Does Total Intravenous Anaesthesia (TIVA) with Propofol-Alfentanil Attenuate the Stress Response? Comparison between TIVA and inhalation anaesthesias

PROPOFOL-ALFENTANIL İLE YAPILAN TOTAL İNTRAVENÖZ ANESTEZİ (TİVA) STRES CEVABINI ZAYIFLATIR MI? TİVA VE İNHALASYON ANESTEZİSİNİN KARŞILAŞTIRILMASI

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Summary

We investigated the effects of total intravenous anaesthesia (TIVA) with propofol-alfentanil and air-oxygen mixture on the endocrine response to stress by comparing with inhalation anaesthesia (IA) using halothane and NoO-oxy'gen. ASA I-II30 adult patients undergoing open uretherolithotomy divided into two groups. All the patients were premedicated with atropine 0.5 nig and diazepam JO mg intramuscularly. In TIVA group (n=15). anaesthesia was induced with alfentanil 25 pg kg-' andpropofol 2 mg kg-', and maintained with the infusion of alfentanil 10 pg kg-' miir' for the first 10 minutes and with 0.5 pg kg-' miir' thereafter and at the same time with propofol 10 mg kg-'Ir' for the first 10 minutes, 8 mgkg-' hour' for the following 10 minutes and 6 mg kg-'lr' there after. Patients were ventilated with oxygen-air mixture. In IA group (n = l5), anaesthesia was induced with thiopentone 6 mgkg-', and maintained with halothane 1 % and NjO 66 % in oxygen. All patients in each group were ventilated mechanically in such a way that the value ofFiOi would be 0.3. The so called "stress hormones" such as Cortisol, ACTH, human growth hormone (hGH), prolactin and insulin as well as blood sugar concentrations were measured the day before surgery (control), 30 and 60 minutes after intubation and 120 minutes after the end of surgery. All samples were taken between 8.00 a.m. and 12.00 a.m. In both groups, Cortisol, ACTH, prolactin and blood sugar concentrations increased significantly compared with the control values (p<0.05). hGH did not change in TIVA group. Insulin did not change in both groups. ACTH and hGH were significantly higher in IA group than TIVA group (p<0.05). We concluded that TIVA was much more capable to supress the endocrine stress response than IA.

Key Words: Anaesthetic techniques: TIVA, Stress response

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Ozet

Bu çalışmada, propofol-alfentanil ve hava-oksijen karışımı ile sağlanan total intravenöz anestezi (TIVA)'nin strese hormonal yanıt üzerindeki etkileri, halotaıı ve NjO-oksijen ile sağlanan inhalasyon anestezisi (İA) ile karşılaştırılarak araştırıldı. Üreterolitotomi geçirecek ASA I-Il 30 yetişkin hasta iki gruba ayrıldı. Hastalar intramüsküler olarak verilen 0.5 mg atropin ve 10 mg diazem ile premedike edildiler. TİVA grubunda (n—15); 25 mg kg-' alfentanil ve 2 mg kg-' propofol ile anestezi indüksiyonu, 10'ar dakikalık sürelerde azalan dozlarda alfentanil (10-0.5 mg kg-' d/c') ve propofol (10-8-6ıng kg-' saat-') infüzyonları ile anestezinin devamlılığı sağlandı. Bu gruptaki hastalar oksijen-hava karışımı ile solutuldular. IA grubunda (n=l5); 6 mg kg-' tiyopenton ile anestezi indüksiyonu sağlandıktan sonra, anestezinin devamı %1 halotaıı ve oksijen içinde % 66 N,0 ile sağlandı. Her iki grupta da huştular, Fi0,: 0.3 olacak şekilde mekanik olarak solutuldu. "Stres hormonları" olarak da bilinen kortizol, ACTH, büyüme hormonu (hGH). prolaktin, insülin ve kan şekeri konsantrasyonları, operasyondan önce (kontrol), entübasyondan 30 ve 60 dakika sonra ve operasyon bittikten 120 dakika sonra ölçüldü. Tüm kan örnekleri saat 8.00 ile 12.00 arasında alındı. Her iki grupta da; kortizol, ACTH, prolaktin ve kan şekeri konsantrasyonları çalışma süresince kontrol değer/erine göre artı (p<0.05). hGH, TİVA grubunda değişmedi. İnsülin ise her iki grupta da değişmedi. ACTH ve hGH değerleri İA grubunda TİVA grubunda olduğundan belirgin olarak daha yüksekti (p<0.05). TİVA'nıı strese hormonal yanıtı iA'dan daha iyi baskılayabildiği kanısına varıldı.

