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Review of dexamethasone administration for management of complications in postoperative third molar surgery

Dr. Ashwin Shravan Kumar[1], Post Graduate Resident, Department of Oral and Maxillofacial Surgery, Sree Balaji Dental College and Hospitals, Bharath Institute of Higher Education and Research, Chennai

Dr. Balakrishnan[2], Professor, Department of Oral and Maxillofacial Surgery, Sree Balaji Dental College and Hospitals, Bharath Institute of Higher Education and Research, Chennai.

Dr. Vijay Ebenezer[3], Professor and Head of the Department, Department of Oral and Maxillofacial Surgery, Sree Balaji Dental College and Hospitals, Bharath Institute of Higher Education and Research, Chennai

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Abstract:

Dexamethasone has been used as an medical aid in third molar surgery to reduce inflammation, trismus and pain. Dexamethasone is a high potent drug helping in the pain pathway. Dexamethasone is responsible for inhibiting the release of inflammatory mediators in the inflammation process to improve patient quality of life after surgical intervention. There are several available routes of administering dexamethasone. This article will help determine the suggested routes of administration, dosage, parameters, and dexamethasone timing for third molar surgeries.

Key words: Administration, Dexamethasone, Techniques, Inflammation, Quality of life

I. Introduction

In the field of oral and maxillofacial surgery, methods for lessening discomfort or complications following surgery have gradually become available throughout time. It is still a prevalent problem in the dentistry environment, though. Following dental procedures, the prescription of medications, particularly opioids, for pain management has become commonplace. Narcotics are an example of an analgesic medication that may not be sufficient for pain management due to the unexpected nature of dental surgery results.

Using corticosteroids, which are among the best drugs for managing postoperative pain and inflammation, is another strategy that has been recommended1, 2. Because of their well-known

ability to control inflammation, glucocorticosteroids are used during oral procedures to lessen swelling, trismus, and pain.

A synthetic glucocorticosteroid with no mineralocorticoid action, dexamethasone 3 is one of the most effective steroidal inflammatory medications. Leukocyte chemotaxis, which shows movement of cells outside the circulatory system towards the site of injury4, is minimally adversely affected by this medication. This glucocorticosteroid is one of the most effective anti-inflammatory medications and has at least 25–50 times the potency of hydrocortisone. Dexamethasone does not have the same sodium-maintaining characteristics as hydrocortisone at inflammatory doses5. Glucocorticoids, including dexamethasone, are similar to hormones generated by the adrenal glands and regulate the pace at which anti-inflammatory genes are synthesised in molecular mechanisms.

Numerous published clinical research studies have examined the benefits of dexamethasone, with particular attention to its administration route and possible applications in the field of oral and maxillofacial surgery. Nonetheless, the effectiveness of the techniques has been questioned in light of the advent of new approaches and channels. As a result, the recommended routes of administration, dosage, parameters, and timing of dexamethasone for third molar operations will be determined with the assistance of this literature review.

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1. Dexamethasone in general use

Dexamethasone is a corticosteroid, which makes it a popular drug because of its demonstrated safety and anti-inflammatory properties. Vascular dilatation and fluid transudation are inhibited, and cell turnover is reduced by inhibiting and chemotacting inflammatory cells, which generate many inflammatory mediators2. Dexamethasone is therefore advised even for significant procedures as orthognathic surgeries8.

There are restrictions on the use of dexamethasone. Diabetes, peptic ulcers, TB, hypertension, ocular herpes, glaucoma, Cushing's disease, renal insufficiency, and pregnancy are contraindications9. The impacts on these circumstances show how dexamethasone affects several metabolic and endocrine processes. The medication may cause the fetus's adrenal glands to be suppressed during pregnancy10. Nonetheless, dexamethasone is commonly used to treat allergies, inflammation, and preoperative and postopera tive supportive therapies[5] and commonly is studied in con junction with surgery.

Dextamethasone has a biological half-life of 36 to 72 hours and a plasma half-life of 100 to 300 minutes. Because it is a corticosteroid, its relative anti-inflammatory potency is 25. Neupert et al. (2011) state that a 4 mg dose can produce five times the body's normal physiological cortisol release. Dexamethasone is thought to start working one to two hours in advance, giving it time to diffuse over the cell membrane12. It is said that corticosteroids are at their peak during the first 24 hours following surgery, and that their effects could extend for up to three days2.Strong vasodilating pro-inflammatory mediators are produced by inflammatory reactions, which in turn cause the postoperative outcomes13. Postoperative swelling is first caused by inflammation, which is a defence mechanism that ultimately results in damage. The following are signs of inflammation: heat, redness, swelling, discomfort, and loss of tissue function14. The body can initiate a chemical signalling cascade upon injury, which triggers responses that ultimately result in the healing of the wounded tissues. The target region will receive a mobilisation of leukocytes by chemotaxis from the systemic circulation15.

