Stress indicators during general anesthesia with opioid analgesics in children

Biljana DRASKOVIC, Danica STANIC, Anna URAM-BENKA, Izabella FABRI*

Clinic of Pediatric Surgery, Institute of Child and Adolescent Health Care of Vojvodina, Medical Faculty, University of Novi Sad, Novi Sad, Serbia

Background/aim: To determine which of the applied opioid analgesics brings the most powerful blockade of the stress response with the fewest side effects in children.

Materials and methods: This was a prospective, observational clinical study. The study included 150 boys, aged 2–5 years, ASA I, who underwent herniectomy or orchidopexy in day case surgery. The introduction and maintenance of anesthesia was intravenous (propofol, rocuronium, and opioids); airway was maintained by laryngeal mask and ventilation by mixture of oxygen/air. Subjects were divided into 3 groups depending on the applied opioid analgesics (fentanyl, alfentanil, remifentanil).

Results: The fentanyl group had the highest blood glucose values (AS = 5.14; SD = 0.47) and the highest increase in cortisone level at the moment of incision and at awakening (AS = 536.09; SD = 198.56). The lowest increase in cortisone was recorded in the remifentanil group. A significant decrease in leptin was registered at awakening in the fentanyl group and at the moment of incision in the remifentanil group (P = 0.939).

Conclusion: Remifentanil is the opioid analgesic with the highest suppressing effect on the stress response to surgical intervention in children.

Key words: Children, stress response, opioid analgesics, surgical intervention

1. Introduction

Surgical interventions cause stress to the organism by significantly violating the normal functioning of organs. The response of the body is manifested in a number of protective mechanisms whose purpose is to restore the physiological balance.

The mechanism of the body's response to stress is very complex, and it is aimed at restoring and maintaining the internal balance of the organism. It represents coordinated activities of organs and organic systems, which are instigated by metabolic, endocrine, and hematological changes (1).

A stressful response to an operation is followed by an increased secretion of pituitary hormones and by the activation of the sympathetic nervous system. Changes in pituitary secretion affect the hormone secretion of target organs.

Cortisone is considered to be the most significant mediator of stress reactions because it maintains vital functions both in normal and stressful circumstances. Cortisone concentration in the blood significantly correlates with the intensity of trauma. From the basic values which oscillate around 400 nmol/L, cortisone concentration can be increased to over 1500 nmol/L, depending on the trauma intensity. Cortisone reaction can be changed by the type of anesthesia.

Cortisone has complex effects on the metabolism of carbohydrates, fats, and proteins by inhibiting the absorption of glucose by cells and therefore increasing the concentration of glucose in the blood (2).

Leptin is a hormone that belongs to the family of cytokines, interleukin-2, interleukin-12, and growth hormone. It is primarily synthesized in the fatty tissue and in slight proportion in the gastric mucosa, skeletal muscles, and the brain. Recent research shows that it plays a role in hypothalamo–hypophysis–adrenocortical (HPA) axis regulation, as well as in angiogenesis and in the immune response. For these reasons leptin is considered to be a significant hormone in the acute stage of the organism's response to stress (3).

The balance of leptin and HPA axis has a clinical significance. Studies have shown that leptin represents the hormone of the acute stage of stress. In the early stage of acute stress the level of leptin decreases with the subsequent

---

* Correspondence: izabellafabri@gmail.com

increase of the cortisone level. This can be explained by the inverse proportion of the 2 neurobiological systems (4).

Blood glucose levels increase following trauma. Catecholamine and cortisone make gluconeogenesis and glycogenolysis easier, with the consequent reduction of glucose intake by muscles and fatty tissue. The level of glucose becomes directly proportional to the level of catecholamines in the blood.

White blood cell (WBC) activation is a part of the defense mechanism of the immune system. Activated WBCs are accumulated in large numbers in the damaged area to limit the harmful effects of trauma.

Opioids are commonly used in general anesthesia. The choice of opioid may be determined by differences in pharmacokinetic, pharmacodynamic, and physiochemical properties.

