Influence of surface anesthesia of the nasal cavity on oral tissues in the anterior region – a pilot study

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Key words

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Abstract

Nasal surface anesthesia is a simple, non-invasive method with a not yet fully understood effect on oral tissues. Should it prove to be successful in dental medicine, it could replace or at least complement the more invasive injection anesthesia, especially in children after dental trauma. The local anesthetic Tenaphin (tetracaine hydrochloride and naphazoline nitrate) was applied to 105 patients prior to ear, nose and throat medical diagnosis or therapy. After different exposure times, the influence on the oral tissues in the anterior region was examined by a dentist in the context of a pilot study. The effect of the mucosal anesthesia increased in the canine and anterior region the further mesial the tooth was located and the longer the application time was. In the buccal and palatinal area the effect increased from apical to incisal. The pulps of the central incisors and the canines were better anesthetized than those of the lateral incisors. Nasal surface anesthesia has the potential to replace the more invasive injection anesthesia in the anterior region of the upper jaw or to complement it. Dosage and exposure time will have to be investigated in more detail.

Introduction

Dental trauma in children is common. One third of all preschool children experience dental trauma in the deciduous dentition, and also many children and adolescents suffer a dental trauma in the permanent dentition (GLENDOR 2008). The incidence for a dental accident is greatest in the first 10 years of life, and then decreases (GLENDOR 2008). Maxillary anterior teeth, especially the central and lateral incisors, are more frequently affected by trauma than lower front teeth (MEECHAN ET AL. 2005, GLENDOR 2008, JOHNSON ET AL. 2010, GAZAL ET AL. 2017). Anesthesia in the anterior region is often painful (GAZAL ET AL. 2017), whereat the palatal infiltration in the anterior area is considered the most painful intraoral injection
(MEECHAN ET AL. 2005). As a possible alternative to conventional infiltration anesthesia in the anterior maxilla, nasal spray anesthesia is discussed (JOHNSON ET AL. 2010).

The maxillary nerve sources from the trigeminal nerve and travels along the lateral wall of the cavernous sinus and passes from the middle cranial fossa into the pterygopalatine fossa via the foramen rotundum. The infraorbital nerve is the continuation of the maxillary nerve. It exits onto the face via the infraorbital foramen. In the infraorbital canal the infraorbital nerve gives rise to the anterior superior alveolar nerve, which supplies the maxillary sinus, maxillary central incisors, lateral incisors and canines, gingiva and the mucosa alongside these teeth. The infraorbital gives as well rise to a small branch of the anterior superior alveolar nerve, which supplies the nasal cavity. The infraorbital nerve also gives rise to the middle superior alveolar nerve (only present in 70%), which supplies the maxillary sinus, maxillary premolars and often the mesiobuccal root of the first maxillary molar, the gingiva and mucosa alongside these teeth. The anterior, middle and posterior superior alveolar nerves form the superior dental plexus to supply the maxillary arch.

The posterior superior alveolar nerve sources from the maxillary nerve in the pterygopalatine fossa, enters the infratemporal surface of the maxilla and descends to form the superior dental plexus. It innervates part of the maxillary sinus and molars with the possible exception of the mesiobuccal root of the first molar.

The nasopalatine nerve (also known as the sphenopalatinal nerve) sources from the maxillary division of the trigeminal nerve, passes through the sphenopalatine foramen to enter the nasal cavity, passes along the superior portion of the nasal cavity to the nasal septum, where it travels anteroinferior to the incisive canal supplying the septum. Once entering the oral cavity through the incisive foramen, it provides sensory innervation to the palatal gingiva and mucosa from central incisor to canine (NORTON 2012, VONARX & LOZANOFF 2015).
The innervation of the maxillary front teeth and the canines as well as the surrounding gingiva and mucosa was relevant for our study. The palatal gingiva and mucosa are innervated through the nasopalatine nerve (NORTON 2012) (Fig. 1, 2). Innervation of the incisors and canines of the maxilla is performed via the anterior superior alveolar branch, which is in close proximity to the nose (GAVIOLA ET AL. 2013, VONARX & LOZANOFF 2015). The close proximity is important for the effect of the nasal anesthesia.