Anahtar Kelimeler: Anestetik teknik: TİVA, Stres yanıt

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Endocrine and metabolic changes occur in response to anaesthesia and surgical stress (1). Endocrine responses to stress are mediated by activation of two major endocrine pathways : The hypothalamopituitary-adrenocortical system and the

sympatlietic-adrenomedullary system. Hypothalamus plays a central role in mediating and controlling the stress response. Several hormones are involved in the neuroendocrine response to stress such as ACTH, human growth hormone (hGH), vasopressin, TSH, Cortisol, insulin, glucagon, prolactin, aldosterone, renin, LH, FSH, adrenaline and noradrenaline (1,2). Stress hormone secretion is not only influenced by trauma itself, but also by direct pharmacological effects of certain anaesthesia (3). This study was planned to investigate the endocrine stress response occurring during total intravenous anaesthesia (TIVA) provided by propofol-alfentanil and air-oxygen by comparing with inhalation anaesthesia provided by halothanc and N_90-oxygen mixture (IA).

Methods

Patients

After obtaining written informed consent, we examined ASA 30 adult patients to undergo open urethcrolithotomy. Patients with known endocrine or neurological disorders and those with conditions likely to alter stress hormones, such as pain, hypovolacmia and hypothermia were excluded from the study.

Procedures

A11 patients were starved for six hours prior to procedure. In this period, 500-700 ml of NaC10.9% were infused to compensate the fluid loss. Central venous pressure and urine output were measured using subclavian catheter and urine catheter respectively to ensure that the patients were normovolemic pre, intra and postoperatively.

Patients were divided randomly into two groups (TIVA and IA). Total intravenous anaesthesia with propofol-alfentanil was applied to TIVA group, whereas the IA group received inhalation anaesthesia with halothanc and N_20. Tabic 1 shows the patients' data and duration of anaesthesia. A11 patients were premedicated with atropine 0.5 mg and diazepam 10 mg intramuscularly, 45 minutes before procedure.

Anaesthetic techniques

In TIVA group (n = 15); alfentanil 25 ug kg-' was given within two minutes and propofol 2 mg kg"' within 30 seconds intravenously for induction. Anaesthesia was maintained with the infusion of alfentanil 10 ug kg-' mm' for the first 10 minutes and 0.5 u,g kg"' min-' thereafter and with propofol 10 mg kg-' h"' for the first 10 minutes, 8 mg kg-' lr' for the next 10 minutes and 6 mg kg-' lr' thereafter by two separate infusion pumps (IVAC 770, SAN DIEGO, CALIFORNIA). Ventilation was provided by the oxygen-air mixture, using a ventilator (Newport Breeze E-150, NEWPORT, CALIFORNIA).

Table 1. Patients' data, duration of anaesthesia and control values of stress parameters (values : mean±SD).

	TIVA(n : 15)	IA(n : 15)
age (yr)	44.8 ± 13.2	45.4 ± 13.0
sex (male/female)	7/8	8/7
weight (kg)	69.8 ± 10.3	67.9 ± 8.4
duration of anaesth.(min)	66.3 ±3.8	66.8 ±8.4
control Cortisol (ng.ml')	131.0 ± 28.6	137.9 ±37.5
control ACTH (pg.ml"')	27.7 ± 8.7	20.9 ±5.7
control hGH (ng.ml"')	1.5 ± 1.6	0.8 ±0.1
control prolactin (mlU.L"')	220.4 ±87.3	234.9 ± 108.9
control insulin (ulU.mr')	11.0 ±6.2	9.1 ±6.0
control blood sugar (mg %)	90.5 ± 10.1	90.3 ±9.0

In IA group (n=15): Anaesthesia was induced with thiopentone 6 mg kg"' and was maintained with halothane 1% and N_20 *66%* in oxygen as end-expiratory concentrations.

