

REVIEW

Present status and future directions—Mechanisms and management of local anaesthetic failures

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Abstract

Aim: To review variables and management techniques that may affect anaesthesia failure during root canal treatment and methods of overcoming anaesthesia failure.

Methodology: The PubMed and Cochran databases were searched for evidence-based investigations regarding pain during needle insertion, pain on injection, efficacy of the anaesthetic solutions and anaesthesia techniques, and premedication.

Results: Variables such as pain on injection, premedication with various types of drugs, volume of anaesthetic solutions, supplemental anaesthetic techniques, and additives to the anaesthetic solutions may influence pain perception during root canal treatment. Differences between teeth with healthy pulps versus those with irreversible pulpitis should be considered when the effects of variables are interpreted. However, there are several concerns regarding the methodology of investigations that have evaluated anaesthesia success rates.

Conclusion: Several variables may influence anaesthesia success rates. There are conditions that may help to predict a patient's pain during endodontic procedures. These conditions could be overcome either by employing methods such as premedication with a non-steroidal anti-inflammatory drug prior to the treatment visit or by using supplementary techniques before or during the treatment. However, investigators need to be more careful when reporting details of their studies to reduce concerns regarding their study bias.

KEYWORDS

anaesthesia, endodontic treatment, irreversible pulpitis, pain, premedication, success, supplemental, technique

INTRODUCTION

Management of dental pain during root canal treatment requires special attention since traditional anaesthetic techniques and solutions do not enable dentists to completely overcome the pain endured by patients during root canal treatment of teeth with irreversible pulpitis (Abbott

& Parirokh, 2018). As a consequence, root canal treatment induces a high level of anxiety amongst patients. A survey of dental patients reported that fear of pain, fear of needles, difficulty in anaesthesia achievement and anxiety are the major factors that produce fear in patients (Huh et al., 2015) may force patients to ask for sedation during treatment (Huh et al., 2015; Setty et al., 2014). From the

patient's point of view, anaesthesia success means no or minimum pain during needle insertion, during injection of the anaesthetic solution and during the treatment procedure. Several hypotheses and variables regarding local anaesthesia in dentistry have been introduced to describe the reasons for anaesthesia failure and the factors that may affect anaesthesia success rates (Drum et al., 2017). However, none of these theories completely describe the reasons of anaesthesia failure nor do they recommend a technique or medication to provide anaesthesia for all teeth in need of root canal treatment. Therefore, it is mandatory for every dental practitioner to be aware of the limitations, reasons for anaesthetic failures, variables that may affect anaesthesia success rates and recommended strategies (i.e. methods, anaesthetic solutions, premedication and techniques) for managing anaesthesia failure. The aim of this review was to explain the reason of anaesthesia failures, variables that may affect anaesthesia success rate as well as shortcomings of previous investigations to help investigators design, perform and report their studies with lower risk of bias.

SEARCH STRATEGY

An electronic search of PubMed and Cochran databases was undertaken. Appropriate MeSH keywords were used—these included: Anaesthetic, local, mandibular nerve, maxillary nerve, anaesthetic solutions, anaesthesia success, therapeutic, anaesthesia techniques, efficacy, injection pain, dental anxiety, pain measurement, pulpitis, needle insertion, pain, premedication, supplementary anaesthesia, intraligamental, intrapulpal, intraosseous, nerve block, periodontal ligament. The selected English papers were published up to June 2021.

CRITERIA FOR ANAESTHESIA SUCCESS

The criteria for anaesthesia success should be divided into two categories—criteria for success of the anaesthesia technique and criteria for success of pulp anaesthesia. Traditionally, for most anaesthesia techniques, soft tissue numbness has been used to determine successful anaesthesia. For instance, following an inferior alveolar nerve block (IANB), lower lip numbness has been considered as a sign of IANB success (Modaresi et al., 2006; Parirokh et al., 2010a, 2010b; Sampaio et al., 2012). However, in crossover studies, no response to pulp sensibility tests has been considered to indicate pulp anaesthesia in teeth without irreversible pulpitis. In teeth with irreversible pulpitis, no or mild pain during access cavity preparation

is often the method of choice to indicate anaesthesia success (Parirokh & Abbott, 2014).

Most patients consider soft tissue numbness as anaesthesia success. However, for instance, most of the time following infiltration injections for maxillary second molars, soft tissue numbness may not be evident and the patient may feel that the anaesthesia was not successful. It would be more appropriate for dental practitioners to consider criteria for anaesthesia success based on scientific evidence. In that case, a lack of response to the cold test would be a more reliable sign of anaesthesia success compared with soft tissue numbness (Hsiao-Wu et al., 2007).

Studies on the success rate of anaesthesia have included either volunteers with sound intact teeth in crossover design studies or randomized clinical trials in patients with irreversible pulpitis. In crossover studies, the success of anaesthesia has been defined as when a volunteer who received anaesthesia does not respond to a cold test or two consecutive maximum outputs of an electric pulp test (EPT) (Dagher et al., 1997; Parirokh & Abbott, 2014). However, in randomized clinical trials of teeth with irreversible pulpitis, neither lip numbness nor lack of responses to cold or EPT guarantee success of anaesthesia during access cavity preparation, pulp exposure or root canal instrumentation (Parirokh et al., 2010a, 2010b; Sampaio et al., 2012). Amongst variables such as sensitivity to cold, lip numbness and pain during access cavity preparation, the latter factor had a significantly higher predictive role compared with either the cold test or lip numbness to pain during pulp removal as the gold standard (Abbott & Parirokh, 2018). It has been reported that despite responding to the electric pulp tester, patients may feel no or mild pain during access cavity preparation and root canal instrumentation (Sampaio et al., 2012). Therefore, lip numbness and either a response or no response to the pulp sensibility tests do not necessarily indicate successful anaesthesia. It has been hypothesized that a lack of response to EPT and the cold test are related to anaesthetizing the fast and slow-silent A δ -fibres, respectively. However, the tetrodotoxin resistance (TTx resistance) sodium channels on C-fibres have no role in the response to sensibility tests, and, for that reason, they cannot be considered to be anaesthetized despite there being no response to sensibility tests following administration of anesthetizing solutions (Parirokh et al., 2010b).

In conclusion, as teeth with irreversible pulpitis are more difficult to anaesthetize during root canal treatment, randomized clinical trials that include teeth with pulpitis provide more accurate results compared to the crossover studies using teeth with healthy pulps. Therefore, systematic reviews and meta-analysis studies on the effects of anaesthetic solutions or techniques should evaluate crossover studies and teeth with irreversible pulpitis separately.

REASONS FOR ANAESTHESIA FAILURE

Several reasons have been described for local anaesthesia failure during root canal treatment. These reasons could be categorized as anatomic and non-anatomic. Amongst the anatomical reasons, the central core theory and the mylohyoid nerve have attracted more attention (Reader & Nusstein, 2002). However, due to the lack of an adequate explanation for failure of anaesthesia for all teeth, non-anatomic reasons have attracted more attention since they may explain reasons of anaesthetic failures for the majority of teeth with irreversible pulpitis. Most of the hypotheses regarding anaesthesia failure have addressed alterations of nerves, including lowering the threshold, expression of tetrodotoxin-resistant sodium channels as well as exited nerve fibres having isoforms of voltage-gated sodium channels in their nerve endings of $\text{Na}_v 1.7$ and $\text{Na}_v 1.8$.

The condition of nerves surrounding tissues may also have an influence on the anaesthetic solution's efficacy since the percentage of the base form of the solution that can effectively penetrate the nerve perineurium would be decreased in inflamed tissues due to a lower pH (Hargreaves & Keiser, 2002). The hypothesis of an acidic environment may be a reasonable explanation for failure of infiltration injections but this theory does not explain why a nerve block injection that administers the anaesthetic solution to a site distant from the inflamed tissue is not successful. It is well documented that pulp inflammation could affect the expression of ion channels, proinflammatory cytokines and prostaglandins at a site distant from the site of inflammation—that is the subnucleus caudalis and trigeminal ganglion (Ballon Romero et al., 2020; Sun et al., 2019). In addition, during inflammation, expression of transient potential vanilloid 1 (TRPV1) receptor would be increased and this will lower the receptor's threshold excitability that finally results in hyperalgesia. Following consumption of oral ibuprofen, the cytokines were down-regulated and microglial and astrocyte activation were prevented (Ballon Romero et al., 2020). This may be a reason for anaesthesia failure despite nerve block administration of an anaesthetic solution since it has been reported that higher levels of the nervous system, such as the trigeminal subnucleus caudalis, were influenced when there was pulp inflammation (Ballon Romero et al., 2020).

It has been reported that during inflammation, neuropeptide and cytokines (such as interleukins IL-2, IL-6, IL-8, IL-10 and tumour necrosis factor), interferon γ and prostaglandins are upregulated (Bletsa et al., 2009; Choi et al., 2013; Elsalhy et al., 2013; Hirsch et al., 2017; Rechenberg et al., 2016; Zhang & An, 2007). In a rat model, it has been reported that 3 days after inducing pulpitis, expression of

extracellular signal-regulated kinases and $\text{Na}_v 1.7$ were increased in the trigeminal ganglion (Sun et al., 2019). All of these factors may affect nerves and may result in nerve sprouting, mechanical allodynia, hyperalgesia and central sensitization that would be difficult to overcome through the administration of local anaesthetic solutions (Cherkas et al., 2012; Kimberly & Byers, 1988; Rossi et al., 2020).

High anxiety increases nerve excitability and lower pain thresholds (Hargreaves & Keiser, 2002). However, despite significantly higher levels of anxiety in women with red hair, no significant difference was found following an IANB between women with red hair and those with dark hair (Droll et al., 2012). A causal relationship has been reported between pain induced by dental injury and anxiety (Shang et al., 2015). Therefore, in addition to changing the quality of life (due to eating and sleeping disturbances and attitude alteration), dental pain may induce anxiety that affects pain management during root canal treatment (Shang et al., 2015). It has been reported that the use of extracellular signal-regulated kinase (ERK) inhibitors not only reduced proinflammatory cytokines but also decreased expression of the tetrodotoxin-sensitive sodium channels and other factors associated with dental pain (Sun et al., 2019). In addition, the medication could mitigate anxiety behaviour in animal models following an intentional pulp injury (Shang et al., 2015).

In conclusion, in addition to the local alteration of nerve fibres, changes in higher levels of nerve pathways (such as the trigeminal subnucleus caudalis) should be considered as one of the reasons for anaesthesia failure. Any hypothesis that is limited to explaining local reasons for failure of pulp anaesthesia cannot be considered comprehensive. Pain management strategies should be based on considering nerve alteration through the nerve pathways to the higher level (such as the trigeminal subnucleus caudalis) neurons.

VARIABLES THAT COULD AFFECT INTRA-OPERATIVE PAIN

Overall the prevalence of anaesthesia failure (considered to be when there is moderate-to-severe pain during root canal treatment) has been reported to range from 11% to 85% (Martín-González et al., 2012; Pak & White, 2011; Parirokh et al., 2010a; Segura-Egea et al., 2009). Several variables have been considered that may affect anaesthesia success rates but there are conflicting results amongst studies regarding their impact (Martín-González et al., 2012; Segura-Egea et al., 2009; Udoye & Jafarzadeh, 2011; Watkins et al., 2002). Several investigations have reported various potential predictors—these include the following: posterior teeth (Segura-Egea et al., 2009), particularly

molars (Kayaoglu et al., 2016), patients aged less than 35 years old (Segura-Egea et al., 2009), presence of irreversible pulpitis with acute apical periodontitis, presence of preoperative pain (Kayaoglu et al., 2016; Segura-Egea et al., 2009), mandibular teeth (Kayaoglu et al., 2016), longer palatal and disto-buccal roots in maxillary molars (Moradi Askarie et al., 2016) and treatment procedures longer than 45 min may significantly induce more severe pain during root canal treatment (Segura-Egea et al., 2009). In addition, gender (females) may be a predictor when premolar teeth are being anaesthetized (Kwon et al., 2014). However, these studies have not been consistent regarding some of the predictors such as gender and age (Kayaoglu et al., 2016; Kwon et al., 2014; Segura-Egea et al., 2009).

In conclusion, it is generally accepted that the presence of preoperative pain and mandibular posterior teeth are the most predictive factors for failure of anaesthesia.

PAIN ON INJECTION

Pain on injection can be induced by the mechanical trauma of needle penetration, administration of the anaesthetic solution and the chemical components of the anaesthetic solution (Ballard, 1968; Kramp et al., 1999).

Topical anaesthesia

There are contraindicatory reports on the efficacy of topical anaesthesia (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). There are reports that favour the use of topical anaesthesia to decrease injection pain and pain during needle insertion, but, in contrast, no significant differences between using topical anaesthesia and placebo controls have been reported by several investigators (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). Irrespective of considering topical anaesthesia as an effective factor for injection pain, it should be noted that employing topical anaesthesia can significantly decrease the pain on needle insertion in patients with high levels of anxiety (Cho et al., 2017).

Most of the attention of investigations that have evaluated topical anaesthesia effects have focused on pain during needle insertion (Meechan John, 2008) although pain on injection has also been investigated following the use of topical anaesthesia (Joshi et al., 2021). However, there is no general agreement regarding the efficacy of topical anaesthesia on pain during needle penetration and anaesthetic solution injection (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). Several investigations have reported a positive effect of some

types of topical anaesthesia on injection pain (Al-Melh & Andersson, 2007; Fukayama et al., 2002; Hersh et al., 1996; Hutchins et al., 1997; Nakanishi et al., 1996; Rosa et al., 1999; Rosivack et al., 1990), whilst, in contrast, others did not report a significant impact of pain reduction during needle penetration or anaesthetic solution injection (Drum et al., 2011; Fukayama et al., 2002; Nusstein & Beck, 2003; Parirokh et al., 2012b). Variables such as the time between topical anaesthetic application and the injection, the site of injection and the type as well as the concentration of the topical anaesthetic agents are all factors that may influence the efficacy of topical anaesthesia (Drum et al., 2011; Fukayama et al., 2002; Meechan John, 2008; Nakanishi et al., 1996; Nusstein & Beck, 2003). In future, new forms of topical anaesthesia with higher permeation may be achievable (Batista da Silva et al., 2021).

Topical anaesthesia should be placed at the injection site at least 2 min in advance of the injection (Meechan John, 2008). The thickness of the keratinized tissues (Meechan John, 2008; Nakanishi et al., 1996) as well as the formulation of the topical anaesthetic may affect the efficacy of topical anaesthesia (Al-Melh & Andersson, 2007; Fukayama et al., 2002). Palatal mucosa with high levels of keratinized tissues prevent a positive effect of topical anaesthetic on injection pain (Meechan John, 2008).

The type of the anaesthetic used for topical anaesthesia as well as the method of placing the topical anaesthetic may influence pain on injection—for example, a patch of 2% lidocaine hydrochloride provided significantly less needle insertion pain compared with 20% ethyl aminobenzoate and a placebo (Nakamura et al., 2013).

Placement of a combination of lidocaine and prilocaine cream at the site of needle insertion of primary intraligamental injections provided significantly lower pain on injection compared with an ointment of 5% lidocaine (Meechan & Thomason, 1999).

In conclusion, topical anaesthesia is not effective in all sites of the oral cavity. However, for psychological reasons, topical anaesthesia could be beneficial since it would indicate that the dentist is doing everything possible to decrease pain during treatment.