Nasal anesthesia is used regularly in ear, nose and throat medicine (ENT) prior to endoscopic examinations (GAVIOLA ET AL. 2013). Numbness in the maxillary has been described as a side effect (CIANCO ET AL. 2013). Nasal application by means of spray or tamponade achieved anesthesia of the teeth in the maxillary (JOHNSON ET AL. 2010). Intranasal anesthesia is a non-invasive method and works within a few minutes in the area of the tonsils, the larynx, the maxillary sinus, the nose and the mouth. The diffuse and large-area distribution of the nasal anesthesia can be discussed as possible disadvantage compared to the more precise syringe anesthesia, especially for dental application (JOHNSON ET AL. 2010). The aim of the present study was to examine in adult patients, whether the use of pain-free nasal spray anesthesia would be feasible in the anterior maxilla instead of conventional infiltration anesthesia. The success of the anesthesia of the gingiva and the pulps were evaluated with a sensitivity test.

**Material and methods**

The present clinical examination was performed at the Department of Otorhinolaryngology, Head and Neck Surgery of the University Hospital Basel. The local ethics committee approved the study (EKNZ 2014/160). The inclusion criterion was that the probands had to be at least 18 years of age. Excluded were patients
lacking the ability to make decisions, for instance patients with dementia. The declaration of consent was signed after the patient was informed, either oral or in writing. The patients received one or two administrations of the nasal spray anesthetic Tenaphin from the treating practitioner, necessary for intubation narcosis treatment. Alternatively, the anesthetic was applied by nasal tamponade. The nasal surface anesthetic Tenaphin is produced in the hospital pharmacy of the University Basel. Tenaphin is a solution, which contains 10 mg tetracaine hydrochloride and 0.2 mg naphazoline nitrate per milliliter. Maximum dose for normal weight patients is 20 mg tetracaine hydrochloride, which is provided by about 14 spray administrations or by 2 ml Tenaphin. Tetracaine hydrochloride blocks tension-dependent sodium channels at the membranes of the nerve fibers and thus leads to the desired anesthesia in the area supplied by the nerve. Naphazoline contracts the blood vessels at the application site (Timmermann 2011). Depending on the indication, the anesthetic was applied on one or two sides (right and/or left nostril). The number of spray applications and the time of application were documented. In case of one-sided anesthesia both sides were examined by the dentist, but only the anesthetized side was evaluated. In addition, the age and medication anamnesis were documented. The time of application was recorded before the medical examination. After the medical examination, the exposure time was calculated, and the dental examination was started. In the schematic picture of the upper anterior area, possible dental restorations were recorded as far as they could be evaluated clinically. Sensitivity test of the pulp was performed with a foam pellet and the cold spray Polar - 45° (ABC dental, Schlieren, CH). The cold foam pellet was held to the tooth for about two seconds, unless the patient indicated a feeling of cold earlier than that. Subsequently, the sensitivity of the gingiva was checked for sharpness or bluntness with a cow horn probe. From buccal the upper anterior front teeth 13 to 23 were examined in apical direction each at 3mm, 8mm
and 13mm, starting at the dento-gingival margin; from palatinal these teeth were examined each at 5mm and 10mm starting again at the dento-gingival margin and documented in the schematic picture (Fig. 1).

The success of the anesthesia was modeled in a logistic mixed effects model with tooth and time since applications as fixed and patient identifier as random effect. Time since application was centralized prior to analysis. As a sensitivity analysis, a generalized additive model was used to estimate a smooth function for the effect of time since application. Furthermore, raw data was displayed graphically. An approximation of the success of anesthesia at each point in time was estimated by interpolating simple moving averages. A score was defined to illustrate the effectiveness of the anesthesia. The primary endpoint was reached when the marginal mucosa (points C and D) was anesthetized.

