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Original Scientific Paper

THE IMPACT OF PREOPERATIVE SALIVARY UREA AND SUPEROXIDE DISMUTASE ACTIVITIES ON POSTOPERATIVE PAIN AFTER SURGICAL REMOVAL OF MANDIBULAR THIRD MOLARS

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SUMMARY – The most frequent surgical procedure in oral surgery is extraction of mandibular third molars, which could be associated with postoperative complications such as pain, swelling, and trismus. We aimed to investigate the association of salivary urea and antioxidative enzyme activities with the intensity of postoperative pain after wisdom tooth extraction. This cross-sectional prospective study included 66 subjects (median age 25, range 17-47 years). Salivary urea and superoxide dismutase (SOD) were determined by enzymatic colorimetric tests. The questionnaire for study participants included demographic and history data, as well as data on personal experience of pain in grade 0-10 according to the visual analog scale (VAS). Grading 1-3 was considered as low (VAS-1), 4-6 mild (VAS-2) and 7-10 as severe pain (VAS-3). Moderate positive correlation was recorded between urea concentration and SOD activity in saliva (r=0.46). Moderate negative correlations were found between urea salivary concentration and VAS grading value reported after 12 hours (r=0.51). The concentrations of urea significantly differed among the three VAS categories (p<0.001), whereas salivary SOD activities did not differ among the categories. Preoperative salivary urea concentration and SOD activity might be associated with postsurgical pain after surgical removal of mandibular third molars.

Key words: *Superoxide dismutase; Urea; Pain; Molar, third; Extraction, tooth*

Introduction

The function of saliva in dental physiology includes remineralization and inhibition of demineralization, lubrication, and buffering. In the last decade, the extravascular fluid has become of interest to laboratory medicine because of its specific composition which includes various metabolites, proteins, enzymes, and others[1]. Additionally, it is significant as a noninvasive sample collection technique in laboratory medicine. The most common surgical procedure in oral and maxillofacial surgery is removal of the mandibular third molar, which may be associated with some postoperative complications such as pain, swelling, and trismus[2].

Anticipation of pain is one of the most important factors in dental care and treatment[3]. Pain after third

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molar extraction (PEP) may be associated with salivary pH and flow rate[4]. The composition of saliva includes the presence of urea which acts as a buffer[5]. Bacterial ureases can hydrolyze it to ammonia and carbon dioxide, causing an increase in pH. It was previously thought that PEP intensity had an inverse correlation with salivary pH[4].

There is evidence that superoxide contributes to pain of various etiologies, as it is involved in peripheral and central sensitization[6]. Pain score on the visual analog scale (VAS) correlated negatively with salivary superoxide dismutase (SOD) activities in subjects undergoing dental implant surgery[1,7]. Therefore, it can also be considered as one of the factors that may contribute to various oral disorders, as well as to pain and other postoperative complications[8].

As it is known from the literature that the pH of some anesthetics affects pain perception, it has been suggested that substances that moderate the oral cavity acidity, such as urea, may be related to pain sensation[9]. Antioxidant enzymes neutralize free radicals and reactive oxygen compounds, which also are associated with pain[10]. Therefore, we hypothesized that changes in salivary urea concentration and antioxidant enzyme activities might be associated with postoperative oral pain. The main objective of the research was to investigate the association of metabolites such as urea and activities of antioxidant enzyme SOD in saliva with the intensity of postoperative pain after surgical removal of the mandibular third molars and to assess the relationship between the level of these parameters and pain intensity.

Material and Methods

Study design and subjects

This prospective cross-sectional study was conducted in collaboration between the Department of Oral and Maxillofacial Surgery, School of Dental Medicine, University of Zagreb, Dubrava University Hospital and Department of Medical Chemistry, Biochemistry and Clinical Chemistry, Zagreb University School of Medicine. The study included healthy individuals who underwent surgical removal of lower third molars at the Department of Oral and Maxillofacial Surgery between February 2018 and July 2019. Oral surgeons selected patients who had no signs of acute inflammation in the molar region preoperatively and had the same angulation and degree of impaction (semi-impaction). According to Parant scale, surgical removal of the third molars with osteotomy and coronal incision (class III) was performed in all patients[11]. Patients were advised not to take painkillers 24 hours before the procedure and to refrain from brushing teeth and consuming chewing gum 2 hours before the procedure.

