, ScienceDirect, EBSCOhost, Wiley Online Library, OVID, Springer, Latin Index, and SCIELO were analyzed. The search algorithm was: (("Preemptive Analgesia"/"Preventive Analgesia"/"Preoperative Analgesia" AND "Dexketoprofen Trometamol" [Mesh]). In addition, the authors hand-searched international peer-reviewed pain and surgery journals.

The authors' names, titles, abstracts, keywords, design, and evaluation length of each reference recovered following the inclusion criteria were objectively and independently screened by two blinded and qualified authors/reviewers (DC-B and VE-V); any difference between these authors was resolved by discussion and consensus, or with the involvement of a third reviewer (AP-G). Selected studies were retrieved as full-text papers and later re-screened in detail by these same reviewers to confirm whether the studies met the inclusion criteria.

Data were extracted independently by the other reviewers (CG-F and DM-I) from the selected papers and pooled on a data extraction sheet (Liberati et al., 2009). If the reviewers had any data-related questions or needed additional information, the authors of the articles were contacted. If one of the reviewers was the author of a publication, the assessment was carried out by a third reviewer, in order to avoid any potential conflict of interest.

2.3 | Quality appraisal

The methodological quality and validity of the included studies were independently assessed by two blinded reviewers using Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Atkins et al., 2004) and Oxford Centre for Evidence-Based Medicine (OCEMB) (Howick et al., 2011) criteria, employing the table reported by Pozos-Guillen, Garcia-Flores, Esparza-Villalpando, and Garrocho-Rangel (2016), both considered suitable for reducing potential biases in terms of quality of RCTs (Pozos-Guillen et al., 2016; Urrútia & Bonfill, 2010). The reviewers scored each scale section based on their judgment and knowledge, in order to determine the weight of the respective section in terms of the final results and conclusions of each individual study. The maximal value was 16; this value was correlated to the quality of the study, but the individual point was assessed for each study (Table 1). If necessary, the corresponding authors of the paper were contacted to obtain additional information on unclear or missing data– e.g., numerical data that were only presented graphically–, which were considered significant by the reviewers, for the purpose of carrying out the meta-analysis.

2.4 | Meta-analysis (quantitative synthesis)

Meta-analysis was performed for the studies considered methodologically homogeneous, which was verified heterogeneity by the Q test and I^2 (Viechtbauer, 2014). Then, an estimated overall-effect size of the

TABLE 1 Quality appraisal

Study	RTC design	Sample calculation 1 = unspecified/ pilot study, 2 = Present.	Randomization 0 = Not present, 1 = Not clear, 2 = Present (homogeneous groups).	Randomization (method) 0 = unsuitable/ not described, 1 = adequate.	Blinding 0 = Not described, 1 = Not clear/ inappropriate, 2 = present and described.	Follow-up 0 = incomplete, 1 = intention to treat/ other methodsof analysis, 2 = full	Response variable 0 = qualitative subjective, 1 = qualitative objective, 2 = quantitative	Concordance of measuring method 0 = Not present, 1 = Not clear, 2 = present/ testing laboratory	Assumptions of the statistical test 0 = Not present, 1 = Not clear/ categorical data, 2 = present and described	Results 0 = incomplete, 1 = complete	Total
Iohom et al. (2002)	P	2	2	0	0	1	2	1	0	1	9
Gülhaş et al. (2011)	P	1	2	1	2	2	2	1	0	1	12
Kara et al. (2011)	P	1	2	0	2	2	2	1	0	1	11
Kesimci et al. (2011)	P	1	2	1	2	2	2	1	2	0	13
Sagiroglu (2011)	P	1	2	0	0	2	2	1	0	1	9
Atalay et al. (2012)	P	2	1	0	1	2	2	1	0	0	9
Ozer et al. (2012)	P	1	2	1	2	2	2	1	0	1	12
Bolat et al. (2013)	P	1	1	1	0	2	2	1	0	0	8
Kadıoğlu et al. (2013)	P	2	2	1	2	2	2	1	1	0	13
Çağiran et al. (2014)	CO	1	2	0	1	2	2	1	0	0	9
Eroglu et al (2014)	CO	1	2	1	0	1	2	1	0	1	9
Kelsaka et al. (2014)	P	2	2	0	1	2	2	1	1	1	12
Esparza-Villalpando et al. (2016)	P	2	2	1	2	2	2	1	1	1	14
Gelir (2016)	P	1	2	1	2	2	2	1	0	1	12

P (Parallel), CO (Crossover).

