



# Do corticosteroids reduce postoperative pain following third molar intervention?

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**Background:** Corticosteroids have been widely used by oral surgeons for reducing swelling caused by wisdom teeth surgery. However, they have not been proven to decrease pain. This study was aimed at analyzing previous studies pertaining to corticosteroids and pain reduction following wisdom teeth surgery.

**Methods:** The Science Direct, PubMed, and MEDLINE databases were searched for relevant journals according to a systematic search strategy (Patient Intervention Comparison Outcome Study). Randomized controlled trials published in English from 1998 to 2017 were extracted.

**Results:** Twenty-seven articles were included, with a total of 36 comparative cases. Methylprednisolone and dexamethasone were the most commonly used corticosteroids. Intramuscular injections of corticosteroids were optimal for pain reduction, regardless of the time of administration.

**Conclusions:** Corticosteroids can be used as an adjuvant for pain reduction following wisdom teeth surgery. Methylprednisolone and dexamethasone delivered via the intramuscular route is the best method for effective pain reduction. The ideal time for administration of corticosteroids is the preoperative period.

**Keywords:** Corticosteroid; Dexamethasone; Mandible; Postoperative Pain; Surgical Removal; Third Molar.



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## INTRODUCTION

Impacted mandibular third molars are usually associated with concomitant pathologies that warrant surgical removal [1-3]. Surgical extraction of the mandibular third molars is the most frequent intervention in the field of oral surgery [4]. However, it is often associated with significant postoperative sequelae [5-6]. In addition to severe complications, such as dysesthesia, infection, fracture, and dry socket, patients frequently present with swelling due to inflammatory responses following

surgery [7].

### 1. Pain from mandibular third molar surgery

Postoperative pain following extraction of the impacted third molars may cause severe patient distress [8]. Analgesics and anti-inflammatory drugs prescribed postoperatively should relieve pain, reduce swelling, and trismus as much as possible and improve healing without undesirable side effects. Therefore, drugs, such as corticosteroids, that exert both analgesic and anti-inflammatory effects should be used [9] for the management of postoperative discomfort.

Received: May 5, 2020 • Revised: July 5, 2020 • Accepted: August 10, 2020

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Table 1. Excluded studies with reasons

Search strategy	Variable	Study	Code	Used Keywords
Population			#1	("third molar" OR "third molar surgery" OR "impacted third molar")
Intervention			#2	("steroid" OR "steroids" OR "corticosteroid")
Comparison			#3	("corticosteroid" OR "placebo effect" OR "analgesic")
Outcome			#4	("pain" OR "postoperative pain")
Study design			#5	Randomized controlled and controlled clinical trials
Search combination				#1 AND #2 AND #3 AND #4 AND #5
Database search				
Language			English	
Electronic database			Scopus, PubMed, and MEDLINE	

Although corticosteroids have been documented to reduce swelling and trismus following wisdom teeth surgery, their role in pain reduction has not been widely reported.

## 2. Comparison of types of corticosteroids

Corticosteroids can be divided into two major groups: glucocorticoids and mineralocorticoids. Glucocorticoids have anti-inflammatory properties with minimal or no influence on the fluid or electrolyte balance; therefore, we investigated only glucocorticosteroids in this study. Hereinafter, "corticosteroids" will be used to imply "glucocorticoids" [10] in this manuscript.

This study was aimed at analyzing the efficacy of corticosteroids in pain management after mandibular third molar surgery through a review of several published scientific studies. We also aimed to obtain knowledge about more effective adjuvant analgesic methods.

## METHODS

### 1. Trial selection

The search methodology was organized using a systematic search strategy (Patient Intervention Comparison Outcome Study), as shown in Table 1. The Scopus, PubMed, and MEDLINE databases were searched from 1998 to 2017 (20 years). We started the study with a suitable title on 2018 and finished it by the

end of that year (2018).