Vibration systems

Vibration of the oral mucosa in advance of the injection of an anaesthetic provides promising results (Ching et al., 2014; Joshi et al., 2021; Tung et al., 2018). DentalVibe is one of the devices that have been used for such vibration. The mechanism of the device's action is based on the gate

control theory—that is, stimulation of larger nerves fibres via vibration prevents pain perception by the patients during injection of the anaesthetic solution. Several studies have confirmed its efficacy for reducing injection pain compared with topical anaesthesia (Ching et al., 2014; Joshi et al., 2021; Tung et al., 2018).

Anaesthetic solutions

There are contraindicatory reports regarding pain on injection when different anaesthetic solutions are used. Several investigations have reported that pain on injection with prilocaine was significantly less than lidocaine with epinephrine (Kramp et al., 1999; Wahl et al., 2006), bupivacaine with epinephrine (Wahl et al., 2002), mepivacaine plain (Wahl et al., 2006) and articaine with epinephrine (Wahl et al., 2006) although one study reported no significant difference between prilocaine plain and lidocaine with epinephrine (Wahl et al., 2001). However, it should be noted that the sites of injections were in different parts of the oral cavity (Kramp et al., 1999; Wahl et al., 2002, 2006). Both 2% mepivacaine with 1:100 000 epinephrine and 4% articaine with 1:100 000 epinephrine for buccal infiltrations significantly induced less pain compared with injecting 2% mepivacaine with 1:100 000 epinephrine for an IANB (Gazal et al., 2015). In addition, no significant difference was found between pain on injection of a combination of 3% mepivacaine and 2% lidocaine with 1:100 000 epinephrine compared with two cartridges of 2% lidocaine with 1:100 000 epinephrine for an IANB (Lammers et al., 2014).

There were also no significant differences between pain on injection of 2% lidocaine with two different concentrations of epinephrine (1:80 000 and 1:200 000) for an IANB (Aggarwal et al., 2014).

Anaesthetic techniques

The technique used for the injection may be another variable that could affect pain on injection. A study that compared IANB, Gow-Gates and Vazirani-Akinosi techniques reported that the former had significantly less pain on needle insertion, needle placement and anaesthetic solution deposition (Shetkar et al., 2016).

Infraorbital blocks and anterior middle superior alveolar nerve blocks induced mild pain and discomfort during injection (Corbett et al., 2010; Saraf et al., 2016). Although the difference was insignificant, the buccal injection for mandibular second molars had the lowest pain level, whereas canine teeth had the more severe pain with buccal injections (Currie et al., 2013).

Speed of injection

It has been assumed that a more rapid speed of injection may increase the distribution of the drug. There has been a suggestion that a faster injection may expose a longer section of the nerve to the anaesthetic solution, and therefore, there may be a higher rate of local anaesthesia success (Hargreaves & Keiser, 2002). Several randomized clinical trials have reported that rapid injections have either significantly lower success rates (Kanaa et al., 2006) or no significant difference for IANB and incisive/mental nerve block success rates (Aggarwal et al., 2012b; Whitworth et al., 2007). However, the faster injections caused greater pain and discomfort during the injections (Aggarwal et al., 2012b; Kanaa et al., 2006; Whitworth et al., 2007) whereas the slow administration of anaesthetic solution reduced the risk of nerve ending stimulation (Aggarwal et al., 2012b; Kanaa et al., 2006; Whitworth et al., 2007).

Use of additives

Adding mannitol to 2% lidocaine with 1:100 000 epinephrine significantly reduced pain on injection for maxillary lateral incisors (Younkin et al., 2014). In contrast, adding diphenhydramine significantly increased pain on injection (Willett et al., 2008).

Devices

It has been reported that needleless injections using a jet device induced significantly less pain on injection compared with the use of conventional syringes and needles (Hameed et al., 2021).

Sedation

The use of nitrous oxide for inhalation sedation may also provide a significant reduction of pain and discomfort during the administration of an anaesthetic solution (Gupta et al., 2019).

Other variables

The pH value of the anaesthetic solution, site of injection and the technique used are other variables that may influence pain on injection (Aggarwal et al., 2012b; Aulestia-Viera et al., 2018; Kanaa et al., 2006; Kramp et al., 1999; Meechan & Day, 2002; Whitworth et al., 2007).

It has been reported that plain anaesthetic solutions with a higher pH provided significantly less pain on injection compared to anaesthetic solutions with lower pH (Kramp et al., 1999; Meechan & Day, 2002).

With the same anaesthetic solution, the site of injection may affect pain on injection. For instance, the presence of epinephrine due to a lower pH was associated with significantly more severe pain in maxillary buccal injections whereas pain induced by palatal injections was not significantly different with the same anaesthetic solutions (Meechan & Day, 2002). In maxillary teeth, no significant difference for injection pain was reported amongst canine, central and lateral incisors during needle insertion and injection (Sharifi et al., 2016). In addition, the volume of anaesthetic solution deposited had no significant impact on injection pain in maxillary teeth (Brunetto et al., 2008; Mikesell et al., 2008; Pfeil et al., 2010).

One may argue that pain on injection may increase a patient's anxiety and therefore anaesthesia failure by lowering the patient's pain threshold but it has been shown that pain during injection has no significant impact on anaesthesia success (Parirokh et al., 2012b). Several devices have been introduced to decrease pain on injection (Aghahi et al., 2017; Shahidi Bonjar, 2011), and a randomized clinical trial on one of these devices introduced a new telescopic needle that significantly decreased pain on injection and post-injection anxiety regarding needle penetration amongst adults (Aghahi et al., 2017).

An interesting finding is the effect of the practitioner's and patient's gender on pain on injection. It has been shown that when male practitioners perform injections for female patients, they may feel significantly higher pain levels during the deposition of the anaesthetic solution (Perry et al., 2015).

A systematic review and meta-analysis based on moderate-quality evidence reported no significant difference on injection pain between 4% articaine and 2% lidocaine with similar amounts of epinephrine (1:100 000) (St George et al., 2018). However, another systematic review and meta-analysis reported significantly less pain on injection for 4% articaine with 1:100 000 epinephrine compared to 2% lidocaine with the same concentration of epinephrine (Su et al., 2016). However, the data in that systematic review and meta-analysis (Su et al., 2016) were derived from only one randomized clinical trial (Kanaa et al., 2012a).

Most studies have had shortcomings of small sample sizes (Gazal et al., 2015; Meechan & Day, 2002; Meechan & Thomason, 1999; Parirokh et al., 2012b; Sharifi et al., 2016), being non-randomized clinical trials (Wahl et al., 2001, 2002), employing volunteers with healthy dental pulps (Corbett et al., 2010; Meechan & Day, 2002; Meechan & Thomason, 1999; Parirokh et al., 2012b; Sharifi et al., 2016;

Younkin et al., 2014) and not explaining the details of the method of randomization and blindness (Gazal et al., 2015). Employing healthy pulps could be a potential shortcoming since the level of anxiety may be different between healthy individuals and patients who are suffering from severe pain such as irreversible pulpitis (Edwards et al., 1999). Furthermore, the use of a single-blinded method may result in detection and performance bias (Aggarwal et al., 2011b, 2012b; Younkin et al., 2014).

It can be concluded that the speed of injection as well as the site of injection may influence pain on injection. In other words, an anaesthetic solution that might have no pain when injected at one site may induce pain on injection at another site. However, since the gender of the clinician who is injecting the anaesthetic solution could be a potential confounding factor (Perry et al., 2015), one may argue that it would be better if a female practitioner injected all anaesthetic solutions in future studies.

ONSET AND DURATION OF ANAESTHESIA

Anaesthetic techniques

The onset of anaesthesia has been reported to be significantly faster for buccal infiltrations compared with IANB (Jung et al., 2008).

In teeth with healthy pulps, 4% articaine with 1:200 000 epinephrine for IANB provided significantly faster onset and longer duration of anaesthesia compared to 2% lidocaine with 1:100 000 epinephrine (Tortamano et al., 2013). When 4% articaine with 1:100 000 epinephrine was used for an IANB for teeth with healthy pulps, the onset of anaesthesia was 8.60 ± 2.12 min and 9.0 ± 1.94 min in molars and canines, respectively (Samdrup et al., 2021).

Type of anaesthetic solutions

There are contraindicatory reports regarding anaesthesia duration when articaine was used as the anaesthetic solution. One study reported that when 4% articaine with different concentrations of epinephrine (1:100 000 and 1:200 000) was used, the duration of anaesthesia was similar and lasted for about 4 h (Lasemi et al., 2015). However, another study reported that the duration of anaesthesia was about 88 min following the use of 4% articaine (Tortamano et al., 2013). The difference is due to the definitions used in each study to evaluate the duration of the anaesthesia. During root canal treatment, the duration of pulp anaesthesia is an important factor but in other branches of dentistry, the duration of

anaesthesia is usually attributed to the soft tissue numbness. This is also how most patients assess the duration of anaesthesia.

When 4% articaine with different concentrations of epinephrine used for a buccal infiltration (BI), no significant difference was found in the onset of anaesthesia between the anaesthetic solutions (McEntire et al., 2011). The onset of injection for 4% articaine with different concentrations of epinephrine (1:100 000 and 1:200 000) when used as a primary buccal infiltration injection was less than 5 min (McEntire et al., 2011).

Plain mepivacaine (3%) provides short duration of anaesthesia in maxillary teeth either when used as intraoral infraorbital nerve block or as an infiltration injection compared to 2% lidocaine with different concentrations of epinephrine (Berberich et al., 2009; Mason et al., 2009).

The type of anaesthetic solution as well as the site of the infiltration injection may influence the onset of anaesthesia. For instance, 0.5% bupivacaine with 1:200 000 epinephrine compared to 2% lidocaine with 1:100 000 provided significantly a slower onset of anaesthesia for maxillary first molars but there was no significant difference between the two anaesthetic solutions when used as infiltration injections for maxillary lateral incisors (Gross et al., 2007). It has also been reported that 0.5% plain ropivacaine (an anaesthetic solution with the similar structure to bupivacaine, but considered to be a safer solution Reiz et al., 1989) provided significantly faster onset of anaesthesia and longer duration for maxillary central and lateral incisors compared to 4% articaine with 1:100 000 epinephrine (Krzemiński et al., 2011).

Site of injection

The onset of anaesthesia when buccal injections are used in the mandible is dependent on the site of injection. When the injection was performed on the buccal aspect of second molars, no anaesthesia was reported for the incisors. However, when the injection was performed at the buccal site of the first molar, the second molar had the fastest median onset time of anaesthesia followed by the second premolar and central incisor. Injections for premolars resulted on slower onset of anaesthesia, whereas second molar injections resulted in the longest median time of onset of anaesthesia (Currie et al., 2013).

Type of device used for anaesthesia

It has been reported that onset of anaesthesia significantly increased when a jet injection device was used for maxillary central incisors (Hameed et al., 2021).

Pulp condition

It should also be noted that the onset of anaesthesia may be influenced by the condition of the pulp. A drawback of most investigations on the onset of anaesthesia is that they usually assess teeth that do not need root canal treatment—that is, they have normal, healthy pulps (Currie et al., 2013; McEntire et al., 2011; Samdrup et al., 2021; Tortamano et al., 2013).

Volume of anaesthesia

Repeated use of infiltration injections significantly increased the duration of anaesthesia of maxillary lateral incisors (Mikesell et al., 2008; Scott et al., 2009). The duration of anaesthesia in maxillary teeth is different for different teeth when infiltration injections were used such that lateral incisors had significantly higher non-continuous anaesthesia. The teeth that received higher volumes of anaesthetic solution had longer duration of anaesthesia (Mikesell et al., 2008). When 2% lidocaine with 1:100 000 was used for posterior superior alveolar nerve blocks, larger volumes of anaesthesia provided significantly longer duration of anaesthesia for the maxillary first molars compared with the use of a smaller volume (1.8 ml) (Pfeil et al., 2010). Injection of anaesthetic solution on the palatal and buccal sides of maxillary molars provided significantly longer anaesthesia (Guglielmo et al., 2011).

Use of additives

It has also been shown that injection of hyaluronidase 30 to 40 min after injecting the anaesthetic solutions (2% lidocaine or 2% mepivacaine) as an IANB can increase the duration of anaesthesia (Satish et al., 2013; Tempestini et al., 2008).

Combining magnesium sulphate with 2% plain lignocaine significantly increased both the onset and duration of anaesthesia following an IANB (Chandrasekaran et al., 2020).

In conclusion, the duration of pulp anaesthesia is not the same when different anaesthetic solutions are used for both maxillary and mandibular teeth. The choice of anaesthetic solution is dependent on the estimated time required for the root canal treatment procedure as well as the need to control bleeding and any systemic conditions of the patients.

NEEDLE GAUGE

Needle Gauge 33 was associated with significantly less pain compared with Gauge 30 needles (Nakamura et al., 2013).

However, the effect of smaller needle gauge size on reducing pain during injection was not supported by an investigation that used needles with Gauges 25, 27 and 30 (Flanagan et al., 2007). Another study on children reported that the size of the needle had no effect on maxillary infiltration injections but there was significantly less discomfort during an IANB injection when needles with a finer gauge were used (Ram et al., 2007). Therefore, the site of injection as well as the needle size may influence pain perception during needle insertion.

In conclusion, there are few results regarding the effect of needle size on injection pain. More investigations focusing on the site of injection and finer needle gauges are needed.

VOLUME OF ANAESTHESIA

There are conflicting results amongst studies that have evaluated the effect of the volume of anaesthetic solutions on the success rate of anaesthesia.

Because of differences between the effects of the volume of anaesthesia when various anaesthetic techniques and pulp status were employed, they have been reviewed separately below.

Mandibular teeth

Inferior alveolar nerve block

In teeth without irreversible pulpitis, studies have reported no significant differences in anaesthesia success of IANB when different volumes of lidocaine with 1:100 000 epinephrine were tested (Nusstein et al., 2002; Vreeland et al., 1989; Wali et al., 2010).

There are conflicting results regarding the effect of the volume of anaesthesia on the success rates of IANB in teeth with irreversible pulpitis (Table 1).

A systematic review and meta-analysis did not reveal a significant impact of using different volumes of anaesthetic solutions on the success rate of IANB with either articaine or lidocaine as the anaesthetic solutions (Corbella et al., 2017). However, three other systematic reviews and meta-analyses reported higher volumes of anaesthetic solutions provided significantly greater success rates of IANB in molars with irreversible pulpitis (Milani et al., 2018; Nagendrababu et al., 2021; Tupyota et al., 2018).

It has been reported that using two cartridges of anaesthetic solution would significantly increase anaesthesia success in both asymptomatic and symptomatic patients who attend for root canal treatment when considering an unsuccessful IANB. However, the authors were more concerned by missing the correct site for the IANB when only one cartridge was used (Fowler et al., 2015).

Buccal infiltration in mandibular molars

As a primary injection, higher volumes of 4% articaine (3.6 ml) provided significantly higher anaesthesia success rates compared with a lower volume (i.e. 1.8 ml) of the same anaesthetic solution in mandibular first molars with healthy pulps (Martin et al., 2011). However, in mandibular teeth with irreversible pulpitis and a failed IANB, a supplementary buccal injection with 3.6 ml of 4% articaine with 1:100 000 epinephrine provided no significant difference compared with 1.8 ml of the same anaesthetic solution (Singla et al., 2015).

