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Articaine efficacy and safety in young children below the age of four years: An equivalent parallel randomized control trial

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Abstract

Background: Pain control is a mandatory aspect in pediatric dentistry office through local anesthesia.

Aim: To assess the safety and efficacy of 4% articaine local anesthetic in young children below four years old.

Design: An equivalent randomized control trial with two parallel arms included 184 young children (92 per group) aged from 36 to 47 months seeking pulpotomy of mandibular primary molars which performed after buccal infiltration injection. The control group received lidocaine hydrochloride 2% with epinephrine 1:100 000. The intervention was articaine hydrochloride 4% with epinephrine 1:100 000. Children's behavior during injection and treatment have assessed using Faces, Legs, Activity, Cry, and Consolability (FLACC) and child's behavior using Frankl Behavior Rating Scale (FBRS). In addition, post-operative complications have been addressed.

Results: Both anesthetic agents were equivalent during the injection phase. During the treatment phase, the absolute risk difference (ARR) between the two groups was 0.120 (95% CI: −0.003; 0.243). The maximum limit of 95% CI surpassed the margin of equivalence, indicating that less pain has been expressed during pulpotomy among children delivered articaine when compared to their counterparts in the lidocaine group. Concerning post-operative complications, no statistically significant difference was detected between the two anesthetic drugs.

Conclusion: The findings supported the efficient and secure use of articaine hydrochloride 4% with epinephrine 1:100 000 to treat children between the ages of 3 and below 4 years old.

KEYWORDS

articaine, buccal infiltration, lidocaine, local anesthesia, pain

1 | INTRODUCTION

One of the most significant determinants of successful accomplishment of dental treatment and shaping the child's later attitude in the dental office is pain control. Adequate local anesthesia has an imperative role in pain elimination throughout the dental setting and subsequent establishment of a positive and effective pediatric treatment triangle.[1] The cardinal aspects of any local anesthetic agent have to be fulfilled are safety and efficacy.[2] Lidocaine as a member of the amide group was primarily introduced in the middle of the preceding century. As a result of its efficient performance and scarce inimical side effect, lidocaine gained ubiquitous

worldwide popularity and considered as the 'gold standard' for comparison with subsequently introduced local anesthetic agents.[3]

In 1969, articaine hydrochloride as new local anesthetic agent emerges. Articaine chemical structure characterized by the existence of a thiophene ring instead of the ordinary benzene ring that presents in other local anesthetics making articaine more lipophilic and subsequently increases its potency. The other exclusive feature is the presence of ester group. These inimitable properties allow the quick hydrolysis of articaine in the blood and minimize the risk of systemic toxicity. In comparison with lidocaine, articaine is 1.5 times more potent and 0.6 times less toxic.[4-6]

Plenty of literature support the use of articaine pediatric patients for its safety and efficiency; however, its use is restricted for children above the age of four years based on the manufacturer's instructions. There is no evidence supports that claim and contraindicate the use of articaine local anesthesia in dental practice for children below the age of four years.[7] Therefore, the current equivalent prospective randomized control trial was conducted to evaluate the safety and efficacy of 4% articaine hydrochloride with epinephrine 1:100 000 in comparison with 2% lidocaine hydrochloride with epinephrine 1:100 000 in young children below four years old.

The null hypothesis of this study (H_0) assumed that the efficiency and safety of articaine and lidocaine were not equivalent. On the other hand, the alternative hypothesis (H_1) supports that both local anesthetic drugs are equivalent.

Why this paper is important to pediatric dentists

- Lidocaine is considered the gold standard of local anesthetic agents. Buccal infiltration in a painful procedure such as pulpotomy, however, may not be sufficient. Therefore, the introduction of another safe and more potent anesthetic drug will be more beneficial.
- Despite the manufacturer's instructions do not recommend the use of articaine in children below the age of four years old, there is no evidence support this claim.
- The current trial revealed the efficiency of articaine administration with comparable results to lidocaine.

2 | MATERIALS AND METHODS

2.1 | Ethical approval

All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee (Ethical approval number of 176) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The trial registered at ClinicalTrials.govPRS (Protocol registration and Result System) under a number of NCT04061265. Informed consent was signed by the participants' parents/legal guardians before launching the procedures.