The keywords used to explore the databases were: "third molar" OR "third molar surgery" OR "impacted third molar" AND "steroid" OR "steroids" OR "corticosteroid" AND "pain" OR "postoperative pain."

Two separate reviewers performed the literature search, and the sifting process was ideally used. Both reviewers agreed on the best practice guidelines in conducting systematic reviews.

### 2. Study criteria

Studies were included if all of the following eligibility criteria were met:

1. Randomized clinical trial (RCT) or controlled clinical trial (CCT)
2. Involving the surgical removal of an impacted mandibular third molar
3. Including corticosteroids as intervention
4. Pain measured on the visual analogue scale (VAS)

### 3. Data extraction

As presented in Table 2 [11-37], data extracted from studies were:

1. Authors and year of publication
2. Study design, number of subjects, and mean age
3. Mean duration of surgery
4. Type of corticosteroid
5. Corticosteroid dosage and route of administration
6. Timing of corticosteroid administration

Table 2. Articles selected for the analysis from 1998 to 2017

No.	Year	Author	Sample size	Mean age (years)	Group	N	Steroid	Dose (mg)	Route	Time	Duration of assessment (day)	pain assessment
1.	2017	Chugh et al. [25]	60	29.7	A	17	Control	0	SM	pre-op	1, 3, 4, 7	VAS
					B	23	Dexamethasone	8	SM	pre-op		VAS
2.	2017	Al-Dajani [30]	32	NR	A	32	Dexamethasone	0.1 mg/kg	IM	pre-op	2, 4, 6	VAS
					B	32	Control	0	IM	pre-op		TAC
3.	2017	Lim & Ngeow [31]	65	25	A	22	Control	0	SM	pre-op	1, 2, 5, 7	VAS
					B	22	Dexamethasone	4	SM	pre-op		VAS
					C	21	Methylprednisolone	40	SM	pre-op		VAS
4.	2016	Saravanan et al. [29]	60	NR	A	20	Control	0	No	No	0, 1, 3, 7	VAS
					B	20	Dexamethasone	8	IV	pre-op		VAS
					C	20	Dexamethasone	8	SM	pre-op		
5.	2014	Chaudhary et al. [11]	200	20.8	A	100	Dexamethasone	4	IV	pre-op	1, 2, 7	VAS
					B	100	Dexamethasone	8	PO	pre-op		TAC
6.	2014	Ilhan et al. [22]	60	NR	A	20	Tenoxicam	x	x	x	1 (q 1 h)	VAS
					B	20	methylprednisolone	80	IV	pre-op		
					C	20	Control	0	IV	pre-op		
7.	2014	Selvaraj et al. [26]	10	NR	A	5	Methylprednisolone	40	IM (massetter)	pre-op	1, 2, 3	VAS
					B	5	Methylprednisolone	40	IM(gluteal)	pre-op		
8.	2013	Alcântara et al. [12]	16	20.3	A	16	Dexamethasone	8	IV	pre-op	1, 2, 3	VAS
					B	16	Methylprednisolone	40	PO	pre-op		TAC
9.	2013	Mehra et al. [18]	80	NR	A	20	Control	0	IV	intra-op	1, 2, 3, 7	VAS
					B	20	Ibuprofen	x	x	x		
					C	20	Dexamethasone	8	IV	intra-op		
					D	20	Dexamethasone/ibuprofen	x	x	x		
10.	2013	Warraich et al. [20]	100	26.9	A	50	Dexamethasone	4	SM	pre-op	2, 10	VAS
					B	50	Control	0	No	No		
11.	2013	Marques et al. [23]	60	23.44	A	30	Betamethasone	12	SM	post-op	1, 2, 3	VAS
					B	30	Control	0	SM	post-op		
12.	2012	Acham et al. [19]	16	23	A	8	Methylprednisolone	40-80 (weight dependent)	PO	pre-op	1, 2, 3, 4, 5, 6, 7	VAS
					B	8	Control	0	PO	pre-op		
13.	2012	Simone et al. [24]	54	NR	A	20	Dexamethasone	8	PO	pre-op	0, 1, 2, 4, 7	VAS
					B	14	Control	0	PO	pre-op		TAC
					C	20	Diclofenac	x	x	x		
					C	20	Methylprednisolone	40	SM	pre-op		VAS
14.	2011	Klongnoi et al. [13]	20	21	A	10	Dexamethasone	8	IM	pre-op	1, 2, 7	VAS
					B	10	Control	0	IM	pre-op		TAC
15.	2011	Boonsirisetth et al. [14]	20	20	A	10	Dexamethasone	8	IM	post-op	1, 2, 3, 4, 5, 6, 7	VAS
					B	10	Dexamethasone	8	PO	post-op		TAC
16.	2011	Majid [16]	33	NR	A	11	Control	0	No	No	0, 1, 3, 7	VAS
					B	11	Dexamethasone	4	IM	post-op		VAS
					C	11	Dexamethasone	4	SM	post-op		
17.	2011	Antunes et al. [21]	67	21	A	18	Dexamethasone	8	IM	pre-op	1, 3, 7	VAS
					B	20	Dexamethasone	8	PO	pre-op		TAC
					C	22	Control	0	No	No		
18.	2010	Majid & Mahmood [17]	30	27	A	10	Control	0	No	No	0, 1, 3, 7	VAS
					B	10	Dexamethasone	4	IM	post-op		VAS
					C	10	Dexamethasone	4	SM	post-op		

