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Ich bedanke mich bei den unten aufgeführten Kolleginnen und Kollegen für ihre wertvolle Mitarbeit, die sie in den vergangenen drei Jahren geleistet haben.

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Comparison of two epinephrine concentrations in an articaine solution for local anesthesia in children

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SUMMARY

Painless dental treatment is of major interest in pediatric dentistry. Local anesthesia contains epinephrine, which prolongs soft tissue anesthesia. This, however, is often a source of discomfort for children and is responsible for certain side effects (e.g., self-inflicted soft tissue lesions).

The aim of this study was to investigate whether an epinephrine-reduced articaine solution could reduce the duration of soft tissue anesthesia and thereby reduce the risk of self-inflicted soft tissue lesions, while still providing an adequate anesthesia.

In a non-interventional clinical study, routine dental treatment was performed on children and adolescents. An articaine 4% solution with an epinephrine-reduced solution (Ubistesin™ mite, 1:400,000) and a conventional epinephrine solution (Ubistesin™ forte, 1:100,000) were compared in terms of duration of soft tissue anesthesia.

One hundred and fifty-eight patients (mite: 75, forte: 83) were treated (80% with infiltration anesthesia). In both groups, the average volume of the injection was comparable (mite: 1.2 ml, forte: 1.1 ml). One patient from each group showed unwanted side effects. In both groups, the local anesthesia was complete or sufficient (96%) to perform the planned treatment. The average treatment time was 24 minutes in the mite group and 28 minutes in the forte group. The difference in mean duration of soft tissue anesthesia was statistically significant ($p = 0.001$, mite: 2.1 h, forte: 2.8 h).

Thanks to its high efficacy, tolerance, and reduced soft tissue anesthesia, the articaine 4% solution with the reduced epinephrine concentration (1:400,000) was considered a safe and suitable drug for routine treatments in pediatric dentistry.

Introduction

Adequate, successful pain and fear management is critically important in modern pediatric dentistry. Thus, it is very important today that a successful elimination of pain include the control of fear. It is now known that until they reach school age, children cannot differentiate between the experience of pain and the feeling of discomfort/anxiety (RAADAL ET AL. 2009). Negative experiences and pain during dental treatment can become anchored in a child's memory. This initiates pain learning processes that manifest in the neuro-matrix (DAUBLÄNDER 2005). Hence, in the interest not only of the patient but also the dentist, this phenomenon should be avoided whenever possible.

Therefore, adequate elimination of pain during dental treatment of children and adolescents is a *conditio sine qua non*. In pediatric dentistry, local anesthesia is still the method of choice for pain elimination and can thus be considered the gold standard (DAUBLÄNDER 2006). Hence, choosing the right local anesthetic is of special significance. Because of its sufficient anesthetic effect in combination with a low level of toxicity, a 4% solution of articaine – which is part of the acid amide complex with a thiophene ring at the aromatic end – is used in routine dental procedures (BADER & LAMBRECHT 2001). Side effects can be avoided by using a weight-based dosage (AHMED & MARTINEZ 2009). In order to prolong the duration of local anesthetics as well as avoid serious systemic side effects due to a lower level of plasma, a vasoconstrictor (LIPP ET AL. 1993, YAGIELA 1995), usually epinephrine, is added to the compound (PAXTON & THOME 2010). However, a child's vegetative nervous system can react very sensitively to systemic side effects caused by epinephrine (ISTAPHANOUS & LOEPKE 2009). Furthermore, epinephrine prolongs the effects of the anesthetic, thus increasing the risk of self-inflicted soft tissue lesions, for example, biting of the tongue or lip (RAM & AMIR 2006).

