

Study Protocol

COMPARATIVE EVALUATION OF 0.5% LEVOBUPIVACAINE V/S 0.5% LEVOBUPIVACAINE MIXED WITH 20µg DEXMEDETOMIDINE IN MANDIBULAR III MOLAR SURGERIES – A DOUBLE BLIND RANDOMISED CONTROLLED TRIAL.

ABSTRACT:

Background: Mandibular third molars (M3M) are the most common impacted teeth in the human dentition. Removal or extraction of these teeth is frightening for the patients owing to the perception of pain. As a result, pain control mechanism like anesthesia is the major factor that needs to be executed appropriately. Using newer local anesthetic drugs minimizes side effects and drug interactions. Levobupivacaine (Levo) is a congener of bupivacaine thereby minimizing the cardiotoxic effects of bupivacaine. Dexmedetomidine (Dex) is an alpha agonist which alongwith Levo is capable of providing prolonged duration of anesthesia decreasing the need for rescue analgesics.

Aim : This study will compare the anesthetic effectiveness between Levo and Levo alongwith Dex during the extraction of impacted M3M..

Methodology : A total of 50 consecutive systemically healthy patients requiring unilateral surgical extraction of impacted M3M with similar orientations will be divided into two groups randomly, one group (L) will receive nerve block with levo while the second group (LD) will receive Levo plus Dex during the extraction procedure.

Results: 'Students t-test' will be used to analyse and evaluate. The patients will be evaluated based on different parameters. The patient will be asked to reciprocate about the first bout of pain experience based on the Visual Analog Scale that will be handed over to patient after the procedure. The other parameters that will be evaluated are Onset on Anesthesia, Depth of Anesthesia , Hemodynamics, Oxygen saturation level, Sedation level and duration of post-operative analgesia. The patient will be evaluated over the time duration after which the patient had to take a rescue analgesic. **Conclusion:** Levo with Dex is more efficient than Levo in providing prolonged duration of anesthesia and has prolonged duration of postoperative analgesia.

Keywords: Impacted mandibular third molars, Anesthesia, Levobupivacaine, Dexmedtomidine, Duration of post operative analgesia.

INTRODUCTION

Pain is experienced as an outcome of stimulation of receptors sensitive to a noxious stimulus. Nociception reaches the cortex and is perceived as pain[1]. In clinical practice, pain is generally managed by numerous methods i.e by eliminating the cause, preventing the pathway of pain impulse, raising the pain threshold and by cortical depression resulting in inhibition of pain perception.

Local anesthetic agents are the major factors in the management of pain control in dentistry. They act by blocking the transmission of pain impulse to the Central Nervous System where it gets interpreted. Local anesthesia was pioneered in 1859, when cocaine was secluded by Niemann [2]. A then renowned Ophthalmologist Koller (1884) was the foremost to utilise Cocaine for topical anesthesia. As far as the oral cavity was concerned, first use of cocaine was performed by the surgeon Halsted, when he removed a wisdom tooth without pain. Since Cocaine gave rise to a number of adverse effects, it was crucial to develop alternative local anesthetic agents. Einhorn (1905) announced the synthesis of first ester type local anesthetic agent – Procaine [3]. Procaine continued to be the conventional local anesthetic for more than 40 years. Lofgren in 1943, introduced the first ever amide derivative local anesthetic agent ‘Lidocaine’ which has since then continued to be the champion amongst all local anesthetic agents in the maxillofacial domain [4].

One of the newer entries in the group of local anesthetic agents is Levobupivacaine. It’s local anesthetic belonging to the amide group and has a prolonged duration of action than the conventionally used Lidocaine. Levo has been consistently less cardiotoxic which is why it was introduced over bupivacaine. It also assures a low risk of CNS toxicity. Levo possesses a faster onset of action. The duration of action is dose-dependent and varies based on the

anesthetic technique. It acts via blockade of voltage-sensitive ion channels in neuronal membranes, preventing transmission of nerve impulses. Levo interferes with the opening of the sodium channel, which inhibits conduction of the action potential and produces localised and reversible anesthesia. Levo provides a significantly prolonged sensory and/or motor block [5]

