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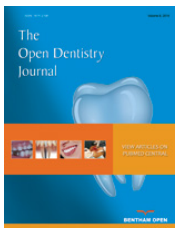

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SYSTEMATIC REVIEW

The Safety and Efficacy of Pre- and Post-Medication for Postoperative Endodontic Pain: A Systematic Review and Network Meta-analysis

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Abstract:

Background:

Postoperative Endodontic Pain is a major concern for dentists and their patients, with pain having been reported to occur in 25%–40% of patients treated. Therefore, the aim of this systematic review and Network Meta-analysis (NMA) was to identify the safety and efficacy of pre- and post-medication for reducing postoperative endodontic pain.

Methods:

A literature search was performed in the SCOPUS, MEDLINE, and ScienceDirect, and Cochrane Central databases until December 2019 with no language restriction. Randomized controlled trials evaluating the efficacy of pre- or post-medications compared with other agents, placebo, or no treatment in adult patients who underwent endodontic surgery for postoperative pain were included. The mean difference of postoperative pain was measured using the Standardized Mean Difference (SMD) with its 95% confidence interval (95% CI).

Results:

This Systematic Review included 62 Articles. Of them, 50 studies were included in the NMA. Among all medications, corticosteroids were ranked as the best treatment for the reduction of postoperative pain at 6 and 12 hours with a significant reduction in postoperative pain scores [SMD= -1.18, 95% CI (-1.51: -0.85)] and [SMD= -1.39, 95% CI (-1.77: -1.02)], respectively. Cyclooxygenase-2 (COX-2) inhibitors were ranked as the best treatment for the reduction of postoperative pain at 8 and 24 hours with a significant reduction in postoperative pain scores [SMD= -2.86, 95% CI (-6.05: -1.66)] and [SMD= -1.27, 95% CI (-2.10: -0.43)], respectively. Non-steroidal anti-inflammatory drugs (NSAIDs) significantly reduced the postoperative pain scores in all durations. For postoperative pain at 6 hours, Indomethacin, Novafen, Naproxen, Prednisolone, Ketorolac, Betamethasone, Dexamethasone, Deflazacort, Rofecoxib, Piroxicam, and Ibuprofen significantly reduced the pain score when compared with a placebo. All of these drugs demonstrated a significant reduction at 12 hours except Ketorolac.

Conclusion:

The current evidence suggests that pre- and post-medication can reduce postoperative pain after nonsurgical root canal treatment. Corticosteroids and COX-2 inhibitors showed significant control of the pain up to 12 hours after administration. However, NSAIDs demonstrated a high efficacy from administration and until two days after treatment. Indomethacin, Novafen, prednisolone, and Naproxen were ranked first in most analyzed durations.

Keywords: Non-steroidal anti-inflammatory drugs, Corticosteroids, Opioids, COX-2 inhibitors, Postendodontic pain, Premedication.

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1. INTRODUCTION

Postoperative pain during root canal therapy is a major undesirable complication for dentists and their patients. Anxiety and fear of pain during root canal treatment are the main reasons that prevent patients from attending dental offices [1]. It was estimated that the prevalence of post-endodontic pain ranges from 3% to 58% [2 - 4]. This condition is linked with the exacerbation of inflammatory response and the activation of inflammatory mediators such as prostaglandins, which cause the periapical activation of sensitive nociceptors [5]. Preoperative and procedural factors such as intracanal medicaments, mechanical instrumentation, microbial effects, and chemical irritants may cause periradicular tissue injury, which in turn causes post-endodontic pain [5, 6]. Endodontic treatment consists of restoring the form and function of teeth and controlling symptoms that address the primary concern of the patient as well as long-term possible complications, such as chronic pain [7]. Therefore, it is highly important to manage discomfort during and after root canal treatment.

In this regard, many drugs have been used to relieve post-endodontic pain, such as Non-steroidal Anti-inflammatory Drugs (NSAIDs), corticosteroids, opioids, cyclooxygenase-2 enzymes (COX-2) inhibitors, and combinations of drugs [8]. Today, the most common types of pharmacological agents prescribed for pain relief in dentistry are NSAIDs and paracetamol (acetaminophen) [9]. NSAIDs decrease inflammation, inhibit cyclooxygenase enzymes, and prevent new prostaglandin molecules, but have no effect on circulating molecules [10]. Moreover, corticosteroids have demonstrated significant efficacy in dentistry pain management [11]. Many randomized control trials were conducted to evaluate the efficacy of various oral pre- and post-medications such as prednisolone [12], ibuprofen [13], lornoxicam [14], indomethacin [15], gabapentin [14], and celecoxib [16]. They reported that premedication is effective for postoperative pain after nonsurgical root canal treatment. However, the best pain-reducing agent is yet to be identified, as these drugs were not to be ranked regarding their efficacy. A recent network meta-analysis was conducted by Nagendrababu and his colleagues, who aimed to identify the most effective oral premedication in reducing pain in adults after nonsurgical root canal therapy [17]. Nevertheless, their study failed to include all available evidence, which eventually affected their conclusion. In this systematic review and network meta-analysis, we aimed to summarize current evidence on the efficacy of pre- and post-medication for the treatment of postoperative endodontic pain and rank the available drugs according to their efficacy.

2. METHODS

This systematic review and network meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for Network Meta-analyses of Health Care Interventions [18].

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2.1. Search Strategy

A computerized search of Medline *via* PubMed, the Cochrane Library, Scopus, and Science direct was conducted using the following keywords “endodontic”, “root canal treatment”, “root canal therapy”, “NSAIDs”, “Non-Steroidal Anti Inflammatory Drugs”, “analgesics”, “paracetamol”, “Steroids”, “corticosteroids”, “Opioid”, “narcotic”, and “postoperative pain”. There was no language or publication date restriction. Additionally, the references of the retrieved trial were hand searched for further relevant articles.

2.2. Inclusion and Exclusion Criteria

We included studies that were eligible according to the following criteria:

(1) Population: studies that enrolled patients who presented with endodontic pain and received a diagnosis of pulpal pathosis necessitating initial nonsurgical endodontic treatment.

(2) Intervention: studies that used oral, intramuscular, supraperiosteal, intraligamentary injection, intracanal or systemic use of NSAIDs, corticosteroids, COX-2 inhibitors, or opioids.

(3) Comparison: placebo-controlled studies.

(4) Outcome: Management of postoperative pain assessed by Visual Analogue Scale (VAS).

(5) Study design: Randomized control trials.

Literature reviews, Opinion papers, systematic reviews, case reports, animal studies, preclinical studies, and clinical guidelines were excluded.

2.3. Study Selection

Eligibility screening was conducted in two steps, each by two independent reviewers: a) title and abstract screening for matching the inclusion criteria, and b) full-text screening for eligibility to meta-analysis. Disagreements were resolved upon the opinion of a third reviewer.

2.4. Data Extraction

Relevant data were abstracted using a standardized extraction form. The form consisted of

(1) Study characteristics (name of the first author, year, country, intervention groups, study sample size, and main findings),

(2) Participant characteristics (age, sex, and VAS score),

(3) Types of intervention and comparator(s) (*i.e.*, drugs NSAIDs, COX-2, Opioids, and corticosteroids) and dosage,

(4) Outcome measures (*i.e.*, the primary outcome: pain scores at different time intervals; immediately after treatment, 6, 8, 12, 24, and 48 hours). Missing information was obtained by contacting the authors of the study. When the means and standard deviations were not mentioned in the text of the published study, values were extracted from the graphs using WebPlotDigitizer (Ankit Rohatgi, Austin, TX, https://automeris.io/WebPlotDigitizer/).

All extracted data were cross-checked by two reviewers, and discrepancies were resolved by consensus.

2.5. Risk of Bias Assessment

The revised Cochrane Collaboration's risk of Bias Assessment Tool (ROB) was used to assess the risk of bias among the included studies [19]. Studies were evaluated for bias and categorized as having low, unknown, or a high risk of bias. The overall quality of the study was based on the 5 domains evaluated for bias: randomization, deviation from intended interventions, missing outcome data, outcome measurement, and selection of results. The overall score was low bias when all five domains were scored as low bias. The presence of at least two concerns in one of the domains rendered the study as having some concerns in bias. A study was evaluated as having high bias when at least one domain was scored to have high bias.

2.6. Data Synthesis and Statistical Analysis

The Standardized Mean Differences (SMD) in postoperative pain scores were calculated as the summary measures in MA. We chose SMD because changes in pain intensity scores were reported by different scales in trials, and the SMD can compare pain intensity scores in a uniform manner. In the case where variance data were not reported as standard deviation, it was estimated with algebraic recalculations or various approximation methods. Means and standard deviations were calculated from the reported medians, ranges, or Confidence Intervals (CIs) when not available. The presence of heterogeneity among the selected studies warranted the use of a random-effects model for the calculation of weighted Mean Differences (MDs) and 95% CIs in MA. The heterogeneity between trials was evaluated using I^2 statistics. Random effects NMA using a consistency model was applied to synthesize the available evidence by combining direct and indirect evidence from different studies.

The global inconsistency test using a fitting design-by-treatment model was used to identify the disagreement between the direct and indirect estimates as a measure of inconsistency. Frequentist method to rank treatments in network "netrank" function was used to rank the various interventions (the higher the P-score, the better the intervention). Moreover, the split direct and indirect evidence in network meta-analysis "netsplit" function was used. Publication bias was assessed using a comparison-adjusted funnel plot. All analyses were performed with R version 1.2.5019 (© 2009-2019 RStudio, Inc.) using the "netmeta" and "meta" packages for NMA [20].

3. RESULTS

3.1. Search Strategy Results

Our search retrieved 1512 unique citations. Following title and abstract screening, 107 full-text articles were retrieved and screened for eligibility. Of them, 45 articles were excluded, and 62 RCTs articles (n= 5412 patients) were included in the systematic review, and 50 articles were included in the final analysis. The flow diagram of study selection for our systematic review and meta-analysis is shown in PRISMA diagram (Fig. **1**). A summary of included studies and baseline characteristics of the populations is shown in Table **1**.

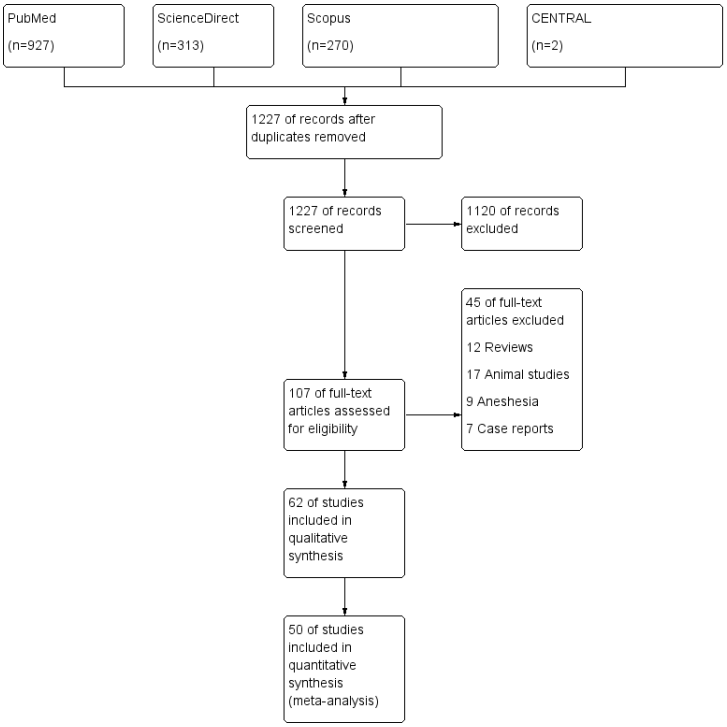

Fig. (1). PRISMA flow diagram.

Table 1. Summary of the included studies.

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Menke *et al.* [1]	1999	USA	14,22	>18	Etodolac	400 mg	12	0, 4, 8, 12, 24, 48, 72	100 mm	Prophylactic ibuprofen significantly reduced post-endodontic pain at four and eight hours after initiation of treatment, when compared to etodolac and a placebo
					Ibuprofen	600 mg	12			
					Placebo		12			
Gopikrishna and Parameswaran [2]	2003	India	29, 16	18–64	Ibuprofen	600 mg	15	4, 8, 12, 24, 48, 72	100 mm	Rofecoxib administration provides an effective reduction in post-endodontic pain
					Rofecoxib	50 mg	15			
					Placebo		15			
Attar *et al.* [3]	2008	USA	7, 7	44.9±4	Ibuprofen tablets	600 mg	15	0, 6, 12, 18, 24	100 mm	Single-dose pretreatment analgesia alone in endodontic pain patients did not significantly reduce postoperative pain below the level of reduction in pain from endodontic treatment of ibuprofen 600 mg and the placebo group
			7, 6	41.6±4.3	Ibuprofen liqui-gels	600 mg	15			
			9, 3	45.8±5.1	Placebo		15			
Saatchi *et al.* [4]	2009	Iran	NR	NR	Ibuprofen	400 mg	30	0, 2, 6, 10, 18, 36, 44, 54, 66, 72	0–10	Diclofenac sodium continuous-release single dose pre-treatment of root canals compared to ibuprofen can prolong pain relief after root canal treatment for a longer period of time.
					Diclofenac sodium	100 mg	30			
					Placebo		30			
Jalalzadeh *et al.* [5]	2010	Iran	14, 6	18–59	Prednisolone	30 mg	20	6, 12, 24	10 cm	Postendodontic pain was substantially reduced by preoperative administration of a single oral dose of prednisolone compared with placebo
			14, 6		Placebo		20			
Arslan *et al.* [6]	2011	Turkey	16, 32	18–52	Tenoxicam	20 mg	16	6, 12, 24, 48, 72	100 mm	A prophylactic single dose of 20 mg tenoxicam or 200 mg Ibuprofen administration before RCT provides effective reduction of post-operative pain at 6 h
					Ibuprofen	200 mg	16			
					Placebo		16			
Ashraf *et al.* [7]	2013	Iran	7, 7	18-57	celecoxib	400mg	15	4, 8, 12, 24, 48	170mm	Prophylactic Celecoxib is not recommended for post-endodontic pain reduction especially in cases with gastrointestinal (GI) problems
			8, 6		Placebo		15			
Atbaei *et al.* [8]	2010	Iran	36, 29	14-65	piroxicam	8mg	35	4, 8, 12, 24, 48	10mm	Piroxicam is highly effective for reducing post-endodontic pain in vital teeth with irreversible pulpitis during the first 48 h. It was found to be much more effective than a similar lidocaine injection in reducing postoperative endodontic pain
					Placebo		30			

(Table 1) contd.....

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Baradaran *et al.* [9]	2014	Iran	26, 19	20-45	ibuprofen	400mg	15	4, 6, 12, 24, 48, 72	10mm	Alprazolam may enhance the analgesic efficacy of ibuprofen in post-endodontic pain
					Ibuprofen+alprazolam	400mg+0.5mg	15			
					Placebo		15			
Douglas [10]	2004	Portugal	3,17	16-61	Rofecoxib	50mg	20	4,8,10,12,24	10mm	Single dose of COX-2 inhibitors maybe sufficient to prevent post-endodontic pain
			4,16		Diclofenac sodium	50mg	20			
			5,15		Placebo		20			
Ehsani *et al.* [11]	2012	Iran	NA	NA	NAC	400mg	20	6, 8, 12, 24	10mm	The prophylactic ibuprofen and NAC failed to clearly reflect their effect on cytokines levels in exudates of chronic periapical lesions. On the other hand, it seems that NAC can be a substitute for ibuprofen in the management of post endodontic pain
					Ibuprofen	400mg	20			
					NAC + Ibuprofen	400 + 200mg	20			
					placebo		20			
Elkhadem *et al.* [12]	2017	Egypt	78, 122	18-35	Prednisolone	40mg	200	6, 12, 24	100mm	A single dose of prednisolone was beneficial to control short-term post-obturation pain in patients with symptomatic irreversible pulpitis reducing pain incidence after 24 h by approximately 30% and postoperative analgesic intake by approximately 55%
			63, 137		placebo		200			
Flath *et al.* [13]	1987	USA	116, 4	20-80	Placebo		29	3, 7, 24	100mm	Endodontic treatment significantly reduced post-operative pain in preoperatively symptomatic patients. Doses of 100 or 200 mg of flurbiprofen resulted in minimal side effects
					Flurbiprofen	100mg	87			
Isik *et al.* [14]	2014	Turkey	7, 23	18-45	Gabapentin	600mg	30	4, 8, 12, 24	100mm	Prophylactic lornoxicam controlled post-endodontic treatment pain more effectively than did the placebo drugs, and gabapentin was more effective in controlling the pain than either lornoxicam or the placebo.
					lornoxicam	8mg	30			
					placebo		30			
Joshi *et al.* [15]	2016	India	11, 11	18-65	piroxicam	40mg	22	4, 8, 12, 24, 48	10 cm	Peroxicam group perceived less post-endodontic pain as compared to placebo at all the time intervals
			12, 10		Placebo		22			
Kaviani *et al.* [16]	2011	Iran	NA	15-45	Ketamine	10mg	18	24	10mm	A low dose of ketamine might be beneficial for enhancing the effect of local anesthetics
					Placebo		18			
Khorasani *et al.* [17]	2011	Iran	8, 8	25-50	ibuprofen	400mg	16	6, 12, 24, 48, 72	100mm	Prophylactic use of Ibuprofen and sulindac for reduction of post-endodontic pain is not suggested
			9, 7		sulindac	200mg	16			
			6, 10		placebo		16			

(Table 1) contd.....