Remifentanil is a selective, ultra-short-acting m-opioid receptor agonist. It has highly predictable onset and offset of action, allowing for easy titration to achieve effective analgesia. Remifentanil does not accumulate and its organ-independent metabolism is not affected by renal or hepatic impairment. Remifentanil-based analgesia has also been associated with sedative-sparing effects (5). Fentanyl and sufentanil are fat-soluble and therefore have a rapid onset of action, but fat solubility also results in increased volume of distribution, thereby increasing the risks for accumulation and delayed recovery after a prolonged administration (6).

Opioid analgesics during anesthesia and local anesthetics as part of regional anesthesia have a leading role in the modulation and suppression of the stress response to surgical trauma.

In our clinic for pediatric surgery we commonly use several opioid analgesics because opioids lower the stress response to the surgical intervention, but we were unsure which opioid was the most effective.

Our aim was to establish the overall effect of opioid analgesics on the organism's stress response to a surgical intervention in proportion to leptin and cortisone levels as well as WBC and blood glucose levels, and to evaluate which opioid analgesic brings the most powerful blockade of the stress response with the fewest side effects.

2. Materials and methods
The protocol for the study was approved by the regional ethics committee and written, informed consent was obtained from the parents or guardians.

This was a prospective, observational clinical study. The study was conducted in a clinic of pediatric surgery in Novi Sad, Serbia, in 2010. The 150 examinees were boys aged 2–5 years of ASA I. They were all operated on for herniectomy or orchidopexy as part of a day surgery. All surgical interventions were performed in the morning between 0830 and 1100 hours to avoid the influence of the daily hormone variations on the organism's stress response. Half an hour prior to the intervention the examinees were given midazolam (0.5 mg/kg) orally. The maintenance of anesthesia was equal in all groups with continuous propofol infusion and rocuronium application as a relaxant; the airway was maintained by laryngeal mask and the ventilation was controlled or assisted by the mixture of oxygen/air at a 1:1 ratio. The applied analgesics were different.

The examinees were divided into 3 groups (50 boys in each), depending on the applied opioid analgesics.

2.1. Fentanyl group
The induction of anesthesia was done with propofol (2.5 mg/kg), rocuronium (0.6 mg/kg), and fentanyl 1 µg/kg. The maintenance of anesthesia was with propofol in a continuous infusion of 5–10 mg kg^{-1} h^{-1}, fentanyl in a continuous infusion of 2–3 µg kg^{-1} h^{-1}, and rocuronium in a single dose of 0.15–0.20 mg/kg.

2.2. Alfentanil group
The induction of anesthesia was with propofol (2.5 mg/kg), rocuronium (0.6 mg/kg), and alfentanil 7 µg/kg. The maintenance of anesthesia was with propofol in a continuous infusion of 5–10 mg kg^{-1} h^{-1}, alfentanil in a continuous infusion of 0.5–1.5 µg kg^{-1} min^{-1}, and rocuronium in a single dose of 0.15–0.20 mg/kg.

2.3. Remifentanil group
The induction of anesthesia was done with propofol (2.5 mg/kg), rocuronium (0.6 mg/kg), and remifentanil 1 µg/kg. The maintenance of anesthesia was with propofol in a continuous infusion of 5–10 mg kg^{-1} h^{-1}, remifentanil in a continuous infusion of 0.25–0.3 µg kg^{-1} min^{-1}, and rocuronium in a single dose of 0.15–0.20 mg/kg. The introductory bolus dosage of remifentanil was 1 µg/kg, then infusion at 0.3–0.5 µg kg^{-1} min^{-1}, and following the surgical incision 0.25 µg kg^{-1} min^{-1} to 0.1 µg kg^{-1} min^{-1}.

The continuous doses of analgesics in all 3 groups were adjusted during the perioperative period according to the hemodynamic parameters of the patients (heart rate, blood pressure).

