

## Assessment of systemic stress in patients undergoing third molar surgery: use of *in situ* cortisol levels as an indicator

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### ABSTRACT

**Objective:** To determine *in situ* serum cortisol levels in patients undergoing third molar surgery. **Materials and methods:** The study population consisted of patients from the University-Teaching Hospital of Chimbote (Hospital Universitario-Docente de Chimbote), who were selected based on inclusion and exclusion criteria. The sample consisted of 30 patients, from whom blood samples were taken at three different times (pre-, intra-, and post-operative) to determine serum cortisol levels using the ELISA technique. The values were transferred to a database and processed using descriptive statistical analysis (mean and standard deviation) and inferential analysis (Kruskal-Wallis and Tukey's tests). **Results:** Preoperatively, 66.7% (n = 20) of patients had serum cortisol levels within the normal range (50-230 ng/mL), while 33.3% (n = 10) had levels above 230 ng/mL. Intraoperatively, 60% (n = 18) of patients presented cortisol levels higher than 230 ng/mL, and postoperatively, this was observed in 56.7% (n = 17). A statistically significant increase in serum cortisol was found intraoperatively ( $285.53 \pm 108.00$  ng/mL) compared to preoperative values ( $198.00 \pm 74.85$  ng/mL), and this elevated level was sustained in the postoperative period ( $280.67 \pm 113.09$  ng/mL), although no statistically significant difference was observed between intra- and postoperative values. **Conclusion:** The present work reports significant *in situ* increases in serum cortisol levels due to the physiological alteration caused by surgical trauma, maintained until the post-operative period.

**Keywords:** oral surgery; cortisol; endocrine system.

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## INTRODUCTION

In clinical practice, any general or oral surgical procedure constitutes a stressful event and a systemic challenge for the patient (1). Third molar surgery is commonly performed on retained or impacted teeth, teeth affected by dental caries, or for orthodontic indications. These procedures can trigger stress responses manifested by increased heart rate, respiratory rate, and body temperature. Regardless of procedural complexity, the internal physiological processes involved generate tissue trauma and an inflammatory reaction that recruit cellular defenses to the site of the noxious stimulus, thereby altering systemic homeostasis and releasing potent mediators that attempt to restore it (2). These responses are physiological, as they activate a coordinated set of systems (neuroendocrine, metabolic, and immunological) that induce a constant state of alertness and facilitate the reestablishment of homeostasis, the success of which depends on the speed and adequacy of the response (3-5). Thus, all events perceived as stressful by the organism, whether exogenous or endogenous, cause a reduction in immune system function, thereby increasing susceptibility to disease and the risk of complications. This aspect is particularly relevant for improving patients' quality of life (1, 5-7).

In this context, one of the indicators of stress in patients is the hormone cortisol. Reports on its use in saliva as a marker of stress during third molar surgeries (both preoperatively and postoperatively) mention evident limitations associated with the difficulty of obtaining an optimal record during surgery, due to saliva manipulation and contamination with blood content (8). Considering this limitation, the present study aimed to quantify the stress level of patients undergoing third molar surgery by measuring serum cortisol levels in blood at different moments of the surgical procedure (pre-, intra-, and postoperative), in order to demonstrate the patient's physiological response.

## MATERIALS AND METHODS

This quasi-experimental study received approval from the Institutional Ethics Committee, and all required authorizations were obtained prior to its implementation at the Hospital Universitario-Docente de Chimbote (Nuevo Chimbote, Santa, Peru) during the period 2015–2016. The study population included patients who attended the Department of Dentistry to undergo third molar surgery due to tooth retention, impaction, advanced dental caries, or orthodontic needs. The study design considered the pre-, intra-, and postoperative moments as the independent variable, and blood cortisol levels—obtained through the ELISA method, which establishes a normal reference range of 50–230 ng/mL—as the dependent variable (9).

A purposive, non-probabilistic sample of 30 patients was selected. After receiving a detailed informational session, all participants voluntarily agreed to take part in the study by signing an informed consent form. This document, prepared in accordance with the principles of the Declaration of Helsinki, included the study objectives, detailed procedures (blood extraction and sampling times), expected benefits, potential risks, and the right to withdraw from the study at any time without adverse consequences.

The inclusion criteria were as follows: individuals aged 18 to 40 years, of either sex, scheduled for the extraction of an intact tooth, not receiving active hormonal therapy, and presenting stable vital signs. Meanwhile, the exclusion criteria included patients with a previous diagnosis of arterial hypertension, diabetes mellitus, hormonal disorders, or those undergoing surgical procedures lasting more than 90 minutes.

