

Peer Review File

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Review Comments

Reviewer A:

Thank you for your detailed comments and suggestions for our manuscript. We are appreciated of your compliments and constructive criticism which would make our paper suitable for publication within the Journal of Oral and Maxillofacial Anesthesia.

Reviewer A commented: “The title of the paper includes both medicine and dentistry, could you please clarify if its either/or? I would encourage you to re-think the title as it needs to reflect the content of the manuscript and relevance to dentistry is only a small component of the paper.”

Author’s response:

We agree with the insight proposed with respect to the manuscript’s title. As such, we have modified the title as per the recommendation suggested by reviewer A. The article has a more heavy focus on the medicine behind local anesthesia in clinical dentistry, so the title will reflect that.

The title previously read:

“Local Anesthetics in Maxillofacial Medicine: Dentistry: Pharmacology, adverse effects, drug interactions and clinical manifestations”

It has been reworded to:

“Local Anesthetics in **Oral and** Maxillofacial Medicine: Pharmacology, adverse effects, drug interactions and clinical manifestations”

Reviewer A commented: “The methods section needs to provide clarity in the platforms used for search, is it limited to the University library system, how were the articles “red, analyzed and interpreted”? How many papers were identified in total that were used for the review? What were the inclusion and exclusion criteria? It would be good to create a flowchart or include a table to demonstrate the process.”

Author’s response:

We agree that the methods section could have been elaborated on more. Therefore, we have included additional information regarding the sources used for identifying useful

papers to reference and the amount of papers identified. A table outlining the inclusion and exclusion criteria was also created.

The section previously read:

“A literature review was conducted to identify the most relevant adverse interactions with common local anaesthetic agents used by general dentists and specialists. Likewise, peer-reviewed articles from the University of Toronto Library System were read, analyzed and interpreted prior to compiling the information displayed in this article. Some of the keywords that were searched in the databases included “local anaesthesia”, “local anaesthetic”, “adverse interactions”, “adverse effects” and “dentistry”. The majority of the content outlined in this paper is derived from sources that were published up to 5 years ago.”

It has been reworded to:

“A literature review was conducted to identify the most relevant adverse interactions with common local anesthetic agents used by general dentists and specialists. Likewise, **the information collection process involved a detailed search** for peer-reviewed **journal** articles from the University of Toronto Library System, **which were thoroughly** read and interpreted prior to compiling the **data** displayed in this article. **The main electronic databases used from the library system were PubMed, MEDLINE, ScienceDirect and the Cochrane Library. Furthermore, physical-copy textbooks from the University of Toronto Dentistry Library were used as a supplementary tool to confirm the accuracy and relevancy of certain clinical details. A total of 560 articles were identified, 105 investigated and 54 cited in this review.** Some of the **major** keywords that were searched in the **online** databases included “local anesthesia”, “local anesthetic **agents**”, “adverse interactions”, “**clinical outcomes**” and “dentistry”. **In addition, over 70% of the content outlined in this paper is derived from scientific reviews and peer-edited manuscripts that were published up to 5 years ago. For a comprehensive depiction of the exclusion and inclusion criteria for choosing pertinent reference articles, refer to the table below.”**

“**Table 1. Inclusion and exclusion criteria for selecting the references utilized in this article”**

Reviewer A commented: “In the discussion section, line 203, how do you define a recreational drug and what does it include? It would be interesting to include the interactions between consumption of alcohol and local anesthesia and its effectiveness.

Author’s response:

A definition of a recreational drug was included to the aforementioned section, including some common examples of drugs. In addition, the interaction between the consumption of alcohol and its effect on local anesthetic efficacy was described.