**Results**

Altogether 105 patients met the inclusion criteria, of whom 47 were male and 58 were female. Five patients, unable to decide for themselves, were excluded. The mean age of the patients was 47.2 years (19-81, SD 16.3). During medication anamnesis seven patients indicated to have taken an analgesic on the day of the examination. 52 patients reported to have taken other medications on the day of the examination (Table 1).

Dental examination was conducted after a mean of 16.5 minutes (6.5-51, SD 7.1) after nasal application of the surface anesthetic. Patients, who only received unilateral anesthesia, were consistently only evaluated unilaterally.
Anesthesia of the gingiva per measuring point

Negative reaction to the sharpness examination per measuring point showed that the anaesthesia buccal (A-C) as well as palatinal (D-E) increased from apical to incisal (p < 0.001) (Fig. 2). The most frequently anesthetized region was buccal close to the gingival margin. The anesthetic effect increased with the exposure time (p=0.006).

Anesthesia of the gingiva, assessment per tooth

When comparing the effect of mucosal anesthesia, the position of individual teeth in the jaw did play a role. Figure 3 shows the comparison of the anesthetic success between the individual positions in the jaw as well as between the palatinal and buccal points. Using tooth 13 as an example, in average 37% of the points A-C and 38% of the points D-E were anesthetized.

Better anesthesia of the mucous membrane was shown the further mesial a tooth was located. Anesthesia of the central incisors was better than that of the lateral incisors (p=0.048). Canines were less anesthetized than lateral incisors (p < 0.001). When comparing the buccal (A-C) and palatinal (D-E) measuring points, no difference could be detected (p=0.128). The anesthetic effect increased with the exposure time (p=0.004).

Sensitivity test

The evaluation of the sensitivity of the pulp showed that the lateral incisors were less frequently anesthetized than the central incisors (p=0.013) and the canines (p=0.005) (Fig. 4). No differences were detectable between left and right (p=0.794).
Anesthesia of the marginal mucosa was defined as primary endpoint (position C and D). Anesthesia of the central incisors was more successful than that of the lateral incisors and canines \((p \leq 0.002)\).

**Discussion**

In the present study, an effect on the anesthesia of the pulp and the surrounding gingiva could already be achieved with a very low concentration of the active ingredient tetracaine. The gingiva was best anesthetized in the incisal area and buccal slightly more than palatinal. Additionally, about one third of the pulps in the central incisors were anesthetized. The anesthetic effect on the pulps is better on the central incisors and the canines than on the lateral incisors (Fig. 4).

Analgesics could have a positive effect on the anesthetic effect. In the present study, seven patients stated to have taken analgesics on the day of examination. Generally, in that case false negative results are possible. Nonetheless, evaluating sharp blunt discrimination and conducting a cold test should be possible, despite taking analgesics.

Another weakness of the study is the varying dosage and contact time of the Tenaphin solution in individual patients. Due to ethical aspects of the good clinical practice the setting of the Otorhinolaryngology, Head and Neck Surgery of the University Hospital Basel was used for the current study. The effects of a medically necessary examination was used, in order to gain knowledge in dental medicine. Nevertheless, the results are valuable for planning a further study design for clinical trials with test persons. Regarding future studies, a standardized dosage of the anesthetics with a defined residence time should be considered.

The study population consisted of patients, who had received an ear, nose and throat medical diagnosis or therapy. The patients were given nasal anesthetic as part of
their examination, which is routinely applied prior to endoscopic examinations (Gaviola et al. 2013). The information used is based on the clinical inspection on the day of the examination. Dental information like specification of restorations (crowns, fillings, root canal fillings, implants) and specification of former dental trauma (obliterations) was not available. Therefore, false negative results could not be excluded due to the possible presence of implants, obliterations and root canal treatments. A further study should include the dental history and the pulp status of its probands as well as a test before the anesthesia.