Periodontal ligament technique

One study reported that a larger volume provided higher anaesthesia success rates in mandibular teeth with irreversible pulpitis that had pain during access cavity

TABLE 1 Studies that compared the efficacy of different volumes of anaesthetic solutions on IANB success rate in mandibular molars with irreversible pulpitis

Authors (Year)	Tooth type	Type of anaesthetic solution	Volume of anaesthetic solution	Comparison (p Value)
Parirokh et al. (2010a)	Mandibular molars	2% lidocaine with 1:80 000 epinephrine	1.8 vs. 3.6 ml	$p > .05$
Aggarwal et al. (2012a)	Mandibular molars	2% lidocaine with 1:200 000 epinephrine	1.8 vs. 3.6 ml	$p < .05$
Fowler and Reader (2013)	Mandibular posterior teeth	2% lidocaine with 1:100 000 epinephrine	1.8 vs. 3.6 ml	$p > .05$
Abazarpour et al. (2015)	Mandibular molars	4% articaine with 1:100 000 epinephrine	1.8 vs. 3.6 ml	$p < .05$
Silva et al. (2019)	Mandibular molars	4% articaine with 1:100 000 epinephrine	1.8 vs. 3.6 ml	$p > .05$

preparation (Aggarwal et al., 2018b). However, another study reported that periodontal ligament (PDL) supplementary injections did not significantly improve the success rate when the volume of primary IANB was increased (Silva et al., 2019).

Maxillary teeth

Infiltration technique

In a crossover study, it has been reported that 1.2 ml of 2% lidocaine with 1:100 000 epinephrine provided significantly greater success rates of anaesthesia compared with smaller volumes (0.6 and 0.9 ml) of the same anaesthetic solution for maxillary canine teeth (Brunetto et al., 2008). However, increasing the volume of the same anaesthetic solution from 1.8 to 3.6 ml did not significantly improve anaesthesia success rates in maxillary teeth (Mikesell et al., 2008).

Posterior superior alveolar nerve block

No significant difference could be observed when 1.8 ml of 2% lidocaine with 1:100 000 epinephrine was compared with 3.6 ml of the same anaesthetic solution following a superior posterior alveolar nerve block (Pfeil et al., 2010).

In conclusion, it seems that the technique used for anaesthesia, the site of injection and the health status of the pulp may have an impact on the efficacy of the volume of anaesthetic solution. Increasing the volume of the anaesthetic solution has the benefit of assuring the patient that his/her dentist is doing everything to overcome the patient's pain during endodontic procedures. Several studies in this field have employed teeth with healthy pulps (Brunetto et al., 2008; Martin et al., 2011; Mikesell et al., 2008; Nusstein et al., 2002; Pfeil et al., 2010). Their results should not be extrapolated for teeth with irreversible pulpitis (Nagendrababu et al., 2021). In addition, detection bias has been reported for two studies (Aggarwal et al., 2012a; Wali et al., 2010) that evaluated the effect of volume of anaesthesia on IANB success rate due to their single-blinded design (Milani et al., 2018). Another shortcoming was the small sample sizes (Wali et al., 2010).

SUPPLEMENTAL TECHNIQUES

One of the reasons that dentistry has gained popularity during the last century was the introduction of local anaesthesia for dental procedures (Grossman, 1982). A survey amongst dentists revealed that 13% of them had failed to

achieve anaesthesia during the working days of one week, and unfortunately, 10% of the dental procedures could not be completed due to anaesthesia failure (Kaufman et al., 1984). IANB injections were the most frequent anaesthesia failures (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). Supplementary techniques have been introduced to overcome anaesthesia failure following conventional administration of anaesthetic solutions (Meechan, 2002).

Intraosseous injection techniques

Both PDL injections and the intraosseous (IO) injections have been classified as intraosseous injections (Meechan, 2002).

Periodontal ligament injection

The PDL injection, also called the intra-ligamentary injection technique (Meechan & Thomason, 1999; Meechan, 2002), is a technique where the anaesthetic solution is injected into the periodontal ligament and reaches the dental pulp via the periodontal ligament or by diffusion through the surrounding bone. The natural cribriform plates of the alveolar socket wall are a route for the anaesthetic solution to reach the dental pulp's nerves (Meechan, 2002). The PDL method has been reported to be the most popular supplementary technique used by members of the American Association of Endodontists as well as general practitioners in the USA (Bangerter et al., 2009; Savani et al., 2014).

Two most important points regarding successful PDL injection are to place the needle at the correct site and to perform the injection with force (Khedari, 1982; Walton & Abbott, 1981). The PDL injection has a rapid onset of anaesthesia of about 30s (Meechan, 2002). Although the PDL injection can be performed with a conventional syringe, several devices have been introduced for this technique. However, there were no significant differences between the conventional syringe compared with a computer-controlled application system in terms of anaesthetic efficacy, pain of injection, quantity of second injections, volume of solution used and duration of local numbness (Kämmerer et al., 2015).

An IANB injection combined with a PDL injection for healthy pulps (Childers et al., 1996), as well as a combination of IANB + buccal infiltration + PDL in teeth with irreversible pulpitis, significantly improved the success rate of anaesthesia (Parirokh et al., 2014). There was no significant difference in injection pain as well as postoperative pain between 2% lidocaine and 4% articaine (both with 1:100 000 epinephrine) used as anaesthetic solutions

for PDL injections (Nusstein et al., 2004a), whilst there was no significant difference in their efficacy of anaesthetizing dental pulps of teeth with irreversible pulpitis (Zargar et al., 2021). It has been reported when PDL injection by 4% articaine with 1:100 000 epinephrine was used as supplementary injection, mandibular second molars had significantly greater anaesthesia success rates compared with mandibular first molars. However, when 2% lidocaine with 1:80 000 epinephrine was used, no significant difference in anaesthesia success rates of the PDL injection was found between mandibular first and second molars (Zargar et al., 2021).

The PDL injection can significantly improve anaesthesia success when mandibular posterior teeth with irreversible pulpitis had signs of IANB failures (Nusstein et al., 2005; Zarei et al., 2012).

The concentration of epinephrine in the anaesthetic solution may influence PDL injection's success rate. It has been reported that 2% lidocaine with 1:80 000 epinephrine provided significantly higher success rates compared to the same anaesthetic solution with 1:200 000 epinephrine (Aggarwal et al., 2020). However, the anaesthesia success rate of 4% articaine compared to 2% lidocaine with 1:80 000 and 1:100 000 epinephrine, respectively, was not significantly different when used as a supplementary PDL injection for mandibular molar teeth with irreversible pulpitis (Aggarwal et al., 2019).

Some dentists have reported that PDL injections were associated with more postoperative pain and discomfort compared with palatal injections for maxillary molars (Jadhav & Mittal, 2016).

As a primary technique, when the PDL injection is performed at four sites around the tooth, it provided significantly higher success rates compared with using just two sites. The authors reported that overall more than 92% of the mandibular molars with chronic irreversible pulpitis were anaesthetized after receiving PDL injections at two and four sites (Lin et al., 2017).

An important shortcoming of most studies was the lack of description of the practitioner's skill and experience regarding the PDL injection (Childers et al., 1996; Nusstein et al., 2004a; Zarei et al., 2012) as well as being non-randomized clinical trials (Nusstein et al., 2005). In addition, there was a difference in methodology that may affect the study results. It should be noted that surveys of dentists' opinions for pain on injection and success rates of anaesthesia should be interpreted with caution since they might be influenced by their own bias (Jadhav & Mittal, 2016).

In conclusion, the PDL injection is an easy and popular method for overcoming anaesthesia failure when conventional injections are used. However, it does not completely provide profound anaesthesia on all occasions.

Intraosseous injection

The IO injection technique is known as one of the most successful supplementary methods following failure of conventional techniques (Bhuyan et al., 2014; Dunbar et al., 1996; Meechan, 2002; Nusstein et al., 1998, 2003; Parente et al., 1998; Sakkir et al., 2014; Zarei et al., 2012).

Several specific devices have been introduced for IO injections—these include the following: the Stabident (Fairfax Dental Inc.), X-Tip (Dentsply International Inc.), IntraFlow (Pro-Dex Inc.), Quick Sleeper 2 (DHT) and the Anesto® (W&H Dentalwerk; Burmoos GmbH) (Bigby et al., 2006; Nilius et al., 2020; Nusstein et al., 2003; Parente et al., 1998; Remmers et al., 2008; Sixou & Barbosa-Rogier, 2008; Zarei et al., 2012) devices. The IO technique is usually used as a supplementary technique (Bhuyan et al., 2014; Dunbar et al., 1996; Meechan, 2002; Nusstein et al., 2003, 1998; Parente et al., 1998; Sakkir et al., 2014; Zarei et al., 2012), but there are several studies that have successfully used IO as the primary anaesthetic technique (Farhad et al., 2018; Jensen et al., 2008; Pereira et al., 2013; Razavian et al., 2013; Remmers et al., 2008; Sixou & Barbosa-Rogier, 2008).

There are contradictory reports regarding the efficacy of IO as a primary injection for teeth with irreversible pulpitis (Farhad et al., 2018; Pereira et al., 2013; Razavian et al., 2013; Remmers et al., 2008). Some investigators have reported very high success rates when the IO technique was used as a primary injection with 4% articaine (Pereira et al., 2013) and significantly greater success than the IANB (Farhad et al., 2018) whilst others have reported no significant differences between IANB with IO in mandibular teeth with irreversible pulpitis (Razavian et al., 2013; Remmers et al., 2008).

No significant difference between 4% articaine with 1:100 000 epinephrine compared to the same anaesthetic solution with 1:200 000 epinephrine was reported when IO was used as a primary anaesthesia technique in mandibular molars with irreversible pulpitis (Pereira et al., 2013). The efficacy of IO when either 2% lidocaine or 4% articaine both with 1:100 000 epinephrine was used as the anaesthetic solution has been confirmed. However, the quality of evidence was very low to moderate (Zanjir et al., 2019). The mean onset of anaesthesia has been reported to be between 10 s and 2.4 min (Meechan, 2002; Vongsavan et al., 2019).

The mean duration for IO efficacy has been reported to range from 13 to 38 min (Nilius et al., 2020; Sixou & Barbosa-Rogier, 2008; Vongsavan et al., 2019).

The success of IO injections is not similar for all teeth. For instance, an investigation that used an electric pulp tester has reported that, unlike mandibular first molars, canine teeth were not successfully anaesthetized by an IO injection. In addition, laser Doppler flowmeter testing

showed that the pulp's blood flow was significantly decreased 1 min after the injection but it had returned to the pre-injection level 45 min following the injection in mandibular first molars. In contrast, the IO injection did not significantly affect the mandibular canine pulp blood flow (Vongsavan et al., 2019).

Several factors such as bone density, bone width and cancellous bone space size may influence the efficacy of IO injections (Meechan, 2002; Nilius et al., 2020). It has been reported that the efficacy of IO injections is related to the size of cancellous bone spaces and because of the difference between these spaces in different parts of the oral cavity, the pulp anaesthesia success rates for IO injections are not the same for all teeth or all patients (Meechan, 2002).

A significant correlation has been found between bone width and the patients' residual pain following IO injections (Nilius et al., 2020).

Heart rate increase (Bigby et al., 2006; Gallatin et al., 2003; Zarei et al., 2012), the need for special equipment, potential of damage to the teeth during drill penetration, pain and discomfort after injection, and difficulty of use in the presence of rubber dam are other drawbacks of the IO injection technique (Meechan, 2002).

A shortcoming of studies that have reported heart rate increases following IO injection might be the rapid speed of injection, since one study reported that a slow IO injection using 4% articaine with either concentration of 1:100 000 or 1:200 000 caused no significant cardiovascular effects (Pereira et al., 2013). In addition, several studies have had small sample sizes which might be the reason for reporting no significant differences between IO and IANB techniques for teeth with irreversible pulpitis (Razavian et al., 2013; Remmers et al., 2008). Most investigations did not report 100% anaesthesia success despite employing IO injections, and there is only one study that did report 100% success following IO injection in teeth (Jensen et al., 2008). Evaluating teeth with healthy pulps using an electric pulp tester as the method for assessing anaesthesia success is the shortcoming of that study since teeth with irreversible pulpitis are much more difficult to anaesthetized (Sampaio et al., 2012). Other shortcomings were detection bias and the performance bias that could be recognized in several investigations because all injections and anaesthesia evaluations were performed by the same operator (Razavian et al., 2013; Remmers et al., 2008).

In conclusion, the IO injection technique has been known as one of the most successful supplemental techniques. However, the practitioner should consider its drawbacks such as the need for special equipment, higher costs, postoperative complications and the potential for systemic effects. In order to reduce the chance of increasing the heart rate, slow administration of the anaesthetic solution during the injection is recommended (Pereira et al., 2013).

Intra-pulp injection

The intra-pulp injection (IP) should be considered as the last technique to achieve pulp anaesthesia, and it is better avoided if other supplementary techniques can successfully achieve anaesthesia. It has been generally accepted that the intra-pulp injection is the most painful injection in endodontics (Parirokh & Abbott, 2014). Adding hyaluronidase to 20% benzocaine gel significantly decreased intra-pulp pain on injection in teeth with irreversible pulpitis (Sooraparaju et al., 2015).

There are several important points when IP anaesthesia is the last technique to anaesthetize an inflamed pulp:

1. The most important point is that the injection should be performed with force/pressure. Without pressure, the injection has no efficacy. It has been shown that even intra-pulp injection of normal saline with force could anaesthetize the pulp (Birchfield & Rosenberg, 1975; Van Gheluwe & Walton, 1997).
2. Since IP injection is painful, it should only be considered when other supplementary techniques have failed to achieve anaesthesia (Parirokh & Abbott, 2014).
3. The duration of anaesthesia is short (Meechan, 2002). Therefore, the dental practitioner should remove the pulp tissues from the root canals as soon and as quickly possible following IP injection.

The anaesthetic solution used for IP injections can reach the apical foramen (Smith & Smith, 1983), and therefore, it is possible to extrude debris and pulp remnants into the periapical tissues. For that reason, IP injection is not recommended in pulps with partial pulp necrosis. In these cases, it has been suggested to use topical anaesthesia inside the root canal space whenever other supplementary techniques have not worked (DeNunzio, 1998). There is the potential for topical anaesthetic gel penetration into the periapical tissues and interaction with root canal filling materials so these factors could be considered as drawbacks for this recommendation. Another technique that could be attempted is to administer an anaesthetic solution into the root canal with no needle binding and without force. In that case, the anaesthetic solution might be applied the pulp tissue by using a hand file with gentle up and down movements.

Buccal infiltration

Buccal infiltration in mandibular posterior teeth could be used either as a primary technique (Aggarwal et al., 2009, 2011a; Akhlaghi et al., 2016; Bhatnagar et al., 2020; Fan et al., 2009; Kanaa et al., 2009; Yadav et al., 2015) or

for supplementary anaesthesia when an IANB has failed to provide no or mild pain during root canal treatment (Ashraf et al., 2013; Gao & Meng, 2020; Matthews et al., 2009; Rosenberg et al., 2007).

As the primary injection techniques, no significant difference was found between anaesthesia success rates of mandibular first molars when IANB + IL injection was compared to IANB + buccal infiltration (Fan et al., 2009).

Most studies have reported that buccal infiltration (BI) injections with 4% articaine either as a primary or supplementary injection significantly improved anaesthesia success in mandibular molars with irreversible pulpitis when compared to 2% lidocaine (Aggarwal et al., 2009; Ashraf et al., 2013; Gao & Meng, 2020). In contrast, another study found no significant difference between lidocaine and articaine for buccal infiltrations (Rosenberg et al., 2007). When 4% articaine with 1:100 000 epinephrine was used as a supplementary technique, the success rate was significantly greater than 2% mepivacaine with 1:100 000 epinephrine (Gao & Meng, 2020). In addition, increasing the volume of 4% articaine with 1:100 000 epinephrine from 1.8 to 3.6 ml for supplemental buccal infiltrations following failed IANB injections for mandibular molars with irreversible pulpitis had no significant impact on improving the anaesthesia success rate (Singla et al., 2015).