### Determination of serum cortisol levels

Prior to the surgical procedure, patients' vital signs were verified for stability, and a peripheral venous line (PVL) was established. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes at three time points: preoperative (baseline), intraoperative (30 minutes after inferior alveolar nerve block anesthesia), and postoperative (after suturing). Each sample was immediately labeled after collection with a unique alphanumeric identifier corresponding to the patient's medical record number and collection time.

To preserve sample integrity, specimens were temporarily stored in refrigerated containers at 4 °C until processing, which was performed in daily batches. In the laboratory, an electronic recording protocol (Excel®) was used to match each sample with its corresponding clinical data. Samples were centrifuged at 3000 rpm for 10 minutes within the first hour after collection, and the resulting serum was aliquoted into properly labeled cryovials. Aliquots were stored at –20 °C until analysis using the ELISA method (10), performed by trained personnel blinded to the surgical moment of origin. Absorbance readings were obtained using a 96-well plate reader ELMR-96 (Scitek®, Scitek Global Co., Jinan City, China) measuring the absorbance of the solutions at 450 nm.

### Statistical analysis

Serum cortisol levels obtained at the three surgical stages were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics (mean and standard deviation), absolute (n) and relative (%) frequencies, and inferential analyses (non-parametric Kruskal-Wallis and Tukey's post-hoc tests) were applied.

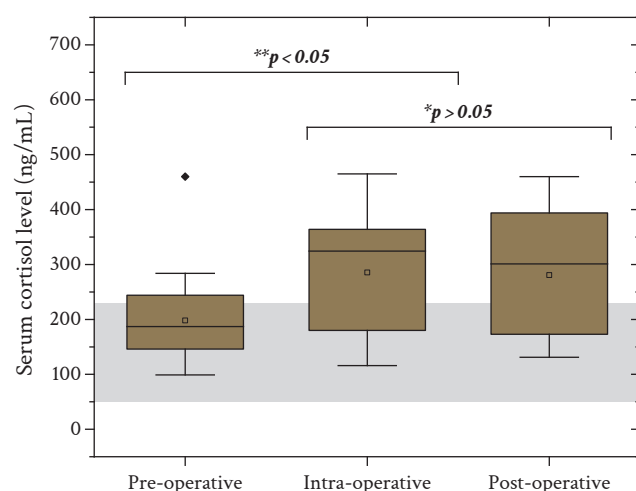
## RESULTS

Statistical analysis revealed variations in serum cortisol concentrations across the three surgical stages. In the preoperative period, 66.7% ( $n = 20$ ) of patients presented cortisol levels within the normal range (50-230 ng/mL), while 33.3% ( $n = 10$ ) exhibited concentrations above 230 ng/mL. During the intraoperative stage, marked fluctuations were observed: only 40.0% ( $n = 12$ ) maintained normal levels, representing a 26.7% decrease compared to the preoperative stage. Conversely, 60.0% ( $n = 18$ ) showed elevated values ( $>230$  ng/mL), indicating an 80.0% relative increase in cortisol concentration compared with the initial stage. In the postoperative period, 43.3% ( $n = 13$ ) showed normal cortisol levels, suggesting partial recovery relative to the intraoperative stage; however, 56.7% ( $n = 17$ ) continued to exhibit elevated concentrations ( $>230$  ng/mL) (Table 1 and Figure 1).

**Table 1.** Serum cortisol levels at pre-, intra-, and postoperative moments in patients undergoing third molar surgery ( $n = 30$ ).

Moment	Cortisol level (ng/mL)*	n	%
Preoperative	50-230	20	66.7
	$>230$	10	33.3
Intraoperative	50-230	12	40.0
	$>230$	18	60.0
Postoperative	50-230	13	43.3
	$>230$	17	56.7

\* Normal values: 50-230 ng/mL



**Figure 1.** Box plot of serum cortisol levels in patients undergoing third molar surgery (the shaded area indicates the range of normal values). \*No statistically significant differences at  $p > 0.05$ . \*\*Statistically significant differences at  $p < 0.05$ .

Descriptive analyses showed a preoperative mean serum cortisol level of  $198.00 \pm 74.85$  ng/mL. During the intraoperative period, the mean concentration increased significantly to  $285.53 \pm 108.00$  ng/mL ( $p < 0.05$ ). In the postoperative moment, a non-significant decrease in the mean value ( $280.67 \pm 113.09$  ng/mL) was observed compared with the intraoperative period ( $p > 0.05$ ). These findings indicate a pronounced physiological stress response during the surgical procedure, followed by a partial trend toward stabilization, although without complete return to baseline levels in the short term (Table 2).