With the application of higher doses of intranasally applied tetracaine solutions, a pain-free filling therapy in the maxilla could be provided after application in 83.3%, and in 90% if the tooth is in the anterior/premolar area. In these cases, no additional anesthesia was necessary apart of the application of the nasal spray (Ciancio et al. 2013). However, the form of application had an influence on the duration of the effect depending on the localization. Thus, it was shown that by infiltration anesthesia on the buccal mucosa, a longer effect was achieved, while the use of a nasal spray showed a longer effect on the palatinal mucosa (Drivas et al. 2007). In the present study it was established that the anesthetic effect increased with exposure time, where both the pulp and the gingival is concerned. The combination of tetracaine spray and a vasoconstrictor showed a significantly better effect in the anterior area than in the premolar area (Ciancio et al. 2016). This is consistent with the results of a study in rats, in which it was shown that the concentration of lidocaine in the pulp was higher in the area of incisors than of molars (Johnson et al. 2010).

It has been postulated that the uptake of the anesthetic is administered along the trigeminal nerve in the area of the posterior naris, the middle concha and the maxillary sinus. The neuronal path functions similar to a pipe system, which not only communicates in the direction of the brain, but also in opposite direction to the connected tissues like teeth and mucosa (Eskandarian et al. 2015). The anterior
superior alveolar branch innervates the incisors and the canines (HERSH ET AL. 2016b). It seems that the nose spray penetrates the maxillary sinus and anesthetizes the anterior and medial nerve branches of the superior alveolar nerve. The posterior branch does not seem to get enough anesthesia, since the spray does not reach the posterior sinus (CIANCIO ET AL. 2013).

The incisors, canines as well as the associated gingiva are supplied by the anterior superior alveolar branch (NORTON 2012). In the anterior region and the associated gingiva the rami overlap in the supply area of the central and lateral incisors leading to cross innervation (YONCHAK ET AL. 2001). The nerve branches form anastomoses which extend beyond the midline. Diffusion may be hindered by the labial frenulum (EVERS 1983), but is usually sufficient, which is why an ipsilateral anesthesia is recommended (HERSH ET AL. 2016a).

There is also an explanation for anesthesia failure of central incisors after an infraorbital block due to cross-innervation via a contralateral anterior superior alveolar nerve branch. It is assumed, that there is additional nerve supply in the anterior palate through accessory bone channels which communicate with the canalis sinuosus and reach the apices of the anterior teeth or perforate the cortex on the palatal side of the anterior teeth. The lower portion of the canalis sinuosus, the piriform canal, reaches the midline and might anastomose with the contralateral side (VON ARX & LOZANOFF 2015).

In case of dental traumata, the upper anterior teeth are affected most often, especially the central incisors (GLENDOR 2008, BOUROLIAS ET AL. 2010, JOHNSON ET AL. 2010). Treatment of direct or delayed consequences of dental accidents requires in many cases adequate anesthesia of the affected teeth and the surrounding soft tissues. At the moment, infiltration anesthesia (buccal infiltration), palatinal block anesthesia and The Wand® (local anesthetic) achieve adequate anesthesia, and are used routinely in dental medicine. The active ingredient articaine in combination with
Epinephrine for vasoconstriction is often used as anesthetic solution. The active ingredient articaine is well tolerated. However, its disadvantage is that it has no superficial anesthetic effect. Absorption of active ingredients through the mucous membranes of the nose is a known phenomenon, and in medicine it is not only used for pain relief, but also in preparation for intubation anesthesia (Eskandarian et al. 2015). Tetracaine shows very good surface effect and the best effect for nasal anesthesia (Noorily et al. 1995, Bizakis et al. 2004, Drivas et al. 2007, Boulolias et al. 2010). Thus, the anesthetic used is well suited for the investigation of the question posed. The dosage used in the present ear, nose and throat medical examinations was about 10 times lower than that of dental comparative studies (Drivas et al. 2007). With this low concentration of anesthetic, it could even be used prior to infiltration as a scope of application. In a comparison between a high-dose tetracaine solution and a lidocaine infiltration, a reliable application of the tetracaine solution in form of a nasal spray could be shown (Drivas et al. 2007). By adding a vasoconstrictor to the anesthetic tetracaine, significantly better anesthesia results were achieved than with the anesthetic alone (Ciancio et al. 2016). Common side-effects of nasal spray anesthesia are rhinorrhea, stuffy nose and an unpleasant feeling in the nose (Ciancio et al. 2016). In summary even a low dose of tetracaine in combination with a vasoconstrictor shows an anesthetic effect, affecting the pulp and particularly the marginal gingival tissue. Thus, treatment in the anterior region would be conceivable after dental accidents. Prevention of a painful pinprick (Timmermann 2011, Ciancio et al. 2013) while considering the diffuse distribution of the anesthetic in large areas (Eskandarian et al. 2015) still needs to be analyzed. The nasal superficial anesthesia could also be used prior to the infiltration anesthesia so prevent the painful prick. Detailed dosage protocols including the determination of the maximum dose, especially for children has to be examined when using this type of application.
Acknowledgements

