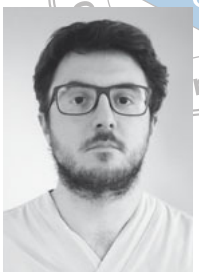

Stefano Corbella

Inferior alveolar nerve block for the treatment of teeth presenting with irreversible pulpitis: A systematic review of the literature and meta-analysis

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Objective: The objective of the present systematic review was to evaluate, in patients with irreversible pulpitis affecting mandibular posterior teeth, if premedication with non-steroidal anti-inflammatory drugs can increase the efficacy of inferior alveolar nerve block (IANB) if compared to placebo administration; if one anesthetic agent is more effective than another; if 1.8 mL injection is more effective than 3.6 mL injection to increase the efficacy of IANB; and if supplementary buccal injection is able to increase the efficacy of IANB as compared to a negative control/placebo group. **Data Sources:** Randomized controlled clinical trials investigating different aspects (technique, premedication with anti-inflammatory drugs, different anesthetic agents) were searched. Success of IANB, as defined in the studies, was considered as the primary outcome. A meta-analysis was performed evaluating relative risks (RRs). Electronic databases (Medline, Embase, Cochrane Central) were searched after preparation of an appropriate search string. After application of selection criteria, a total of 37 studies were included; 19 of them were considered in the meta-analysis. There was evidence of a difference in favor of the use of premedication with anti-inflammatory drugs (RR, 1.80; CI 95%, 1.50–2.14; $P < .0001$). There was no evidence of a difference between articaine and lidocaine (RR, 1.05; CI 95%, 0.91–1.21; $P = .94$). With regard to the volume of anesthetic infiltrated, the computed RR was 1.17 (CI, 0.73–1.88) without any significant difference between the use of one or two cartridges ($P = .52$). The estimated RR for a supplementary buccal infiltration was 1.56 (CI, 1.00–2.42; $P = .05$). **Conclusion:** The use of premedication with anti-inflammatory drugs before IANB can increase the efficacy of the IANB. The type of anesthetic agent, the volume of anesthetic, and the use of a supplemental buccal infiltration do not seem to affect the efficacy of anesthesia. *(Quintessence Int 2017;48:69–82; doi: 10.3290/j.qi.a37131)*

Key words: inferior alveolar nerve block, local anesthesia, pulpitis, systematic review

Anesthetics have been used in dentistry since the last decades of the 19th century to achieve the block of nerves supplying teeth and oral mucosa.[1] In particular, inferior alveolar nerve block (IANB) is commonly used to obtain the anesthesia of posterior mandibular teeth, for various dental purposes including endodontic procedures, reconstructive procedures, and tooth extraction.[2,3]

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Even when a proper technique is adopted and lip numbness is obtained, the failure of IANB at the pulp level can be observed.[4] The percentage of failure of IANB reported in the scientific literature is extremely variable, ranging from 88%[5] to 3.2%.[6] A number of mechanisms have been suggested as conditions that could alter the efficacy of IANB, such as anatomical variations, accessory innervation of the posterior mandible, the decrease of local pH due to infection, and local activation of nociceptors.[7]

Symptomatic irreversible pulpitis (SIP) is a clinical condition, defined based on subjective and objective findings, that is characterized by "sharp pain upon thermal stimulus, lingering pain (often 30 seconds or longer after stimulus removal), unprovoked and referred pain," as indicated by the guidelines provided by American Academy of Endodontics.[8] Root canal treatment is the most indicated solution for this condition because of the incapacity of the inflamed vital pulp to heal spontaneously at this point.[8] In the presence of SIP, IANB in mandibular posterior teeth could be less effective than for noninflamed teeth.[4-7]

A recent paper reported the results of a study on a large sample size (3,169 teeth included) about IANB efficacy when performed either on symptomatic or asymptomatic patients.[9] Considering lip numbness as the success criterion, no differences could be found between symptomatic and asymptomatic subjects.[9] However, considering pain during the treatment as the failure criterion, it has been shown that obtaining pulp anesthesia can be more difficult in symptomatic than asymptomatic teeth.[7,10]

The present systematic review of the literature was intended to address the population, intervention, comparison, outcomes (PICO) question that follows: In patients with SIP affecting mandibular posterior teeth needing endodontic treatment:

- is premedication with anti-inflammatory drugs able to increase the efficacy of IANB if compared to placebo administration?
- is one anesthetic agent more effective than another one?
- is 1.8 mL injection more effective than 3.6 mL injection to increase the efficacy of IANB?
- is supplementary buccal injection (to obtain long buccal nerve block) able to increase the efficacy of IANB as compared to a negative control/placebo group?

DATA SOURCES

The present study is reported following the PRISMA statement (http://www.prisma-statement.org).

Eligibility criteria

Only randomized controlled clinical trials (RCTs) with both parallel and split-mouth design assessing the efficacy of one type, technique, or drug in the IANB of patients suffering from SIP in mandibular posterior teeth (molars and premolars), thus requiring endodontic treatment, were included. Both studies with placebo group and comparing two or more experimental groups were included. Only studies treating at least 10 patients per each group were considered eligible.

Studies not reporting the characteristics of the drug used (anesthetic agent and its concentration) as well as information regarding the used success criteria, were excluded.

Search strategy

A literature search was performed on electronic databases (Medline through PubMed interface, Embase, Cochrane Central Register of Controlled Trials) using a search string created ad hoc and then adapted to each electronic database: ("inferior alveolar nerve" OR "IAN" OR "mandibular" OR "molar" OR "first molar" OR "second molar") AND ("pulpitis" OR "irreversible pulpitis" OR "inflammation" OR "pain") AND ("anesthesia" OR "block" OR "anaesthesia").