**Table 2.** Descriptive statistics of serum cortisol levels (ng/mL) in patients undergoing third molar surgery ( $n = 30$ ).

Moment	Mean	SD	Min.	Max.
Preoperative	198.00 <sup>a</sup>	74.85	99	460
Intraoperative	285.53 <sup>b</sup>	108.00	116	465
Postoperative	280.67 <sup>b</sup>	113.09	131	460

<sup>a, b</sup> Different letters indicate groups that differ significantly from each other, while identical letters denote no significant difference at  $p = 0.05$ .

SD: standard deviation; Min.: minimum; Max.: maximum.

## DISCUSSION

The study focused on measuring serum cortisol levels, widely regarded as one of the most reliable biomarkers for quantifying physiological stress in clinical contexts (5, 11). Normal cortisol levels range from 50 to 230 ng/mL; values above this range indicate that the patient is considered to be in a state of stress. Participants who underwent third molar extraction surgery under local anesthesia were alert and oriented in time and space during the three evaluation moments (pre-, intra-, and postoperative), and exhibited variations in serum cortisol levels. These variations reflect the activation of endocrine pathways that have been well documented for nearly a century in general surgery contexts (12, 13); however, in dental surgeries, there are no detailed records of patients undergoing invasive procedures while remaining conscious.

The physiological responses triggered by stress may appear in patients from the moment they agree to undergo a surgical procedure, whether for aesthetic, rehabilitative, and/or preventive reasons, raising questions regarding the duration, procedure, prognosis, etc.; nonetheless, only 33.3% of the population may exhibit elevated stress levels. This indicates that the psychological factor affects certain patients, as reflected in the activation of the hypothalamic–pituitary–adrenal (HPA) axis, which allows determining the level of stress present at the preoperative moment (12, 14).

During the intraoperative stage, beginning after local anesthesia administration, the HPA axis and the sympathetic nervous system immediately receive the systemic alert that triggers an increase in plasma cortisol, regardless of the psychological factor (12, 15-17). According to the reported results, the values obtained at this moment showed statistically significant differences compared with the preoperative moment, and, as stated in the literature, such elevations may persist only for a few minutes. This increase may be influenced by the complexity of the surgical procedure, the lack of control, and the degree of assistance the patient receives (18-20).

Reports on the physiological causes that generate changes in serum cortisol levels during the postoperative moment show a tendency toward a decrease associated with the physiological stress of these intrinsic processes (depending on modern anesthetic and surgical techniques), with levels remaining elevated even up to the second day after the intervention (21-23).

Understanding these changes in serum cortisol levels allows for adequate management during the recovery period and provides potential benefits for the surgical outcome (24, 25). Major surgical procedures, both medical and maxillofacial (for example, fractures of the maxillary, mandibular, and zygomatic-maxillary complex, or surgeries for the treatment of tumors and odontogenic cysts), currently prescribe a single dose of hydrocortisone (1-2 mg/kg of body weight, up to a maximum of 100 mg per dose), administered during the intraoperative or immediate postoperative moment to modulate the early inflammatory response to surgical trauma (23). Although corticosteroids are standard in postoperative care for general surgery, their use in oral

and maxillofacial surgery is still not part of the standard protocol (26).

One limitation of this study is the restricted age range (18-40 years), determined by the need to evaluate subjects under baseline health conditions, free from systemic comorbidities or hormonal imbalances that could interfere with physiological parameters. Although this methodological restriction was necessary to ensure the stability of preoperative vital signs, it limits the extrapolation of results to pediatric and geriatric populations, and those with underlying medical conditions. Moreover, the lack of previous literature on serum cortisol quantification in oral and maxillofacial surgical procedures poses a comparative challenge. In addition, the small sample size and the lack of standardization in cortisol measurement times may limit the generalizability of the findings. In addition, excluding other stress biomarkers limited the ability to perform a multifactorial analysis of the physiological response. Despite these limitations, the study highlights the importance of documenting the surgical stress response *in situ* using this biomarker, providing a reference framework for future research aimed at exploring the correlation between physiological stress and clinical variables in this context, preferably through longitudinal designs and more diverse samples.

## CONCLUSIONS

This study found significant intraoperative increases in *in situ* serum cortisol levels, reflecting the physiological alterations associated with third molar surgery when compared with the preoperative stage.

### Conflict of interest:

The authors declare no conflict of interest.

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### Ethics approval:

This study was approved by Universidad Nacional de Trujillo (RD No. 0651-2016-EPG).

### Author contributions:

**KHM:** conceptualization, research, methodology, formal analysis, writing – review & editing.

**SBG:** data curation, software, visualization, writing – original draft.

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