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Mehrvarzfar *et al.* [18]	2016	Iran	9, 11	32+4.6	placebo		20	6, 12, 24	170mm	Pretreatment PDL injection of dexamethasone can significantly reduce the post-treatment endodontic pain in patients with symptomatic irreversible pulpitis.
			10, 10	26.1+9.8	lidocaine	0.2ml	20			
			8, 12	30.3+4.2	dexamethasone	8 mg	20			
Mehrvarzfar *et al.* [19]	2012	Iran	15, 9	31.4+10.7	placebo		24	6, 12, 24	10mm	A single oral dose of Naproxen, Novafen and Tramadol taken immediately after treatment reduced postoperative pain following pulpectomy and root canal preparation of teeth with irreversible pulpitis.
			13, 11	29.5+6.9	tramadol	100mg	24			
			11, 12	29.6+8.1	Novafen	325 mg of paracetamol, 200 mg ibuprofen and 40 mg caffeine anhydrous)	23			
			14, 10	28.4+7.6	naproxen	500mg	24			
Menhinick *et al.* [20]	2004	USA	8, 11	24-80	placebo		19	4, 8	100mm	The results demonstrate that the combination of ibuprofen with acetaminophen may be more effective than ibuprofen alone for the management of postoperative endodontic pain.
			6, 14	21-61	ibuprofen	600	20			
			2, 16	19-58	ibuprofen + paracetamol	600mg + 1000mg	18			
Mirzaie *et al.* [21]	2011	Iran	56, 34	18-65	Celecoxib	200mg	30	4, 8, 12, 24, 48	100 mm	Use of Gelofen or Celecoxib before treatment reduces post-endodontic pain. These drugs can be prescribed before initiation of treatment as effective agents for the reduction of post-endodontic pain.
					Gelofen	400mg	30			
					Placebo		30			
Mokhtari *et al.* [22]	2016	Turkey	9, 13	19-0	Ibuprofen	400mg	22	8, 12, 24	100mm	Premedication with ibuprofen and indomethacin can effectively control short term post-operative pain; the lower incidence of side effects and greater analgesic power of ibuprofen make it a superior choice.
			7, 15		Indomethacin	25mg	22			
			13, 9		Placebo		22			
Negm 1st group [23]	1989	Egypt	NA	16-71	Piroxicam	20mg	48	2, 4, 8	1 to 4	Piroxicam was more effective than diclofenac or the placebo. Diclofenac required a longer time to reach maximum effectiveness. Piroxicam's superiority was greater at the first and second days after the initial dose of medication was taken.
					Diclofenac sodium	50mg	52			
					Placebo		43			
Negm 2nd group [23]					Piroxicam	20mg	45			
					diclofenac sodium	50mg	40			
					placebo		40			

(Table 1) contd.....

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Negm 1st group [24]	1994	Egypt	NA	18-78	diclofenac	75mg	65^	2, 4, 8, 12	1 to 4	Post-endodontic pain occurred with less frequency when the teeth were treated with diclofenac, but diclofenac-treated and ketoprofen-treated cases were not significantly different in controlling post-endodontic pain. An increase in the number of patients who reported a complete absence of pain was recorded when hyaluronidase was added to the study medications. However, the difference between the medications and medication-hyaluronidase was not of statistical significance.
					diclofenac-hyaluronidase	75mg + 1500 iu	63^			
					Ketoprofen	100mg	60^			
					Ketoprofen-hyaluronidase	100mg + 1500 iu	70^			
					Placebo		58^			
					Placebo-hyaluronidase	1500 iu	51^			
Negm 2nd group [24]					diclofenac	75mg	73^			
					diclofenac-hyaluronidase	75mg + 1500 iu	70^			
					Ketoprofen	100mg	66^			
					Ketoprofen-hyaluronidase	100mg + 1500 iu	60^			
					Placebo		60^			
					Placebo-hyaluronidase	1500 iu	64^			
Nekoofar *et al.* [25]	2003	USA	NA	>15	meloxicam	15mg	17	8, 24	9cm	Based on the two-way repeated measures ANOVA, the reduction in pain with meloxicam, piroxicam, and placebo was not significantly different (p=0.058), although the mean change of pain was greater with meloxicam over piroxicam and greater with piroxicam than placebo.
					piroxicam	20mg	17			
					placebo		17			
Praveen *et al.* [26]	2017	India	15, 14	18-50	Ketorolac	20mg	31	0, 6, 12, 24, 48	10 cm	Single pre-treatment dose of prednisolone has a more sustained effect in reducing post-endodontic pain compared with placebo or ketorolac.
			16, 14		prednisolone	30mg	31			
			13, 14		placebo		31			
Ramazani *et al.* [27]	2013	Iran	15, 12	18-65	ibuprofen	400mg	30	4, 8, 12, 24, 48, 72	100mm	The obtained results of the trial revealed that prophylactic use of 2 g Zintoma is not an effective pain-relieving agent.
			13, 11		zintoma	2000mg	30			
			10, 11		placebo		30			
Rashka *et al.* [28]	2013	India	NA	NA	diclofenac sodium	30mg	26	4, 8, 12, 24, 48	10mm	Diclofenac Sodium was found to be highly effective in reducing post-endodontic pain of vital teeth with irreversible pulpitis during the first 48 h.
					placebo		26			

(Table 1) contd.....

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Ryan *et al.* [29]	2008	USA	6, 8	NA	placebo		14	0, 6, 12, 18, 24	NA	Statistical analysis of the data showed that ibuprofen 600 mg provided statistically significantly greater analgesic effect than placebo at 6 and 12 hours (P=0.0014 and 0.0024), and pentazocine/naloxone provided statistically significantly greater analgesic effect than placebo at 12 hours (P =0.0084).
			8, 7		ibuprofen	600mg	15			
			6, 8		talwin	50mg	14			
Salarpoor *et al.* [30]	2013	Iran	6, 13	31.3	ibuprofen	400mg	19	6, 12, 24, 48	10mm	The results demonstrate that betamethasone and indomethacin may be more effective than ibuprofen for the management of post-operative pain after nonsurgical endodontic treatment when patients present with moderate to severe pain
			4, 17	24.5	betamethasone	2mg	21			
			7, 15	28	indomethacin	75mg	22			
			6, 14	29	placebo		20			
Sethi *et al.* [31]	2014	India	12, 6	18-60	Tapentadol	100mg	20	0, 6, 12, 18, 24	10cm	Single oral dose of 10 mg of ketorolac and 100mg of tapentadol as a pretreatment analgesic significantly reduced postoperative endodontic pain in patients with symptomatic irreversible pulpitis when compared to 400 mg of etodolac
					Etodolac	400mg	20			
					Ketorolac	10mg	20			
Elzaki *et al.* [32]	2016	Sudan	66, 104	33+10.5	paracetamol	1000mg	34	1, 2, 3, 4, 6, 8	NA	The combination of ibuprofen/paracetamol, taken immediately after initial endodontic therapy and root canal preparation in teeth with irreversible pulpitis, reduced post-endodontic pain
					Ibuprofen + paracetamol	600 + 1000mg	33			
					Mefenamic acid + paracetamol	500mg + 1000mg	34			
					Diclofenac K + paracetamol	50mg + 1000mg	35			
					Placebo		34			
Jorge-Araújo *et al.* [33]	2018	Brazil	7, 12	18-66	Placebo		20	4, 8, 12, 24, 48	NA	Preoperative administration of Ibuprofen or dexamethasone reduces post-endodontic pain and discomfort in comparison with a placebo. Premedication with anti-inflammatory drugs could contribute to control of the post-endodontic pain, mainly in patients more sensitive towards pain
			7, 12		Ibuprofen	400mg	20			
			7, 11		Dexamethasone	8mg	20			
Jenarthanan *et al.* [34]	2018	India	7,3	30±6	Oral diclofenac sodium	75mg	10	6,12,24,48	10cm	In patients with low pain threshold, intra-ligamentary route of administration is effective in controlling pain of endodontic origin postoperatively.
			5,5	26±9	Intraligamentary route of diclofenac sodium	NA	10			
			6,4	28±7	Placebo		10			

(Table 1) contd.....

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Yavari *et al.* [35]	2019	Iran	NA	20-50	Placebo		64	6, 12, 24, 48, 72	0-10	Infiltration of long-acting betamethasone and dexamethasone resulted in decreased postoperative pain experience. Dexamethasone was more effective in alleviating pain within the first 24-hour period after treatment. Infiltration of long-acting betamethasone and dexamethasone exhibited the same efficacy in 48 hours. The efficacy of long-acting betamethasone in pain relief lasted for 7 days. The QOL in the 2 groups receiving corticosteroids was higher than that in the placebo group.
					Betamethasone	0.7 mL	66			
					Dexamethasone	4mg	64			
Makkar *et al.* [36]	2012	India	7,3	39.6 yrs	Ibuprofen and paracetamol	400 mg,325 mg	10	6,12,24	10 cm	A single oral dose of diclofenac sodium and paracetamol and ibuprofen and paracetamol combination reduced postoperative pain following pulpectomy and root canal preparation of teeth with irreversible pulpitis.
			6,4	41.3 yrs	Diclofenac sodium and paracetamol	50 mg, 500mg	10			
			6,4	37.9 yrs	Placebo		10			
Doroschak *et al.* [37]	1999	USA	NA	18-65	Tramadol	100 mg	12	1,2,3	100 mm	NSAID/opiate combination, together with endodontic therapy, may be useful in the management of endodontic pain.
					Flurbiprofen	100 mg	12			
					Tramadol/Flurbiprofen	100 mg	13			
					Placebo		12			
Konagala *et al.* [38]	2019	India	62,70	18-50	Piroxicam	20 mg	30	6,12,24,48,72	100 mm	Preoperative single oral dose of piroxicam or dexamethasone or deflazacort is equally effective in controlling post-endodontic pain.
					dexamethasone	4 mg	30			
					deflazacort	30 mg	30			
					Placebo		30			
Ashraf [39]	2002	Iran	NA	NA	Rofecoxib	NA	60	12	100mm	NA
					Ibuprofen					
					Placebo					
Chance *et al.* [40]	1987	USA	NA	NA	prednisolone	NA	158	NA	NA	The corticosteroid was effective in significantly reducing the incidence of postoperative pain in teeth where vital pulp was present.
					Placebo		142			
Glassman *et al.* [41]	1989	USA	NA	NA	Dexamethasone	4 mg	19	NA	NA	oral dexamethasone is sufficient to significantly reduce endodontic interappointment pain for teeth with asymptomatic vital-inflamed pulps.
					Placebo		18			

(Table 1) contd.....

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Kaufman *et al.* [42]	1994	Israel	16,29	19-71	Methylprednisolone	8 mg	18	24	NA	The tested drug significantly reduced the frequency and intensity of postoperative pain sequelae in the experimental set-up.
					Mepivacaine	NA	17			
					Placebo	NA	10			
Krasner *et al.* [43]	1986	USA	NA	NA	Dexamethasone	5.25mg	25	8,24	100 mm	Post-treatment endodontic pain was substantially reduced by administration of oral dexamethasone. The risks to the otherwise healthy patient seem to be minimal and acceptable
					Placebo		25			
Liesinger *et al.* [44]	1993	USA	NA	NA	Dexamethasone	8 mg	106	1,4,8,24,48,72	9 cm	Patients who received dexamethasone took significantly fewer posttreatment pain medications than those who received the placebo
					Placebo					
Marshall *et al.* [45]	1984	USA	NA	NA	Dexamethasone	4 mg	50	4,24	NA	Injection of the steroid (dexamethasone, 4 mg) significantly reduced both the incidence and severity of pain at 4 h post-treatment and reduced pain at 24 h post-treatment.
					Placebo					
Mehrvarzfar *et al.* [46]	2008	Iran	34,66	21-58	Dexamethasone	4 mg	50	6,12,24,48	NA	Dexamethasone was considerably effective in controlling the severity of pain during the first 24 h; in contrast, there was no difference between dexamethasone and placebo groups 48 h after the first appointment.
					Placebo		50			
Pochapski *et al.* [47]	2009	Brazil	26,24	18-67	Dexamethasone	4 mg	25	4,6,12,24	NA	Preoperative single oral dose of dexamethasone substantially reduced post-endodontic pain
					Placebo		23			
Rogers *et al.* [48]	1999	USA	NA	NA	Dexamethasone	4mg	12	6,12,24,48	100 mm	At the 12-h period, both dexamethasone and ketorolac provided statistically significant better pain relief than placebo. At the 24-h period, only ketorolac demonstrated better pain relief than the placebo. There were no statistically significant differences among the groups at 6 and 48 h.
					Ketorolac tromethamine	30 mg	12			
					Ibuprofen	600 mg	12			
					placebo		12			
Shantiaee *et al.* [49]	2012	Iran	30,60	18-42	Dexamethasone	4 mg	30	4,8,24,48	9cm	Periapical infiltration of dexamethasone and morphine led to a considerable decrease in postoperative endodontic pain during the first 24 h after operation. Dexamethasone was more effective than morphine in pain reduction.
					Morphine	1 mg	30			
					Placebo		30			

(Table 1) contd.....

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Zarrabi	2003	Iran	NA	NA	betamethasone	4 mg	50	6,12,24	NA	NA
					Placebo		50			
Zarrabi *et al.* [50]	2007	Iran	NA	NA	betamethasone	2 mg	20	6,12,24	NA	NA
					Placebo		20			
Sharma *et al.* [51]	2015	India	NA	NA	dexamethasone	4 mg	20	6,12,24	100 mm	NSAID resulted in significantly less post-operative endodontic pain at all time-intervals. Preoperative oral administration of Dexamethasone performed best in reducing pain post operatively.
					Placebo		20			
Eftekhar *et al.* [52]	2013	NA	NA	NA	Triamcinolone	1 mg	40	NA	NA	NA
					Placebo		40			
Moradi *et al.* [53]	2013	Iran	NA	NA	dexamethasone	4 mg	15	6,12,24,48	10 cm	Administration of dexamethasone did not reduce post-operative pain severity in the first 12hours after endodontic treatment
					Placebo		15			
Ahangari	2009	Iran	NA	NA	dexamethasone	0.5 mg	20	6,12,24	10 cm	NA
					Placebo		20			
Fava [54]	1998	NA	NA	28-64	Otosporin	NA	30	48 h/1 w	NA	No difference was observed in the incidence of post-operative pain between the two groups.
					Placebo		30			
Ehrmann *et al.* [55]	2003	Australia	NA	NA	Triamcinolone acetonide		58	4,24,48,72	100 mm	Ledermix is an effective intracanal medicament for the control of postoperative pain associated with acute apical periodontitis, with a rapid onset of pain reduction.
					Placebo		71			
Negm *et al.* [56]	2001	Egypt	NA	15-75	Kenacomb	NA	245	24	100 mm	intracanal use of corticosteroid-antibiotic combination for controlling posttreatment endodontic pain.
					Placebo		230			
Wells *et al.* [57]	2011	USA	17,16	34.3±14.0	Ibuprofen/acetaminophen	600 mg/1000 mg	35	24,48,72	100 mm	There were decreases in pain levels and analgesic use over time in the ibuprofen and ibuprofen/acetaminophen groups.
			20,15	37.3± 14.7	Ibuprofen	600 mg	36			
Battrum *et al.* [58]	1996	USA	NA	NA	Ketorolac	10 mg	10	6,24	100mm	There was no significant difference in pain relief between the two groups treated with different drug regimens
					Placebo		10			
Torabinejad *et al.* [59]	1994	NA	NA	NA	Salicylic acid	650 mg	50	30, 36, 42, 48, 54, 60, 66, 72	90mm	Ibuprofen, ketoprofen, erythromycin base, penicillin, and methylprednisolone plus penicillin were more effective than placebo within the first 48 h following complete instrumentation.
					Acetaminophen	650 mg	57			
					Ibuprofen	400 mg	57			
					Ketoprofen 50 mg	50 mg	53			
					Acetaminophen + codeine	325 mg/60 mg	48			

(Table 1) contd.....