Smaller sample sizes and asking the patients to rate their pain as the method of evaluating anaesthesia efficacy after the supplemental injections might be the reason for the different reported results since previous dental experiences, emotional, psychological, gender, genetic and ethnicity may be important factors that influence a patient's reaction to pain during root canal treatment (Parirokh et al., 2021; Rosenberg et al., 2007). However, it should be noted that most studies on the efficacy of anaesthesia success have evaluated pain at different treatment stages such as access cavity preparation and root canal instrumentation (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014).

The type of teeth being treated may affect the success of BI supplementary injections. In teeth with irreversible pulpitis, BI had significantly higher success rates for mandibular premolars with irreversible pulpitis compared to molar teeth with the same condition (Fowler et al., 2016). However, lingual infiltrations did not significantly improve anaesthesia success obtained with IANB in combination with BI injection (Dou et al., 2013). In addition, supplemental buccal infiltration for mandibular second molars showed significantly higher success rates with 4% articaine compared to 2% lidocaine whereas no significant difference was found between these two anaesthetic solutions for mandibular first molars (Rogers et al., 2014; Shapiro et al., 2018). It has been reported that buccal injections for mandibular second molars have been associated with significantly higher failure rates compared to

mandibular first molars when 2% lidocaine with 1:80 000 epinephrine was used for either buccal or buccal and lingual infiltrations (Rogers et al., 2014; Shapiro et al., 2018; Yadav et al., 2015). The authors attribute this difference to the anatomic difference between the teeth and inability of lidocaine to reach the tooth.

It is important to consider the methodology of studies that used buccal infiltrations in combination with IANB as a primary technique for anesthetizing mandibular posterior teeth. Several investigations have used the buccal injection immediately or a short time following the IANB injection (Aggarwal et al., 2009; Akhlaghi et al., 2016; Bhatnagar et al., 2020; Kanaa et al., 2009; Parirokh et al., 2010a). Due to the lip numbness induced by the latter technique, a missed IANB would not be recognized. Administration of a buccal injection 5–10 min following an IANB injection would be a good approach to be sure about the success of the IANB injection (Dou et al., 2013).

Based on several systematic reviews and meta-analyses, the solution of choice for supplementary BI for mandibular molar teeth with irreversible pulpitis is 4% articaine with 1:100 000 epinephrine as it has been shown to provide significantly higher anaesthesia success rates compared to 2% lidocaine (Brandt et al., 2011; Kung et al., 2015; Su et al., 2016).

Lingual infiltration

A lingual infiltration (LI) injection as a supplementary technique is usually performed in combination with a BI (Aggarwal et al., 2009; Dou et al., 2013). There are conflicting results regarding the efficacy of LI injections. One study reported LI significantly improved anaesthesia success (Aggarwal et al., 2009) whereas another study did not show an improvement (Dou et al., 2013). The time elapsed between the supplemental injections and commencing the treatment may be a variable that can affect a study's results. In one study, the time between injection and commencing the treatment was 5 min (Dou et al., 2013) whereas in the other study, the time was about 13 min (Aggarwal et al., 2009). The type of primary technique may also be an important variable on the efficacy of supplementary lingual infiltration injections. In a study on mandibular molars with irreversible pulpitis when IANB was used as the primary injection technique, a lingual infiltration as a supplemental injection provided significantly higher pain reduction compared to using the Gow-Gates mandibular block injection as the primary technique with the same supplementary injections (Ghoddusi et al., 2018).

These studies were not similar in their methodology since two different aims were followed. In two studies (Aggarwal et al., 2009; Dou et al., 2013), the buccal and

lingual infiltration techniques were used as a primary technique and in advance of commencing the treatment whilst in the other study (Ghoddusi et al., 2018), the supplemental injection was performed when the primary technique had failed to provide adequate anaesthesia.

Intra-septal injection

Intra-septal injections as either a primary or supplemental injection did not significantly improve anaesthesia success (Bonar et al., 2017; Webster et al., 2016). There was no significant difference for intra-septal anaesthesia success rates when either 2% lidocaine or 4% articaine was used as the anaesthetic solutions (Bonar et al., 2017). Intra-septal injection success rates when used as supplementary anaesthesia (Webster et al., 2016) were lower than the rates reported in studies that used other previously mentioned supplemental techniques (Aggarwal et al., 2018b; Zarei et al., 2012).

Retromolar canal infiltration

One of the reasons for anaesthesia failure in mandibular molars has been attributed to the anatomic variations. It has been claimed that the retromolar canal or foramen may be present and may provide a neurovascular network that innervates mandibular posterior teeth, particularly third molars. An uncontrolled clinical trial has reported that the anaesthesia success rate significantly increased when retromolar injections were used as supplementary injections for mandibular first molars with acute irreversible pulpitis (Karamifar et al., 2021). However, the study had a high risk of bias since it was uncontrolled and there was no comparison with other supplementary injections. In addition, only one operator did all procedures (i.e. injections, pulp sensibility tests, access cavity preparation and root canal treatment) without blinding. Therefore, the chance of detection bias and performance bias may be increased.

In summary, systematic reviews and meta-analyses have reported that supplementary injections can significantly improve anaesthesia success rates (Brandt et al., 2011; Kung et al., 2015; Sivaramakrishnan et al., 2019; Su et al., 2016). However, small sample sizes could be considered as the major shortcomings of studies that have evaluated the effects of anaesthesia techniques and solutions (Corbett et al., 2008; Currie et al., 2013; Jung et al., 2008). In addition to a lack of precise inclusion criteria (Corbett et al., 2008; Currie et al., 2013), no explanation has been reported for the method of randomization (Aggarwal et al., 2010b; Corbett et al., 2008; Jung et al., 2008).

CLINICAL POINTS REGARDING SUPPLEMENTARY TECHNIQUES

1. None of the supplemental techniques can completely overcome pain during root canal treatment. It has been reported that, even following the use of supplementary infiltration techniques, about 6% of patients may still suffer pain during root canal treatment (Kayaoglu et al., 2016).
2. Most patients can be managed with current anaesthetic supplementary techniques (Parirokh & Abbott, 2014).
3. Comparisons between supplementary articaine BI, lidocaine IO, lidocaine PDL and repeated lidocaine IANB have demonstrated that the two former techniques have significantly higher success rates for mandibular teeth with irreversible pulpitis when the primary IANB injection has failed to provide anaesthesia during root canal treatment (Kanaa et al., 2012b).
4. When a BI injection is going to be used, 4% articaine is the first choice of solution (Brandt et al., 2011; Kung et al., 2015; Su et al., 2016).

ANAESTHETIC TECHNIQUES

The clinician should always follow the simplest method to achieve the highest rate of anaesthesia (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). For instance, no significant difference was found between buccal infiltration injection, combination of buccal and palatal infiltration injection, and posterior superior alveolar nerve block for maxillary molars with irreversible pulpitis (Aggarwal et al., 2011b). Therefore, choosing just a buccal injection is the more favourable anaesthesia technique for maxillary molar teeth. In the case of an unsuccessful attempt, the practitioner can employ the palatal or other supplementary techniques (Atasoy Ulusoy & Alaçam, 2014). However, when the preoperative periapical radiograph shows long roots of a maxillary molar with irreversible pulpitis, the practitioner should consider adding another anaesthetic technique to the traditional buccal infiltration injection before commencing root canal treatment (Moradi Askari et al., 2016). Another example is the use of simple labial and lingual infiltration injections that provide better anaesthesia compared with only one of these injections to anaesthetize mandibular anterior teeth (Meehan & Ledvinka, 2002; Nuzum et al., 2010) although both of these studies evaluated teeth with healthy pulps.

Techniques for maxillary teeth

Various anaesthetic techniques have been used for pulp anaesthesia of maxillary teeth. However, all of these

techniques may have some limitations. A clinician should know the advantages and disadvantages of these techniques and choose them based on knowing their risks and benefits. For instance, the palatal-anterior superior alveolar (P-ASA) injection could anaesthetize maxillary incisors and canines with one injection but pain during needle insertion, pain during injection, temporary numbness/paresthesia, incisive papilla swelling or tenderness and post-injection discomfort are disadvantages of this technique (Nusstein et al., 2004b). Another example is the greater palatine and high tuberosity second division nerve blocks that can be used to anaesthetize maxillary molars. However, the latter technique caused significantly higher postoperative discomfort one day following the injection. In contrast, the greater palatine injection had significantly more severe pain on needle insertion and anaesthetic solution deposition (Broering et al., 2009).

The infraorbital block produced more rapid and better anaesthesia of maxillary canine and premolar teeth compared to the anterior middle superior alveolar nerve block. In contrast, for maxillary central and lateral incisors, the anterior middle superior alveolar nerve block had significantly more success compared with the infraorbital block. There was no significant difference regarding pain on injection (Corbett et al., 2010). However, all of the teeth in this study had healthy pulps and 57.1% of the central incisors was not anaesthetized when the anterior middle superior alveolar nerve block was used. For maxillary anterior and premolar teeth in need of root canal treatment, the anterior middle superior alveolar nerve block with 4% articaine provided more rapid onset compared to an infraorbital block with 2% lidocaine (Saraf et al., 2016). Unfortunately, in that study, the success rate of anaesthesia during root canal treatment was not investigated and the degree of anaesthesia was only evaluated with an electric pulp tester.

Mandibular teeth

Inferior alveolar nerve block versus Gow-Gates block

Several techniques have been described for anaesthetizing the inferior alveolar nerve—these include the Gow-Gates, Vazirani-Akinosi, direct and indirect IANB injections. In teeth with irreversible pulpitis, both lip numbness and pulp anaesthesia were significantly better achieved by the Gow-Gates technique compared with the Vazirani-Akinosi technique (Click et al., 2015) but there are conflicting results regarding the efficacy of the Gow-Gates mandibular nerve block technique compared with IANB block. One investigation reported higher success rates of

anaesthesia for the Gow-Gates mandibular nerve block compared with either a conventional IANB or buccal and lingual infiltrations (Aggarwal et al., 2010b). However, three other studies found no significant differences between these techniques for mandibular molars (Ghoddusi et al., 2018; Goldberg et al., 2008; Montagnese et al., 1984).

Other techniques such as frequency-dependent stimulation (a continuous electrical current) for blocking the inferior alveolar nerve following IANB could not significantly improve pulp anaesthesia of mandibular teeth (Hutchison et al., 2011).

A systematic review and meta-analysis that compared a low risk of bias investigation reported no significant difference between the Gow-Gates mandibular nerve block and the IANB for anesthetizing mandibular teeth with irreversible pulpitis (Nagendrababu et al., 2019b).

In conclusion, a practitioner should be aware of the advantages and disadvantages of all anaesthetic techniques, and then choose the one that would provide less injection and post-injection pain and discomfort as well as higher success rates. Several previous investigations on various anaesthetic techniques have evaluated their efficacy on teeth with healthy pulps (Broering et al., 2009; Goldberg et al., 2008; Hutchison et al., 2011). Therefore, in future, research should be focused on investigations employing teeth with irreversible pulpitis.

Mental/incisive nerve block

No significant difference was found between the success rates of 4% articaine with 1:100 000 epinephrine when used for an IANB compared to a Mental/incisive nerve block (MINB) for mandibular premolars with irreversible pulpitis. The onset of anaesthesia was faster and pain on injection was significantly less when the MINB was used. However, post-injection pain was higher compared with the IANB (Ghabraei et al., 2019). It has been reported that for anesthetizing mandibular incisor teeth with irreversible pulpitis, bilateral MINB with 2% lidocaine with 1:80 000 epinephrine significantly improved the success rate of anaesthesia compared to a unilateral MINB injection (Kumar et al., 2020). However, that study only used teeth with healthy pulps.

For mandibular second premolars with irreversible pulpitis, the IANB had no significant advantage in anaesthesia success rate compared with buccal infiltration injections. However, the buccal infiltration was associated with a significantly higher heart rate compared to the IANB (Yilmaz et al., 2018).

Several investigations have evaluated mental/incisive nerve block efficacy. It has also been reported that swelling is an adverse side effect of this anaesthetic technique.

Only a few studies have compared IANB to MINB. A systematic review and meta-analysis that compared various anaesthetic techniques reported that, due to the limited number of studies that have compared the Vazirani-Akinosi and mental incisive nerve block efficacy to that of the IANB, a meta-analysis could not be performed (Nagendrababu et al., 2019b).

Buccal and lingual infiltration as the primary technique

Teeth with healthy pulps

It has been reported that BI injection of 4% articaine with 1:100 000 epinephrine has provided significantly higher anaesthesia success rates compared to 2% lidocaine with 1:100 000 epinephrine for mandibular posterior teeth (Robertson et al., 2007). No significant difference between either 2% lidocaine with 1:80 000 epinephrine or 4% articaine with 1:100 000 epinephrine as the anaesthetic solution for IANB was found when compared to 4% articaine with 1:100 000 epinephrine for BI (Corbett et al., 2008; Jung et al., 2008).

A comparison between 4% articaine with different concentrations of epinephrine (i.e. 1:100 000 and 1:200 000 epinephrine) as a primary buccal infiltration for asymptomatic teeth showed no significant difference in anaesthesia success (McEntire et al., 2011).

As a BI injection, there was also no significant difference in anaesthesia success rates between 1.8 ml of 2% lidocaine with 1:100 000 epinephrine compared to the same volume of the anaesthetic solution when separately injected in buccal and lingual sites of mandibular first molars (0.9 ml on the buccal and 0.9 ml on the lingual) (Meechan et al., 2006).

The site of an infiltration injection may have some impact on the success of anaesthesia for mandibular teeth. It may imply that infiltration injections on the buccal side of a tooth provide significantly better anaesthesia when compared to teeth that were far from the injection site. Buccal infiltration injections of 4% articaine with 1:100 000 epinephrine for the mandibular first molar provided significantly lower anaesthesia success rates for lateral incisors compared with the injection of the same anaesthetic solution at the canine buccal tissues. However, there was no significant difference for the mandibular first premolar teeth with either injection at the first molar or the canine sites. When an infiltration on the buccal side of the mandibular second molar was performed, both the first and second molars had higher anaesthesia success rates compared with the first premolars (Currie et al., 2013). On the contrary, buccal infiltrations were significantly more effective than lingual

infiltrations when 4% articaine with 1:100 000 epinephrine were used (Meechan et al., 2011).

Teeth with irreversible pulpitis

A study reported no significant difference between BI injections of 4% articaine compared to 2% lidocaine (as IANB), both with 1:100 000 epinephrine for teeth with irreversible pulpitis (Poorni et al., 2011).

In children, a comparison between 2% lidocaine as an IANB and 4% articaine as a buccal infiltration, both with 1:100 000 epinephrine, showed no significant difference in onset and duration of anaesthesia between the groups. However, buccal injection with articaine provided a significantly lower need for supplementary injections during access cavity preparation of primary molars compared to IANB with the lidocaine (Arali & Mytri, 2015). In adults, no significant difference was found between BI and LI of 4% articaine with 1:100 000 epinephrine compared to IANB with the same anaesthetic solution (Aggarwal et al., 2010b).

No significant difference was found between anaesthesia success rates for mandibular first molars when IANB + PDL injections were compared to IANB + buccal infiltrations as primary injections (Fan et al., 2009).