2. Dexamethasone in third molar surgeries

In dentistry, third molar operations are typically reviewed during treatment with dexamethasone. One of the most frequent procedures performed by oral and maxillofacial surgeons is the extraction of the third molar. Third molar extractions typically necessitate flap reflection, tooth sectioning, and bone removal. The quality of life of the patient is negatively impacted by injuries resulting from manipulation of the surrounding tissue and in conjunction with postoperative sequelae such discomfort, swelling, and trismus. Analgesics are typically administered for patients who are in moderate to severe pain. The type and quantity of analgesics must be carefully chosen to prevent potential adverse effects because non-steroidal anti-inflammatory medicines (NSAID) have the potential to promote acidity, which in certain patients causes a more severe side effect.16.

Inflammation after third molar operations is the main cause of pain, swelling, and trismus. Tissue injury-related inflammation is the source of pain17, 18. Postoperative pain has a significant impact on wound health and healing predictability19, as well as increasing the patient's anxiety and suffering. Despite the limited validity of the many pain metrics, patient suffering should be appropriately described by them20. The visual analogue scale is one of the most commonly used metrics (VAS). Patients' subjective pain experiences are measured using this criterion, particularly those who have had oral and maxillofacial surgery21. VAS has been used in numerous studies7,13,22-28 to measure pain response when dexamethasone is administered. In order to determine pain levels, some studies have used the VAS in conjunction with analgesic intake7,23. A study by Laureano Filho et al.22 Gozali et al.23emphasised that dexamethasone has a significant impact on swelling and trismus but had a negligible effect on discomfort.

Where the mucosa, gingiva, and bone are moved during a lengthy surgical procedure, swelling may result. Swelling cannot be quantified by a single technique since linear estimations are not repeatable29. Dexamethasone-related studies often involve measuring the amount of swelling directly at six anatomical locations and calculating the mean of the linear dimensions (mandibular angle, tragus, lip commissure, nasal border, pogonion, and lateral to the outer canthus of the eye). The planes from the tragus of the ear to the corner of the mouth, the gonion to the commissure of the lips, and the outer canthus of the eye to the gonion are typically used to characterise the points13,22,24, and 28. Only four sites based on plane from the tragus of the ear were assessed in a few investigations[25-27,30]. The two measurements from the eye's tragus to the midline (pogonion) and from the eye's outer canthus to the gonion were measured by Majid and Mahmood31.

Trismus has been measured in a number of dexamethasone-related research by using a ruler or calliper to measure the interincisal distance. The measurement of this parameter often involves calculating the separation between the maxillary and mandibular central incisors' incisal angles at their maximum opening (13, 22–28). Al-Shamiri et al.13, on the other hand, developed an alternative method by figuring out the difference between the maximal openness before and after surgery.

It has been noted that when steroids like dexa methasone are administered, patients need to take less analgesics, such as NSAIDs. This is because dexamethasone has been shown in certain trials to potentially lessen post-operative pain23,33,34. According to Bamgbose et al.35, treating postoperative sequelae with corticosteroids and NSAIDs together, such as dexamethasone, is beneficial for minimising side effects. However, the use of corticosteroids depends on how difficult the process is, therefore it shouldn't be used for every third-molar surgery36.

Dexamethasone has also been used in third-molar research to evaluate quality of life. Majid19 defines quality of life as the patient's capacity to understand how the conditions they are dealing with will affect their everyday functioning, social skills, and physical and mental health. This instrument is typically made up of questionnaires that are tailored to a certain circumstance and can be answered subjectively, either by standardisation or modification37. Patients' quality of life has been linked to the results of third molar surgical extractions. Intravenous cortisol could improve a patient's quality of life by reducing pain and edema, according to Tiwana et

al. 38.