In an attempt to further minimize the effects of local anesthetics and prolong the duration of intraoperative and postoperative analgesia various adjuvants like vasoconstrictors, opioids, alpha-2 agonists have been used [5]. Dex is a highly selective alpha 2 adrenergic receptor agonist. The hypnotic and supraspinal analgesic effects of Dex are mediated by the hyperpolarization of noradrenergic neurons, which suppresses neuronal firing in the locus coeruleus along with inhibition of norepinephrine release. This suppression of inhibitory control stimulates neurotransmitters that decrease histamine secretion producing hypnosis similar to normal sleep without ventilatory depression. It is neuroprotective and attenuates post-operative pain without causing any cardio-respiratory depression and ensuring faster, neuromuscular recovery and sedation. It possesses cardio-protective modulation. Dex prolongs the duration of sensory block of local anesthetics [7].

Levo is a preferred local anesthetic because of its early onset and prolonged duration of sensory block, shorter duration of motor block and lower cardiac toxicity. Addition of Dex to Levo produces effective analgesia and prolonged duration of motor and sensory block along with improved post-operative analgesia and fewer side effects. The time of onset of sensory block is decreased due to the addition of Dex. The combination provides a longer duration of post-operative analgesia. Lesser number of doses of rescue analgesics are required.

Hence the present study will be designed to compare and analyse the efficacy and safety of Levo and Levo with Dex in impacted mandibular third molar surgery based on the

hypothesis that **Levo is administered along with Dex** it provides potent prolonged anesthesia and post-operative analgesia with minimal cardiotoxicity.

Objectives: -

- To evaluate and compare the latency, profoundness, duration of anesthesia and requirement of post op analgesics following classic inferior alveolar nerve block in two groups.
- To compare the hemodynamic changes in two groups.
- To compare the total number of analgesics consumed in two groups..

METHODOLOGY: -

SAMPLE SIZE CALCULATION:

The sample size was calculated using OpenEpi, Version 3. Open source calculator SS Mean. A total of 50 consecutive systemically healthy patients requiring unilateral surgical removal of impacted mandibular third molars with similar difficulty (Moderate to Very Difficult according to Modified Pederson's Index) from October 2019 to May 2021 are to be included in the study.

Criteria for inclusion:

- 1) Individuals with ASA Gr I status
- 2) Individuals between 18 to 40 years
- 3) Presence of at least one asymptomatic impacted mandibular third molar having moderate to very difficult ,difficulty index (Modified Pederson's Scoring)

Criteria for exclusion:

1. History of drug dependence
2. Patients with systemic disease such as HTN, DM, blood dyscrasias, immune-compromised status.
3. Patients who chronic smokers
4. Patients on cardio-selective antihypertensive drugs.
5. Patients with allergy to local anesthetic agents used in the study
6. Pregnant and nursing mothers
7. Females on oral contraceptives
8. Patients undergoing treatment with antibiotics, anti-inflammatory drugs
9. Presence of any local infection like pericoronitis/pterygomandibular space infection
10. Presence of any chronic facial pain on the side of intervention
11. Radiologic evidence of Inferior alveolar canal approximation
12. Patients with Congenital Heart Disease.
13. Patients who are have any psychiatric illness.

STUDY DESIGN:

The study is scheduled to be conducted at Department of Oral and Maxillofacial Surgery, Sharad Pawar Dental College and Hospital, Sawangi (M), Wardha

STUDY PROCEDURE:

Fifty systemically healthy subjects (ASA Class I status) aged between 18-40 years were included in the study with a presence of at least one asymptomatic lower impacted third molar devoid of any pathologies having similar angulations/orientations