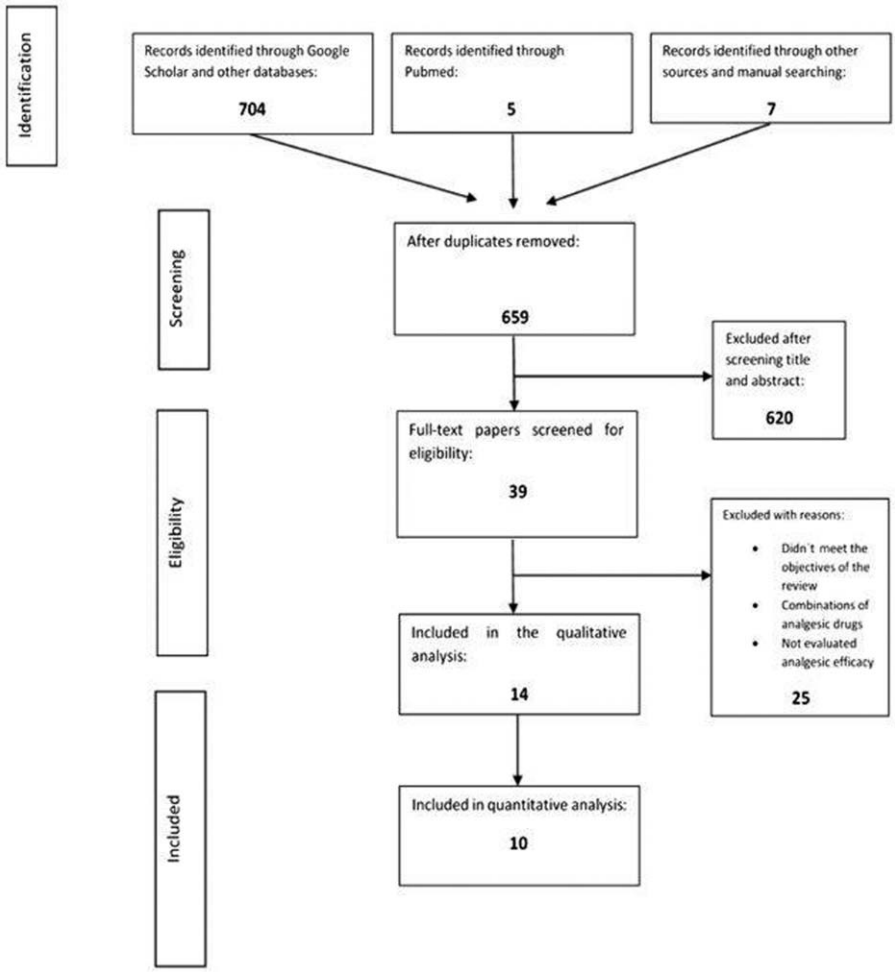

FIGURE 1 Search strategy flowchart

papers included in the analysis was obtained. Summary measures (means and standard deviations [SD]) were extracted from the results expressed as continuous data in the study groups. The standardized mean difference was chosen as the estimate point with its 95% Confidence Interval (95% CI), calculated from a restricted maximum likelihood model. A significant difference was assumed (null hypothesis rejected) if the lower limit of the 95% CI with regard to the pool estimate was greater than zero. A size effect of the averaged outcomes for each individual study was graphically presented in a forest plot. Statistical software R ver. 3.3.1 and R packages META and METAFOR were used, with the alpha value established set at 0.05.