The last electronic search was performed on 30 April 2016. A hand search was performed on the following journals: Journal of Dentistry, Journal of Dental Research, International Endodontic Journal, Journal of Endodontics, International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, Oral Surgery Oral Medicine Oral Pathology Oral Radiol-

ogy, European Journal of Oral Sciences, British Dental Journal, Journal of American Dental Association.

The reference list of all included studies and of pertinent reviews was also screened for potential inclusion of cited papers. No language restriction was placed.

Data collection

Two of the authors (SC, ST) independently screened titles and abstracts of the initially retrieved articles. Cohen's Kappa coefficient was used to assess the concordance between the reviewers. If the abstracts did not provide sufficient information to decide for inclusion the full-texts were retrieved and evaluated. Any disagreement was resolved by discussion. Full-texts of all studies of possible relevance were independently screened by the same two reviewers to check if they met all inclusion criteria and to decide for potential inclusion. Reasons for exclusion were recorded.

All relevant data from included studies were independently extracted and recorded on a spreadsheet by two reviewers (SC, MDF). A joint evaluation was taken to resolve all cases of disagreement.

Primary outcome measure was the success of IANB as reported by authors of the studies measured after the evidence of lip numbness.

Risk of bias assessment

All studies included in the present systematic review were subjected to risk of bias evaluation, which was performed independently by two reviewers (SC, MDF). Any disagreement was resolved by discussion between the two reviewers. The guidelines reported in the Cochrane Handbook for Systematic Reviews of Interventions (2011) were used as criteria to assess the risk of bias. The considered parameters were:

- selection bias (randomization methods and allocation concealment)
- performance bias (blinding of participants and personnel)
- detection bias (blinding of outcome assessment)
- attrition bias (incomplete outcome data)
- reporting bias (selective reporting)
- other bias.

In cases of incomplete information provided in the articles, the authors of included studies were contacted to provide explanations or missing information as needed. A study was considered at low risk of bias when all items were met; it was considered at moderate risk of bias if one of the items was not adequate; and it was considered at high risk of bias if at least one parameter was judged as not adequate. Studies that were judged at high risk of bias were excluded from the meta-analysis.

Data analysis

Data about frequency of success of IANB were extracted from the included articles.

Articles were grouped according to the PICO questions posed in the aims of the review. For such groups, when two or more articles presented the same comparison, a meta-analysis (fixed effects assuming that differences among studies were due only to a play of chance (Cochrane Handbook for Systematic Review for Interventions, 2001). Mantel-Haenszel method was performed using the software RevMan (Review Manager Version 5.3, 2014; The Nordic Cochrane Center, The Cochrane Collaboration) estimating the risk ratio (RR). Heterogeneity among studies included in the meta-analysis was calculated through I^2 statistics. Other studies were analyzed separately.

A value of $P < .05$ was considered as statistically significant.

REVIEW

Manual search resulted in 33 articles, while electronic search found 948 papers. After removal of duplicates, a total of 953 article titles and abstracts were screened. A total of 65 articles were eligible, while 888 papers were excluded. After full-text evaluation, a total of 38 articles were included in the present review. The Cohen's kappa for concordance in article selection process of the authors was 0.92. All selected articles were included in the qualitative analysis, while 20 were included in the quantitative synthesis. The main characteristics of included studies are summarized in Table 1. Consider-

Table 1 General characteristics of included studies

Study	Year	No. subjects	Teeth	Scale	Success criteria
Abazarpoor et al[11]	2015	80	First molars	HP VAS scale	Total success rate presented
Aggarwal et al[12]	2009	84	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Aggarwal et al[13]	2010	69	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Aggarwal et al[14]	2011	94	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Aggarwal et al[15]	2012	59	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Aggarwal et al[16]	2012	55	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Aggarwal et al[17]	2013	62	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Akhlaghi et al[18]	2016	40	Molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Ashraf et al[19]	2013	125	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Bigby et al[5]	2007	48	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Claffey et al[20]	2004	72	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Click et al[21]	2015	98	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Dou et al[22]	2013	80	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Fan et al[23]	2009	57	First molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Fullmer et al[24]	2014	70	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Ianiro et al[25]	2007	40	NS	Cold spray (before treat-ment)	"Pain" before treatment (cold spray) or during treatment
Jalali et al[26]	2015	40	First molars/ second molars	VAS 100 mm	Pain > 20 mm during treatment
Kennedy et al[27]	2003	64	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Khademi et al[28]	2012	60	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment

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Comparison*			
Treatment A	**Treatment B**	**Treatment C**	**Treatment D**
IANB: Ar 4% + epi 1:100 1.8 mL	IANB: Ar 4% + epi 1:100 3.6 mL		
IANB: Li 2% + 1:200 1.8 mL	IANB: Li 2% + 1:200 1.8 mL; B&L (2 mins after IANB): Ar 4% + epi 1:200 1.8 mL	IANB: Li 2% + 1:200 1.8 mL; B&L (2 mins after IANB): Li 2% + epi 1:200 1.8 mL	
Placebo (1 h before); IANB: Li 2% + epi 1:200 1.8 mL	Ibuprofen 300 mg (1 h before); IANB: Li 2% + epi 1:200 1.8 mL	Ketorolac 10 mg (1 h before); IANB: Li 2% + epi 1:200 1.8 mL	
IANB: Li 2% + epi 1:200 1.8 mL	IANB: Li 2% + epi 1:200 1.8 mL; B: Ar 4% + epi 1:100 1.8 mL	IANB: Li 2% + epi 1:200 1.8 mL; B: Ar 4% + epi 1:100 1.8 mL; B: 1 mL/30 mg ketorolac	IANB: Li 2% + epi 1:200 1.8 mL; B: Ar 4% + epi 1:100 1.8 mL; B: 5 mL/4 mg dexamethasone
IANB: Li 2% + 1:200 3.6 mL; 120 s	IANB: Li 2% + 1:200 3.6 mL; 30 s		
IANB: Li 2% + epi 1:200 1.8 mL	IANB: Li 2% + epi 1:200 3.6 mL		
IANB: Li 2% + epi 1:80 1.8 mL	IANB: Li 2% + epi 1:200 1.8 mL		
IANB: Ar 4% + epi 1:100 1.8 mL; after 20 min 30 mg/mL ketorolac (periapical)	IANB: Ar 4% + epi 1:100 1.8 mL; after 20 min 30 mg/mL placebo (periapical)		
IANB + B: Li 2% + 1:100 1.5 mL + 0.3 mL; INF: Li 2% + 1:100 1.8 mL	IANB + B: Ar 4% + 1:100 1.5 mL + 0.3 mL; INF: Ar 4% + 1:100 1.8 mL		
IANB: Li 2% + epi 1:100 1.8 mL	IANB: Li 2% + epi 1:100 1.8 mL + 2% meperidine + epi 1:100 1.8 mL		
IANB: Ar 4% + epi 1:100 2.2 mL	IANB: Li 2% + epi 1:100 2.2 mL		
Gow Gates -> IANB: Li 2% + epi 1:100 3.6 mL; B: 2% Li + epi 1:100	Vazirani-Akinosi -> IANB: Li 2% + epi 1:100 3.6 mL; B: 2% Li + epi 1:100 3.6 mL		
IANB: Li 2% + 1:200 4.0 mL; B: Ar 4% + epi 1:100 0.9 mL	IANB: Li 2% + 1:200 4.0 mL; B: Ar 4% + epi 1:100 0.9 mL; L: Ar 4% + epi 1:100 0.9 mL		
IANB: Ar 4% + epi 1:100 1.7 mL; B: Ar 4% + epi 1:100 0.2 mL	IANB: Ar 4% + epi 1:100 1.7 mL; PDL: Ar 4% + epi 1:100 0.2 mL		
Placebo (1 h before); IANB: Li 2% + epi 1:100 1.7 mL; B: Li 2% + epi 1:100 0.9 mL	1,000 mg acetaminophen + 10 mg hydrocodone (1 h before); IANB: Li 2% + epi 1:100 1.7 mL; B: Li 2% + epi 1:100 0.9 mL		
Placebo (30 min before); IANB: Li 2% + epi 1:100 3.6 mL	1,000 mg acetaminophen (30 min before); IANB: Li 2% + epi 1:100 3.6 mL	1,000 mg acetaminophen + 600 mg ibuprofen (30 min before); IANB: Li 2% + epi 1:100 3.6 mL	
Acupuncture (15 min); IANB: Li 2% + epi 1:80 1.8 mL	Placebo (15 min); IANB: Li 2% + epi 1:80 1.8 mL		
IANB: Li 2% + 1:80 2.8 mL (needle bevel far from the ramus)	IANB: Li 2% + 1:80 2.8 mL (bidirectional-needle-rotational [Wand II])		
0.5 mg alprazolam (45 min); IANB: Li 2% + epi 1:100 1.8 mL	0.5 mg placebo (45 min); IANB: Li 2% + epi 1:100 1.8 mL		

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Kreimer et al[29]	2012	55/51	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Monteiro et al[30]	2015	50	First molars/ second molars	Self-reported pain	Endodontic treatment
Noguera-Gonzalez et al[31]	2013	50	First molars/ second molars	Cold test; self-reported pain	Endodontic treatment
Oleson et al[32]	2010	100	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Parirokh et al[33]	2010	150	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation; details presented
Parirokh et al[34]	2010	81	First molars	Self-reported pain	Endodontic treatment
Poorni et al[35]	2011	156	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation; details presented
Prasanna et al[36]	2010	114	First molars/ second molars	Self-reported pain	No pain during endodontic access preparation and root canal instrumentation
Rodriguez-Wong et al[37]	2015	56	First molars/ second molars	HP VAS scale (100 mm)	"No pain"during endodontic endodontic treatment; details presented
Saatchi et al[38]	2015	80	First molars/ second molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Saha et al[39]	2016	126	Molars	HP VAS scale	No pain during treatment
Sampaio et al[40]	2012	70	First molars/ second molars	Self-reported pain	"No pain" or "weak/mild pain" during endodontic treatment
Schellenberg et al[41]	2015	100	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic access preparation and instrumentation
Shahi et al[42]	2013	165	First molars/ second molars	VAS 100 mm	"No pain" or "weak/mild pain" VAS < 21 during endodontic access preparation and instrumentation
Sherman et al[43]	2008	40	NS	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Shetty et al[44]	2015	100	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Simpson et al[45]	2011	100	Premolars/ molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment
Sood et al[46]	2014	100	Premolars/ molars	VAS (0–3)	VAS score 0 or 1; access phase
Tortamano et al[47]	2009	40	Premolars/ molars	VAS (0–3)	VAS score 0 or 1; access phase
Yadav et al[48]	2015	150	Molars	HP VAS scale	"No pain" or "weak/mild pain" HP VAS < 55 during endodontic treatment

*1:80 stands for 1:80,000; 1:100 stands for 1:100,000; 1:200 stands for 1:200,000.
Ar, articaine; B, buccal injection; Bu, bupivacaine; epi, epinephrine; G1, group 1; HP, Heft Parker; IANB, inferior alveolar nerve block; INF, inferior; L, lingual injection; Li, lidocaine; Me, mepivacaine; USP, US Pharmacopeial Convention; VAS, visual analog scale.