2.2 | Setting, design, and sample size calculation

This trial carried in the outpatient clinic, Pediatric Dentistry Department, Faculty of Dentistry, Minia University. The trial was held between August 2019 and completed in January 2020. The study was equivalent randomized control trial with two parallel arms (1:1 allocation ratio). The sample size per group was calculated according to the following equation for binary outcomes; $N = 2*(Z_{\alpha/2} + Z_{\beta})^2*p(1-p)/\delta^2$.[8] Based on the results of previous studies,[9] the difference in efficiency between the two local anesthetic agents ($\pm\delta$) specified at ± 0.2 and prevalence (p) of success in the two groups was equal and defined at 0.7. The level of significance and the power of the trial adjusted at 5% ($P < .05$) and 80% ($\beta = 0.2$), respectively. An additional 10% of participants were added to compensate for the withdrawal bias. Therefore, 92 children per group (total of 184 children) were suitable to declare the difference if present between the two local anesthetic agents at 95% confidence level (95% CI).

2.3 | Randomization, allocation, and blinding

As illustrated in Figure 1, out of examined 239 children, 184 children who met the inclusion criteria were selected. An independent clinician was responsible for generating a random allocation sequence that kept hidden from all the trial participants. Based on local anesthetic drugs, the participants were assigned equally into two groups using a computer-generated block randomization technique. Randomization was performed using online databases for clinical trials at https://www.sealedenvelope.com/simple-randomiser/v1/lists. The printed letters were folded several times and placed within an aluminum foil. An additional task performed with the independent nurse was the peeling of the manufacture's local anesthetic cartridge and relabeled with an identification code. The letter and relabeled local anesthetic cartridge placed inside an opaque sealed and stapled envelope, including patient's identification code, name, time, and date. The nature of treatment was masked for the patient/parents, chief investigator who