A11 patients received atracurium with a bolus dose of 0.5 mg kg*'; followed by an infusion with a rate of 0,4 mg kg-' lr' atracurium for the neuromuscular block (IVAC 770, SAN DIEGO, CALIFORNIA). When the twitch depression reached 90% (TOF-GUARD INMT, ODENSE, DENMARK), endotracheal intubation was performed. In both groups, ventilation was mechanically conducted with IPPV in such a way that the values would be ; $ETco_2$: 34±4 lmnHg and FiO_2:0.3. The adequacy of anaesthesia was evaluated according to the presence of significant variations in mean arterial pressures and the heart rates (>%25, <%25), at the same time to the presence of the symptoms of autonomic nervous system stimulation such as sweating and lacrimation.

Atracurium administration was discontinued 20 minutes before the expected end of surgery.

Cessation of alfcntanil infusion was 15 minutes before the end, whereas propofol infusion was stopped during the last skin sutures. Neostigmin 0,07 mg kg"[1] and glycopyroíate 0,01 mg kg-' were administered intravenously to the patients with continuing neuromuscular blockage. If spontaneous ventilation was still inefficient ($ETco_2$>45 mmHg), naloxone was given in TIVA group according to the patient's response. In both groups, postoperative analgesia was evaluated by Visual Analogue Scale (VAS: 0-10 cm). Patients received meperidine hydrochloride 50 mg intramuscularly for postoperative analgesia when VAS>5 cm. No patient received blood or blood components during the study.

Monitorization

Mean arterial pressure, central venous pressure, heart rate, ECG, transcutaneus oxygen saturation ($Sp0_2$), inspiratory oxygen ($Fi0_2$), end-tidal carbon dioxide concentrations (ETco-,), end-tidal N_20 concentrations (ET_{N_2O}), end-tidal halolhanc concentrations ($ET_{Halothane}$) and rectal temperature were monitored by Datascope passport, (PARAMUS, NEW JERSEY) and Datex capnomac ultima (HELSINKI, FINLAND).

Blood sampling

Serum Cortisol, ACTH, human Growth hormone (hGH), prolactin, insulin and blood sugar concentrations were measured at 10.00 a.m. on the day before surgery (control) (T_1), 30 (T_2) and 60 (T_3) minutes after intubation and 120 minutes after the end of surgery (T_4) by radioimmunoassay. A11 samples were taken between 8.00 and 12.00 a.m.

Cortisol : (CORTCTK-125, SOR1N Biomedica, Vercelli, ITALY)
ACTH : (ACTH Controls DPC®, Los Angeles, CA)
hGH : (hGH : Human Growth Hormone DPC®, Los Angeles, CA)
Prolactin : (IRMA-mat Prolactin BYK Sangtec Diagnostica mbH & Co. KG von Hevesy-Strasse)
Insulin : (Insulin Coat-A-Count DPC®, Los Angeles, CA)
Blood,sugar : (Cobas Miras, SWITZERLAND)

Data analysis

Patient's data, duration of anaesthesia and control values of stress parameters were analysed with the Student's t test. Blood sugar and endocrine data within group were statistically evaluated with repeated measures analysis of variance test. Comparisons between the groups were analysed with Mamı Whitney U test. $p<0.05$ was considered significant. A11 statistical analysis were performed by statistical package for social sciences for windows V[50] (SPSS INC., 1989-1992).

Results

Patient data

The patients' data, duration of anaesthesia and control values of stress parameters are shown in Table 1. There was no significant difference between two groups. The changes in hacmodynamic variables, body temperature and other parameters monitored were within the acceptable clinical limits during this study. Blood loss did not exceed 200-300 ml, and neither blood nor blood components were given.

Endocrine data

Cortisol. Cortisol concentrations increased promptly at T_2 and T_3 after the induction of anaesthesia, reached a maximum at T_4 in both groups ($p<0.05$) (Figure 1). There was no significant difference in Cortisol concentrations between two groups in the course of the study.

