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Original Article

Responses of salivary cortisol levels and sedation score to oral hydroxyzine premedication in children undergoing outpatient surgery

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ABSTRACT

Aim: To evaluate the sedation score response and salivary cortisol levels (SC) to premedication with sedative hydroxyzine in children with outpatient surgery and the relationships between the two.

Methods: Eighty-seven ASA 1 classified patients (American Society of Anesthesiologists Classification 1, normal healthy patients), aged 4-13 years, were randomly and prospectively allocated into the study. Children having outpatient surgery (e.g. inguinal/abdominal surgery, circumcision) either did not have a premedication or received oral hydroxyzine (2 h before the surgery) as a sedative drug. All patients were evaluated for the level of sedation by Ramsay sedation score [RSS, from 1 (awake, anxious, restless or both) to 6 (asleep, exhibits no response)] by an independent anesthesiologist. Salivary samples taken during the assessment of sedation score were analyzed for cortisol levels.

Results: SC increased significantly by increasing age *(r=0.447; p<0.001)*. Premedication with hydroxyzine produced higher sedation scores *(1.73 vs 1.46, p=0.014)* and patients with higher sedation scores had lower SC *(p<0.01)*. Circumcised children had similar SC to hernia/inguinal surgery *(p>0.05)*.

Conclusion: The data suggest that salivary cortisol increases by increased age and provide evidence that sedation is associated with suppressed cortisol levels. Moreover, different types of surgery appear to be perceived as similar threats by the children.

Keywords: Outpatient surgery, conscious sedation, sedation score, salivary cortisol levels, child.

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Introduction

Undergoing a surgical operation is a stressful event for most of the people but it has much pronounced effects in pediatric patients [1]. Children are more sensitive to being separated from their parents and unfamiliar surgical environment poses more stress on them, resulting in intense fear, stress and anxiety. In order to overcome this problem, presence of parents before anesthesia has been preferred by the patients, parents and surgeons. However, some studies showed that this method reduced anxiety and improved patient cooperation but the others expressed their concerns as it caused negative behaviors in children (e.g. exaggerated response to stress) and parents (e.g. emotional outcomes) [2,3].

Sedative premedication might be the other way to alleviate fear, stress and anxiety in children undergoing surgery. The major objectives of premedication are to decrease the stress response with preservation of hemodynamic parameters, to facilitate anesthesia induction and to produce amnesia [1,3]. Commonly used premedications include benzodiazepines, opioids, phenothiazines, barbiturates, and antihistaminics (diphenhydramine, hydroxyzine) [4]. In general, most of them are long acting, physiologically more disturbing and requires parenteral administration [1]. However, availability of oral drugs for premedication has increased their usage, especially in children. Hydroxyzine is one of those orally used drugs and has anxiolytic, antihistaminic, antispasmodic, antiemetic, and secretion lowering effects with minimal respiratory and circulatory changes [5,6]. Level of sedation before surgery, whether induced by premedication or not, is crucial for successful accomplishment of anesthesia and surgery.

Fear, anxiety and stress activate the hypothalamo-pituitary-adrenal (HPA) axis and increases cortisol levels in blood circulation [7]. Therefore, its measurement in blood might provide valuable information about the stress-induced activity of this system. However, blood cortisol is not preferred as it reflects total cortisol (free plus bound cortisol) and as blood sampling by a needle itself activates stress axis. Measurement of cortisol in saliva has taken precedence over blood cortisol, not only due to its non-invasive sampling but also due to its representation of free, or active, cortisol [8]. Also, routine free cortisol measurement in blood is very uncommon and requires labor-intensive analyses and calculations based on assumptions. Moreover, salivary cortisol is preferable as cortisol freely passes from blood to saliva without being affected by salivary flow rate.