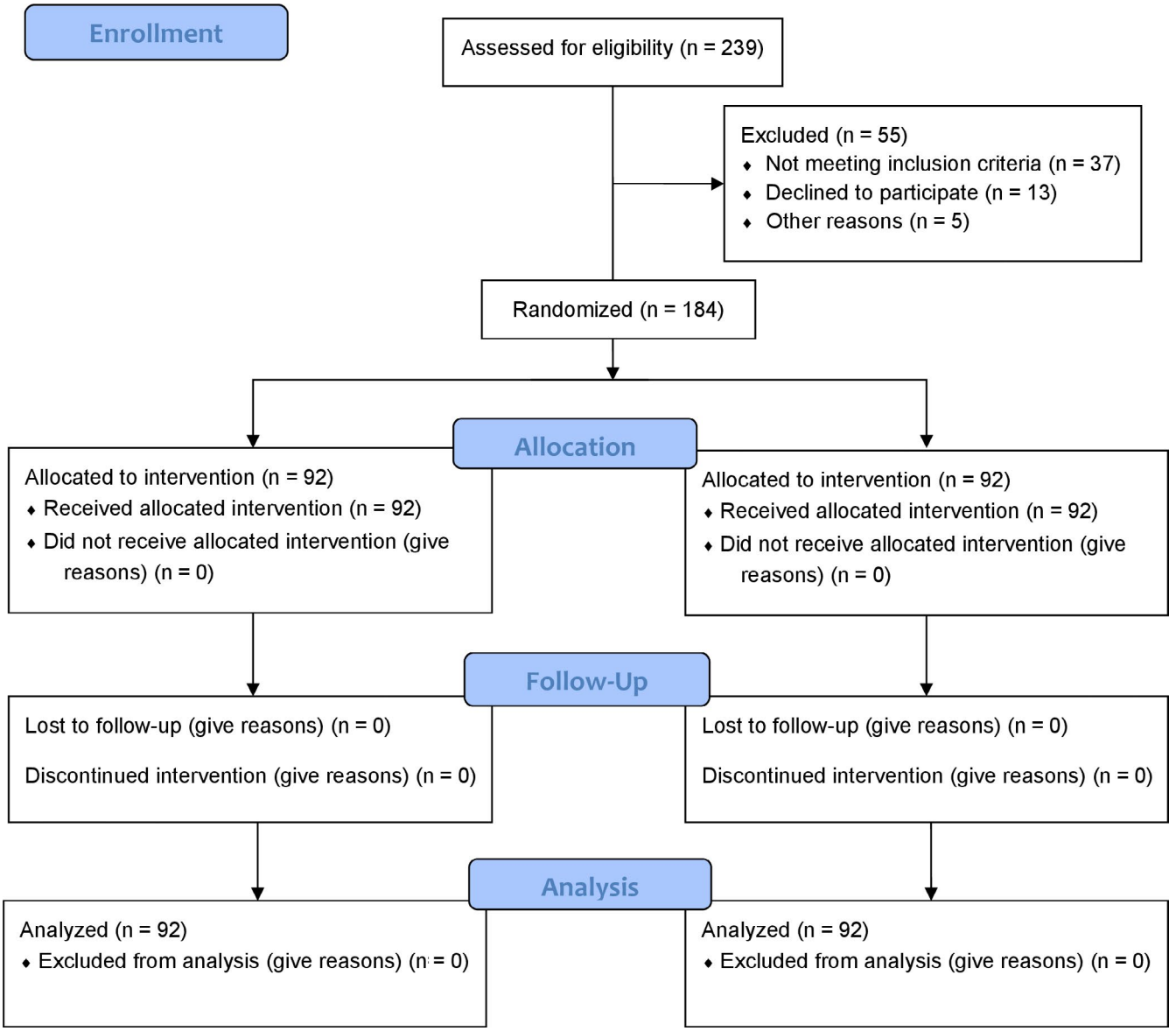

FIGURE 1 CONSORT flow diagram of the randomized control trial

performed the clinical procedures and the two dental clinicians who assess the child's behavior and pain intensity.

2.4 | Eligibility standards

2.4.1 | Inclusion standards

- Class I and Class II relaying on ASA classification
- Child's age was between 36 and 47 months inclusive
- Intellectually qualified for communication
- Child's body weight must be at least 15 kg
- Mandibular primary molars indicted for pulpotomy (ie, carious teeth with vital pulp exposure, normal clinical, and radiographic findings with no evidence of pulp degeneration).[10]

2.4.2 | Exclusion standards

- History or signs of swelling, inflammation, mobility, fistulous tract, or periapical lesion, which confirmed with pre-operative periapical radiograph at or close to the injection site
- Intellectual or severe emotional problems
- Considerable behavior problems
- Parents refuse participation in the trial
- History of previous dental experience
- Past dental visit to not influence child perception

2.5 | Standardization and calibration

Before launching the investigation, all dental staff (clinicians and assistants) took part in the investigation trained for one

day on the clinical steps and assessment scale. The local anesthetic injection and pulpotomy conducted by one investigator. Two pediatric dentists with at least 5 years of experience evaluated and recorded the scores of a pain assessment tool using Faces, Legs, Activity, Cry, and Consolability (FLACC) and child's behavior using Frankl Behavior Rating Scale (FBRS).[11] The inter-observer reliability (Cohen's kappa coefficient χ) was calculated.

2.6 | Clinical procedures and post-operative negative reaction evaluation

The dose of each local anesthetic drug adjusted based on each child's weight taking part in the investigation. Topical anesthesia did not apply to allow accurate calculation of the drug dose and obviate drug toxicity. Alternatively, non-pharmacological behavior management such as a distraction technique was considered. Aspirating syringe with a 30-gauge short needle (Sirio, Tecnofar, Italy 0.30 × 12 mm) was used for buccal infiltration injection. The anesthetic solution injected near the distal root apex of the intended mandibular primary molar at a rate of 1 mL/min. Local anesthetic drugs were lidocaine hydrochloride 2% and epinephrine 1:100 000 (Lignospan® standard, 1.7 mL, SEPTODONT Ltd) for the control group. The intervention group received articaine hydrochloride 4% and epinephrine 1:100 000 (Septocaine® 1.7 mL, SEPTODONT Ltd). The maximum recommended dose for lidocaine and articaine calculated according to the AAPD guidelines was 4.4 and 5 mg/kg, respectively.[12] The maximum dose, however, adopted for articaine was 5 mg/kg.[9] The treatment deemed to be unsuccessful in case of failure to complete the pulpotomy procedures and reschedule.

Vital signs including blood pressure, heart rate, and respiratory rate were measured at three occasions; the first before injection, the second was 5 minutes following the injection, and the third occasion was immediately after finishing the pulpotomy procedures. After 24 hours, the chief investigator inquired from the parent about the child's post-operative pain using as parents' post-operative pain measure (PPPM) and any undesired adverse effects.[9,13]

2.7 | Definition of different study outcomes

The different scales used in this trial defined based on binary outcomes as follows:

- Faces, Legs, Activity, Cry, and Consolability (FLACC) dichotomized into no or mild pain (0-3) and moderate to severe pain (4-10)
- Frankl Behavior Rating Scale (FBRS) dichotomized into positive (behavior rating 3 or 4) and negative (behavior rating 1 or 2)
- Local anesthesia delivery success dichotomized into no (0) and yes (1)
- Parents' post-operative pain measure (PPPM) dichotomized into absent (0-5) and present (6-15)
- Post-operative lip pr cheek biting, use of medication and/or others dichotomized into no (0) and yes (1)

2.8 | Statistical analysis

The descriptive baseline characteristics of the participants in the experimental and control groups were analyzed using frequency tables, mean and standard deviation (SD), chi-square test, and *t* test. To test the equivalence between the two local anesthetic agents, on the basis of success rates of articaine and lidocaine from previous literature, the margin of equivalence ($\pm\delta$) was adjusted at 20%.[3,9] The absolute risk difference (ARR) of success rates of the two anesthetic drugs was calculated at 95% confidence interval (95% CI) and 5% cut-off point of the level of significance ($P < .05$). Equivalence was announced when the ARR exited within the margins of equivalence ($\pm\delta = 0.2$). Statistical Package for the Social Sciences (SPSS) version 20 and STATA version 14 have been used for statistical analysis.

3 | RESULTS

3.1 | Baseline characteristics of children, tooth type, and dental procedures

The inter-observer reliability (Cohen's kappa coefficient χ) was high (0.88). The children's baseline characteristics showed no statistically significant difference between the two groups. Age and weight mean values (SD) were close. The mean age was 41.79 ($\pm$2.89) months for the control group and 41.58 ($\pm$2.60) months for the experimental group. The mean weight of children in lidocaine and articaine was 15.46 ($\pm$0.49) and 15.53 ($\pm$0.58) repectively. In the two groups, the second primary molar proportion had a higher proportion than first primary molars (Table 1).

3.2 | Vital signs assessments

With reference to hemodynamics, there were no statistically significant differences between the two anesthetic drugs in systolic/diastolic blood pressure, heart rate, or respiratory rate at the selected points for measurements (Table 2).

TABLE 1 Baseline characteristics of the children (n = 184)

Predictors	Lidocaine group	Articaine group	*P*-value*
Gender N(%)			
Boys	42 (45.7)	40 (43.5)	.771
Girls	50 (54.3)	52 (56.5)	
Age in months			
Mean(SD)	41.79 (2.89)	41.58 (2.60)	.962
Tooth N (%)			
First primary molars	36 (39.1)	26 (28.3)	.122
Second primary molars	56 (60.9)	66 (71.7)	
Weight in kilograms			
Mean(SD)	15.46 (0.49)	15.53 (0.58)	.930

*Chi-square test, level of significance $P < .05$.

3.3 | Treatment assessment

3.3.1 | Face, legs, activity, cry, and consolability scale FLACC pain scale evaluation

During local anesthetic injection and treatment, the FLACC pain scale scores showed no statistically significant difference between the control and test groups ($P > .05$). The ARR between the two groups during drug delivery was −0.011 which lies within the equivalent range. Throughout the treatment procedures, the ARR between the test group and the control group was 0.120 (95% CI: −0.003; 0.243). The maximum limit of 95% CI surpassed the margin of equivalence, showing that both local anesthetic agents were not equivalent (Table 3).

3.4 | Frankl's Behavior Rating Scale (FBRS) evaluation

The success rate of articaine during injection and throughout pulpotomy was 81.5% and 87%, respectively. Although the success rate in the lidocaine group was 79.3% at local anesthetic administration and 78.3% during the treatment, absolute risk difference between articaine and lidocaine groups during local anesthetic administration and treatment procedures was 0.022 (95% CI −0.093; 0.136) and 0.087 (−0.023; 0.196), respectively. Both 95% CI limits were within the margin of equivalence boundaries ($\pm\delta = 0.2$) suggesting that the two anesthetic drugs were equivalent.

3.5 | Post-operative complications

Post-operative adverse effects in terms of signs, symptoms, or the need for systemic analgesics have shown no statistically significant difference between the two anesthetic agents. Pain in the lidocaine group and soft tissue injuries in the articaine group were the common complaints (7.6%). Other post-operative adverse reactions were illustrated in Table 4.

