A. Libonati*, R. Nardi**, G. Gallusi**, V. Angotti**, S. Caruso***, F. Coniglione*, G. Marzo***, A. Mattei***, S. Tecco****, L. Paglia*****, V. Campanella**

*Department of Surgical Sciences, Dental School, Catholic University of Our Lady of Good Counsel of Tirane, Tirane, Albania
**Department of Clinical and Translational Medicine, Dental School, University of Rome "Tor Vergata", Rome, Italy
***Department of Life, Health and Environmental Sciences, Dental School, University of L'Aquila, L'Aquila, Italy
**** Dental School "Vita-Salute San Raffaele" University, Milan, Italy
*****Department of Paediatric Dentistry, Istituto Stomatologico Italiano (ISI), Milan, Italy

e-mail: vincenzo.campanella@uniroma2.it,

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Pain and anxiety associated with Computer-Controlled Local Anaesthesia: systematic review and meta-analysis of cross-over studies

ABSTRACT

Aim *This review focuses on Computer-Controlled Local Anaesthesia Delivery systems (CCLAD), in comparison with conventional carpule anaesthesia in means of pain and anxiety.*

Methods *Medline, Embase, Web of Science and Cochrane Database for Systematic Reviews were searched up to August 2018. Only cross-over split-mouth design studies aimed to clinically compare CCLAD with a conventional carpule anaesthesia are included. Data about pain and anxiety associated with anaesthesia were sought. The authors performed meta-analysis where appropriate.*

Results *A total of 20 studies are included in the systematic review (n = 973 subjects). Quantitative synthesis (conducted on VAS scores from 8 studies) shows that pain intensity is over 9 points lower in CCLAD than in conventional anaesthesia on a scale from 0 to 100 (95% confidence interval, –12.90 to –5,53; P<.001). The systematic review showed no differences between the two techniques according to the physiological parameters of pain (heart rate or blood pressure), and the data about anxiety are inconsistent.*

Conclusion *CCLAD results in significantly slightly less pain perception with respect to conventional injection and is a promising device to help patients. The literature needs to be expanded, mostly regarding anxiety.*

Keywords *Anxiety, CCLAD Dental anaesthesia, Pain.*

Introduction

Dental treatments are associated with pain and anxiety [Ring, 1985; Cianetti et al., 2017; Libonati et al., 2018a; Libonati et al., 2018b], but their acceptance is facilitated by hypodermic injection of procaine and lidocaine amide as anaesthetic agents, since the early 20th century [Ring, 1985]. At any rate, many patients associate injection with pain [Asarch et al., 1999; Matthews et al., 2001], due to the mechanical trauma of needle insertion [Meechan et al., 2005] or to the sudden distention of the tissues by the anaesthetic agent, especially during a rapid discharge of anaesthetic [Meechan et al., 2005]. Thus, pain can also be stimulated after the first few drops of the injection [Meechan et al., 2005]. Therefore, painless anaesthesia is a critical issue to inspire confidence among patients toward the operator during the procedure [San Martin-Lopez et al., 2005; Bernardi et al., 2013]. According to the American Dental Association, fear of pain can prevent patients from visiting their dentists [Newton and Buck, 2000; Matthews et al., 2001], and anaesthetic injection is the most anxiety-provoking procedure for both children and adult patients [Caprara et al., 2003; Giannetti et al., 2018]. Between all different conventional local anesthetic techniques such as infiltration, nerve block, intrapulpal injection, periodontal ligament injection (PDL injection) and others, some are intrinsically more painful than others. Each technique has potential drawbacks and side effects and, in some cases, can lead to tissue damage [Libonati et al., 2017]. Many measures to alleviate pain during injection have been tried: use of topical anaesthetic [Hersh et al., 1996], warming anaesthesia solution to body temperature [Ram et al., 2002], or increasing injection time [Maragakis and Musselman, 1996]. Recently, computer-controlled local anaesthesia delivery systems (CCLAD) have been proposed to reduce pain and associated anxiety, because they deliver a constant flow rate of local anaesthetic regardless of the location, density and resiliency of the soft tissues in the injection site [Hochman et al., 1997].

Many studies have compared pain levels between

conventional techniques and CCLAD [Yesilyurt et al., 2008; Feda et al., 2010; Langthasa et al., 2012; Mummolo et al., 2014]. However, results are still unclear, and,- to the authors' knowledge, there is a lack of systematic review to clarify existing data.

This systematic review of cross-over studies with split-mouth design focuses on the question whether CCLAD is "less painful" and/or less "anxiety-inducing" than conventional anaesthesia.

Methods

The adopted protocol is based on the PRISMA statement [Liberati et al., 2009] and the review has been registered on PROSPERO (registration number CRD42016037560).

Eligibility criteria

The eligibility criteria for studies are as follows.