When 4% articaine with 1:100 000 epinephrine used for an IANB and buccal infiltration compared with 2% lidocaine with 1:100 000 epinephrine with the same technique, the articaine provided significantly higher success rates for mandibular molars with irreversible pulpitis (Khan et al., 2021).

Combination of anaesthetic techniques

For overcoming anaesthesia failure, investigators have used combinations of anaesthetic techniques. For instance, it has been shown that administration of a combination of a Gow-Gates and IANB could significantly improve anaesthesia success rates compared to each of these techniques used alone for mandibular molar teeth with irreversible pulpitis (Saatchi et al., 2018).

In addition to the combination of IANB + PDL injection and IANB + buccal infiltration (Shahi et al., 2018), combinations of IANB + buccal infiltration + PDL injections can also significantly improve anaesthesia success in mandibular molars with irreversible pulpitis (Parirokh et al., 2014). The combination of a mental/incisive nerve block (MINB) and an IANB using 2% lidocaine with 1:200 000 epinephrine significantly improved pulp anaesthesia in mandibular premolars with irreversible pulpitis (Aggarwal et al., 2016). However, the results of the combination anaesthesia may be underestimated since the authors did not mention a time lapse between the IANB and

MINB injections. In that case, due to lip numbness from the MIAB, the practitioner may not be aware of an IANB that has not been successful.

The combination of IANB with 2% lidocaine with 1:100 000 epinephrine + buccal injection of 4% articaine with 1:100 000 epinephrine + an inter-septal injection of 4% articaine with 1:100 000 epinephrine provided significantly higher success rates compared to either 2% lidocaine or 2% lidocaine +4% articaine as IANB and buccal infiltration injections, respectively (Dianat et al., 2020).

TYPE OF ANAESTHETIC SOLUTIONS

Studies evaluating the efficacy of anaesthetic solutions on pulp anaesthesia have used either healthy intact pulps via crossover studies or teeth with irreversible pulpitis via randomized clinical trials (Parirokh & Abbott, 2014). It should be noted that maxillary teeth are easier to anaesthetize compared with mandibular teeth (Nusstein et al., 2010). Table 2 present results of these studies.

There are scarce results regarding the efficacy of various anaesthetic solutions for maxillary teeth when testing healthy pulps although several studies have reported that different types of teeth as well as different techniques might give different responses to the various anaesthetic formulations in terms of anaesthesia success and duration (Burns et al., 2004; Evans et al., 2008; Forloine et al., 2010; Mason et al., 2009). In addition, results of separate studies confirmed that mepivacaine significantly increases the risk of anaesthesia with short duration (Berberich et al., 2009; Forloine et al., 2010; Mason et al., 2009). Since the type of tooth in maxillary arch may influence anaesthesia success (Evans et al., 2008), it would be better to only choose a certain type of the tooth when different anaesthetic solutions are going to be compared.

A systematic review and meta-analysis reported no significant difference between the efficacy of 2% lidocaine and 4% articaine for maxillary infiltrations (Kung et al., 2015). In contrast, two other systematic reviews and meta-analyses have reported that articaine is superior to lidocaine for anesthetizing maxillary teeth (St George et al., 2018; Su et al., 2016).

A network systematic review and meta-analysis reported that articaine was the most, and lidocaine was the least, effective anaesthetic solution for IANB in patients with irreversible pulpitis (Larocca de Geus et al., 2020).

There are contradictory results when separate systematic reviews and meta-analyses reported their results comparing various anaesthetic solutions. A systematic review and meta-analysis reported no significant difference between lidocaine and mepivacaine as anaesthetic solutions

for IANB (Vieira et al., 2018). Another systematic review and meta-analysis with a low risk of bias reported that mepivacaine and articaine were the anaesthetic solutions that could significantly improve IANB anaesthesia compared with lidocaine, but there was no significant difference for IANB success rates when other anaesthetic solutions (i.e. articaine, bupivacaine, prilocaine) were compared to mepivacaine. Prilocaine and bupivacaine had no significant difference compared with lidocaine when used for IANB injections (Nagendrababu et al., 2019a). The results of three other systematic reviews and meta-analyses also reported that 4% articaine was a significantly better choice compared to lidocaine for IANB (Brandt et al., 2011; Katyal, 2010; Larocca de Geus et al., 2020; Su et al., 2016).

In contrast, another systematic review and meta-analysis reported that for IANB and maxillary infiltration, there was no significant difference between articaine and lidocaine. However, after successful IANB, administration of an articaine buccal infiltration as a supplemental injection was significantly better than lidocaine (Kung et al., 2015).

An umbrella review has also supported the superiority of 4% articaine compared to 2% lidocaine for successful anaesthesia, irrespective of the techniques used for delivery of the anaesthetic solutions (i.e. supplemental, IANB and infiltration injections). However, they reported that, despite a more rapid onset of anaesthesia, less injection pain and fewer adverse effects with 4% articaine compared to 2% lidocaine, only a small number of systematic reviews and meta-analyses have reported these effects, and therefore, there is limited evidence to support these advantages (Nagendrababu et al., 2019a).

Based on low-quality evidence, a Cochrane review reported superiority of 4% articaine with 1:100 000 epinephrine compared to 2% lidocaine with the same vasoconstrictor concentration when anesthetizing posterior teeth with irreversible pulpitis (St George et al., 2018).

Most previous investigations have drawbacks in the comprehensive reporting of their trials. It is important to consider the following parameters in the reports of clinical trials regarding anaesthesia success rate: sample size calculation, diagnosis, inclusion/exclusion criteria, the type of anaesthetic solution used and the method and details of its delivery, method of randomization, blinding, length of time between injection and commencing the treatment, details of outcome measurement, and reporting systemic or local adverse effects. In addition, a power analysis to calculate the required sample size should be performed, based on the difference between success rate of either anaesthetic solutions or techniques, to prevent the study from being underpowered (Nagendrababu et al., 2019a).

When a specific technique or equipment is going to be used, details regarding the experience of the practitioner

TABLE 2 Studies evaluating the efficacy of different types of anaesthetic solutions on pulp anaesthesia

Authors (Year)	Tooth	Type of anaesthetic solutions	Volume of anaesthetic solutions	Technique of administration	Study design	Pulp status	Comparison to placebo (p Value)
Haas et al., 1990	Mandibular and maxillary canine	4% prilocaine with 1:200 000 epinephrine 4% articaine with 1:200 000 epinephrine	1.5 ml	Buccal infiltration	Crossover	Normal	$p > .05$
McLean et al., 1993	Mandibular first molar, first premolar, lateral incisor	4% prilocaine 3% mepivacaine 2% lidocaine with 1:100 000 epinephrine	1.8 ml	IANB	Crossover	Normal	$p > .05$
Cohen et al., 1993	Mandibular molars	3% mepivacaine HCL 2% lidocaine HCl with 1:100 000 epinephrine	1.8 ml	IANB	Randomized clinical trial	Irreversible pulpitis	$p > .05$
Burns et al., 2004	Maxillary incisors and canine	3% mepivacaine *2% lidocaine with 1:100 000 epinephrine	1.4 ml	Palatal–anterior superior alveolar nerve block	Crossover	Normal	$p < .05$
Claffey et al., 2004	Mandibular posterior teeth	4% articaine with 1:100 000 epinephrine 2% lidocaine with 1:100 000 epinephrine	2.2 ml	IANB	Randomized clinical trial	Irreversible pulpitis	$p > .05$
Gross et al., 2007	Maxillary lateral incisors* and first molars	0.5% bupivacaine with 1:200 000 epinephrine *2% lidocaine with 1:100 000 epinephrine	1.8 ml	Buccal infiltration	Crossover	Normal	$p > .05$ * $p > .05$
Corbett et al., 2008	Mandibular first molar	4% articaine with 1:100 000 epinephrine 2% lidocaine with 1:80 000 epinephrine	1.8 ml BI 0.9 ml BI and LI 2 ml IANB	Buccal infiltration buccal and lingual infiltration compared with IANB	Crossover	Normal	$p > .05$
Evans et al., 2008	Maxillary lateral incisor* and first molar	*4% articaine with 1:100 000 epinephrine 2% lidocaine with 1:100 000 epinephrine	1.8 ml	Buccal infiltration	Crossover	Normal	* $p < .05$

(Continues)

TABLE 2 (Continued)

Authors (Year)	Tooth	Type of anaesthetic solutions	Volume of anaesthetic solutions	Technique of administration	Study design	Pulp status	Comparison to placebo (p Value)
Sherman et al., 2008	Mandibular and maxillary posterior teeth	4% articaine with 1:100 000 epinephrine 2% lidocaine with 1:100 000 epinephrine	1.7 ml 1.8 ml	Gow-Gates blocks and maxillary infiltrations	Randomized clinical trial	Irreversible pulpitis	$p > .05$
Berberich et al., 2009	Maxillary incisors, Canine premolars, and first molar	2% lidocaine with 1:100 000 epinephrine 2% lidocaine with 1:50 000 epinephrine 3% mepivacaine	1.8 ml	Intraoral, infraorbital nerve block	Crossover	Normal	$p > .05$
Mason et al., 2009	Maxillary lateral incisors and first molars	2% lidocaine with 1:100 000 epinephrine 2% lidocaine with 1:50 000 epinephrine 3% mepivacaine	1.8 ml	Buccal infiltration	Crossover	Normal	$p > .05$
Forloine et al., 2010	Maxillary anterior, premolar, and molar teeth	2% lidocaine with 1:100 000 epinephrine 3% mepivacaine	3.6 ml	Maxillary high tuberosity second division nerve block	Crossover	Normal	$p > .05$
Lawaty et al., 2010	Maxillary central incisors and first molars	2% mepivacaine with 1:20 000 levonordefrin 2% lidocaine with 1:100 000 epinephrine	1.8 ml	Infiltration	Crossover	Normal	$p > .05$
Batista da Silva et al., 2010	Mandibular lateral incisor, canine, premolars	*4% articaine with 1:100 000 epinephrine 2% lidocaine with 1:100 000 epinephrine	0.6 ml	Incisive/mental nerve block	Crossover	Normal	$*d > .05$
Krzemiński et al., 2011	Maxillary central and lateral incisors, canine	0.5% plain ropivacaine 4% articaine with epinephrine 1:100 000	1.8 ml	Infiltration	Randomized clinical trial	Normal	$p > .05$
Poorni et al., 2011	Mandibular molars	2% lidocaine with 1:100 000 4% articaine with 1:100 000 epinephrine	1.8 ml	IANB IANB or Buccal infiltration	Randomized clinical trial	Irreversible pulpitis	$p > .05$

TABLE 2 (Continued)

Authors (Year)	Tooth	Type of anaesthetic solutions	Volume of anaesthetic solutions	Technique of administration	Study design	Pulp status	Comparison to placebo (p Value)
Vilchez-Pérez et al., 2012	Lateral incisor	0.5 bupivacaine with 1:200 000 adrenaline 4% articaine with 1:200 000 adrenaline	0.9 ml	Buccal infiltration	Crossover	Normal	$p > .05$
Kanaa et al., 2012a	Maxillary teeth	4% Articaine with 1:100 000 epinephrine 2% Lidocaine with 1:80 000 epinephrine	2.0 ml	Buccal infiltration	Randomized clinical trial	Irreversible Pulpitis	$p > .05$
Ashraf et al., 2013	Mandibular first and second molars	2% lidocaine with 1:100 000 epinephrine 4% articaine with 1:100 000 epinephrine	1.5 ml for IANB 0.3 ml for long buccal infiltration 1.8 ml for buccal infiltration	IANB IANB +Buccal infiltration of lidocaine or articaine* (as supplementary injection)	Randomized clinical trial	Irreversible Pulpitis	$*p < .05$
Sood et al., 2014	Mandibular posterior teeth	2% lidocaine with 1:80 000 epinephrine 4% articaine with 1:100 000 epinephrine	1.8 ml	IANB	Randomized clinical trial	Irreversible Pulpitis	$p > .05$
Atasoy Ulusoy & Alaçam, 2014	Maxillary first molar	4% articaine HCl with 1:100000 epinephrine 4% articaine HCl with 1:100 000 epinephrine 100 000 epinephrine bitartrate	1.5 ml	Buccal infiltration	Randomized clinical trial	Irreversible Pulpitis	$p > .05$
Nydegger et al., 2014	Mandibular first molar	*4% articaine with 1:100 000 epinephrine 4% lidocaine with 1:100 000 epinephrine 4% prilocaine with 1:200 000 epinephrine	1.8 ml	Buccal infiltration	Crossover	Normal	$*p > .05$

(Continues)

TABLE 2 (Continued)

Authors (Year)	Tooth	Type of anaesthetic solutions	Volume of anaesthetic solutions	Technique of administration	Study design	Pulp status	Comparison to placebo (p Value)
Parirokh et al., 2015	Mandibular molars	2% lidocaine with 1:80 000 epinephrine 0.5% bupivacaine with 1:200 000 epinephrine	1.8 ml	IANB	Randomized clinical trial	Irreversible Pulpitis	$p > .05$
Hosseini et al., 2016	Maxillary first molar	2% lidocaine with 1:80 000 epinephrine 4% articaine with 1:100 000 epinephrine	1.8 ml	Buccal infiltration	Randomized clinical trial	Irreversible Pulpitis	$p > .05$
Visconti et al., 2016	Mandibular molars	2% lidocaine with 1:100 000 epinephrine *2% mepivacaine with 1:100 000 epinephrine	1.8 or 3.6 ml	IANB	Randomized clinical trial	Irreversible Pulpitis	$*p > .05$
Allegretti et al., 2016	Mandibular first and second molars	4% articaine with 1:100 000 epinephrine 2% lidocaine with 1:100 000 epinephrine 2% mepivacaine with 1:100 000 epinephrine	3.6 ml	IANB	Randomized clinical trial	Irreversible Pulpitis	$p > .05$
Aggarwal et al., 2017	Mandibular first and second molars	2% lidocaine with 1:200 000 4% articaine with 1:100 000 epinephrine 0.5% bupivacaine with 1:200 000 epinephrine	1.8 ml	IANB	Randomized clinical trial	Irreversible Pulpitis	$p > .05$
Jouhar et al., 2020	Mandibular first and second molars	2% lidocaine with 1:80 000 epinephrine *0.5% bupivacaine with 1:200 000 epinephrine	1.8 ml	IANB	Randomized clinical trial	Irreversible Pulpitis	$*p > .05$

Note: Direction of significance.

All anaesthetic solution with * had significant effect on anesthesia success rate.

who used either the equipment or the technique should be outlined. In addition, in order to prevent detection and performance bias, the practitioner who is going to inject the anaesthetic solution should be different to the one who is going to evaluate the efficacy of the anaesthetic solution, technique or equipment.

In conclusion, most systematic reviews and meta-analyses support the superiority of articaine versus lidocaine in terms of anaesthesia success rates for irreversible pulpitis, particularly in mandibular posterior teeth.

DIFFERENT CONCENTRATION OF EPINEPHRINE

The success rates of anaesthesia with 2% lidocaine with three different concentrations of epinephrine (1:80 000, 1:100 000 and 1:200 000) were not significantly different when used for IANB injections for mandibular molars with healthy pulps or irreversible pulpitis (Aggarwal et al., 2014).

COMBINATION OF ANAESTHETIC SOLUTIONS

A combination of 1.8 ml 2% lidocaine with 1:100 000 epinephrine and 1.8 ml 3% plain mepivacaine did not significantly improve IANB anaesthesia success compared to 3.6 ml 2% lidocaine with 1:100 000 epinephrine in mandibular teeth with healthy pulps (Lammers et al., 2014).

