



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

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Dexamethasone has been used in oral and maxillofacial surgery for postoperative pain, swelling, and trismus following third molar surgeries. It is a potent and powerful drug that can alleviate the aforementioned postoperative sequelae. 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

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I. Introduction

Techniques for reducing pain or postoperative complications in the field of oral and maxillofacial surgery have emerged progressively over the years. However, it remains a common issue in the dental setting. Prescription of drugs pertaining to pain control, especially narcotics, has been widespread after dental surgeries. However, since the outcomes of dental surgeries are unpredictable, analgesic drugs like narcotics can be inadequate for pain relief.

Another method suggested is the use of corticosteroids, one of the most effective medications to control postoperative pain and inflammation^{1,2}. Glucocorticosteroids are well known to suppress inflammation and are utilized in oral surgeries to relieve pain and reduce trismus and swelling.

One of the most potent steroidal inflammatory drugs is dexamethasone³, a synthetic glucocorticosteroid that has no mineralocorticoid effect. This drug has a minimal unfavorable impact on leukocyte chemotaxis, which indicates movement of cells outside the circulatory system toward the site of injury⁴. This glucocorticosteroid is at least 25 to 50 times more potent than hydrocortisone and is one of the most potent anti-inflammatory drugs. At inflammatory doses, dexamethasone lacks the sodium-maintaining properties of hydrocortisone⁵. Glucocorticoids such as dexamethasone also control the rate of synthesis of anti-inflammatory genes in molecular mechanisms⁶ and are similar to hormones produced by the adrenal glands⁷.

There have been many published clinical trials on the capabilities of dexamethasone, emphasizing the route of administration and potential contributions to the field of oral and maxillofacial surgery. However, the introduction of new approaches and pathways has called into question the efficacy among the methods. Consequently, this literature review will help determine the suggested routes of administration, dosage, parameters, and dexamethasone timing for third molar surgeries.

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1. Dexamethasone in general use

Since dexamethasone is a corticosteroid, it is used widely due to its anti-inflammatory activity and proven safety. It inhibits vascular dilation and fluid transudation and decreases cell turnover through inhibition and chemotaxis of inflammatory cells that produce several inflammatory mediators². For this reason, dexamethasone is suggested even for major procedures such as orthognathic surgeries⁸.

The application of dexamethasone is not without limitations. Contraindications are diabetes mellitus, peptic ulcers, tuberculosis, hypertension, ocular herpes, glaucoma, Cushing's syndrome, renal insufficiency, and pregnancy⁹. The effects on these conditions indicate the impact of dexamethasone on various endocrine and metabolic functions. In pregnancy, the drug can lead to adrenal suppression of the fetus¹⁰. However, dexamethasone is accepted widely as a treatment for allergies, inflammation, and preoperative and postoperative supportive therapies⁵ and commonly is studied in conjunction with surgery.

Dexamethasone has a relative anti-inflammatory potency of 25 with a plasma half-life of 100 to 300 minutes and a biological half-life of 36 to 72 hours. According to Neupert et al.¹¹, a 4 mg dose can generate five times the body's standard physiological output of cortisol. The onset of dexamethasone is presumed to be 1 to 2 hours—enough time to disperse along the cell membrane¹². Corticosteroids are claimed to be functioning at their full potential during the first 24 hours after surgery, with the effects potentially lasting for three days². The postoperative outcomes are triggered by inflammatory responses that lead to strong vasodilating pro-inflammatory mediators¹³. Initially, postoperative swelling is due to inflammation, a protective response that eventually leads to injury. Characteristics of inflammation are as follows: redness, swelling, heat, pain, and loss of tissue function¹⁴. Upon injury, the body has the capability of inducing a chemical signaling cascade that activates responses that will lead to healing of the injured tissues. Leukocyte chemotaxis will mobilize from the systemic circulation to the target area¹⁵.

