Clin Oral Invest (2012) 16:1289–1295
DOI 10.1007/s00784-011-0608-x

ORIGINAL ARTICLE

Clinical use of an epinephrine-reduced (1/400,000) articaine solution in short-time dental routine treatments—a multicenter study

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Received: 20 March 2011 / Accepted: 10 August 2011 / Published online: 23 August 2011

Abstract The addition of epinephrine in dental local anaesthesia results in a longer and deeper anaesthesia under almost ischemic conditions. For short-time dental treatments, epinephrine-reduced anaesthetics may offer shorter and more individual anaesthesia with reduced potential side effects. The aim of this study was a clinical evaluation of anaesthetic potency and adverse effects of an epinephrine-reduced articaine formulation in dental patients undergoing short-time routine treatment. In a prospective clinical, not interventional, study between January 2008 and February 2009, 908 patients undergoing short-time dental treatment in five medical centers were anaesthetized with 4% articaine 1:400,000 epinephrine (Ubistesin™, 3M/ESPE, Seefeld, Germany). Efficacy and safety in clinical use were evaluated. A follow-up after 1 day was conducted by telephone survey. A mean amount of 1.3-ml anaesthetic solution was needed to achieve a complete or sufficient anaesthesia in 97% (n=876) of cases. A second injection had to be done in 3.7% (n=34) before and in 11.9% (n=108) during treatment. Here, the second injection had to be applied after a mean of 48.6 min. The mean duration of soft tissue anaesthesia after infiltration was 146.6 min, after nerve block 187.7 min. The painful treatment took a mean of 50.2 min and the total treatment time summed up to 68.8 min. In 1.7% cases (n=15), unwanted side effects were observed. The results indicate that a lower concentration of epinephrine in combination with the 4% articaine solution leads to a high success rate of efficacy. The clinical use of a 4% articaine 1:400,000 epinephrine solution can be stated as safe and effective in short dental routine treatments. Reconsiderations concerning limitations of indication or additional contra-indications are not necessary.

Keywords Dental local anaesthesia · Epinephrine · Articaine · Dental treatment · Routine procedures

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Introduction

Dental pain constitutes a major problem for patients and dental care providers [1, 2]. Pain control is an important factor to

reduce fear and anxiety associated with dental procedures [3]. Improvements in agents and techniques for local anaesthesia may improve the dental treatment. An adjustment of depth and quality of local anaesthesia to treatment modalities and individual patients' needs are desirable.

Articaine, an amide-type local anaesthetic, is unique among clinically used local anaesthetics because of its thiophene ring with an ester linkage. There is evidence that it is the local anaesthetic that best diffuses within soft and hard tissues even if the contributing factors are not understood yet [4–6]. Because of its vasodilatation properties and the increase of the anaesthetic efficacy, articaine is often used in association with a vasoconstrictor [7]. Clinically, vasoconstrictors, especially epinephrine, are combined with local anaesthetics such as articaine to provide local ischemia in the region of treatment and to reduce the systemic toxicity of the anaesthetic agent [8]. A delay in absorption of the local anaesthetic can be achieved [9]. A low concentration of epinephrine 1:400,000 has shown to be sufficient for adequate pain control and haemostasis while minimizing potential side effects caused by epinephrine [9–12]. The same concentration has been evaluated to prolong systemic absorption of the anaesthetic solution [13]. Though, the reduced concentration of epinephrine shortens the time of local numbness and can be used to adapt local anaesthesia to the duration of selected treatment. This may also enhance patients' subjective well-being after short-time dental treatments. Especially for nonsurgical or minor surgical treatments, most patients may prefer a local anaesthesia that suites the dental treatment in extension of soft tissue anaesthesia and duration. Besides, in order to reduce the risk of systemic adverse reactions, local anaesthetic solutions should contain the minimum concentration of vasoconstrictors possible [14–17].

Epinephrine-reduced Ubistesin™ 1/400,000 (3M/ESPE, Seefeld, Germany) contains 4% articaine and epinephrine in a dilution of 1/400,000. According to the manufacturers' information, it is applicable for infiltration and nerve block anaesthesia for dental routine treatments expected lasting not longer than 30 min. The low concentration of epinephrine is characteristic. Therefore, minor effects on the cardiovascular system as well as a reduced intensity and duration of soft tissue anaesthesia compared with other local anaesthetics can be expected.