4 | DISCUSSION

One of the crucial aspects of behavior management in the dental office is pain hindering.[14] Most dental procedures relay on local anesthesia for pain control. However, Local anesthetic injection, represents the major source of anxiety stimulation especially in pediatric patients.[15] Despite the wide use of articaine in pediatric dentistry because of its proved effectiveness and safety, articaine application in children below the age of four years is still argumentative. Concerning the use of articaine in very young children, the available data are still very deficient.[5,7] Therefore, the current prospective equivalent trial has been conducted to examine the safety and effectiveness of articaine in pulpotomy procedures in children aged 3- to 4-year-old. The scientific background of this study based on the results of a retrospective study records conducted on 211 pediatric children under the age of four from two pediatric dental offices in Canada. Children have been assigned into two groups, the first group treated under sedation with the use of articaine local anesthesia and in the second group children have received articaine local anesthesia solely. The findings in both groups revealed no systemic adverse reactions.[16] Another article has been conducted to test the effectiveness of infiltration anesthesia using 4% articaine in comparison with mepivacaine hydrochloride 2%, prilocaine hydrochloride for cavity preparation and rubber dam application among 66 young children aged between 42- and 72- month-old.[17]

TABLE 2 Vital signs of children in lidocaine and articaine groups at three different occasions (the first before injection, the second was 5 min following the injection, and the third occasion was immediately after finishing the pulpotomy procedures)

Predictors	Lidocaine group	Articaine group	*P*-value*
Systolic blood pressure Mean (±SD)			
First occasion	98.23 (7.63)	100.23 (8.10)	.089
Second occasion	101.35 (7.65)	103.30 (7.62)	.321
Third occasion	102.78 (7.11)	104.31 (7.95)	.171
Diastolic blood pressure Mean (±SD)			
First occasion	66.54 (5.62)	65.45 (4.36)	.143
Second occasion	68.25 (6.03)	67.70 (5.84)	.350
Third occasion	69.79 (5.44)	69.25 (6.22)	.532
Heart rate Mean (±SD)			
First occasion	98.26 (12.61)	97.65 (14.21)	.759
Second occasion	101.22 (13.11)	100.58 (13.55)	.745
Third occasion	101.65 (14.55)	103.99 (13.80)	.285
Respiratory rate Mean (±SD)			
First occasion	22.12 (5.29)	21.94 (4.88)	.811
Second occasion	24.80 (5.82)	23.87 (4.57)	.266
Third occasion	25.23 (4.96)	24.01 (4.63)	.086

*t Test. Level of significance $P < .05$.

TABLE 3 Success and failure rates of lidocaine and articaine at administration and during pulpotomy

Predictors	Lidocaine N (%)	Articaine N (%)	Absolute difference (95% CI)	*P*-value
FLACC				
1. At injection				
No/mild pain	71 (77.2)	70 (76.1)	−0.011 (−0.133; 0.111)	.862
Moderate/severe pain	21 (22.8)	22 (23.9)		
2. At treatment				
No/ mild pain	64 (69.6)	75 (79.3)	0.120 (−0.003; 0.243)	.059
Moderate/severe pain	28 (30.4)	17 (20.7)		
FBRS				
1. At injection				
Positive	73 (79.3)	75 (81.5)	0.022 (−0.093; 0.136)	.710
Negative	19 (20.7)	17 (18.5)		
2. At treatment				
Positive	72 (78.3)	80 (87.0)	0.087 (−0.023; 0.196)	.119
Negative	20 (21.7)	12 (13.0)		

Abbreviations: FLACC: Face, Legs, Activity, Cry, and Consolability scale; Frankl's Behavior Rating Scale.
Level of significance $P < .05$.

For standardizations, only one painful procedure (ie, pulpotomy of the mandibular primary molars) using infiltration anesthesia has been adopted to perform this study. Although the self-reported subjective scales are the benchmark of pain assessment such as the Visual Analogue Scale (VAS), these scales are usually used at age five or older to ensure the

TABLE 4 Post-operative side effects of lidocaine and articaine

Predictors	Lidocaine N (%)	Articaine N (%)	Absolute difference (95% CI)	*P*-value
PPPM N(%)				
Absent	85 (92.4)	88 (95.7)	0.033 (−0.036;0.101)	.351
Present	7 (7.6)	4 (4.3)		
Post-operative soft tissue injury N (%)				
No	90 (97.8)	85 (92.4)	−0.054 (−0. 116;0.007)	.088
Yes	2 (2.2)	7 (7.6)		
Post-operative analgesic N (%)				
No	87 (94.6)	85 (92.4)	−0.022 (−0.093;0.050)	.550
Yes	5 (5.4)	7 (7.6)		

Abbreviation: PPPM, Parents' post-operative pain measure.