The Ubistesin™ mite injection solution is approved by the manufacturer (3M ESPE, Seefeld, Germany) for dental therapy in children above the age of four and adolescents with certain approved indications. The drug consists of articaine hydrochloride (40 mg/ml) and epinephrine as hydrochloride (2.5 µg/ml in a corresponding dilution of 1:400,000). What makes Ubistesin™ mite different from the conventional compounds is its low level of epinephrine (Ubistesin™ forte: 1:100,000, Ubistesin™ 1:200,000). Therefore, the effects on the circulatory system are expected to be less severe when administering the compound accordingly. Additionally, one can assume that a lower concentration of the vasoconstrictor reduces the duration of the soft tissue anesthesia. To supplement previously published studies of other local anesthetics with higher concentrations of epinephrine used in children, the purpose of this observational study was to specifically document the effects profile and compatibility when treating children and adolescents in terms of lower epinephrine concentrations and the duration of the soft tissue anesthesia.

The aim of this study was to examine and compare the clinical benefits of Ubistesin™ mite and Ubistesin™ forte injection solution on children and adolescents under routine conditions in a dental practice. The criteria for success were the effectiveness, duration, tolerability, and safety of the chosen anesthetic. Simultaneously, the side effect profile on children and adolescents and the areas of application in restorative dentistry were recorded.

Materials and Methods

Study design and selection of patients

To meet the ethical requirements of such a study, the patients or their parents were informed in writing about the purpose, content, and data security of the study. Participation in the study was voluntary, and patients had the right to revoke their participation at any time without stating reasons. The ethics votum of the Cantonal Ethics Commission was positive.

This was an observational study without intervention in the usual clinical treatment of the patients. The monocentric clinical study examined 176 patients (87 mite, 89 forte) who were recruited in the third quarter of 2011 at a study center (Clinic for Orthodontics and Pediatric dentistry, University of Zurich) with several satellite clinics (school dental clinics of the City of Zurich).

All patients aged 4 to 17 (the main target group was ages 4 to 12) and their parents/legal guardians were asked to participate in the study if infiltration, block or intra-ligament anesthesia was planned for a routine treatment, thus making the selection of patients random. The allocation into the two groups was done by drawing lots, with the exception of a very few, more extensive surgical cases. Neither the patients nor their parents/guardians were told which group they were sorted into. The routine treatments to be included were those in the deciduous and permanent dentition that were not expected to take longer than 30 minutes: presumably easy extractions, treatment of lesions to the dentin caused by trauma, endodontic procedures, inserting stainless steel crowns, and cavity and crown-stump preparations. Suitable consecutive patients who had given their consent were included in the study. Each patient was included in the observational study only once. Therefore, if a patient took part in the study, it had to be noted in his or her medical history. Reasons for excluding patients were all the absolute contraindications mentioned in Ubistesin's™ product information sheet. Other criteria for exclusion from the study were suspected drug addictions, chronic or spontaneous ingestion of painkillers or psychotherapeutic drugs at the time of dental treatment, and cardiovascular diseases as well as sub-optimal general health with risk classifications of ASA 3 (American Society of Anesthesiology) and ASA 4. Further reasons for exclusion of patients were relative contraindication of the test substance, as well as mucogingival surgery (labial or lingual frenulum surgery), surgical exposure of impacted teeth, extraction of the 12-year molar, a planned osteotomy, the treatment of acute trauma-related lesions as well as surgical procedures that called for postoperative analgesia over several hours and prolonged vasoconstriction for ischemia.

The local anesthetics used were 4% articaine in 1.7-ml cartridges with an epinephrine concentration of either 1:100,000 (Ubistesin™ forte) or 1:400,000 (Ubistesin™ mite).