COMBINATIONS OF ANAESTHETIC SOLUTIONS AND OTHER AGENTS

Meperidine

The combination of lidocaine and meperidine did not significantly improve anaesthesia success for mandibular teeth with irreversible pulpitis when used either as an IANB or a PDL injection (Bigby et al., 2007; Mohajeri et al., 2015).

Buffering of anaesthetic solutions

One of the hypotheses regarding anaesthesia failure is the acidic environment at the site of inflammation. Therefore, alkalization of anaesthetic solutions may increase dissociation of solutions that are usually acidic. This process

will increase the uncharged form of the anaesthetic solution which is responsible for crossing the neural sheet and therefore improving the efficacy of the anaesthetic solution. The studies on buffered anaesthetic solutions have reported contradictory results. Two investigations reported a positive impact on the onset of anaesthesia and pain on injection following IANB, buccal and lingual infiltration injections (Kashyap et al., 2011; Malamed et al., 2013) but two other studies reported that buffering of 2% lidocaine did not significantly change the pain on injection or the onset of anaesthesia following maxillary canine infiltration injections and IANB (Hobeich et al., 2013; Whitcomb et al., 2010).

Several investigations have evaluated the success rates of anaesthesia following buffering of the anaesthetic solutions (Saatchi et al., 2015, 2016; Schellenberg et al., 2015; Shurtz et al., 2015; Whitcomb et al., 2010). It has been reported that sodium bicarbonate in combination with lidocaine did not significantly increase the success rate of IANB in teeth with either normal pulps (Whitcomb et al., 2010) or teeth with acute irreversible pulpitis (Saatchi et al., 2015; Schellenberg et al., 2015), as well as buccal infiltration of 4% articaine with 1:100 000 epinephrine for mandibular first molars with normal pulps (Shurtz et al., 2015). In addition, buffering either 2% or 4% lidocaine with 1:100 000 epinephrine had no significant reduction of pain on needle insertion and injection as well as pain of incision and drainage in patients who had infected root canals and swellings associated with acute apical abscesses (Balasco et al., 2013; Harreld et al., 2015).

Most previous investigations on the buffering of anaesthetic solutions have used the buffering agent simultaneously with the anaesthetic solutions (Parirokh, 2016; Saatchi et al., 2015; Schellenberg et al., 2015; Shurtz et al., 2015; Whitcomb et al., 2010). However, when the buffering agent in combination with 2% lidocaine was administered via an infiltration injection 15 min prior to the IANB administration, a significantly greater anaesthetic success rate was achieved for mandibular first molars with irreversible pulpitis (Saatchi et al., 2016). Addition of lidocaine to sodium bicarbonate is important since injecting the latter agent is very painful (Saatchi et al., 2016).

Mannitol

The addition of mannitol to an anaesthetic solution has been suggested to increase the success rate of anaesthesia due to the ability of mannitol to change the perineural permeability (Antonijevic et al., 1995). The efficacy of adding mannitol depends on the arch and the type

as well as the volume of the anaesthetic solution used. When 2% lidocaine with 1:100 000 epinephrine was used as the anaesthetic solution for IANB, a significant positive impact in increasing the success rate of pulp anaesthesia in mandibular teeth was reported for both healthy pulps and teeth with irreversible pulpitis (Kreimer et al., 2012; Wolf et al., 2011). However, adding mannitol to 4% articaine with 1:200 000 epinephrine did not improve the success rate of IANB for mandibular first molars with irreversible pulpitis (Shakoui et al., 2019). A higher volume of lidocaine as a anaesthetic solution in combination with mannitol also provided significantly greater anaesthesia success following IANB when compared with less volume of the same anaesthetic solution (Wolf et al., 2011).

In contrast to mandibular posterior teeth, mannitol significantly reduced anaesthesia success rates in maxillary lateral incisors (Younkin et al., 2014).

It has been reported that adding mannitol to lidocaine with epinephrine provided either significantly lower or no significant impacts on injection pain (Kreimer et al., 2012; Wolf et al., 2011; Younkin et al., 2014). However, pain on injection has not been investigated when mannitol was added to 4% articaine (Shakoui et al., 2019).

Diphenhydramine

It had been hypothesized that diphenhydramine due to its action on the sodium channels could have the potential to be used in combination with anaesthetic solutions to increase their success rates (Parirokh & Abbott, 2014). However, a study reported that lidocaine alone was more effective than when combined with diphenhydramine. More severe pain levels on injection and post-injection discomfort were adverse effects of this combination of lidocaine and diphenhydramine (Willett et al., 2008).

Dexamethasone

It has been reported that either a combination of 4% dexamethasone plus 2% lidocaine with 1:200 000 epinephrine for IANB (Kaushik et al., 2020) or buccal infiltration of the corticosteroid following IANB with the lidocaine did not significantly improve anaesthesia success in mandibular molars with irreversible pulpitis compared to the control IANB (Aggarwal et al., 2011a). It would have been more relevant if the authors had also evaluated pain on injection. Several drawbacks such as difficulty in blinding and the time differences between administration of anaesthesia amongst the test and the control groups have been reported (Aggarwal et al., 2011a).

Hyaluronidase

Hyaluronidase is another example of an unsuccessful hypothesis for combining an enzyme with an anaesthetic solution in order to enhance the diffusion and efficacy of the anaesthetic solution. This combination also caused trismus and postoperative discomfort (Ridenour et al., 2001).

Fentanyl

The mixture of fentanyl, a synthetic opioid more potent than morphine and a synthetic agonist of μ receptors, and 2% lidocaine with 1:80 000 epinephrine did not enhance the anaesthetic efficacy of infiltration injections for maxillary molars with irreversible pulpitis (Mehrvarzfar et al., 2014).

In conclusion, some additives may have a positive effect on anaesthesia success rates but more studies of their possible benefits and risks are needed. In addition, if a combination was effective at increasing the success rates of anaesthesia, the patients should be monitored for some time afterwards in order to be sure there are no adverse side effects.

PREMEDICATION

There are numerous studies that have evaluated the effects of premedication on the success rates of anaesthesia. The medications used to increase anaesthesia success rates include the following: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) (such as ketorolac, ibuprofen, sodium diclofenac, piroxicam, meloxicam), benzodiazepines (triazolam, alprazolam and diazepam), tramadol, antagonists of N-methyl-D-aspartate (NMDA) receptors and corticosteroids (Aggarwal et al., 2010a; Ehrich et al., 1997; Ianiro et al., 2007; Jena & Shashirekha, 2013; Khademi et al., 2012; Lindemann et al., 2008; Modaresi et al., 2006; Oleson et al., 2010; Parirokh et al., 2010b; Paul et al., 2021; Prasanna et al., 2011; Ramachandran et al., 2012; Shahi et al., 2013; Shetty et al., 2015; Simpson et al., 2011). Most of these studies have been used to evaluate the effects on the success rates of IANB injections (Table 3).

Acetaminophen

It seems that premedication with acetaminophen has no significant impact on IANB success rates (Fullmer et al., 2014; Ianiro et al., 2007; Shirvani et al., 2017) even following combination with either ibuprofen (Ianiro et al.,

TABLE 3 Studies that evaluated the effect of NSAIDs on local anaesthesia compared with the placebo

Authors (Year)	Tooth	Type of anaesthetic solution/ Technique	Type of medication and dosage	Medication form	Comparison to placebo (p Value)
Ianiro et al. (2007)	Mandibular posterior teeth	3.6 ml 2% lidocaine with 1:100 000 epinephrine (IANB)	1000 mg Acetaminophen 600 mg ibuprofen+ 1000 mg Acetaminophen	Oral	$p > .05$
Aggarwal et al. (2010a)	Mandibular molars	1.7 ml 2% lidocaine with 1:200 000 epinephrine (IANB)	10 mg ketorolac 300 mg Ibuprofen	Oral	$p > .05$
Oleson et al. (2010)	Mandibular posterior teeth	3.6 ml 2% lidocaine with 1:100 000 epinephrine for IANB + 0.9 ml 2% lidocaine with 1:100 000 for long buccal	800 mg ibuprofen	Oral	$p > .05$
Parirokh et al. (2010b)	Mandibular molars	1.8 ml 2% Lidocaine with 1:80 000 epinephrine (IANB)	600 mg ibuprofen 75 mg Indomethacin	Oral	$p < .05$
Prasanna et al. (2011)	Mandibular molars	1.8 ml 2% Lidocaine with 1:200 000 epinephrine (IANB)	8 mg lornoxicam 50 mg diclofenac potassium*	Oral	$p < .05$ $*p > .05$
Simpson et al. (2011)	Mandibular posterior teeth	3.6 ml 2% lidocaine with 1:100 000 epinephrine for IANB + 0.9 ml 2% lidocaine with 1:100 000 for long buccal	800 mg ibuprofen+ 1000 mg acetaminophen	Oral	$p > .05$
Aggarwal et al. (2011a)	Mandibular molars	1.8 ml 2% lidocaine with 1:200 000 epinephrine (IANB) + 0.9 ml of 4% articaine (Buccal infiltration)	1 ml/30 mg of ketorolac tromethamine	Buccal injection	$p < .05$
Ramachandran et al. (2012)	Maxillary first molar	1.8 ml 2% Lidocaine with 1:200 000 epinephrine (Buccal infiltration)	1000 mg paracetamol 800 mg ibuprofen 100 mg aceclofenac	Oral	$p < .05$
Jena and Shashirekha, (2013)	Mandibular molars	2% lignocaine with 1:100 000 adrenaline (IANB)	600 mg ibuprofen 10 mg ketorolac 400 mg etodolac + 500 mg paracetamol 100 mg aceclofenac with 500 mg paracetamol	Oral	$p > .05$
Shahi et al. (2013)	Mandibular molars	1.8 ml 2% Lidocaine with 1:80 000 epinephrine (IANB)	400 mg ibuprofen	Oral	$p > .05$
Noguera-Gonzalez et al. (2013)	Mandibular molars	1.8 ml 2% mepivacaine with 1:100 000 epinephrine (IANB)	600 mg ibuprofen	Oral	$p < .05$

(Continues)

TABLE 3 (Continued)

Authors (Year)	Tooth	Type of anaesthetic solution/ Technique	Type of medication and dosage	Medication form	Comparison to placebo (p Value)
Yadav et al. (2015)	Mandibular molars	1.8 ml 4% articaine with 1:100 000 epinephrine for IANB + 0.9 ml buccal and lingual infiltration of either lidocaine or articaine** 1.8 ml 2% lidocaine with 1:80 000 epinephrine for IANB + 0.9 ml buccal and lingual infiltration of either lidocaine or articaine 1.8 ml 2% lidocaine or articaine as IANB	10 mg ketorolac**	Oral	$p < .05^{**}$ $p > .05$
Saha et al. (2016)	Mandibular molars	1.8 ml 2% lidocaine with 1:200 000 epinephrine (IANB)	10 mg ketorolac 50 mg diclofenac potassium	Oral	$p < .05$
Akhlaghi et al. (2016)	Mandibular molars	1.8 ml 4% articaine with 1:100 000 epinephrine for IANB + 0.9 ml articaine for buccal injection	30 mg/ml ketorolac	Buccal injection	$p < .05$
Shantiaee et al. (2017)	Mandibular first molar	1.8 ml of 2% lidocaine with 1:100 000 epinephrine	600 mg ibuprofen 7.5 meloxicam	Oral	$p < .05$
Bidar et al. (2017)	Mandibular molars	1.8 ml of 2% lidocaine with 1:80 000 epinephrine (IANB)	400 mg ibuprofen	Oral	$p < .05$
Stentz et al. (2018)	Mandibular posterior teeth	3.6 ml 2% lidocaine with 1:100 000 epinephrine for IANB + 0.4 ml 2% lidocaine with 1:100 000 epinephrine as buccal injection + nitrous oxide/oxygen administration	31.5 mg ketorolac	Intranasal	$p > .05$
Kaladi et al. (2019)	Mandibular molars	2% lidocaine with 1:80 000 epinephrine (IANB)	400 mg ibuprofen 20 mg ketorolac	Oral	$p < .05$
Nivedha et al., 2020	Mandibular molars	2.5 ml 2% lignocaine with 1:80 000 adrenaline 2.5 ml 4% articaine with 1:100 000 adrenaline	10 mg ketorolac	Oral	$p > .05$
Paul et al. (2021)	Mandibular molars	1.8 ml 2% lignocaine with epinephrine 1:80 000 (IANB) + 0.9 ml lignocaine (buccal infiltration)	40 mg/2ml piroxicam	Buccal injection	$p < .05$
Kumar et al. (2021)	Mandibular molars	1.8 ml 2% lignocaine with 1:200 000 adrenaline (IANB)	800 mg ibuprofen* 800 mg ibuprofen + 0.5 mg dexamethasone	Oral	$p > .05^{*}$ $p < .05$
Aggarwal et al. (2021)	Mandibular molars	1.8 ml 2% lidocaine and 1:80 000 epinephrine (IANB)	1.8 ml diclofenac sodium from a 3ml vial 75 mg/3 ml	Periodontal ligament injection	$p > .05$

Note: * No statistically significant difference; ** Statistically significant difference.

2007; Simpson et al., 2011), etodolac or aceclofenac (Jena & Shashirekha, 2013). Despite these studies, a systematic review and meta-analysis reported that a combination of ibuprofen and paracetamol could significantly improve IANB success rates (Sivaramakrishnan et al., 2019). However, when used as a premedication before infiltration injections for maxillary molars with irreversible pulpitis, acetaminophen significantly improved anaesthesia success rates (Ramachandran et al., 2012). Small sample sizes may be the reason for the non-significant differences in anaesthesia success rates in some studies (Ianiro et al., 2007; Jena & Shashirekha, 2013).

Non-steroidal anti-inflammatory drugs

It has been confirmed that increasing the level of prostaglandins (PG) in tissues can affect the tetrodotoxin-resistant sodium channels (Hargreaves & Keiser, 2002; Henry & Hargreaves, 2007). Therefore, if a medication can decrease PG levels in tissues, it could potentially increase the efficacy of anaesthetic solutions. Prescription of an NSAID prior to administration of an anaesthetic solution is the rationale for reducing PG levels and increasing the efficacy of the anaesthetic (Gould et al., 2004). In addition, it has been shown that the level of proinflammatory mediators such as PGE₂, TNF- α , IL-6 and IFN- γ decreased following premedication with an NSAID (Nguyen et al., 2020).

There are studies that have supported the use of premedication with NSAIDs (Aggarwal et al., 2011a; Akhlaghi et al., 2016; Modaresi et al., 2006; Parirokh et al., 2010b; Prasanna et al., 2011; Ramachandran et al., 2012; Saha et al., 2016; Yadav et al., 2015) but there are also other studies that have not reported a significant difference between premedication with NSAIDs and placebo (Aggarwal et al., 2010a; Ianiro et al., 2007; Jena & Shashirekha, 2013; Oleson et al., 2010; Shahi et al., 2013; Simpson et al., 2011). Differences in the inclusion criteria as well the potency of the NSAIDs tested may be reasons for the variable results (Li et al., 2012; Parirokh et al., 2010b; Prasanna et al., 2011).

Results of studies on the efficacy of various NSAIDs on anaesthesia success are summarized in Table 3.

There are reports regarding severe pain on injection of ketorolac (Aggarwal et al., 2011a; Mellor et al., 2005). Premedication with ketorolac in injection form should be performed several minutes following the anaesthesia to prevent the pain associated with injection of this medication (Aggarwal et al., 2011a; Akhlaghi et al., 2016). In addition, in order to overcome pain during ketorolac injection, some investigators have recommended that in addition to

performing an IANB with lidocaine, a combination of the medication and 4% articaine with 1:100 000 epinephrine should be used as a buccal infiltration for mandibular molars (Aggarwal et al., 2011a).