Level of significance $P < .05$.

development of children's cognitive ability for discrimination between different pain intensity scales.[18] For that reason, the present trial depended on an objective measure to assess pain at injection and during treatment. FLACC pain scale has been nominated to fulfill such task for several rationales including the following: (a) suitable objective tool for the age group from two months up to seven-year-old, (b) improved to have excellent reliability and validity,[11] and (c) has appropriate psychometric properties.[19] To evaluate the anxiety in dental sitting, FBRS has been applied in the present trial because of its simplicity, higher reliability, and its immense use of literature.[20,21]

A direct comparison between the findings of previously published literature was an intractable issue for a group of considerations. For instance, (a) the limited number of investigations concerned with age below of four years, (b) the diversity in study design, sample size, and inclusion specifications,[22] and finally (c) the use of variable tools for pain assessment. Nevertheless, it might be beneficial to highlight some of the previous literatures' outcomes. Concerning articaine efficacy, most published articles among pediatric patients pointed out that articaine infiltration showed comparable or higher results over lidocaine, which was in line with the findings of this study. For instance, a former trial has reported a 71% successful buccal infiltration anesthesia of articaine versus 64% for lignocaine among 56 children with an average age of 12.9 years.[9] Another prospective random trial was conducted on 62 children aged from 5 to 13 years old recorded that no difference in pain using Wong-Baker FACES pain rating scale between 2% lidocaine with 1:100 000 epinephrine and articaine 4% with 1:200 000 epinephrine.[23] Furthermore, an equivalent randomized controlled trial reported that the success rate of 4% articaine mandibular buccal infiltration was 73.5% using Visual Analogue Scale (VAS) and 79.6% for lidocaine group using the same subjective assessment tool.[3]

Articaine and lidocaine were equivalent during anesthetic injection. While during treatment, the two anesthetic drugs were not equivalent with little number of cases expressed pain in the articaine group in comparison with those received lidocaine anesthetic agent. These findings were opposite to Alzahrani et al, who reported non-equivalence while the anesthetic drug was administrated via buccal infiltration and inferior alveolar nerve block. On the other hand, equivalence has been detected during treatment procedures.[3] Pain severity associated with inferior alveolar nerve block was higher compared to infiltration injection.[24,25] Another article concluded that the efficacy of lidocaine and articaine was similar during buccal infiltration and inferior alveolar nerve block of 62 children with an age group ranged from 5 to 13 years.[23] With respect to vital signs, this study displayed that there was no statistically significant difference between articaine and lidocaine. These findings were in line with the finding of Odabaş,et al who concluded that blood pressure, heart rate, or oxygen saturation were within the normal range immediately after maxillary injection and post-intervention with articaine 4% with 1:200,000 epinephrine.[26] In addition, Mitta et al reported no statistically significant difference in the hemodynamic records when compared the efficacy of lidocaine to articaine during extraction of maxillary primary molars, and these observations were suitable with the findings of this study.[27]

Regarding the post-operative negative reactions, no significant differences between the articaine and lidocaine groups have been identified. Post-operative pain and analgesics were likely attributed to the self-injurious lip/buccal mucosa or the pulpotomy procedure itself and not be connected to the type of local anesthetic agent. Previous literature studied the

post-operative reactions after articaine injection for 50 children between 4 and 13 years old, only one case suffered from accidental lip-biting which less than recorded in this study.[4] This might be due to the younger age of children recruited in this study.

The current trial has several merits for instance; (a) the adequate number of participants, which ensured sample representativeness, (b) the dependence on objective tools with high reliability and validity for pain assessment, (c) the inter-observer reliability was high, and finally (d) the rigorous actions have been taken to avoid any bias such as double-blinding and assessment unprejudiced candidates. The main limitation in this study was the lack of assessment of the pharmacokinetics of the articaine, furthermore the short follow-up period (24 hours). 24 hours, however, was an enough time to address delayed complications after the treatment session, to determine whether any adverse reactions occurred[28] and also, the onset of classic presentation of local anesthetic systemic toxicity (prodromes, central nervous system, and cardiovascular system syndromes) is <5 minutes.[29] All participants' parents/caregivers had the phone number of the chief operator for emergency and/or any inquiry.

5 | CONCLUSIONS

In sum, the findings of this study supported the secure use of articaine hydrochloride 4% with epinephrine 1:100 000 for treatment of children between the age of 3 and below 4 years old. Its safety was comparable to lidocaine hydrochloride 2% and epinephrine 1:100 000.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

EAA conceived the ideas; analyzed the data; and led the writing.

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