Examination procedure

Before the study began, every patient and/or their parent/guardian gave their written consent that they had been informed about the study in detail and that all questions they might have had been answered to their satisfaction. After reviewing the patients' medical history and determining their weight, the findings (tooth, area, indication) were documented on the patient datasheet in preparation for dental treatment. The decision whether or not to sedate the patient in addition to applying the local anesthesia was left up to the dentist. Here, type, drug, and concentration were documented. Depending

on the indication the appropriate technique of application was chosen (infiltration, block or intra-ligament anesthesia). The time of injection of the anesthetic, as well as the amount and injection technique were documented. If several areas were anesthetized, only one tooth or area of up to three neighboring teeth was observed and documented. In these cases, the quadrant that was treated first was included in the study. If a second injection was necessary, time, amount, and anesthetic used as well as the technique of application were noted. The length of the entire treatment was documented by the treating dentist. The treating dentist also evaluated the anesthesia using certain scores:

- Score 3: completely effective (treatment is completely painless)
- Score 2: sufficiently effective (slightly painful treatment, yet no additional injection necessary)
- Score 1: insufficiently effective (painful treatment, and depending on the intensity of the pain, second injection necessary)
- Score 0: no effect (second injection necessary)
- Evaluation not possible (treatment could begin only at least ten minutes after the first injection, uncertain whether effects had worn off)

Until an evaluation was made, a latency period of 5 to 7 minutes was allowed to elapse. A premature termination of the planned treatment as well as its reasons had to be documented. The time point at which restored, complete, normal sensation was ascertained – which marks the end of the soft tissue anesthesia – as well as possible unwanted events (systemic or local) were documented by contacting the patients/their parents via telephone on the day of the treatment or the following day. Unwanted local events were, for example, hematomas and bite lesions (cheek, lip, tongue). In the examination report, every harmful incident that befell the patient after the drug was administered, regardless of whether or not it could be linked to the treatment, was defined as an unwanted event. However, in cases of unwanted drug effects, equal to side effects, a causal link between the unwanted event and the drug was assumed. The entire period of observation was 14 days.

Statistical evaluation

All parameters of this open, explorative observational study were evaluated using descriptive statistics.

To analyze the reduced duration of the soft tissue anesthesia in the two groups (Ubistesin™ mite and Ubistesin™ forte), the results were subjected to a parametric two-sample t-test.

The sample size was determined using a power sample-size test. Assuming a standard deviation of +/-60 minutes and an expected difference of 25 to 30 minutes, an accuracy of 75% with a mean difference of 25 minutes could be expected, but with a mean difference of 30 minutes, an accuracy of 88% could be expected with 80 patients. Based on these calculations and the acceptance of an accuracy of about 80%, the number of patients per group was set at 80.

Results

Patients

Of the 176 patients (87 Ubistesin™ mite, 89 Ubistesin™ forte), 12 patients from the mite group and 6 patients from the forte group could not be included in the evaluation due to inadequacies in informed-consent forms or not meeting the inclusion

criteria. In two cases, the treatment of a patient from the mite group had to be discontinued and in one case from the forte group. These patients were not included in the evaluation of the time needed for the treatment or the duration of the effects of the anesthesia; they were, however, included in the other descriptive evaluations. The set age requirement of 4 to 17 years was fulfilled in both groups and the distribution of gender was even (mite: 38 female, 37 male; age: \bar{x} = 8.37 years, 4–15, SD = 2.42; forte: 39 female, 44 male; age: \bar{x} = 7.99 years, 4–16, SD = 2.30). In the end, the data of a total of 158 patients (mite: 75, forte: 83) were evaluated who had been treated at the six study centers within the third quarter of 2011. In both groups 60% of the examinations were conducted in three study centers (Schulzahnklinik Nord, Schulzahnklinik Unterstrass, and Schulzahnklinik Aussersihl). The patients' average weight was 31.25 kg in the mite group (18–79, SD = 11.41) and 29.87 kg in the forte group (15.6–76.5, SD = 11.82). There were no known allergic reactions to the local anesthetic or its components in any of the patients.

Indications for treatment/areas of application

In about 90% of the cases in both study groups, the following indications for treatment were listed. Mite: 49/75: preparation of cavities at the D3 level; 16/75: extractions of primary teeth (70% posterior teeth, 30% anterior teeth); 4/75: preparation of cavities at the D3/D4 level; other indications for treatment: 8%. Forte: 51/83: preparation of cavities at the D3 level; 16/83: extractions of primary teeth (60% posterior teeth, 40% anterior teeth); 8/83: preparation of cavities at the D3/D4 level; other indications for treatment: under 10%.