3. Dexamethasone mechanism

In inflammation, injuries create cell membrane dysfunction to allow conversion of phospholipids into arachidonic acid by enzyme phospholipase A (PLA2), an essential chemical mediator that plays a crucial role in the cellular phospholipid bilayer. This transition will lead to synthesis of prostaglan dins and thromboxane by cyclooxygenase (COX) of and leu kotrienes through lipoxygenase and other related substances that trigger inflammatory responses in the initial phases[24,39,40]. These responses are responsible for peripheral sensitization, which increases the excitability of dorsal horn neurons, fol lowed by central sensitization. Once central sensitization is established, signals transmitted through Aβ fibers from low threshold mechanoreceptors are perceived as pain at dorsal horn neurons with high excitability. In addition, since Aδ fi bers and C fibers from nociceptors are under peripheral sensi tization, the pain is enhanced and sustained. Once this central sensitization is established, patients will respond poorly to analgesics[41].

In the concept of pre-emptive analgesia, postoperative pain is minimized by preventing central sensitization before sur gery. When pre-emptive analgesia is provided before surgery, central sensitization is suppressed, and postoperative hyper esthesia does not occur[42]. Other mediators that play a crucial role in inducing inflammation are bradykinin, prostaglandins, and leukotrienes[43-45]. According to Lerner et al.[46], bradykinin is a nonapeptide that activates prostaglandin. Corticosteroids like dexamethasone have been observed to inhibit the release of bradykinin-produced prostaglandin (PGE2), reducing inflammation at the early stages. On the other hand, leukotri enes have a hypoalgesia effect that is essential in modulating inflammatory pain caused by kinins in the system[45].

Inflammatory responses such as swelling occur gradually, with a peak at 48 hours after surgical removal of the teeth[44,47]. Corticosteroids and NSAIDs block on of the same pathways leading to an inflammatory reaction[7]. NSAIDs block the cy
clooxygenase system, while corticosteroids block both the cyclooxygenase and lipoxygenase systems[40]. Based on this, corticosteroids are superior in reducing the effects of chemi cal mediators and can decrease swelling and trismus com pared to NSAIDs[22].

II. Routes of Administration

There are several routes to administering dexamethasone that had been attempted and studied in surgeries of different teeth. There remains no definite consensus about the best treatment approach because advantages and disadvantages exist in every method tested[48,49]. The administration of corti
costeroids through submucosal, intramuscular, intra-alveolar, or intravenous route reduced postoperative pain after third molar surgery[50].

1. Oral route

According to Al-Shamiri et al.[13], 8 mg oral dexamethasone either preoperatively or postoperatively lessens the postop erative complications of third molar surgeries, with their find ings leaning toward preoperative administration. Sabhlok et al.[50] used 4 mg of oral dexamethasone postoperatively every day for five days, demonstrating that it is useful for treating pain and trismus. Moreover, de Sousa Santos et al.[51] con-

cluded that oral dexamethasone with tramadol has favorable effects in controlling the postoperative complications of third molar surgeries. The oral route depends on patient compli ance and repeated intake to regulate blood level for success ful outcomes, rendering it a debatable course of

administra tion[52].

2. Submucosal route

According to Grossi et al.[44], submucosally-administered dexamethasone can achieve positive postoperative edema results compared to other administration routes. Furthermore, they also stated that the submucosal route is advantageous from both the operator and patient point of view because of the ease of administration. Arora et al.[53] found the same re
sults using dexamethasone through the same route. Support ing the conclusions drawn by Grossi et al.[44] and Arora et al.[53], Khalida et al.[25] demonstrated the positive effects of dexa methasone submucosally through reduction of discomfort fol lowing surgery. They mentioned that a sub-therapeutic dose of 4 mg has nonsignificant systemic outcomes[25]. Likewise, Shah et al.[33] stated that dexamethasone through this route im proves patient quality of life. However, the intervention was performed for apicectomy in anterior maxillary teeth, not for third molar surgery[33]. These studies demonstrate the submu cosal route as a widely popular technique[54]. In a 2016 meta analysis by Moraschini et al.[55] on submucosal administration of dexamethasone after third molar surgeries, there was sig nificant decrease of swelling and pain in all studies but was no difference in trismus.

According to Deo[56], quality of life decreased immediately after third molar surgery, leading to his conclusion that sub mucosal dexamethasone can maintain the quality of life. Other studies support this conclusion regarding submucosal dexamethasone[19,31,57].