Studies have shown that sedative premedication before anesthesia facilitates patient cooperation, separation from the parents, and eases anesthesia induction [3]. We postulate that this might be due to suppression of stress axis, and therefore, might be associated with reduced salivary cortisol levels. To test this hypothesis, the sedation scores of children undergoing outpatient surgery (whether premedicated or not) were evaluated and then compared with salivary cortisol levels.

Materials and Methods

The study was carried out following ethical approval *(Date:* 2016*; Decision number:* 8-57*)* by the local ethics committee (Erzurum Regional Education and Research Hospital Ethics Committee). Written informed consents were obtained from the parents of all patients. The study was conducted prospectively in the Erzurum Regional Education and Research Hospital between October 2016 and June 2017. In the pediatric surgery clinic, 87 patients (4 to 13-year-old) with ASA I scores (American Society of Anesthesiologists) undergoing elective outpatient surgery were included in the study. Patients with any chronic disease, drug use or allergic history were excluded from the study.

The patients either did not receive any premedication or received hydroxyzine groups. The latter group of patients received oral hydroxyzine HCl (Atarax syrup, 2 mg / ml, 200 ml, UCB Pharma, Turkey) 2 hours before the surgery at a 1 ml/kg doses in 10 ml of injectable water. None of the patients were given psychotherapy to reduce anxiety or fear. All the patients were taken to the operation room and the sedation scores were assessed by using Ramsay Sedation Score scale (RSS, *Score 1: Awake, anxious, restless or both; 2: Awake, cooperative, oriented and tranquil; 3: Responds to commands only; 4: A brisk response to a light glabellar tap; 5: A sluggish response to a light glabellar tap; 6: No response, asleep*) by an anesthesiologist who was unaware of the premedication. Then, the saliva samples were taken from the patients by the surgeon who was going to perform the operation.

Children taken into the surgery should normally wake up early in the morning (presumably at 07.00 am) in order to finish their pre-surgery official procedures in the hospital between 08:30-09:00 am. They had their surgery between 10:00-11:30 am. Although, salivary cortisol have a diurnal rhythm, Petrowski et al. [9] has shown that the rise associated with cortisol awakening response (CAR) settle back to a relatively stable level approximately 3 hours post-awakening. Therefore, the time points for cortisol samplings in the current study coincide with a relatively stable cortisol level. The cortisol awakening response (CAR) is normally associated with a peak cortisol levels between 15-45 min post-awakenings, followed by a decline afterwards. Saliva samples (0.5-1.0 ml) were taken with the help of Pasteur pipette into the micro centrifuge vials. After taking the sample, the tube was sealed, labeled and stored at -20 °C until analysis. As a strict routine before the surgery, the children were not permitted to eat or drink before the surgery. Salivary cortisol levels were analyzed by a validated ELISA (enzyme-linked immunosorbent assay) method reported by Ozgocer et al (10).

Of 87 cases, 41 did not receive premedication and 46 received hydroxyzine. Of the children with premedication, 89.1% were male (n=41) and this ratio was 100% in the children who had no premedication (n=41). Number of female patients was 5 and they were all among premedication patients. The mean age was 8.0 (range 4 to 12 years old) in the children who had premedication while it was 8.1 (range 4 to13 years old) in the children who did not have it. All patients underwent a outpatient surgery including inguinal hernia repair, circumcision, hydrocele etc., and were discharged on the same day postoperatively. The demographic characteristics of the patients are shown in Table 1.

For the surgery type, only the patients having either inguinal/hernia surgery (n=35) or circumcision (n=45) were compared as there was sufficient number of patients under these grouping. Patients (n=7) who could not be included in either groups (such as anal fissure, hypospadias etc.) were within premedication group and were not included in the inguinal/hernia surgery vs. circumcision comparisons. Additionally, patients with multiple operations, such as hernia plus circumcision (n=4), were included in the inguinal/hernia surgery group.