3 | RESULTS

3.1 | Literature findings

The search of the literature was performed between July 2016 and June 2017. The electronic databases and journal handmade searches identified a total of 716 potential citations. The selection of final references was carried out as described in Figure 1. After eliminating duplicates or supplementary reports ($n = 57$) and articles with titles and abstracts not complying with inclusion criteria ($n = 620$), the full-text of the remaining 39 citations was retrieved and screened in more detail, and assessed for eligibility. Finally, 14 relevant studies were identified for inclusion in the systematic review, and 12 in the meta-analysis.

3.2 | Characteristics of included studies

Table 2 summarizes the characteristics of the included articles. The 14 studies were RTC (12 parallel trials and 2 cross-over trials), published in the English and Turkish languages between 2002 and 2017. Follow-up periods ranged from 4, 6, 8, 24, and 48 hr. All trials measured outcome result as Acute Pain Level (APL) (VAS, NRS, VRS), time for requiring a second dose of DEX or analgesic emergency and consumption of opioids via Patient-Controlled Analgesia (PCA). However, some trials did not report complete information on the outcome measurements (Table 2). The studies were divided into two categories for qualitative and quantitative syntheses:

- **Category A** ($n = 11$): DEX was compared with a different drug or placebo at the same time (comparison between preoperative administration of DEX vs. preoperative administration of a different drug or placebo).

TABLE 2 Characteristic of the included trials

Study	RTC design (Type)	Surgical condition	Administered via/time of administration	Subjects	Experimental groups		N	Response variables	
Iohom et al. (2002)	P (A)	Elective arthroplasty	Oral T1 = 24 hr before/ 48 hr after surgery	30 patients ASA I-II (47–70 years)	T1= Placebo		14	Morphine total consumption (mg) Time second dose (min)	VAS (mm)
					T1= 25 mg DXTP		15		
Gülhaş et al. (2011)	P (A)	Hysterectomy	IV. T1 = 30 min before surgery	120 patients ASA I-II (18–85 years)	T1= Placebo		30	Fentanyl total consumption (mg)	VAS (mm)
					T1= 50 mg DXTP		30		
					T1= 8 mg LORXM		30		
					T1= 1 g PCTMOL		30		
Kara et al. (2011)	P (A)	Plastic surgery	Oral T1 = 1 hr before surgery	50 patients ASA I-II (33.8 mean years)	T1= Placebo		25	Tramadol total consumption	VAS (mm)
					T1= 25 mg DXTP		25		
Kesimci et al. (2011)	P (A)	Lumbar disc surgery	Oral T=1 30 min before surgery	75 patients ASA I-II (18–65 years)	T1= Placebo		25	Morphine total consumption (mg)	
					T1= 25 mg DXTP		25		
					T1= 500 mg PCTMOL		25		
Sagiroglu (2011)	P (A)	Mediastino-scopy	IV. T1 = 20 min before surgery	40 patients ASA I-II (22–52 years)	T1= 8 mg LORXM		20	VAS (mm)	
					T1= 25 mg DXTP		20		
Atalay et al. (2012)	P (A)	Abdominal Hysterect-omy	IV. T1 = 30 min before surgery	40 patients ASA I-II (55 mean years)	T1= Placebo		20	Fentanyl totalconsumption (mg)	
					T1= Placebo		20		
Ozer et al. (2012)	P (B)	Septum Rhinoplasty	IV. T1 = 30 min before surgery. T2 = 30 min before surgery completion	120 patients ASA I-II (27 mean years)	T1= Placebo	T2 = Placebo	25	Tramadol total consumption (mg)	VAS (mm)
					T1= 50 mg DXTP	T2 = Placebo	25		
					T1= Placebo	T2 = 50 mg DXTP	25		
					T1= 25 mg DXTP	T2 = 25 mg DXTP	25		

(Continues)

TABLE 2 (Continued)