During anesthesia and in the early phase of recovery the values of WBCs, the blood glucose level, and the levels of cortisone and leptin in the serum were measured. These parameters were measured at the following 3 stages in the study: before the introduction into anesthesia, after the surgical incision, and during awakening. The values obtained before the introduction were taken as baseline values.

All statistical analyses were performed using SPSS 11.5 for Windows (SPSS, Chicago, IL, USA) and STATISTICS 5.0. Statistical analysis was carried out by analysis of variance (ANOVA)for parametric data, descriptive statistical methods, and post hoc analysis for data evaluation. Statistical significance was set at $P < 0.05$, with a confidence interval of 95%.

3. Results

3.1. Basic data about patients - age and body mass
One hundred and fifty boys, aged 2–5 years, participated in the study. The average age of the examinees was 3.8 ± 1.09 years. Analyzing the age structure of the examinees and their body mass, it was established that there were no statistically significant differences among the groups (P > 0.05) (Table 1).

3.2. The operation and duration of anesthesia
There were no statistically significant differences in the length of surgical intervention and anesthesia among the groups (Table 2).

3.3. Observation of the analyzed parameters

3.3.1. WBCs
There were significant differences in the number of WBCs in relation to the introduction, incision, and awakening for the entire sample. The post hoc tests (Table 3) registered a statistically significant difference between the fentanyl and remifentanil groups and between the alfentanil and remifentanil groups. They showed that there was no significant difference between the fentanyl and alfentanil groups in proportion to the number of WBCs at all 3 measuring stages.

The results showed that the highest WBC values were in the alfentanil group at all 3 measuring stages (Figure 1). The most indicative period was the moment of awakening. Namely, at awakening both the fentanyl and alfentanil groups had the same level of increase in WBC count.

3.3.2. Blood glucose level
In the whole sample there were significant differences in the values of blood glucose in proportion to the introduction, incision, and awakening. Those differences varied among the examined groups. The post hoc tests (Table 4) showed

Table 1. Age and body mass of the subjects (ANOVA).

Group	n	Age (years)		Body mass	
		AS	SD	AS	SD
Fentanyl	50	3.6000	1.14286	3.6000	1.14286
Alfentanil	50	3.7600	1.09842	3.7600	1.09842
Remifentanil	50	4.0600	.99816	4.0600	.99816
Total	150	3.8067	1.09113	3.8067	1.09113

Table 2. Duration of operation and anesthesia (ANOVA).

Group	Operation duration (min)			Anesthesia duration (min)		
	AS	SD	P	AS	SD	P
Fentanyl	24.52	9.08		35.60	9.96	
Alfentanil	23.92	11.00		34.10	11.80	
Remifentanil	23.70	10.64	0.918	35.50	10.63	0.741
Total	24.04	10.21		35.06	10.77	

Table 3. The Scheffe post hoc test: WBCs (×10⁹/L).

Group	Group	Differences AS	Standard error	P
Fentanyl <	Alfentanil	−0.088	0.35955	0.970
	Remifentanil	1.004	0.35955	0.022
Alfentanil <	Fentanyl	0.088	0.35955	0.970
	Remifentanil	1.092	0.35955	0.011
Remifentanil <	Fentanyl	−1.004	0.35955	0.022
	Alfentanil	−1.092	0.35955	0.011

Table 4. The Scheffe post hoc test: glucose level in blood (g/L).

Group		Group	Differences AS	Standard error	P
Fentanyl	<	Alfentanil	0.551	0.09691	0.000
		Remifentanil	0.826	0.09691	0.000
Alfentanil	<	Fentanyl	−0.551	0.09691	0.000
		Remifentanil	0.275	0.09642	0.019
Remifentanil	<	Fentanyl	−0.826	0.09691	0.000
		Alfentanil	−0.275	0.09642	0.019

that statistically significant differences were registered among all 3 groups in proportion to the glucose values at all 3 stages of measuring.

The results showed that the highest glucose values in blood occurred in the fentanyl group at all 3 stages of measuring (Figure 2). The highest increase of blood glucose level occurred in the fentanyl group at awakening (from the anesthesia).