The purpose of this study was an evaluation of the clinical use of an epinephrine-reduced local anaesthetic solution in routine short-time dental treatment regarding the amount of anaesthetic agent needed, efficacy and duration of anaesthesia, rate and profile of adverse effects to specify the indication in restorative and prosthodontic dentistry, as well as in minor oral surgery in dental practice. Obtained data were compared with the literature.

Materials and methods

Study design and patient selection

A prospective, clinical, noninterventional multicenter study was performed at five study sites (University Medical Centre Mainz, University of Heidelberg, University of Frankfurt, and two external resident centers (Wiesbaden and Neuhofen)) between 2008 and 2009. In 908 patients, short-duration routine dental treatments after anaesthesia with epinephrine-reduced Ubistesin™ 1/400,000 (4% articaine, epinephrine 1/400,000; 3M/ESPE, Seefeld, Germany) were carried out. The study was conducted with the approval of the local ethics committee and in accordance with the Declaration of Helsinki. All patients signed an informed consent prior to the initiation of the dental treatment. Inclusion criteria were the following: patients with at least 18 years of age and with clinical indication for dental local anaesthesia (preparation of dental cavities, curettage, endodontic treatment, preparation of dental crowns, extractions of teeth). Exclusion criteria were contraindications for components of anaesthetic solution (articaine, epinephrine, sulfite), limited activity of plasma cholinesterase, patients with American Society of Anaesthesiologist classification >2, chronic or spontaneous taking of psychotropic drugs in temporal context with the dental treatment, lacking compliance, as well as infections in the area of injection. The local anaesthetic solutions were supplied in capsules by 3M/ESPE (Seefeld, Germany).

Treatment protocol

After taking the medical history of the patient and explaining the purpose of the study to get informed consent, the sensitivity of the teeth planned to be treated were tested with a pulp tester. Anaesthesia was induced carefully after aspiration and under slow injection. After onset of anaesthesia, the depth of anaesthesia was tested. If needed, a second injection was given. A maximum of three adjacent teeth were anaesthetized. The treatment started after successful anaesthesia and lasted until the completion of the dental procedure. Patients were asked to remain seated for several minutes after the completion of the dental treatment. The efficacy of anaesthesia was evaluated by the patient and investigator (complete, sufficient, insufficient, and no effect). The following day, the patients were contacted via telephone and asked regarding the duration of soft tissue anaesthesia and adverse effects.

Statistics

All statistics were done in an explorative manner. Data were calculated descriptively only.

Results

Patients

Nine hundred eight patients with a mean age of 42.6 years (18–88; standard deviation (SD) 16.6), a mean size of 171.9 cm (147–206; SD 9.8) and a mean weight of 74.15 kg (42–160; SD 15.7) could be included. Forty-four percent (n=400) of the patients were male, 56% (n=508) female. Sixteen percent of the patients (n=154) complained pain prior to treatment, 3.6% (n=33) reported previous use of oral analgesics. In 29.2% (n=265), concomitant diseases (Fig. 1) was reported. With 15.6% of the patients (n=142), the group with cardiovascular diseases was the most prominent, followed by diseases of the thyroid gland with 6.8% (n=62). Further concomitant diseases were diabetes mellitus (3.1%; n=28), allergies (1.8%; n=16), mental (1.7%; n=15) as well as renal (1.1%; n=10) and lung diseases (0.9%; n=8). In 28% (n=254) of patients, concomitant permanent medications could be evaluated. Indications for dental treatment were dental filling therapy (42.7%; n=388), endodontic treatment (8.6%; n=78), prosthetic treatment (19.2%; n=174), periodontal therapy (14.5%; n=132), minor surgery (12.3%; n=112), and other reasons (2.6%; n=24).

Treatment

The techniques of anaesthesia were infiltration, nerve block, infiltration in combination with nerve block as well as combination of nerve block and other techniques (Fig. 2). When doing infiltration anaesthesia, a mean amount of 1.2-ml local anaesthetic (SD 0.5) and when doing nerve block a mean amount of 1.5-ml (SD 0.3) solution was used. An average amount of 1.3 ml (SD 0.48) was injected. The subjective rating of anaesthetic efficacy of patients and investigators using a predefined ordinal scale is shown in Fig. 3.

