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Evaluation of intraosseous computerized injection system (QuickSleeper™) versus conventional infiltration anaesthesia in paediatric oral healthcare: a multicenter, single-blind, combined split-mouth and parallel-arm randomized controlled trial

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Acknowledgments

Conflict of Interest

Author contributions

V.S.F., F.C and M.M.B conceived the ideas; V.S.F. collected the data; V.S.F and J.L.S. analyzed the data; and V.S.F., F.C., M.M.B. and J.L.S. all contributed to the writing.

Summary

Background Conventional infiltration anaesthesia (CIA) is the most frequently used in paediatric oral healthcare. However, other techniques are available, such as intraosseous anaesthesia (IOA), that can beneficiate from newly developed technologies. **Aim** To compare the pain caused by CIA and IOA delivered by the computerized system (QuickSleeper™) in children. **Design** We used an innovative design consisting in simultaneously conducting a multicenter split-mouth and parallel-arm randomized controlled trial (RCT) to allow for increased power. The primary outcome was pain reported by the patient on a visual analogue scale (0-10 cm) concerning the insertion of the needle and injection. **Results** A total of 30 children were included in the split-mouth RCT and 128 in the parallel-arm RCT. We combined treatment effect estimates by using an inverse-variance weighting

meta-analysis approach. Pain scores were significantly decreased with IOA vs CIA (mean difference -0.69 cm, 95% confidence intervals -1.13 to -0.25 cm). For each patient enrolled in the split-mouth RCT, about 5 were enrolled in the parallel-arm RCT, which allowed for not losing any eligible patients. **Conclusion** Pain during the insertion of the needle and injection was less with IOA versus CIA in children. The design of this study allowed for increasing statistical power and using all generated evidence. (ClinicalTrials.gov NCT02084433)

Introduction

Local anaesthesia is frequently indicated in paediatric oral healthcare [1]. Two types of anaesthesia exist: conventional intra-mucosal infiltration anaesthesia (CIA), frequently used by practitioners, and intraosseous anaesthesia (IOA), which delivers the local anesthetic within the spongy bone adjacent to the tooth to anesthetize. Needle- and injection-related fear are common sources of dental anxiety in children in case of CIA. Indeed, the needle is not only visible, but also injecting too quickly in the mucosa can lead to pain or discomfort. With IOA, the fear of the needle would be decreased because the pen grip is very close to the needle. Also, pain during injection would be decreased because IOA can be delivered by a computerized system (QuickSleeper™ system), which delivers local anaesthesia at a constant rate and pressure. Indeed, some authors showed that 83,9% of 50 children felt no pain or only mild discomfort with QuickSleeper™ system (scores 0 to 2 on the visual analogue scale [VAS]) [2], and that 69,7% of 30 patients preferred IOA compared to CIA [3]. To our best knowledge, IOA studies of pain felt by children have been only observational or non-

randomized comparative studies. Moreover, a recent systematic review and Evidence-Based Clinical Practice Guidelines showed insufficient evidence supporting the injection technique as superior to others and concluded that more rigorous and high-quality studies are needed [1, 4].

The randomized controlled trial (RCT) is the gold standard for evaluating the effectiveness of interventions [5]. The design most frequently used is the parallel-arm RCT [6], but the split-mouth RCT is also commonly used in dental clinical trials [7]. Because every patient receives each intervention, the split-mouth design allows for removing a lot of inter-individual variability from the estimates of the treatment effect and increasing the statistical power. Nevertheless, recruitment in a split-mouth RCT requires patients to have symmetrical disorders (e.g., carious lesions on at least two first permanent molars) to allow random allocation of the interventions [8]. Conducting simultaneously a parallel-arm RCT and a split-mouth RCT would allow enrolling all patients and maximizing power.

In this study, we aimed to compare pain during the insertion of the needle and injection with IOA against CIA for treating first permanent molars with deep carious lesions or moderate to high severity (MIH) lesions in children and adolescents. Secondary objectives were to compare the two anaesthesia types in terms of pain latency, the need for additional anaesthesia and pain felt during the treatment. We hypothesized that intraosseous anaesthesia delivered by the QuickSleeper™ may reduce pain more than anaesthesia delivered by the conventional infiltration technique. We used an innovative approach, by simultaneously conducted a parallel-arm RCT and a split-mouth RCT.

Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol of the trial was approved by the local research ethics committee (no. 13466) and the national authorities regulating confidentiality (no. 14.217). We communicated any important protocol modifications to the ethics committee. The protocol was prospectively registered in ClinicalTrials.gov (NCT02084433) and was published [9]. The study was conducted in paediatric dentistry departments of three French universities (Nice, Paris and Rennes). This manuscript was written following the guidelines of CONSORT (Consolidated Standards of Reporting Trials) (Supplementary Table S1).

Study design

The study design consisted in simultaneously conducting a multicentric split-mouth RCT and a parallel-arm RCT. For the split-mouth RCT, two permanent first molars belonging to the same dental arch were included per patient, and for the parallel-arm RCT, only one permanent first molar was included per patient.