3.3.3. Cortisone

There were significant differences in cortisone values in the serum during introduction, incision, and awakening. The post hoc tests (Table 5) showed that statistically significant differences were registered among all 3 groups in proportion to the cortisone levels at the 3 measuring stages. The highest cortisone values in the serum were

in the fentanyl group at all 3 measuring times (Figure 3). The moment of awakening was the most indicative period. The fentanyl group had the highest increase of cortisone level.

3.3.4. Leptin

There were significant differences in leptin values in the serum between the analyzed groups at all 3 times. The post hoc tests (Table 6) did not register a statistically significant difference among the 3 groups in proportion to the leptin values at all 3 measuring stages.

The results showed, at the scope of descriptive indicators, that leptin values in the serum registered the greatest decrease in the fentanyl group at the moment of awakening and in the remifentanil group at the moment of incision (Figure 4).
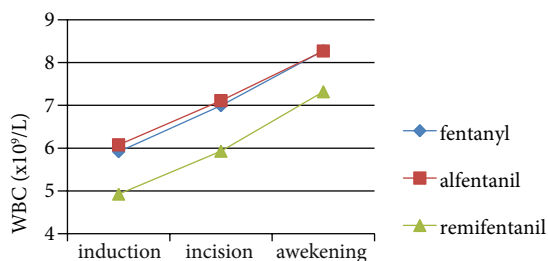

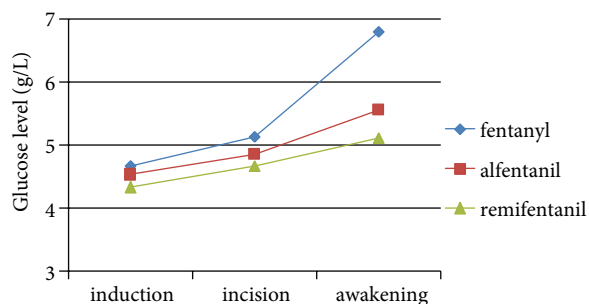**Figure 1.** The average WBC values in all 3 groups at 3 measuring stages (10^9/L).

Figure 2. The average glucose values in blood in all 3 groups at 3 measuring stages.

Table 5. The Scheffe post hoc test: cortisone (nmol/L).

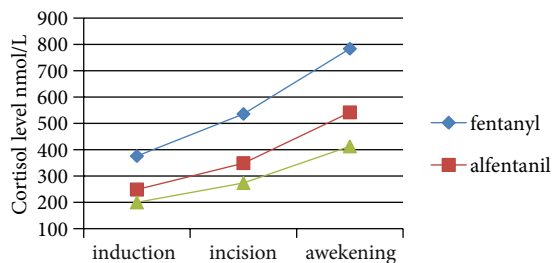| Group		Group	Differences AS	Standard error	P
Fentanyl	<	Alfentanil	185.52	26.94464	0.000
		Remifentanil	269.78	26.94464	0.000
Alfentanil	<	Fentanyl	−185.52	26.94464	0.000
		Remifentanil	84.25	26.94464	0.009
Remifentanil	<	Fentanyl	−269.78	26.94464	0.000
		Alfentanil	−84.25	26.94464	0.009

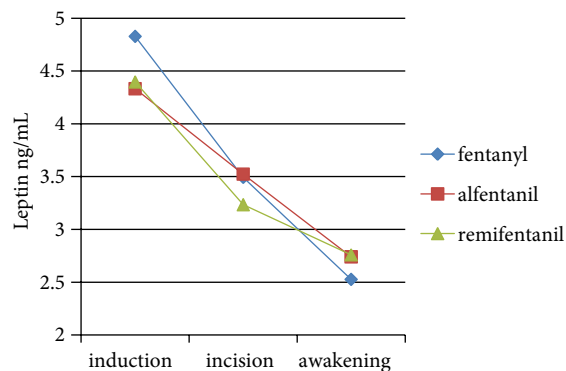**Figure 3.** The average cortisone values in all 3 groups at the 3 measuring stages.