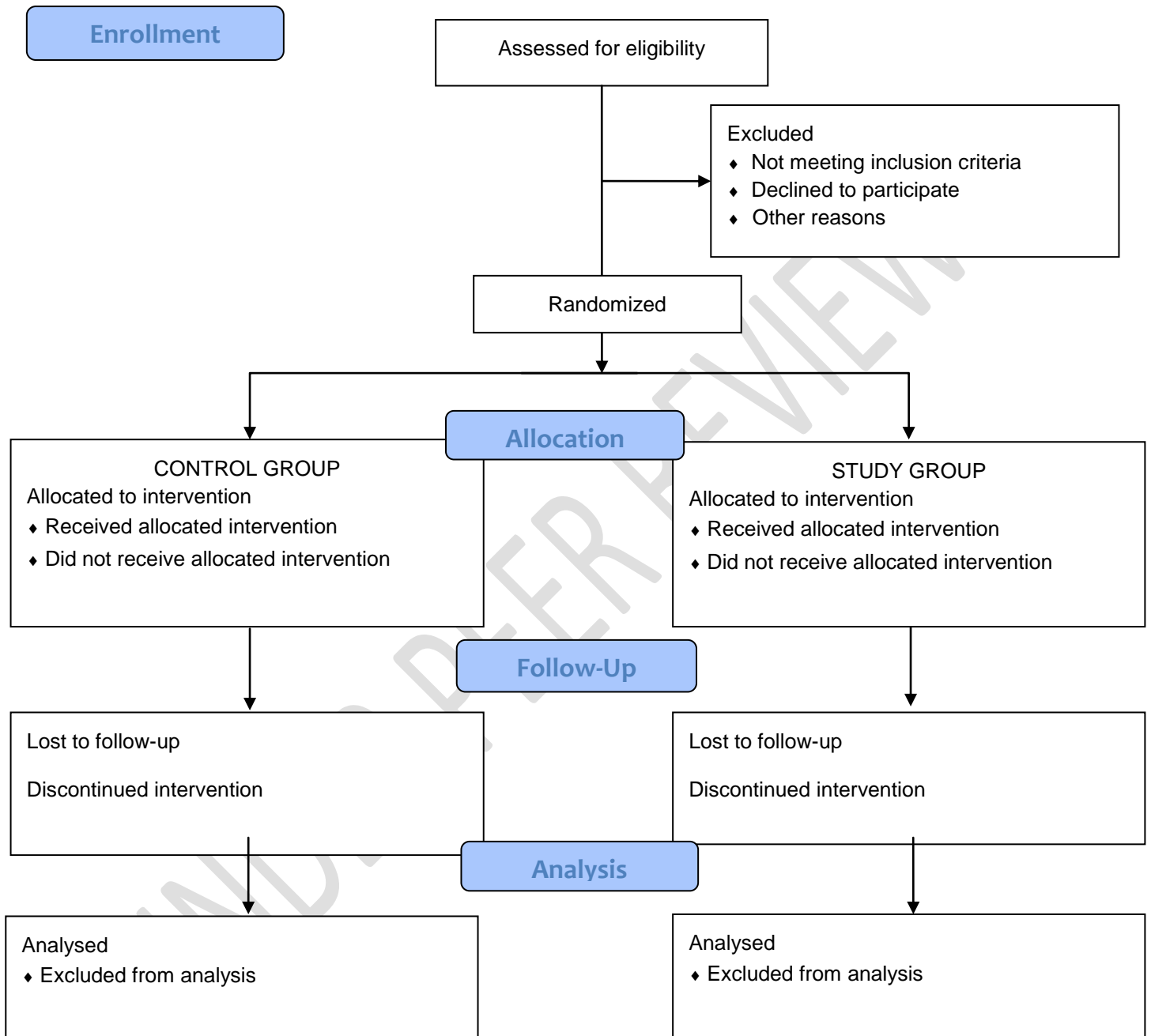
(Moderate to Very Difficult according to Modified Pederson's Index) from October 2019 to May 2021 are to be included in the study.

These 50 patients will be randomised into two groups based on a lottery system (n=25 each).

- Group L : Subjects (n=25) requiring impacted third molar surgery with Levoas the local anesthetic agent.
- Group LD : Subjects (n=25) requiring impacted third molar surgery with Levoand Dex as the local anesthetic agent.

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CONSORT(Consolidated Standards Of Reporting Trials) 2010 Flow Diagram



A detailed case history of the patient will be taken and the procedure of the study will be explained to the patient. After receiving a written consent for the procedure from the patient, the patient will be taken up for the surgery and prepared according to the protocols.

The study is a double blind study wherein the clinician administering the local anesthetic solution, and the evaluator, both will be unaware of the solution being administered. The solution of Levo and Dex will be mixed in the concentration of 1.8ml of Levo+ 0.2ml of Dex in a syringe. The sister on duty who will be handing over the local anesthesia loaded into a syringe to the clinician will be aware of the solution being deposited and will keep a record.