Study	RTC design (Type)	Surgical condition	Administered via/time of administration	Subjects	Experimental groups		N	Response variables	
Bolat et al. (2013)	P (A)	Varicocelect-omy/Sperm extraction	IV. T1 = Before anesthetic induction	60 patients ASA I-II (18–65 years)	T1= Placebo		30	Time Second dose (min)	
					T1= 50 mg DXTP		30		
Kadıoğlu et al. (2013)	P (B)	Laparotomy	IV. T1 = 30 min before surgery T2 = 30 min before surgery completion	90 patients ASA I-II (20–70 years)	T1 = 50 mg DXTP	T2 = Placebo	30	N/A	
					T1 = Placebo	T2 = 50 mg DXTP	30		
					T1 = Placebo	T2 = Placebo	30		
Çağiran et al. (2014)	CO (A)	Third Molar Surgery	IV. T1 = 15 min before surgery	20 patients ASA I-II (18–35 years)	T1 = Placebo		20	N/A	
					T1= 50 mg DXTP		20		
Eroglu et al. (2014)	CO (A)	Third Molar Surgery	Oral. T1 = 1 hr before surgery	21 patients ASA I (18–35 years)	T1= 12.5 mg DXTP		15	VAS (mm)	
					T1 = 500 mg PCTMOL		15		
Kelsaka et al. (2014)	P (A)	Laminectomy	IV. T1 = 10 min before surgery	50 patients ASA I-II (18–70 years)	T1= Placebo		25	VAS (mm)	
					T1= 50 mg DXTP		25		
Esparza-Villalpando et al. (2016)	P (B)	Third Molar Surgery	Oral T1 = 30 min before surgery T2 = Immediately after surgery	60 patients ASA I (18–30 years)	T1= 25 mg DXKT T2 = Placebo		30	Time second dose (min)	NRS (mm)
					T1= Placebo T2 = 25 mg DXKT		30		
Gelir (2016)	P (A)	Hysterectomy	IV. T1 = 30 min before surgery	50 patients ASA I-II (18–60 years)	T1= Placebo		25	Time second dose (min)	VAS (mm)
					T1= 50 mg DXTP		25		

Type of the article.
(A) Preoperative administration of dexketoprofen vs the preoperative administration of other drug or placebo.
(B) Preoperative administration of dexketoprofen vs the posoperative administration of dexketoprofen.
Time of the operatory administration:.
(T1) Preoperative.
(T2) Postoperative.
DEX (Dexketoprofen Trometamol), PCTMOL (Paracetamol), LORXM (Lornoxicam), P (Parallel), CO (Crossover).

- **Category B** ($n = 3$): When the difference was the time of administration and only DEX was used (comparison between the preoperative administration of DEX vs. postoperative administration of the same drug).

For studies categorized as B, where two different times are considered, both Times (T) were sub-classified: T1 (with administration of DEX, different drug, or placebo was administered prior to the surgical procedure, meaning preoperatively), and T2 (when the administration of DEX, a different drug, or placebo was administered after the surgical procedure (meaning standard postoperative administration).

The surgical protocol and the administration routes were different between the studies. Five studies evaluated oral administration (p.o.) of DEX (Eroglu, Durmus, & Kiresi, 2014; Esparza-Villalpando et al., 2016; Iohom, Walsh, Higgins, & Shorten, 2002; Kara, Tuncer, Erol, & Reisli, 2011; Kesimci, Gümüs, & Kanbak, 2011), while the other studies employed intravenous (i.v.) administration (Atalay, Dogan, & Kizilkaya, 2012; Bolat, Erhan, & Deniz, 2013; Çağiran, Eyigör, & Sezer, 2014; Gelir, 2016; Gülhaş et al., 2011; Kadıoğlu, Tüker, Gurbet, Demirci, & Hülagü, 2013; Kelsaka, Guldogus, & Cetinoglu, 2014; Sagiroglu, 2011; Ozer et al., 2012). Eight studies utilized DEX 50 mg (Atalay et al., 2012; Bolat et al., 2013; Çağiran et al., 2014; Gelir, 2016; Gülhaş et al., 2011; Kadıoğlu et al., 2013; Kelsaka et al., 2014; Ozer et al., 2012), while the remaining studies evaluated DEX 25 mg (Esparza-Villalpando et al., 2016; Iohom et al., 2002; Kara et al., 2011; Kesimci et al., 2011; Ozer et al., 2012; Sagiroglu, 2011). Only one study (Eroglu et al., 2014) evaluated 12.5 mg DEX. In category A, the comparator drug included placebo, paracetamol, and lornoxicam (Table 2), independently of the route of administration or the surgical procedure, the main goal of this systematic review was the effectiveness comparison between preoperative administrations of DEX vs postoperative administration of DEX.

