

## Twin Mix Inferior Alveolar Nerve Anaesthesia for Transalveolar Extraction of Mandibular Third Molar Surgery: Review of Current Evidence

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### Abstract

Utmost recurrent surgical process executed in oral & maxillofacial surgery is transalveolar extraction (TAE) of mandibular impacted 3<sup>rd</sup> molar which consequences to surgical trauma to surrounding soft & hard tissues during the process of tooth removal. Post-operative sequelae like pain, facial swelling & sometimes trismus follow TAE. Dexamethasone is commonly used steroid post-operatively and studies have revealed clinical aids in refining patients' quality of life (QoL). To improve the QoL after TAE of third molars, use of twin-mix anaesthesia is proposed, where a combination of local anaesthetic solution and steroid is administered as a single injection, thus, negating the requirement of additional route of administration for dexamethasone. The advantages for this technique are, solitary method for dual drug delivery, reduced sensation of sting while injecting owing to altered pH of solution, short latency period, prolonged duration of anaesthesia & amended QoL post operatively. Twin Mix inferior alveolar nerve anaesthesia is found beneficial by reducing patient discomfort and enhancing patient compliance for surgeries of the mandible.



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### Introduction


The common surgical process executed in oral & maxillofacial surgery is transalveolar extraction (TAE) of mandibular impacted 3<sup>rd</sup> molar which consequences to trauma of surrounding soft and hard tissues and has associated sequelae that may

include post-operative pain, swelling on the face and at times trismus.<sup>1</sup> These problems greatly affect the patient's daily activities like mastication and speech. Anti-inflammatory drugs are usually prescribed post operatively to ease patient's discomfort.

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Steroids are potent anti-inflammatory drugs, widely used to relieve patients from post-operative sequelae following surgical extraction of mandibular 3<sup>rd</sup> molars.<sup>2</sup> Dexamethasone is the commonly used steroid post-surgery and studies have shown significant clinical advantages in improving the patient's quality of life (QoL).<sup>3</sup> In available drug trials, it is confirmed that dexamethasone is found beneficial in reducing the post-surgery pain and facial swelling, with certain effect on trismus.<sup>3,4</sup> It is also established that there is no clinical indication of persistent perineural damage or its functional amendment or alteration after administration of anaesthesia along with a steroid perineurally.<sup>5</sup> Many clinical trials have been carried out evaluating the steroid administration via intravenous and intramuscular routes following the surgical procedure.<sup>6,7</sup> Maxillofacial surgeons are generally competent with administration of steroids via parental routes but is uncommon for general dental surgeons as they are adequately trained only for intraoral administration.<sup>8</sup> In order to ease administration of steroid using an intra-space access instead of intra-venous (IV) or intramuscular (IM) route and to reduce discomfort to the patient by an additional injection. Authors advocate twin-mix technique in which the local anaesthetic solution and steroid is administered as an intra-space injection via inferior alveolar nerve block (IANB), thus, negating the requirement of supplementary route of administration for dexamethasone.<sup>9</sup> The advantages of using twin mix solution as anesthetic are ease of drug administration utilizing single prick method for dual drug delivery, reduced sting sensation on injecting due to altered pH, short latency period, prolonged duration of anesthesia and post-operative improved QoL.<sup>10</sup>

#### Data Extraction and Method of Analysis

Two authors reviewed the data (DB, BS), who had research experience with Twin Mix Inferior Alveolar Nerve Anaesthesia, and independently mined the data using data extraction data utilizing online search platforms that included PubMed/MEDLINE and Google Scholar. The search terms used were "Twin Mix", "Twin Mix Inferior Alveolar Nerve Anaesthesia", "Twin Mix Anaesthesia", "Twin Mix Anaesthesia Minor Oral Surgery" and "Twin Mix Transalveolar Extraction of Mandibular Third Molar Surgery". The information retrieved from the relevant scholarly search articles was: author(s),

year of publication, study details, intervention(s), and outcomes.