The Blood pressure and the heart rate will be monitored carefully.

The Blood pressure will be monitored using a manual sphygmomanometer at regular intervals.

The heart rate will be monitored using a Pulse Oximeter .

The necessary surgical procedure will be carried out and all the parameters will be evaluated during the procedure.

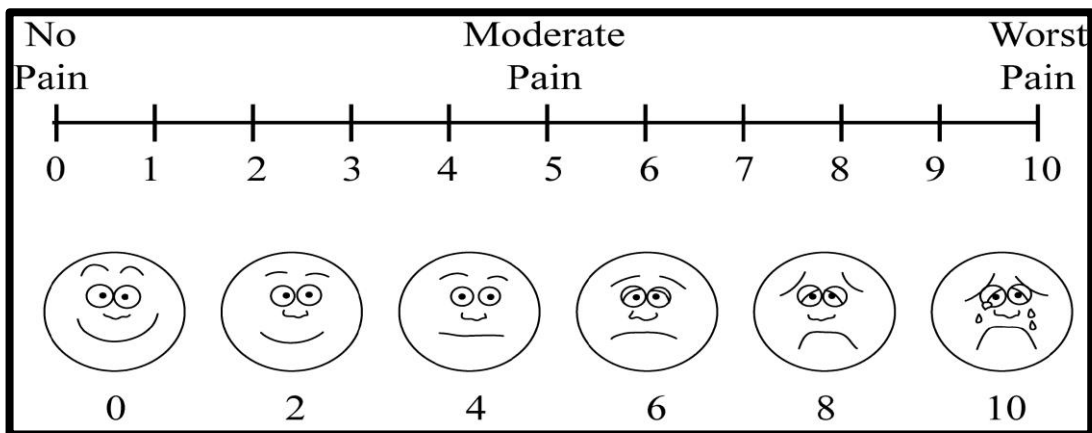
The depth of anesthesia will be evaluated using Facial Pain Scale.



After the procedure and the necessary assessment and evaluation ,the patient will be advised postoperative instructions and necessary medications will be prescribed.

(Analgesic – Aceclofenac 100mg 12 hourly)

The patient will be given a printed card with the Visual Analogue Scale printed on it for further assessment and will be relieved.



The patient will be asked to reciprocate about the reading of the Visual Analogue Scale over a telephonic conversation when the first bout of pain is experienced postoperatively thereby assessing the pain intensity and the duration of postoperative analgesia.

The patients will be evaluated on the following parameters –

- 1) Onset of anesthesia
- 2) Depth of anesthesia
- 3) Hemodynamic parameters
- 4) Duration of postoperative analgesia

STATISTICAL ANALYSIS:

The values evaluated will be represented in number and mean +/- standard deviation. The statistical test used for analysis will be standard paired and unpaired t test, chi square test to find out various results based on the aim and objectives of study.

EXPECTED OUTCOME:

The efficacy and safety of using a long acting local anesthetic with the addition of an alpha-2 agonist for alleviating post surgical pain without any undesirable side-effects. Advantage of prolonged duration of anesthesia, prolonged duration of postoperative analgesia and faster onset of anesthesia.

DISCUSSION:

Pain control after M3M surgery has been a challenge due to the variable amount of inflammatory response. There is a continual burgeoning search for a pharmacological agent with optimal therapeutic efficacy and minimal side effects. Dex is a promising pharmacologically active dextro-isomer of medetomidine that shows specific and selective α_2 adrenoceptor agonism. Clinically, it not only prolongs the duration of anesthesia but also help reduce anxiety, induce arousable sedation and analgesia. When used as an adjunct to local anesthetic shortens the latency period and prolongs the duration of local anesthetic, maintains homeostasis induces haemostasis and helps provide better subject satisfaction. The present study is deliberated with an aim to compare and evaluate the anesthetic efficacy and safety of Levo with or without Dex in IANB for surgical removal of M3M.

In the present study, we will be selecting a homogenous sample having well-controlled determinants of post-operative pain and inflammation in the extraction of M3M, viz; age, gender, asymptomatic, similarly oriented M3M, surgeon's experience and the quantity of the local anesthetic used.