Study	Year	Country	Sex (M,F)	Age	Treatment Groups	Dose (mg)	Sample Size	Follow-up Period (h)	VAS Scale	Conclusion
Moskow *et al.* [60]	1984	NA	NA	NA	Dexamethasone	4 mg	26	24,48,72	100 mm	A statistically significant decreased incidence of pain was reported for the corticosteroid cases as compared to the control at the 24-hour time period ($p<0.05$)
					Placebo		24			

3.2. Characteristics and Quality of the Included Studies

A total of 5412 patients, including males and females between the ages of 15 and 80 years, from the included studies, formed the sample size for the NMA. The origin countries of included studies were Iran (n=21), USA (n=15), India (n=9), Egypt (n=3), Turkey (n=3), Brazil (n=2), Israel (n=1), Portugal (n=1), Sudan (n=1), and Australia (n=1), and four studies were found to be non-reported. Negm study consists of two trials; therefore, each one is considered as a separate study. The quality of the 62 included studies is described in Table **2**. Thirty-seven studies had a low risk of bias, 10 studies had a high risk of bias, and 15 studies had some concerns.

Table 2. Risk of bias of included studies.

Study	Year	Randomization	Allocation Concealment	Blinding of Participants and Personnel	blinding of Outcome Assessors	Attrition Bias	Selection Bias	Other Bias	Overall
Arslan *et al.*	2011	low	unclear	low	low	low	low	low	Low
Ashraf *et al.*	2013	low	unclear	low	low	low	low	low	Low
Atbaei *et al.*	2010	low	unclear	low	unclear	low	low	low	Some concerns
Attar *et al.*	2008	low	unclear	low	low	low	low	low	Low
Baradaran	2014	low	unclear	low	low	low	low	low	Low
Douglas	2004	low	unclear	low	low	low	low	low	Low
Ehsani	2012	low	unclear	low	low	low	low	low	Low
Elkhadem	2017	low	low	low	low	low	low	low	Low
Elzaki	2016	low	unclear	low	low	low	low	low	Low
Flath	1987	low	unclear	low	low	low	low	low	Low
Gopikrishna and Parameswaran	2003	low	unclear	low	low	low	low	low	Low
Isik	2014	low	unclear	low	low	low	low	low	Low
Jalalzadeh *et al.*	2010	low	unclear	low	low	low	low	low	Low
Jorge-Araújo	2018	low	low	low	low	low	low	low	Low
Joshi	2016	low	unclear	low	low	low	low	low	Low
Kaviani	2011	low	unclear	low	low	low	low	low	Low
Khorasani	2011	low	unclear	low	low	low	low	low	Low
Mehrvarzfar	2012	low	unclear	low	low	low	low	low	Low
Mehrvarzfar	2016	low	unclear	low	low	low	low	low	Low
Menhinick	2004	low	unclear	low	low	low	low	low	Low
Menke *et al.*	1999	low	unclear	low	unclear	low	low	low	Some concerns
Mirzaie	2011	low	unclear	low	low	low	low	low	Low
mokhtari	2016	low	unclear	low	low	low	low	low	Low
Negm	1989	low	unclear	low	unclear	low	low	low	Some concerns
Negm	1994	low	unclear	low	unclear	low	low	low	Some concerns
Nekoofar	2003	low	unclear	low	low	low	low	low	Low
Praveen	2017	low	low	low	low	low	low	low	Low
Ramazani	2013	low	unclear	low	low	low	low	low	Low
Rashka	2013	low	unclear	unclear	low	low	low	low	Some concerns
Ryan	2008	low	unclear	low	low	low	low	low	Low
Saatchi *et al.*	2009	low	unclear	low	low	low	low	low	Low

Study	Year	Randomization	Allocation Concealment	Blinding of Participants and Personnel	blinding of Outcome Assessors	Attrition Bias	Selection Bias	Other Bias	Overall
Salarpoor	2013	low	unclear	low	low	low	low	low	Low
Sethi	2014	low	unclear	low	low	low	low	low	Low
Yavari	2019	low	low	low	low	low	low	low	Low
Makkar	2012	low	unclear	low	low	low	low	low	Low
Doroschak	1999	low	unclear	low	low	low	low	low	Low
Konagala	2019	low	low	low	low	low	low	unclear	Low
Jenarthanan	2018	low	unclear	unclear	unclear	low	low	low	Some concerns
Ashraf *et al.*	2002	low	unclear	low	low	low	low	low	Low
Chance	1987	unclear	low	unclear	low	low	unclear	unclear	Some concerns
Glassman	1989	unclear	low	unclear	unclear	low	unclear	unclear	Some concerns
Kaufman	1994	low	unclear	unclear	unclear	low	unclear	unclear	Some concerns
Krasner	1986	low	low	low	unclear	low	low	unclear	Some concerns
Liesinger	1993	unclear	unclear	low	low	low	low	low	Some concerns
Marshall	1984	low	unclear	low	low	low	low	low	Low
Mehrvarzfar *et al.*	2008	low	unclear	low	low	low	unclear	low	Some concerns
Pochapski	2009	low	unclear	low	low	low	unclear	low	Some concerns
Rogers	1999	low	unclear	unclear	unclear	low	low	low	Some concerns
Shantiaee	2012	low	unclear	low	low	low	low	low	Low
Zarrabi	2003	low	unclear	low	high	low	low	high	High
Zarrabi	2007	low	unclear	low	low	high	low	low	High
Sharma	2015	low	unclear	low	low	high	low	low	High
Eftekhar	2013	low	unclear	low	low	high	low	low	High
Moradi	2013	low	unclear	low	low	high	low	low	High
Ahangari	2009	low	unclear	low	low	high	unclear	low	High
Fava	1998	low	unclear	high	high	high	unclear	low	High
Ehrmann	2003	unclear	unclear	unclear	unclear	low	low	low	Some concerns
Negm	2001	low	low	low	low	low	low	low	Low
Wells	2011	low	unclear	low	low	low	low	low	Low
Battrum	1996	unclear	unclear	high	high	high	low	low	High
Torabinejad	1994	high	high	low	unclear	low	low	low	High
Moskow	1984	low	high	high	unclear	low	low	low	High

3.3. Effects on the Primary Outcomes

3.3.1. Postoperative Pain for Treatment Intervention Categorized by Pharmacologic Group

Immediately after procedure: Among all medications, opioids were ranked as the best treatment for the reduction of postoperative pain [SMD= -1.16, 95% CI (-1.96: -0.36), P-score= 0.91]. Moreover, NSAIDs showed a significant reduction in pain after endodontic treatment [SMD= -0.63, 95% CI (-0.89: -0.36), P-score= 0.61]. On the other hand, there was no significant difference between corticosteroids, COX-2 inhibitors, and placebo in this period. Pooled analysis was heterogeneous (Q=373.01; I^2=84.7%; P<0.0001) due to the significant variation among the analyzed categories (Fig. **2a**). Publication bias analysis showed that there was no detected bias according to the Egger test (p=0.07). Split analysis demonstrated that there was no significant difference between corticosteroid *vs*. placebo or NSAIDs (Appendix Fig. **1**). Network ranking graph showed the rank of categories immediately after the procedure (Fig. **3a**). League table is presented in Appendix Table **1**.

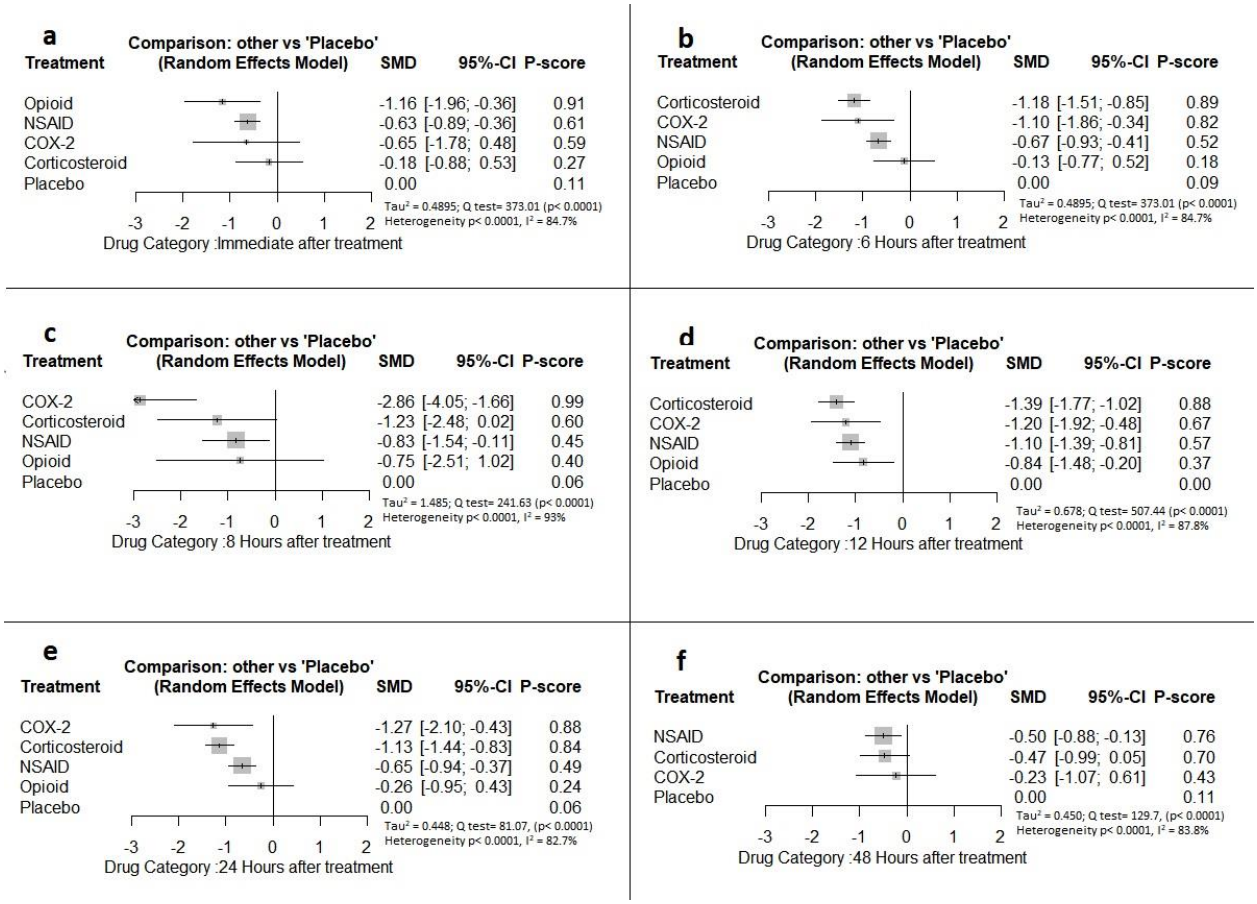

Fig. (2). Forest plot of the effect of Treatment Intervention Categorized by Pharmacologic Group on Postoperative Pain: **a**) Immediately after Procedure, **b**) Six Hours after Procedure, **c**) Eight Hours after Procedure. **d**) Twelve Hours after Procedure, **e**) Twenty-four Hours after Procedure, **f**) Forty-eight Hours after Procedure.

Six Hours after Procedure: Interestingly, the efficacy of corticosteroids dramatically increased, reaching the first rank in terms of the best treatment for the reduction of postoperative pain [SMD= -1.18, 95% CI (-1.51: -0.85), P-score= 0.89], and the efficacy of opioids dramatically decreased, scoring the fourth rank [SMD= -0.13, 95% CI (-0.77: 0.52), P-score= 0.18]. NSAIDs showed a significant reduction in pain after endodontic treatment [SMD= -0.67, 95% CI (-0.93: -0.41), P-score= 0.52]; however, it scored the third rank after the COX-2 inhibitors [SMD= -1.10, 95% CI (-1.86: -0.34), P-score= 0.82]. Pooled analysis was heterogeneous (Q=373.01; I^2=84.7%; P<0.0001) due to the significant variation among the analyzed categories (Fig. **2b**). Publication bias analysis showed a detected bias according to the Egger test (p=0.005). Split analysis demonstrated no significant difference between NSAIDs *vs*. COX-2 inhibitors or *vs*. Opioids (Appendix Fig. **2**). Network ranking graph showed the rank of categories at 6 hours after the procedure (Fig. **3b**). League table is presented in Appendix Table **2**.

Eight Hours after Procedure: at this period, only COX-2 inhibitors and NSAIDs showed a significant effect in reducing the postoperative pain [SMD= -2.86, 95% CI (-4.05:-1.66), P-score= 0.99] and [SMD= -0.83, 95% CI (-1.54:-0.11), P-score= 0.45], respectively. Pooled analysis was heterogeneous (Q=241.63; I^2=93%; P<0.0001) due to the significant variation among the analyzed categories (Fig. **2c**). Publication bias analysis showed that there was no detected bias according to the Egger test (p=0.60). Split analysis demonstrated no significant difference between NSAIDs *vs*. corticosteroids or *vs*. Opioids (Appendix Fig. **3**). Network ranking graph showed the rank of categories at 8 hours after the procedure (Fig. **3c**). League table is presented in Appendix Table **3**.

Twelve Hours after Procedure: All medication showed a significant reduction when compared to placebo; Corticosteroids (SMD= -1.39), COX-2 inhibitors (SMD= -1.20), NSAIDs (SMD= -1.10), and Opioids (SMD= -0.84). Pooled analysis was heterogeneous (Q=507.44; I^2=87.8%; P<0.0001) due to the significant variation among the analyzed categories (Fig. **2d**). Publication bias analysis showed that there was a detected bias according to the Egger test (p=0.0001). Split analysis demonstrated that there was no significant difference between NSAIDs *vs*. corticosteroids, Opioids, and COX-2 inhibitors (Appendix Fig. **4**). Network ranking graph showed the rank of categories at 12 hours after the procedure (Fig. **3d**). League table is presented in Appendix Table **4**.

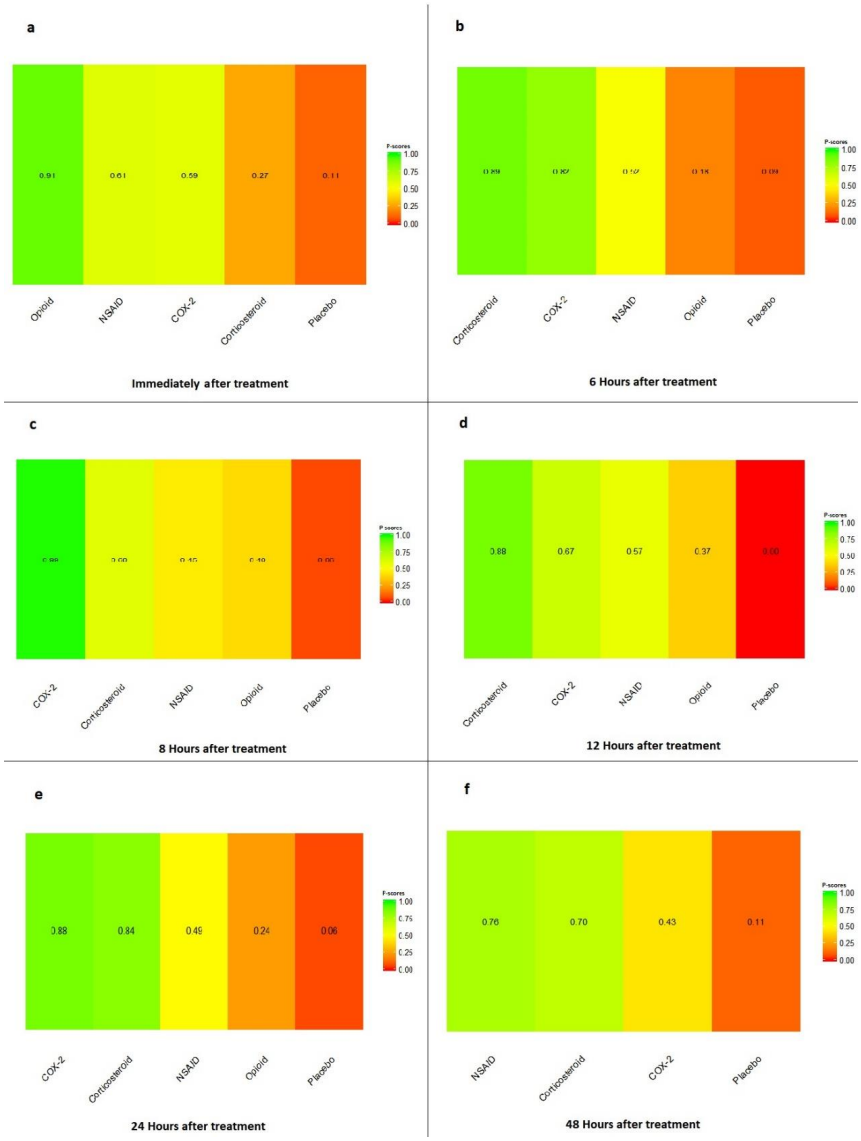

Fig. (3). Network ranking graph showed the rank of categories for the primary analysis Categorized by Pharmacologic Group: **a**) Immediately after procedure, **b**) Six Hours after Procedure, **c**) Eight Hours after Procedure. **d**) Twelve Hours after Procedure, **e**) Twenty-four Hours after Procedure, **f**) Forty-eight Hours after Procedure.