Statistical analysis

Data were analyzed by using Minitab 18 statistical package (PA, USA). Distribution of the data was analyzed by using Anderson-Darling test. Cortisol data did not have a normal distribution and therefore they were converted into log 10 scale. One patient's log 10 cortisol value (male, 7 year-old, and circumcised child) was removed from cortisol analyses following Grubbs' outlier test. Consequently, log transformed data had normal distribution and were used for statistical analyses. The effects of age, surgery type and sedation score on salivary cortisol levels were analyzed separately by t-test. Effect of gender could not be assessed as the number of females were low (n=5). Effects of premedication on salivary cortisol levels were analyzed by t-test. The effects of sedation score on salivary cortisol levels also were assessed by t-test. This data was re-analyzed by following adjusting for age, gender, premedication and type of surgery in GLM (Generalized linear model) analysis (alone or in combination). Same method was also applied to type of surgery comparison for cortisol levels.

Non-parametric sedation scores were compared by Kruskal-Wallis test. Two patients (2 males, both with inguinal hernia surgery) did not have their RSS records and were not included in RSS analyses. Pearson correlations were carried out to find the relationships between the study parameters. An alpha level less than 0.05 was accepted as statistically significant and all data are presented as mean±SEM unless otherwise stated. Salivary cortisol levels are presented as log 10 transformed values.

Results

The demographic characteristics of the patients were presented in table 1.

Table 1. Demographic characteristics of the patients.

Parameters	No-pre med N=41	Pre med N=46
Age **(years)**	8.1 (4-13)	8.0 (4-12)
Gender		
Male	41 (100%)	41 (89.1%)
Female	0 (0%)	5 (9.9%)
Surgical procedure*		
Inguinal/hernia surgery	7 (17.1%)	28 (71.8%)
Circumcision	34 (82.9%)	11 (28.2%)

Pre med: Pre medication.

Ramsay sedation score was either 1 or 2 and none of the patients had a sedation score of 3 or more as expected. Premedication caused significantly higher sedation scores (1.73 and 1.46, respectively, $p<0.05$). In the premedication group, sedation score was 2 (awake, calm, watching the environment) in 33 patients (71.7%) but it was score 1 (awake, restless and / or crying) in 11 patients (29.3%). In the other patients without premedication, 19 patients (37.4%) were in score 2 while 22 patients (63.6%) were in score 1 (Table 2). Sedation score did not differ between the genders, between the ages of children or between the type of surgery $(p>0.05)$.

Table 2. Ramsay sedation scores (RSS) of the patients.

RSS	No-pre med	Pre med	*p value*
Median (mean)	1 (1.46)	2 (1.73)	*<0.05*
Min-max	1-2	1-2	
Score 1 (n, %)	22 (53,7)	11 (25,0)	
Score 2 (n, %)	19 (46,3)	33 (75,0)	

Pre med: Pre medication.

Premedication did not affect SC $(p>0.05)$ (Figure 1A). Type of the surgery also did not affect SC $(p>0.05)$ (Figure 1B). However, the age of the children was significantly, positively and linearly correlated with SC $(r=0.447; p<0.001)$ (Figure 1C)

Children with a Ramsay sedation score (RSS) of 2 had significantly lower SC $(p<0.001)$ than that of children who had a RSS of 1 $(p<0.001)$ (Figure 2). This trend persisted when the data were adjusted for age, type of surgery, gender and premedication, alone or in combination $(p<0.001)$.