IANB: Li 2% + epi 1:200 3.18 mL	IANB: Li 2% + epi 1:200 3.18 mL + 0.5 mol/L mannitol 1.82 mL	IANB: Li 4% + epi 1:200 1.9 mL	IANB: Li 4% + epi 1:200 1.9 mL + 0.5 mol/L mannitol 1.1 mL
IANB: Li 2% + epi 1:100 1.8 mL	B: Ar 4% + epi 1:100 1.8 mL		
600 mg ibuprofen (1 h); IANB: Me 2% + epi 1:100 1.8 mL	Placebo (1 h); IANB: Me 2% + epi 1:100 1.8 mL		
800 mg ibuprofen (1 h); IANB: LI 2% + epi 1:100 3.6 mL; B: LI 2% + epi 1:100 0.9 mL	Placebo (1 h); IANB: LI 2% + epi 1:100 3.6 mL; B: LI 2% + epi 1:100 0.9 mL		
600 mg ibuprofen (1 h); IANB: Li 2% + epi 1:80 1.8 mL	75 mg indomethacin (1 h); IANB: Li 2% + epi 1:80 1.8 mL	Placebo (1 h); IANB: Li 2% + epi 1:80 1.8 mL	
IANB: Li 2% + epi 1:80 1.8 mL	IANB: Li 2% + epi 1:80 3.6 mL	IANB: Li 2% + epi 1:80 1.8 mL; B: Li 2% + epi 1:80 1.8 mL	
IANB: Ar 4% + epi 1:100	B: Ar 4% + epi 1:100	IANB: Li 2% + epi 1:100	
Placebo (1 h); IANB: Li 2% + epi 1:200 1.8 mL	Lanoxicam 8 mg (1 h); IANB: Li 2% + epi 1:200 1.8 mL	Diclofenac potassium 50 mg (1 h); IANB: Li 2% + epi 1:200 1.8 mL	
IANB: Me 2% + epi 1:100 1.3 mL; 50 mg / mL tramadol 0.5 mL	IANB: Me 2% + epi 1:100 1.8 mL		
IANB: Li 2% + epi 1:80 1.62 mL; sodium bicarbonate 8.4% 0.18 mL	IANB: Li 2% + epi 1:80 1.62 mL; saline solution 0.18 mL		
Ketorolac tablet (1h); Li 2% 1:200 1.8 mL	Diclofenac potassium tablet (1h); Li 2% 1:200 1.8 mL	Placebo tablet (1h); Li 2% 1:200 1.8 mL	
IANB: Li 2% + epi 1:100 3.6 mL	IANB: Bu 0.5% + epi 1:200 3.6 mL		
IANB: Li 4% + epi 1:100 2.8 mL	IANB: Li 4% + epi 1:100; sodium bicarbonate 8.4% 2.8 mL		
Placebo (1 h); IANB: Li 2% + epi 1:80 1.8 mL	Dexamethasone 0.5 mg (1 h); IANB: Li 2% + epi 1:80 1.8 mL	Ibuprofen 400 mg (1 h); IANB: Li 2% + epi 1:80 1.8 mL	
IANB (Gow Gates): Ar 4% + epi 1:100 1.7 mL	IANB (Gow Gates): Li 2% + epi 1:100 1.7 mL		
Magnesium sulfate USP 50% 1 mL (1 h); IANB: Li 2% + epi 1:100 1.8 mL	Distilled water 1 mL (1 h); IANB: Li 2% + epi 1:100 1.8 mL		
Ibuprofen 800 mg + acetaminophen 1,000 mg (1 h); IANB: Li 2 % + epi 1:100 3.6 mL; B: Li 2% + epi 1:100 0.9 mL	Placebo (1 h); IANB: Li 2 % + epi 1:100 3.6 mL; B: Li 2% + epi 1:100 0.9 mL		
IANB: Li 2% + epi 1:80 1.8 mL	IANB: Ar 4% + epi 1:100 1.8 mL		
IANB: Ar 4% + epi 1:100 3.6 mL	IANB: Li 2% + epi 1:100 3.6 mL		
G1: IANB: Ar 4% + epi 1:100 1.8 mL; G1A: B: 0.9 mL + L: 0.9 mL Ar 4% or Li 2%; G1B: Premedication with ketorolac 10 mg; G1C: Premedication with ketorolac 10 mg + B: 0.9 mL + L: 0.9 mL Ar 4% or Li 2%	G1: IANB: Li 2% + epi 1:80 1.8 mL; G1A: B: 0.9 mL + L: 0.9 mL Ar 4% or Li 2%; G1B: Premedication with ketorolac 10 mg; G1C: Premedication with ketorolac 10 mg + B: 0.9 mL + L: 0.9 mL Ar 4% or Li 2%		