Figure 4. The average leptin values in the 3 groups at the 3 measuring stages.

Table 6. The Scheffe post hoc test: leptin (ng/mL).

Group		Group	Differences AS	Standard error	P
Fentanyl	<	Alfentanil	0.0835	0.42956	0.981
		Remifentanil	0.1522	0.42956	0.939
Alfentanil	<	Fentanyl	−0.0835	0.42956	0.981
		Remifentanil	0.0687	0.42956	0.987
Remifentanil	<	Fentanyl	−0.1522	0.42956	0.939
		Alfentanil	−0.0687	0.42956	0.987

Analyzing the side effects and complications during the perioperative period, we found that there were no complications registered in the remifentanil group, and the highest number of complications was found in the alfentanil group (Table 7).

Analyzing the hemodynamic response of the children in the examined groups, we found that during the perioperative period the children in the fentanyl group had the highest values of systolic blood pressure and heart rate and in the remifentanil group the highest values of

Table 7. Complications during anesthesia.

Complications		Group			In total
		Fentanyl	Alfentanil	Remifentanil	
No complication	f (%)	44 (88.0%)	31 (62.0%)	50 (100.0%)	125 (83.3%)
Bradycardia	f (%)	6 (12.0%)	6 (12.0%)	0 (0%)	12 (8.0%)
Bradyarrhythmia	f (%)	0 (0%)	12 (24.0%)	0 (0%)	12 (8.0%)
SVEs*	f (%)	0 (0%)	1 (2.0%)	0 (0%)	1 (0.7%)
In total	f	50	50	50	150
	%	100%	100%	100%	100%

Chi-square test = 36.528, df = 6, P = 0.00.
*SVEs: supraventricular extrasystoles.

diastolic blood pressure (Figures 5 and 6). We found the greatest decrease of all 3 hemodynamic parameters (heart rate and systolic and diastolic blood pressure) in the remifentanil group (Figure 7).

4. Discussion

This observational clinical study was prospective. The results indicate that the examinees in each group were of the same age, body mass, and preoperative health condition (ASA I). The type and duration of the surgical intervention as well as the length of anesthesia were not

Figure 5. Average values of systolic blood pressure in the 3 groups at the 3 measuring stages.

Figure 6. Average values of diastolic blood pressure in the 3 groups at the 3 measuring stages.

Figure 7. Average values of heart rate in the 3 groups at the 3 measuring stages.

statistically different among the groups. In this way, all potential differences regarding the age and other pathologic conditions, as well as the degree of the forthcoming surgical stress, were excluded and all secondary effects on the body's response to stress were excluded.

It is well known that stress induces an increase in WBC count. The activated WBCs accumulate in the damaged area to restrict the harmful effects of trauma (1). In this study the measured number of leukocytes at the moment of incision was significantly higher in the alfentanil group. The lowest increase of WBCs occurred in the remifentanil group. Analyzing all groups, the results showed that the WBC values in the alfentanil group were the highest at all 3 measured stages.

A group of Japanese researchers found that immediately following a surgical intervention the number of WBC increased significantly. They also found that the level of WBC production, particularly of monocytes, reflects the degree of surgical stress (7). The Wilcox test showed that the WBC values statistically significantly increased in proportion to the baseline values in each group at all measuring stages.

The remifentanil group had the greatest increase at awakening (+32.69%). This can be explained by pharmacodynamic drug properties, rapid concentration decrease, and rapid termination of effect after the application (8). It is of great importance to have experience and knowledge of the remifentanil properties because a prompt analgesic treatment of postoperative pain is required, often to be started during the surgical intervention.

During a surgical intervention the blood glucose level increases. It is caused by rising epinephrine, glucagon, and cortisone, which act synergistically on the increase of gluconeogenesis and inhibit the peripheral usability of glucose. The measured glucose values in blood at the moment of incision as well as the moment of awakening were the highest in the fentanyl group and the lowest in the remifentanil group.