Inclusion criteria

The following inclusion criteria were established: patients between 7-15 years of age; mentally and generally disease-free; cooperative (score 0 to 2 on the Venham distress scale) [10]; with one (for the parallel-arm trial) or at least two (for the split-mouth trial) first permanent molars with deep caries (i.e., dentinal lesion involving more than 50% of the entire dentin thickness evaluated by radiography) or MIH lesion, with preserved pulp vitality as determined by clinical and radiographic

observations (treatments could be conservative or endodontic limited to pulpotomy); without use of analgesic drug for 48 hr before randomization. The non-inclusion criteria were periodontal alterations (periodontal pockets or dental mobility) or radiological defects (bone loss, furcation or periapical radiolucency). The exclusion criteria were per-operative clinical and radiographic observations of irreversible radicular pulpal inflammation or pulpal necrosis. All patients and parents received oral and written information about the study, which was carried out according to the Declaration of Helsinki, following approval of the local research ethics committee. Oral agreement was obtained from all individual patients and parents included in the study.

Interventions

Before both types of anaesthesia, we applied the topical anaesthesia Xylocaïne® visqueuse 2% (AstraZeneca, Rueil Malmaison, France) for 1 to 2 min on previously dried mucosa. For CIA, we used a 16-mm-long needle for para-apical maxillary anaesthesia, and a 35-mm-long needle for locoregional mandibular anaesthesia. IOA was carried out using the QuickSleeper™ system (Dental Hi Tec, Cholet, France) following the three-step procedure described by the manufacturer [11]. For IOA, we used a 30-gauge, 9 or 16-mm-long needle. The anesthetic solution used in both techniques was 4% articaine with 1: 200,000 adrenalin. Anaesthesia in all cases was carried out by a single practitioner (one of the four investigators) in each of the three centers.

Outcomes

All outcomes were recorded on the day of the intervention. The primary outcome measure was pain felt during the insertion of the needle and injection of the anesthetic, assessed at the end of the anaesthesia, with a VAS ranging from 0 cm (no pain) to 10 cm (very much pain) [12]. We evaluated three secondary outcomes: latency, the need for additional anaesthesia during the treatment and

pain felt during the treatment. The latency was assessed examining the sensitivity of the vestibular sulcus for CIA or lingual sulcus for IOA by using a probe at the end of the injection (an exam was conducted every minute until the sulcus was insensitive to the probe). Patient assessed the pain felt during the treatment with the VAS at the end of the dental treatment session.

Sample size

For the split-mouth RCT, we estimated the sample size for the primary outcome by taking into account the correlation induced by paired nature of the data. In a previous trial, the corresponding standard deviation in the VAS score was estimated at 1.2 [2]. Assuming that the standard deviation is equal in the two randomization groups and that the correlation between the pain scores for the same subject in the first and second treatment is 0.6, the difference in VAS scores would have a standard deviation of 1.10. With a type I error risk of 0.05, we needed 30 patients to guarantee 80% power to detect a minimum true difference of 0.6 points in mean pain experienced during IOA and CIA. For the parallel-arm RCT, under the same assumptions described previously, we estimated the sample size at 128.

Assignment of interventions

For anaesthesia allocation, we used a computer-generated, permuted-block randomization sequence, with two block sizes randomly varied. The random sequences were stratified by center for both RCTs and by dental arch for the parallel-arm RCT. The practitioner obtained each randomization allocation via a centralized, secure web-based interface (RandoWeb). For the split-mouth RCT, one permanent first molar was randomly allocated to one of the techniques (e.g. IOA) and the other permanent first molar belonging to the same dental arch in the same child was allocated to the other technique (e.g. CIA). A 7- to 21-day interval was established between the two procedures. For

the parallel-arm RCT, one patient with one permanent molar first was randomly allocated to one of the techniques (IOA or CIA). Patients — evaluators — were unaware of which of the two techniques was used, whereas practitioners were not.

Data collection and management

First, data were collected by investigators by using a paper form. The form was pilot-tested by the coordinating center. Second, data were entered electronically by the coordinating center. Participant files were stored in a secure and accessible place and manner. A Data Monitoring Committee was not needed because of the short duration of patient participation and known minimal risks. Adverse events were collected and reported.

Statistical methods

The unit of analysis was the tooth for the split-mouth RCT, and the patient for the parallel-arm RCT. For pain and latency, we reported the mean differences between groups and the associated 95% confidence intervals (95% CI). For the need of additional anaesthesia, we reported odds ratio between groups and the associated 95% CI. For the split-mouth RCT, the results were analyzed by Student's *t* test for paired samples (because of the paired nature of data). We also compared intervention effect estimates between the split-mouth and parallel-arm RCTs by z ratio tests (the difference in effect estimates between the two RCTs divided by its standard error). Because the effect estimates from the two RCTs were consistent, we combined them by using an inverse-variance weighting meta-analysis approach: the combined effect estimate is a weighted average of the two effect estimates, each effect estimate being weighted by the inverse of its variance [8, 13, 14]. We also performed a subgroup analysis by arch (the same statistical methods were applied). For the primary outcome, we did an exploratory post hoc subgroup analysis by type of disorders (deep

caries, MIH, or both deep caries and MIH) (the same statistical methods were applied). Finally, we compared the pain felt by boys versus girls and assessed the role of age using a post hoc multivariate analysis. All the analyses followed the intention-to-treat principle [15]. We did not plan any interim analysis and early stopping.