3. Intravenous route

Bamgbose et al.[35] conducted a study using intravenous dexamethasone with a maximum of 16 mg within 24 hours. Their findings complemented the amplified effects of dexa methasone when used with diclofenac sodium after third molar surgery[35]. Another study by Moore et al.[58] concluded that a co-therapy of 10 mg intravenous dexamethasone (pre operatively) with 50 mg rofecoxib (intraoperative) was the most efficient in combating pain and trismus after third molar surgery compared to using intravenous dexamethasone intra
operatively.

4. Intramuscular route

Intramuscular injections were found to exhibit similar ef fects to the intravenous route. Klongnoi et al.[48] mentioned enhanced postoperative pain relief and reduced swelling in impacted lower third molar surgeries with preoperative 8 mg intramuscular dexamethasone injection in the deltoid muscle. Al-Dajani[59] concluded that a single preoperative intramus cular dose of dexamethasone successfully minimized post operative sequelae after surgical removal of third molar and improved comfort in performing day to day activities.

Coupled by the findings corresponding to intravenous and intramuscular administration, Majid and Mahmood's findings[31] support the conclusion that intravenous and intra muscular routes of dexamethasone have positive effect on swelling and pain compared to other administration routes due to the higher plasma concentrations and long-lasting anti inflammatory effects of intramuscular injection.

In comparing the three routes cited above, in 2017, Vivek et al.[60] studied 8 mg dexamethasone through the three routes of administration of intravenous, intramuscular, and submucosal and determined that, aside from the faster onset and greater bioavailability of intravenous administration, the submucosal and intramuscular routes also can be used for control of pain and swelling with fewer possible complications compared to the intravenous route.

5. Other novel approaches

The administration of dexamethasone through the pterygo mandibular space was studied by Latt et al.[61] in 2016. It was perceived that an 8 mg dexamethasone dose administered through this route was sufficient in reducing swelling, pain, and trismus after third molar surgery[61].

The sublingual route of dexamethasone was

recommended by Gozali et al.[23] for patient comfort in 2017. It was claimed to have a faster onset and, at the 8 mg dose, was believed to be advantageous compared to the intramuscular method to al
leviate effectively pain symptoms[23].

Validating the evidence presented by Latt et al.[61] and Go zali et al.[23], a 2019 study by Moranon et al.[62] found that injec tions of 8 mg dexamethasone into the pterygomandibular or sublingual space were effective similarly in easing postopera tive sequelae after third molar surgeries.

Graziani et al.[36] studied dexamethasone in endo alveolar

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powder and submucosal routes and found comparable results for postoperative pain, swelling, and trismus. It is important to note that the topical dexamethasone used in their study had a more significant effect on trismus[36].

The intra-masseteric approach was investigated by Nandi ni[52] using 8 mg dexamethasone, and they claimed that it was another way to reduce postoperative sequelae compared to the systemic approach. Moreover, some studies stated that the intra-masseteric and submucosal routes were more effective because the drug injection site is in proximity to the surgical area, allowing greater localized absorption with nonsignifi cant side effects[52,56].

Another new method was reported in 2020, where the in traosseous route was utilized and compared to the submuco sal route. Kaewkumnert et al.[27] found that the latter was more efficacious than the former due to the possibility of height ened tension with discomfort created by intraosseous injec tion in the alveolar bone. A summary of respective techniques were presented in Table 1.

III. Dosages

The ideal dose of dexamethasone has yet to be deter mined[50]. According to Antunes et al.[3], the dosing is arbitrary

Table 1. Summary of the latest clinical trials with the use of dexamethasone through different routeS

Results

Evaluated parameters	Sample size and mean age (yr)
Submucosal more favorable than intramuscular	
Pain, swelling, trismus, quality of life	33 patients; mean age, 26.9
Intramuscular and oral equally effective	
Pain, swelling, trismus	67 patients; mean age, 21
Intramuscular (masseter)	

Intramuscular and oral equally effective	Pain, swelling, trismus	20 patients; mean age, 20	
Intramuscular (deltoid) Submucosal more favorable than intramuscular	Pain, swelling, trismus, quality of life	30 patients; mean age, 25.6	
Intravenous and oral equally effective	Pain, swelling, trismus	200 patients; mean age, 20.8	
Oral favorable to intramuscular	Pain, swelling, trismus	60 patients; mean age not mentioned	
Intramuscular (masseter) Intravenous, submucosal, and intramuscular equally effective (Intravenous is faster)	Pain, swelling, trismus	45 patients; mean age, 27	
Intramuscular (masseter) Pterygomandibular and sublingual routes equally effective	Pain, swelling, trismus	30 patients; mean age, 21	
Pterygomandibular space Submucosal favorable to intraosseous	Pain, swelling, trismus		

56 patients; mean age not mentioned

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administration depending on the severity of the issue and patient tolerance.