The section previously read:

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">• Peer-reviewed articles• Written in English, or possess a copy translated to English• Preference for publications released from 2017 onward• Papers displaying objectively measured outcomes of study	<ul style="list-style-type: none">• Papers which were not peer-reviewed• Not written in English, or do not possess a copy translated to English• Journals not accessible online• Duplicate publications• Editorials and letters• Papers displaying self-reported outcomes of study

“A scientific theory has recently been proposed regarding the reasoning as to why recreational drug use is associated with recalcitrant local anaesthesia. Specifically, difficulty in achieving effective local anaesthesia has been observed clinically in recreational drug users. The pharmacodynamic factors of regional numbing has effects on both peripheral nerve sensitization and central sensitization. Some researchers believe that past or current drug use may be altering the emotional perception of pain, leading patients to normalize their pain threshold to a new set point. Another theory suggests that, since many recreational drugs produce dysphoric states of mind, patients consuming such drugs may enter a state of hyperalgesia.²¹ All in all, experts believe that patients who are current or past users of recreational drugs may have an altered sensory system and a lower overall pain threshold, meaning that they often require more local anaesthetic and are predisposed to local anaesthetic toxicity.^{21,22}”

It has been modified to:

“A scientific theory has recently been proposed regarding the reasoning as to why recreational drug use is associated with recalcitrant local anesthesia. A recreational drug is typically defined as a chemical substance that is taken for psychoactive effects rather than for medical reasons. Further, these agents can be found naturally, or they can be synthesized in a laboratory setting. Some examples of recreational drugs used worldwide include, but are not limited to, marijuana, cocaine, morphine, MDMA (ecstasy), heroin, LSD, ketamine, amphetamines, methamphetamines, magic mushrooms, as well as volatile substances such as gases, aerosols and glues. Difficulty in achieving effective local anesthesia has been observed clinically in recreational drug users. The pharmacodynamic factors of regional numbing has effects on both peripheral nerve sensitization and central sensitization. Some researchers believe that past or current drug use may be altering the emotional perception of pain, leading patients to normalize their pain threshold to a new set point. Another theory suggests that, since many recreational drugs produce dysphoric states of mind, patients consuming such drugs may enter a state of hyperalgesia.²¹ All in all, experts believe that patients who are current or past users of recreational drugs may have an altered sensory system and a lower overall pain threshold, meaning that they often require more local anesthetic and are predisposed to local anesthetic toxicity.^{21,22, 45”}

This section has been added as the last paragraph of the “Key Drug Interactions with Vasoconstrictors:

“It has been known for decades that alcoholic patients may exhibit a variable response to drugs commonly used in clinical dentistry.⁴⁶ As these patients develop a tolerance to ethanol through routine consumption, they also raise their tolerance for sedative agents such as general and local anesthetics. In other words, this population of patients will likely require greater than average doses in order to achieve the appropriate degree of anesthesia for dental procedures. Interestingly, alcoholics may experience physiological alterations in the way drugs are metabolized, particularly for drugs which are mainly processed in the liver. The chronic consumption of alcohol-containing beverages results in a cumulative elevation of the mixed-function oxidase system enzymes, which are grouped into a super-family commonly known as cytochrome P450; these proteins are responsible for the metabolism of drugs within the liver. Ultimately, this can result in an accelerated drug metabolism cascade, leading to a shortened substance half-life and a potential reduction in the agent's effectiveness. Typically, alcoholics with healthy livers tend to metabolize drugs faster than the average population due to enzyme induction. On the other hand, those with less severe liver conditions, such as fatty liver, usually maintain normal metabolic efficiency. Further,

individuals with more advanced liver diseases, such as hepatitis or chronic cirrhosis, often experience a slower-than-normal metabolic rate due to the loss of these essential enzymes.^{46,47} Overall, predicting the impact of these physiological differences in individual patients can be very challenging.