#### Composition of the Twin-Mix Solution

Twin mix solution for local anaesthesia (LA) is prepared freshly using 1.8 ml of 2% Lignocaine containing 1:200000 adrenaline & 1 ml of 4 mg dexamethasone. The final mixture results in 2.8 ml solution, containing lignocaine upto 38.3 mg, adrenaline of 0.009 mg & 4 mg dexamethasone.<sup>9</sup> 1.8 ml of anaesthetic solution is composed of 21.3 mg/ml of Lignocaine hydrochloride, 0.005 mg/ml of Adrenaline, 6.0 mg/ml of Sodium chloride, 0.5 mg/ml of Sodium metabisulphite, 1.0 mg/ml of Methylparaben and distil water as a vehicle for injection.<sup>9</sup>

Lignocaine is amide local anaesthetic agent, chemically it is 2(*diethylamino*) N (2,6*dimethylphenyl*) acetamide. The mechanism of action for lignocaine is it produced by stalling or blocking voltage gated sodium(Na) channels present in cell membranes of the post synaptic neurons, thus preventing the depolarisation of neurons and inhibiting neural impulse generation or propagation.<sup>12,13</sup> The added 1 ml of dexamethasone solution for the combination consists of- 4mg/ml of Dexamethasone sodium phosphate, 0.15% w/v of sodium methylparaben, 0.02% w/v of sodium propylparaben and distilled water for injection.<sup>11,12,13,14</sup>

Dexamethasone is a powerful anti-inflammatory and immunosuppressive corticosteroid. When compared to cortisol, it has a 20–30 times anti-inflammatory effectiveness. It produces anti-inflammatory action through stimulating synthesis of endogenous proteins that inturn prevents phospholipase A2 from being activated enzymatically. Thus, preventing the release of arachidonic acid by cell membrane, as well as synthesis of prostaglandins, leukotrienes, and thromboxane-related compounds. It also suppresses degranulation by blocking superoxide generation & lysosomal enzyme release in the human polymorpho nuclear neutrophils (PMNN).

#### Stability of Twin Mix Solution

Physical compatibility of various components in the twin mix solution is established by studies examining presence of a precipitous against black background &/or any colour change against

white backdrop in mixture, which demonstrated no physical incompatibility between parent solutions. A spectro-photometric analysis studies have been conducted to assess chemical stability of twin mix experimental solutions. When comparing twin-mix anesthetic solution, control local anaesthetic (lignocaine) solution, & dexamethasone solution, the double-beam UV visible spectro-photometry (UV: 1700, Shimadzu, Japan) revealed no significant differences in the individual solution wavelengths (max) and there was no deterioration in active pharmacological compounds on examination. Another benefit of twin mix is that it changes the pH of the LA solution, reducing the sting during injection.<sup>15,16,17</sup> The resultant pH of mixture shifts to a more basic nature (pH:6) when dexamethasone is added to 2 percent lignocaine hydrochloride solution with 1:200,000 epinephrine. At this modified pH in the twin mix solution, basic uncharged (nonionised) cationic form, which is lipid soluble/lipophilic, & charged (ionised) cationic form, which is water soluble/hydrophilic, remain in the equilibrium in the solution. The non-ionized, lipid soluble form of local anesthetic infiltrates neural sheath & membrane (& is responsible for tissue penetration). The ionised variant of the local anesthetic in the solution attaches to the sodium channels, preventing impulse propagation (and is responsible for the clinical action). Changing pH to a more basic for the solution, as in case of the twin mix, increases percentage of non-ionised form compared to ionised form, thereby, hastening the commencement of action of the local anesthetic. Studies using high performance liquid chromatography have demonstrated that the portions of dexamethasone in plasma with twin-mix injection is equivalent to as seen with its systemic absorption via other routes of administration. Pharmacokinetics following intra-space pterygomandibular twin-mix injection has demonstrated that dexamethasone can attain statistically similar plasma concentration as when same dose is administered intramuscularly with comparable clinical consequence.<sup>32</sup>