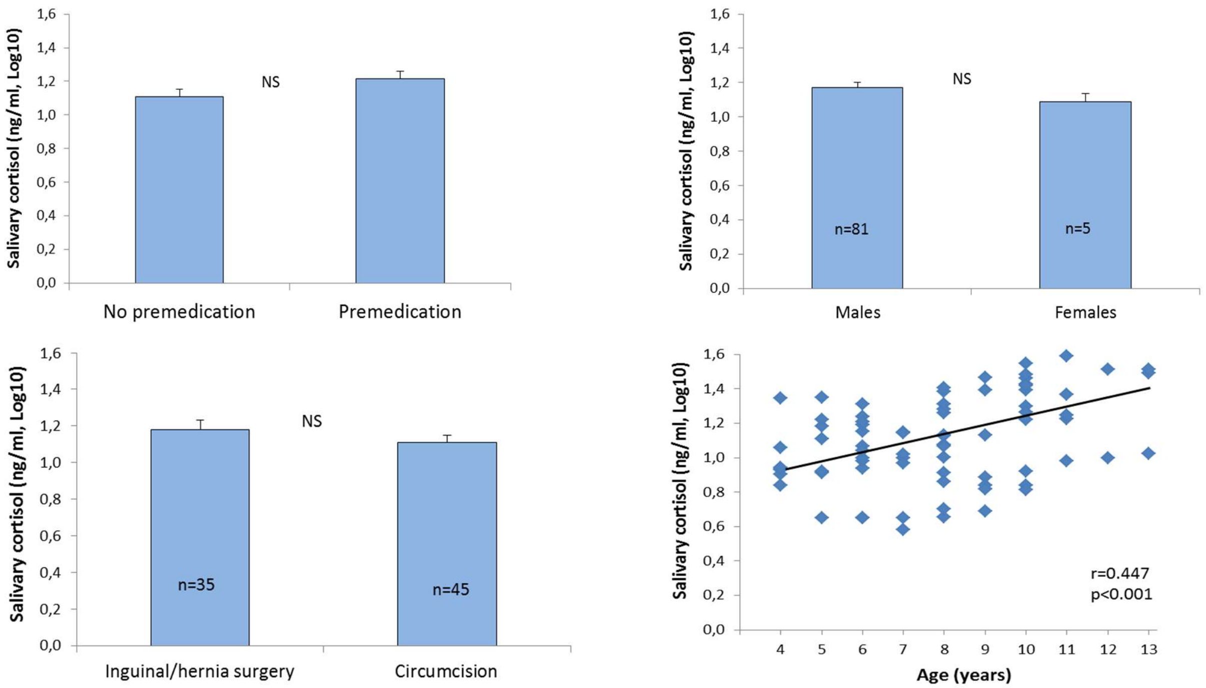

Figure 1. A. Salivary cortisol (SC) did not differ between patients who had premedication or not *(p>0.05).* B. SC did not also differ between males and females *(p>0.05)*. C. Type of surgery did not have an effect on SC *(p>0.05)*, B. Age of the children significantly, linearly and positively correlated with SC *(r=0.447; p<0.001).* NS, non-significant. Data are presented as log10 mean ± S.E.M.

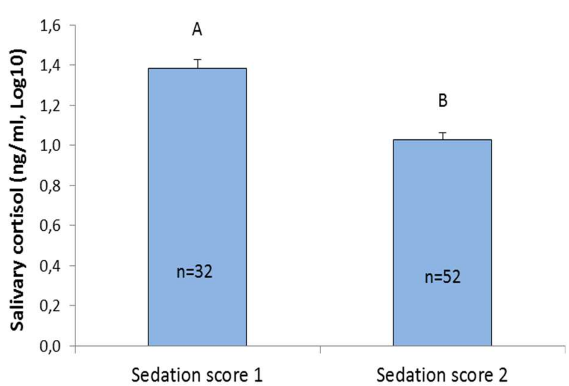

Figure 2. Children with higher Ramsay sedation scores (RSS) had lower SC *(p<0.001).* This trend did not change in significance when the data were adjusted for age, type of surgery, premedication and gender in GLM analyses (alone or in combinations). Data are presented as log 10 mean ± S.E.M. Different letters denote significant difference at *p<0.001*.

Discussion

This study evaluated preoperative sedation level and stress axis in children by non-invasive means (salivary cortisol) and provided evidence to support the hypothesis that higher sedation scores (score 2 vs. score 1), irrespective of premedication use, are associated with suppressed salivary cortisol levels. Features of the patients, sedation scores and salivary cortisol levels are separately discussed below.