There are several shortcomings in study designs including buccal infiltration injections of the anaesthetic solution immediately following the IANB (Akhlaghi et al., 2016). Since a buccal infiltration causes lip numbness, the practitioner will not be able to determine whether the IANB injection was successful or not. It has been recommended to delay the buccal infiltration for up to 10 min following an IANB in order to be sure of the success of the IANB injection (Aggarwal et al., 2011a; Parirokh & Abbott, 2014).

The results of systematic reviews and meta-analyses were contradictory. A systematic review and meta-analysis reported no significant impact of ketorolac (Li et al., 2012) whilst another systematic review and meta-analysis reported that preoperative consumption of ketorolac significantly improved the success rate of IANB for mandibular teeth with irreversible pulpitis (Nagendrababu et al., 2018).

Several systematic reviews and meta-analyses have confirmed the benefits of prescribing ibuprofen before commencing the root canal treatment to improve IANB success rates (de Geus et al., 2019; Nagendrababu et al., 2018; Pulikkotil et al., 2018). Two systematic reviews and meta-analyses have confirmed the dose dependence of ibuprofen as a premedication for increasing IANB success rates. The results revealed that doses of ibuprofen higher than 400 mg significantly increased the success rates of anaesthesia in teeth with irreversible pulpitis (Nagendrababu et al., 2018; Pulikkotil et al., 2018).

It has also been reported that a combination of acetaminophen with an NSAID could significantly increase anaesthesia success. However, when acetaminophen was used alone, it had no significant impact on increasing anaesthesia success rate (Shirvani et al., 2017).

Two separate systematic reviews and meta-analyses reported that the type of anaesthetic solution may be important when used with NSAID premedication. Four per cent articaine (Shirvani et al., 2017) and 2% mepivacaine in combination with preoperative NSAID (Zanjir et al., 2019) may be a good approach to reach greater anaesthesia success rates but further research is required.

In conclusion, most systematic reviews and meta-analyses have supported the use of NSAIDs as premedication to help increase the success rates of IANB injections (Corbella et al., 2017; de Geus et al., 2019; Li et al., 2012; Nagendrababu et al., 2018; Pulikkotil et al., 2018; Shirvani et al., 2017; Tupyota et al., 2018; Zanjir et al., 2019). However, the recommendations from previous systematic reviews and meta-analyses might change

by including the results of new randomized clinical trials in a new systematic review and meta-analysis. For instance, despite no significant effect of ketorolac in the systematic review and meta-analysis conducted by Li et al. (2012), three studies that have subsequently been published have confirmed the effect of this medication on anaesthesia success rates for mandibular molars with irreversible pulpitis (Akhlaghi et al., 2016; Kaladi et al., 2019; Yadav et al., 2015).

Dexamethasone

Several investigations have used different doses (from 0.5 mg to 4 mg) and routes of administration of dexamethasone (oral, buccal and PDL injections) to evaluate its efficacy on IANB anaesthesia success rates (Aggarwal et al., 2011a, 2021; Bidar et al., 2017; Shahi et al., 2013). However, conflicting results have been reported regarding its efficacy when used in conjunction with IANB injections for teeth with irreversible pulpitis. Two studies reported no significant impact of premedication with dexamethasone compared to the control group (Aggarwal et al., 2011a; Kumar et al., 2021), whereas three other studies reported significantly higher IANB anaesthesia success rates compared with the placebo (Aggarwal et al., 2021; Bidar et al., 2017; Shahi et al., 2013). A recent investigation reported that a combination of dexamethasone and ibuprofen provided significantly higher IANB success rates compared with the individual use of each of these medications for premedication (Kumar et al., 2021).

Tramadol

The type of anaesthetic solution may affect the efficacy of tramadol for IANB anaesthesia success rates. When tramadol was used with 4% articaine with 1:100 000 epinephrine for IANB, the anaesthesia success rate of mandibular molar with irreversible pulpitis was significantly improved (De Pedro-Muñoz & Mena-Álvarez, 2017), however, using tramadol with either 2% lidocaine with 1:80 000 epinephrine or 2% mepivacaine with 1:100 000 epinephrine as anaesthetic solutions did not improve the success of IANB for mandibular molars with irreversible pulpitis (Aksoy & Ege, 2020; Rodríguez-Wong et al., 2016).

A systematic review reported that premedication with dexamethasone, NSAIDs or tramadol can significantly improve anaesthesia success rates of IANB for teeth with irreversible pulpitis (Pulikkotil et al., 2018).

Since the type of the anaesthetic solutions used in these studies was not similar, future studies should focus

on comparing different anaesthetic solutions when tramadol is used as a premedication.

Benzodiazepines

It has been assumed that anxiety may adversely affect the success rates of anaesthesia (Hargreaves & Keiser, 2002; Wong, 2001). However, no significant impact on increasing anaesthesia success rate has been reported, so far, by premedication with benzodiazepines (Ehrich et al., 1997; Khademi et al., 2012; Lindemann et al., 2008).

Notwithstanding the above, premedication with a combination of sodium diclofenac and alprazolam as well as employing the Gow-Gates mandibular block technique provided a significantly higher success rate of pulp anaesthesia for mandibular molars with irreversible pulpitis compared to either IANB or the Vazirani-Akinosi block with and without premedication (Shetkar et al., 2016).

Nitrous oxide

In anxious patients, nitrous oxide inhalation significantly improved the success rate of IANB and decreased the levels of anxiety compared with the controls. In addition, postoperative anxiety was significantly less in the test group compared with the control group (Gupta et al., 2019).

Magnesium sulphate

It has been proposed that an increase in the N-methyl-D-aspartate (NDMA) receptor is one of the reasons for central sensitization (Hargreaves & Keiser, 2002). Magnesium sulphate is known as a non-competitive antagonist of NDMA receptors, and therefore, it may be useful for preventing central sensitization. Three studies have evaluated the use of magnesium sulphate either one hour prior to anaesthetic solution injection or in combination with anaesthetic solution for IANB technique. Results showed that magnesium sulphate significantly improved the anaesthesia success rate of IANB for mandibular molar teeth with irreversible pulpitis (Chandrasekaran et al., 2020; Mousavi et al., 2020; Shetty et al., 2015). In addition, it was interesting to note that none of the patients when either 75 mg or 150 mg of magnesium sulphate was used needed any supplementary injections in one of these studies (Chandrasekaran et al., 2020).

The amount of magnesium sulphate used was not the same in these studies (75–500 mg). However, since a

minimum dose of 75 mg magnesium sulphate has shown a significant impact on anaesthesia success, it can be considered as the preferred dose to be combined with an anaesthetic solution. Higher magnesium sulphate doses increase the duration of anaesthesia, and therefore, the selection of the magnesium sulphate dose should be based on the duration of the procedure (Chandrasekaran et al., 2020).

ANXIETY CONTROL

It has been reported that root canal treatment is associated with moderate anxiety in patients (Khan et al., 2016). Several resources have been cited to explain dental fear and anxiety, including genetics, using verbal treats in the family, ethnic background, unpleasant previous experiences and listening to unpleasant experiences of friends and relatives (Carter et al., 2015; Parirokh & Abbott, 2014).

Performing root canal treatment as painlessly as possible and listening to music have been recommended to decrease anxiety during root canal treatment (Di Nasso et al., 2016; Parirokh & Abbott, 2014).

In addition to patient anxiety, dental practitioners may also suffer from occupation anxiety. Delivery of anaesthesia for patients, and particularly for children, has been reported to be the most stressful procedure for general practitioners and specialists in dentistry (Davidovich et al., 2015).

REVERSING ANAESTHESIA

Some patients may complain about long-lasting soft tissue numbness following treatment. Phentolamine mesylate (OraVerse; Septodont Inc.), a reversible non-selective α -adrenergic antagonist, has been successfully used to reverse both pulp and soft tissue anaesthesia (Elmore et al., 2013; Fowler et al., 2011). The effect of reducing anaesthesia by phentolamine mesylate in maxillary soft tissues (lip/cheek) has been significantly greater than for lower lip numbness following mandibular injections (Fowler et al., 2011). The effect of phentolamine mesylate on reducing the duration of anaesthesia is not similar for all anaesthetic solutions. For instance, 0.5% bupivacaine with 1:200 000 epinephrine had significantly more reduction compared to 2% lidocaine with 1:80 000 epinephrine and 4% articaine with 1: 200 000 epinephrine (Gago-García et al., 2021).

However, there is a possibility that reversing soft tissue anaesthesia may adversely affect postoperative pain following root canal treatment since bupivacaine, used as a long-acting anaesthetic solution, significantly reduced

postoperative pain for up to 12 h following root canal treatment (Parirokh et al., 2012a). Furthermore, several side effects such as pain at the site of injection, headache, high volume of bleeding and tachycardia have been reported when phentolamine mesylate was used to reverse the anaesthesia (Gago-García et al., 2021).

ACUPUNCTURE

The use of acupuncture prior to administration of 2% lidocaine with 1:80 000 epinephrine as an IANB significantly improved the anaesthesia success rate for teeth with irreversible pulpitis when used prior to the injection (Jalali et al., 2015). In an animal study, it has been shown that electroacupuncture could restrain microglia and astrocytes excitement and inhibit the formation and suppress the production of paramount proinflammatory cytokines following intentional dental pulp injury (Ballon Romero et al., 2020).

CRYOTHERAPY

Several investigators have reported positive impacts on anaesthesia success rates after placing a small pack containing ice at the buccal vestibule of teeth with irreversible pulpitis following IANB injections (Topçuoğlu et al., 2019). However, in that study, due to the nature of the cryotherapy, the patients could not be blinded (Brignardello-Petersen, 2019).

PHOTOBIMODULATION

Irradiation with soft tissue lasers at the buccal site of mandibular molar teeth with irreversible pulpitis may increase IANB efficacy during root canal treatment (Ghabraei et al., 2017). However, another investigation reported that diode laser irradiation at the supposed periapex and the crown of the teeth with irreversible pulpitis adversely affected anaesthesia success (Ramalho et al., 2016). The differences between wavelengths and the power of the laser may be reasons for the different outcomes on anaesthesia success rates.

OTHER VARIABLES

Position of patients during and after IANB injection

The patient's position during injection, head position following the injection and aromatherapy are variables that

have been investigated (Aggarwal et al., 2018a; Crowley et al., 2018; Jadhav & Mittal, 2020). One study reported that injection of IANB with the patient in a supine position significantly improved anaesthesia success for mandibular first and second premolars. However, it did not significantly improve the anaesthesia success rate for mandibular molars and anterior teeth (Crowley et al., 2018). Another study requested the patients to tilt their head in the direction or against the direction of the IANB administration following the injection. Results showed that no significant difference between the two study groups (Aggarwal et al., 2018a).

Aromatherapy

Using a pleasant fragrance called aromatherapy during root canal treatment resulted lowering the patients' anxiety and improving the IANB anaesthesia success rate (Jadhav & Mittal, 2020).

POST-INJECTION COMPLICATIONS AND SIDE EFFECTS

Although rare, several side effects have been reported following the use of various types of anaesthetic solutions. Paraesthesia, methemoglobinemia, cardiac and central nervous system toxicity, oedema, haematoma, dizziness, nausea, allergy and shock have all been reported as common side effects of local anaesthetic solutions. However, the risk of each of these is not similar. It is extremely important that all complications and side effects of any medications, techniques and interventions should be reported in clinical trials. One of the shortcomings of previously published investigations was not reporting complications following the use of anaesthetic solutions, techniques and premedication (Aggarwal et al., 2018b; Gupta et al., 2019; Kaladi et al., 2019). Future studies should more focus on these subjects.

Most complications when anaesthetic solutions were used as buccal infiltrations for posterior mandibular teeth were initial tenderness, intraoral bruising and slight swelling at the site of the injection (McEntire et al., 2011). Paraesthesia, cardiac and central nervous system toxicity have been more prominent with bupivacaine (Sambrook & Goss, 2011; Sambrook et al., 2011; Su et al., 2016).

There are concerns regarding possible adverse effects of articaine and prilocaine versus lidocaine when used as anaesthetic solutions in dentistry (Batista da Silva et al., 2021; Becker & Reed, 2012; Sambrook & Goss, 2011). In contrast to these reports, two systematic reviews and

meta-analyses did not show a significant difference in adverse effects between 2% lidocaine and 4% articaine (Katyal et al., 2010; Su et al., 2016).

MAJOR SHORTCOMINGS AND NEW DIRECTIONS OF STUDIES ON ANAESTHESIA SUCCESS RATES

An important point regarding anaesthesia success and failure is the difference between the scientific and professional perceptions regarding anaesthesia success. As a rule, moderate pain or pain at more than 54 mm in the Heft-Parker VAS during any steps of access cavity preparation has been considered as failure of anaesthesia (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). However, as a practitioner, it would be successful when a supplementary injection, such as a PDL injection, helps to overcome the pain during dentine penetration, on reaching the pulp and administering an intra-pulp injection. An important subject in dentistry is to appreciate the patient's desire to have treatment that is as painless as possible. From a practitioner's point of view, each safe method that helps the patients to have either no or minimum pain during root canal procedure would be most welcome. Therefore, it is mandatory to select and perform treatment modalities that have higher success rates, whilst also being safe, and reducing pain and discomfort during and after the treatment.

One of the confusing points regarding buccal infiltrations is that there is often no clear description regarding whether the buccal infiltration injection is used as a supplemental or primary technique (Aggarwal et al., 2009; Rosenberg et al., 2007). Several studies have used supplemental injections as the rescue injections that were performed when an initial injection(s) produced signs of successful anaesthesia (such as soft tissue numbness and no response to pulp sensibility tests) but the patient complained of pain during access cavity preparation or root canal instrumentation (Ashraf et al., 2013; Fowler et al., 2016; Matthews et al., 2009; Rogers et al., 2014; Rosenberg et al., 2007; Shapiro et al., 2018; Silva et al., 2019; Singla et al., 2015). In contrast, other studies have used a buccal infiltration following the IANB technique prior to commencing access cavity preparation (Aggarwal et al., 2009; Bhatnagar et al., 2020; Dou et al., 2013; Drum et al., 2011; Kanaa et al., 2009). In studies with the latter approach, the investigators have considered that any anaesthetic injection other than the IANB to be supplemental whereas they were actually used as a primary technique. It is very important to define the terms of primary and supplemental injections so their use in future studies does not confuse the readers. Since dental practitioners should do

everything possible to prevent pain during root canal treatment, and the buccal infiltration has been shown to be a useful method to increase anaesthesia success, it should be considered as a primary technique and dentists should not wait to use it only in the case of IANB failure. The authors of this paper are suggesting that the techniques used after failure of the primary techniques to overcome pain and discomfort during access cavity preparation and root canal instrumentation should be considered as the supplementary injections.

Naturally, methods and materials of studies that have evaluated anaesthesia success rates may potentially provide unreliable outcomes. A systematic review of the effect of premedication on success rates of IANB in teeth with irreversible pulpitis confirmed that most studies of that topic have had moderate to high risks of bias (Karapinar-Kazandag et al., 2019). In order to prevent risk of bias in future studies, the researchers should employ more precise methods and materials.

Ideally, double-blinded studies are more favourable in terms of study design. However, particularly when different techniques are compared, it may not be possible to design a double blinded study. Several investigations have been single-blinded although they could have been planned to be double blinded (Aggarwal et al., 2012a, 2018b).