19.	2010	Kang et al. [27]	60	NR	A	96	Control	0	No	No	1, 2, 3, 4, 5, 6	VAS
					B	60	Prednisolone	10	PO	pre-op		
					C	64	Prednisolone	20	PO	pre-op		
20.	2009	Chopra et al. [28]	150	28	A	30	Control	0	PO	pre-op	1, 3, 5, 7	VAS
					B	30	Paracetamol	x	x	x		
					C	30	Serrapeptidase	x	x	x		
					D	30	Ibuprofen	x	x	x		
					E	30	Betamethasone	0.5	PO	post-op		
21.	2008	Vegas-Bustamante et al. [15]	40	25	A	20	Methylprednisolone	40	IM	post-op	1, 2, 3	VAS
					B	20	Control	0	No	No		
22.	2008	Zandi [32]	22	NR	A	11	Drain	0	No	No	2, 7	4 point scale
					B	11	Dexamethasone	8	IV	pre-op		
					C	22	Control	0	No	No		
23.	2006	Buyukkurt et al. [36]	45	22.87	A	15	Prednisolone	25	IM	post-op	1 (q 1 hr.)	VAS
					B	15	prednisolone/ diclofenac	25	IM	post-op		
					C	15	Control	0	IM	post-op		
24.	2005	Graziani et al. [33]	43	24	A	14	Dexamethasone	4	endo-alveolar powder	intraop	2, 7	VAS
					B	14	Dexamethasone	10	endo-alveolar powder	intraop		
					C	15	Dexamethasone	10	SM	intraop		
					D	43	Control	0	No	No		
25.	2004	Moore et al. [37]	29	22.8	A	8	Control	0	PO/IV	pre-op/ intra-op	1, 2, 3, 7	VAS
					B	5	Rofecoxib/placebo	PO/IV	pre-op/ intra-op			
					C	9	Placebo/ dexamethasone	10	PO/IV	pre-op/ intra-op		
					D	7	Rofecoxib/ dexamethasone	PO/IV	pre-op/intra-op			
26.	2003	Üstün et al. [34]	20	21.9	A	20	Methylprednisolone	1.5 mg/kg	IV	pre-op	1, 2, 3, 4, 5, 6, 7	VAS
					B	20	Methylprednisolone	3 mg/kg	IV	pre-op		
27.	1998	Claseman et al. [35]	34	NR	A	8	Control	0	IV	pre-op	1 (q 2 h)	VAS
					B	9	Ketorolac	30	IV	pre-op		
					C	8	Dexamethasone	8	IV	pre-op		
					D	9	Ketorolac	30	IV	pre-op		
							Dexamethasone	8	IV	pre-op		

REMARK: NR, no report; X, Data were not collected; IM, intramuscular; IV, intravenous; SM, submucosal; PO, per oral.