Sixty-six patients were enrolled in the study. There were 42 women (median age 25, range 17-47 years) and 24 men (median age 24.5, 18-45 years). The study participants were asked to answer the questionnaire before surgical intervention. The questionnaire contained data on age, sex, and medical history, which included patient knowledge of congenital diseases, diseases of the cardiovascular system, diseases of the central nervous system, diseases of the digestive system, diseases of the genital and genitourinary systems, allergies, pregnancy/breastfeeding, and medication use (including analgesics and contraceptives). After this part of the questionnaire, all patients who denied any of the previously listed conditions were included in the study. After tooth extraction, the oral surgeon recorded data on the duration of surgery and anesthesia. At 24, 48 and 72 hours after surgery, patients were asked to report data on personal pain perception in levels 0-10 according to VAS. Grading between 1 and 3 was considered as low (category VAS-1), from 4 to 6 as mild (category VAS-2) and ≥7 as severe (category VAS-3). Three-day pain averages were also calculated for each patient. Patients also reported data on postoperative analgesic therapy. They were advised to use only ibuprofen tablets (Neofen forte 400 mg, Belupo, Koprivnica, Croatia) in a daily dose according to the manufacturer's recommendation, maximal 1200 mg divided in 3 doses. Excluded were five individuals who disclosed using other analgesics such as ketoprofen or diclofenac, and those who required antimicrobial medication.

The study was approved by the Ethics Committee of Dubrava University Hospital. Each study participant voluntarily participated in the study and signed an informed consent form. All procedures performed in the study were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Saliva collection

Sampling was performed according to a modified method previously described by Kanehira *et al.*[12],

before surgery between 8 a.m. and 10 a.m. by expectoration to conical sterile Falcon™ 15 mL Conical Centrifuge Tubes (Fisher Scientific, Hampton, New Hampshire, USA). Prior to sampling, patients rinsed the oral cavity with 10 mL of saline according to modification of the saline collection method described in the manuscript. Samples were immediately frozen at -20 ˚C until processing. Before centrifugation at 4˚, 1000 g/20 min, the samples were thawed at room temperature and the supernatant was used for analysis.

Surgical procedure

Surgery was performed under local anesthesia (inferior alveolar nerve block) with 1 mL suspension containing 40 mg articaine chloride and 0.005 mg epinephrine in the form of epinephrine chloride (Ubistesin-articaine, 3M ESPE, Neuss, Germany). The operations were performed by the same surgeon. The surgery started with elevation of the mucoperiosteal flap, followed by osteotomy, coronal incision, and extraction of the third molar. The wound was sutured with 3-0 silk (Johnson & Johnson Medical Ltd., Simpson Parkway, Krikton Campus, Livingston, UK). The sutures were removed seven days after the procedure.

Methods

Urea was determined by urea liquicolor enzymatic colorimetric tests (HUMAN Gesellschaft für Biochemica und Diagnostica GmbH, Wiesbaden, Germany), and SOD by RANSOD (Randox Laboratories Ltd., Crumlin, UK) on an Abbott Architect c4000 biochemical analyzer (Abbott GmbH, Wiesbaden, Germany).

Statistics

Statistical analyses were performed using Statistica, Version 13.5.0.17 TIBCO Software. Normality of distribution was tested using the Kolmogorov-Smirnov test. Nonparametric statistical tests were performed because the continuous data of urea concentration and SOD activities were not normally distributed, while other parameters determined were presented as ordinal data. Spearman correlation coefficient was used for ranking testing the association between two ranked variables. Urea concentrations and SOD activities among three VAS categories were compared using the Kruskal Wallis test and Mann-Whitney test. The values of $p<0.05$ were considered significant. Bonferroni correction was performed for testing between paired categories, and therefore the values of $p<0.017$ were considered significant.