Some local anesthetic substances that are significantly metabolized by the liver include both lidocaine and mepivacaine, which are medications that are very commonly employed prior to routine operative dentistry. Therefore, it is important for the treating dental clinician to consult with the patient's physician to outline the safe dosages according to their liver function. Dental anesthesiologists typically advise the utilization of ester-type local anesthetics for individuals with alcoholic cirrhosis because of their more consistent metabolic processing rates. For instance, a local anesthetic cartridge containing 0.4% propoxycaine hydrochloride (Ravocaine) combined with 2% procaine hydrochloride (Novocain) is available on the market, with a total volume of 1.8 ml per cartridge. These ester formulations, which belong to the para-amino benzoic acid family, undergo rapid breakdown via plasma cholinesterase hydrolysis, and the liver processes them to a lesser extent compared to the amide-type local anesthetic agents.⁴⁷

Reviewer A commented: "Evidence of the local anesthesia injection technique: how one could be better than the other in terms of outcomes in achieving anesthesia with reduced adverse effects."

Author's response:

We agree that this section should be included in the discussion as it adds value and variety to the paper. A sub-section was added to the discussion following the section titled "Vasoconstrictor Precautions and Contraindications".

This section has been added:

"Clinical differences between Local Anesthesia Injection Techniques

With the evolution of clinical dentistry, dental practitioners have increasingly diversified their methods of achieving anesthesia within the oral cavity. Despite the large variety of approaches discovered over the years, the choice of local anesthetic injection technique mainly depends on the type of dental procedure being performed, the risk of adverse consequences unique to each patient, and the extent of analgesia required.

Firstly, one of the most common techniques used to anesthetize a specific tooth or small area in the mouth is the infiltration method, which involves injecting

the local anesthetic solution directly into the tissues surrounding the teeth that require treatment. Although this technique is relatively safe to execute, some common adverse effects could include, but are not limited to, post-injection swelling and damage to nearby oral tissues if the needle penetration is not precise. Secondly, nerve blocks are employed in order to achieve more profound anesthesia of multiple teeth in a quadrant and their surrounding soft tissues; this is done by injecting the anesthetic fluid near a major nerve that supplies a larger surface area of the oral cavity. Similarly, some studies have shown that nerve blocks are more effective than infiltrations in terms of providing long-lasting analgesia for procedures such as extractions or root canal therapies, but this evidence is not conclusive and varies among different research articles according to their unique experimental criteria.⁵² Generally speaking, current research suggests that infiltrations lead to faster analgesia and a more tolerable peri-operative pain level compared to nerve blocks, which are only more effective with respect to duration of action compared to infiltrations. Due to their more invasive and penetrative nature, nerve blocks also possess a greater risk of nerve damage, trismus, needle breakage, facial paralysis, paraesthesia, ocular manifestations, accidental intravascular injection leading to systemic effects, and possible hematoma formation.

In terms of the mandibular nerve blocks, the Gow-Gates technique is often deemed as the most promising injection, with a close-to 99% success rate when performed by experienced dentists. Although it is viewed as a difficult technique to master, it possesses a smaller risk of facial paralysis following imprecise technique execution, hematoma formation and vascular contact compared to the traditional inferior alveolar nerve block (IANB). With the IANB, published success rates are between 80% to 92%, and efficacy can be improved by injecting the anesthetic solution more slowly, waiting for a longer period of time post-injection for the analgesic effect to work, using an adequate needle gauge, and promoting relaxation prior to injecting.⁵³ In addition, the Vazirani-Akinosi technique has the same indications as the Gow-Gates technique and the IANB, but it is often recommended when the patient has trismus or cannot open their mouth wide enough, when it is difficult to visualize the anatomic landmarks, when there is a history of failure with other mandibular blocks, and when there is accessory innervation present. Lastly, maxillary nerve blocks are considered to be extremely effective in anesthetizing regions of the maxillary jaw when appropriately administered, but they do present with their own risks and clinical complications, such as trismus, hematoma formation, intravascular injection, and ocular disturbances. The latter risk is especially important to note for maxillary nerve block techniques such as the greater palatine approach, the high tuberosity approach and the posterior superior alveolar approach, whereby

diplopia (double vision), esotropia (cross-eyed) and amaurosis (blindness) have been previously reported.⁵⁴