- Crossover design, which is aimed to clinically compare CCLAD with conventional carpule anaesthesia.
- Studies with a split-mouth design, so each patient served as his/her own control. As pain perception is subjective, both systems had to be tested on the same patient and on the same or in similar and comparable intraoral sites (e.g., left and right first upper molars).

No language restriction was applied and printed or online studies were both included.

Information sources

Sources included the following databases: Ovid Embase (from 1980 to 2018, week 21), Ovid Medline (from 1950 to August 2018, week 4), Web of Science and Cochrane databases for Systematic Reviews (2005 to August 2018, week 4).

Search

A search strategy was developed for Medline and adapted to the other databases with the assistance of a Health Sciences Reference Librarian. Three groups of keywords were used; keywords in each group were combined by the boolean term "or" (Table 1). The first group included terms associated with "electronic"; the second group included words related to "dental"; and the third group included terms related to "anaesthesia". The three groups were then combined together using the boolean term "and". Additionally, hand searching was applied to the reference list of retrieved articles, and to all issues of core dental journals, related to general dentistry, published over the previous five years.

Study selection

Two reviewers (AL and GG) independently screened the studies. They independently coded the list of titles and abstracts for possible inclusion in systematic review and, if applicable, in the meta-analysis, which was confirmed after obtaining the full-text versions. The kappa value between the two operators was 0.83, indicating good agreement. Any disagreement between them was resolved through discussion, or by consulting a third reviewer (VC).

Data collection

The reviewers, independently — in duplicate, and following a piloted form — extracted the following data from each report: the authors, the year of publication, the sample size, the range of age, the CCLAD (commercial product used), the time interval between the traditional injection and the CCLAD use, the dental treatment following the anaesthesia (if present or absent; and, when present, the type of treatment), and the number of operators.

Data items

The following items were sought: pain; anxiety. Pain is defined as the sensation of pain experienced during the act of local anaesthesia as measured by units of subjective relief (visual analogue scales, VAS, or verbal rating scale) or objective parameters (heart rate, blood pressure, body temperature). Anxiety is defined as the pre-operative anxiety associated with anaesthesia. Anxiety assessment was collected as present or not; when present, the scale and the scores were reported.

Risk of bias in individual studies

Special attention was given to the blinding procedure of patients in individual reports, to avoid bias related to the patient's sensation at seeing the anaesthetic device.

Summary measures

The summary measures in this systematic review are the means of pain and anxiety, evaluated for conventional anaesthesia and for CCLAD in the studies.

Quantitative analysis (meta-analysis)

A decision to perform a meta-analysis was taken when sufficient similarities between studies, types of participants, type of anesthesia - with conventional system or CCLAD - and outcomes were observed. Pooled effect sizes were possible only on the results of pain intensity

Search no.	Keywords involved
#1	Wand
#2	Anaeject
#3	QuickSleeper
#4	Comfort Control Syringe
#5	electronic*
#6	computer *
#7	1 or 2 or 3 or 4 or 5 or 6
#8	Dent*
#9	anaesthesia
#10	anaesthesia
#11	injection*
#12	9 or 10 or 11
#13	7 and 8 and 12

TABLE 1 Search strategy.

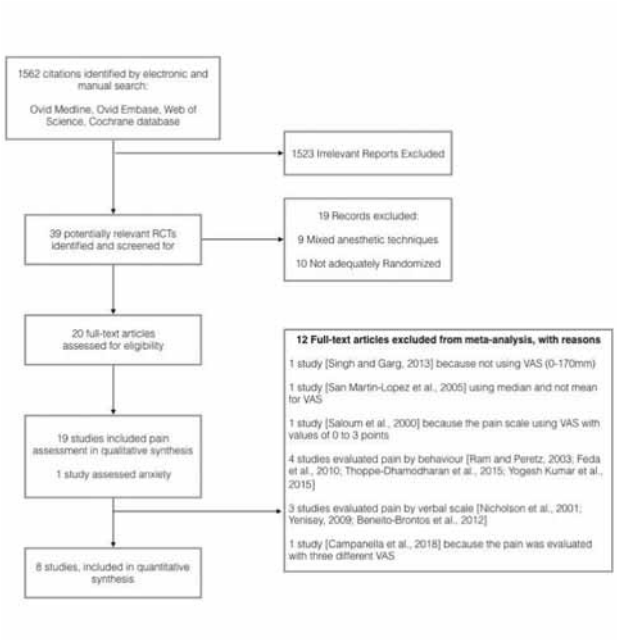

FIG. 1 The studies eligible for systematic review.