Results

Basic characteristics of study participants are shown in Table 1. It is noted that the parameters examined did not differ significantly between male and female participants. Therefore, correlation analyses were performed together for the whole group (Table 2).

Moderate positive correlation was recorded between urea concentration and SOD activity in saliva ($r=0.46$). Moderate negative correlations were found between urea salivary concentration and VAS grading value reported after 12 hours ($r=0.51$).

Table 3 illustrates median values for urea and SOD according to VAS categories. Urea concentrations differed significantly among the three VAS categories ($p<0.001$). When we performed two group comparison tests, there was no significant difference between VAS-1 and VAS-2 ($p=0.398$), whereas there were significant differences between VAS-2 and VAS-3 and between VAS-1 and VAS-3 ($p<0.001$ both). SOD activities did not differ among VAS categories.

Discussion

To the best of our knowledge and available literature data, there is no study on the relationship between salivary urea concentration, SOD activity, and postoperative pain after mandibular third molar surgical removal, but it has been demonstrated that salivary urea concentration and SOD activity may be related to oral pain, dental and periodontal disease[4,13-15]. We demonstrated that preoperative urea concentration might be associated with postoperative pain after surgical removal of mandibular third molars. Urea concentration negatively correlated with pain intensity, while positive correlation was demonstrated between urea concentration and SOD activity.

Urea is the main metabolic product of the breakdown of nitrogenous substances in the body. It is synthesized in the liver and excreted in the urine. The concentration of urea in saliva is similar to its concentration in serum and is about 1 to 10 mmol/L[16].

Table 1. Characteristics of study participants

Men, N (ratio)		24 (0.36)	
Age, median (range)	All (N=66)	25 (17-47)	
	Men (N=24)	25 (18-45)	0.951
	Women (N=42)	25 (17-47)	
Urea, median (25th; 75th percentiles), mol/L	All (N=66)	6.96 (6.47; 9.12)	
	Men (N=24)	6.96 (6.49; 8.69)	0.931
	Women (N=42)	6.97 (6.43; 9.12)	
SOD, median (25th; 75th percentiles), U/mL	All (N=66)	0.26 (0.16; 0.43)	
	Men (N=24)	0.24 (0.13; 0.41)	0.436
	Women (N=42)	0.26 (0.21; 0.47)	
Body mass, median (25th; 75th percentiles), kg	All (N=66)	72 (62; 81)	
	Men (N=24)	83 (75; 95)	>0.001
	Women (N=42)	65 (58; 72)	
Therapy*	Appropriate, N	61	
	Inappropriate, N	5	
VAS, after 12 h, median (25th; 75th percentiles)**	All (N=61)	5.0 (3.0; 7.0)	
	Men (N=22)	5.0 (3.0; 7.0)	0.976
	Women (N=39)	5.5 (3.0; 8.0)	

*Participants taking inappropriate therapy were excluded from further statistical analyses that included pain, swelling and trismus;

**Patients provided information on personal experience of pain in grades 0-10. For each patient, VAS values after 12 hours were taken into account;

SOD = superoxide dismutase; VAS = visual analog scale

Table 2. Spearman rank order correlations (N=61)

	N	Spearman p (95% CI)	p
Urea (mmol/L) and SOD (U/mL)	61	0.46 (0.24; 0,64)	<0.001
Urea (mmol/L) and VAS after 12 hours	61	-0.51 (-0.68; -0.30)	<0.001
SOD (U/mL) and VAS after 12 hours	61	-0.21. (-0.44; -0.04)	0.101

CI = confidence interval; SOD = superoxide dismutase; VAS = visual analog scale

Table 3. Comparison of urea concentrations and SOD activities according to VAS categories