Twenty-four Hours after Procedure: Among all medications, COX-2 inhibitors were ranked as the best treatment for the reduction of postoperative pain when compared to placebo [SMD=-1.27, 95% CI (-2.10: -0.43), P-score=0.88]. Corticosteroids and NSAIDs also showed a significant reduction in pain score (SMD= -1.13 and SMD= -0.65, respectively). Pooled analysis was heterogeneous (Q=81.07; I^2=82.7%; P<0.0001) due to the significant variation among the analyzed categories (Fig. **2e**). Publication bias analysis showed a detected bias according to the Egger test (p=0.0008). Split analysis demonstrated that there was no significant difference between NSAIDs *vs*. Opioids and COX-2 inhibitors (Appendix Fig. **5**). Network ranking graph showed the rank of categories at 24 hours after the procedure (Fig. **3e**). League table is presented in Appendix Table **5**.

Forty-eight Hours after Procedure: Among all medications, only NSAIDs demonstrated a significant reduction in postoperative pain when compared to placebo [SMD=-0.50, 95% CI (-0.88: -0.13), P-score=0.76]. Pooled analysis was heterogeneous (Q=129.7; I^2=83.8%; P<0.0001) due to the significant variation among the analyzed categories (Fig. **2f**). Publication bias analysis showed that there was no detected bias according to the Egger test (p=0.16). Split analysis demonstrated that there was no significant difference among NSAIDs, Corticosteroids or COX-2 inhibitors (Appendix Fig. **6**). Network ranking graph displayed the rank of categories at 24 hours after the procedure (Fig. **3f**). League table is presented in Appendix Table **6**.

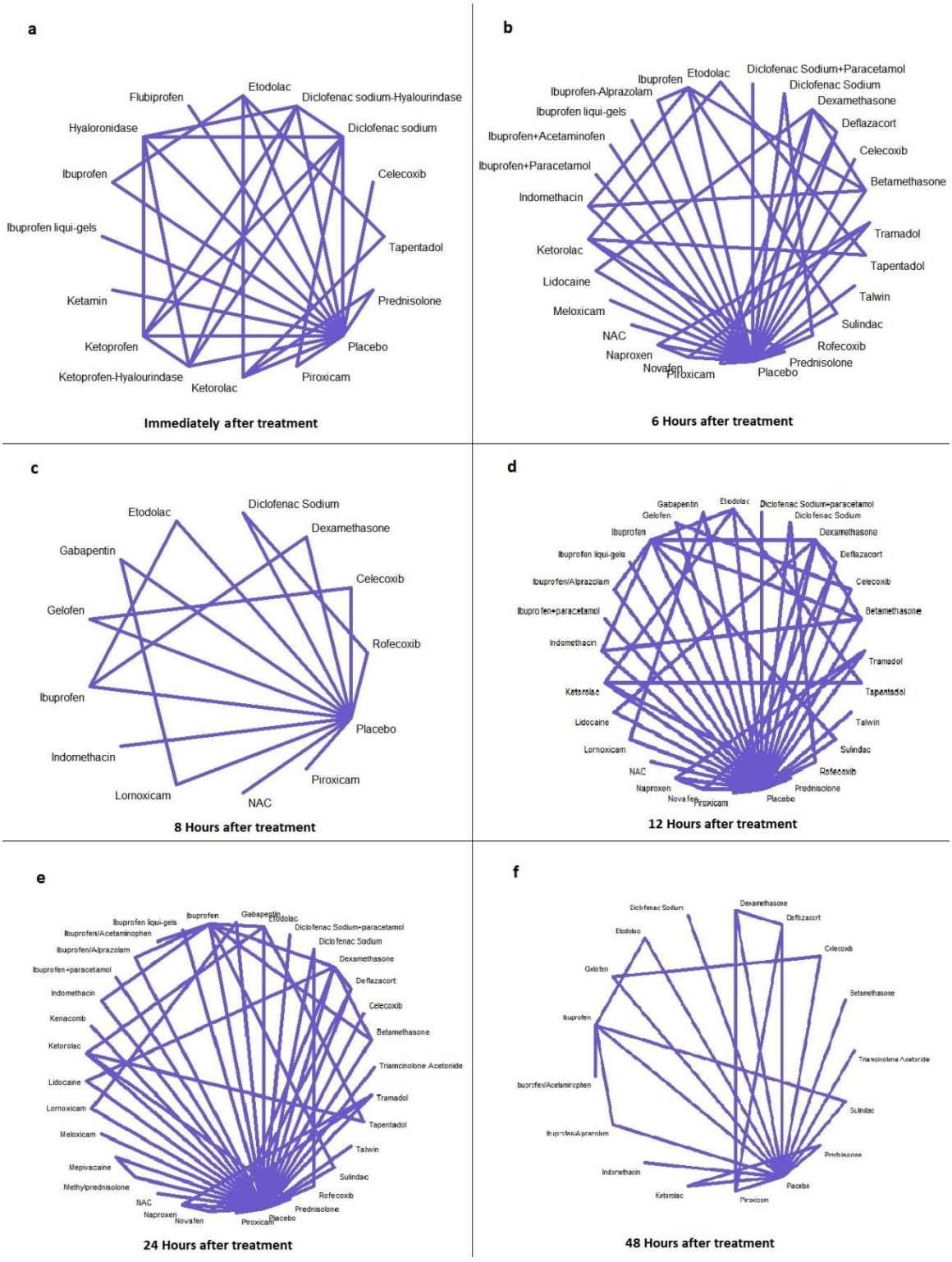

Fig. (4). Network diagrams of all the eligible comparisons for primary outcomes according to the chemical name: **a**) Immediately after procedure, **b**) Six Hours after Procedure, **c**) Eight Hours after Procedure. **d**) Twelve Hours after Procedure, **e**) Twenty-four Hours after Procedure, **f**) Forty-eight Hours after Procedure.

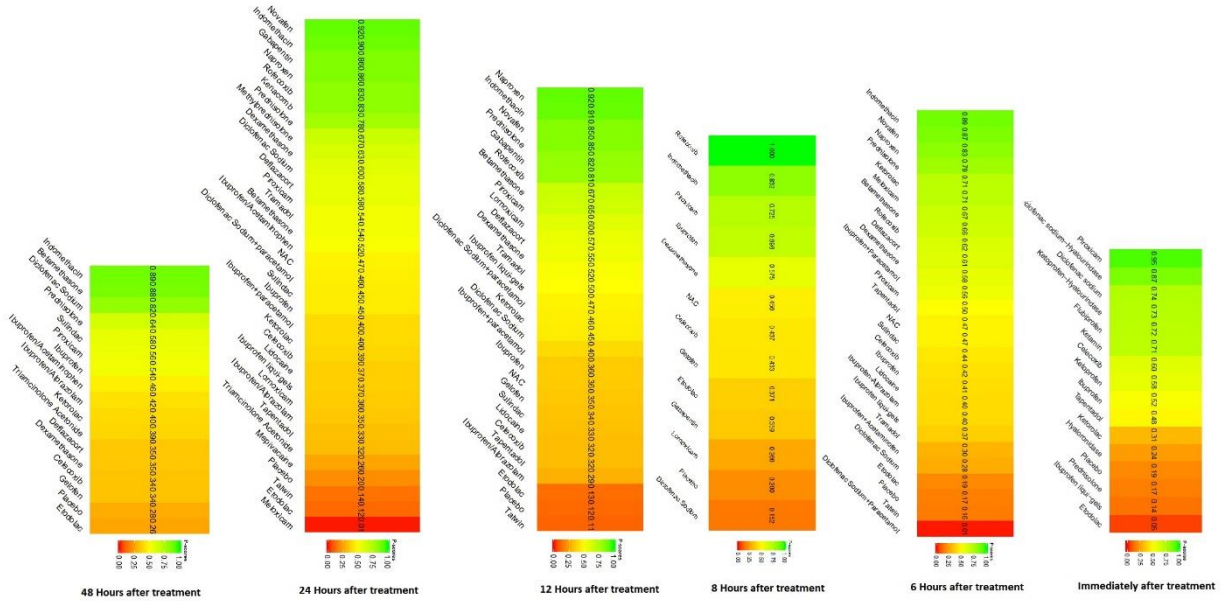

Fig. (5). Network ranking graph showed the rank of categories for the primary analysis Categorized by the chemical name: **a**) Immediately after procedure, **b**) Six Hours after Procedure, **c**) Eight Hours after Procedure. **d**) Twelve Hours after Procedure, **e**) Twenty-four Hours after Procedure, **f**) Forty-eight Hours after Procedure.

3.3.2. Postoperative Pain for Treatment Intervention Categorized by Chemical Name

Network diagrams of all the eligible comparisons for primary outcomes according to the chemical name are presented in Fig. (**4a-f**).

Immediately after procedure: Among all medications, Piroxicam was ranked as the best treatment for the reduction of postoperative pain [SMD= -1.20, 95% CI (-1.53: -0.86), P-score= 0.95]. Moreover, Diclofenac sodium, Flubiprofen, Ketamin, Ketoprofen, and Ibuprofen showed a significant reduction in pain after endodontic treatment. Pooled analysis was found to be homogenous (Q=23.89; I^2=20.5%; P<0.97) (Appendix Fig. **7**). Publication bias analysis showed that there was no detected bias according to the Egger test (p=0.66). The split analysis is presented in Appendix Fig. (**8**). Network ranking graph showed the rank of drugs immediately after the procedure (Fig. **5a**).

Six hours after procedure: Indomethacin was ranked as the best treatment for the reduction of postoperative pain [SMD= -1.79, 95% CI (-2.55: -1.02), P-score= 0.89]. Furthermore, Novafen, Naproxen, Prednisolone, Ketorolac, Betamethasone, Dexamethasone, Rofecoxib, Piroxicam, and Ibuprofen showed a significant reduction in pain after 6 hours of endodontic treatment. Pooled analysis was heterogeneous (Q=252.22; I^2=82.6%; P<0.0001) due to the significant variation among the analyzed drugs (Appendix Fig. **9**). Publication bias analysis showed a detected bias according to the Egger test (p<0.0001). The split analysis is presented in Appendix Fig. (**10**). Network ranking graph showed the rank of drugs 6 hours after the procedure (Fig. **5b**).

Eight hours after procedure: At this period, only four drugs significantly reduced post-endodontic pain; Rofecoxib [SMD= -6.65, 95% CI (-8.53: -4.78), P-score= 1.00], Indomethacin [SMD= -2.39, 95% CI (-4.36: -0.42), P-score= 0.83], Piroxicam [SMD= -1.61, 95% CI (-2.97: -0.25), P-score= 0.72], and Ibuprofen [SMD= -1.41, 95% CI (-2.42: -0.41), P-score= 0.70]. Pooled analysis was heterogeneous (Q=82.04; I^2=87.8%; P<0.0001) due to the significant variation among the analyzed drugs (Appendix Fig. **11**). Publication bias analysis showed that there was no detected bias according to Egger test (p<0.15). The split analysis is presented in Appendix Fig. (**12**). Network ranking graph showed the rank of drugs 8 hours after the procedure (Fig. **5c**).

Twelve hours after procedure: Naproxen was ranked as the best treatment for the reduction of postoperative pain [SMD= -2.67, 95% CI (-3.90: -1.44), P-score= 0.92]. Furthermore, Novafen, Indomethacin, Prednisolone, Gabapentin, Betamethasone, Dexamethasone, Rofecoxib, Piroxicam, and Ibuprofen showed a significant reduction in pain after 12 hours of endodontic treatment. Pooled analysis was found to be heterogeneous (Q=377.76; I^2=86.8%; P<0.0001) due to the significant variation among the analyzed drugs (Appendix Fig. **13**). Publication bias analysis showed that there was a detected bias according to the Egger test (p<0.0001). The split analysis is presented in Appendix Fig. (**14**). Network ranking graph showed the rank of drugs 12 hours after the procedure (Fig. **5d**).

Twenty-four hours after procedure: Novafen was ranked as the best treatment for the reduction of postoperative pain [SMD= -2.13, 95% CI (-3.18: -1.08), P-score= 0.92]. Furthermore, Naproxen, Indomethacin, Prednisolone, Gabapentin, Diclofenac sodium, Betamethasone, Dexamethasone, Rofecoxib, Kenacomb, Piroxicam, and

Ibuprofen showed a significant reduction in pain after 24 hours of endodontic treatment. Pooled analysis was observed to be heterogeneous (Q=321; I^2=84.4%; P<0.0001) due to the significant variation among the analyzed drugs (Appendix Fig. **15**). Publication bias analysis showed that there was a detected bias according to the Egger test (p=0.003). The split analysis is presented in Appendix Fig. (**16**). Network ranking graph showed the rank of drugs 24 hours after the procedure (Fig. **5e**).

Forty-eight hours after procedure: Only indomethacin and betamethasone showed a significant reduction in postoperative pain [SMD= -1.66, 95% CI (-3.15: -0.18), P-score= 0.89] and [SMD= -1.64, 95% CI (-3.13: -0.15), P-score= 0.88], respectively. Pooled analysis was heterogeneous (Q=81; I^2=82.7%; P<0.0001) due to the significant variation among the analyzed drugs (Appendix Fig. **17**). Publication bias analysis showed that there was no detected bias according to the Egger test (p=0.32). The split analysis is presented in Appendix Fig. (**18**). Network ranking graph showed the rank of drugs 48 hours after the procedure (Fig. **5f**).

3.4. Secondary Outcome: Adverse Events

3.4.1. Nausea

Our analysis showed that only five studies reported data regarding nausea [21 - 25]. Network graph included the following drugs: Indomethacin, ibuprofen, tramadol, betamethasone, flurbiprofen, and placebo (Appendix Fig. **19**). Interestingly, among the tested drugs, no drug showed a significant increase in the risk/incidence of nausea, as shown in Appendix Fig. (**20**). Moreover, the ranking analysis demonstrated ibuprofen as the lowest drug associated with risk/incidence of nausea (Appendix Fig. **21**). The split analysis is presented in Appendix Fig. (**22**).

3.4.2. Headache

Only four studies reported data regarding headache [21 - 24]. Network graph included the following drugs: Indomethacin, ibuprofen, tramadol, betamethasone, flurbiprofen, and placebo (Appendix Fig. **23**). Betamethasone and Ibuprofen showed a significant reduction in the risk/incidence of headache [OR= 0.10, 95% CI (0.01: 0.90), P-score= 0.87] and [OR= 0.31, 95% CI (0.11: 0.89), P-score= 0.63], respectively (Appendix Fig. **24**). Moreover, the ranking analysis demonstrated that betamethasone was the lowest drug associated with risk/incidence of headache (Appendix Fig. **25**). The split analysis is presented in Appendix Fig. **26**.