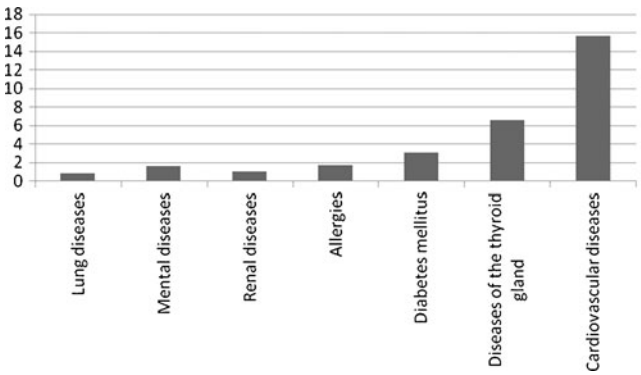

Fig. 1 Percentage of concomitant diseases (in percent; n=265 patients) related to the whole test group (n=908)

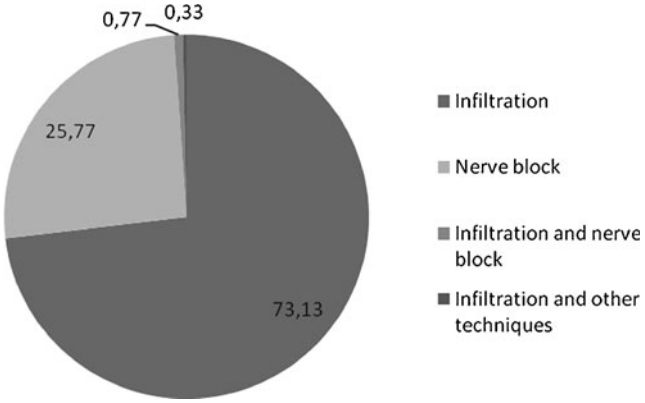

Fig. 2 Use of different anaesthesia techniques in percent (n=908)

In 96.3% (n=874) of cases, the first injection was sufficient to start treatment. With one single injection, 84.5% (n=767) of treatments could be completed successfully. In 3.7% (n=34), a second injection was necessary before treatment which was mostly done by infiltration. In 11.9% (n=108), a second injection had to be done during treatment. The second injection had to be applied after a mean of 48.6 min (5–165). This injection was not sufficient in 4% of cases when done between 10 and 30 min after the beginning of treatment. When done after >30 min, the injection was not sufficient in 1.5% of cases. A summary of efficacy associated to the technique of anaesthesia is shown in Fig. 4. Figure 5 shows which kind of anaesthesia technique was used in which kind of dental treatment.

A mean time of 7.3 min (0–40; SD 4.9) was seen to attain local anaesthetic effectiveness. After infiltration, a mean duration of soft tissue anaesthesia of 146.6 min (17–685 min; SD 70.14) could be measured. The patient with the duration of 685 min is suspicious for a failure in the metabolism of local anaesthetics but not yet tested. She is reacting always in that way. After nerve block, the mean duration was 187.7 min (55–440 min; SD 65.31;

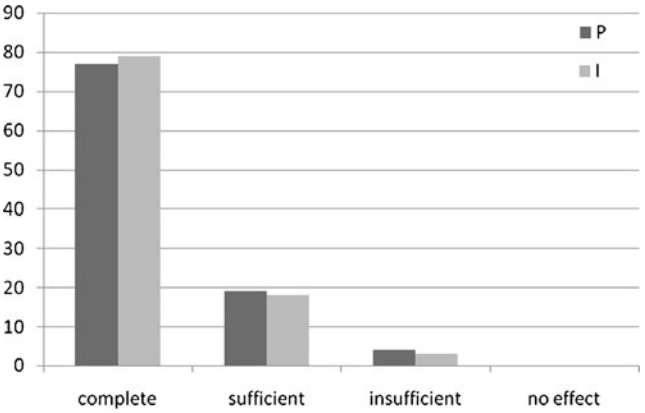

Fig. 3 Efficacy of anaesthesia assessed by patients (P) and investigators (I); values are given in percent