7. Time of pain assessment

8. Method of pain assessment, mean VAS score, and p-values

#### 4. Statistical Analysis

Descriptive analysis and Spearman correlation coefficients were used to analyze the correlation.

## RESULTS

The initial search yielded 99 articles. After title screening, 36 articles were selected for abstract screening. Subsequently, seven studies were excluded for following reasons:

1. Unclear data on the patient selection, treatment, route of administration, dose, or surgical procedure

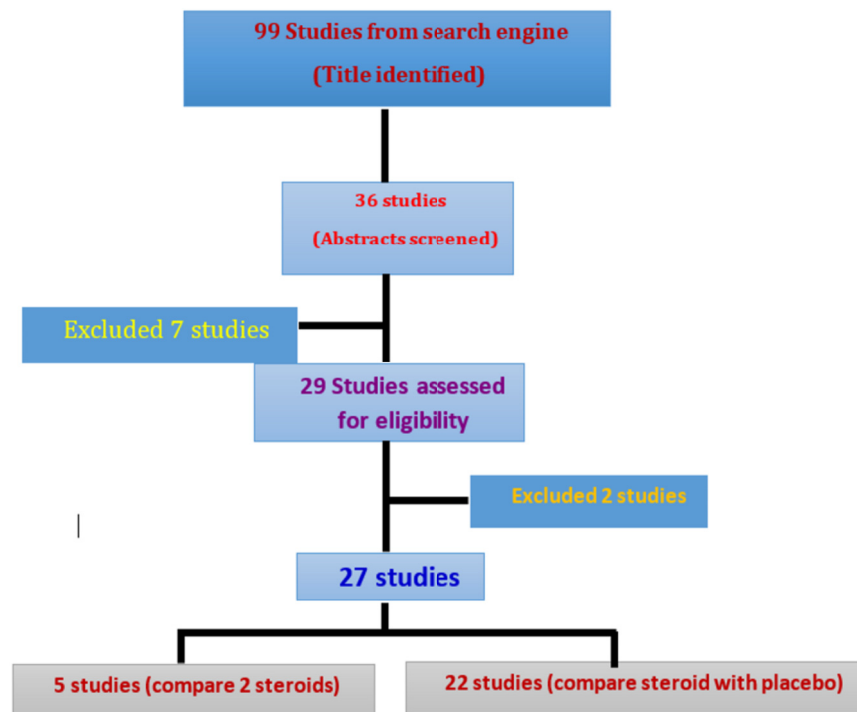


Fig. 1. The number of articles extracted from the search that were excluded or included in this analysis are shown in a flowchart.

2. Improper evaluation of pain or inadequate information of pain outcomes
3. Comparison of corticosteroids with other drugs

Two articles were later excluded because the study had not used VAS for pain assessment.

Finally, 27 articles were chosen for the analysis. Fig. 1 illustrates a flow chart of the 27 case studies that were selected. The effects of varying concentrations of corticosteroids compared to placebo were assessed in 22 studies. The other five previous studies compared types of corticosteroids in terms of the VAS score after surgical removal of the mandibular third molar (Table 2). The corticosteroids used were dexamethasone, methylprednisolone, betamethasone, prednisolone, and placebo/dexamethasone in 64%, 19%, 6%, 8%, and 3%, respectively.