3.4.3. Other Adverse Events

Salapoor *et al.* [24] reported one case and Menhinick *et al.* [21]reported three cases of sweating due to using ibuprofen. Regarding dizziness, Shantiaee *et al.* [24] reported three cases with dexamethasone, and Sethi *et al.* [23]reported four cases with Tapentadol and Etodolac. In terms of vomiting and heartburn, three cases were recorded for each Tapentadol and Etodolac [23].

4. DISCUSSION

To the best of our knowledge, this is the largest and most updated systematic review and network meta-analysis that was conducted to evaluate the current evidence regarding the effect of pre- and postmedication for reducing the postendodontic pain. In this study, we included a total of 62 RCTs in the systematic review. Out of them, 50 studies were included in the network meta-analysis (NMA). NMA was conducted on the basis of pharmacological or chemical name groupings in order to identify the effect of classification of the medications given pre- or postendodontic care on postoperative pain during the following periods: immediately, 6, 8, 12, 24, 48 hours after the procedure. Opioids were ranked first in the pharmacologic group for reducing pain immediately after the procedure. Moreover, it showed a significant reduction at 12 hours after the procedure. Corticosteroids were ranked first as the best treatment for the reduction of postoperative pain at 6 and 12 hours with a significant reduction in postoperative pain scores [SMD= -1.18, 95% CI (-1.51: -0.85)] and [SMD= -1.39, 95% CI (-1.77: -1.02)], respectively. COX-2 were ranked as the best treatment for the reduction of postoperative pain at 8 and 24 hours with a significant reduction in postoperative pain scores [SMD= -2.86, 95% CI (-6.05: -1.66)] and [SMD= -1.27, 95% CI (-2.10: -0.43)], respectively. NSAIDs significantly reduced the postoperative pain scores in all durations. Based on the chemical name, piroxicam was superior immediately after the procedure, whereas indomethacin followed by novafen, naproxen, and prednisolone was found to be effective at 6 hours. At 12 and 24 hours, naproxen and Novafen followed by indomethacin were ranked first. However, at 48 hours, only indomethacin and betamethasone were effective. The safety profile of test drugs was acceptable except for some events of nausea, vomiting, and headache.

Clinically, it has been reported that patients with periapical diagnosis of an Acute Apical Periodontitis (APP) or Phoenix Abscess are more likely to require additional medication to relieve post-endodontic pain compared to a periapical diagnosis of a Normal Periapex, a Chronic Apical Periodontitis (CAP), or a Chronic Apical Abscess (CAA) [26, 27]. Therefore, it seems rational to minimize occlusion after root canal therapy on the tooth, which is harmful to percussion. Occlusal reduction in patients with teeth that initially show pulp vitality, percussion sensitivity, preoperative pain and/or absence of periradicular radiolucency has been recommended to prevent postoperative pain [28]. On the other hand, CAA or CAP consists of a radiolucency at the root apex, a draining fistula (sinus tract), and usually no pain in percussion.

Nagendrababu *et al.* [17] conducted NMA for the same purpose; however, they only included 16 RCTs and reported results for only three durations. In terms of adverse events, they reported a descriptive result and did not conduct a pooled analysis. In conclusion, they stated that the use of piroxicam or prednisolone would be the premedication of choice. We agree that these drugs are promising and show a significant effect; however, we believe that indomethacin, Novafen, naproxen, betamethasone have a better effect and longer duration.

In the NMA of Shirvani and colleagues, they aimed to investigate the efficacy of NSAIDs and paracetamol in

reducing postendodontic pain. They did not include corticosteroids or opioids; therefore, they enrolled only 27 articles. They analyzed the data at four durations immediately, 6, 12, and 24 hours after the procedure. They performed a meta-regression which demonstrated that combination therapy did not reduce the pain significantly (OR= -0.88, 95% CI (-2.05, 0.28), p= 0.1). Moreover, they showed that the systemic administration was more efficient than oral administration (OR= -1.17, 95% CI (-1.93, -0.41), p= 0.004) and (OR= 4.24, 95% CI (2.62, 5.86), p<0.001), respectively. Finally, they recommended the use of multiple-dose regimens of NSAIDs during the postoperative period to achieve most efficacy (29). Smith *et al.* (30) found that the elimination of 6 hours of postendodontic pain with ibuprofen 600 mg and ibuprofen 600 mg + acetaminophen 1000 mg was more effective than placebo. They analyzed studies that evaluated the efficacy of pre- and postmedication for endodontic treatment on pain. They showed that ketoprofen 50 mg and naproxen 500 mg might be more effective than ibuprofen 600 mg at 6 hours postoperative.

5. Limitations

This study possessed some limitations: 1) Heterogeneity was observed in all analyses, which can be explained by the extensive variation in types of drugs, dosage, mechanism of action, and mode of administration. Moreover, the different types of teeth of participants with varied demographics may influence the applicability of our findings. However, all studies were conducted in hospitals, universities or clinics where the numbers and experience of operators were diversified, which could further encourage our findings to be generalized. 2) We could not conduct a subgroup analysis according to the regimen doses because of insufficient data.

CONCLUSION

In conclusion, the current evidence suggests that pre- and postmedication have the ability to reduce postoperative pain after nonsurgical root canal treatment. Corticosteroids and COX-2 inhibitors showed significant control of the pain up to 12 hours after administration. However, NSAIDs demonstrated a high efficacy from administration and until two days after treatment. Indomethacin, Novafen, prednisolone, and Naproxen were ranked as first in most analyzed durations. The use of narcotic agents before and post-nonsurgical root canal procedures for postoperative pain control and improving the quality of life needs further research.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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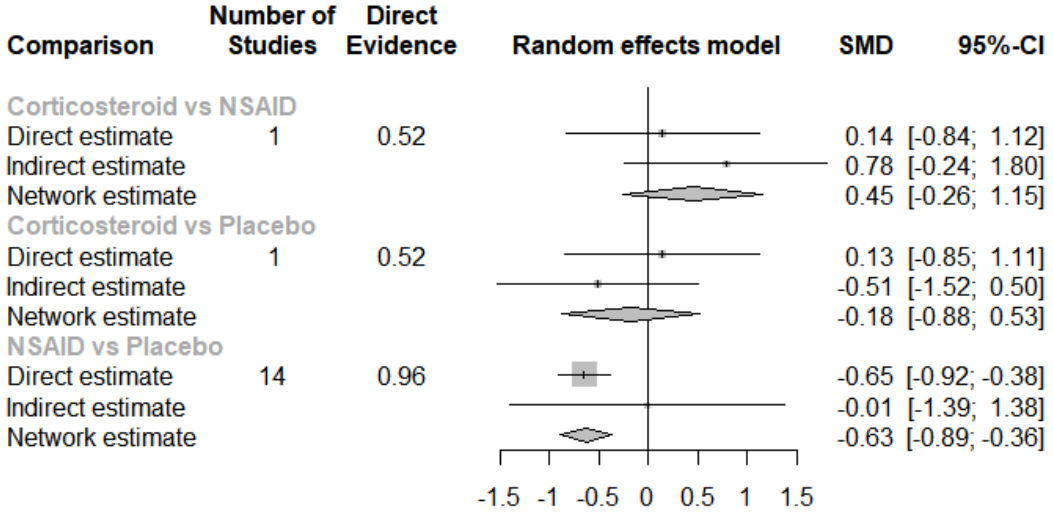
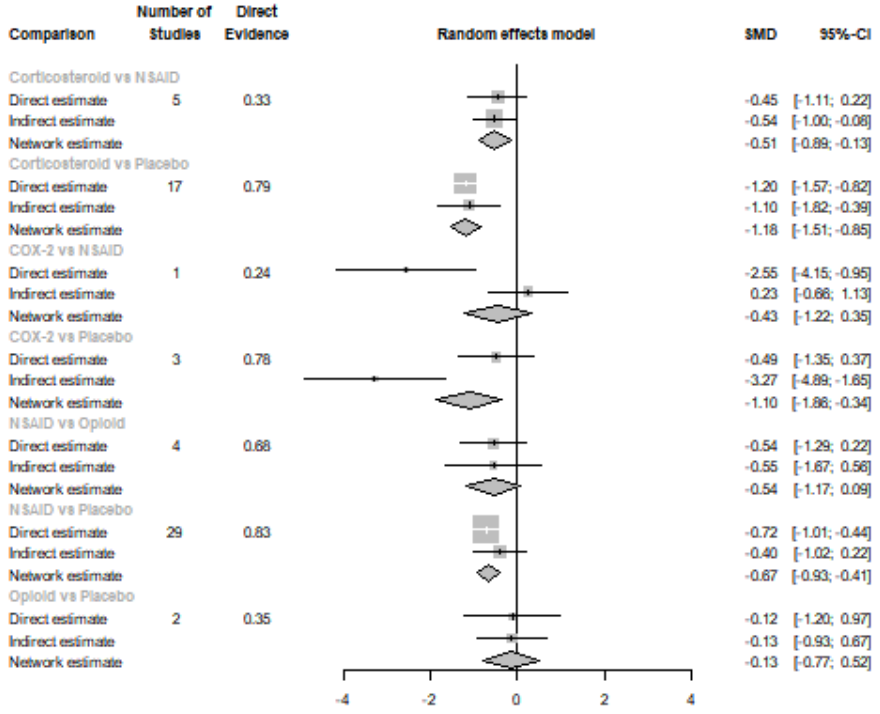
APPENDIX

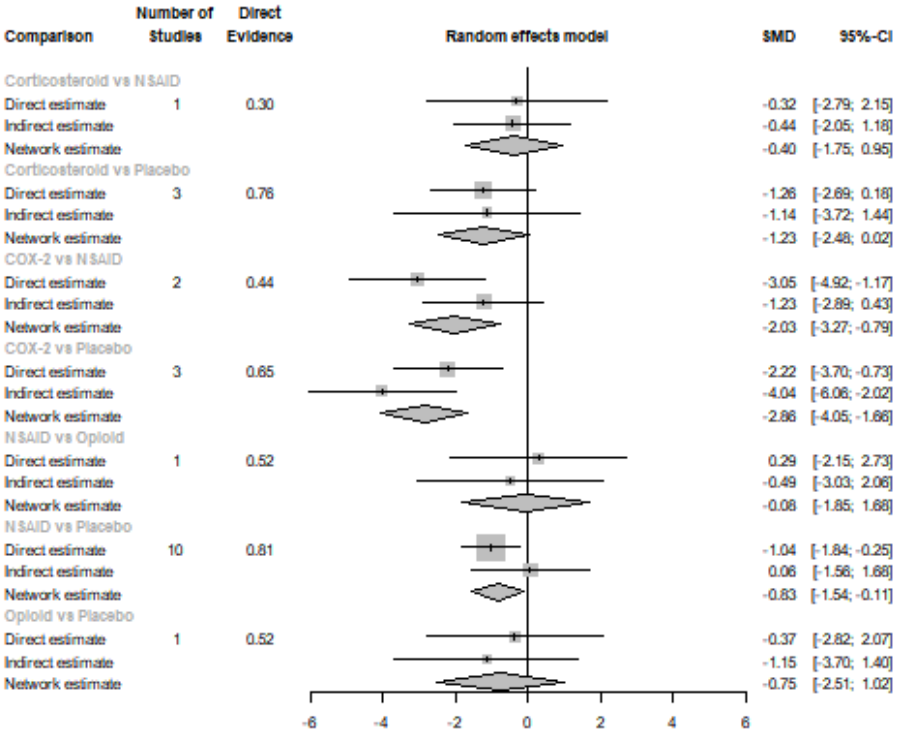
Primary outcome: Postoperative Pain Treatment Intervention Categorized by Pharmacologic Group



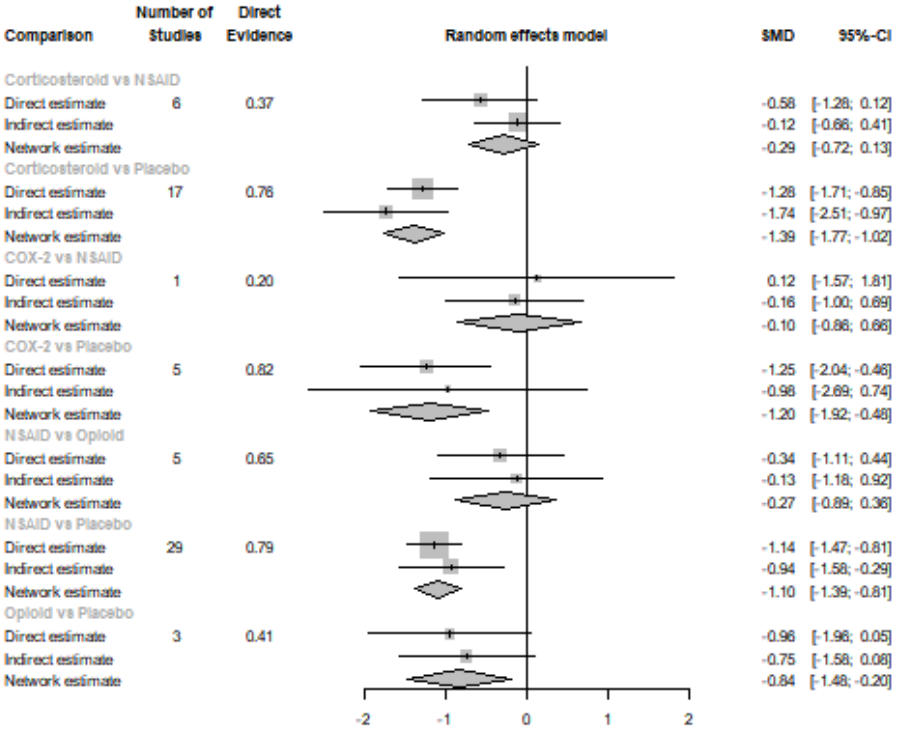
Appendix Fig. (1). Split analysis of the effect of Treatment Intervention Categorized by Pharmacologic Group on Postoperative Pain Immediately after the procedure.



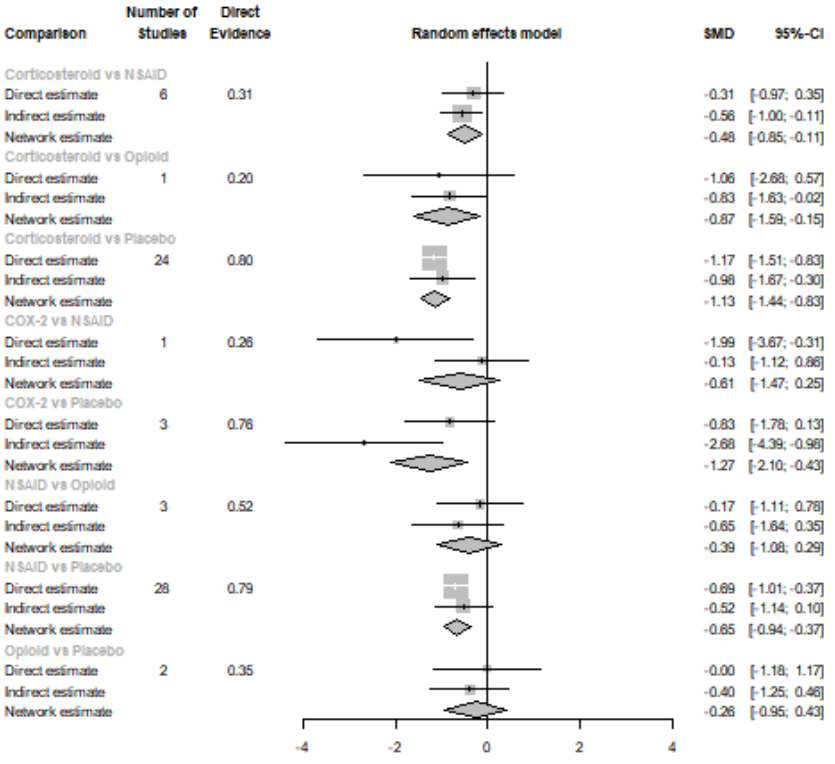
Appendix Fig. (2). Split analysis of the effect of Treatment Intervention Categorized by Pharmacologic Group on Postoperative Pain at 6 hours after the procedure.