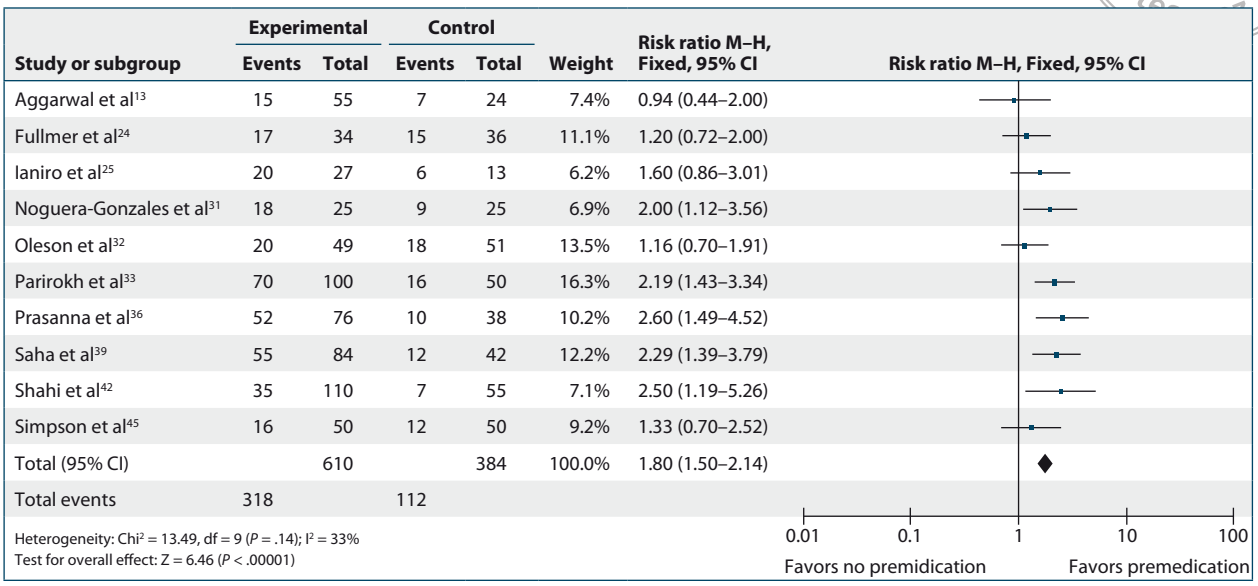

Fig 1 Forest plot: premedication with anti-inflammatory drugs vs no premedication.

ing all included studies, results from a total of 3,221 teeth were considered in the review.

Two articles evaluated only mandibular first molars, 23 evaluated mandibular first and second molars, 13 evaluated premolars and molars, and two articles did not present details about teeth characteristics.

As shown in Table 1, most of the studies used a Heft-Parker Visual Analog Scale (VAS) to measure pain intensity, while other studies used self-reported pain.

Risk of bias

Three studies were found to be at high risk of bias because of inadequate allocation concealment,[11,26,29] and were excluded from the quantitative synthesis.

Is premedication with anti-inflammatory drug able to increase the efficacy of IANB if compared to placebo administration?

A total of 10 studies, accounting for 994 teeth, were considered (Fig 1). The computed RR was 1.80 (confidence interval [CI], 1.50 to 2.14), favoring the use of a premedication, and the difference was statistically significant ($P < .0001$). The computed heterogeneity I^2 was 33%.

Ibuprofen (taken alone 1 hour prior to the treatment) was evaluated in five studies, using different doses, ranging from 300 mg to 800 mg. Acetaminophen 1,000 mg was studied (taken alone or in combination with other drugs) in three papers, and it was taken both 30 minutes and 1 hour prior to intervention. Ketorolac 10 mg 1 hour before, indomethacin 75 mg 1 hour before, lanoxicam 8 mg 1 hour before, diclofenac potassium 50 mg 1 hour before, and dexamethasone 0.5 mg 1 hour before were also used in the included articles.

Is one anesthetic agent more effective than another one?

Six studies (371 teeth) were considered comparing articaine to lidocaine for IANB (Fig 2). The computed RR was 1.00 (CI, 0.88 to 1.15), without any significant difference between articaine and lidocaine ($P = .97$). The computed heterogeneity I^2 was 0%.

Is 1.8 mL injection more effective than 3.6 mL injection to increase the efficacy of IANB?

Two studies were considered in the comparison between the use of 1.8 mL or 3.6 mL of anesthetic (Fig 3). The computed RR was 1.17 (CI, 0.73 to 1.88), without any significant difference between the two groups ($P = .52$). Moreover, in this particular comparison, the heterogeneity I^2 was 79%.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M–H, Fixed, 95% CI
Ashraf et al[19]	8	17	9	17	7.6%	0.89 (0.45–1.75)
Claffey et al[20]	9	37	8	35	6.9%	1.06 (0.46–2.45)
Poorni et al[35]	39	52	36	52	30.3%	1.08 (0.85–1.38)
Sherman et al[43]	9	10	8	11	6.4%	1.24 (0.82–1.88)
Sood et al[46]	41	50	44	50	37.0%	0.93 (0.79–1.10)
Tortamano et al[47]	13	20	14	20	11.8%	0.93 (0.60–1.43)
Total (95% CI)		186		185	100.0%	1.00 (0.88–1.15)
Total events	119		119			

Heterogeneity: Chi² = 2.40, df = 5 (*P* = .79); I² = 0%
Test for overall effect: Z = .04 (*P* = .97)