(expressed through a VAS). STATA 12.0 Software was used to summarise the effects (i.e., pooled weighted mean differences [WMD]) and construct the forest plots for all comparisons. A random-effects model (Der Sirmonian and Laird model) on the assumption of the presence of inter-studies variability — to provide a more conservative estimate of the true effect — with corresponding Z-statistics, p values, and 95% confidence interval (CI), was also calculated. A test for heterogeneity was also performed. For this test, the I2 statistic describes the proportion of total variation due to heterogeneity, where 0% indicates no heterogeneity, and 100% indicates maximal heterogeneity among the studies included in the meta-analysis. The forest plots for each meta-analysis present: (a) the raw data (means, standard deviations [SD], and sample sizes) for each study; (b) point estimates and the CI for the chosen effect measure (represented as blocks and lines, respectively); (c) heterogeneity statistic (I2); (d) the total number of participants for each study, the overall average effect (WMD and Z-statistics) in the random-effects model, and the percent weight given to each study. Meanwhile, the differences between means of the combined scores for injection type (PSA, IA and LB) for paired data were investigated using the Wilcoxon signed-rank test, when paired analyses were not available.

Results

Study selection

A total of 1,562 reports were screened, and 20 studies were eventually deemed eligible for systematic review (Fig. 1). Eight studies were finally included in the meta-analysis.

Study characteristics

The characteristics of the 20 studies are reported in Table 2. The last study was conducted in 2018, and the earliest in 2000. The total number of participants who were interviewed within the 20 studies is 973. The studies include patients from 3 to 70 years of age. The 20 surveys are from 12 different countries: United States, Israel, India, Mexico, Turkey, Saudi Arabia, Spain, Denmark, Korea, Brasil, Italy and Sweden. Furthermore, all studies include males and females in their survey. These 20 articles analyze six different CCLAD: Wand Injection system, Anaject, Quicksleeper, Comfort Control Syringe, Morpheus and CNR (Table 2). The interval between CCLAD and conventional anaesthesia varies from 1-2 minutes [Saloum et al., 2000; Shah et al., 2012], 24 hours [Langthasa et al., 2012; Campanella et al., 2018], 5 days [Yesilyurt et al., 2008;], to 1 week [Nusstein et al., 2004; Feda et al., 2010; Beneito-Brotons et al., 2012; Mummolo et al., 2014].

Only eight studies [Ram and Peretz, 2003; Loomer and Perry, 2004; Yenisey, 2009; Beneito-Brotons et al., 2012; Shah et al., 2012; Jälevik and Klingberg, 2014; Araújo et al., 2015; Chang et al., 2016] include a dental treatment after the anaesthesia.

Risk of bias in individual studies

All 20 studies adopted a randomized sequence for each patient receiving the two types of anaesthesia, to avoid bias. All patients were blinded to the order of the technique to be used; they were randomly assigned an anaesthetic device (traditional or CCLAD) at the first appointment, and received the other anaesthetic technique at the second appointment.

Results of individual studies

- Outcome: anxiety assessment; anxiety is evaluated in 6 studies over 14 [Saloum et al., 2000; Nusstein et al., 2004; Yesilyurt et al., 2008; Queiroz et al., 2015; Thoppe-Dhamodharan et al., 2015; Chang et al., 2016]. Three studies [Nusstein et al., 2004; Yesilyurt et al., 2008; Chang et al., 2016] use the Corah's DAS (dental anxiety scale) [Corah, 1988] at both appointments. These report no correlation among DAS value, pain and type of anaesthesia.
  Two reports [Saloum et al., 2000; Yenisey, 2009] evaluate anxiety only before the beginning of the first appointment. Saloum et al. [2000] uses only two questions (yes/no) and relates the anxiety to pain perception during anaesthesia, concluding that "a history of anxiety" or an "immediate pre-operative anxiety" does not have a significant effect on the patient's pain sensation during anaesthesia. However, their results are not generalisable, as the sample consisted of dental professionals, with a level of anxiety generally lower than that of the general population.
  Queiroz et al. [2015] used the State-Trait Anxiety Inventory for Children (STAIC) and the salivary cortisol levels before and after each anaesthetic technique. They

