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Relationship between salivary biomarkers and postoperative swelling after the extraction of impacted lower third molars

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Abstract. Many authors have studied various different parameters in relation to postoperative anxiety after the extraction of third molars. However, the effect that the acute inflammatory process occurring post extraction could have on these parameters has not been studied. Certain salivary biomarkers, although not specifically inflammatory, may be affected by the acute inflammatory process occurring following the extraction of a retained lower third molar. Three biomarkers were assessed in this study: total protein, immunoglobulin A (IgA), and alpha-amylase. A total of 15 patients were recruited. Four samples of saliva were taken from each patient: before extraction, immediately after extraction, at 2 h after extraction, and at 7 days after extraction. The concentrations of the proteins in the saliva were measured. The average values of each marker were compared across the different stages of the study. Statistical analysis revealed that of the three salivary biomarkers, only alpha-amylase was associated with an inflammatory response to the surgery ($P < 0.05$). These results suggest the possibility that salivary alpha-amylase levels may be affected by the acute inflammation occurring post extraction; therefore, this would not be an appropriate marker to use in the study of other situations, unless this interference is controlled for.

Key words: oral swelling; third molar surgery; alpha-amylase; immunoglobulin A; total proteins.

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The extraction of impacted lower third molars is one of the most common surgical techniques performed in the oral cavity. This procedure may result in postoperative pain, inflammation, and/or trismus. The inflammatory process is usually characterized by soft tissue swelling and subsequent facial deformity, and a degree of trismus is also sometimes observed. The postoperative recovery process generally takes around 7 days, with inflammation being the primary side effect during the healing period.[1,2]

Multiple factors can influence patient discomfort, including the complexity and duration of the surgery, the surgeon's technique, iatrogenic complications, etc. Minimizing these factors increases satisfaction with the treatment, improves the patient's quality of life, and reduces the fear of surgical interventions.[3] Postoperative symptom management has improved considerably over the past few years due to a better understanding of not only the

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pathophysiological causes of pain and inflammation, but also the mechanisms of action and pharmacodynamics of the analgesics and anti-inflammatories used to treat them. Therefore, greater emphasis is now placed on the importance of preventing both pain and inflammation. Pain and inflammation are typically brief and peak in intensity during the early postoperative period, within the first 24 h post extraction; swelling generally appears within 48–72 h after the surgery.[4]

Human saliva is a biological fluid with enormous diagnostic potential. As it can be collected non-invasively, it presents a viable alternative to blood, serum, or plasma.[5–10] Human saliva contains a variety of proteins,[11] hormones,[12] antibodies,[13] drugs,[14] and cytokines[15] that enter the saliva through the blood, so most compounds found in the blood are also present in saliva. Many of these arrays of proteins are useful for the detection and treatment of oral and systemic diseases.[5] As the composition of saliva can be influenced by systemic changes, specific biomarkers could help identify certain disease conditions.[11] Recent studies have demonstrated how saliva can aid in the diagnosis of cardiovascular disease, systemic and local inflammation, hepatic damage, autoimmune disease, and insulin resistance.[11,16–19]

Current clinical diagnostic methods are unable to detect the onset of periodontal inflammation or to identify those patients at greatest risk of periodontal disease progression.[20] Biomarkers from oral fluids have been used to evaluate the response to therapies such as periodontal surgery combined with matrix metalloproteinase inhibition.[21] The analysis of recent data supports the use of salivary biomarkers associated with matrix destruction, inflammation, the host response, and bone turnover in the diagnosis of periodontal disease progression.[22]

Salivary alpha-amylase has been proposed as an important biomarker of stress in terms of autonomic dysregulation, as it increases in response to both physical and psychological stress via interactions with the autonomic nervous system.[23] On the other hand, one of the major antibodies present in saliva is immunoglobulin A (IgA), which is generally synthesized by plasma cells in the salivary glands and then exported by an epithelial receptor-mediated mechanism.[24] Secretory IgA levels in the saliva have also been proposed as a potentially useful immunological marker of stress.[25] Finally, human saliva also contains clinically relevant proteins, many of which come from the blood and may also prove useful in clinical applications.[26,27]