Route of Sublingual space Intramuscular Intramuscular Intraosseous Submucosal Submucosal Submucosal Submucosal Intravenous Intravenous

1. 4 mg dosage

Oral Oral Oral Oral

Neupert et al.[11] reported that 4 mg of intravenous dexa methasone exhibited no statistical differences in swelling and

Postoperative Postoperative Postoperative Postoperative Postoperative administration Preoperative Preoperative Preoperative Preoperative Time of

trismus compared to the sterile water control. On the other hand, Majid and Mahmood[63] in 2011, concluded that 4 mg dexamethasone through the submucosal route effectively controlled pain, swelling, and trismus compared to the intra

Randomized Randomized Randomized muscular route. Another interesting study by Arora et al.[53]

Design in 2018 stated that no significant differences were observed when 4 mg

or 8 mg was third molar used after third molar surgeries, and that 4 mg was sufficient in reducing edema after

Dose (mg) surgeries.

4 8 8

2. 8 mg

dosage

(2011) A study by Laureano Filho et al.[22] in 2008, comparing the

Antunes et al.[3]

Study							
Majid[19] (2011)	effectiveness of dosages of dexamethasone, indicated that 8	Boonsiriseth et al.[26] (2012)	mg dexamethasone is more efficient in minimizing trismus and swelling compared to the lower dose of 4	Majid and Mahmood[63] (2011)	Randomized 4 (IV) 8 (oral)	Chaudhary et al.[64] (2015)	Randomized 4	Vivek et al.[60] (2017)	Randomized 8	Kaewkumnert et al.[27] (2020)	Randomized 4
			mg. Chaudhary et al.[64], however, assessed 8 mg oral dexamethasone and 4		Randomized 4	Sabhlok et al.[50] (2015)	Randomized 8	Moranon et al.[62]			

mg intravenous dexamethasone. Their results demonstrated that the former was as valuable as the latter in combating postoperative issues after third molar surgeries even if the two routes differed[64]. To date, there are no other studies to supplement the finding that 8 mg dexamethasone is more effective than the 4 mg option through a consistent route of administration. A supporting study of the two dosages was conducted by Grossi et al.[44] and suggested that 4 mg and 8 mg were effective equally in terms of eliminating edema.

IV. Timing of Administration

Regarding whether we should use dexamethasone preop eratively, perioperatively, or postoperatively, Simone et al.[7] indicated that the preoperative combination of dexametha sone and anti-inflammatory drugs was effective in minimiz ing pain during the postoperative period.

1. Preoperative

Ngeow and Lim[65] also mentioned that corticosteroids were preferred before surgery before of commencement of inflam matory activity. Specifically, the rationale for preoperative use of dexamethasone includes preventing establishment of central sensitization caused by peripheral nociception activity secondary to surgical trauma. In the absence of local anesthe sia, this process begins at the incision and continues during the intraoperative and postoperative periods[7]. Preoperative administration was favorable among studies comparing peri operative and postoperative administration[13,66,67].

2. Perioperative

A systemic review and meta-analysis by Markiewicz et al.[68] deduced that perioperative corticosteroids, in general, can lessen edema and trismus more than the control group in a mild to moderate manner, but with no conclusive evi dence regarding pain outcomes. Graziani et al.[36] reinforced this claim using dexamethasone, mentioning that the ease of operation with timing can decrease morbidity after surgery. Similarly, Mehra et al.[69] stated that a perioperative dosage of dexamethasone had a tremendous impact by lessening post operative side effects, but only for a short duration.

3. Postoperative

Studies regarding postoperative use of dexamethasone alone in preventing adverse effects on third molar surgeries are limited. Lima et al.[70] used 4 mg oral dexamethasone fol lowing third molar surgery in a clinical setting and found that all the postoperative sequelae had been addressed in contrast to the use of diclofenac sodium. Furthermore, concerning the timing, it is important to note that some studies found that dexamethasone injections before or after third molar surger

ies to be equitably efficacious[24,71]. The comparisons between the different timing of administration are shown in Table 2.