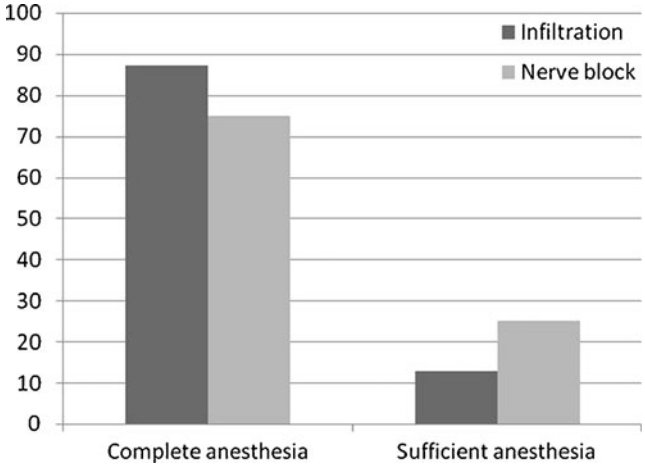

Fig. 4 Mean effectiveness of anaesthesia associated with technique in percent

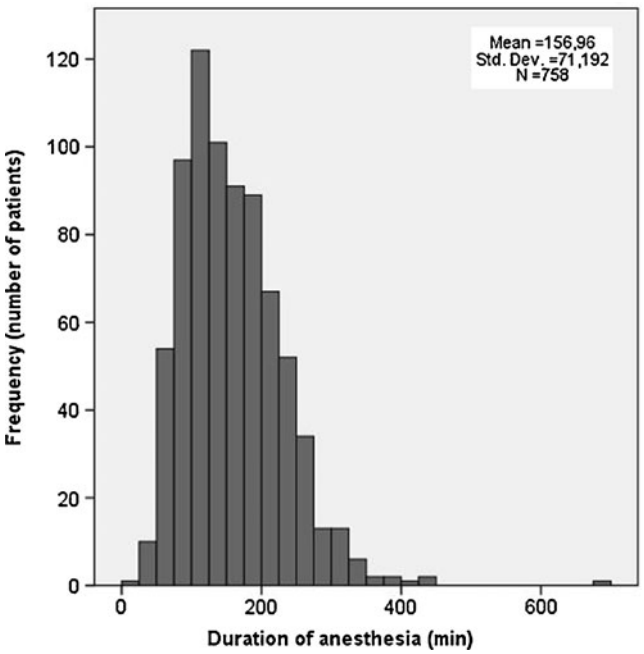

Fig. 6 Total duration of anaesthesia in minutes. Mean value as well as standard deviation and total patient numbers are given

Figs. 6, 7, and 8). The painful treatment of the patients with only one initial injection took a mean of 50.2 min (5–253 min; SD 44.3). The total treatment time in these patients summed up to 68.8 min (7–305 min; SD 54.4).

Adverse effects

In 1.7% of cases (n=15), unwanted side effects were observed. They could be separated into systemically, nonspecific symptoms (headache, dizziness, tremor, skin efflorescence's, and vasovagal syncope) into systemically specific symptoms (buzzing feeling in the back of the head) and into local symptoms (tooth ache, pain in the mandible, painful opening of the mouth, bleeding episodes). One case of prolonged numbness after injection close to the greater palatine nerve lasted up to 4 months. Only in nine cases causality with the local anaesthetic solution was really assumed by the investigator, which means an incidence rate of 1% for the drug. Medical and medicinal interventions were necessary in five cases.

Discussion

In several European countries, articaine hydrochloride is the most widely used local anaesthetic agent in dentistry. The actual duration of anaesthesia obtained varies with the local anaesthetic, its concentration, the type, the site of injection as well as the concentration of the vasoconstrictor [16]. Vasoconstriction influences duration and intensity of sensory block by delaying the absorption of local anaesthetic

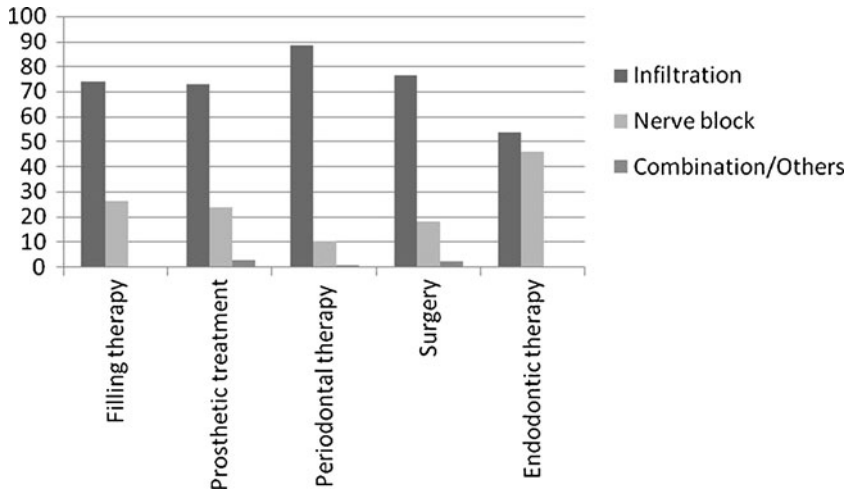

Fig. 5 Assignment of anaesthesia technique to different kinds of dental treatment. Values are shown in percent