Ref.	Sample size and age	Devices compared and type of anaesthesia	Pain assessment	Pre-operative Anxiety assesment
Shah et al, 2012	10, from 30 to 65 years	Wand: AMSA Carpule:AMSA	VAS 100 mm length	N
Saloum et al, 2000	40, from 21 to 36 years	Wand: AMSA, IANB and palatal infiltration Carpule: AMSA, IANB and palatal infiltration	4 points VAS	Two questions with "yes" or "no" answers regarding fear and dental anxiety
Campanella et al, 2018	80, from 18 to 70 years	Wand: AMSA Carpule: AMSA, IANB	VAS 100 mm length	Corah's Dental Anxiety Scale Questionnaire
San Martin Lopez et al. 2005	64 from 9 to 12 years	Wand: Buccal and palatal infiltrations Carpule: Buccal and palatal infiltrations	10 points VAS and hearth rate	N
Feda et al 2010	40 from 7 to 10 years	Wand: AMSA Carpule: buccal and palatal infiltration	Sounds, eyes and motor (SEM) scale for pain reaction and modified Eland color scale	N
Yenisey, 2009	16 from 27 to 64 years	Wand: AMSA Carpule: buccal infiltration	5 points likert scale	N
Loomer & Perry, 2004	20	Wand: IA, LB, AMSA and PSA Carpule: IA, LB, MSA, PSA, ASA, GP, NP	100 mm VAS and 5 points verbal scale	N
Nicholson et al 2001	30 from 23 to 54 years	Wand: maxillary infiltration and IANB Carpule: maxillary infiltration and IANB	Verbal scale from 0 to 10	N
Yesilyurt et al, 2008	40 from 18 to 30 years	Wand: IANB Carpule: IANB	100 mm VAS length and 4 levels likert scale	Corah's Dental Anxiety Scale
Palm et al, 2004	33 from 7 to 18 years	Wand: IANB Carpule: IANB	10 point VAS	N
Ram & Peretz 2003	102 from 3 to 10 years	Wand: Infiltration and IANB Carpule: Infiltration and IANB	Behaviour reaction	N
Beneito-Brotons et al, 2012	30 from 18 to 65 years	Quicksleeper: Intraosseus anaesthesia Carpule: IANB and local infiltration	Four points verbal scale	N
Singh & Garg 2013	90 from 20 to 65 years	Anaeject: supraperiosteal maxillary Carpule: supraperiosteal maxillary	170 mm length Heft Parker VAS	N
Langhtasa et al 2012	50 from 6 to 14 years	Comfort control syringe: infiltration Carpule: Infiltration	VAS, face pain rating scale, hearth rate blood pressure and temperature	N
Yogesh Kumar et al 2015	110 from 7 to 11 years	Wand: STA Carpule: Infiltration	Facial image scale (FIS),face legs activity cry consolability (FLACC) scale, hearth rate blood pressure	N
Queiroz et al 2015	20 from 7 to 12 years	Wand: infiltration Carpule: local infiltration	N	Pre- and post-operative Salivary cortisol levels, State-trait anxiety inventory for children (STAIC)
Thoppe-Dhamodharan et al 2015	110 from 7 to 11 years	Wand: STA Carpule: Infiltration	Facial image scale (FIS),face legs activity cry consolability (FLACC) scale, hearth rate blood pressure	N
Jälevik & Klingberg 2014	28 from 11 to 18 years	Wand: AMSA, P-SA Carpule: Buccal fold and palatal infiltration	100mm VAS	Pre-operative Children'Fear Survey Schedule-Dental Subscale (CFSS-DS)
Araújo et al. 2015	29 from 18to 40 years	Morpheus: inferior alveolar nerve block Carpule: inferior alveolar nerve block	100mmVAS and five points Likert Scale, pulse rate, oxygen saturation and blood pressure	N
Chang et al, 2016	31 from 34 to 66 years	CNR: Supraperiosteal injection Carpule: Supraperiosteal injection	100mm VAS	Pre-operative Corah's Dental Anxiety Scale

TABLE 2A Search results.

Ref.	Amount of time between two injections	Treatment after injection	Number of operators	Evaluation of postoperative discomfort
Shah et al., 2012	2 minutes	Periodontal surgical treatment procedures	1	N
Saloum et al., 2000	1-2 minutes	No treatment	1	N
Campanella et al., 2018	1 week	Restorative or endodontic treatment	5	Y
San Martin Lopez et al., 2005	--	No treatment	1	N
Feda et al., 2010	1 week	---	1	N
Yenisey, 2009	---	Prosthodontic treatment	1	Y
Loomer & Perry, 2004	---	Scaling and root planing	3	N
Nicholson et al. 2001	--	No treatment	2	y
Yesilyurt et al., 2008	At most 5 days	No treatment?	1	N
Palm et al., 2004	--	No treatment?	1	N
Ram & Peretz, 2003	--	Restorative procedures		N
Beneito-Brotons et al, 2012	1 week	Reconstructions with composite, root canal treatments of teeth with vital pulp tissue and simple extractions	1	N
Singh & Garg, 2013	24 hours	No treatment?	--	N
Langhtasa et al., 2012	24 hours	--	--	N
Yogesh Kumar et al., 2015	1 week	No treatment	1	N
Queiroz et al., 2015	Not reported	No treatment	1	N
Thoppe- Dhamodharan et al., 2015	1 week	No treatment	1	N
Jälevik & Klingberg, 2014	Not reported	Minor maxillary surgical treatment	Not reported	Y
Araújo et al., 2015	Not reported	Third molar removal	1	N
Chang et al., 2016	Not reported	Surgical periodontal therapy: open flap debridement	3	N

TABLE 2B Search results.

failed to find statistically significant differences between the two techniques, with respect to cortisol levels and psychological analysis.