The lack of precise inclusion criteria has been an important shortcoming of many studies that have evaluated success rates of anaesthesia. This may potentially result in selection bias as well as leading to performance bias (Fleming et al., 2014). Furthermore, a high risk of bias may occur because of unreasonable blinding and impaired randomization with concealment resulting in selection bias (Fleming et al., 2014).

It has been generally accepted that the presence of preoperative pain is one of the major predictors of anaesthesia failure (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). In other words, those patients with emergency conditions have lower anaesthetic success rates. On the contrary, systemic reviews and meta-analyses have shown that oral premedication with NSAIDs can significantly improve the success rate of anaesthesia (Corbella et al., 2017; Nagendrababu et al., 2018; Pulikkotil et al., 2018; Shirvani et al., 2017; Tupyota et al., 2018). Since patients may take analgesics for their dental pain in advance of their attendance for treatment, a recent consumption of analgesics should be considered as one of the exclusion criteria if their effect was not considered as one of the main objectives of the study. In several studies, the authors have not mentioned that they excluded these patients from their studies or whether they were excluded if they took analgesics within a specific time (6–48 h) before attending for root

canal treatment (Claffey et al., 2004; Kanaa et al., 2012a, 2012b; Srinivasan et al., 2009).

Another dilemma in studies that have evaluated anaesthesia success rates for teeth with irreversible pulpitis is whether they have included patients with severe pain (Claffey et al., 2004; Fowler & Reader, 2013; Sampaio et al., 2012; Srinivasan et al., 2009) or patients who had irreversible pulpitis with a history of spontaneous pain plus lingering pain following a cold test (Moradi Askari et al., 2016; Parirokh et al., 2010b). It is more likely to assume that patients with the latter condition had no history of analgesic consumption during a short period of time prior to the root canal treatment. However, it seems unlikely that patients with a real emergency condition (i.e. severe pain) were able to cope with the pain and not take any analgesics during the 6–24 h of period before seeking root canal treatment. In addition, if a lack of response to the cold test was considered as one of criteria for anaesthesia success, the authors should have excluded the volunteers or patients who took NSAIDs, particularly ibuprofen, since it has been reported that this medication can mask cold test results by up to 25% (Read et al., 2014).

It is generally accepted that no response to cold or electric pulp tests does not guarantee the success of anaesthesia (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). It has been recommended that a positive response to a sensibility test following injection of an anaesthetic should be assumed as anaesthesia failure and another supplemental anaesthetic technique should be used to overcome this problem (Abbott & Parirokh, 2018). However, it is also true that a positive response to a pulp sensibility test may be a 'false-positive' response (Sampaio et al., 2012). Therefore, a positive response to a pulp sensibility test may not necessarily be considered as failure of anaesthesia (Chavarría-Bolaños et al., 2017; Sampaio et al., 2012). For that reason, several studies have not considered using pulp sensibility tests as an indicator of anaesthesia success before commencing root canal treatment (Aggarwal et al., 2010a, 2018a, 2018b, 2019). This is very important to note because it may lead to underestimations of the anaesthesia success rates. In crossover studies on teeth with healthy pulps, there would be no other way than pulp sensibility tests to evaluate anaesthesia success. However, in teeth with irreversible pulpitis, no or mild pain during root canal treatment has been used as the criteria for success of anaesthesia.

One of the most important points that is a matter of debate is the pulp status before starting the treatment. Most investigations, especially in the last decade, that have evaluated different anaesthetic solutions and techniques have used the terms 'symptomatic' and 'asymptomatic' irreversible pulpitis although some of them have not mentioned exact definitions of their terminology (Abbott & Parirokh,

2018; Parirokh & Abbott, 2014). Several studies have used the term 'emergency' patients or the patients presented in an emergency department which likely means the patients had spontaneous and severe pain (Claffey et al., 2004; Fowler & Reader, 2013; Kanaa et al., 2012a, 2012b; Sampaio et al., 2012; Srinivasan et al., 2009). It has been suggested that the terms 'acute' and 'chronic' would be better diagnostic terms to distinguish between patients with severe pain and those having episodes of pain that may be tolerable (Bestall et al., 2020). One may argue that 'acute' and 'chronic' are histopathologic terms and should not be used as clinical terminology. However, these terms are commonly used in all branches of dentistry (e.g. acute necrotizing gingivitis and chronic marginal periodontitis), as well as in medicine, as clinical terms (e.g. acute appendicitis and chronic malaria). If the terms are adequately defined, then they can be used clinically as reported in a survey of Australian dentists which clearly showed that the terms 'chronic' and 'acute' resulted in significantly more practical decisions to treat the presenting condition compared to when 'symptomatic' and 'asymptomatic' were used (Bestall et al., 2020).

Several studies have had some exclusion criteria that may limit their external validity. For instance, patients aged more than 65 years old have been considered as an exclusion criteria (Evans et al., 2008; Lammers et al., 2014). The reason for this has not been mentioned although it may be related to systemic diseases and/or drug interactions being more likely in older patients. In addition, most studies have excluded patients under the age of 18 years which may be because their consent form need to be signed by their parents or guardians. Despite this, there are investigators that have included patients under 18 years of age (Kanaa et al., 2012a).

Almost all investigations on anaesthesia success rates employing various techniques, solutions and devices have included type I and II American Society of Anesthesiologists (ASA) as an inclusion criterion. However, this inclusion criterion may reduce external validity of these studies, particularly when the general population is getting older and they may have more systemic diseases (Umino & Nagao, 1993). The number of patients with systemic diseases and in older age groups that are in need of root canal treatment has been increased (Walton, 2015). Therefore, practitioners ideally need more information regarding the efficacy and safety of anaesthetic solutions and techniques in these patients with systemic diseases and older ages. Since performing randomized clinical trials for patients with ASA III or IV may be unethical or these confounding factors may interfere with the study design, prospective cross-sectional observational studies with large sample sizes may be more practical. This would give the researchers more information regarding the variables that

may affect anaesthesia success rates in patients with systemic diseases (Kayaoglu et al., 2016). For instance, a recent investigation evaluating predictive factors reported that practitioners with lower level of experience, diabetes and preoperative pain affecting daily activities had been associated with significantly higher anaesthesia failure (Weitz et al., 2021). However, these studies would have a lower level of evidence.

Another major shortcoming is the probability of detection bias. No or mild pain during access cavity preparation has been assumed as the indicator of successful anaesthesia, whilst moderate-to-severe pain is assumed as anaesthesia failure. Therefore, if the clinician fills out an evaluation form based on the patient's report, he/she might have bias, particularly if it was not possible to blind him/her due to the nature of the study for all procedures from randomization and implementation as well as injection and evaluation performed by the same operator. In that regard, before starting the study, both the personnel and researchers who are involved in the study should receive sufficient training and advice (Fleming et al., 2014). In addition, the responsibility of guiding the patients about how to fill-out the VAS form should be taken by researchers who are not involved in the clinical procedure to prevent and limit detection bias (Aggarwal et al., 2010a, 2011b).

In addition to small sample sizes (Berberich et al., 2009; Haas et al., 1990; Visconti et al., 2016), there are several other shortcomings that research papers have missed from the CONSORT check list (Schulz et al., 2010). These include no description of the method of sample size calculation (Gross et al., 2007), no explanation of randomization/implementation (Gross et al., 2007), no report of any possible adverse effects (Gross et al., 2007; Mason et al., 2009; Singla et al., 2015) and reporting no statistical data interpretation in terms of the level of significance (Matthews et al., 2009).

Another important point is employing proper power analysis for sample size calculation. Power analysis should be based on previous studies and their clinical significance as well as sample sizes in order to prevent type II errors that may result from small sample sizes employed by previous investigations (Nagendrababu et al., 2020a, 2020b).

In studies on teeth with irreversible pulpitis, some researchers believe that it would be more reasonable to include patients who have only one tooth with active pain due to irreversible pulpitis (Aggarwal et al., 2012b, 2014, 2018b; Singla et al., 2015). The rationale for this exclusion may be that the patients falsely felt pain from the other tooth with pulp pathosis that could be considered as failure of the anaesthesia. It is true that mandibular teeth with irreversible pulpitis have had different success rates following anaesthesia (Fowler et al., 2016; Parirokh et al.,

2010a, 2010b), but placing a dental dam on the tooth receiving the root canal treatment would usually prevent irritation of the other involved teeth during the treatment. Another reason may be that there is a greater possibility of inducing central sensitization (Khan et al., 2007).

There are variables that might influence study results but these variables need to be investigated further to determine whether they should be considered as the standard method for studies on anaesthesia success rates. These variables include the position of the patient during the injection (Crowley et al., 2018) and the gender of the practitioner who is administering the injection (Perry et al., 2015).

Several investigators believe that the patients' anxiety should be considered during research studies evaluating success rates of anaesthesia with various anaesthetic solutions and techniques (Karapinar-Kazandag et al., 2019). In other words, a high anxiety level may influence the success of anaesthesia because a correlation has been reported between higher pain levels and greater dental anxiety (Klages et al., 2004). Therefore, it has been suggested that patients with high anxiety levels should be excluded from study evaluation anaesthesia success.

An important variable that may act as a confounding factor is the inclusion criteria and the diagnosis of irreversible pulpitis. Several investigations have included patients with a history of spontaneous pain and prolonged response to cold tests (Parirokh et al., 2010a, 2010b, 2014), whereas others have only included emergency patients (in terms of feeling pain) (Fowler et al., 2016; Fowler & Reader, 2013; Schellenberg et al., 2015). Greater preoperative pain is a predictor for anaesthesia failure (Abbott & Parirokh, 2018; Parirokh & Abbott, 2014). Therefore, the results of studies with different inclusion criteria should not be mixed together for a systematic review and meta-analysis regarding success rate of anaesthesia.

Ignoring the baseline patients' pain measurements in advance of the injection or intervention is another important shortcoming (Modaresi et al., 2006), as is measuring but not reporting the preoperative pain of the armed groups (Shahi et al., 2013) since a significant difference in preoperative baseline pain levels between the armed groups may influence final outcomes (Aggarwal et al., 2015). Several studies have evaluated the sensitivity of teeth to electric pulp testing in order to compare the effect of their intervention (Chandrasekaran et al., 2020; Kaladi et al., 2019; Modaresi et al., 2006). However, since pulp sensibility test responses may not be in accordance with the patient's response during root canal treatment, asking patients to rate their pain would be more reliable (Nagendrababu et al., 2020a, 2020b).

It is assumed that pain levels equal to or lower than 54 mm in the Heft-Parker VAS are considered to be

mild pain, whilst higher pain levels are assumed to be moderate-to-severe pain (Heft & Parker, 1984). In studies evaluating anaesthesia success rate, firstly, the preoperative pain should be compared between the study's groups and it should be reported that there was no significant difference for the baseline pain levels. For instance, in one study based on a VAS form, the average preoperative pain in one group was reported as mild whilst the other group was moderate, although the difference was not statistically different (Aggarwal et al., 2014). A study on patients with different preoperative pain has shown that patients with severe preoperative pain were significantly associated with higher anaesthesia failure rates compared to the patients with mild preoperative pain (Aggarwal et al., 2015). Therefore, a controlled randomized clinical trial should also consider baseline preoperative pain to prevent this confounding factor. Future studies should evaluate this further since it may affect the final outcome as well as lead to unjustified conclusions.

There are differences in the quality of investigations with the subject of anaesthesia success rate (Nagendrababu et al., 2018). For instance, the quality of investigations of the efficacy of various anaesthetic solutions on success rates of IANB in patients with irreversible pulpitis is low to moderate (Nagendrababu et al., 2019a) compared to the studies, with high quality, that evaluated the effect of premedication on the success rate of anaesthesia (Nagendrababu et al., 2018). The authors should be given notice that if they prepare their papers with more details, then their investigation will be considered to have low risk of bias in future systematic reviews and meta-analyses, whereas brief explanations of methods and materials may lead to doubts and different types of risk of bias such as attrition bias, detection bias and performance bias (Karapinar-Kazandag et al., 2019; Milani et al., 2018). However, there was no agreement regarding the level of risk of bias amongst studies that evaluated the efficacy of premedication on IANB success rate (Karapinar-Kazandag et al., 2019; Nagendrababu et al., 2018). Importantly, it should be also noted that the study design may influence the outcome of studies. For instance, studies that reported no significant difference regarding efficacy of bupivacaine as IANB anaesthetic solution had a double-blinded design (Aggarwal et al., 2017; Parirokh et al., 2015), whereas the study that showed higher efficacy of bupivacaine was a single-blinded study (Jouhar et al., 2020). Therefore, the risk of bias for the latter study is much higher.

One may question why systematic reviews and meta-analyses with similar subjects provide different results. The difference between systematic reviews and meta-analyses results may be due to two major reasons: (1) including recently published clinical trials that were not included in previous systematic reviews and meta-analyses and (2)

excluding studies that may be included in other systematic reviews due to the study eligibility criteria and method of outcome measures (Nagendrababu et al., 2020a, 2020b, 2021). For instance, a systematic review included all randomized clinical trials using either pulp sensibility tests or VAS as the outcome measurement tool (Kung et al., 2015) but another systematic review and meta-analysis only included studies that used the VAS for the outcome measurement during endodontic intervention (Nagendrababu et al., 2019a).

An important recommendation for future studies should be employing precise method and materials and reporting details to prevent higher risk of bias.

CONCLUSION

Several anaesthetic solutions and techniques have been recommended to increase anaesthesia success rates. However, despite encouraging results for various approaches, there is still no unique method of choice that can predictably and completely overcome pain during root canal treatment, especially for teeth (and particularly mandibular molars) with irreversible pulpitis. There are several shortcomings in previously published studies in terms of various types of biases. Future investigations should consider these variables as confounding factors that may influence their study outcomes. Future studies on anaesthesia success rates should precisely determine the inclusion criteria as well as the method of evaluating the success of anaesthesia in order to allow future systematic reviews and meta-analyses to include studies with lower heterogeneity as well as low risk of biases. Some heterogeneity is unavoidable such as geographic location. However, standardizing other factors such as proper sample size calculation, including only 'acute' or 'chronic' patients with irreversible pulpitis, using a VAS during endodontic intervention as the outcome measure tool, and considering all variables that may affect the outcomes of pulp anaesthesia can prevent further heterogeneity.

Furthermore, comprehensive descriptions of the methods and materials based on the PRIRATE 2020 reporting guidelines (Nagendrababu et al., 2020b) and the CONSORT checklist (Schulz et al., 2010) and explaining any adverse effects would reduce the risk of bias and help to allow future systematic reviews and meta-analyses with more reliable outcomes.

Therefore, the method of diagnosis of irreversible pulpitis, the periapical status of the teeth, the devices and techniques used to diagnose the pulp status, experience of all practitioners who perform clinical procedures (examination, radiographic interpretation, clinical treatment), inclusion as well as exclusion criteria, the type of

anaesthetic solution(s), technique(s) employed for administration, randomization, blinding, time lapse between anaesthesia administration and assessing the anaesthesia success or commencing the root canal treatment, method of outcome measurement, considering power analysis in order to reach a clinical significance, if there was any, and finally any immediate or delayed adverse effects following injection of the anaesthetic.

CONFLICT OF INTEREST

The authors have stated explicitly that there is no conflict of interests in connection with this article.

ETHICAL APPROVAL

There are no ethical considerations since this is a review article discussing previously published papers. This review article does not report any new study involving either humans or animals.

AUTHOR CONTRIBUTION

Both authors contributed to the development of the ideas and the writing and editing of this paper.

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