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Zusammenfassung

Einleitung
Unfallbedingte Verletzungen im Bereich der Oberkieferfrontzähne treten bei Kindern und Jugendlichen häufiger auf. Die Lokalanästhesie ist in diesem Bereich, insbesondere palatinal, schmerzhaft.


Material und Methoden
Das nasale Oberflächenanästhetikum Tenaphin (Tetracainhydrochlorid und Naphazolinnitrat) wurde 105 Patienten vor einer Hals-Nasen-Ohren-Diagnostik und -Therapie appliziert. Die in die vorliegende Untersuchung eingeschlossenen Personen mussten volljährig und urteilsfähig sein. Die Patienten erhielten entweder einen oder zwei Stösse des Oberflächenanästhetikum oder (je nach Indikation) eine Tamponade. Nach unterschiedlichen Einwirkzeiten wurde der Einfluss auf die oralen Gewebe im anterioren Oberkieferbereich (Zähne 13 bis 23 sowie die zugehörige Gingiva) untersucht. Dafür wurde ein Sensibilitätstest der Pulpen sowie eine spitz/stumpf Überprüfung der Gingiva mit einer Kuhhornsonde an 3 Stellen bukkal (3mm, 8mm und 13mm ab dento-gingivaler Grenze) und an 2 Stellen palatinal (5mm und 10mm ab dento-gingivaler Grenze) durchgeführt.
Resultate

Der Anästhesieerfolg der Gingiva nahm im Bereich der Frontzähne zu, je weiter mesial der Zahn lokalisiert und je länger die Einwirkzeit war (p=0.004). Sowohl bukkal als auch palatinal nahm der Effekt von apikal nach inzisal zu (p < 0.001). Der Anästhesieerfolg vergrößerte sich mit der Einwirkzeit (p=0.006). Die Pulpen der lateralen Inzisiven waren schlechter anästhesiert als diejenigen der zentralen Inzisiven (p=0.013) und der Eckzähne (p=0.005). Der primäre Endpunkt (Anästhesieerfolg der marginalen Mukosa) war im Bereich der zentralen Inzisiven erfolgreicher als im Bereich der lateralen Inzisiven und der Eckzähne (p ≤ 0.002). Im Durchschnitt fand die Untersuchung der Wirkung der Anästhesie nach 16.5 Minuten statt (6.5-51, SD 7.1)

Diskussion

Résumé

Introduction
Les blessures accidentelles à l’aire des dents maxillaires antérieures surviennent le plus fréquemment chez les enfants et les adolescents. L’anesthésie locale pour cette zone, surtout l’anesthésie palatine, est une anesthésie douloureuse. Les incisives et les canines sont innervées par le nerf alvéolaire supérieur antérieur qui est à proche proximité du nez. L’anesthésie superficielle nasale est une méthode non invasive dont l’efficacité au tissu oral n’a pas été recherchée totalement. Si cette méthode d’anesthésie s’avère efficace pour la médecine dentaire, elle pourrait remplacer ou parfaire les anesthésies par injection plus invasives. La thèse présentée ici vise à évaluer si l’anesthésie indolore superficielle du nez peut remplacer la méthode conventionnelle de l’anesthésie par infiltration dans la région antérieure de la mâchoire supérieure.