Postoperative pain reduced significantly in patients who took corticosteroids in comparison with those who took a placebo drug. When methylprednisolone and dexamethasone were compared, no significant difference in postoperative pain was found (Table 3). These results suggested that all corticosteroids (glucocorticoids) offered

the same efficacy in pain reduction following surgical removal of the mandibular third molars. This study also focused on articles that reported no steroid treatment or placebo. There were 31 case studies with four features: steroid, dose, route, and time.

We applied one hot methodology and Spearman correlation to determine the key factors contributing to pain reduction and found that the route of drug delivery (max of corr. = 0.3727) is the most important factor, followed by the type of steroid (max of corr. = 0.1667) and time (max of corr. = 0.1373; Table 4).

The percentages of pain reduction in patients administered with corticosteroids intramuscularly, intravenously, and via other routes (submucosal, PO, and endo-alveolar powder) were 100%, 83.33%, and 50%, respectively.

Methylprednisolone, dexamethasone, betamethasone, and prednisolone reduced pain in 75% (three of four), 72.72% (16 of 22), 50% (one of two), and 33% (one of three) of patients, respectively.

The optimal administration timing for corticosteroids was postoperative (77.77%, seven of nine), followed by

**Table 3.** Studies that compared different types or doses of steroids

Author	year	No of study	Type of Steroid and dose (mg)	Route	Time	Result
Ma'aïta & Alwrikat [2]	2000	16	Dexamethasone (8) vs. Methylprednisolone (40)	IV vs. PO	pre-op	ND
Laureano Filho et al. [4]	2008	10	Dexamethasone (8)	IM vs. PO	post-op	ND
Majid [16]	2011	5	Methylprednisolone (40)	IM (masseter vs. gluteal)	pre-op	ND
McCoy [1]	2012	100	Dexamethasone (4 vs. 8)	IV vs. PO	pre-op	ND
Simone [24]	2013	20	Methylprednisolone (1.5 mg/kg vs. 3 mg/kg)	IV	pre-op	ND

REMARK: vs, versus; IM, intramuscular; IV, intravenous; PO, per oral; pre-op, preoperatively; post-op, postoperatively; ND, No difference.

**Table 4.** Spearman correlation for studies on non-steroid use

Result	1.0000	-0.0997	0.1667	0.0598	0.2409	0.3727	0.1634	0.1859	0.2619	0.0997	0.2602	0.1373	0.0671
Betamethasone	-0.0997	1.0000	-0.4106	-0.1011	-0.0860	-0.1418	-0.1287	0.2037	0.0997	-0.0690	-0.1152	0.1213	-0.0255
Dexamethasone	0.1667	-0.4106	1.0000	-0.6018	-0.5118	0.1755	0.1335	-0.4062	0.0147	0.1680	0.2805	-0.0606	-0.1520
Methyl-prednisolone	0.0598	-0.1011	-0.6018	1.0000	-0.1260	-0.2079	0.0550	0.0550	0.1461	-0.1011	-0.1688	0.0342	0.1559
Prednisolone	0.2409	-0.0860	-0.5118	-0.1260	1.0000	0.0842	-0.1604	0.3920	-0.2259	-0.0860	-0.1435	0.0310	0.0778
IM	0.3727	-0.1418	0.1755	-0.2079	0.0842	1.0000	-0.2646	-0.2646	-0.3727	-0.1418	-0.2368	0.3345	0.1300
IV	0.1634	-0.1287	0.1335	0.0550	-0.1604	-0.2646	1.0000	-0.2400	-0.3381	-0.1287	0.2292	-0.3133	0.1164
PO	0.1859	0.2037	-0.4062	0.0550	0.3920	-0.2646	-0.2400	1.0000	-0.3381	-0.1287	-0.2148	-0.1335	0.2805
SM	0.2619	0.0997	0.0147	0.1461	-0.2259	-0.3727	-0.3381	-0.3381	1.0000	-0.1812	-0.1150	0.1667	-0.0671
Endo-alveolar powder	0.0997	-0.0690	0.1680	-0.1011	-0.0860	-0.1418	-0.1287	-0.1287	-0.1812	1.0000	0.5988	-0.1680	-0.2894
Intra-operatively	0.2602	-0.1152	0.2805	-0.1688	-0.1435	-0.2368	0.2292	-0.2148	-0.1150	0.5988	1.0000	-0.2805	-0.4832
Post-operatively	0.1373	0.1213	-0.0606	0.0342	0.0310	0.3345	-0.3133	-0.1335	0.1667	-0.1680	-0.2805	1.0000	-0.7084
Pre-operatively	0.0671	-0.0255	-0.1520	0.1559	0.0778	0.1300	0.1164	0.2805	-0.0617	-0.2894	-0.4832	-0.7084	1.0000
	Result	Betamethasone	Dexamethasone	Methylprednisolone	Prednisolone	IM	IV	PO	SM	Endo-alveolar powder	Intra-operatively	Post-operatively	Pre-operatively