- Outcome: pain assessment; pain is evaluated in 19 over 20 reports with different methods: VAS [Saloum et al., 2000; Nusstein et al., 2004; Palm et al., 2004; Yesilyurt et al., 2008; Langthasa et al., 2012; Shah et al., 2012; Jälevik and Klingberg 2014; Araújo et al., 2015; Chang et al., 2016; Campanella et al., 2018], heart rate [Loomer and Perry 2004; San Martin-Lopez et al., 2005; Langthasa et al., 2012; Araújo et al., 2015; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015], blood pressure [Nusstein et al., 2004; Araújo et al., 2015; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015], oxygen saturation [Nusstein et al., 2004; Araújo et al., 2015] and temperature response [Langthasa et al., 2012], behaviour (e.g., crying, facial expression, hand, legs and torso movements) [Ram and Peretz, 2003; Feda et al., 2010; Mummolo et al., 2014; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015], or verbal scale [Nicholson et al., 2001; Yenisey, 2009; Beneito-Brotons et al., 2012]. Three studies [Yesilyurt et al., 2008; Yenisey, 2009; Campanella et al., 2018] consider separately the two phases of anaesthesia: needle insertion and infusion of the anaesthetic (Table 3). Four reports evaluate the sensation of discomfort, in addition to pain [Nicholson et al., 2001; Nusstein et al., 2004; Yenisey, 2009; Jälevik and Klingberg 2014].

Quantitative analysis

Of the 19 articles evaluating pain, 11 full-text articles [Saloum et al., 2000; Nicholson et al., 2001; Ram and Peretz, 2003; Nusstein et al., 2004; San Martin-Lopez et al., 2005; Yenisey, 2009; Feda et al., 2010; Beneito-Brotons et al., 2012; Mummolo et al., 2014; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015; Campanella et al., 2018] were excluded from quantitative analysis for the methods used to evaluate pain: VAS by Heft–Parker [Campanella et al., 2018]; VAS with values of 0 to 3 points [Saloum et al., 2000]; median of VAS [San Martin-Lopez et al., 2005]; behavior [Ram and Peretz, 2003; Feda et al., 2010; Mummolo et al., 2014; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015] (e.g., crying, facial expression, hand, legs and torso movements); verbal scale [Nicholson et al., 2001; Loomer and Perry 2004; Beneito-Brotons et al., 2012]; pain evaluated in three modes of expression [Nusstein et al., 2004].

Eight trials - using cross-over design, providing data on pain intensity as evaluated by VAS, during injection -

Ref.	Results
Shah et al., 2012	No significant differences between the two techniques
Saloum et al., 2000	Wand generally less painful, but significant only in 4 patients
Campanella et al., 2018	Pain and discomfort are lower with Wand treatment than with Conventional treatment The vital parameters induced by Wand are lower than Conventional anaesthesia
SanMartin Lopez et al., 2005	According to the mean heart rate and to the VAS the computerised device is painless
Feda et al., 2010	Wand had significantly lower mean pain reaction scores than traditional buccal and palatal injections
Yenisey, 2009	Wand had significantly lower pain at needle insertion and during anaesthetic solution delivery phase. No differences between the two techniques for pain level during tooth preparation
Loomer & Perry, 2004	No significant difference for the IA or LB in the mandibular arch. AMSA injection with wand less painful than conventional NP injecton (VAS) and GP (VRS) scores for conventional injections in the maxillary arch were higher than scores for the AMSA computer-controlled injection (VAS + VRS)
Nicholson et al., 2001	No differences in injection discomfort; postoperative discomfort for mandibular block was significantly less using Wand system
Yesilyurt et al., 2008	Wand was significantly painless for needle insertion and during injection
Palm et al., 2004	Pain ratings were significantly higher after the traditional injection than after The Wand injection; a significant greater reduction in perceived pain was found in those patients with a high pain perception during traditional injection
Ram & Peretz 2003	No differences
Beneito-Brotons et al, 2012	No significant differences between the two techniques
Singh & Garg 2013	Anaeject, technique during needle prick and local anaesthetic delivery phaseis significantly painless than the traditional syringes
Langhtasa et al 2012	Comfort Control syringe significantly painless than conventional anaesthesia according to VAS and face pain rating scale. No significant differences in the physiological parameters between the two techniques
Yogesh Kumar et al 2015	Wand was significantly painless according to FIS and produced lesser disruptive behavior and pulse rate. No significant differences in the physiological parameters between the two techniques during injection
Queiroz et al 2015	No significant differences were found between the two techniques in the salivary cortisol levels or psychological assessment before and after anaesthesia
Thoppe- Dhamodharan et al., 2015	No significant differences between the two techniques at first visit. At second visit there was a significant increase in FIS, FLACC and heart rate with traditional syringes
Jälevik & Klingberg, 2014	Wand was significantly painless according to VAS. No differences between the two types of computerized anaesthesia. No differences in the global pain report for the total treatment procedure. Pain assessments for all injections were high compared with the pain for the treatment procedure
Araújo et al., 2015	No statistically significant differences between the two anaesthetic techniques in pain perception, oxygen saturation and pulse rate
Chang et al., 2016	CNR was significantly painless according to VAS regardless of the order in which anaesthetic procedures were applied

TABLE 2C Search results.