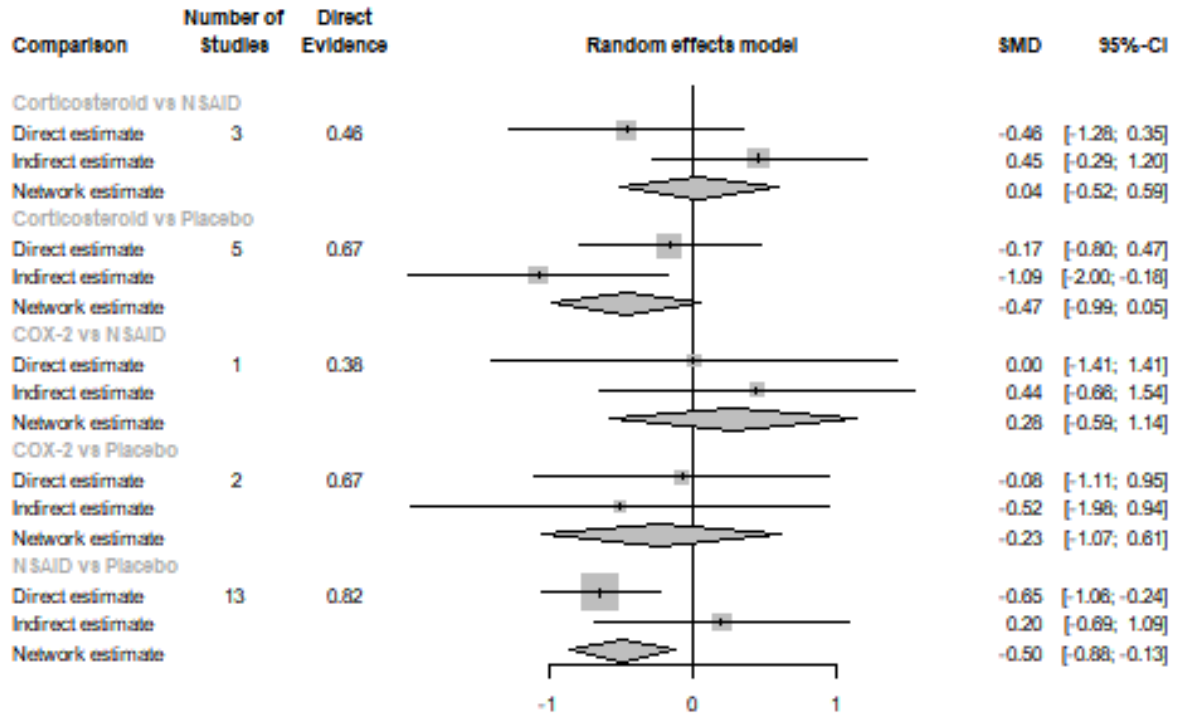
Appendix Fig. (3). Split analysis of the effect of treatment Intervention Categorized by Pharmacologic Group on Postoperative Pain at 8 hours after the procedure.



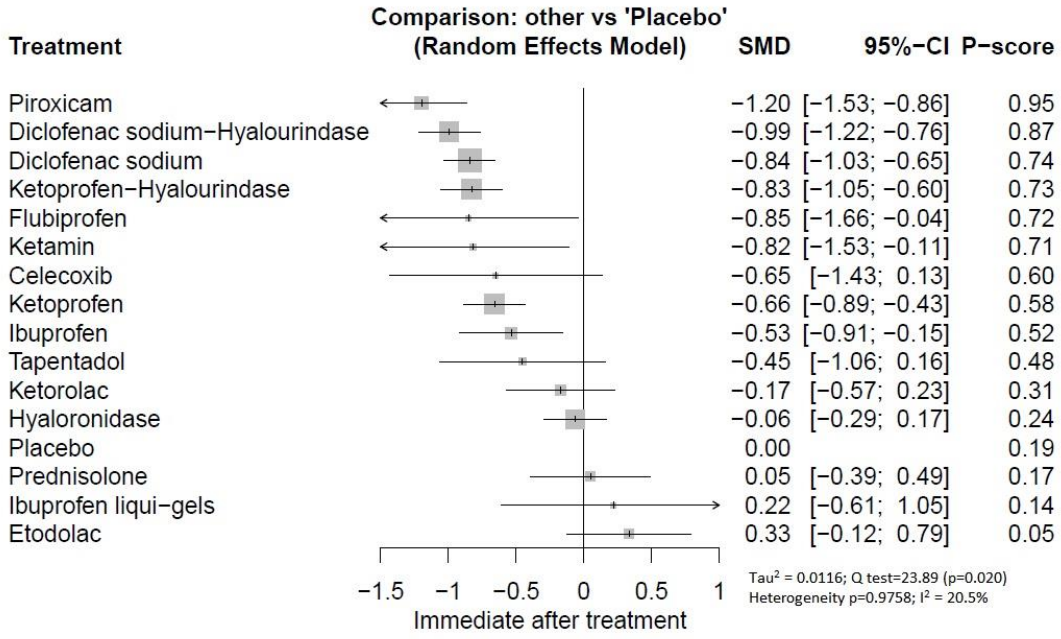
Appendix Fig. (4). Split analysis of the effect of treatment Intervention Categorized by Pharmacologic Group on Postoperative Pain at 12 hours after the procedure.



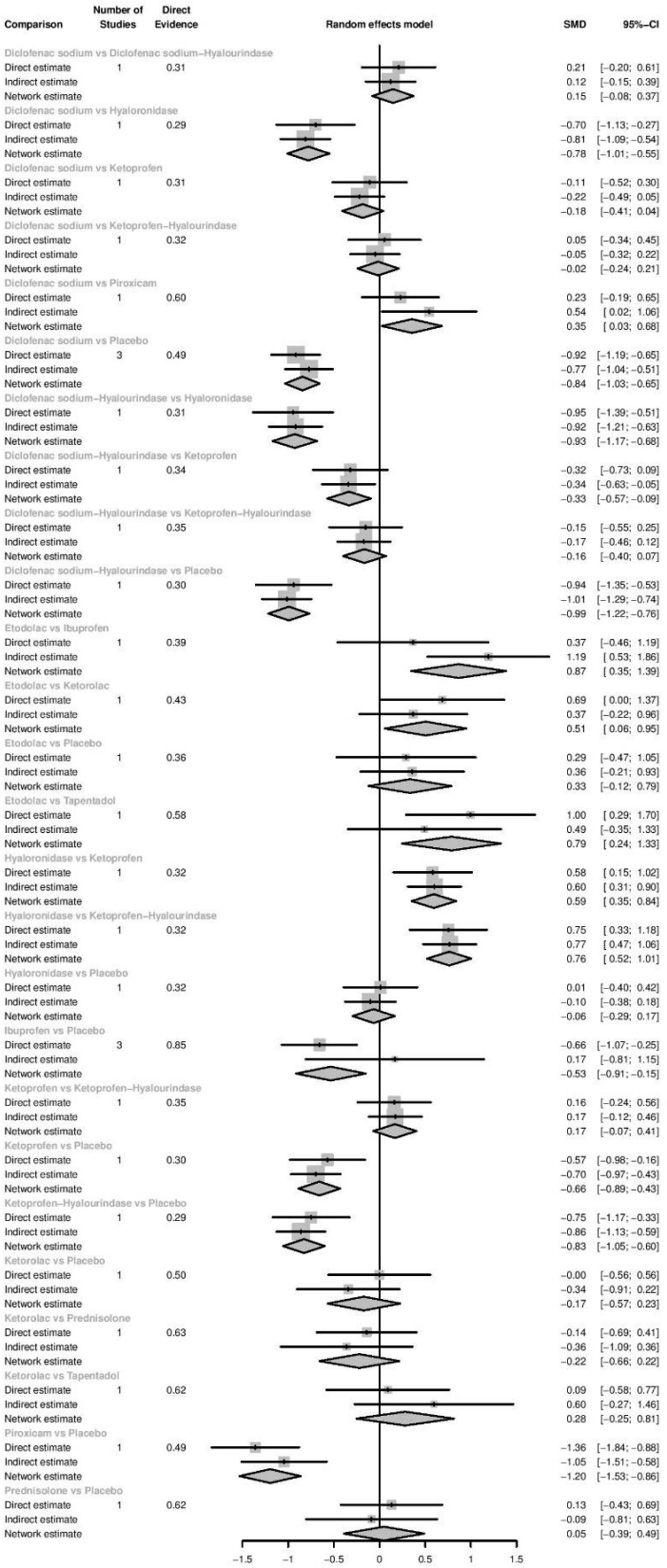
Appendix Fig. (5). Split analysis of the effect of treatment Intervention Categorized by Pharmacologic Group on Postoperative Pain at 24 hours after the procedure.



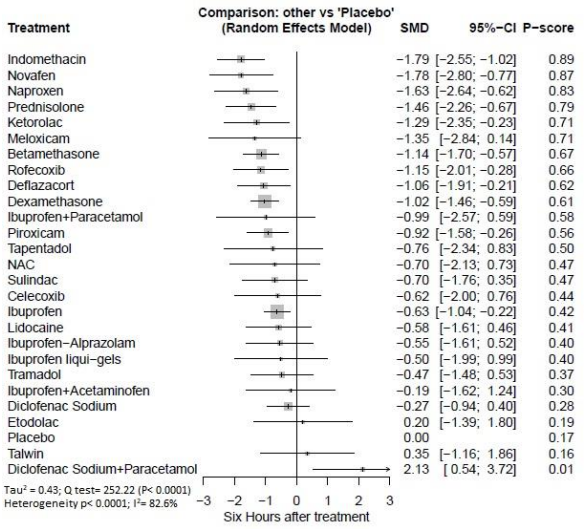
Appendix Fig. (6). Split analysis of the effect of treatment Intervention Categorized by Pharmacologic Group on Postoperative Pain at 48 hours after the procedure.



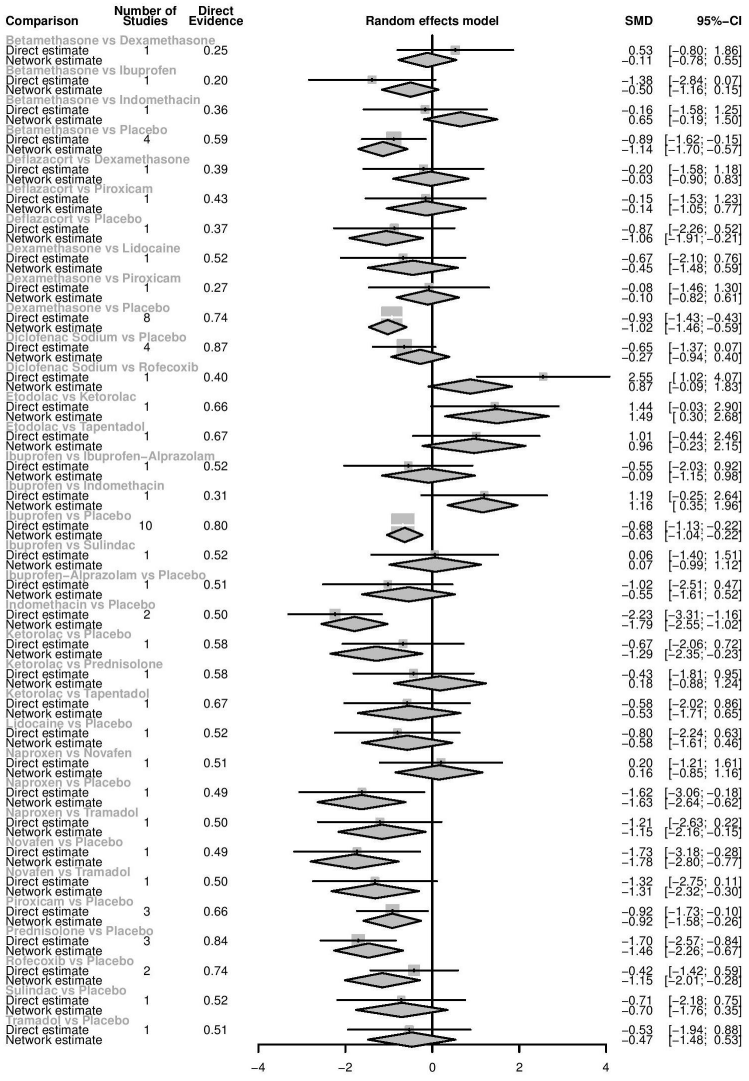
Appendix Fig. (7). Forest plot of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain immediately after the procedure.



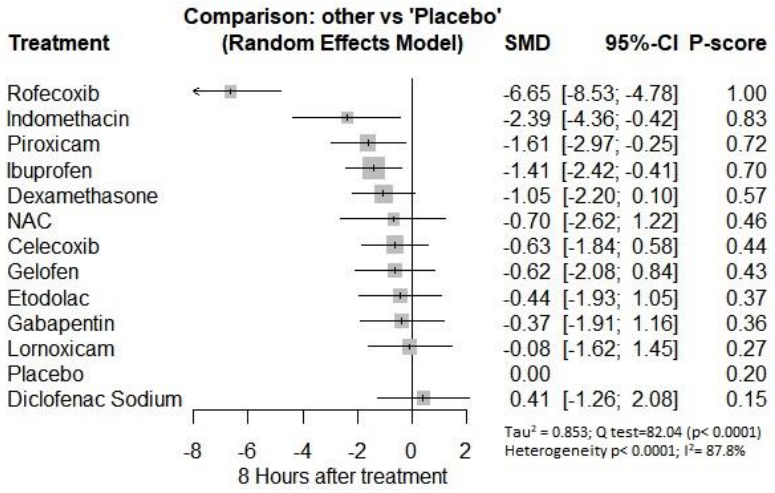
Appendix Fig. (8). Split analysis of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain immediately after procedure.



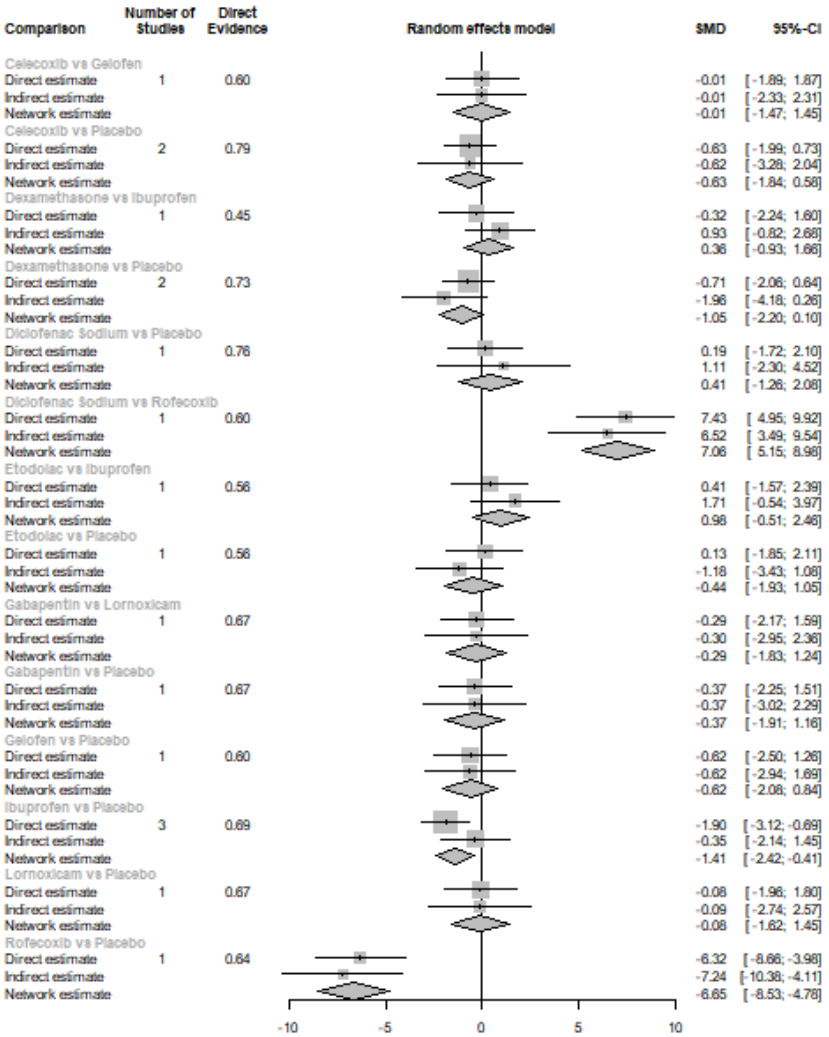
Appendix Fig. (9). Forest plot of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 6 hours after the procedure.