4 | QUALITATIVE SYNTHESIS

4.1 | Category A studies

4.1.1 | Comparison of DEX vs. Placebo

Nine articles reported this comparison (Atalay et al.,2012; Bolat et al., 2013; Çağiran et al., 2014; Gelir, 2016; Gülhaş et al., 2011; Iohom et al., 2002; Kara et al., 2011; Kesimci et al., 2011; Kelsaka et al., 2014). Age of the patients included in these studies ranged from 18 to 85 years. The pain models evaluated in this comparison are described in Table 2. Eight studies reported lower opioid consumption and postoperative pain, as well as a longer time requiring a second dose of the drug, favoring preoperative administration of DEX. One study (Bolat et al., 2013) reported no difference in the same comparison previously described. However, this study did not report the total data of the study. The mean of the quality appraisal of this comparison was 10.56 ± 1.81 (Table 1).

4.1.2 | Comparison of DEX vs. Paracetamol

Three studies reported this comparison (Eroglu et al., 2014; Gülhaş et al., 2011; Kesimci et al., 2011). The age range was 18–85 years. The pain models employed in this comparison are presented in Table 2. Two articles reported lower opioid consumption and postoperative pain, favoring preoperative administration of DEX. These studies evaluated a 500-mg dose of paracetamol. Only one article (Gülhaş et al., 2011) reported no difference in the comparison previously described. In this study, 1 g of paracetamol was compared with 50 mg of DEX on hysterectomy postoperative pain. The mean quality appraisal of this comparison was 10.75 ± 2.06 (Table 1).

4.1.3 | Comparison of DEX vs. Lornoxicam

Two studies reported this comparison (Gülhaş et al., 2011; Sagiroglu, 2011). These articles reported opposite results. Gülhaş et al. (2011) reported lower opioid consumption and postoperative pain, favoring preoperative Lornoxicam. On the other hand, Sagiroglu (2011) reported lower postoperative pain favoring preoperative administration of DEX. The mean quality appraisal of this comparison was 10.5 ± 2.12 (Table 1).

4.2 | Category B studies

4.2.1 | Comparison of preoperative DEX preoperative vs. postoperative DEX

Three articles reported this comparison (Esparza-Villalpando et al., 2016; Kadıoğlu et al., 2013; Ozer et al., 2012). All of the T1 times in the studies were 30 min prior to the surgical procedure, while T2 times differed. Two studies reported postoperative i.v. administration of DEX 30 min prior to complete suturing, and one (Esparza-Villalpando et al., 2016) reported p.o. administration of DEX immediately after surgery. The range of age was 18–70 years. All studies reported no significant difference in postoperative pain level, nor in opioid consumption. Ozer et al. (2012) did not report differences between groups. On the other hand, Kadıoğlu et al. (2013) reported lower consumption on preoperative administration of DEX. The mean quality appraisal of this comparison was 13 ± 1 (see Table 1).