Painless anaesthesia with CCLAD: 12 studies over 20 [Loomer & Perry, 2004; Nusstein et al., 2004; Palm et al., 2004; Yesilyurt et al., 2008; Yenisey, 2009; Feda et al., 2010; Langthasa et al., 2012; Jälevik & Klingberg, 2014; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015; Chang et al., 2016; Campanella et al., 2018] reported less pain with CCLAD, respect to conventional anesthesia, using different methods	Methods to measure pain	- VAS [Palm et al., 2004; Langthasa et al., 2012; Jälevik and Klingberg, 2014; Chang et al., 2016; Campanella et al., 2018] - Behaviour (sounds, eyes and motor scale for pain reaction) [Feda et al., 2010] - facial image scale (FIS), face legs activity cry consolability (FLACC) scale [Yogesh Kumar et al., 2015] - Hearth rate [San Martin-Lopez et al., 2005; Yogesh Kumar et al., 2015] - Blood pressure [Yogesh Kumar et al., 2015]
	Pain during needle insertion and solution deposition:	CCLAD resulted significantly painless respect to conventional system: - during needle insertion [Yesilyurt et al., 2008; Yenisey, 2009; Campanella et al., 2018] - during solution deposition [Nusstein et al., 2004; Yesilyurt et al., 2008; Yenisey, 2009; Campanella et al., 2018] In addition, one study reported significant pain reduction with the injections with CCLAD in maxillary arch, while no difference during mandibular block [Beneito-Brotons et al., 2012]
No difference between the two systems: 9 studies over 20 [Nicholson et al., 2001; Ram and Peretz, 2003; Nusstein et al., 2004; Beneito-Brotons et al., 2012; Langthasa et al., 2012; Shah et al., 2012; Araújo et al., 2015; Queiroz et al., 2015; Thoppe-Dhamodharan et al., 2015] reported no difference between the conventional and CCLAD systems using different methods	Methods to measure pain:	- VAS [Shah et al., 2012; Araújo et al., 2015] - Behaviour (e.g. crying, facial expression, hand, legs and torso movement) [Ram and Peretz, 2003] - Facial image scale (FIS), face legs activity cry consolability (FLACC) scale [Thoppe-Dhamodharan et al., 2015] - Verbal scale [Nicholson et al., 2001; Beneito-Brotons et al., 2012] - Physiological parameters [Langthasa et al., 2012; Araújo et al., 2015; Thoppe-Dhamodharan et al., 2015]
	Pain during needle insertion and solution deposition:	No difference between the two systems during the phase of needle insertion [Campanella et al., 2018]

TABLE 3 Systematic review of data about pain, from the 20 reports (main results).

Source	No.	Mean (SD)	No.	Mean (SD)	WMD (95% CI)	% Weight
Adults						
Loomer et al., 2004	20	13.83 (13.46)	20	18.53 (17.43)	-4.70 (-14.35 to 4.95)	12.5
Yesilyurt et al., 2008	40	8.5 (14.5)	40	15.9 (18.9)	-7.40 (-14.78 to -0.02)	19.4
Shah et al., 2012	10	15 (9.72)	10	18 (12.29)	-3.00 (-12.71 to 6.71)	12.4
Chang et al. 2016	31	22.8 (16.3)	31	40.9 (24.6)	-18.1 (-28.48 to -7.71)	15.1
Araujo et al., 2015	29	28.6 (19.6)	29	34.5 (27.3)	-5.9 (-18.13 to 6.33)	12.2
Subtotal (95% CI)	130		130	-7.69 (-12.59 to -2.78)		
Test for heterogeneity: $\chi 2$= 5.21, df= 4, (p=0.26), I2 =23.2% Tau2 = 7.29 Test for overall effect: Z= 3.07 (p= 0.002)						
Children						
Palm et al., 2004	33	27 (17.3)	33	43 (18.4)		
Langhtasa et al., 2012	50	20 (20.4)	50	28.2 (28.88)		
Jalevick et al. 2014	28	31.4 (21.1)	28	41.5 (22.60)		
Subtotal (95% CI)	111		111			
Test for heterogeneity: $\chi 2$= 1.51, df= 2, (p=0.317), Tau2 =4.09 Test for overall effect: Z= 4.17 (p<0.001)						
Total	241		241		-9.21 (-12.90 to -5.53)	100
Test for heterogeneity: $\chi 2$= 8.18, df= 7, Tau2 = 4.09,), I2 =0.00% (p= 0.309) Test for overall effect: Z= 4.90 (p< 0.001)						

TABLE 4A

were finally included in the meta-analysis: Loomer and Perry [2004], Palm et al. [2004], Yesilyurt et al. [2008], Langhtasa et al. [2012], Shah et al. [2012], Jälevik and Klingberg [2014], Araújo et al. [2015], Chang et al. [2016].