2. Dexamethasone in third molar surgeries

In dentistry, dexamethasone usually is studied with third molar surgeries. Third molar extraction is one of the most common procedures carried out by oral and maxillofacial surgeons. Surgical removal of third molars usually requires bone removal, flap reflection, and tooth sectioning. Injuries

caused by manipulation of the surrounding tissue and association with postoperative sequelae such as pain, edema, and trismus reduce the quality of life of the patient. Typically, with a patient experiencing moderate to severe pain, analgesics are prescribed. Given the potential of non-steroidal anti-inflammatory drugs (NSAID) to cause acidity that induces a more severe side effect in some patients, the type and amount of analgesics must be selected carefully to avoid potential adverse side effects¹⁶.

Pain, swelling, and trismus occur predominantly because of inflammation following third molar surgeries. Pain is a result of inflammation caused by tissue injury^{17,18}. Postoperative pain increases the patient's anxiety and suffering and significantly influences wound health and healing predictability¹⁹. Although the various pain measurements have limited validity, they should accurately describe patient pain²⁰. One of the most applied measurements is the visual analogue scale (VAS). This parameter is utilized to determine the subjective pain experience of patients, especially those who underwent oral and maxillofacial surgeries²¹. Multiple studies have used VAS to indicate pain response with dexamethasone administration^{7,13,22–28}. Other studies have relied on analgesic intake along with VAS in determining pain levels^{7,23}. It was emphasized in a study by Laureano Filho et al.²² that dexamethasone has a minimal effect on pain but a large influence on swelling and trismus. Additionally, VAS results by Gozali et al.²³ showed pain reduction only with the sublingual route.

Swelling can occur where the bone, gingiva, and mucosa are manipulated during prolonged surgery. There is no single method to measure swelling because linear estimations are not reproducible²⁹. Studies involving dexamethasone usually contain direct swelling measurements at six anatomical points and determining the mean of the linear dimensions (angle of the mandible, tragus, commissure of the lips, nasal border, pogonion, and lateral to the outer canthus of the eye). The points generally are described based on planes from the tragus of the ear to the corner of the mouth, from the gonion to the commissure of the lips, and from the outer canthus of the eye to the gonion^{13,22,24,28}. Several studies only measured four points based on planes from the tragus of the ear to the commissure of the mouth, outer canthus of the eye, and angle of the mandible or gonion^{25–27,30}. Majid and Mahmood³¹ assessed the two measurements from the tragus of the eye to the midline (pogonion) and to the outer canthus of the eye to the gonion.

Trismus is limitation in mouth opening caused by immobilized facial musculature and nervous structures to reduce

discomfort after surgery^{13,22,32}. Several studies involving dexamethasone have quantified trismus by measuring the interincisal distance with a ruler or a caliper. This parameter usually is measured as the distance between the incisal angles of the maxillary and mandibular central incisors at maximum opening^{13,22-28}. However, Al-Shamiri et al.¹³ created a different approach by calculating the difference between maximum opening preoperatively and postoperatively.

It has been reported that patients require a smaller intake of analgesics like NSAIDs when steroids such as dexamethasone are prescribed. The reason for this is because dexamethasone in some studies appears to reduce pain after surgery^{23,33,34}. Bamgbose et al.³⁵ suggested that combined treatment with NSAIDs and corticosteroids like dexamethasone is advantageous in reducing postoperative sequelae without complications. Nonetheless, the intake of corticosteroids depends on procedure difficulty and should not be applied in all cases of third molar surgeries³⁶.

Quality of life also has been assessed with dexamethasone in third molar studies. As defined by Majid¹⁹, quality of life is the patient's ability to perceive the outcomes of the conditions they are experiencing and involves impacts on daily life, social abilities, and physical and mental well-being. This tool usually is comprised of standardized or modified questionnaires that apply to a particular situation and usually are answered subjectively³⁷. The outcomes of third molar surgical extractions have been correlated with the quality of life of the patients. Tiwana et al.³⁸ mentioned that intravenous corticosteroids could decrease pain and swelling, thus improving patient quality of life.

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 prostaglandins and thromboxane by cyclooxygenase (COX) of and leukotrienes 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, followed by central sensitization. Once central sensitization is established, signals transmitted through A β fibers from low-threshold mechanoreceptors are perceived as pain at dorsal horn neurons with high excitability. In addition, since A δ fi-

bers and C fibers from nociceptors are under peripheral sensitization, the pain is enhanced and sustained. Once this central sensitization is established, patients will respond poorly to analgesics⁴¹.