In proportion to the glucose values at each measuring stage among the 3 groups of examinees it was established that the fentanyl group had the highest blood glucose values. Keeping records of the range of glucose in the blood in proportion to the baseline values, its level increased in all 3 groups, but the greatest deviations were recorded in the fentanyl group, as was also found by Demirbilek et al. (9).

There are various data in the literature about the influence of fentanyl and remifentanil on the blood glucose level in relation to the body's response to stress. Weale et al. (11) showed that the application of fentanyl infusion of 1 μg kg^{-1} min^{-1} in children of up to 5 years of age leads to a significant suppression of the increase of the blood glucose level. This is in accordance with the results
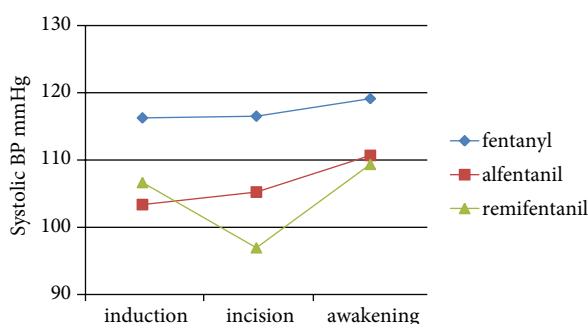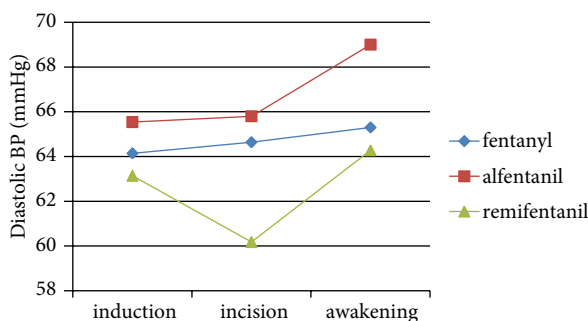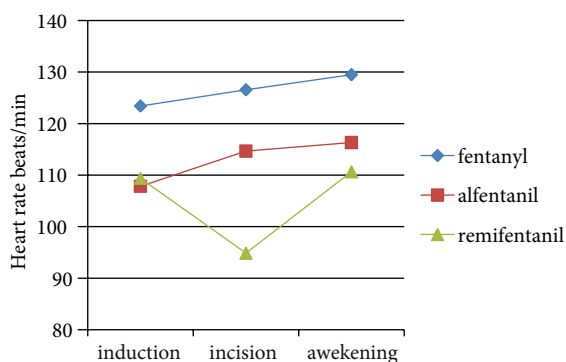
achieved in our research and contrary to results presented by Bell et al. (10).

The neuroendocrine system and cytokine secretion are activated by surgical intervention and remain active after its cessation. Cortisone is considered to be one of the best stress indicators and its role is of vital importance in the course of stress. It directs glucose exploitation from the muscles to the brain, supports the effect of catecholamine, and prevents an exaggerated reaction of the immune system in a damaged area.

The size and length of growth of intra- and postoperative adrenocorticotropic hormone and cortisone concentration is considered to be proportional to the degree of surgical trauma (12). In comparison with the other groups, the examinees from the fentanyl group had the highest increase of the cortisone level in the blood, both at the moment of incision and at the time of awakening. The lowest level of cortisone was recorded in the remifentanil group.

The statistically significant increase in the cortisone level was registered at all 3 measuring stages in the fentanyl group. Several studies mention that fentanyl is an opioid analgesic that does not satisfactorily reduce the hormonal and metabolic stress response. Buyukkocak et al. came to the conclusion that recommended fentanyl doses do not sufficiently affect the decrease of the cortisone level in the course of stress. They also found that a considerable increase of the dosage would be followed by side effects and a prolonged awakening from anesthesia (13).