Among these studies, three reports enroll young patients (children), and five trials enroll adult patients. In all of these studies, the patient's pain perception to each technique is investigated immediately after the anaesthesia.

Three trials [Loomer and Perry, 2004; Shah et al., 2012; Araújo et al., 2015] report no significant difference in pain intensity between CCLAD and conventional system. In the study by Loomer and Perry [2004] the mean values of the combined scores for injection type (PSA, IA and LB) were compared with the Wilcoxon signed-rank test, because paired analyses were not available (p=0.362). In the study of Shah et al. [2012] data were normalised to a 0- to 100-mm VAS. The remaining five trials [Palm et al., 2004; Yesilyurt et al., 2008; Langhtasa et al., 2012; Jälevik and Klingberg, 2014; Chang et al., 2016] show statistically significant differences between conventional and CCLAD; according to VAS scores, pain intensity results lower in CCLAD than in conventional systems.

Data from these 8 articles with a total of 241 patients are combinable for a meta-analysis, since they report the means and standard deviations for pain intensity after injection with CCLAD or conventional system. The $\chi 2$ value for heterogeneity was 8.18 (p=0.309), indicating a high degree of homogeneity between and within studies (Table 4). The overall mean difference in the last measured pain intensity for CCLAD versus conventional injection is over 9 points lower (on a 0-100 VAS scale) (95% CI, –12.90 to –5.53; P<.001). Data from 3 trials, involving a total of 111 children, and from 5 trials, involving 130 adult patients, were combinable for a further meta-analysis. For young patients, the final pain intensity following CCLAD is about 12 points lower than that after placebo (95% CI, –17.65 to –5; P<0.001), whereas for adults patients, the difference is –5 points (95%CI,–10 to –0.5; P=0.002) (Table 4).

Additional analysis

In this study no meta-regression was performed because of the small number of trials included in the quantitative analysis.

Discussion

The aim of the study is to review data about pain and anxiety associated with local anaesthesia with CCLAD, in comparison with conventional anaesthesia.

None of the 20 studies included in this systematic review report painless anaesthesia with conventional systems, respect to CCLAD (Table 3). A meta-analysis of results extracted by 8 eligible studies shows that the overall mean difference in the last measured pain intensity for CCLAD versus conventional injection is over 9 points lower (on a 0-100 VAS) (95% CI, –12.90 to –5.53; p <.001). In children, the final pain intensity following CCLAD is about 12 points lower than that after placebo (95% CI, –17,65 to –6,35; p<0.001), whereas in adult patients the difference is –7.69 points (95% CI, –10 to –0.5; p=0.002) (Table 4).

No difference was generally found between the two techniques when compared through objective physiological parameters indicating pain (e.g., heart rate and pressure) [Nusstein et al., 2004; Langhtasa et al., 2012; Araújo et al., 2015; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015]. The data about anxiety - as published in the current literature - fail to indicate any difference between conventional system and CCLAD.

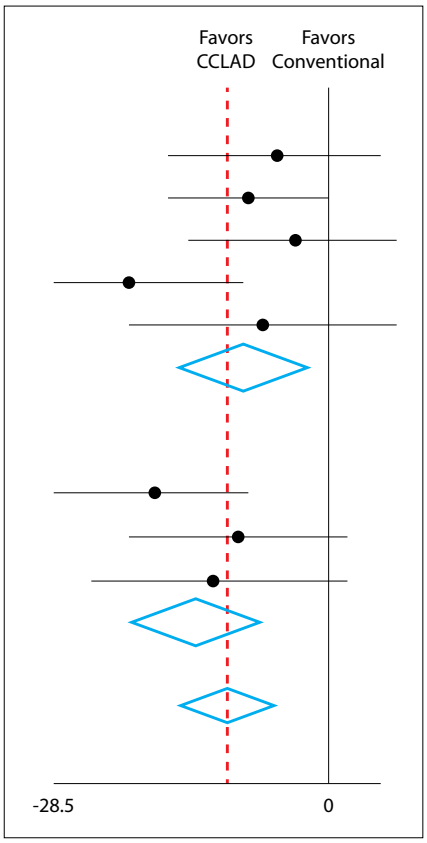

TABLE 4B

Interpretation of data

The pain perceived during the administration of a local anaesthetic is a two-part phenomenon [Zilinsky et al., 2005]. The first sensation is caused by the needle puncture, which causes a short, intense pain. The second pain involves activation of nociceptors, responding to both the chemicals of the infiltrated agent, and rapid distention of the tissue. This second sensation is more intense and more prolonged [Zilinsky et al., 2005]. According to the literature on traditional injection, a careful needle insertion and a slow anaesthetic advancement are common tricks used to reduce the two-part pain process, during the administration of conventional injection [Zilinsky et al., 2005; Liberati et al., 2009].