In the concept of pre-emptive analgesia, postoperative pain is minimized by preventing central sensitization before surgery. When pre-emptive analgesia is provided before surgery, central sensitization is suppressed, and postoperative hyperesthesia does not occur⁴². Other mediators that play a crucial role in inducing inflammation are bradykinin, prostaglandins, and leukotrienes⁴³⁻⁴⁵. 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, leukotrienes have a hypoalgesia effect that is essential in modulating inflammatory pain caused by kinins in the system⁴⁵.

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 reaction⁷. NSAIDs block the cyclooxygenase system, while corticosteroids block both the cyclooxygenase and lipoxygenase systems⁴⁰. Based on this, corticosteroids are superior in reducing the effects of chemical mediators and can decrease swelling and trismus compared to NSAIDs²².

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 corticosteroids through submucosal, intramuscular, intra-alveolar, or intravenous route reduced postoperative pain after third molar surgery⁵⁰.

1. Oral route

According to Al-Shamiri et al.¹³, 8 mg oral dexamethasone either preoperatively or postoperatively lessens the postoperative complications of third molar surgeries, with their findings 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 compliance and repeated intake to regulate blood level for successful outcomes, rendering it a debatable course of administration⁵².

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 results using dexamethasone through the same route. Supporting the conclusions drawn by Grossi et al.⁴⁴ and Arora et al.⁵³, Khalida et al.²⁵ demonstrated the positive effects of dexamethasone submucosally through reduction of discomfort following surgery. They mentioned that a sub-therapeutic dose of 4 mg has nonsignificant systemic outcomes²⁵. Likewise, Shah et al.³³ stated that dexamethasone through this route improves patient quality of life. However, the intervention was performed for apicectomy in anterior maxillary teeth, not for third molar surgery³³. These studies demonstrate the submucosal route as a widely popular technique⁵⁴. In a 2016 meta-analysis by Moraschini et al.⁵⁵ on submucosal administration of dexamethasone after third molar surgeries, there was significant decrease of swelling and pain in all studies but was no difference in trismus.

According to Deo⁵⁶, quality of life decreased immediately after third molar surgery, leading to his conclusion that submucosal 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 dexamethasone when used with diclofenac sodium after third molar surgery³⁵. Another study by Moore et al.⁵⁸ concluded that a co-therapy of 10 mg intravenous dexamethasone (preoperatively) 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 effects 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-Dajani⁵⁹ concluded that a single preoperative intramuscular dose of dexamethasone successfully minimized postoperative 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 findings³¹ support the conclusion that intravenous and intramuscular 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 pterygomandibular 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 surgery⁶¹.

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 alleviate effectively pain symptoms²³.

Validating the evidence presented by Latt et al.⁶¹ and Gozali et al.²³, a 2019 study by Moranon et al.⁶² found that injections of 8 mg dexamethasone into the pterygomandibular or sublingual space were effective similarly in easing postoperative sequelae after third molar surgeries.

Graziani et al.³⁶ studied dexamethasone in endo alveolar

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 trismus³⁶.

The intra-masseteric approach was investigated by Nandini⁵² 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 nonsignificant side effects^{52,56}.

Another new method was reported in 2020, where the intraosseous route was utilized and compared to the submucosal route. Kaewkumnert et al.²⁷ found that the latter was more efficacious than the former due to the possibility of heightened tension with discomfort created by intraosseous injection 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 determined⁵⁰. According to Antunes et al.³, the dosing is arbitrary depending on the severity of the issue and patient tolerance.

1. 4 mg dosage

Neupert et al.¹¹ reported that 4 mg of intravenous dexamethasone exhibited no statistical differences in swelling and trismus compared to the sterile water control. On the other hand, Majid and Mahmood⁶³ in 2011, concluded that 4 mg dexamethasone through the submucosal route effectively controlled pain, swelling, and trismus compared to the intramuscular route. Another interesting study by Arora et al.⁵³ in 2018 stated that no significant differences were observed when 4 mg or 8 mg was used after third molar surgeries, and that 4 mg was sufficient in reducing edema after third molar surgeries.