The pain associated with lidocaine infiltration is reduced when the pH of the drug is raised.<sup>9,16</sup> when dexamethasone is mixed with local anesthetic solution pH of resultant solution is increased from 4.5 to 6. This change in pH, clinically demonstrates quicker onset of anesthesia & increases the duration with resultant lesser sensation of sting

on injection.<sup>9</sup> Apart from the change in pH, steroid induced shorter latency/onset & prolonged duration could be owing to vasoconstriction feature of the dexamethasone itself or an upsurge in activity of inhibitory potassium channels on nociceptive C-fibres (through glucocorticoid receptors), thus lowering their activity.<sup>17,18</sup> Additionally, dexamethasone demonstrates analgesic properties through the increased activation of inhibitory potassium channels on nociceptive C-fibres, according to already established scientific data available.<sup>19,20</sup> Another important school of thought is that glucocorticoids cause vasoconstriction, which reduces LA absorption and so prolongs LA nerve contact time.<sup>21,22</sup>

### Route of Administration

The twin mix solution for mandibular LA is freshly prepared just before the injection for intraoral nerve block. It is injected in pterygomandibular space following the steps for conventional IANB technique. The subjective symptoms usually confirm the successful nerve block and surgical procedure may be carried out after onset of subjective & objective symptoms and signs respectively. Long buccal nerve block would require a separate injection.

There are several other documented routes of administration for corticosteroids post-surgery that include sub-mucosal, intra-venous (IV), intramuscular (IM) and peroral to prevent post-op sequelae. The intra-space administration of twin mix solution is beneficial as it eases the administration and has similar clinical effects when compared to other methods.<sup>9,11</sup>

### Complications

Dexamethasone has a known property of vasoconstriction which can be of concern as it may induce ischaemia and related changes in the neural tissues when deposited or injected in the nerve proximity. Drug dose of 4mg dexamethasone is considered safe and effective, but it should be cautiously used for doses of 8 mg or more.<sup>23</sup> There are several animal studies in the literature opining that restraint is mandatory when administering large doses of steroids in the nerve proximity as it may unfavourably affect nerve conduction due to its resultant vascular effects.<sup>24</sup> It is established through animal studies that there are dose dependent minimal changes in neural blood flow with histologic changes in rat nerve fibres model. Contrary to the

animal studies, there are no adverse effects reported including neurotoxicity with perineural use of steroids in human trials.<sup>25</sup> It is evident that the intra-space administration of steroid is safe with visible clinical benefits provided the permissible drug dosage is maintained as documented.

### Discussion

Twin mix anaesthesia for mandibular nerve block is an anaesthetic technique which involves the admixture of drugs including local anaesthetics with dexamethasone to harness the clinical benefits of the principal ingredients. The studies relevant to the use of twin-mix solution are summarized in table 1.<sup>9,10,11,26,27,28,29,30,31,32</sup>

Bhargava D *et al.* first proposed clinical use of the twin mix anaesthesia for mandibular nerve block in 2013 by evaluating this anaesthetic technique and the admixture of drugs through their prospective clinical randomized double-blind study to evaluate latency & efficacy of twin-mix solution & 2% lignocaine with 1:200,000 adrenaline for the transalveolar extraction of impacted mandibular third molars.<sup>9</sup>

Gaur S *et al.* conducted a randomized controlled trial evaluating the altered twin mix local anaesthesia using two long acting amide local anesthetic solutions: bupivacaine & ropivacaine with/without 4 mg/ml dexamethasone solution for patients undergoing 3<sup>rd</sup> molar surgical extraction. The authors concluded that the intraoperative & postoperative outcome parameters in both trial groups were better than those for the control group subjects, thereby endorsing clinical efficacy of either modified or altered twin mix solutions for use as anesthetics for the transalveolar extraction of mandibular third molars.<sup>26</sup>