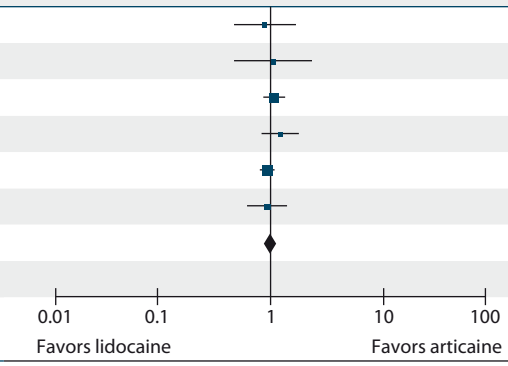

Fig 2 Forest plot: lidocaine vs articaine.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M–H, Fixed, 95% CI
Aggarwal et al[16]	12	28	15	27	78.9%	0.77 (0.45–1.33)
Parirokh et al[34]	11	28	4	27	21.1%	2.65 (0.96–7.32)
Total (95% CI)		56		54	100.0%	1.17 (0.73–1.88)
Total events	23		19			

Heterogeneity: Chi² = 4.73, df = 1 (*P* = .03); I² = 79%
Test for overall effect: Z = .64 (*P* = .52)

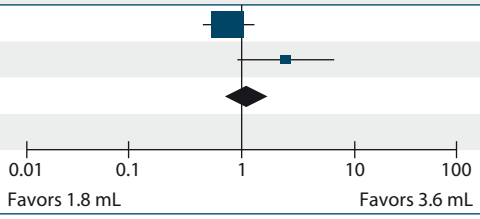

Fig 3 Forest plot: 1.8 mL vs 3.6 mL.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M–H, Fixed, 95% CI
Aggarwal et al[12]	13	24	9	23	44.6%	1.38 (0.74–2.60)
Aggarwal et al[14]	34	60	8	24	55.4%	1.70 (0.93–3.12)
Total (95% CI)		84		47	100.0%	1.56 (1.00–2.42)
Total events	47		17			

Heterogeneity: Chi² = 0.22, df = 1 (*P* = .64); I² = 0%
Test for overall effect: Z = 1.98 (*P* = .05)

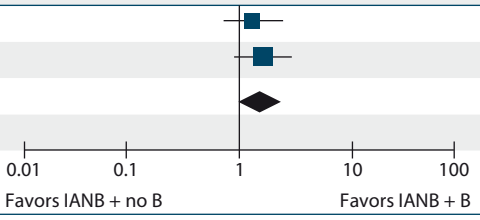

Fig 4 Forest plot: supplemental buccal infiltration (B) vs no supplemental infiltration.

Is supplementary buccal injection (to obtain long buccal nerve block) able to increase the efficacy of IANB as compared to a negative control/placebo group?

Two studies, of the same research group, evaluated the efficacy of a supplementary buccal injection in IANB (Fig 4). The computed RR was 1.56 (CI, 1.00 to 2.42) without any significant difference (*P* = .05). The computed heterogeneity I^2 was 0%.

Other findings

Other findings are summarized in Table 2.

In one study by Aggarwal et al,[16] it was found that injection time had a low effect on increasing the efficacy of IANB. Bigby et al[5] found no effect in infiltrating adjunctive meperidine 2%. Regarding the used technique, Gow-Gates was found to be more effective than Vazirani-Akinosi technique.[21] An adjunctive lingual injection was not effective, as reported in one study published in 2013.[22] Moreover, no superior effect was

Table 2 Summary of findings of studies not included in the meta-analysis

Investigation	Study	Year	Treatment A*	n	Success
Time for injection	Aggarwal et al[15]	2012	IANB: Li 2% + 1:200 3.6 mL; 30 s	30	43%
Adjunctive periapical ketorolac	Akhlaghi et al[18]	2016	IANB: Ar 4% + epi 1:100 1.8 mL; after 20 min 30 mg/mL ketorolac (periapical)	20	40%
IANB + Buccal injection Ar 4% versus Li 2%	Ashraf et al[19]	2013	IANB: Ar 4% + epi 1:100 1.5 mL; B: Ar 4% + epi 1:100 0.3 mL; supplemental infiltration: Ar 4% + epi 1:100	58	71%
Adjunctive meperidine 2%	Bigby et al[5]	2007	IANB: Li 2% + epi 1:100 1.8 mL	23	26%
Gow Gates versus Vazirani-Akinosi technique	Click et al[21]	2015	Gow Gates → IANB: Li 2% + epi 1:100 3.6 mL; B: 2% Li + epi 1:100	60	35%
Adjunctive lingual injection	Dou et al[22]	2013	IANB: Li 2% + 1:200 4.0 mL; B: Ar 4% + epi 1:100 0.9 mL	40	70%
Buccal versus intraligamentary adjunctive injection	Fan et al[23]	2009	IANB: Ar 4% + epi 1:100 1.7 mL; B: Ar 4% + epi 1:100 0.2 mL	27	81.5%
Acupuncture	Jalali et al[26]	2015	Acupuncture (15 min); IANB: Li 2% + epi 1:80 1.8 mL	20	60%
Needle position	Kennedy et al[27]	2003	IANB: Li 2% + 1:80 2.8 mL (needle bevel far from the ramus)	32	50%
Premedication with benzodiazepine	Khademi et al[28]	2012	0.5 mg alprazolam (45 min); IANB: Li 2% + epi 1:100 1.8 mL	30	53%
Adjuctive mannitol	Kreimer et al[29]	2012	IANB: Li 2% + epi 1:200 3.18 mL	27	37%
			IANB: Li 4% + epi 1:200 1.9 mL	23	13%
Premedication with opioid	Rodriguez-Wong et al[37]	2015	IANB: Me 2% + epi 1:100 1.3 mL; 50 mg/mL tramadol 0.5 mL	28	82.1% (cold test); 57.1% (pulp tissue access)
Effect of buffering solution	Saatchi et al[38]	2015	IANB: Li 2% + epi 1:80 1.62 mL; sodium bicarbonate 8.4% 0.18 mL	40	62.5%
	Schellenberg et al[41]	2015	IANB: Li 4% + epi 1:100 2.8 mL	50	40%
Li versus Bu	Sampaio et al[40]	2012	IANB: Li 2% + epi 1:100 3.6 mL	35	42.9% (pulp tester); 62.9% (pulpectomy)
Effect of adjunctive magnesium sulfate solution	Shetty et al[44]	2015	Magnesium sulfate USP 50% 1 mL (1 h); IANB: Li 2% + epi 1:100 1.8 mL	50	58%
Ar + B/L versus Li + B/L	Yadav et al[48]	2015	IANB: Ar 4% + epi 1:100 1.8 mL; B: 0.9 mL + L: 0.9 mL Ar 4% or Li 2%	25	48%
Ketorolac premedication + Ar versus ketorolac premedication + Li	Yadav et al[48]	2015	Ketorolac 10 mg; IANB: Ar 4% + epi 1:100 1.8 mL	25	76%
Ketorolac premedication + Ar + B/L versus ketorolac premedication + Li + B/L	Yadav et al[48]	2015	Ketorolac 10 mg; IANB: Ar 4% + epi 1:100 1.8 mL; B: 0.9 mL + L: 0.9 mL Ar 4% or Li 2%	25	64%