Results

Patient recruitment started in January 2015 and stopped in February 2017. The flow of participants in the trial is in Figure 1. For each patient enrolled in the split-mouth RCT, about 5 were enrolled in the parallel-arm RCT, which allowed for not losing any eligible patients. In total, 158 children aged 7 to 15 years for whom parental consent had been obtained were deemed eligible for inclusion. Of these, 30 (mean age 9.0 years, SD 2.3) participated to the split-mouth RCT and 128 (mean age 10.4 years, SD 2.5) to the parallel-arm RCT and randomly allocated to IOA (n = 63) or CIA (n = 65). On average, one cartridge containing the anesthetic solution was injected per anaesthesia. Finally, no harm was detected. Patient characteristics are in Table 1.

Split mouth RCT

The main results are shown in Table 2.

Primary outcome

The mean VAS scores were 0.73 ± 1.31 cm for the IOA and 1.43 ± 1.45 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.70 ± 0.36 cm (-1.44 to 0.04), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, but this difference was not statistically significant (p = 0.06).

Secondary outcomes

Latency

The mean latency was 1.07 ± 0.25 min for the IOA and 2.83 ± 2.64 min for the CIA groups. The mean (95% CI) for the difference in paired proportions was -1.77 ± 0.51 (-2.77 to -0.77), indicating that latency was statistically decreased with IOA compared to CIA with a statistically significant difference (p = 0.001).

Need for additional anaesthesia during the treatment

Four patients needed additional anaesthesia: two in IOA group (one additional intrapulpal anaesthesia and one additional intraligamentary anaesthesia in mandibular arch), and two patients in CIA group (one additional IOA on maxillary arch and one para-apical anaesthesia in mandibular arch). There was no statistically significant difference between the two groups (odd ratio (OR) = 1.00, 95%CI 0.15 to 6.74, p = 1.00).

Pain felt during the treatment

The mean VAS scores were 1.07 ± 1.76 cm for the IOA and 0.53 ± 0.82 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was 0.53 ± 0.37 cm (-0.19 to 1.25), indicating that patients felt less pain during treatment with CIA compared to IOA, but this difference was not statistically significant (p = 0.14).

Subgroup analysis

Results are summarized in Supplementary Table S2.

Primary outcome

On the maxillary arch, the mean VAS scores were 0.53 ± 1.19 cm for the IOA and 1.33 ± 1.54 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.81 ± 0.51 cm (-1.89 to 0.29), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, but this difference was not statistically significant (p = 0.14).

On the mandibular arch, the mean VAS scores were 0.93 ± 1.44 cm for the IOA and 1.53 ± 1.41 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.60 ± 0.53 cm (-1.74 to 0.54), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, but this difference was not statistically significant (p = 0.28).

Secondary outcomes

On the maxillary arch, the mean latency was 1.07 ± 0.26 min for the IOA and 2.33 ± 1.05 min for the CIA groups. The mean (95% CI) for the difference in paired proportions was -1.27± 0.29 (-1.84 to -0.69), indicating that latency was statistically decreased with IOA compared to CIA with a statistically significant difference (p = 0.0003). On the mandibular arch, the mean latency was 1.07 ± 0.26 min for the IOA and 3.33 ± 3.58 min for the CIA groups. The mean (95% CI) for the difference in paired proportions was -2.27 ± 1.03 (-4.28 to -0.25), indicating that latency was statistically decreased with IOA compared to CIA with a statistically significant difference (p = 0.03).

On the maxillary arch, the mean VAS scores were 0.93 ± 2.02 cm for the IOA and 0.20 ± 0.56 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was 0.73 ± 0.56 cm (-0.36 to 1.83), indicating that patients felt less pain during the treatment with CIA compared to IOA, but this difference was not statistically significant (p = 0.17). On the mandibular arch, the mean VAS

scores were 1.20 ± 1.52 cm for the IOA and 0.87 ± 0.92 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was 0.33 ± 0.54 cm (-0.73 to 1.39), indicating that patients felt less pain during the treatment with CIA compared to IOA, but this difference was not statistically significant (p = 0.51).

Post hoc subgroup analysis for the primary outcome

Results are summarized in Supplementary Table S5.

For the subgroup "deep caries", the mean VAS scores were 1.43 ± 1.90 cm for the IOA and 1.43 ± 1.51 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was 0 cm (-2.14 to 2.14, p=1).

For the subgroup "MIH", the mean VAS scores were 1 ± 1.41 cm for the IOA and 1.41 ± 1.58 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.33 cm (-2.09 to 1.42), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, but this difference was not statistically significant (p = 0.67).

For the subgroup "both deep caries and MIH", the mean VAS scores were 0.21 ± 0.58 cm for the IOA and 1.50 ± 1.45 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -1.29 cm (-2.18 to -0.40), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, with a statistically significant difference (p = 0.008).

Parallel-arm RCT

The main results are shown in Table 2.

Primary outcome

The mean VAS scores were 1.17 ± 1.40 cm for the IOA and 1.86± 1.81 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.69 ± 0.29 cm (-1.25 to -0.12), indicating that patients felt statistically less pain on the insertion of the needle and the injection with IOA compared to CIA statistically significant, with a statistically significant difference (p = 0.02).

Secondary outcomes

Latency

The mean latency was 1.63 ± 0.97 min for the IOA and 3.08± 2.11 min for the CIA groups. The mean (95% CI) for the difference in paired proportions was -1.44 ± 0.29 (-2.02 to -0.87), indicating that latency was statistically decreased with IOA compared to CIA with a statistically significant difference (p = $2.87.10^{-6}$).