5 | QUANTITATIVE SYNTHESIS

5.1 | Meta-analysis of preoperative DEX vs. Other drugs preoperatively

Two meta-analyses were conducted for the studies categorized as A. The comparators were preoperative administration of DEX vs. preoperative administration of the other drugs (placebo, paracetamol, and lornoxicam: (Eroglu et al., 2014; Gelir 2016; Gülhaş et al., 2011; Iohom et al., 2002; Kara et al., 2011; Kelsaka et al., 2014, which exhibited sufficient raw data, and possible outcomes were included. Due to the studies having different evaluation times, an evaluation period was assumed to be 6–8 hr in the same analysis. These combined studies (Figure 2) did not demonstrate significant heterogeneity ($Q = 2.59$; degrees of freedom (df) $= 7$; $p = .9199$), according to the restricted maximum likelihood model. Estimators for both models were the same: the SMD estimator was -0.7283 (95% CI $= -0.9341$; -0.5224), with a z-statistic of -6.93 and a p value of $<.0001$. The tests exhibited significant differences in favor of preoperative administration of DEX

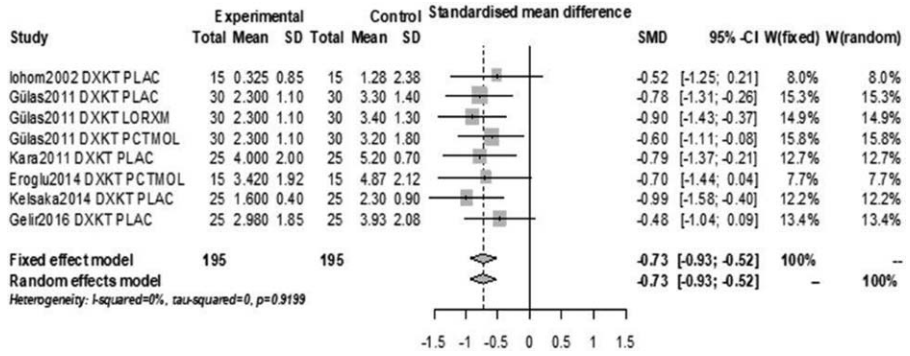

FIGURE 2 Forest plot: preoperative DEX vs. preoperative administration of other drugs

when compared with the other drugs or placebo, showing lower levels of postoperative pain in different types of surgical procedures.

5.2 | Meta-analysis of preoperative DEX vs. Postoperative DEX

Category B studies were involved in the second comparison. The studies considered in this comparison were Ozer et al. (2012) and Esparza-Villalpando et al. (2016), which exhibited sufficient raw data, and possible outcomes were included. Because the studies had different evaluation times, an evaluation period of 6–8 hr was assumed in the same analysis. These combined studies (Figure 3) did not demonstrate significant heterogeneity ($Q = 1.99$; $df = 3$; $p = .5739$), according to the restricted maximum likelihood model. The estimators for both models were the same: the estimator of SMD was −0.0739 (95% CI = −0.3389; 0.1911), with a z-statistic of −0.55 and a p value of .5846. The test analysis proved no-significant differences between preoperative administration of DEX and postoperative administration of DEX, both regimens exhibiting the same levels of postoperative pain in different types of surgical procedures.

6 | DISCUSSION

The present systematic review and meta-analysis focused on the efficacy of preoperative administration of DEX in a variety of surgical procedures. "Preemptive" or "preventive" protocols were defined in terms of time of the administration of the drug. According to these definitions and adjusting in terms of the evidence available, preoperative DEX was compared with two possible scenarios as follows: preoperative use of a different molecule (drugs or placebo treatment) or postoperative administration of the same DEX. Independently of the multiple pain conditions, designs, surgical approaches, and dosage regimens, the superiority of DEX over the control and other drug groups was demonstrated.

When the comparator was paracetamol, lornoxicam, or placebo, an increased effect was recognized. Interestingly, three different groups of compounds were included (from an inactive control, to a weak analgesic without anti-inflammatory properties, to another NSAID), diminishing the possibility of bias and not favoring DEX. The efficacy of preoperative administration of DEX can be a direct or indirect consequence of different conditions, where the potency and pharmacodynamic profile of DEX may play a key role (Burke & Bannister, 2003; Hanna et al., 2003; Moore & Barden, 2008; Moore et al., 2015). Such particular response supports the overall results derived from this meta-analysis. However, these studies only demonstrate the effect of DEX against these drugs when used preoperatively, but the timing effect cannot be demonstrated under these designs.