Anesthesia

In 80% of the cases, dental treatment was conducted without additional sedation. With almost 20% of the mite patients (13/75) and a good 10% (9/83) of the forte patients, inhalation sedation was implemented with nitrous oxide.

The most commonly used injection technique was infiltration anesthesia. This type of anesthesia was performed on about 80% of the patients (mite group: 60/75; forte group: 66/83). Block anesthesia was used in 13% of the cases in the mite group (10/75), and with Ubistesin™ forte in about 11% of the cases (9/83). Furthermore, combinations of injection techniques were done, for instance the combination of infiltration and block anesthesia (mite 2/75; forte 7/83), and the combination of infiltration and intra-ligament anesthesia (mite 2/75; forte 1/83). In both groups, the mean amount injected was about the same (mite: 1.2 ml, SD = 0.29; forte: 1.1 ml, SD = 0.30).

Side effects

In each group, one patient showed unwanted side effects. These were rated as non-serious: one patient from the mite group was diagnosed with nausea post-operatively (1/75), which, however, disappeared spontaneously. One patient from the forte group complained of a headache (1/83), which also spontaneously wore off. The dentist who had performed the treatment rated the causal link as non-assessable.

Efficacy and duration of soft tissue anesthesia

In both study groups, complete to sufficient effectiveness of the anesthesia was achieved in 96% of the cases (mite: 72/75; forte: 80/83) (Fig. 1). Three patients from each group judged the effects of the anesthesia as insufficient. In the mite group, two

(2/75) second injections were applied, where subsequently one treatment could be conducted completely, but the other had to be prematurely discontinued due to persistent pain. The treatment of one patient had to be terminated prematurely due to a lack of cooperation. In three cases, patients from the forte group also judged the effects of the anesthesia as being insufficient (3/83), and all three patients were given a second injection. In two cases, this led to a successful conclusion of the treatment. Due to poor cooperation, the treatment of one patient had to be terminated prematurely.

The mean time required for the treatment was 24 minutes (SD = 10.2) for the Ubistesin™ mite group, and 28.4 minutes (SD = 12.7) for the Ubistesin™ forte group. In the mite group, the treatment time for cavity preparation at the D3 level with one to two adjoining teeth was an average of 27 minutes (SD = 9.4), the treatment time for the extraction of one to two adjoining deciduous teeth was a mean of 13 minutes (SD = 6.5). In the forte group, the treatment time for cavity preparation at the D3 level

under the same circumstances was about 28 minutes (SD = 8.2), and an extraction of one to two adjoining deciduous teeth took about 23 minutes (SD = 19.5).

The datasets for the mean duration of the effects of the anesthesia and thus the duration of the soft tissue anesthesia showed that the effects of Ubistesin™ mite lasted for 126.2 minutes (SD = 64.1), and those of the forte compound lasted for 166.0 minutes (SD = 94.2). The differences are statistically significant ($p = 0.001$) (Fig. 2).