Kaushik M *et al.* compared the effectiveness of twin mix and lidocaine for inferior alveolar nerve blocks in patients with symptomatic irreversible pulpitis. This randomized case controlled double-blind prospective clinical study assessed anaesthetic efficacy of 2% lidocaine with 1:200,000 adrenaline with an admixture of 2% lidocaine with 1:200,000 adrenaline & 1mL solution containing 4mg dexamethasone (twin mix anesthetic solution) for inferior alveolar nerve block in patients with symptomatic mandibular molars with irreversible

pulpitis. The stated inferior alveolar nerve block success rates for lidocaine group & twin mix group in the study were 66% and 68% respectively.<sup>27</sup>

Albert D *et al.* through their randomised controlled double blinded study compared twin mix and revamped twin mix for mandibular wisdom tooth transalveolar surgery. The intraspace injection of dexamethasone mixed with 2% lignocaine and 0.5% centbucridine labelled as 'Twin Mix' (TM) and 'Revamped Twin Mix' (RTM) respectively were evaluated. Authors concluded that RTM can be used as an alternative to TM considering its comparable properties.<sup>28</sup>

Bhargava D *et al.* conducted a clinical prospective randomized trial to evaluate post-operative quality of life (QoL) in patients undergoing surgical intervention for isolated vertically undisplaced parasymphysis mandibular fracture with twin mix (TM) anesthetic solution and concluded that the 'TM' solution proves to be more advantageous as compared to the conventional local anaesthetic solution as the former provides an improved clinical outcomes with enhanced the post-operative QoL in patients undergoing open reduction & internal fixation (ORIF under LA) for an undisplaced parasymphysis fractures.<sup>29</sup> This data is in consistence with effects observed with minor oral surgical procedures like transalveolar extractions.

Sahu S *et al.* assessed the efficacy & latency of twin-mix and 2% lignocaine hydrochloride solution with 1:80000 adrenaline in surgical/ transalveolar extractions of mandibular impacted 3<sup>rd</sup> molars, & concluded that the addition of dexamethasone to lignocaine & its administration as an intraspace injection demonstrates shorter latency with prolonged duration of soft tissue mandibular anaesthesia. Patients also demonstrated amended quality of life (QoL) in postoperative phase after the surgical extraction of 3<sup>rd</sup> molars.<sup>30</sup>

Beena S *et al.* conducted randomized triple blind split mouth clinical trial with limited subjects to assess latency & duration of local-anaesthesia with twin-mix solution (1.8 ml 2% lignocaine with 1:200,000 adrenaline & 1 ml/4mg dexamethasone) and the modified twin mix solution (1.7 ml of 4% articaine with 1:100,000 adrenaline & 1ml/4mg dexamethasone) and compared the two with to conventional standard

local anesthesia solutions. Authors concluded that the intraspace pterygomandibular administration of twin mix & modified twin mix solutions were clinically effective when used for anesthesia in transalveolar

surgery. Authors also reported noticeable beneficial clinical outcomes postoperatively with the use of dexamethasone-anesthetic admixtures.<sup>31</sup>