When the comparator was the same drug (DEX) before and after the surgery, the superiority of preoperative administration of DEX was not established. However, caution must be exercised not to diminish the effectiveness of this drug, but to understand that its analgesic effect is not favored nor affected by the timing regimen. In other words, by isolating some of the variables previously identified, administration time was the only factor evaluated, demonstrating no significant impact on the clinical pain outcome. However, the studies included in this comparison reported a slight tendency favoring preoperative

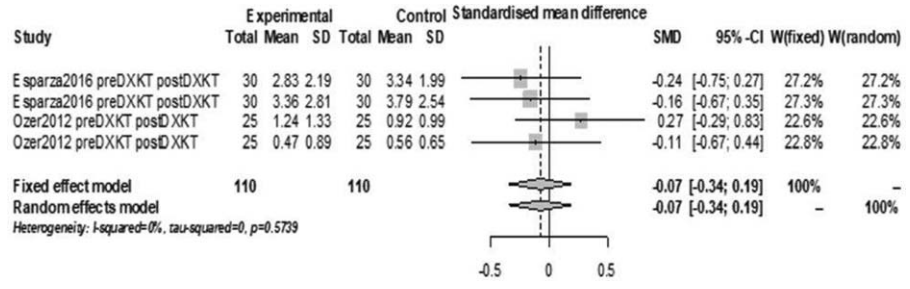

FIGURE 3 Forest plot: preoperative DEX vs. postoperative DEX

administration, which revealed lower pain intensity. New RCTs designed to evaluate specifically the timing effect may contribute to the confirmation of this observation.

The preoperative administration of analgesic drugs under postoperative pain conditions is related with the terms "preemptive" or "preventive". Ong, Lirk, Seymour, and Jenkins, (2005) reported a possible efficacy of preemptive analgesia in selected regimens, a conclusion explained by evidence that included a range of study designs, response variables, and different types of drug. However, the conclusion of this review derived from a different approach that was not exclusive to preemptive intervention, but to the broad preventive philosophy (Ong et al., 2005). Sáez takes preemptive and preventive analgesia as a single term, creating a confusing mixture of designs and approaches that lead to inconclusive data (Sáez, 2012). Especially when the purpose is to collect different information (i.e., performance of meta-analysis), the clear classification of data and results is mandatory. In the same field, Yamaguchi and Sano (2013) suggest the effectiveness of preemptive analgesia in third-molar surgery, reporting promising conclusive results derived from mixed unclassified studies. Similar findings were reported by Penprase, Brunetto, Dahmani, Forthoffer, and Kapoor (2015) who concluded a positive effect of the preemptive use of NSAIDs. Again, preemptive and preventive designs were not classified, thus, the timing variable was not demonstrated (Penprase et al., 2015). Costa et al. (2015) concluded that preemptive analgesia did not exert a significant effect in reducing postoperative pain after removal of lower impacted third molars, but the results were derived from a placebo comparison thus precluding the evaluation of preemptive efficacy (Costa et al., 2015).

It is important to recognize the difference among study designs in promoting a high quality of evidence (Schulz, Altman, Moher, & Group, 2010), in order to elucidate the real benefit expected from analgesic administration. Even when preoperative administration of DEX showed benefits in terms of reduction of postoperative pain (independently of the design, type of surgery, or administration route), the limitations derived from the individual studies must be recognized to avoid overestimation of this conclusion.

To obtain a greater understanding and confirmation of preoperative DEX in surgical treatment, access to information derived from well-designed RCTs with a wider variety of compounds tested (i.e., dual analgesics, opioids, or more potent NSAIDs) will help to fill possible knowledge voids. Finally, new RCTs with larger and heterogeneous populations will confirm whether the effects reported continue to be in the same direction.

The analgesic efficacy of preoperative administration of DEX when compared to placebo, lornoxicam, and paracetamol on postoperative pain was evident, and preoperative administration of DEX compared to postoperative administration of the same drug exhibits the same analgesic effect.

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CONFLICT OF INTEREST

All authors declare no competing interests.

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