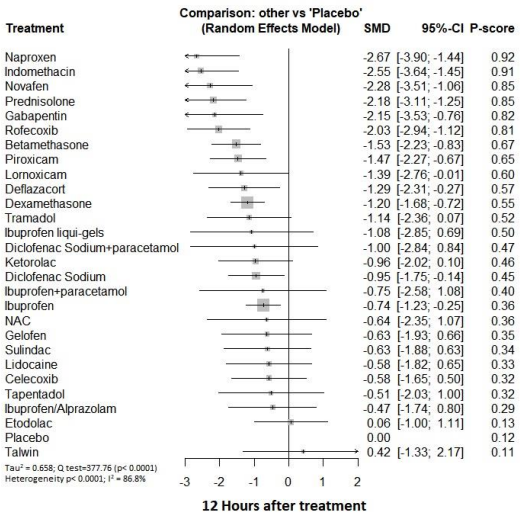
Appendix Fig. (10). Split analysis of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 6 hours after the procedure.



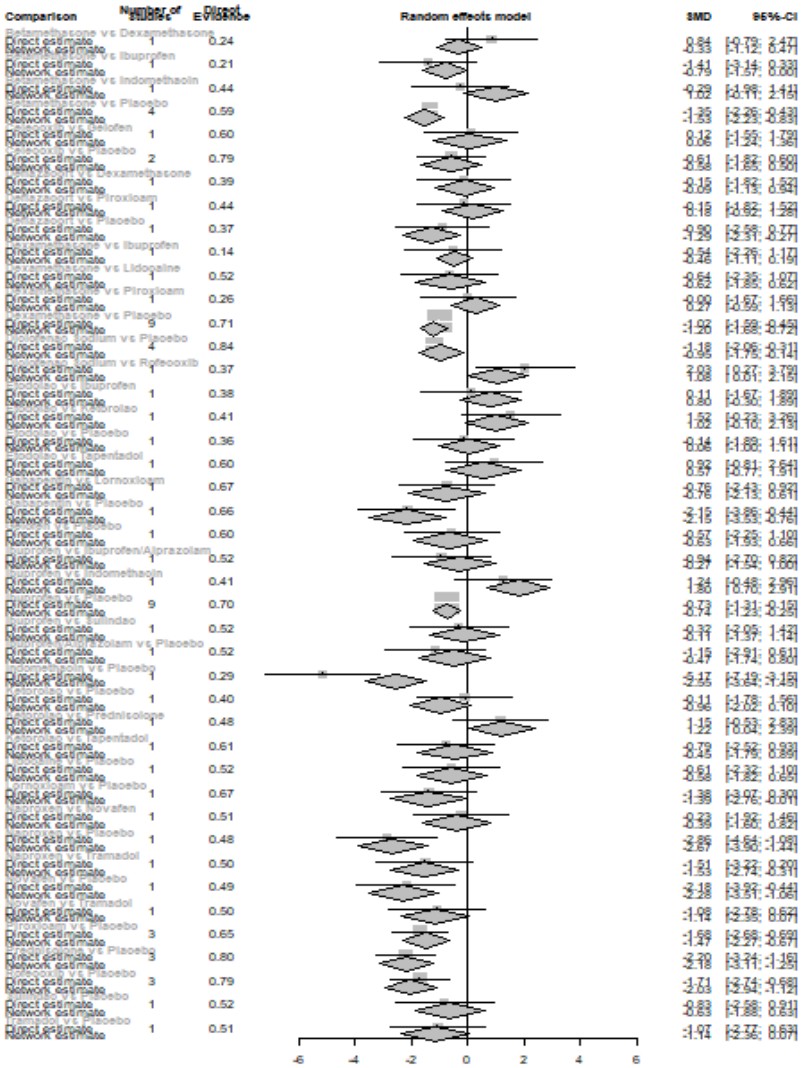
Appendix Fig. (11). Forest plot of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 8 hours after the procedure.



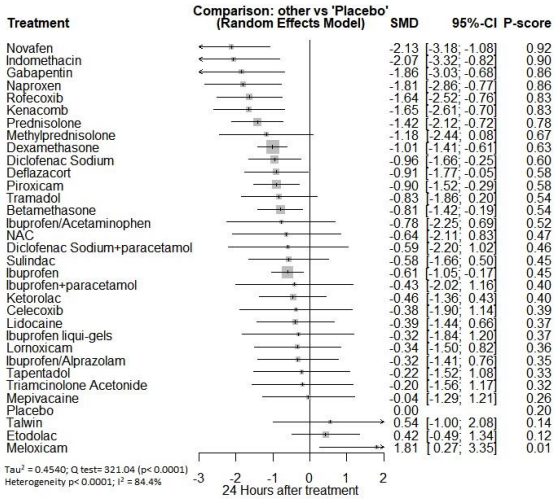
Appendix Fig. (12). Split analysis of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 6 hours after the procedure.



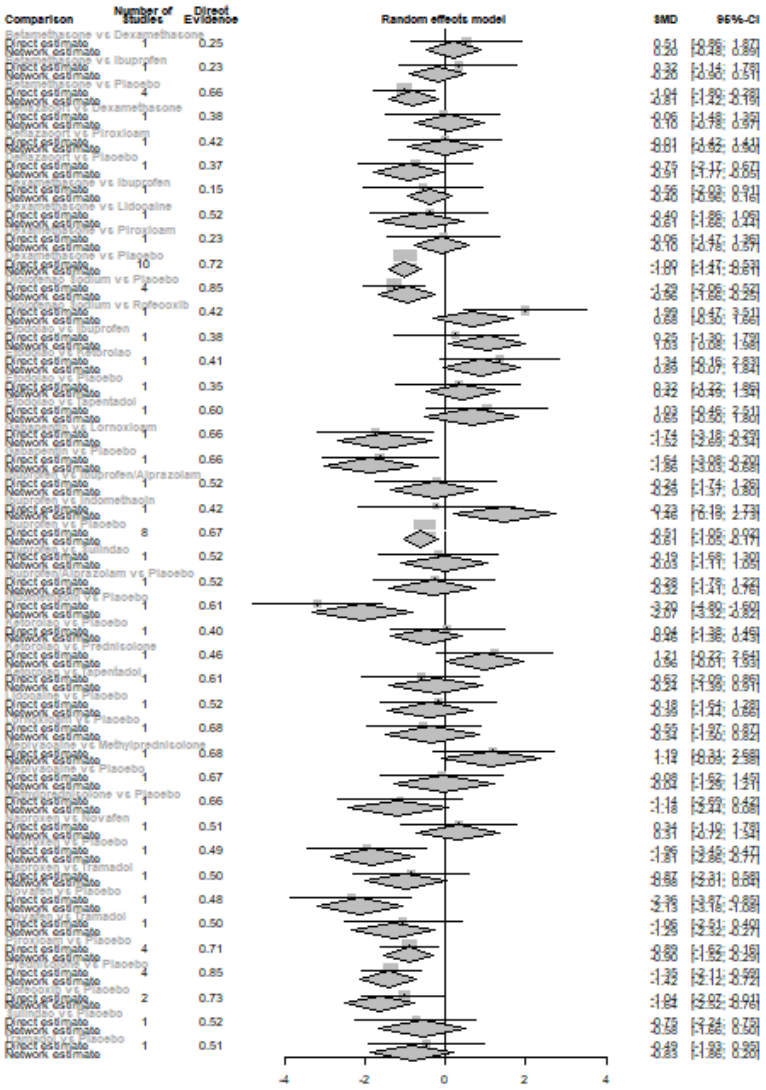
Appendix Fig. (13). Forest plot of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 12 hours after the procedure.



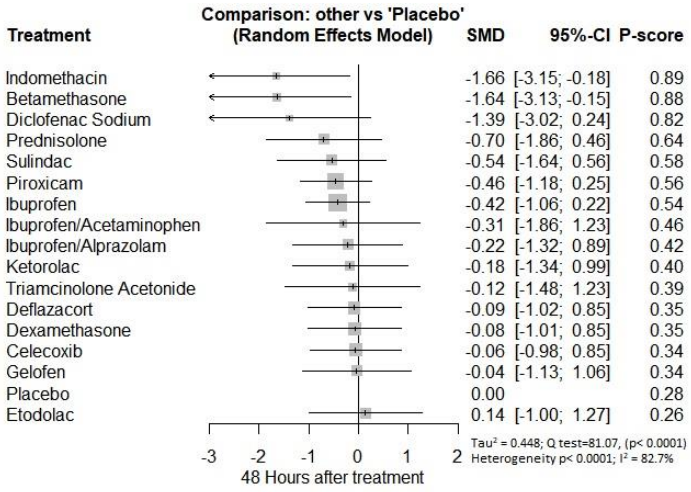
Appendix Fig. (14). Split analysis of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 12 hours after the procedure.



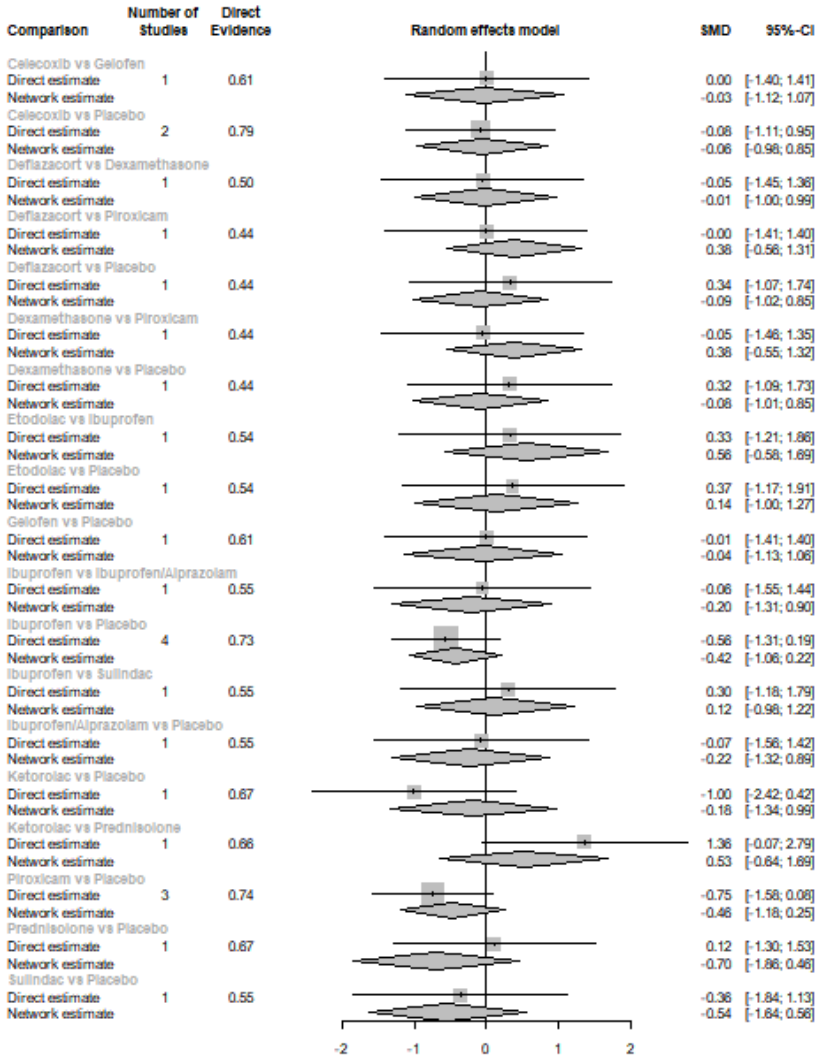
Appendix Fig. (15). Forest plot of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 24 hours after the procedure.



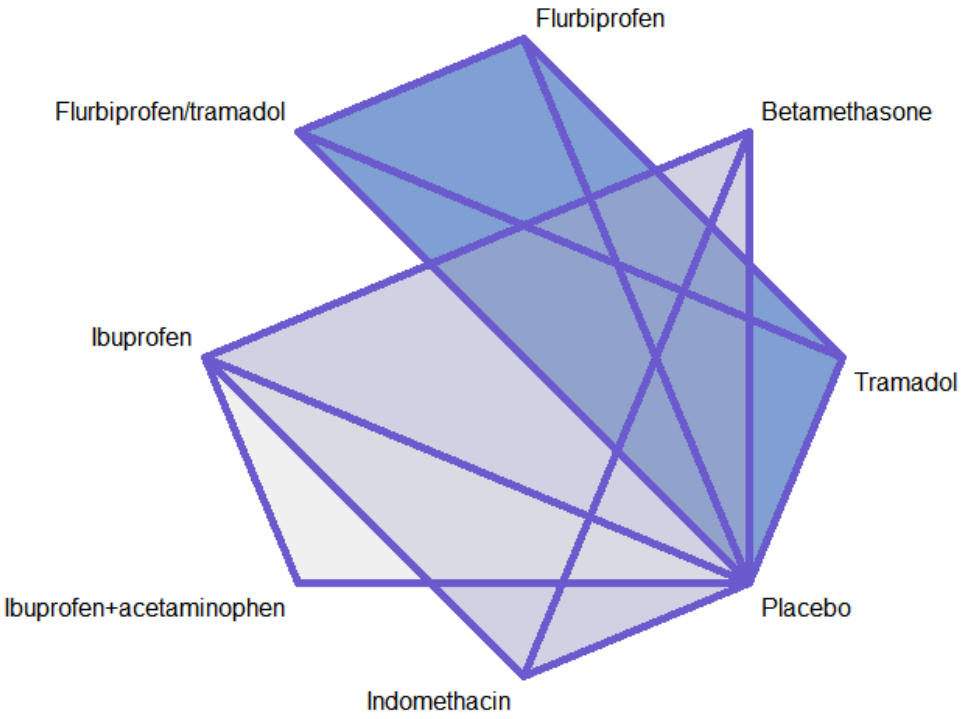
Appendix Fig. (16). Split analysis of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 24 hours after the procedure.



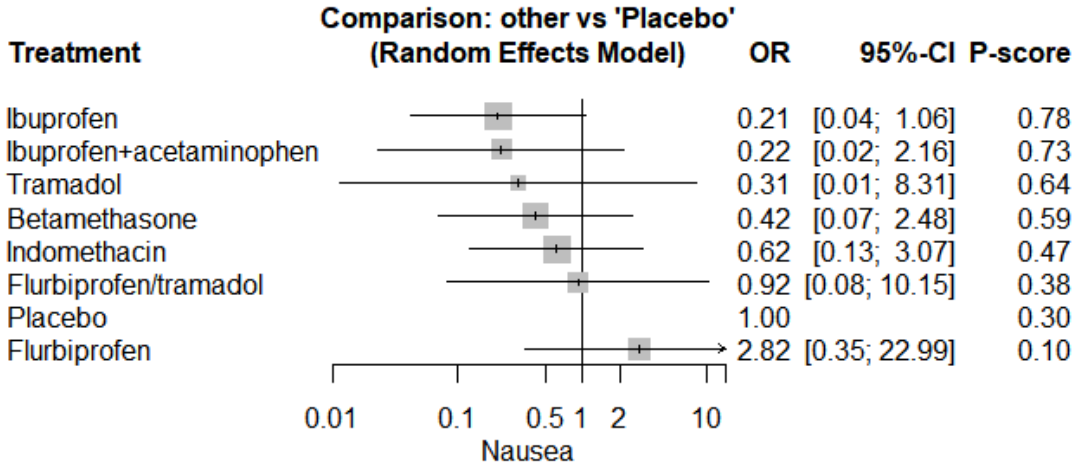
Appendix Fig. (17). Forest plot of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 48 hours after the procedure.



