Anxiety and cortisol levels during circumcision

Duygu Kara1, Erkan Cem Celik1, Yener Yesiltepe2, Fatih Ozdemir3
1Anesthesiology and Reanimation Unit, 2Biochemistry Unit, 3Urology Unit, Palandoken Government Hospital, Erzurum, Turkey

Abstract
Aim: In this study, we aimed to investigate whether circumcision is a stressor ambulatory surgical intervention for children and demonstrate the relationship between pre- and post-operative anxiety levels, blood cortisol levels (BCL), and salivary cortisol levels (SCL) in these children. Material and Method: Boys aged between 5 and 17 years, with a plan of circumcision, were prospectively included. Their preoperative anxiety levels, salivary cortisol levels (SCL), and blood total cortisol levels (BCL) were measured. After the operation, the same parameters were measured and preoperative values were compared with postoperative values. Also, the correlation between anxiety scores, SCL, and BCL was assessed. The Yale Preoperative Anxiety Scale was used to calculate the anxiety scores. Results: The mean age of 81 patients was 6.62 ± 1.40 years. The preoperative anxiety scores, SCL, and BCL were significantly lower than post-operative values (p<0.001 for each). The preoperative SCL were positively correlated with BCL and anxiety scores. Postoperative SCL were positively correlated with BCL and anxiety scores. Discussion: Circumcision is a cause of increment in anxiety, serum, and salivary cortisol levels in children. Salivary cortisol levels were correlated with simultaneously drawn serum cortisol levels. The preoperative and postoperative anxiety scores were correlated with BCL and SCL in children with circumcision operation.

Keywords
Anxiety Score; Circumcision; Salivary Cortisol; Serum Cortisol
Introduction
Circumcision is the surgical removal of the foreskin of the penis. Motivation arising from either some personal or religious reasons makes the procedure prevalent in especially Muslim and Jewish populations. It is also one of the oldest surgical procedures, performed for medical indications, such as phimosis, balanitis xerotica obliterans, recurrent balanoposthitis, paraphimosis, and urine outlet obstruction, as well [1]. Recommendations of American Academy of Pediatrics, American College of Obstetricians and Gynecologists, Centers for Disease Control and Prevention, and World Health Organization are present, based on its long-term benefits which outweigh any risks [2].

Circumcision is performed as an ambulatory surgery, which can provide more improved patient satisfaction, reduced complications, and more efficient care. Anyway, as well as many other surgical procedures, circumcision is a source of anxiety, fear, and pain for children [3]. Increased preoperative anxiety levels result in negative consequences, such as challenges in the induction of anesthesia, increase in the need of anesthetic drugs during the operation and analgesic drugs after the operation, and increased risk of infections [4]. Following any surgical interventions and trauma, the stress response is triggered by impulses sent from the injured site to the hypothalamus. As well as activation of hypothalamic-pituitary-adrenal (HPA) axis, the serum levels of glucagon, catecholamines, and host of inflammatory cytokines are increased [5].

Total serum cortisol is the main parameter that is routinely measured in the assessment of HPA axis. Due to the changes in levels of the affinity of corticosteroid-binding globulin and misinterpreting in some patient groups, underestimation of the cortisol response in stress may happen [6]. Measuring salivary cortisol level (SCL) is a promising alternative, because of its strong correlation with serum-free cortisol, hence safe, easy, and non-invasive, and rapid method that is especially appropriate for pediatric patients [7]. Previously, SCL has been shown to reflect the stress in obstructive sleep apnea syndrome, dental caries, and burn wounds in children [8-10].

In this study, we aimed to investigate and confirm whether circumcision is a stressor ambulatory surgical intervention for children, and also we aimed to demonstrate the relationship between pre- and post-operative anxiety levels and blood and salivary cortisol levels in these children.

Material and Methods
A prospective, observational study was planned to conduct in Erzurum Palandoken Government Hospital, between January 1, 2017 and December 31, 2017. Boys aged between 5 and 17 years, with a plan of circumcision, were included. Children with a known chronic disease (cardiac, respiratory, endocrinologic, and neurologic, etc.) and history of receiving any kind of corticosteroid therapy during the last month, were excluded. Local ethical committee approved the study protocol (Date:06/21/2016, Number: 2016/12-79) and the patients were included in the study after written informed consent was obtained from the parents of each child.

Preoperative anxiety levels of all children were calculated with the short form (M-YPAS-SF), just 30 minutes before the surgery [11]. Additionally, salivary cortisol levels (SCL) and blood total cortisol levels (BCL) of all children were measured three times; between 08.00-13.00, on the day before the surgery (basal level); 30 minutes before the surgery (preoperative level); 2 hours after the surgery (postoperative level).

For sedation of the children, the protocol for anesthetic drugs was as follows: midazolam (after an initial intravenous dose (0.05 mg/kg), careful titration up to 0.4 mg/kg total dose was used (not exceeding 10 mg) until appropriate sedation and anxiolysis were achieved before the procedure); propofol (repeated bolus method; after an initial intravenous induction dose (2 mg/kg, 0.5 mg/kg) was given, additional bolus doses in every 3-5 minutes were applied until moderate sedation could be achieved).