*1:80 stands for 1:80,000; 1:100 stands for 1:100,000; 1:200 stands for 1:200,000.
Ar, articaine; B, buccal injection; Bu, bupivacaine; epi, epinephrine; L, lingual injection; Li, lidocaine; HP, Heft Parker; IANB, inferior alveolar nerve block; PDS, periodontal ligament; USP, US Pharmacopeial Convention.

reported for adjunctive buccal versus adjunctive intraligamentary injection.[23]

Articaine 4% was found in one study to be more effective than lidocaine 2% in inducing anesthesia when used for adjunctive periapical infiltration after IANB and long buccal block.[19] One study evaluated the application of acupuncture technique to increase the efficacy of IANB.[26] Interestingly, the authors found a significant beneficial effect of acupuncture. The position of the needle bevel was reported not to influence the efficacy of IANB, as highlighted in one study.[27] One study published by Khademi et al[28] in 2012 found that

Treatment B*	n	Success
IANB: Li 2% + 1:200 3.6 mL; 120 s	29	51%
IANB: Ar 4% + epi 1:100 1.8 mL; after 20 min 30 mg/mL placebo (periapical)	20	15%
IANB: Li 2% + epi 1:100 1.5 mL; B: Li 2% + epi 1:100 0.3 mL; supplemental infiltration: Li 2% + epi 1:100	58	29%
IANB: Li 2% + epi 1:100 1.8 mL + 2% meperidine + epi 1:100 1.8 mL	25	12%
Vazirani Akinosi → IANB: Li 2% + epi 1:100 3.6 mL; B: 2% Li + epi 1:100	38	16%
IANB: Li 2% + 1:200 4.0 mL; B: Ar 4% + epi 1:100 0.9 mL; L: Ar 4% + epi 1:100 0.9 mL	40	62.5%
IANB: Ar 4% + epi 1:100 1.7 mL; PDL: Ar 4% + epi 1:100 0.2 mL	30	83.3%
Placebo (15 min); IANB: Li 2% + epi 1:80 1.8 mL	20	20%
IANB: Li 2% + 1:80 2.8 mL (bidirectional-needle-rotational [Wand II])	32	56%
0.5 mg placebo (45 min); IANB: Li 2% + epi 1:100 1.8 mL	30	40%
IANB: Li 2% + epi 1:200 3.18 mL + 0.5 mol/L mannitol 1.82 mL	28	54%
IANB: Li 4% + epi 1:200 1.9 mL + 0.5 mol/L mannitol 1.1 mL	28	39%
IANB: Me 2% + epi 1:100 1.8 mL	28	67.9% (cold test); 46.4% (pulp tissue access)
IANB: Li 2% + epi 1:80 1.62 mL; saline solution 0.18 mL	40	47.5%
IANB: Li 4% + epi 1:100; sodium bicarbonate 8.4% 2.8 mL	50	32%
IANB: Bu 0.5% + epi 1:200 3.6 mL	35	20% (pulp tester); 80% (pulpectomy)
Distilled water 1 mL (1 h); IANB: Li 2% + epi 1:100 1.8 mL	50	32%
IANB: Li 2% + epi 1:100 1.8 mL; B: 0.9 mL + L: 0.9 mL Ar 4% or Li 2%	25	40%
Ketorolac 10 mg; IANB: Li 2% + epi 1:80 1.8 mL	25	56%
Ketorolac 10 mg; IANB: Li 2% + epi 1:80 1.8 mL; B: 0.9 mL + L: 0.9 mL Ar 4% or Li 2%	25	32%

premedication with benzodiazepine (alprazolam) could significantly increase the efficacy of IANB if compared to a placebo group. Also, premedication with an opioid (tramadol) increased the IANB success for pulpal anesthesia in one study.[37] One study reported that adjunctive mannitol could be useful to increase the efficacy of IANB.[29] One paper reported that adjunctive periapical injection of ketorolac could increase the efficacy of IANB as compared to placebo.[18]

Buffering solutions were tested for their efficacy if associated with anesthetic solutions in IANB in two studies, but the results were not unequivocal.[38,41] In contrast, the adjunctive use of magnesium sulfate increased the efficacy of IANB, as reported in one study.[44] Bupivacaine 0.5% was not found to be more effective than lidocaine 2%.[40] Finally, another study found that articaine demonstrated higher success rate of IANB as compared with lidocaine, with adjunctive buccal and lingual injection or with premedication with ketorolac.[48]

DISCUSSION

A systematic review attempts to collect all empirical evidence in order to respond to a specific question postulated a priori. Methods of systematic reviews are chosen in order to minimize the potential biases, allowing extrapolation of a conclusion from the results obtained.