The present study will demonstrate that addition of dex to levo shortens the latency significantly. It could be due to independent action of individual drugs working synergistically. The shorter latency in the group D can be attributed to the blockage of pre-synaptic α_2 receptors by dex which inhibits the release of norepinephrine which ultimately terminates the propagation of pain signals and prolongs the hyperpolarization which prevents the nerve to return to the resting membrane potential.

We will evaluate pain as an individual unit and it won't be associated to other perceptions such as temperature, proprioception and pressure, so the total duration of anesthesia and time to pain onset during the post-operative period won't be comparable. The mean number of analgesics that would be taken by subjects of group D would show a significant difference. Results of the study would indicate that subjects of group D would demonstrate a prolonged time to pain onset and require fewer analgesics than group L. The results would indicate the analgesic potency and prolonged duration of action of dex can be attributed to its anti-inflammatory and local vasoconstriction effects respectively. Dex acts centrally by inhibition of discharge of substance P by activation of α_2 receptors at locus coeruleus.

Hemodynamic parameters such as HR and BP have multifactorial influence. In the present study, all the nerve blocks and surgical procedures would be carried out by the same surgeon in a well-controlled operatory using standard protocol. Perineurally administered dex in various doses have found to have minimal haemodynamic alterations.

These alterations are greatly affected by the route of administration, dose of the drug and the rate of drug delivery. In a recent meta-analysis, it was concluded that perineural doses ranging from 2 - 50 μg and intra venous doses upto 3 $\mu\text{gm/kg}$ does not influence hemodynamic response [8]. The results imply that, haemodynamic stability is an complemented advantage of dex.

To the best of our knowledge, no earlier studies attempted to evaluate the effects of dex along with levo on post-operative analgesia in M3M surgery. The blend of dex and lb will provide prolonged and profound post operative analgesia with fewer number of analgesic tablets requirement in the acute post-operative period.

G.A Chalkiadis et al (2004)[9] carried out an open-label phase 2 study to examine the pharmacokinetics of levo0.25% after it's single shot administration into caudal epidural space in 49 children aged less than 2 years. Plasma concentrations were determined at intervals upto 60min after caudal injection. Time to peak plasma concentration ranged between 5 and 60 mins and was reached later in children aged less than 3 months.

Despoina D. Kakagia et al (2007) [10] carried out a double blind study to compare the analgesic properties of locally infiltrated levowith those of ropivacaine in fleur-de-lys abdominoplasty. A total of 46 patients subjected to fleur-de-lys abdominoplasty were included out of which 15 were given 100ml of 0.9% saline. 15 were given 50ml of ropivacaine 0.75% in 50ml of saline 0.9%. 16 were given 60ml levo0.25% in 40ml of saline 0.9%. Adequate analgesia is achieved postoperatively with either of the two agents.

Julide Ergil et al (2012) [11] performed a study to evaluate the use of preincisional plain levobupivacaine, lidocaine adrenaline and saline for perioperative blood loss and post

operative analgesia in pediatric tonsillectomy patients. Ninety patients were randomly assigned into 3 groups. Levohas a vasoconstrictive effect in 0.25% concentration that is beneficial in tonsillectomy.

P. Miranda et al (2016) [12] conducted a study to characterize levoabsorption pharmacokinetics, with and without epinephrine and estimate the risk of LAST, based on a previously reported toxic threshold. 11 healthy male volunteers underwent ultrasound guided TAP blocks on two independent, randomly assigned occasions. Epinephrine prolongs the levoabsorption half-life.

Saadawy et al(2009) [13] conducted a study to evaluate the effect of Dex on the characteristics of bupivacaine in a caudal block in pediatric patients. Sixty children were randomly allocated to two groups. Group B received a caudal injection of bupivacaine 2.5mg/ml while group BD received the same dose of bupivacaine mixed with Dex during sevoflurane anesthesia. Group BD was associated with extended duration of post operative pain relief.