No additional sedatives were used. During the monitorization, the duration of procedure, sedation, and recovery, and the doses of propofol and midazolam were recorded. And after the surgery, the Aldrete (recovery) scores were calculated [12]. Deep sedation/general anesthesia was defined as the state of blunted consciousness produced by anesthetic medications, resulting in partial loss of protective reflexes and purposeful responses to various stimuli [13]. During and after the surgery, complications such as apnea, O2 desaturation, bradycardia, hypotension, cough, nausea, and vomiting were recorded and managed accordingly.

All SCL samples were drawn from the patients after at least 6 hours of fasting. For basal SCL samples, patients rinsed their mouth or drank water 10 minutes before sampling, between 08.00-13.00 am. Examination of cortisol levels (ng/ml) in saliva were performed in clarified saliva supernatants, which centrifuged (at 3500xg for 20 minutes) after sampling and stored at -80°C until analysis. ELISA kit (DRG Salivary Cortisol ELISA; DRG International, Inc., USA) was used following the manufacturer’s instructions. BCL’s were measured by Cobas e 601 (Roche Diagnostics GmbH; Manheim, Germany). Blood samples were centrifuged (at 3500 rpm for 10 minutes) and serum samples were stored at -80°C until analysis.

The statistical analyses of the data of the present study were performed by means of IBM SPSS 20.0 software. The Kolmogorov–Smirnov test was used to evaluate the data distribution. To evaluate the changes in anxiety and cortisol levels, paired samples T-test was used to check differences before and after the surgery, at a significance level of 5% for normally distributed continuous variables. The correlation between anxiety, blood, and salivary cortisol levels was evaluated with the Pearson correlation test. Differences were considered significant if the p-value was < 0.05. Descriptive statistics were expressed as a mean ± SD.

Results
Eighty-one patients were included in the study. Mean age of the patients was 6.62 ± 1.40 years. The data regarding the intra- and post-operative properties of the children were shown in Table 1. The preoperative anxiety scores, SCL, and BCL were significantly lower than post-operative values (p<0.001 for each) (Table-2). The pre-operative SCL were positively correlated with BCL and anxiety scores (Table 3). Similarly, post-operative SCL

| Duration of sedation (min) | 13.50±1.05 |
| -------------------------- | ---------- |
| Duration of operation (min) | 11.48±0.96 |
| Duration of recovery (min) | 4.58±1.17 |
| Aldrete score             | 12.00±0   |
| Dose of propofol (mg/kg)  | 90.60±19.32 |
| Dose of midazolam (mg/kg) | 1.48±0.31 |

* Mean ± standard deviation
Anxiety in circumcision

In this study, preoperative anxiety, blood, and salivary cortisol levels were higher than preoperative levels. It is expected that a surgical procedure can induce a physiological stress response. Nevertheless, an increased level of anxiety may reflect the surgical and anesthetic experience. Increased postoperative cortisol levels are assumed as instant values without long-term effects. A healthy and functional HPA axis has been proven in ambulatory surgery. The authors declare that they are responsible for the article's scientific content

Table 2. Comparison of salivary cortisol, blood cortisol, and anxiety scores before and after surgery

|                         | Before Surgery | After surgery | p       |
|-------------------------|----------------|---------------|---------|
| Salivary cortisol level (µg/ml) | 0.320±0.22     | 0.589±0.35    | <0.001  |
| Blood cortisol level, (3-21 µg/dL) | 5.93±4.19      | 9.36±6.10     | <0.001  |
| Anxiety Score           | 24.60±2.15     | 34.58±5.27    | <0.001  |

Table 3. Correlation of salivary cortisol, blood cortisol, and anxiety scores before and after surgery*

|                         | Before Surgery | After surgery | r      | p       |
|-------------------------|----------------|---------------|--------|---------|
| Salivary cortisol       | 1              | 0.88          | 0.54   | <0.001* |
| Blood cortisol          | <0.001*        | 1             | 0.46   | <0.001* |
| Anxiety score           | 0.54           | 0.46          | 1      |         |
| Salivary cortisol       | <0.001*        | 1             | 0.52   | <0.001* |
| Blood cortisol          | <0.001*        | 1             | 0.45   | <0.001* |
| Anxiety score           | 0.52           | 0.45          | 1      |         |

*, all analyses were presented by r (correlation coefficient) and p (probability) values; *: statistically significant

were positively correlated with BCL and anxiety scores. During and after the surgery, no serious complications, such as hypotension, arrhythmia, and cardiopulmonary arrest were experienced. Fifteen (18.5%) patients had a cough and 12 (14.8%) patients had nausea and vomiting in the post-operative period.

Discussion

In this study, postoperative anxiety, blood, and salivary cortisol levels were higher than preoperative levels. It is expected that a surgical procedure can induce a physiological stress response. Nevertheless, an increased level of anxiety may reflect the surgical and anesthetic experience. Increased postoperative cortisol levels are assumed as instant values without long-term effects. A healthy and functional HPA axis has been proven in ambulatory surgery. The authors declare that they are responsible for the article's scientific content

As a conclusion, the results of this study have shown that circumcision induced an increment in anxiety, serum, and salivary cortisol levels in children. Salivary cortisol levels were in correlation with simultaneously drawn serum cortisol levels. Also, the preoperative and postoperative anxiety scores were correlated with BCL and SCL in children with circumcision operation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.
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