The Wilcoxon test shows that a statistically significant increase in the hormone level is present at all measuring stages and in all 3 groups. It is most explicit at the awakening stage in the fentanyl group with a 54.12% increase in comparison with the baseline values, while the smallest increase is in the remifentanil group at 51.6%.

The research done by Demirbilek showed that remifentanil and alfentanil have similar effects on the endocrine response to stress. Plasma concentration of cortisone kept growing for 30 min after the incision (9).

Weale et al. declared in their study that the impact of remifentanil on cortisone level increase is dose-dependent; they found that a dose of 0.25 μg kg^{-1} min^{-1} suppresses cortisone concentration growth in the blood, which is in accordance with the results in our research (11).

Leptin plays a role in the regulation of the HPA axis, immune response, and angiogenesis, which were all confirmed by this study. Because of these responses the role of leptin is considered to be essential in the acute phase of stress response (3,14).

Contemporary research shows the ability of leptin to alleviate the activation of the HPA axis, which is induced by stress. It can affect the hypothalamus by inhibiting the corticotropin-releasing hormone (CRH) release. It is shown that leptin and cortisone are in a reciprocal, highly negative correlation—the increase of cortisone causes the decrease of leptin blood levels in the course of a stressful situation. Leptin has an inhibitory effect on the cortisone secretion, a long-term inhibitory effect on the adrenal secretion, and excitatory effects on the hypothalamus. A high level of leptin inhibits the HPA axis response to acute stress (15).

In our research the leptin values in the serum were similar in all 3 groups at the moment of surgical incision and the time of awakening.

The greatest decrease was recorded in the fentanyl group at the awakening time. In comparison to the baseline values of leptin, a statistically significant decrease was recorded in all examinees, at all measured stages. The greatest decrease was recorded in the fentanyl group following surgical incision (–27.59%) and during recovery (–47.72%).

Karayiannakis et al. found that leptin levels in blood decrease slightly 30 min after the surgical incision (16).

Some authors, such as Marana et al., limit the importance of determining the leptin levels in the course of stressful procedures. They consider that the choice of anesthetic does not affect the level of leptin in the blood, but it influences the release of other markers of stress response (15).

The subjects from the fentanyl group had the most significant decrease of leptin, but the same examinees also had the highest cortisone increase, which confirms the data published in the literature that there is a significant negative correlation between the leptin and cortisone levels. Modan-Moses et al. came to the same results in their research, which proves an inverse relation between leptin and cortisone (17).

The literature points to a significant role of leptin in the HPA axis. Circulating leptin can restrict the HPA axis activity, inhibiting the release of CRH. In the course of acute and chronic stress leptin secretion can decrease in order to reduce the HPA axis responsibility, which is important for the survival of the organism (18).

In our study we found a connection between alfentanil and the greatest number of complications. This cardiodepressive effect of alfentanil has been reported in other studies (19).

Remifentanil lowered the hemodynamic response to surgical trauma in all 3 groups examined in our study, and this effect was also observed in studies of other authors (20).

In conclusion, analyzing the level of stress indicators during general anesthesia in children, we found a significant increase of glucose blood level and cortisone in the fentanyl group and a decrease in the level of leptin at the time of surgical incision and awakening. The largest

number of WBCs in all 3 levels of measurement was found in the alfentanil group. The increase of glucose and cortisone levels in the blood and the decrease of leptin were moderate. The laboratory stress indicators (WBCs, glucose, and cortisone) had the smallest increase in the remifentanil group when compared with the other 2 groups, while the decrease of leptin was equal in all 3 groups.

Based on these results we may conclude that remifentanil is the opioid analgesic with the highest suppressing effect on the stress response to surgical intervention in children.

References

1. Tomić V. Odgovor organizma na stres izazvan hirurškom traumom. In: Jović M. Priručnik vaskularne anestezije. Begrade, Serbia: Alta Nova; 2004. pp. 145–160 (in Serbian).

2. Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000; 85: 109–117.

3. Ahima RS, Flier JS. Leptin. Annu Rev Physiol 2000; 62: 413–437.

4. Charmandari E, Kino T, Souvatzoglou E, Chrousos GP. Pediatric stress: hormonal mediators and human development. Horm Res 2003; 59: 161–179.