preoperative (70.58%, 12 of 15) and intraoperative (40%).

In Fig. 2 the decision flow chart shows three factors that influenced the effectiveness of corticosteroids for reducing pain (route, type, and timing). This study found the intramuscular route to be extremely effective for reducing pain, consistent with previous studies. We also found five studies that documented 100% efficacy of corticosteroids in pain reduction and four studies that reported no effect in pain reduction.

However, one major limitation of the present study was the extremely small sample size, including six of nine studies that showed 100% effectiveness or no effect at

all for reducing pain. Although oral prednisolone was assessed in two case studies, the timing of drug administration was not considered.

From the decision tree, we found three studies with a 50% probability of effective reduction in pain with any corticosteroid administered via the endo-alveolar route, dexamethasone via the oral route, and any corticosteroid via the intravenous route intraoperatively. Meanwhile, dexamethasone via a submucosal injection postoperatively as effectively reduced pain as a submucosal injection preoperatively at the same dose.

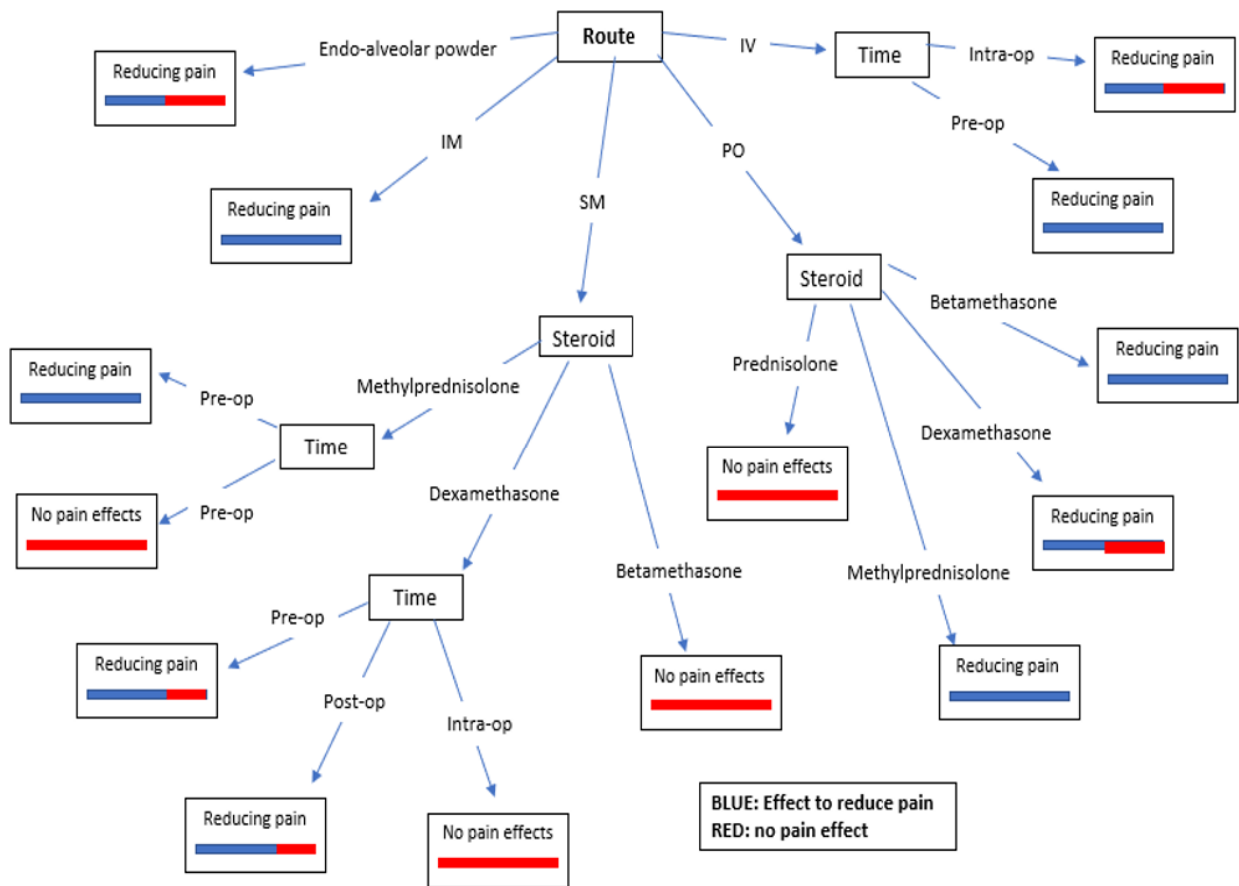


Fig. 2. The decision tree included three factors affecting pain reduction (route, type of steroid, and timing).

## DISCUSSION

Patients are usually afraid of having their wisdom teeth removed because of the fear of pain. Postoperative pain could be managed with analgesics, which reduce pain to a bearable level. Although the role of corticosteroids has mainly been of reducing postoperative swelling and limited mouth opening, corticosteroids also have analgesic properties if administered at the right time of the procedure and via an ideal route of drug administration.