**Table 1: Studies relevant to the use Twin Mix Inferior Alveolar Nerve Anaesthesia for minor oral surgical procedures**

S.No.	Author and Year	Study	Outcome and Conclusion(s)
1	Bhargava D <i>et al.</i> 2013 <sup>9</sup>	A prospective randomized double-blind study to assess the latency and efficacy of twin-mix and 2% lignocaine with 1:200,000 epinephrine in surgical removal of impacted mandibular third molars: a pilot study.	Addition of dexamethasone to lignocaine and its administration as an intra-space injection significantly shortens the latency and prolongs the duration of the soft tissue anaesthesia, with improved quality of life in the postoperative period
2	Bhargava D <i>et al.</i> 2014 <sup>11</sup>	Effects of intra-space injection of Twin mix versus intraoral-submucosal, intramuscular, intravenous and per-oral administration of dexamethasone on post-operative sequelae after mandibular impacted third molar surgery: a preliminary clinical comparative study.	Intra-space injection of dexamethasone in pterygomandibular space as Twin mix was found to have similar clinical effects as conventional methods of administering steroids via intraoral-submucosal, intramuscular, intravenous and per-oral routes.
3	Bhargava D <i>et al.</i> 2015 <sup>10</sup>	Validation of data on the use of twin mix in minor oral surgery: comparative evaluation of efficacy of twin mix versus 2 % lignocaine with 1:200000 epinephrine based on power analysis and an UV spectrometry study for chemical stability of the mixture	Apart from the clinical benefits, the UV spectrometry analysis for dexamethasone and local anaesthetic in the twin-mix solution indicated no change in the active pharmacological agents.
4	Bhargava D <i>et al.</i> 2016 <sup>32</sup>	High performance liquid chromatography determination of dexamethasone in plasma to evaluate its systemic absorption following intra-space pterygomandibular injection of twin-mix (mixture of 2 % lignocaine with 1:200,000 epinephrine and 4 mg dexamethasone): randomized control trial	Pterygomandibular space administration of dexamethasone can achieve similar plasma concentration as when the same dose is administered intramuscularly
5	Bhargava D <i>et al.</i> 2018 <sup>33</sup>	A preliminary study on plasma concentration achieved following intra pterygomandibular space injection of dexamethasone as a route of drug delivery with lignocaine inferior alveolar nerve block-correlation of clinical effects	Intraspace route of drug administration can be utilized to deliver dexamethasone local anesthetics safely with predictable clinical effects
6	Dyna Albert <i>et al.</i> 2020 <sup>28</sup>	Comparison of twin mix and revamped twin mix (1.8ml of 0.5%	Efficacy of Revamped Twin Mix is comparable to Twin Mix with respect to

		Centbucridine 1ml of 4mg dexameth-its anesthetic properties and in its ability asone) in mandibular third molar surgery - A randomised controlled double blinded study	to enhance the postoperative quality of life
7	Sahu S <i>et al.</i> 2020 <sup>30</sup>	Comparative evaluation of efficacy and latency of twin mix vs 2% lignocaine HCL with 1:80000 epinephrine in surgical removal of impacted mandibular third molar	The addition of dexamethasone to lignocaine and its administration as an intraspaces injection shortens the latency and prolongs the duration of the soft tissue anesthesia
8	Beena S <i>et al.</i> 2020 <sup>31</sup>	Comparison of latency and efficacy of twin mix and modified twin mix in impacted mandibular third molar surgery - A Preliminary Randomized Triple Blind Split Mouth Clinical Study	Intra-space administration of twin mix (1.7ml of 4% articaine with 1:100,000 epinephrine and 1ml/4mg dexamethasone) is clinically efficacious in impacted mandibular third molars surgery with better clinical outcomes postoperatively.
9	Gaur S <i>et al.</i> 2021 <sup>26</sup>	Twin Mixed Local Anesthesia in Third Molar Surgery - Randomized Controlled Trial	Modified twin mixes, 1.8 mL of 0.5% bupivacaine hydrochloride + 1mL/4mg dexamethasone and 0.75% ropivacaine hydrochloride + 1 mL/4mg dexamethasone demonstrated promising clinical outcome.

### Conclusion

The potent anti-inflammatory effects of steroid, combined with LA has an obvious benefit of reducing post-operative oedema and discomfort for patients undergoing mandibular minor oral surgical procedures, where indicated. The duration and depth of the anesthetic effect with the twin-mix solution for IANB has been found to be greater than that of lignocaine solution alone. Other major benefits include administration of dexamethasone and local anesthetic as a single needle prick, less sting on injection, short latency of LA & persistent period of soft tissue mandibular anaesthesia, & improved postoperative QoL. Where indicated, in cases of anticipated post-surgical edema, pain and trismus, the twin mix solution is safe to use after TAE

of mandibular third molars and other minor oral surgical procedures with reduced patient discomfort and enhanced QoL. Any predetermined contraindication for the use of steroids in a case specific manner, should be considered before utilizing twin mix solution as local anesthetic for minor oral surgery.

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### Conflict of Interest

The authors do not have any conflict of interest.

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