2. 8 mg dosage

A study by Laureano Filho et al.²² in 2008, comparing the effectiveness of dosages of dexamethasone, indicated that 8 mg dexamethasone is more efficient in minimizing trismus and swelling compared to the lower dose of 4 mg. Chaudhary et al.⁶⁴, however, assessed 8 mg oral dexamethasone and 4

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

Study	Dose (mg)	Design	Time of administration	Route of administration	Sample size and mean age (yr)	Evaluated parameters	Results
Majid ¹⁰ (2011)	4	Randomized	Postoperative	Submucosal	33 patients; mean age, 26.9	Pain, swelling, trismus, quality of life	Submucosal more favorable than intramuscular
Antunes et al. ³ (2011)	8	Randomized	Preoperative	Intramuscular Intramuscular (masseter)	67 patients; mean age, 21	Pain, swelling, trismus	Intramuscular and oral equally effective
Boonsiriseth et al. ²⁶ (2012)	8	Randomized	Postoperative	Oral Intramuscular (deltoid)	20 patients; mean age, 20	Pain, swelling, trismus	Intramuscular and oral equally effective
Majid and Mahmood ⁶³ (2011)	4	Randomized	Postoperative	Submucosal	30 patients; mean age, 25.6	Pain, swelling, trismus, quality of life	Submucosal more favorable than intramuscular
Chaudhary et al. ⁶⁴ (2015)	4 (IV) 8 (oral)	Randomized	Preoperative	Intramuscular Intravenous	200 patients; mean age, 20.8	Pain, swelling, trismus	Intravenous and oral equally effective
Sabhlok et al. ⁵⁰ (2015)	4	Randomized	Postoperative	Oral Intramuscular (masseter)	60 patients; mean age not mentioned	Pain, swelling, trismus	Oral favorable to intramuscular
Vivek et al. ⁶⁰ (2017)	8	Randomized	Postoperative	Intravenous Submucosal	45 patients; mean age, 27	Pain, swelling, trismus	Intravenous, submucosal, and intramuscular equally effective (Intravenous is faster)
Moranon et al. ⁶² (2019)	8	Randomized	Preoperative	Intramuscular (masseter) Pterygomandibular space	30 patients; mean age, 21	Pain, swelling, trismus	Pterygomandibular and sublingual routes equally effective
Kaewkumnert et al. ²⁷ (2020)	4	Randomized	Preoperative	Sublingual space Submucosal Intraosseous	56 patients; mean age not mentioned	Pain, swelling, trismus	Submucosal favorable to intraosseous

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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 differed⁶⁴. 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 preoperatively, perioperatively, or postoperatively, Simone et al.⁷ indicated that the preoperative combination of dexamethasone and anti-inflammatory drugs was effective in minimizing pain during the postoperative period.

1. Preoperative

Ngeow and Lim⁶⁵ also mentioned that corticosteroids were preferred before surgery before of commencement of inflammatory 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 anesthesia, this process begins at the incision and continues during the intraoperative and postoperative periods⁷. Preoperative administration was favorable among studies comparing preoperative 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 postoperative 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 following 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 surgeries 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 Difficulty 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 criteria 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 administration 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.
Sithisongkhram 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)

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general anesthesia¹⁵. 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 decreasing 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 combination of NSAIDs and glucocorticoids is stated to increase the risk for peptic ulcer disease. Therefore, it is advised that patients who take them should undergo prophylactic doses with a proton pump inhibitor.

According to Bebawy⁷⁷, gastric stress is more frequent during the perioperative periods. The immunological effects of dexamethasone are said to have possible apoptotic consequences 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 administration, dosage, and timing. Dexamethasone is a corticosteroid that is highly potent for anti-inflammatory use since it suppresses effectively inflammatory mediators. Among all the elements reviewed, preoperative administration and submucosal 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 efficient drug.

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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. conceptualized 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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