Need for additional anaesthesia during the treatment

Eighteen patients needed additional anaesthesia: seven in IOA group (two additional IOA, two additional para-apical anaesthesia, two additional intraligamentary anaesthesia and one additional intrapulpal anaesthesia), and eleven patients in CIA group (four additional IOA, two additional para-apical anaesthesia, and five additional intraligamentary anaesthesia). There was no statistically significant difference between the two groups (odd ratio (OR) = 0.61, 95%CI 0.22 to 1.70, p = 0.34).

Pain felt during the treatment

The mean VAS scores were 0.90 ± 1.51 cm for the IOA and 0.88 ± 1.64 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was 0.03 ± 0.28 cm (-0.52 to 0.58), indicating that patients felt less pain during treatment with CIA compared to IOA, but this difference was not statistically significant (p = 0.92).

Subgroup analysis

Results are summarized in Supplementary Table S3.

Primary outcome

On the maxillary arch, the mean VAS scores were 1.25 ± 1.40 cm for the IOA and 1.64 ± 1.65 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.40 ± 0.41 cm (-1.21 to 0.42), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, but this difference was not statistically significant (p = 0.34).

On the mandibular arch, the mean VAS scores were 1.11 ± 1.41 cm for the IOA and 2.06 ± 1.91 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.94 ± 0.40 cm (-1.75 to -0.14), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, with a statistically significant difference (p = 0.02).

Secondary outcomes

On the maxillary arch, the mean latency was 1.57 ± 0.92 min for the IOA and 2.81 ± 1.80 min for the CIA groups. The mean (95% CI) for the difference in paired proportions was -1.24 ± 0.38 (-1.97 to -

0.50), indicating that latency was statistically decreased with IOA compared to CIA with a statistically significant difference (p = 0.002). On the mandibular arch, the mean latency was 1.69 ± 1.02 min for the IOA and 3.32 ± 2.36 min for the CIA groups. The mean (95% CI) for the difference in paired proportions was -1.64 ± 0.45 (-2.52 to -0.75), indicating that latency was statistically decreased with IOA compared to CIA with a statistically significant difference (p = 0.0005).

On the maxillary arch, five patients needed additional anaesthesia: one in IOA group and four patients in CIA group. There was no statistically significant difference between the two groups (mean OR = 0.61, 95% CI 0.22 to 1.70, p = 0.20). On the mandibular arch, 13 patients needed additional anaesthesia: six in IOA group and seven patients in CIA group. There was no statistically significant difference between the two groups (mean OR = 0.61, 95% CI 0.22 to 1.70, p = 0.72).

On the maxillary arch, the mean VAS scores were 1.18 ± 1.49 cm for the IOA and 0.87 ± 1.98 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was 0.31 ± 0.47cm (-0.61 to 1.23), indicating that patients felt less pain during the treatment with CIA compared to IOA, but this difference was not statistically significant (p = 0.51). On the mandibular arch, the mean VAS scores were 0.69 ± 1.51 cm for the IOA and 0.88 ± 1.30 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.20 ± 0.35 cm (-0.87 to 0.48), indicating that patients felt less pain during the treatment with IOA compared to CIA, but this difference was not statistically significant (p = 0.56).

Post hoc subgroup analysis for the primary outcome

Results are summarized in Supplementary Table S5.

For the subgroup "deep caries", the mean VAS scores were 1.31 ± 1.57 cm for the IOA and 1.79 ± 1.83 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.47 cm (-1.24 to 0.29), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, but this difference was not statistically significant (p = 0.22).

For the subgroup "MIH", the mean VAS scores were 0.86 ± 0.90 cm for the IOA and 2.80 ± 1.93 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -1.94 cm (-3.62 to -0.26), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, with a statistically significant difference (p = 0.03).

For the subgroup "both deep caries and MIH", the mean VAS scores were 0.93 ± 1.03 cm for the IOA and 1.47 ± 1.59 cm for the CIA groups. The mean (95% CI) for the difference in paired proportions was -0.54 cm (-1.52 to 0.44), indicating that patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, with a statistically significant difference (p = 0.04).

Combined treatment effect from split-mouth and parallel-arm RCTs

For all outcomes, findings from the two types of trials were consistent: for pain felt during insertion of the needle and injection, p value was equal to 0.98; for latency, p value was equal to 0.58; for need for additional anaesthesia, p value was equal to 0.66; and for pain felt during treatment, p value was equal to 0.27. Consequently, for all outcomes, findings could be combined by using an inverse-variance weighting meta-analysis approach (*see* forest plots in Figure 2). The main results are shown in Table 3.

Primary outcome

Based on VAS score, patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, with a statistically significant mean difference of -0.69 (95% CI 1.13 to -0.25, p = 0.002) with a reduction of half of one standard deviation.

Secondary outcomes

For secondary outcomes, latency was statistically decreased with IOA compared to CIA (mean difference -1.52, 95% CI -2.02 to -1.03, p = $1.99.10^{-9}$). We found no statistically significant differences for need for additional anaesthesia (mean OR 0.68, 95% CI 0.28 to 1.68, p = 0.41) and pain felt during treatment (mean difference 0.22, 95% CI -0.22 to 0.65, p = 0.33).

Subgroup analysis

Results are summarized in Supplementary Table S4.