In theory, the pain perception with CCLAD systems is supposed to be less than that in the traditional technique, because of the larger gauge needle, the pre-puncture technique [Krochak and Friedman, 1998], and the pen-like grasp tool. This tool allows users to easily rotate the needle - while it is introduced into tissues - producing a coring penetration that minimises needle deflection, allowing a slow rate of anaesthetic flow, thereby maintaining a constant pressure and controlled volume of solution, regardless of the tissue resistance [Hochman et al., 1997]. With traditional anaesthesia, it is difficult - although not impossible - to achieve the same result, because the manual control of a syringe is objectively more difficult, owing to the wide variance in soft tissue elasticity, that unavoidably influences injection pressures (especially in the palatal area) which may require pressures as high as 660 psi [Nicholson et al., 2001]. This results in a practical advantage for CCLAD, for which the pressure control is computerised. The comparative forest plot of the meta-analysis between CCLAD and conventional systems shows over 9 points of difference between the two systems.

These findings are relevant for clinicians, who must take into account the fact that the use of CCLAD does not always guarantee less painful anaesthesia than the traditional technique. There is a noticeable proportion of clinical cases for which the two techniques are equivalent, in terms of pain, during the injection. In addition, data about anxiety associated with the two techniques are actually inconsistent and warrant further investigations.

From a practical point of view, the commercial CCLAD systems analysed in the 8 reports eligible for the meta-analysis are WAND system (used in 5 studies) [Loomer and Perry 2004; Palm et al., 2004; Yesilyurt et al., 2008; Shah et al., 2012; Jälevik and Klingberg, 2014], Comfort Control system [Hochman et al., 1997], Morpheus [Araújo et al., 2015] and CNR [Chang et al., 2016] (Table 2). This observation could be useful for clinicians, as they need to be aware from which device come the most robust data in the literature. This finding could guide clinicians on the type of instrument to follow in the literature; moreover, it can be useful for researchers to implement clinical studies on these systems.

Other information

The possible confounding variables in this review are operator ability and use of pre-anaesthetic. In 12 over 20 studies [Saloum et al., 2000; Palm et al., 2004; San Martin-Lopez et al., 2005; Yesilyurt et al., 2008; Yenisey, 2009; Feda et al., 2010; Beneito-Brotons et al., 2012; Shah et al., 2012; Araújo et al., 2015; Queiroz et al., 2015; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015] the anaesthetic procedure was performed by only one operator, to avoid effects due to hand ability. Operator ability may influence the result of a study; for example, it is possible that a right-handed operator might be unconsciously more comfortable and better in delivering injections to the left side of the mouth, as compared to the right side [Saloum et al., 2000]. Operator ability may ultimately influence pain perception, even in palatal injections, which are generally the most painful ones [Friedman and Hochman, 2001].

In 10 of 20 studies [Saloum et al., 2000; Loomer and Perry 2004; Nusstein et al., 2004; Yesilyurt et al., 2008; Shah et al., 2012; Jälevik and Klingberg, 2014; Queiroz et al., 2015; Thoppe-Dhamodharan et al., 2015; Yogesh Kumar et al., 2015; Campanella et al., 2018] topical pre-injection anaesthetics were not used to avoid the effects of subjective response to pain after the topical application of an anaesthetic. Topical anaesthetic is the most widely used method to reduce pain associated with dental injections. Consequently, most patients are accustomed to topical agents being applied before injections; they can taste the anaesthetic agent and can feel its effect on their soft tissue. Topical anaesthetic can increase the subjective

anaesthetic effect and can serve to reduce the anticipatory anxiety associated with dental injections [Martin et al., 1994; Bernardi et al., 2016].

Limitation

Considerable variation between studies in injection site assessment allowed only limited quantitative synthesis of data.

Conclusions

Based on the results of this review, it can be assumed that a computerized system of anaesthetic injection results in significantly less pain perception (VAS score) when compared with the conventional injection during solution deposition, both on adult patients and in children. However, physiological parameters do not confirm this data about pain. The CCLAD seems to be a promising device, offering a less painful method of anaesthesia administration; however, further research is necessary to verify this and to better evaluate anxiety associated with anaesthesia.

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