The present systematic review of the literature about IANB of posterior mandibular teeth affected by symptomatic irreversible pulpitis found substantial scientific evidence to support the use of premedication with anti-inflammatory drugs before IANB.

In order to allow adequate interpretation of the results, the main limitations of the present study should be considered. First, in the meta-analysis, studies with not identical treatment protocols were pooled together, including different premedication drugs (ibuprofen, acetaminophen, diclofenac, ketorolac, and others). The first aim was to understand the effect of premedication in general without focusing on any single anesthetic agent. The hypothetical mechanisms of action of anti-inflammatory drugs in augmenting the efficacy of IANB in symptomatic teeth could be postulated to be substantially identical among different anesthetic agents. One further limitation was the low number of articles in two of the considered comparisons (volume of anesthetics and supplemental buccal infiltration efficacy). Finally, and probably the most

important limitation, is the frequent use of self-reported pain sensation, which could have limited the comparability of results among studies.

As was found in the meta-analysis, the preventive use of anti-inflammatory drugs could increase significantly the success rate of IANB for teeth affected by SIP. These findings confirm those presented in a previously published systematic review.[49] The reason for such effect should be searched for in the pathways of pain generation due to inflammation. Inflammation, through stimulation of the release of arachidonic acid from cell membranes and metabolism by the cyclooxygenase pathway, induces the production of prostaglandins, which are mainly involved in pain generation and amplification.[50,51] In addition, in subjects suffering from symptomatic pulpitis, there is substantial hyperactivation of nociceptors due to inflammation itself, and this mechanism could severely limit the efficacy of anesthetics.[7] In this situation, the premedication with selective inhibitors of the cyclooxygenase pathway could lower the activation level of nociceptors, reducing inflammation.[13,24,32] On the basis of the results, even though a specific analysis was not performed, it seemed that the assumption of one single dose of ibuprofen 600 mg or 800 mg 1 hour before treatment could increase the efficacy of IANB. With regard to the premedication with molecules acting centrally, such as benzodiazepine (alprazolam) and opioids (tramadol, hydrocodone), few studies were found, although these did support premedication with such drugs in order to increase the efficacy of IANB.

The present review found no evidence of a higher efficacy of articaine when compared to lidocaine for IANB. One systematic review and meta-analysis, published by Brandt et al[52] in 2011, aimed to compare the pulpal anesthetic efficacy of these two anesthetic agents, considering both mandibular and maxillary teeth. Interestingly, the authors found superior efficacy of articaine if compared to lidocaine. Most of the computed effect was due to studies not regarding symptomatic mandibular teeth.[53-55] This important aspect might suggest that the inflammatory status could have masked importantly potential differences among different anesthetic agents for IANB. This assumption was confirmed in the review by Brandt et al,[52] when a subgroup analysis on inflamed teeth only was performed. A more recent systematic review by Kung et al[56] found no advantage in the use of articaine over lidocaine when used for IANB in mandibular teeth with symptomatic irreversible pulpitis.

Some authors found no difference in efficacy when increasing the volume of anesthetics for IANB in uninflamed teeth.[3,57] Similarly, the present review found no evidence that the success rate of IANB changes when increasing the volume (number of cartridges used) of anesthetics.

Buccal anesthesia can be administered in the mandible in order to obtain the block of buccal nerves (mainly ramification of long buccal nerve) that could provide an accessory innervation of posterior, molar teeth.[7,58] However, as reported previously,[7] there is a lack of evidence about the importance of such accessory innervations (from lingual and buccal nerves) in determining pain during treatment, and this is indirectly confirmed by the results of the present review on two studies,[12,14] performed by the same research group, that showed an absence of evidence of a beneficial effect in increasing the efficacy of IANB. Indeed, since statistical significance for this comparison was borderline, it can be hypothesized that a wider sample size is needed in order to clarify this particular aspect.

With regard to other findings, too few studies were selected to allow a generalization of their findings. Nonetheless, some considerations could be made. The use of buffered solutions of anesthetics, used to reduce the effect of local pH, did not result in an increased efficacy of IANB if compared to placebo groups,[38,41] probably because IANB was not usually performed in the inflamed region in cases of pulpitis. The adjunct of molecules affecting the nerve conduction (mannitol[29] and magnesium sulfate[44]) led to a higher success rate for IANB as compared to placebo groups. However, the results on mannitol infiltration, which were similar to those from studies about IANB in asymptomatic teeth,[58] were not confirmed from data about maxillary infiltrations.[60]

CONCLUSION

In conclusion, within the limitations of the present paper we can assume that premedication with anti-inflammatory drugs can increase the efficacy of IANB for teeth with SIP. Further RCTs with large sample size are needed to better understand the effect of different anesthetic agents and concentrations. In particular, studies evaluating, through a randomized comparative design, the effect of premedication with different anesthetic agents could add important information to the topic addressed in the present review.

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