Matériel et méthodes
L’anesthésique de surface pour cavité nasale Tenaphin (tétracaïnhydrochlorure et naphazolinnitrate), fut appliquée à 105 patients précédant un examen et thérapie ORL. Les participants devaient être majeurs et capables de discernement. Les patients reçurent soit une à deux coups de vaporisateur de Tenaphin, soit (selon indication) par tamponnement. Après différents temps d’action, les effets sur les tissus orales dans la région antérieure de la mâchoire supérieure (dents 13 à 23 ainsi que la gencive correspondante) furent mesurés. A cette fin, un test de sensibilité des pulpes ainsi qu’un examen de la gencive avec une sonde dentaire furent effectués en trois points vestibulaires (3mm, 8mm et 13mm à partir de la frontière entre la
Résultats

L’efficacité de l’anesthésie locale de la gencive augmente au niveau des dents antérieures plus la dent est localisée mesialement et plus le temps d’action est long (p=0.004). L’efficacité croît buccal et palatal de l’apical à l’incisal (p< 0.001).

L’efficacité de l’anesthésie augmente avec le temps d’action (p=0.006). L’anesthésie est moins efficace pour les pulpes des incisives latérales que pour celles des incisives centrales (p=0.013) et des canines (p=0.005). L’efficacité de l’anesthésie des muqueuses marginales, le critère d’évaluation primaire dans cette étude, est plus prononcée au niveau des incisives centrales qu’au niveau des incisives latérales et des canines (p” 0.002). Les effets de l’anesthésie furent en moyenne mesurés après 16.5 minutes (6.5-51, SD 7.1).

Discussion

Les résultats de cette étude montrent qu’une anesthésie des pulpes et des gencives avoisinantes peuvent être effectuée avec une faible dose de Tenaphin. L’efficacité de l’anesthésie croît avec le temps d’action. L’anesthésie superficielle du nez a le potentiel de remplacer au du moins de parfaire la méthode invasive de l’anesthésie par infiltration dans la région antérieure de la mâchoire supérieure. Le dosage et le temps d’action doivent être étudiés de plus près. Afin d’exclure des faux-négatifs (les dents ayant reçu un traitement endodontique, implants, oblitérations, couronnes etc.), un contrôle dentaire, y compris des radiographies, devraient être effectué avant l’examen, ce qui n’était pas possible ici.
References


ESKANDARIAN T, ARABZADE MOGHADAM S, REZA GHAEMI S, BAYANI M: The effect of nasal midazolam premedication on parents-child separation and recovery time in


Captions

**Figure 1** Anatomical schematic picture of the course of trigeminal nerve

**Figure 2** Anatomical schematic picture of the anatomy of nasopalatinal nerve

**Figure 3** Schematic picture of the anterior maxilla to note the results after the examination for sharpness or bluntness

**Figure 4** Negative reaction of sharpness per measuring point, n=579 for A, B, C, n=576 for D and E

**Figure 5** Negative reaction of sharpness per tooth, n=475 for 13, 12, 11, n=488 for 21, 22, 23

**Figure 6** Negative sensibility of the pulp per tooth, n=87 for 13, n= 78 for 12 and 11, n=90 for 21 and 23, n=89 for 22
### Tables

**Anamnesis of drugs**

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<td>analgesics (celecoxib, paracetamol, ibuprofen, acetylsalicylic acid, oxycodon</td>
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<tr>
<td></td>
<td>hydrochlorid/naloxon hydrochlorid, lornoxicam, mefenamin acid)</td>
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<tr>
<td>&gt; 10</td>
<td>antihypertensive</td>
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<tr>
<td>&gt;= 5</td>
<td>Antirheumatic, rhinologics, cholesterol-lowering drugs</td>
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<td>&lt; 5</td>
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**Table I** Anamnesis of drugs