VAS category*	N	Urea, median (25th; 75th percentiles), mmol/L	p**	SOD, median (25th; 75th percentiles), U/mL	p**
VAS-1	20	7.87 (6.81; 10.7)	<0.001	0.31 (0.28; 0.69	0.148
VAS-2	20	7.98 (6.65; 9.95)		0.29 (0.21; 0.39)	
VAS-3	21	6.58 (6.04; 6.82)		0.24 (0.12; 0.29)	

*Grading between 1 and 3 was considered as low (VAS-1), from 4 to 6 as mild (VAS-2) and ≥7 as severe (VAS-3);

**Comparison of median concentrations of urea and SOD activities among three VAS categories.

SOD = superoxide dismutase; VAS = visual analog scale

The main role of urea in the oral cavity is to maintain the acid-base balance of saliva by breaking it down into ammonia and carbon dioxide with the help of urease, either bacterial urease or urease which is otherwise a component of human saliva[17]. Its buffering activity leads to alkalinization of saliva, which then negatively affects the metabolism and proliferation of acidogenic and aciduric bacteria (*Streptococcus mutans, Lactobacillus* spp.) associated with caries formation[18]. Dawes and Dibdin were the first to describe an increase in salivary pH by the addition of urea[19]. Salivary alkalinization favors the proliferation of less acid-forming bacteria, which maintain the pH of plaque homeostasis and the balance between mineralization and demineralization of teeth[14]. Therefore, it can be concluded that urea could indirectly lead to a reduction in salivary acidity and maintenance of oral health. Salivary concentrations of urea were significantly higher in Slovak subjects with periodontitis than in control subjects[20]. Higher concentrations of salivary urea were determined in subjects with low decay-missing-filled indices (DMFT indices)[18]. These results suggest a protective role of urea against dental and periodontal diseases due to buffering properties, as it was found that PEP can be higher at lower salivary pH[4,14]. In the analysis of our results, a negative correlation was found between the intensity of post-extraction pain and urea concentration. Although there is a study in the literature on the direct effect of urea on neuropathic pain, the association of salivary urea concentration and pain might presume the relationship with nociceptors, which has not been studied so far[21]. A cell culture study showed that treatment of neurons with urea might reduce the numbers of neurons[21]. Numerous studies confirm the existence of multiple proton-sensitive nociceptors that are activated by a decrease in extracellular pH. These receptors may additionally be influenced by a number of mediators, the most important of which are inflammatory mediators, which may also activate them directly. In response to lowered pH, the acid-sensing ion channel (ASIC) and the transient receptor potential channel (TRP) coordinate cation influx, contributing to the depolarization of nociceptors[22,23]. In their study, Steen *et al.* demonstrated a strong, potentially allogeneic interaction between acidic pH and inflammatory mediators in relation to the prevalence and strength of nociceptor excitation in inflamed rat skin[23]. Based on the results obtained, we conclude that urea indirectly reduces the sensitivity of proton-sensitive nociceptors and consequently pain intensity by shifting the pH value towards alkaline. Reactive oxygen species (ROS) are molecules or ions involved in the processes regulating cell growth and differentiation and inflammatory and immune responses, formed as a byproduct of cellular respiration, in which the electron is transported to oxygen, resulting in the formation of superoxide anions[24]. The process of ROS formation occurs within mitochondria and at membranes of many cells in the process of NADPH oxidase (NOX), an enzymatic reaction called oxidative burst[25]. Among the group of ROS formed, superoxide radical anion is most abundant and is also the starting point for the formation of other ROS[26]. The conversion of superoxide anion into a less 'dangerous' radical occurs with the help of the biocatalyst SOD in the reaction of dismutation of two molecules of

superoxide anion (* O2) to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2)[26]. The optimal pH at which the enzyme activity of SOD is most pronounced is between 7 and 9.5[27]. Today, the role of the TRP ion channel family in the development of nociceptive pain is well known[28]. TRP channels can be directly activated by ROS. Activated TRP channels not only trigger pain sensation but also generate other ROS that support the inflammatory process and thus pain[29-32]. Although ROS can have many beneficial effects in wound healing by helping fight microorganisms and mutual communication between cells, their excessive formation leads to oxidative damage and prolongs the healing process[33,34]. ROS have been shown to play an important role in the development of periodontitis and the etiology of orofacial pain[35,36].