Reviewer A commented: “Suggestions for relevance to the dental practice, it would be valuable to include how a dentist should manage an adverse reaction if patient used illicit drugs such as cocaine before the dental appointment and does not inform the dentist about it. Another relevance to dental practice is the use of LA for management of acute pain as an alternative to prescribing opioids both in dental and medical practice and mentioning the long-acting LA that could be used for these situations”

Author’s response:

We agree on the recommendations here, as they are very relevant to the modern dental practice and increasing popularity of discrete drug use among patients. We have added a section that explains the importance of screening patients who are substance users and the protocol in dealing with an adverse response in the dental chair. Also, a separate subsection was added to describe the usefulness of using local anesthetics in managing acute pain in dentistry, as well as in some medical circumstances.

The sections that were added to “Relevance to the Dental Practice”

“Recent studies have indicated that dentists and specialists within the field who incorporate substance abuse screening tools into their practices, and who possess a thorough understanding of the addiction process, are more likely to make inquiries related to substance misuse when interacting with their patients on a day-to-day basis. Despite the existence of valid screening programs designed for unique clinical situations, additional investigation is imperative to establish the most effective screening methodologies within the realm of dental practice. As a result, a demand exists for comprehensive education among dental clinicians with respect to the pre-, peri- and post-operative management of the addicted patient.⁴⁸

In the event that a patient consumed illicit substances prior to a dental appointment, and has not informed the dentist about it, a cascade of negative events could occur if the clinician has not been trained to detect the physiological signs and symptoms of an adverse drug reaction. In order to effectively manage these types of situations, such as when a patient has cocaine in their system, the dentist should begin by assessing the patient's physical condition in the dental chair. Specifically, the clinician should focus on signs such as tachycardia, excessive perfusion, hypertension,

anxiety, restlessness and confusion. Following this initial emergency assessment, the dentist or surrounding staff should call for immediate assistance, especially if the patient's physical status appears to be severely compromised or deteriorating rapidly; this may include contacting nearby emergency medical services or a local hospital department. While waiting for medical assistance to arrive to the dental office, it is important to keep the patient calm, conscious if possible, and to reassure them that help is on the way. If the patient's physical status worsens drastically and they become totally unresponsive, it may be necessary to commence basic life support techniques, such as CPR, if the dentist or any dental staff members are properly trained to do so.⁴⁹ After the patient receives the appropriate medical attention, the treating dentist should attempt to communicate with the patient in a supportive and empathetic manner. This form of doctor-patient interaction can help promote open and honest dialogue about the substance use, which could aid in ensuring the continuity of dental care following the incident. For the prevention of such unforeseeable emergencies in the future, dental offices should consider incorporating a routine and non-judgmental substance use screening program as part of their new patient intake process. By doing so, this can help identify those who could be at risk for adverse reactions in the dental office due to their undisclosed substance abuse.^{48,49}

Administering local anesthetics for acute pain management a promising alternative to the traditional practice of prescribing opioids to patients, both within the dental and medical sectors.^{50,51} This modern clinical approach, while slightly more invasive, offers a means to reduce pain symptoms while mitigating the risks linked to opioid misuse, which include dependence, addiction, and the cascade of physiological consequences as a result of over-consumption.

In clinical dentistry, one notable solution for alleviating pain is the use of long-acting local anesthetic agents, such as bupivacaine, tetracaine and etidocaine. Since these drugs have a longer duration of action (i.e., between 2 to 4 hours), they can effectively offer pain relief for an extended period of time, making them especially advantageous for post-procedural pain management following endodontic therapies, tooth extractions, or periodontal surgeries. Interestingly, bupivacaine has been shown to be superior with respect to the amount of post-operative analgesic consumption and time to analgesic consumption compared to short-acting anesthetics such as lidocaine with epinephrine and mepivacaine.⁵⁰ This suggest that, compared to short-acting local anesthetics, bupivacaine yields a substantially lower pain response after invasive operations. Therefore, it is clear that the advent of long-acting local anesthetics like bupivacaine has now allowed for general dentists and specialist clinicians to enhance patient comfort while also minimizing the need for opioid prescriptions.⁵⁰ Similarly, in