For all outcomes, findings from the two types of trials were consistent. On the maxillary arch, for pain felt during insertion of the needle and injection, p value was equal to 0.54; for latency, p value was equal to 0.95; and for need for additional anaesthesia, p value was equal to 0.56. On the mandibular arch, for pain felt during insertion of the needle and injection, p value was equal to 0.61; for latency, p value was equal to 0.58; and for need for additional anaesthesia, p value was equal to 0.41. Consequently, for all outcomes, findings could be combined by using an inverse-variance weighting meta-analysis approach (*see* forest plots in Supplementary Figure S1).

Primary outcome

On the maxillary arch, based on VAS score, patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, but the mean difference was not statistically significant (-0.55, 95% CI -1.18 to 0.07, p = 0.08). On the mandibular arch, based on VAS score, patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, with a statistically significant mean difference (-0.82, 95% CI -1.45 to -0.19, p = 0.01).

Secondary outcomes

On the maxillary arch, the latency was statistically decreased with IOA compared to CIA with a statistically significant difference (mean difference -1.25, 95% CI -1.71 to -0.80, p = $5.32.10^{-8}$). On the mandibular arch, the latency was statistically decreased with IOA compared to CIA with a statistically significant difference (mean difference -1.74, 95% CI -2.55 to -0.93, p = $2.60.10^{-5}$).

On the maxillary arch, patients felt less pain during the treatment with CIA compared to IOA, but this difference was not statistically significant (mean difference 0.48, 95% CI -0.22 to 1.19, p = 0.51). On the mandibular arch, patients felt less pain during the treatment with IOA compared to CIA, but this difference was not statistically significant (mean difference -0.04, 95% CI -0.61 to 0.53, p = 0.88).

Post hoc subgroup analysis for the primary outcome

Results are summarized in Supplementary Table S5.

Findings from the two types of trials were consistent: for the subgroup "deep caries", p value was equal to 0.62; for the subgroup "MIH", p value was equal to 0.14; for the subgroup "both deep caries

and MIH", p value was equal to 0.24. Consequently, findings could be combined by using an inverse-variance weighting meta-analysis approach.

For the subgroup "deep caries", patients felt less pain during the treatment with IOA compared to CIA, but this difference was not statistically significant (mean difference -0.40, 95% CI -1.08 to 0.29, p = 0.26). For the subgroup "MIH", patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, with a statistically significant mean difference (-1.11, 95% CI -2.18 to -0.40, p = 0.04). For the subgroup "both deep caries and MIH", patients felt less pain on the insertion of the needle and the injection with IOA compared to CIA, with a statistically significant mean difference (-0.97, 95% CI -1.58 to -0.36, p = 0.002).

Post hoc multivariate analysis

After combining individual data from both studies, we assessed the VAS score at beginning with a negative binomial model controlled on age, gender, anesthesia type, tooth treated (upper or lower molar), study design (parallel-arm RCT versus split-mouth RCT) and inclusion criteria (MIH/deep caries). In this post hoc multivariate analysis, CIA was significantly associated with pain on the insertion of the needle and the injection (RR 1.78, 95% CI 1.24 to 2.56, p = 0.002), which supports our main results. In particular, we did not find a difference between the pain felt by boys versus girls (RR 1.06, 95% CI 0.74 to 1.52, p = 0.734), and age was not a factor (RR 1.09, 95% CI 1.00 to 1.18, p = 0.053).

Discussion

To our best knowledge, this well-powered, multicenter RCT is the first to include a split-mouth RCT and a parallel-arm RCT to assess how children and adolescents felt pain during IOA compared to CIA. Our results showed a statistically significant difference in favor of IOA, with a reduction of half of one standard deviation.

Conducting simultaneously both trials allowed for enrolling all eligible patients. In fact, patients who did have symmetrical disorder (ie deep carious lesions or MIH or both on two first permanent molars) were included in the split-mouth RCT, and patients who did have asymmetrical disorder (ie deep carious lesions or MIH or both on one first permanent molar) were included in the parallel-arm RCT. Our results showed that for each patient enrolled in the split-mouth RCT, about 5 were enrolled in the parallel-arm RCT. Although it may seem surprising, this result highlights one of the strengths of our study, that is the use of combined split-mouth and parallel-arm RCT allowed for not losing any eligible patients. Indeed, patients who did not have symmetrical disorders (therefore were not eligible for the split-mouth RCT) were included in the parallel-arm RCT. Because we enrolled patients with both symmetrical disorder (deep carious lesions or MIH or both on two first permanent molars) or asymmetrical disorder (deep carious lesions or MIH or both on one first permanent molar), our findings are generalizable to any type of patients. Moreover, conducting simultaneously both trials offered advantages in terms of statistical power and applicability of findings. Indeed, the two types of trials provided similar results, allowing for pooling the findings of both trials by using an inverse-variance weighting meta-analysis approach: the combined effect estimate is a weighted average of the two effect estimates, each effect estimate being weighted by the inverse of its variance. This indicates that it is "reproducible" and that the superiority of the IOA method is reliable and valid. As the sample size increases, the Type I error risk (false positive) is bounded by the pre-specified alpha level (5%), whereas the Type II error risk (false negative) decreases, increasing power. Furthermore,

we solely reported the mean differences between groups and the associated 95% confidence intervals (and not the combined variables for each of the two anaesthesia methods), because estimating the weighted VAS score during anaesthesia across the IOA groups from the split-mouth and the parallel-arm RCTs, and then estimating the weighted VAS score during anaesthesia across the CIA groups from the two RCTs would break randomization and may lead to erroneous results (Simpson's paradox). Instead, we followed the typical meta-analysis process: we first calculated the mean difference for each RCT, then we calculated the combined effect estimate as a weighted average of the treatment effects estimated in the individual RCT.