This study was randomized prospective study and most of the patients attending to clinic were boys (94.3%). When the patients who were circumcised were excluded (as it is a seasonal event coinciding with the study period), again the vast majority of the patients (88.1%) were boys. This appears to be due to the fact that inguinal hernia or inguinal operations are more common in boys [11].

As expected, RSS was higher in patients who had premedication (a mean score of 1.73 vs. 1.46). Additionally, sedation scores were either 1 (awake, restless and / or crying) or 2 (awake, cooperative, oriented and tranquil) and none of the patients had a score 3 or more. These scores were also expected when drugs like hydroxyzine was used for premedication. Some patients in premedication group had lower RSS while some of the patients in non-premedication group had higher RSS. Both situations may suggest that sedation itself is likely to be a trait feature but hydroxyzine is effective in inducing sedation in most patients. Moreover, type of the surgical operation, age and gender did not have an effect on sedation score [12].

Salivary cortisol levels represent free cortisol, which is the bioactive fraction of total circulating cortisol levels [13,14]. Therefore, it has been considered more appropriate measure than total blood cortisol and it has been accepted as a useful tool to measure anxiety and stress in a non-invasive manner [15,16]. Likewise, in the current study, salivary samples were taken non-invasively before the surgery to assess the activity of the stress axis, i.e. the hypothalamo-pituitary-adrenal axis (HPA).

The age of the children was one of the most important factor affecting salivary cortisol levels. This is in accordance with the study of Bäumler et al. [17] who observed a linear increase in awakening cortisol levels in children aged 2-87 month (7.25 year-old). The current study adds that the increase was also evident from 4 to 13 years. Moreover, the current study did not measure awakening response but instead it utilized sample taken later in the day. This sample is expected to have lower cortisol concentration as awakening response is the highest response during the daytime. Even so, age-dependent increase was still evident. Furthermore, all children knew that they were going to have a surgical operation when they gave their saliva samples. From that point of view, it appears that stress reactivity against a surgical operation also increases by age. It might be speculated that awareness about the consequences of a surgical operation may increase by age and this, in turn, may translate into higher stress reactivity in older children. An alternative explanation might be "maturation of the HPA axis" by increasing age [18]. Altogether, data suggest that maturation of HPA axis or awareness of threats increases by increasing age. Moreover, data in the current study shows that this "maturation" or "reactivity" appears to cover not only the neonatal or early childhood period but also continues until late childhood (early teenage). Our hypothesis was that higher sedation scores would be associated with lower salivary cortisol levels. The data in the current study provides support for this hypothesis and suggest that suppression of HPA axis might be an integral part of sedation. Higher sedation scores (score 2) was not only seen in premedication group but also in control group, suggesting that suppression of HPA axis may be a trait feature like sedation scores. In line with this, Hsu et al. [19] observed no change in cortisol levels in drug-induced sedation group over the control. This suggests that lower salivary cortisol levels in higher sedation scores might be due to personal traits rather than direct effects of sedatives. In the current study, total number of girls was quite low (n=5) and therefore it has not been possible to draw conclusions in terms of effects of gender on salivary cortisol levels. Nevertheless, Lindfors et al [20] who found no difference between girls and boys in their response to perceived stress or in relation to recurrent pain such as headache, stomach ache, back pain etc. Additionally, it seems that circumcision, a relatively simple surgery, evokes similar stress responses observed in hernia/inguinal surgery. This might suggest that both groups of surgeries are perceived as similar threats by the children.

Conclusion

This study suggests that sedation in children appears to be associated with suppression of salivary cortisol levels. Moreover increased age of the children is associated with increased salivary cortisol levels suggesting that maturation or reactivity of the HPA axis might increase by increasing age.

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All procedures performed in studies involving human participants 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.