5. Wolfram W, Kreuer K. The place for short-acting opioids: special emphasis on remifentanil. Crit Care 2008; 12 (Suppl. 3): S5.

6. Gommers D, Bakker J. Medications for analgesia and sedation in the intensive care unit: an overview. Crit Care 2008; 12 (Suppl. 3): S4.

7. Aosasa S, Ono S, Mochizuki H, Tsujimoto H, Osada S, Takayama E, Seki S, Hiraide H. Activation of monocytes and endothelial cells depends on the severity of surgical stress. World J Surg 2000; 24: 10–16.

8. Samartino M, Garra R, Sbaraglia F, De Riso M, Continolo N. Remifentanil in children. Paediatr Anaesth 2010; 20: 246–255.

9. Demirbilek S, Ganida S, Aksoy N, Becerik C, Baysal Z. The effects of remifentanil and alfentanil-based total intravenous anesthesia (TIVA) on the endocrine response to the abdominal hysterectomy. J Clin Anesth 2004; 16: 358–363.

10. Bell G, Dickson U, Arana A, Robinson D, Marshall C, Morton N. Remifentanil vs fentanyl/morphine for pain and stress control during pediatric cardiac surgery. Paediatr Anesth 2004; 14: 856–860.

11. Weale NK, Rogers CA, Cooper R, Nolan J, Wolf AR. Effect of remifentanil infusion rate on stress response to the pre-bypass phase of paediatric cardiac surgery. Br J Anaesth 2004; 92: 187–194.

12. Srinivas R, Brown SD, Chang YF, Garcia-Fillion P, Adelson PD. Endocrine function in children acutely following severe traumatic brain injury. Childs Nerv Syst 2010; 26: 647–653.

13. Buyukkocak U, Caglayan O, Cagatay D, Aydinuraz K, Saygun O, Kaya T, Agalar F. Similar effects of general and spinal anaesthesia on perioperative stress response in patients undergoing haemorrhoidectomy. Mediators Inflamm 2006; 1: 1–5.

14. Ghizzoni L, Mastorakos G. Interactions of leptin, GH and cortisol in normal children. Ann N Y Acad Sci 2003; 997: 56–63.

15. Marana E, Scambia G, Colicci S, Maviglia R, Maussier ML, Marana R, Proietti R. Leptin and perioperative neuroendocrine stress response with two different anaesthetic techniques. Acta Anaesthesiol Scand 2008; 52: 541–546.

16. Karayiannakis AJ, Asimakopoulos B, Efthimiadou A, Tsaroucha AK, Polychronidis A, Simopoulos C. Serum leptin levels and their response during laparoscopic and open cholecystectomy. Eur Cytokine Netw 2005; 16: 91–96.

17. Modan-Moses D, Ehrlich S, Kanety H, Dagan O, Pariente C, Esrahi N, Lotan D, Vishne T, Barzilay Z, Paret G. Circulating leptin and the perioperative neuroendocrinological stress response after pediatric cardiac surgery. Crit Care Med 2001; 29: 2377–2382.

18. Michalaki M, Vagenakis AG, Argentou M, Mylonas P, Kalfarentzos F, Kyriazopoulou V. Dissociation of thyrotropin and leptin secretion in acute surgical stress in severely obese patients. Obes Surg 2009; 19: 1424–1429.

19. Cicek M, Koroglu S, Demirbilek H, Teksan H, Ersoy MO. Comparison of propofol-alfentanil and propofol-remifentanil anaesthesia in percutaneous nephrolithotripsy. Eur J Anaesthesiol 2005; 22: 683–688.

20. Chanavaz C, Tirel O, Wodey E, Bansard JY, Senhadji L, Robert JC, Ecoffey C. Haemodynamic effects of remifentanil in children with and without intravenous atropine. An echocardiographic study. Br J Anaesth 2005; 94: 74–79.