Previous papers about studies performed in children and adults using computer controlled needle rotation and injection suggested that IOA could be could be selected instead of CIA because the anesthetic agent is injected directly in the cancellous bone close to the tooth needing to be anaesthetized [2, 3, 16-19], even for hot teeth such as MIH teeth [20]. Although the difference in pain scores between IOA and CIA was statistically significant, it corresponded to less than one unit on the VAS, which limits its clinical relevance. This extent of reduction in pain observed statistically with IOA was not considerable clinically. Nevertheless, any benefit in terms of pain is not to be neglected in the interest of the patient, especially when we know that pain due to anaesthesia is a failure factor in health care. Moreover, this advantage is added to the other IOA advantages that have been demonstrated in adults or children when using a computer-controlled pen-shaped plastic-made device compared to injection in soft tissues using metal syringes. Anxiety may be reduced due to a less scary physical appearance of the injector with a physical appearance of plastic needle [21]. The QuickSleeper™ system facilitates injection because the practitioner does not have to stay focused on the amount of pressure applied throughout the injection and does not have to apply force. The pen-shaped device allows better support points close to the injection site and therefore leads to easier and less painful needle penetration. IAO is associated to less soft-tissue anesthetic

effect because the anesthetic solution is directly placed in the cancellous bone adjacent to the tooth programmed for anaesthesia, thereby not affecting the surrounding soft tissues [18] reducing the risk of soft tissue nibbling and therefore of self-biting.

The subgroup analysis by arch suggested that the difference was statistically significant for the mandibular arch only (comparison between IOA and locoregional mandibular anaesthesia). Our results are consistent with those of previous studies, showing that locoregional mandibular anaesthesia performed with a metal syringe yielded significantly more discomfort than local infiltration in children whatever the method or the device used [22-24] possibly leading to a higher risk of children's opposition to a subsequent dental visit [25].

Results of the post hoc multivariate analysis seemed to support our main results. In particular, age would not be a factor, although it seems there would be a possible trend toward significance (RR 1.09, 95%CI 1.00 to 1.18, p = 0.053). It might suggest that older patients would feel more pain on the insertion of the needle and the injection. An explanation might be a previous negative dental experience as a source of dental anxiety, as suggested by some authors [26, 27]. Moreover, we did not find a difference between the pain felt by boys versus girls. Contrary to our results, some studies showed significantly higher dental anxiety in girls as compared to boys [28, 29].

For the secondary outcomes, we found statistically significant evidence in favor of IOA for latency, about 1.5 min. However, we did not assess injection time, which could be longer for IOA because it was delivered by a computerized system at a constant rate and pressure. We found no statistically significant differences for the other secondary outcomes.

Our study has some limitations. First, although we expected that the proportion of different types of disorders (deep caries, MIH, or both deep caries and MIH) would be the same in both RCTs, our results showed that there was more deep caries on the parallel-arm RCT than the split-mouth RCT (p<0.0001), and our design was not performed to detect an interaction on outcome. This difference may not be explainable by chance alone, nor by selection bias. However, some reasons may explain this difference: perhaps it is a pattern that patients who develop bilateral symmetrical caries usually have shallower caries, while those whom caries are not bilateral develop deeper caries; or perhaps bilateral caries develop due to general reasons that make them milder, while unilateral caries have local but severer etiologies. Another reason might be that bilateral caries might be detected sooner (thus bilateral caries might be shallower), because the chance of detecting caries in two teeth is greater than one tooth; unilateral caries would therefore be deeper, remaining hidden for a longer time. Finally, we did not collect information about contralateral tooth for patients included in the parallel-arm RCT. Indeed, patients who did have asymmetrical disorder could have a missing or restored contralateral tooth; if this is a common occurrence, we would expect the parallel-arm RCT to have a higher disease severity due to cross-median similarities. Second, operators could not be blinded to the randomization because of the different devices used for the two anaesthesia techniques. However, children were very likely unaware which of the two techniques was used. Thus, the lack of blinding of the operator probably did not affect the primary outcome (ie, pain felt during the insertion of the needle and injection of the anesthetic). Third, the trial was conducted in three French hospital dental departments specialized in treating children and adolescents, which may affect the generalizability of findings to different settings. However, in general, a child's perception of pain mostly depends on the operator and behavioral management and having three different operators prevented the study from being single-operator-related. Fourth, we did not assess pain based on objective evaluation, with signs and body and face movements, such as the Modified Behavior Pain Scale, Sound Eye Motor scale, Faces Legs Activity Cry and Consolability, or Children's Hospital of Eastern Ontario Pain Scale. Nevertheless, we used VAS to subjectively evaluate