As ROS in the induction of pain stimuli attract increasing attention of researchers today, SOD mimetics are being developed for topical application to reduce the inflammatory response and pain[37,38]. Previous studies have confirmed the potential benefit of using SOD mimetics in the treatment of many diseases[39]. Our results show that in patients with more severe pain intensity, preoperative salivary SOD levels were lower. We could explain this fact by the increased production of superoxide anions due to tissue trauma caused by surgery and in the process of wound healing. Degradation of superoxide anions is also reduced due to the lower SOD activity. Although we did not find a statistically significant relationship of pain and SOD activity, we could explain this by general pharmacokinetics of natural SOD molecule which has low bioavailability and different dose-response curve with respect to SOD mimetics[39]. In addition, we demonstrated a direct correlation between SOD and urea in saliva and their effect on pain. Namely, in a patient with lower pain intensity, in addition to the direct effect of SOD on ROS neutralization, alkalinization of saliva as a consequence of increased urea levels directly locally optimizes pH levels at which the activity of SOD is more pronounced, further reducing pain stimuli.

The added value of the presented study indicates that some biochemical parameters of saliva might predict postoperative complications after surgical removal of mandibular third molars. A limitation of the study could be related to differences in the subjective evaluation of pain sensation. Verification of the test in salivary specimen also should be performed. It is necessary to perform further studies on larger cohorts and with different complications after surgery.

Conclusion

Preoperative urea concentration might be associated with the intensity of postoperative pain after surgical removal of mandibular third molars. Urea concentration negatively correlated with pain intensity. In addition, positive correlation was demonstrated between urea concentration and SOD activity, which could be explained by the effect of urea on salivary alkalinization and the consequent creation of optimal conditions for SOD activity.

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Sažetak

UTJECAJ PRIJEOPERACIJSKE SALIVARNE UREJE I AKTIVNOSTI SUPEROKSID DISMUTAZE NA POSLIJEOPERACIJSKU BOL NAKON KIRURŠKOG ODSTRANJIVANJA TREĆIH MOLARA MANDIBULE

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Najčešći kirurški zahvat u oralnoj kirurgiji je ekstrakcija trećih molara donje čeljusti, što može biti povezano s poslijeoperacijskim komplikacijama kao što su bol, oteklina i trizmus. Cilj nam je bio istražiti povezanost aktivnosti ureje i antioksidativnih enzima u slini s intenzitetom poslijeoperacijske boli nakon vađenja umnjaka. Ova presječna prospektivna studija uključivala je 66 ispitanika (srednja dob 25 godina, raspon 17-47 godina). Ureja u slini i superoksid dismutaza (SOD) određivane su enzimskim kolorimetrijskim testovima. Upitnik za sudionike istraživanja uključivao je demografske podatke i podatke o anamnezi, kao i podatke o osobnom iskustvu boli u stupnju 0-10 prema vizualnoj analognoj ljestvici (VAS). Ocjene 1-3 smatrane su niskom (VAS-1), 4-6 blagom (VAS-2), a 7-10 jakom boli (VAS-3). Zabilježena je umjerena pozitivna korelacija između koncentracije ureje i aktivnosti SOD u slini (r=0,46). Nađene su umjerene negativne korelacije između koncentracije ureje u slini i vrijednosti VAS ocjenjivanja prijavljenih nakon 12 sati (r=0,51). Koncentracije ureje značajno su se razlikovale između tri kategorije VAS (p<0,001), dok se aktivnosti SOD u slini nisu razlikovale među kategorijama. Koncentracija ureje u slini prije operacije i aktivnost SOD mogu biti povezane s poslijeoperacijskom boli nakon kirurškog uklanjanja trećih kutnjaka mandibule.

Ključne riječi: *Superoksid dismutaza; Ureja; Bol; Molar, treći; Vađenje zuba*