Corticosteroids act by suppressing each phase of the initial inflammatory response, thereby decreasing cellular permeability and capillary dilatation by inhibiting the production of vasoactive substances and diminishing the amount of cytokines [38,39]. Furthermore, the generation of prostaglandin is repressed by corticosteroids, resulting

in an analgesic effect [40,41].

We reviewed 27 previous articles (36 study groups) reporting RCTs involving corticosteroids in comparison with placebo (31 study groups) or comparison of different corticosteroids (five study groups). This study found dexamethasone and methylprednisolone to be the most used corticosteroids because of their pure glucocorticoid nature with no mineralocorticoid effects. These corticosteroids have been used widely in dento-alveolar surgery with minimal adverse effects on leukocyte chemotaxis; their half-life is of an intermediate duration (18–36 h) and potency greater than that of hydrocortisone[42].

There was no significant difference in postoperative pain score across corticosteroid types and doses. Chaudhary et al. [11] found good pain relief with the use of dexamethasone via oral or intravenous administration. Their study found no significant difference in post-

operative pain between 4 and 8 mg of intravenous dexamethasone.

Boonsiriseth et al. [14] reported that the VAS scores for pain assessment showed no significant difference between 8 mg intramuscular and oral dexamethasone following impacted third molar extraction.

An 8-mg single dose of preoperative intramuscular dexamethasone for impacted mandibular third molar surgery was used in the study by Klongnoi et al., which revealed no significant difference between dexamethasone and placebo in pain assessment on VAS [13].