V. Difficulty of Surgery

According to several authors, the Pell and Gregory Dif ficulty index exhibits questionable reliability. However, it is an important part of predicting postoperative ramifications after surgical removal of third molars when administered with dexamethasone[36,42]. The most common inclusion cri teria in dexamethasone trials were Class II and Position B[3,42,44,49,60,64,72,73]. The use of corticosteroids, in general, is not applicable for every third molar surgery. Nevertheless, its ad ministration can be important in cases of a certain degree of complexity[74,75].

VI. Adverse Effects

Dexamethasone has been utilized in different conditions, including reducing postoperative nausea and pain after

Table 2. Studies on dexamethasone comparing preoperative and postoperative administrations for third molar surgeries

Study Design	Dose (mg)	Time of administration	Route	Sample size and mean age (yr)	Results
Al-Shamiri et al.[13] (2017)	RCT	8	Preop. or Postop.	Oral	24 patients; N/A	Preop.>Postop.
Latif Shah et al.[66] (2018)	RCT	8	Preop. or Postop.	Intramuscular	150 patients; N/A	Preop.>Postop.
Giri et al.[24] (2019)	RCT	8	Preop. or Postop.	Intravenous	100 patients; 27.7±9.7	Preop.=Postop.
Núñez-Díaz et al.[67] (2020)	RCT	4	Preop. or Postop.	Intramuscular	60 patients; N/A	Preop.>Postop.
Sitthisongkhram et al.[71] (2020)	RCT	4	Preop. or Postop.	Pterygomandibular	27 patients; N/A	Preop.=Postop.

(RCT: randomized controlled trial, Preop.: preoperative, Postop.: postoperative, N/A: mean ages not mentioned) *Diane Isabel Selvido et al: Review of dexamethasone administration for management of complications in postoperative third molar surgery. J Korean Assoc Oral Maxillofac Surg 2021*

general anesthesia[15]. For a long time, it has been utilized as a drug for reduction of postoperative sequelae. As general knowledge, most drugs have different adverse effects as they enter the body, regardless of administration route. While dexamethasone has been indicated to help with third molar surgeries because of its enhanced analgesic effects and de
creasing discomfort during the postoperative period, it also has adverse effects that can impact healing.

In a systemic review and meta-analysis by Waldron et al.[12], 45 studies exhibited routine wound healing without infection but increased blood glucose that was not sufficient to create drastic outcomes.

A review article by Caplan et al.[76] states that patients taking glucocorticoids can encounter gastric irritation. Still, it was not enough to be at risk for peptic ulcer disease. A combina tion of NSAIDs and glucocorticoids is stated to increase the risk for peptic ulcer disease. Therefore, it is advised that pa tients who take them should undergo prophylactic doses with a proton pump inhibitor.

According to Bebawy[77], gastric stress is more frequent during the perioperative periods. The immunological effects of dexamethasone are said to have possible apoptotic conse quences on T lymphocytes and decrease the quantities of β cells

in moderate to high doses. In contrast to these findings, many studies have stated that there were no adverse reactions experienced by most of the participants in each study[31,35,78]. This evidence supports the finding that dexamethasone can be used safely and effectively.

VII. Conclusion

With the evidence presented, dexamethasone used in third molar surgeries is effective regardless of route of administra tion, dosage, and timing. Dexamethasone is a corticosteroid that is highly potent for anti-inflammatory use since it sup presses effectively inflammatory mediators. Among all the elements reviewed, preoperative administration and submu cosal route with a dosage of 4 to 8 mg had the most impact on outcomes from most clinical trials. The results can vary by study and chosen parameters. Therefore, further studies are encouraged to maximize the effectiveness of this highly ef ficient drug.

ORCID

Diane Isabel Selvido, https://orcid.org/0000-0001-6232-6477 Bishwa Prakash Bhattarai, https://orcid.org/0000-0003-3359-9032

Nattisa Niyomtham, https://orcid.org/0000-0003-2233- 918X

Apiwat Riddhabhaya, https://orcid.org/0000-0002-9093- 2316

Kadkao Vongsawan, https://orcid.org/0000-0002-0537- 2896

Verasak Pairuchvej, https://orcid.org/0000-0002-9566-2407 Natthamet Wongsirichat, https://orcid.org/0000-0003-3005- 2680

Authors' Contributions

D.I.S. designed and wrote the manuscript. B.P.B. reviewed and edited the manuscript and tables. N.N. participated in the coordination of this review. N.W., V.P., K.V., and A.R. con ceptualized and supervised the project. All authors read and approved the final manuscript.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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