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References

[1]Abdallah C, Hannallah R. Premedication of the child undergoing surgery. Middle East J Anaesthesiol. 2011; 21(2): 165-74.

[2]Kain ZN, Mayes LC, Caldwell-Andrews AA, et al. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. Pediatrics. 2006;118(2):651-58.

[3]Vinita S, Manu P, Singh GP. Oral midazolam and oral butorphanol premedication. Indian J Pediatr. 2005;72(9):741-44.

[4]Merriman HM. The techniques used to sedate ventilated patients. A survey of methods used in 34 ICUs in Great Britain. Intensive Care Med. 1981;7(5):217-24.

[5] Shapira J, Kupietzky A, Kadari A, et al. Comparison of oral midazolam with and without hydroxyzine in the sedation of pediatric dental patients. Pediatr Dent. 2004; 26(6):492-96.

[6]Kupietzky A, Holan, G, Shapiro J. Intranasal midazolam better at effecting amnesia after sedation than oral hydroxyzine: A pilot study. Pediatr Dent. 1996;18(8):32-34.

[7]Kara D, Bayrak NA, Volkan B, et al. Anxiety and Salivary Cortisol Levels in Children Undergoing Esophago-Gastro-Duodenoscopy Under Sedation. J Pediatr Gastroenterol Nutr. 2019;68(1):3-6.

[8]Blair C, Raver CC. Closing the achievement gap through modification of neurocognitive and neuroendocrine function: Results from a cluster randomized controlled trial of an ınnovative approach to the education of children in kindergarten. PloS one. 2014; 9(11): e112393.

[9]Petrowski K, Schmalbach B, Niedling M, et al. The effects of post-awakening light exposure on the cortisol awakening response in healthy male individuals. Psychoneuroendocrinology. 2019;108:28-34.

[10]Ozgocer T, Yildiz S, Uçar C. Development and validation of an enzyme-linked immunosorbent assay for detection of cortisol in human saliva. J Immunoassay Immunochem. 2017; 38(2): 147-64.

[11]Le Rouxa F, Lipskerb A, Mesureurc S, et al. Inguinal hernia repair in children: Surgical technique. J Visc Surg. 2016; 153 (2): 121-25.

[12]Köner O1, Türe H, Mercan A, et al. Effects of hydroxyzine-midazolam premedication on sevoflurane-induced paediatric emergence agitation: a prospective

randomised clinical trial. Eur J Anaesthesiol. 2011; 28(9): 640-45.

[13] Kudielka BM, Hellhammer DH, Wüst S. Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. Psychoneuroendocrinology. 2009; 34(1): 2-18.

[14] Gatti R, Antonelli G, Prearo M, et al. Cortisol assays and diagnostic laboratory procedures in human biological fluids. Clin Biochem. 2009; 42(12): 1205-17.

[15] Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. 2009; 34(2): 163-71.

[16] Stalder T, Kirschbaum C, Kudielka BM, et all. Assessment of the cortisol awakening response: Expert consensus guidelines. Psychoneuroendocrinology. 2016; 63: 414-32.

[17] Bäumler D, Kirschbaum C, Kliegel M, et al. The cortisol awakening response in toddlers and young children. Psychoneuroendocrinology. 2013; 38(11): 2485-92.

[18] Saridjan NS, Huizink AC, Koetsier JA, et al. Do social disadvantage and early family adversity affect the diurnal cortisol rhythm in infants? The Generation R Study. Horm Behav. 2010; 57(2): 247-54.

[19] Hsu AA, von Elten K, Chan D, et al. Characterization of the cortisol stress response to sedation and anesthesia in children. J Clin Endocrinol Metab. 2012; 97(10): 1830-35.

[20] Lindfors P, Folkesson Hellstadius L, Östberg V. Perceived stress, recurrent pain, and aggregate salivary cortisol measures in mid-adolescent girls and boys. Scand J Psychol. 2017; 58(1): 36-42.