Ahmed Sobhy Basuni, Hoda Alsaïd Ahmed Ezz (2014) [14] conducted a study to evaluate the efficiency of Dex to low dose levospinal anaesthesia in patients undergoing knee arthroscopy. Sixty adult patients were randomized into two groups. Group F received fentanyl while group D received Dex. The pain free period was more prolonged and visual analog scale for pain was lower during postoperative hours in group D

Amar Prakash Kataria et al(2019) [6] carried out a study in order to compare between levoand levowith Dex in infraumbilical surgeries under spinal anesthesia. Sixty adult patients were selected randomly and divided into two groups. Group L were given levobupivaine while group LD were given Levowith Dex. Group LD has early onset and prolonged duration of sensory and motor block and longer duration of postoperative analgesia than Group L.

Conclusion:

When used as an adjunct to a long acting local anesthetic like Levobupivacaine, dexmedetomidine will enhance the latency and profoundness of anesthesia. It will prolong the duration of post-operative analgesia with minimal cardiovascular and neurocognitive actions. This in turn shall lead to decreased consumption of analgesics in the post-operative period thereby avoiding the undesirable side effects of the commonly used analgesics. It would conclude that dexmedetomidine in a single IANB block with local anesthetic may be effective and advantageous in providing adequate anesthesia and prolonged duration of post-operative analgesia and fewer analgesic requirements with minimal side effect

References:

1. Bahl R. Local anesthesia in dentistry. *Anesthesia progress*. 2004;51(4):138.
2. Calatayud J, González Á. History of the development and evolution of local anesthesia since the coca leaf. *The Journal of the American Society of Anesthesiologists*. 2003 Jun 1;98(6):1503-8.
3. Bezerra MM, Leao RA, Miranda LS, de Souza RO. A brief history behind the most used local anesthetics. *Tetrahedron*. 2020 Oct 9:131628.
4. Rahn R, Ball B. Local anesthesia in dentistry-Articaine and epinephrine for dental anesthesia. *3M Espe*. 2001.
5. Foster RH, Markham A. Levobupivacaine. *Drugs*. 2000 Mar 1;59(3):551-79.
6. Kumar M, Gupta KK, Kataria AP. Comparison of caudal ropivacaine 0.2% with bupivacaine 0.2% in pediatric patients—a randomized controlled trial. *Anaesthesia, Pain & Intensive Care*. 2019 Jan 26:141-6.
7. Grewal A. Dex: new avenues. *Journal of anaesthesiology, clinical pharmacology*. 2011 Jul;27(3):297.
8. Cai H, Fan X, Feng P, Wang X, Xie Y. Optimal dose of perineural dexmedetomidine to prolong analgesia after brachial plexus blockade: a systematic review and Meta-analysis of 57 randomized clinical trials. *BMC anesthesiology*. 2021 Dec;21(1):1-20.
9. Chalkiadis GA, Eyres RL, Cranswick N, Taylor RH, Austin S. Pharmacokinetics of levo0.25% following caudal administration in children under 2 years of age. *British journal of anaesthesia*. 2004 Feb 1;92(2):218-22.
10. Kakagia DD, Fotiadis S, Tripsiannis G, Tsoutsos D. Postoperative analgesic effect of locally infiltrated levoin fleur-de-lys abdominoplasty. *Aesthetic plastic surgery*. 2007 Apr 1;31(2):128-32.
11. Ergil J, Akkaya T, Gozaydin O, Gunsoy B, Alicura S, Aladag E, Gumus H, Akin I. Vasoconstrictive and analgesic efficacy of locally infiltrated levoin tonsillectomy patients. *International journal of pediatric otorhinolaryngology*. 2012 Oct 1;76(10):1429-33.
12. Miranda P, Corvetto MA, Altermatt FR, Araneda A, Echevarría GC, Cortínez LI. Levoabsorption pharmacokinetics with and without epinephrine during TAP block: analysis of doses based on the associated risk of local anaesthetic toxicity. *European journal of clinical pharmacology*. 2016 Oct 1;72(10):1221-7.

13. Saadawy I, Boker A, Elshahawy MA, Almazrooa A, Melibary S, Abdellatif AA, Afifi W. Effect of dex on the characteristics of bupivacaine in a caudal block in pediatrics. *Acta Anaesthesiologica Scandinavica*. 2009 Feb;53(2):251-6.
14. Basuni AS, Ezz HA. Dex as supplement to low-dose levospinal anesthesia for knee arthroscopy. *Egyptian Journal of Anaesthesia*. 2014 Apr 1;30(2):149-53.

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