clinical medicine, long-acting local anesthetics are frequently used to address acute or sporadic pain in a wide array of scenarios, ranging from minor surgical interventions to generalized post-operative discomfort. Likewise, this approach aligns with the medical community's growing commitment to reduce opioid dependence and overprescribing, which has become a widespread issue over the last few decades as seen with the opioid crisis. Local anesthetics such as ropivacaine, with its extended analgesic effect, are valuable options in many contexts within the field of medicine.⁵¹ Ropivacaine has been shown to last between 2.5 to 6 hours when administered epidurally, while its effective analgesia could last between 8 to 13 hours when used for peripheral nerve blocks. While long-acting local anesthetic agents are extremely effective in a diverse amount of situations, they should be used with extreme care because overdose or improper administration can lead to severe complications. Thus, healthcare providers are required to possess the necessary clinical knowledge and training in order to safely use this strategy for pain alleviation.^{50,51}

Reviewer B:

Thank you for your comments on the paper. We are very delighted that you are considering this article as a publication in your journal. Therefore, we have taken into account your recommendations and have made some changes in order to make the manuscript even more suitable for the Journal of Oral and Maxillofacial Anesthesia.

Reviewer B commented: “- Title: The authors should use the following title “Local Anesthetics in Maxillofacial Medicine and Dentistry: Pharmacology, adverse effects, drug interactions and clinical manifestations.”

Author’s response:

We agree with your suggestion for the title. Since the paper reflects more on the medicine behind local anesthetics and their effects, we are leaning toward using the title suggested by Reviewer A. However, we are open and willing to use either title.

Reviewer B commented: “- Introduction (pag 2 – line 40): Please, make it clearer the meaning of “nature of dental surgeries”.

Author’s response:

We agreed that the meaning of “nature of dental surgeries” should have been worded more clearly. Therefore, we refined that section of the introduction.

The section previously read:

“...Although anaesthetics have been used for over 175 years, patient factors and the nature of dental surgeries have drastically changed with time. Therefore, it is paramount for current dental practitioners to comprehend how these locally administered preparations interact with both exogenously delivered drugs, as well as naturally occurring compounds within the body.”

It has been modified to:

“...Although anesthetics have been used for over 175 years, **individual** patient factors and the **clinical scope** of dental surgeries have drastically changed with time. Therefore, it is paramount for current dental practitioners to comprehend how these locally administered preparations interact with both exogenously delivered drugs, as well as naturally occurring compounds within the body.”

Reviewer B commented: “- Introduction (pag 3 – line 52): The terms “pain is largely perception” do not seem to be suitable. I recommend rewriting them.”

Author’s response:

We agreed that this statement would benefit from being described in a less vague manner. Therefore, this section has been refined as well.

The section previously read:

“...In general, pain is largely perception, and the experience of a painful stimulus essentially defines this unwanted feeling...”

It has been modified to:

“...**Despite pain being dictated by many intricate sensory pathways, this unpleasant signal or feeling is also largely guided by the complex experience of perception.**”

Reviewer B commented: “- Discussion (pag 8 – line 172): The authors should check the information “...the fat-soluble form of the preparation is favoured...”.

Author’s response:

This was an accidental error in writing that has been modified to the correct information.