After surgery, there is a systemic reaction that encompasses endocrine, immunological, and haematological changes.[28] Certain studies have investigated the value of IgA, alpha-amylase, and the total protein in saliva as indicators of dental anxiety during the extraction of retained lower third molars.[23,25,29] However, the effect that the acute inflammatory process occurring post extraction could have on the values of these biomarkers has not been studied. In view of this possible relationship, the results of these previous studies should be interpreted with caution, as this possible interference was not controlled for . The present study was designed to evaluate the levels of salivary alpha-amylase, IgA, and total protein in the saliva as biomarkers for inflammation after lower third molar surgery.

Patients and methods

A total of 20 patients requiring impacted third molar extractions were initially considered for inclusion. The final study sample comprised 15 subjects between 20 and 37 years of age. The other individuals did not complete the study due to a lack of compliance with the protocol. The surgical extractions took place in the oral and maxillofacial clinic of a hospital in Seville, Spain. Third-year residents of a master's degree programme in oral surgery performed the procedures.

Each patient underwent an exhaustive radiographic study (a panoramic radiograph was used to classify the lower third molars based on Winter's classification: mesioangular, distoangular, vertical, and horizontal impactions) and diagnosis to ensure that the surgery was as simple as possible. In addition, the purpose of the clinical study was explained to each patient to make them aware of the importance of their collaboration.

Complete case histories were collected: age, sex, and smoking status (smoker or non-smoker), among others. Written informed consent forms were signed by all patients who agreed to participate in the study. The inclusion criteria for the study were the following: patient with impacted lower third molars with a moderate degree of difficulty (5–7 Koerner classification); no relevant systemic pathology (ASA I as per the American Society of Anesthesiologists classification). A complete periodontal examination was also included; it was imperative that the patient did not have periodontitis or any oral infection prior to the surgery. The study was approved by the institutional ethics committee.

Variables and data measurement

One researcher was responsible for collecting data on the following variables: age, sex, smoking status, depth of impaction using the Pell and Gregory classification, position using Winter's classification, and whether the patient was taking any medication.

One tooth extraction was performed per session, with an interval of 15 days between interventions to allow the tissues to heal and recover from the first extraction. The first specimen of saliva was collected before the third molar was removed. The patient was asked to refrain from smoking and vigorous exercise for 2 h prior to the collection of saliva. Saliva was allowed to flow in the floor of mouth and 1 ml was then collected using an auto-aspiration pipette tip. After this, the patient received local anaesthetic (articaine 4% and epinephrine 1:100,000). Due to the position and localization of the third molar, all cases required an osteotomy, which was performed using a 20,000-rpm hand piece under irrigation . Some cases required tooth sectioning . At the end of the intervention a 3–0 suture was used to facilitate soft tissue healing and avoid infections in the area. The patient demographic data and the Koerner index for the extracted teeth are shown in Table 1.

The time taken to perform the extraction ranged from 7 to 25 min (if it was longer than 30 min, the patient was excluded from the study). A second saliva sample was taken immediately after extraction, trying to avoid any blood. The patient then remained in the waiting room for 2 h without eating or drinking anything, after which a third saliva sample was taken. The final saliva sample was taken 7 days later, before the stitches were removed.

Ibuprofen (600 mg every 8 h for 7 days) and amoxicillin/clavulanate (875 mg/125 mg every 8 h for 5 days) were

Table 1. Clinical and demographic patient data.

Sex	
Male	8 patients
Female	7 patients
Age range	20–37 years
Smoker	
Yes	7 patients
No	8 patients
Koerner index	
5	6 teeth
6	15 teeth
7	9 teeth

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