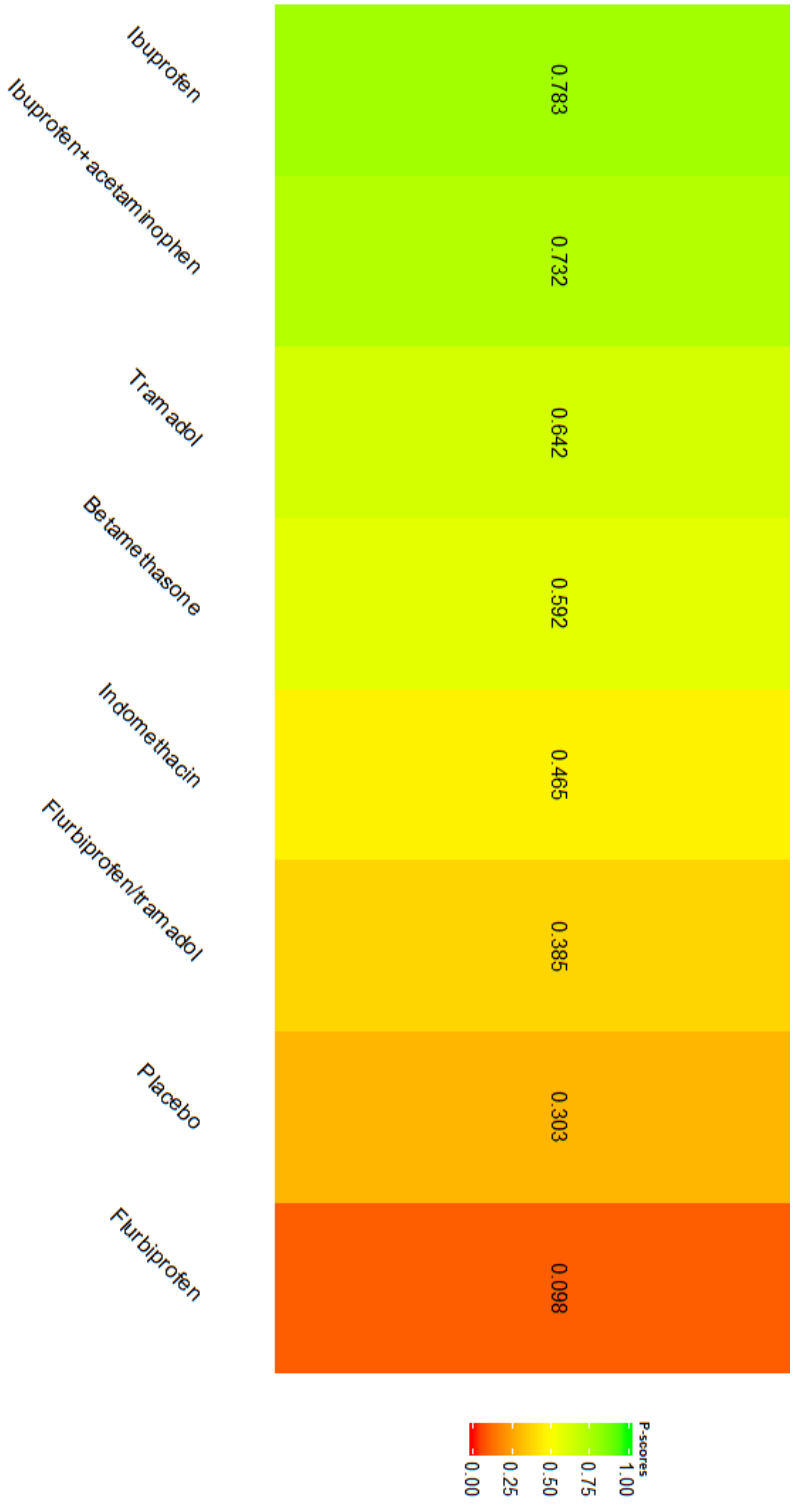
Appendix Fig. (18). Split analysis of the effect of treatment Intervention Categorized by chemical name on Postoperative Pain at 48 hours after the procedure.



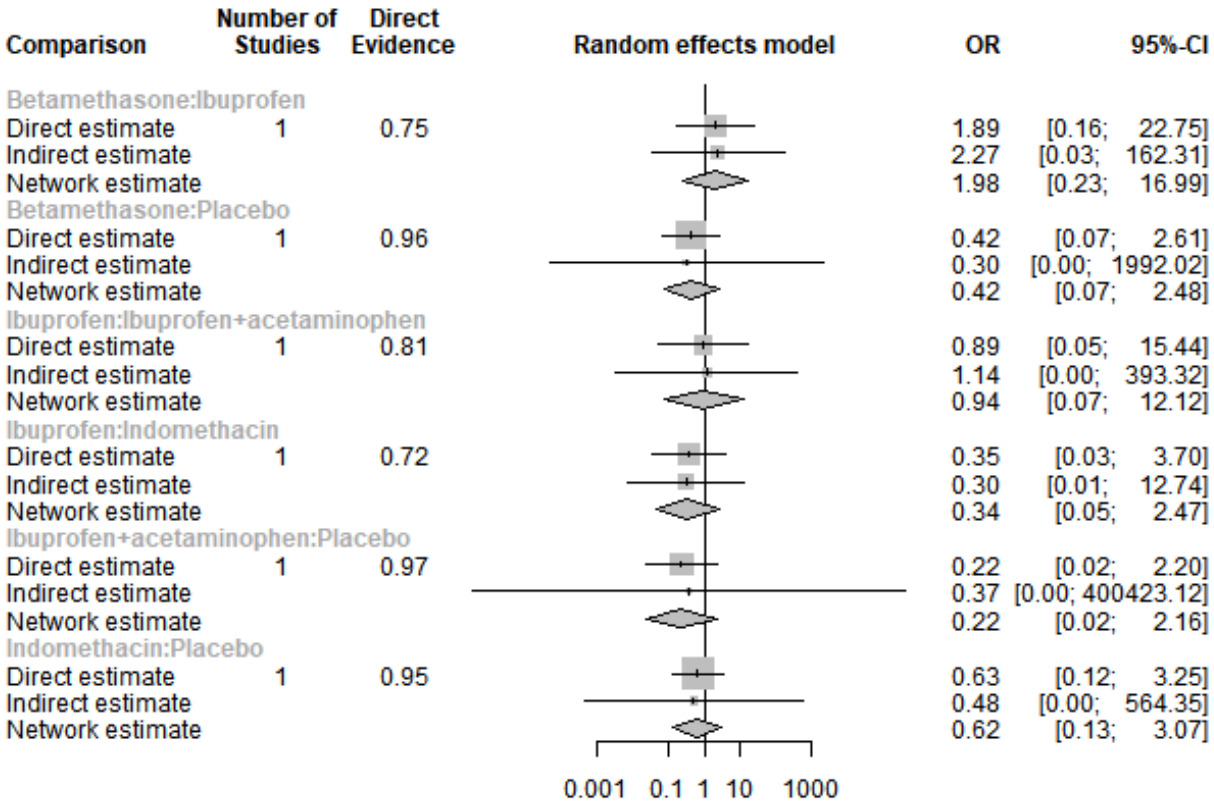
Appendix Fig. (19). Network graph of nausea.



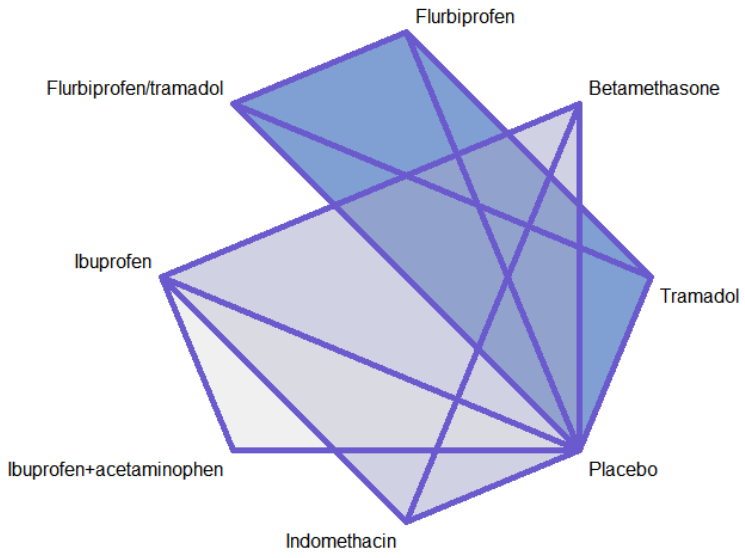
Appendix Fig. (20). Forest plot of nausea.



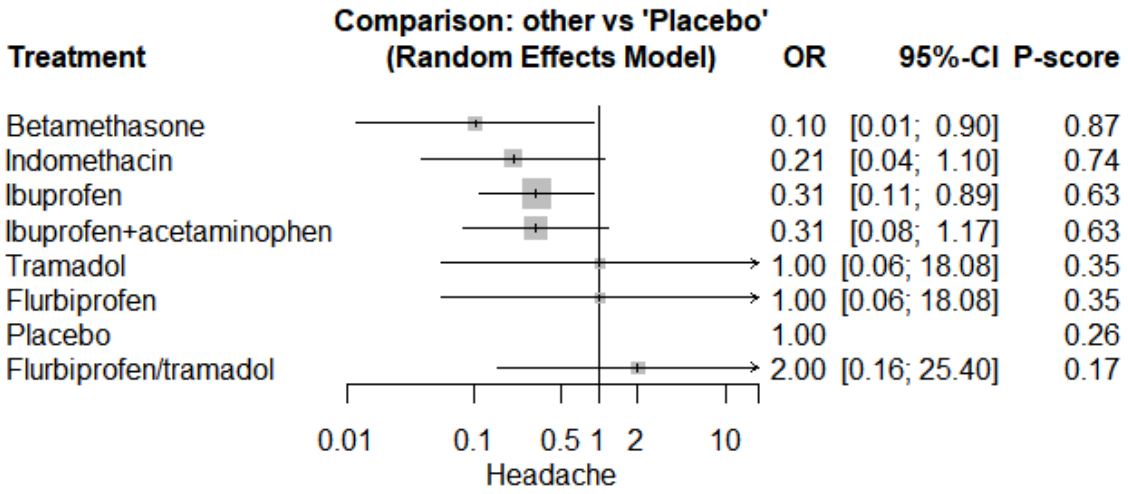
Appendix Fig. (21). Ranking plot of nausea.



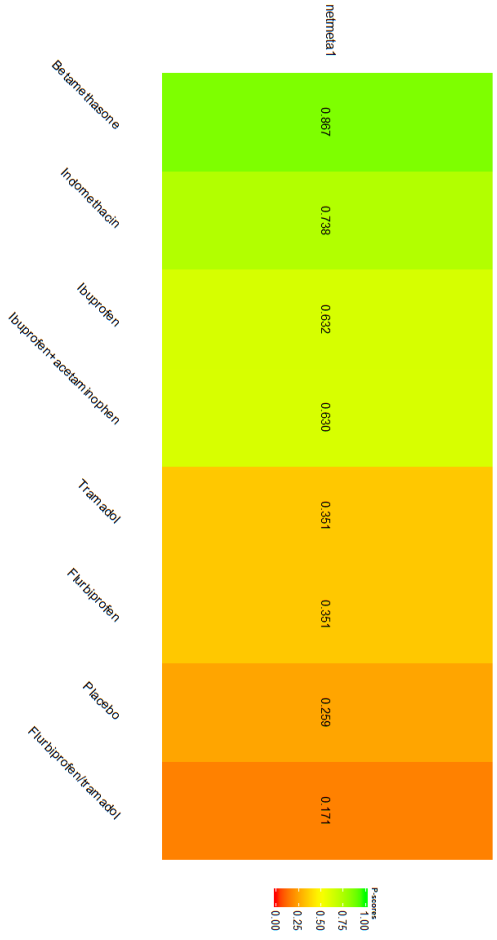
Appendix Fig. (22). Split analysis of nausea.



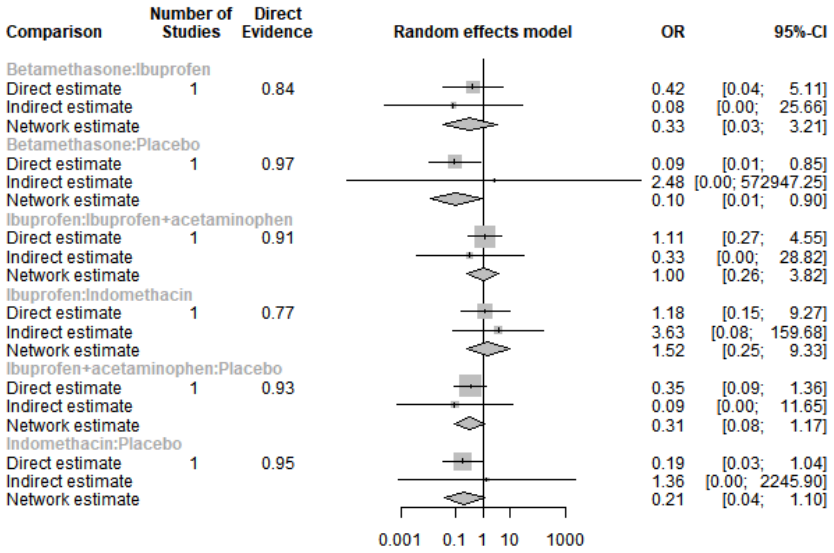
Appendix Fig. (23). Network graph of headache.



Appendix Fig. (24). Forest plot of headache.



Appendix Fig. (25). Ranking plot of headache.



Appendix Fig. (26). Split analysis of headache.

Appendix Table 1. League table of the effect of treatment intervention categorized by pharmacologic group on postoperative pain immediately after the procedure.

Corticosteroid	-	-	-	-
0.47 (-0.86; 1.80)	COX-2	-	-	-
0.45 (-0.26; 1.15)	-0.02 (-1.18; 1.13)	NSAID	-	-
0.98 (-0.05; 2.01)	0.51 (-0.87; 1.89)	0.53 (-0.22; 1.29)	Opioid	-
-0.18 (-0.88; 0.53)	-0.65 (-1.78; 0.48)	**-0.63 (-0.89; -0.36)**	**-1.16 (-1.96; -0.36)**	Placebo

Appendix Table 2. League table of the effect of treatment intervention categorized by pharmacologic group on postoperative pain at 6 hours after the procedure.

Corticosteroid	-	-	-	-
-0.07 (-0.90; 0.75)	COX-2	-	-	-
-0.51 (-0.89; -0.13)	-0.43 (-1.22; 0.35)	NSAID	-	-
-1.05 (-1.76; -0.34)	-0.98 (-1.96; 0.01)	-0.54 (-1.17; 0.09)	Opioid	-
-1.18 (-1.51; -0.85)	**-1.10 (-1.86; -0.34)**	**-0.67 (-0.93; -0.41)**	-0.13 (-0.77; 0.52)	Placebo

Appendix Table 3. League table of the effect of treatment intervention categorized by pharmacologic group on postoperative pain at 8 hours after the procedure.

Corticosteroid	-	-	-	-
1.63 (-0.07; 3.33)	COX-2	-	-	-
-0.40 (-1.75; 0.95)	**-2.03 (-3.27; -0.79)**	NSAID	-	-
-0.48 (-2.62; 1.65)	**-2.11 (-4.20; -0.03)**	-0.08 (-1.85; 1.68)	Opioid	-
-1.23 (-2.48; 0.02)	**-2.86 (-4.05; -1.66)**	**-0.83 (-1.54; -0.11)**	-0.75 (-2.51; 1.02)	Placebo

Appendix Table 4. League table of the effect of treatment intervention categorized by pharmacologic group on postoperative pain at 12 hours after the procedure.

Corticosteroid	-	-	-	-
-0.19 (-1.00; 0.62)	COX-2	-	-	-
-0.29 (-0.72; 0.13)	-0.10 (-0.86; 0.66)	NSAID	-	-

(Table 4) contd.....

Corticosteroid	-	-	-	-
-0.56 (-1.28; 0.16)	-0.37 (-1.32; 0.59)	-0.27 (-0.89; 0.36)	Opioid	-
-1.39 (-1.77; -1.02)	**-1.20 (-1.92; -0.48)**	**-1.10 (-1.39; -0.81)**	**-0.84 (-1.48; -0.20)**	Placebo

Appendix Table 5. League table of the effect of treatment intervention categorized by pharmacologic group on postoperative pain at 24 hours after the procedure.

Corticosteroid	-	-	-	-
0.13 (-0.75; 1.01)	COX-2	-	-	-
-0.48 (-0.85; -0.11)	-0.61 (-1.47; 0.25)	NSAID	-	-
-0.87 (-1.59; -0.15)	-1.01 (-2.08; 0.07)	-0.39 (-1.08; 0.29)	Opioid	-
-1.13 (-1.44; -0.83)	**-1.27 (-2.10; -0.43)**	**-0.65 (-0.94; -0.37)**	-0.26 (-0.95; 0.43)	Placebo

Appendix Table 6. League table of the effect of treatment intervention categorized by pharmacologic group on postoperative pain at 48 hours after the procedure.

Corticosteroid	-		
-0.24 (-1.21; 0.73)	COX-2		
0.04 (-0.52; 0.59)	0.28 (-0.59; 1.14)	NSAID	
-0.47 (-0.99; 0.05)	-0.23 (-1.07; 0.61)	**-0.50 (-0.88; -0.13)**	Placebo

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