Moreover, a study by Alcântara et al. [12] showed no statistically significant difference in pain scores between 8 mg intravenous dexamethasone and 40 mg PO methylprednisolone following surgical third molar removal. There is no statistically significant difference between the intrabuccal approach for a masseteric muscle injection and gluteal muscle injection of methylprednisolone [26]. Simultaneously, a study by Üstün et al. investigated pain between the groups of 1.5 and 3 mg/kg of methylprednisolone via an intravenous injection and reported no statistically significant difference between the two doses [34]. Postoperative pain was relieved with corticosteroids compared to placebo in 21 of 31 cases (67.74%) and using corticosteroids via intramuscular injections could be the most effective drug delivery administration for postoperative pain control when compared to another administration via another route.

A single dose of pre- or postoperative intramuscular administration [13] can deliver stable plasma drug concentrations and extended anti-inflammatory activity. Masseter and deltoid muscle injections are the most effective.

From this study, the intravenous injection of corticosteroids preoperatively provides decreased postoperative pain better than intraoperative or postoperative intravenous injections. The preoperative intravenous injection provides immediate therapeutic drug concentrations in the blood before actual surgical trauma [43]. Nonetheless, the distinct disadvantage of both intramuscular and intra-

venous injections is an additional discomfort or pain at the injection site.

In the scholarly articles reviewed, the use of corticosteroids aided in exerting an additional analgesic effect. However, the use of analgesics for pain control is still recommended.

It is difficult to draw finite conclusions from all these studies because of the varying skills of surgeons and depth and angulation of the wisdom teeth. Furthermore, postoperative pain measurements were performed in different time periods. The objective and subjective factors, such as degree of surgical trauma, duration of surgery, and experience of the surgeon, as well as the anxiety, pain tolerance, pain expectation, or analgesic drug use of the patient can affect the outcome of pain evaluation following impacted third molar surgery [44]. The sociocultural background may also affect the pain outcome, tolerance, and expectations, which could differ among individuals from developed countries to those from underdeveloped nations.

Although our study found many articles that mentioned pain reduction with corticosteroids, the exact mechanism for this effect is not yet defined. The authors assume that corticosteroids work by reducing prostaglandin synthesis, which suppresses the vascular events that lead to the cardinal signs of inflammation, thereby reducing swelling, redness, heat, and pain.

Steroids are an analgesic adjuvant. They have shown analgesic properties in some painful situations, although their use is mostly outside pain management. With different mechanisms of action, there are many names of these drugs, such as secondary analgesics, co-analgesics, auxiliary analgesics, and non-indication drugs. Therefore, most steroids are only adjuvant agents for preventing inflammation and edema of the oral soft tissue, which contribute to the development of pain.

In conclusion, corticosteroids can have analgesic properties but are not analgesic drugs because of the indirect analgesic effects. They can be used in combination with analgesics to reduce inflammatory symptoms, including pain. Methylprednisolone and dexamethasone



are the suggested drugs that can effectively decrease pain after impacted mandibular third molar surgery. The intramuscular and intravenous routes are the most effective for pain reduction. The perfect timing for injection to obtain maximum benefit from corticosteroids for pain reduction is the preoperative period.

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**Lee Kian Khoo:** Methodology, Visualization, Writing - review & editing

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**Natthamet Wongsirichat:** Conceptualization, Supervision, Writing - review & editing

**ACKNOWLEDGMENTS:** The authors would like to thank the staff, colleagues, and dental assistants, including co-workers, at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Mahidol University. Finally, the authors would like to thank Christian Estacio for editing and revising the language of this manuscript.

**DECLARATION OF PATIENT CONSENT:** No patient consent was required because of the retrospective study design.

**FUNDING, CONFLICTS OF INTEREST, ETHICAL APPROVAL**

**FUNDING AND SPONSORSHIP:** This research study did not receive funding from any sponsor or scholarship

**CONFLICTS OF INTEREST:** The authors declared a conflict of interest.

**ETHICS APPROVAL FOR CLINICAL STUDY:** This study did not require approval from the Faculty of Dentistry/Faculty of Pharmacy, Mahidol University, Institutional Review

Board (MU-DT/PY-IRB), because of the retrospective study design.

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