pain for children aged 7 years and older, and VAS has been shown by some authors to be reliable for use by children aged 5 years and older and for other authors, by children aged 7 years and older [30, 31]. Fifth, we did not record heart rate (with a pulse oximeter), a physiological indicator of pain response, before, during and after local anaesthesia. However, some authors showed a significant transient increase in heart rate up to 3 min after IOA with other non-computer-controlled devices, but only with 2% lidocaine or 4% articaine with adrenalin, 1: 100,000, in IOA [32-34]. Two studies performed in adults using the Quick Sleeper™ system showed no heart increase using 4% articaine with adrenalin, 1: 100,000 [35] or a slight increase of short duration using 2% lidocaine with adrenalin 1: 80,000 [17]. In our trial, we used an anesthetic solution of 4% articaine with adrenalin, 1: 200,000, and recent studies have not shown a significant transient increase in heart rate with this combination even with devices without computer control of intraosseous penetration or injection [36, 37]. In addition, our study included only healthy patients, and some authors found that a transient increase in heart rate would not be clinically significant in most healthy patients [34]. Finally, a study suggested that a transient increase in heart rate could be related to the speed of injection [37]. Sixth, we assessed pain on low-anxious children only (score 0 to 2 on the Venham scale). Therefore, our findings cannot be generalised to high-anxious children. However, the post hoc subgroup analysis requested by the reviewer would suggest that patients with MIH would feel less pain on the insertion of the needle and the injection with IOA compared to CIA. As regards a study showing that dental fear and anxiety were more common in children with MIH [38], our post hoc analysis might mean that patients who were more anxious could benefit from use of IOA rather than CIA. Contrary to our results, Versloot et al showed that only low-anxious children seemed to benefit from use of a computerized anaesthesia delivery system in free mucosa rather than the traditional syringe in receiving local anaesthesia, with no differences found in the high-anxious group [39]. Another study confirmed that computer-control injection of anaesthetics in soft tissues was not associated to lower pain scores in anxious children [40]. However, these two studies did not assess intra-osseous anaesthesia.

Conclusion

This study provided new evidence on reduced pain associated with IOA versus CIA in paediatric oral health care. These results can help clinicians in the choice of local anaesthesia technique for helping alleviate patients' anxiety. Although the difference in pain scores between IOA and CIA was statistically significant, it corresponded to less than one unit on the VAS, which limits its clinical relevance. Nevertheless, any benefit in terms of pain is not to be neglected in the interest of the patient, especially when we know that pain due to anaesthesia is a failure factor in health care. Moreover, this advantage is added to the other IOA advantages that have been demonstrated in adults or children: reduced anxiety due to a less scary physical appearance of the needle; the ease in using the QuickSleeper™ system; less soft-tissue anesthetic effect; shorter latency; and efficacy in cases of MIH or severe pulpal inflammation. Finally, this study showed that a novel clinical trial design combining a split-mouth RCT and parallel-arm RCT allowed for increasing statistical power and using all generated evidence.

Why this paper is important for paediatric dentistry

- This study has provided new evidence that pain associated with IOA delivered by the QuickSleeper™ is reduced compared to conventional infiltration in paediatric oral healthcare.

- This advantage is added to the others : reduced anxiety due to a less scary physical appearance of the needle, the ease in using the QuickSleeper™ system, less soft-tissue anesthetic effect, shorter latency, and efficacy in cases of MIH or severe pulpal inflammation.

- The design of this multicenter, well powered study is innovative because it involved a split-mouth RCT and a parallel-arm RCT: patients who did not have symmetrical disorders

(therefore were not eligible for the split-mouth RCT) were included in the parallel-arm RCT. For each patient enrolled in the split-mouth RCT, about 5 were enrolled in the parallel-arm RCT, which allowed for not losing any eligible patients. Therefore, conducting simultaneously both trials offered advantages in terms of statistical power and applicability of findings.

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Table 1. Patient characteristics

Characteristics	Split-mouth RCT			Parallel-arm RCT		
	IOA (n=30)	CIA (n=30)	Total (n=60, N=30)	IOA (n=63)	CIA (n=65)	Total (n=N=128)
Sex: male N (%)			15 (50)	28 (44)	34 (52)	62 (48)
Arch n (%)						
Maxillary			30 (50)	28 (44)	31 (48)	59 (46)
Mandibular			30 (50)	35 (56)	34 (52)	69 (54)
Severity n (%)						
Deep caries	6 (20)	7 (12)	13 (22)	41 (65)	38 (59)	79 (62)
MIH	8 (27)	9 (15)	17 (28)	7 (11)	10 (15)	17 (13)
Both deep caries and MIH	16 (53)	14 (23)	30 (50)	15 (24)	17 (26)	32 (25)
Treatment n (%)						
Conservative treatment	27 (90)	29 (97)	56 (93)	55 (87)	62 (95)	117 (91)
Pulpotomy	3 (10)	1 (3)	4 (6)	8 (13)	3 (5)	11 (9)

RCT: randomized controlled trial; IOA: intraosseous anaesthesia; CIA: conventional infiltration anaesthesia; MIH: molar-incisor hypomineralisation, moderate to high severity lesion; N: number of patients; n: number of teeth