Discussion

In pediatric dentistry, it is mandatory to recognize pain and treat it, as well as to take preventive measures against pain. Being a conventional tool of dentistry, local anesthetics are one of the most frequently administered drugs (MALAMED 1990). Articaine chloride with an added vasoconstrictor is quite popular for local pain elimination in the dental treatment of children and adolescents. The added epinephrine reduces the risk of intoxication through delayed washout, which increases the available threshold quantity. Safe pulp and soft tissue anesthesia offers a wide range of indications for conservative-surgical treatment of children. Bite lesions due to prolonged soft tissue anesthesia, however, pose a relatively common problem that should not be underestimated. In their study, ADEWUMI ET AL. (2008) examined the side effects that occurred in connection with articaine, and reported an increased number of transient sensation disturbances. Forty percent of the patients complained of numbness three hours after treatment, and after five hours, 11% still complained of numbness. Accordingly, 14% of the children incurred bite lesions, mainly of the lip. These unwanted accompanying events can be partially attributed to the vasoconstrictor (MEECHAN ET AL. 2001). To date, the safety and effect of a 4% articaine and a 2% lidocaine solution with a 1:100,000 and 1:200,000 addition of epinephrine have been examined in several studies (DUDKIEWICZ ET AL. 1987, WRIGHT ET AL. 1989, WRIGHT ET AL. 1991). BOYNES ET AL. (2013) published a paper in which the rate of complications after the injection of a vasoconstrictor (phentolamine) that shortens the duration of the soft tissue anesthesia was examined. The duration of numbness of cheeks, lips, and tongue could be reduced by almost half by a second injection into the anesthetized area at the end of the dental treatment. So far, this alpha-adrenergic antagonist is only approved in the USA and Germany. A recently published paper showed the clinical benefits of a 4% articaine solution with epinephrine at a concentration of 1:400,000 (KÄMMERER ET AL. 2013). However, there is no data to date comparing the two drugs directly. Thus, the question at hand was whether or not the length of the paresthesia, which caused the bite lesions in children, could be verifiably reduced by using an epinephrine-reduced anesthetic (1:400,000) instead of the usual compound (1:100,000).

The age and gender distribution as well as the indications for treatment were similar in the mite and the forte group. In both groups, about two-thirds of the cases (mite: 49/75, forte: 51/83) were preparations of cavities at the D3 level. The second most common area of application was the extraction of deciduous teeth, with about 20% in both groups (mite: 16/75, forte: 16/83). Therefore, the differences that appeared in the evaluation were discarded as irrelevant. The data concerning the additional sedation through inhalation were, however, less similar. In the mite group, nitrous oxide was used almost twice as often as in the other group (mite: 13/75, forte 9/83).

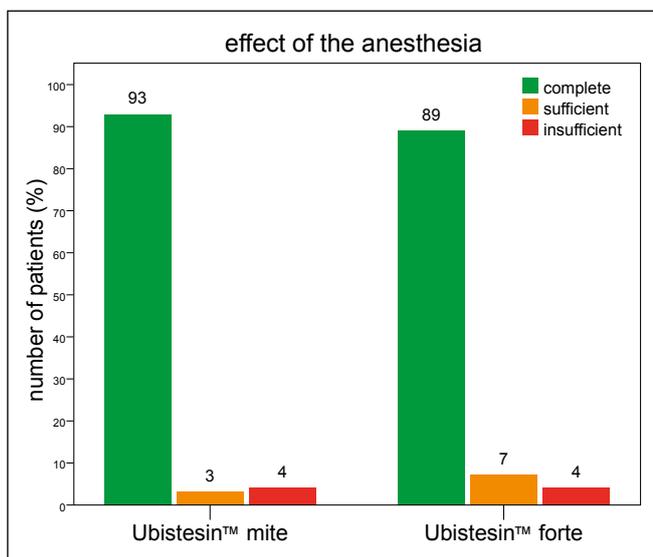


Fig. 1 Results of the effect of the anesthesia in percent for Ubistesin™ mite and Ubistesin™ forte