The section previously read:

“...Since the pH of the oral cavity becomes more acidic in the presence of an inflammatory response, the fat-soluble form of the preparation is favoured, which

would ultimately lead to less molecules infiltrating the nerve and reaching their target site on the ionophores...^{16,17}

It has been modified to:

“...Since the pH of the oral cavity becomes more acidic in the presence of an inflammatory response, the **water**-soluble form of the preparation is favoured, which would ultimately lead to less molecules infiltrating the nerve and reaching their target site on the ionophores.^{16,17}”

Reviewer B commented: “- I suggest avoiding using the word "one" throughout the text, as in this sentence: “Of the altered sensations one could experience...”. Please, use a more scientific writing.”

Author’s response:

We agree with the suggestion of replacing the word “one” with more scientific terminology. When the word “one” was used in this context, it was replaced with words such as “patient”, or the sentence was reformulated to not include the word “one”.

Reviewer B commented: “- Discussion (pag 14 – line 320): The authors should describe as follows: “...could be an accumulation of epinephrine or levonordefrin...”.

Author’s response:

We agreed that this sentence required some elaboration for contextual clarity. Therefore, some extra information was added to this section to explain the process of increased cardiovascular activity when a patient takes TCAs.

The section previously read:

“...With the tricyclic antidepressant’s ability to block the non-adrenergic reuptake channel, there could be an accumulation of epinephrine or levonordefrin in proximity to the postsynaptic alpha- and beta-adrenergic receptors, leading to increased cardiovascular activity...”

It has been modified to:

“...With the tricyclic antidepressant’s ability to block the non-adrenergic reuptake channels, **this would lead to an elevated concentration** of epinephrine, levonordefrin **and serotonin within the synaptic cleft. Ultimately, this would cause an increase in cardiovascular activity as a result of summative anticholinergic effects at the neuronal**

level. When these agents interact with exogenous vasoconstrictors, enhanced sympathomimetic effects, increased blood pressure, and a greater risk of postural hypotension could be witnessed as well.”

Reviewer B commented: “- Discussion (pag 14 – line 331): The sentence “Similarly, norepinephrine reuptake inhibitors (atomoxetine) and amphetamine-like stimulants such as attention deficit hyperactivity disorder medications augment the release of norepinephrine and catecholamines, while blocking their reuptake.” should be rewritten more clearly.”

Author’s response:

We agree that the aforementioned sentence was confusing to read at first, so we attempted to reword it in a more clear and concise manner.

The section previously read:

“Similarly, norepinephrine reuptake inhibitors (atomoxetine) and amphetamine-like stimulants such as attention deficit hyperactivity disorder medications augment the release of norepinephrine and catecholamines, while blocking their reuptake. The latter two drugs may be used in children and adults with normal heart rates and blood pressures.³⁵”

It has been modified to:

“Similarly, norepinephrine reuptake inhibitors and amphetamine-like stimulants, such as attention deficit hyperactivity disorder medications, are able to augment the release of norepinephrine and catecholamines while also chemically blocking their reuptake. The latter two drug classes may be used in children and adults with normal heart rates and blood pressures.³⁵”

Reviewer B commented: “- Discussion (pag 15 – line 350): Please, write THC in full too.”

Author’s response:

We agree and have added the full scientific name of THC.

The sentence previously read:

“All in all, recent research has concluded that the additive effects of epinephrine and THC increase the overall risk of stroke or myocardial infarction in those who have used cannabis immediately prior to their dental visit.³⁷”

It has been modified to:

“All in all, recent research has concluded that the additive effects of epinephrine and **delta-9-tetrahydrocannabinol** increase the overall risk of stroke or myocardial infarction in those who have used cannabis immediately prior to their dental visit.³⁷”

Reviewer B commented: “- Discussion (pag 16 – line 370): Please, make a new sentence as follows: Then, the cautious use of epinephrine-containing local anaesthetic preparations is strongly suggested.”

Author’s response:

We accept the suggestion to add the aforementioned sentence to the manuscript.

The section previously read:

“...the cautious use of epinephrine-containing local anaesthetic preparations is strongly suggested.³⁵”

It has been modified to:

“Then, the cautious use of epinephrine-containing local anesthetic preparations is strongly suggested.³⁵”