Table 2. Main results for split-mouth RCT and parallel-arm RCT

	Split-mouth RCT			*Parallel-arm RCT*		
	Mean±SD	**Mean difference (95% CI)**	**p value**	**Mean±SD**	**Mean difference (95% CI)**	**p value**
Mean VAS score during anaesthesia, cm	IOA: 0.73 ± 1.31 CIA: 1.43 ± 1.45	-0.70 (-1.44 to 0.04)	0.06	IOA: 1.17 ± 1.40 CIA: 1.86 ± 1.81	-0.69 (-1.25 to -0.12)	0.02
Latency, min	IOA: 1.07 ± 0.25 CIA: 2.83 ± 2.64	-1.77 (-2.77 to -0.77)	0.001	IOA: 1.63 ± 0.97 CIA: 3.08 ± 2.11	-1.44 (-2.02 to -0.87)	<0.0001
Need for additional anaesthesia during treatment	IOA: 2 cases CIA: 2 cases	1.00* (0.15 to 6.74)	1.00	IOA: 7 cases CIA: 11 cases	0.61* (0.22 to 1.70)	0.34
Mean VAS score during treatment, cm	IOA: 1.07 ± 1.76 CIA: 0.53 ± 0.82	0.53 (-0.19 to 1.25)	0.14	IOA: 0.90 ± 1.51 CIA: 0.88 ± 1.64	0.03 (-0.52 to 0.58)	0.92

RCT: randomized controlled trial

IOA: intraosseous anaesthesia

CIA: conventional infiltration anaesthesia

CI: confidence interval

VAS: visual analog scale

* Odds ratio

Table 3. Main results for combined analysis of split-mouth and parallel-arm RCTs

	Mean difference (95% CI)	p value
VAS score during anaesthesia, cm	-0.69 (-1.13 to -0.25)	0.002
Latency, min	-1.52 (-2.02 to -1.03)	<0.0001
Need for additional anaesthesia during treatment	0.68* (0.28 to 1.68)	0.41
VAS score during treatment, cm	0.22 (-0.22 to 0.65)	0.33

In the combined analysis, we combined the two effect estimates of the split-mouth and parallel-arm RCTs by using an inverse-variance weighting meta-analysis approach: for each outcome, the combined effect estimate is a weighted average of the two effect estimates, each effect estimate being weighted by the inverse of its variance

CI: confidence interval

VAS: visual analog scale

*Data are mean differences for IA compared to CIA, except for the need for additional anaesthesia during treatment, the effect measure is the Odds ratio for IA compared with CIA

Figure legends

Fig. 1. Flow of participants in the trial

Fig. 2. Combined treatment effect from split-mouth and parallel-arm

RCTs (forest plots)

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                          ┌─────────────────────┐
                          │   Eligible children │
                          │       N=158         │
                          └─────────────────────┘
                           ╱                    ╲
            ┌─────────────────────┐      ┌─────────────────────┐
            │   Split-mouth RCT   │      │   Parallel-arm RCT  │
            │        N=30         │      │        N=128        │
            └─────────────────────┘      └─────────────────────┘
            ┌─────────────────────┐      ┌─────────────────────┐
            │    Randomization    │      │    Randomization    │
            │        N=30         │      │        N=128        │
            └─────────────────────┘      └─────────────────────┘
             ╱              ╲              ╱              ╲
    ┌──────────────┐ ┌──────────────┐ ┌──────────────┐ ┌──────────────┐
    │ Received IOA │ │ Received CIA │ │ Received IOA │ │ Received CIA │
    │   (n=30)     │ │   (n=30)     │ │   (n=63)     │ │   (n=65)     │
    └──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘
    ┌──────────────┐ ┌──────────────┐ ┌──────────────┐ ┌──────────────┐
    │Lost to       │ │Lost to       │ │Lost to       │ │Lost to       │
    │follow-up     │ │follow-up     │ │follow-up     │ │follow-up     │
    │   (n=0)      │ │   (n=0)      │ │   (n=0)      │ │   (n=0)      │
    └──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘
    ┌──────────────┐ ┌──────────────┐ ┌──────────────┐ ┌──────────────┐
    │  Analysed    │ │  Analysed    │ │  Analysed    │ │  Analysed    │
    │   (n=30)     │ │   (n=30)     │ │   (n=63)     │ │   (n=65)     │
    └──────────────┘ └──────────────┘ └──────────────┘ └──────────────┘
```

1. VAS (end of anesthesia)

Parallel ⊢──▲──┤ -0.69 (-1.25 to -0.12)

Split ⊢───■───┤ -0.70 (-1.44 to 0.04)

Combined ⊢──●──┤ -0.69 (-1.13 to -0.25)

Favor IOA ⋮ Favor CIA

Mean difference

-2   -1   0   1   2

2. Latency

Parallel ⊢─▲─┤ -1.44 (-2.02 to -0.87)

Split ⊢───■──┤ -1.77 (-2.77 to -0.77)

Combined ⊢─●─┤ -1.52 (-2.02 to -1.03)

Favor IOA ⋮ Favor CIA

Mean difference (minutes)

-3 -2 -1 0 1 2 3

3. Need for additional anesthesia

Parallel ⊢──▲──┤ 0.61 (0.22 to 1.70)

Split ⊢─────■─────┤ 1.00 (0.15 to 6.74)

Combined ⊢──●──┤ 0.68 (0.28 to 1.68)

Favor IOA ⋮ Favor CIA

Odds Ratio

0.1   1   10

4. VAS (end of dental treatment session)

Parallel ⊢───▲───┤ 0.03 (-0.52 to 0.58)

Split ⊢───■───┤ 0.53 (-0.19 to 1.25)

Combined ⊢──●──┤ 0.22 (-0.22 to 0.65)

Favor IOA ⋮ Favor CIA

Mean difference

-2   -1   0   1   2