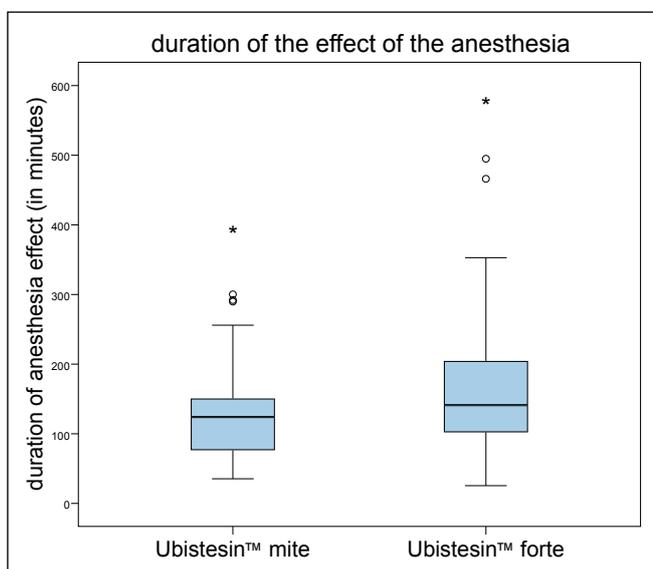


Fig. 2 Boxplot of the duration of the effect of the anesthesia in minutes of Ubistesin™ mite and Ubistesin™ forte

The injection technique, however, was the same in both groups again. For about 80% of the treatments, an infiltration technique was used. About every tenth anesthesia was performed by blocking the inferior alveolar nerve (mite: 10/75, forte: 9/83). Almost the same amount of anesthetic was administered in both groups (mite: 1.2 ml, forte: 1.1 ml). The occurrence of unwanted side effects (1%) was also identical; in both groups, one patient showed a non-serious, spontaneously subsiding event. These results match those of a recently published Australian study that examined serious unwanted events due to local anesthesia and found that such events are very rare (SAMBROOK ET AL. 2011). In our study, no damage to the soft tissue caused by biting was reported.

A success rate of 97% of the initial injection in the mite group and 96% in the forte group, as well as successful completion of treatment of 97% in the mite group and 99% in the forte group prove a very high efficacy for both of the tested anesthetics. The success rate of the initial injection in the mite group was even higher than in a comparable study by KÄMMERER ET AL. 2013. The higher success of the mite group may be explained by the fact that the treating dentist automatically used Ubistesin™ forte if more demanding surgical procedures were necessary. This created a bias. Through a strictly randomized assignment of the patients, the resulting difference might change. The same thoughts apply to the following results: due to two particular cases that were more time consuming, the average time needed for treatment was slightly longer in the forte group than in the mite group (mite: 24.0 minutes, forte: 28.4 minutes). The treatment of patients from the forte group tended to take slightly longer. If the data from those two cases were eliminated, the rest of the data stayed within a normal distribution. The mean was reduced to 27.4 minutes (SD = 10.3), and the time needed for the treatments was equally long. The time required for the preparation of a cavity was almost identical (mite: 27 minutes, forte: 28 minutes). However, this was not the case for the time required for extractions. While an extraction of one to two adjoining deciduous teeth took 13 minutes in the mite group, the average time needed for an extraction in the forte group was about ten minutes longer, thus being 23 minutes.

One of the most important results of this study was the correlation between the concentration of epinephrine in the anesthetic and the duration of the soft tissue anesthesia. It was proven that the patients from the mite group experienced a significantly shorter duration of soft tissue anesthesia than did the patients from the forte group ($p = 0.001$). Furthermore, the boxplot indicates that the outliers of the forte group are more extreme. This is a very important issue for pediatric dentistry which should not be underestimated, because a large number of postoperative complications comprise the self-inflicted lesions commonly seen in dental practices. These mostly involve the lips, but also the tongue and cheeks, due to the prolonged paresthesia. This observation could, however, not be confirmed definitively in clinical studies (RAM & AMIR 2006); these authors reported the effects of the anesthetic to persist for 3.43 (SD = 0.7) hours. KÄMMERER ET AL. (2013) reported a duration of 2.19 hours when using a 4% articaine solution with 1:400,000. Our results were 2.1 hours for the mite group and 2.8 hours for the forte group. Differentiation based on type of local anesthesia used was not possible on account of the small number of cases. Therefore, a total mean was determined with a comparable distribution in both groups. Consequently, the use of an epinephrine-reduced compound shortens the duration of soft

tissue anesthesia, a condition which is both unpleasant and dangerous for children. In contrast to other studies (ADEWUMI ET AL. 2008, BOYNES ET AL. 2013), none of the patients in our study showed any unwanted local events, probably owing to the fact that the children were informed in such detail about these risks, and watched closely to prevent lesions of this kind.