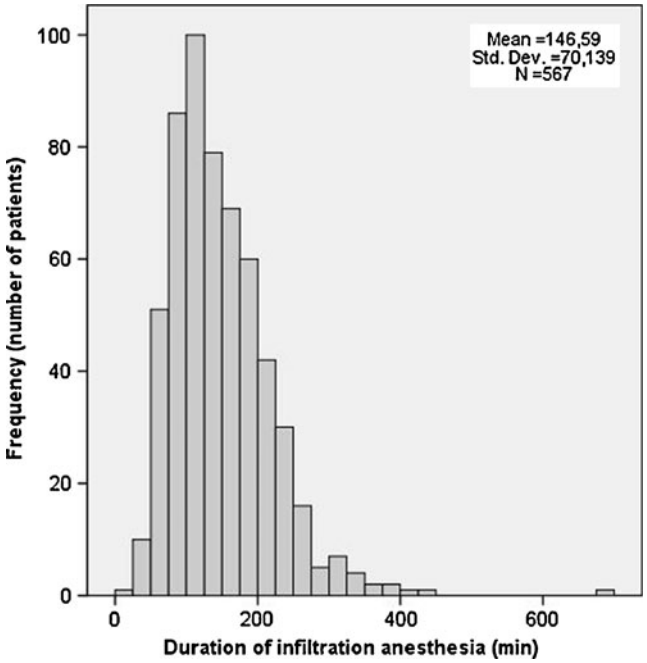

Fig. 7 Duration of infiltration anaesthesia in minutes. Mean value as well as standard deviation and total patient numbers are given

from the injection site. Epinephrine causes vasoconstriction by stimulating alpha-1 and alpha-2 membrane-bound receptors on vascular smooth muscle cells [18]. A reduction of epinephrine concentration can minimize potential side effects, shorten anaesthesia duration, and adapt the anaesthetic agent to the needs of practitioner and patient. Petrikas et al. studied the effect on pulpal anaesthesia of 4% articaine with different epinephrine concentrations, amongst others 1:400,000, in a smaller group of healthy volunteers without dental treatment. They concluded that the reduction in epinephrine concentration had only slightly reduced its effects but had not excluded them at all. In contrast, the articaine solution without epinephrine could not induce a relevant pulpal anaesthesia [19]. To the best of our knowledge, for 4% articaine with epinephrine in the dilution 1:400,000, no clinical studies regarding efficacy and safety in dental treatment have been published.

To answer the question on how much epinephrine is needed in dental local anaesthesia, in several clinical studies, the dilutions 1:100,000 and 1:200,000 have been compared. The anaesthetic efficacy and mean duration of anaesthesia were similar for 1:100,000 and 1:200,000 epinephrine-containing formulations whereas in subjects who received a formulation containing no epinephrine, the success rate for profound anaesthesia was significantly less [17, 20]. Abdulwahab et al. could not evaluate significant differences in pulpal anaesthesia between 4% articaine solutions with the different concentrations of epinephrine [21]. Accordingly, no differences were seen for lower third molar extraction with or without bone removal [22], whereas a better visualization of the surgical field and less bleeding could be seen for 4% articaine 1:100,000 epinephrine formulation in periodontal surgery [23]. In buccal vestibule–palatal anaesthesia, a more effective anaesthesia could be studied for 4% articaine with epinephrine 1:100,000 compared to epinephrine 1:200,000 [6]. The success rates in experimental clinical trials of Moore et al. with 4% articaine and epinephrine 1:100,000 and 1:200,000 were 95.2% and 93.5%, respectively, after maxillary infiltration [20]. Due to technical reasons, the success rate of the inferior alveolar block is lower, in this study 47.6% and 54.8%, respectively. In our study, infiltration was the predominant technique and showed a higher level of complete anaesthesia than nerve block. This may be due to the rate of failure of inferior alveolar nerve block mostly due to accessory innervations and anatomical variability [24, 25]. Compared to these numbers and other studies measuring the success rate of dental local anaesthesia [26–30], the overall efficacy of anaesthesia with a single injection of 4% articaine 1:400,000 epinephrine (Ubistesin™, 3M/ESPE, Seefeld, Germany) of 96.3% is high. The duration of pulpal anaesthesia was not tested separately. But the mean duration of 50.2 min of suggested painful treatment is in some respect a count for adequate pulpal anaesthesia. Accordingly, in 108 patients, a second injection had to be done after a mean time of 48.6 min. The results of the experimental clinical study of Moore et al. showed a duration of pulpal anaesthesia of 45.6 min (SD, 23.6), respectively,