In the present study, the clinical benefits of both anesthetics were examined and compared. The epinephrine-reduced compound proved to be effective, sufficient in duration, and tolerable. The 4% articaine solution with an added vasoconstrictor of 1:400,000 is clearly advantageous for pediatric dentistry, where insuring adequate elimination of pain with as few side effects as possible is of vital importance.

In accordance with the study protocol, the mite compound with a pulp anesthesia time of about 30 minutes is recommended without restriction for the shorter routine treatments in pediatric dentistry. Using this compound for indications that require a prolonged pre- and postoperative period of anesthesia or an ischemia should be evaluated critically. However, the use of the conventional compound with a higher level of epinephrine is still recommended for treatments that require prolonged pulp anesthesia as well as treatments where restricted blood flow and prolonged elimination of pain through local anesthetics is necessary postoperatively. Although it contradicts the established university consensus, many private practices and – according to the manufacturer – about 96% of pediatric dentists use the forte compound as a rule in their daily routine, because the name forte implies a strong and reliable effect. In truth, however, the higher level of epinephrine prolongs the effective only insignificantly. In comparing the two epinephrine concentrations, which differed by a factor of 4, the study was able to show that even the mite compound is sufficiently effect for the practice of pediatric dentistry. This should make it clear to the practitioner that the forte compound should be used only in certain exceptional cases, and that an epinephrine concentration of 1:200,000 is more than enough for a standard compound. In general, it is important to weigh the advantages and disadvantages when choosing the right anesthetic, in order to ensure pain-free treatment while keeping the burden borne by the patient to a minimum. Patients who have had experiences with both compounds would clearly prefer Ubistesin™ mite for future treatments.

Conflict of interests

Consulting services were provided by 3M ESPE, supervisor of the sponsored study.

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Résumé

En médecine dentaire pédiatrique, la minimisation de la douleur pendant le traitement est de grande importance. Pourtant, l'anesthésiant local contient de l'adrénaline, qui est responsable pour l'anesthésie prolongée des tissus mous. Ceci n'engendre pas seulement une sensation désagréable pour les enfants, mais est aussi associé à un taux élevé d'effets secondaires (p. ex. blessures par morsure). Le but de l'étude était d'évaluer, si la réduction d'adrénaline dans l'anesthésiant local peut réduire le temps d'anesthésie des tissus mous et ainsi le risque

de morsures, tout en préservant une profondeur et durée d'anesthésie suffisante.

Dans une étude clinique, qui a été menée dans le cadre de traitements routiniers d'enfants et d'adolescents, la durée d'anesthésie d'une solution de 4% d'Articaïne avec un taux réduit d'adrénaline (Ubistesin™ mite, 1:400 000) a été comparée à une solution avec un taux d'adrénaline normale (Ubistesin™ forte, 1:100 000).

158 patients (*mite*: 75, *forte*: 83) ont été traités (80% avec anesthésie d'infiltration). Le volume d'injection moyen était comparable dans les deux groupes (*mite*: 1,2 ml, *forte*: 1,1 ml).

Dans chacun des deux groupes, un patient a subi des effets secondaires. Dans chacun des deux groupes, une anesthésie complète ou suffisante a été obtenue dans 96% des cas. Le temps de traitement moyen a été de 24 minutes dans le groupe *mite* et 28 minutes dans le groupe *forte*. Concernant la durée d'anesthésie des tissus mous, une différence statistiquement significative a été trouvée ($p = 0,001$, *mite*: 2,1 h, *forte*: 2,8 h).

En raison de la bonne efficacité et tolérance ainsi que de la réduction de la durée d'anesthésie, la solution d'Articaïne de 4% avec un taux d'adrénaline réduit constitue un anesthésiant local adéquat pour la médecine dentaire pédiatrique.

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