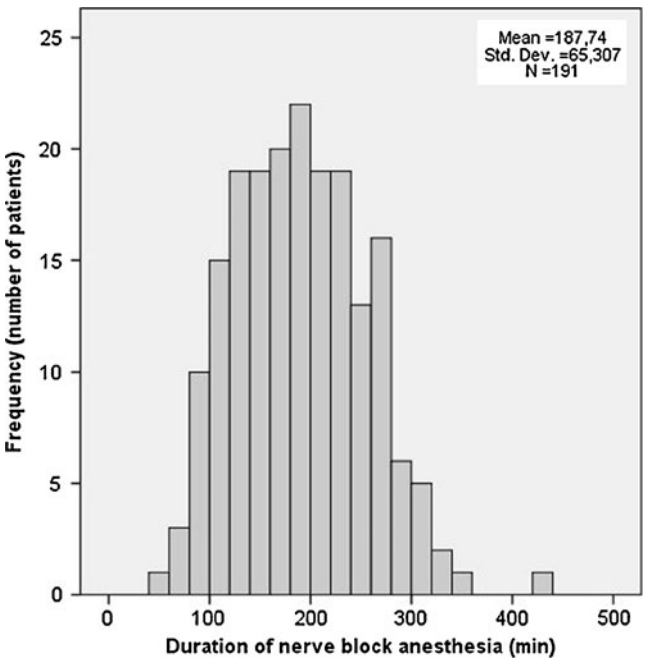

Fig. 8 Total duration of nerve block anaesthesia in minutes. Mean value as well as standard deviation and total patient numbers are given

41.6 min (SD, 21.1) after infiltration and 61.8 min (SD, 59) and 51.2 min (SD, 55.9) after inferior alveolar block with the 1:100,000, respectively, 1:200,000 solution. That means a decrease of duration of anaesthesia due to the reduced epinephrine concentration but still enough time for routine dental treatment that lasts mostly in less than 30 min. Accordingly, the duration of soft tissue anaesthesia after 4% articaine 1:400,000 epinephrine (Ubistesin™, 3M/ESPE, Seefeld, Germany) injection was shorter as seen in other studies with higher epinephrine concentrations [17, 22, 31]. The amount of needed local anaesthetic (mean 1.3 ml) is in accordance to the literature [17, 32, 33].

In contrast to the benefits of local anaesthesia, the usage of vasoconstrictive epinephrine leads to systemic side effects. For articaine with higher concentrations of epinephrine, more frequent adverse effects were reported [34, 35]. One study showed the relationship between the amount of the epinephrine concentration used and the number of specific complications. The articaine 4% solution with epinephrine 1:100,000 led to an incidence rate of 6.1% and the 1:200,000 solution of 3.1% [34]. The numbers of patients in this study were also comparable to the present study (1,057 and 1,404 patients, respectively); the fraction of patients with preexisting diseases somewhat higher but comparable in both groups. In the recent study, the frequency of side effects after 4% articaine 1:400,000 epinephrine (Ubistesin™, 3M/ESPE, Seefeld, Germany) administration was 1.7% (n=15). That means a further reduction due to the reduced epinephrine concentration. The most frequently observed complications were transient in nature and did not require treatment. As only in nine cases the causality with the local anaesthetic has been strongly assumed, the incidence rate for the drug was only 1%. One case of prolonged numbness of the palate and the left cheek for approximately 4 months after injection at the palatal foramen was the most serious event but did not require a specific additional treatment besides caring for the patient and invite him to a periodical recall. Our explanation for that incidence is a penetration of the cannula and the local anaesthetic into the fossa pterygopalatine. The results show a good tolerability of the drug even in medically compromised patients (29.2% of the included patients).

Conclusion

It could be evaluated that the 4% articaine 1:400,000 epinephrine formulation (Ubistesin^{TM}) is a safe and effective local anaesthetic in dental short-time routine procedures. The results indicate that a lower concentration of epinephrine in combination with the 4 % articaine solution leads to a high success rate of efficacy.

The duration of soft tissue anaesthesia is reduced especially when infiltration anaesthesia is used. Patients may benefit from shorter numbness. The incidence rate of the reported adverse events is low and reflects the good tolerability of the solution.

Conflicts of interest The authors declare that they have no conflict of interest.

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