ACTH. ACTH concentrations increased immediately after the induction of anaesthesia (T_2, T_3), remained elevated in the postoperative period (T_4) in both groups. In IA group these increases

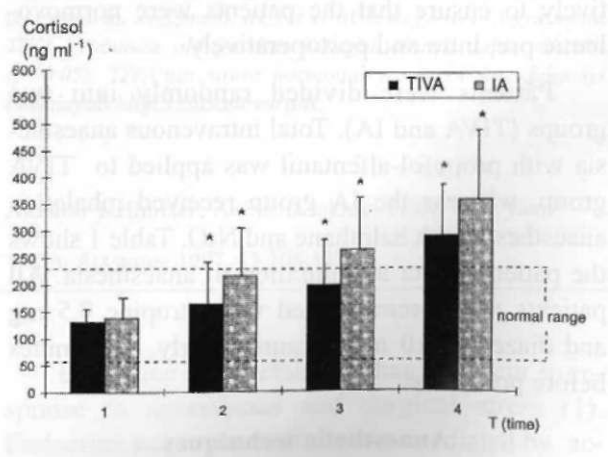

Figure 1. Serum Cortisol concentrations (mean±SD)
*: $p < 0.05$ (with T1), Y : $p < 0.05$ (between TIVA and IA)

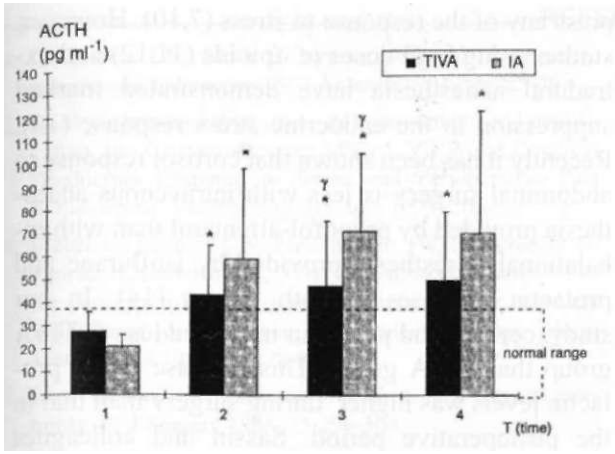

Figure 2. Serum ACTH concentrations (mean±SD).
*: p < 0.05 (with TI), y : p < 0.05 (between TIVA and IA)

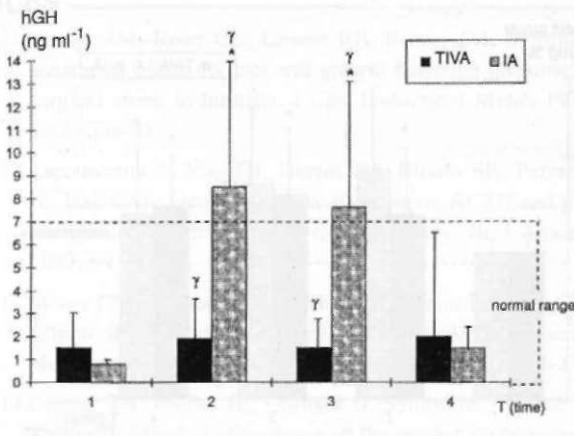

Figure 3. Serum hGH concentrations (mean±SD).
*: p < 0.05 (with Tl), y : p < 0.05 (between TTVA and IA)

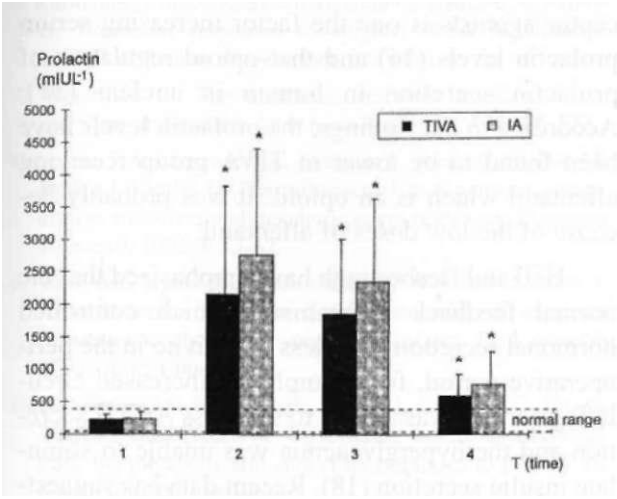

Figure 4. Scram prolactin concentrations (mean±SD).
*: p < 0.05 (with T1), Y : P < 0.05 (between TIVA and IA)

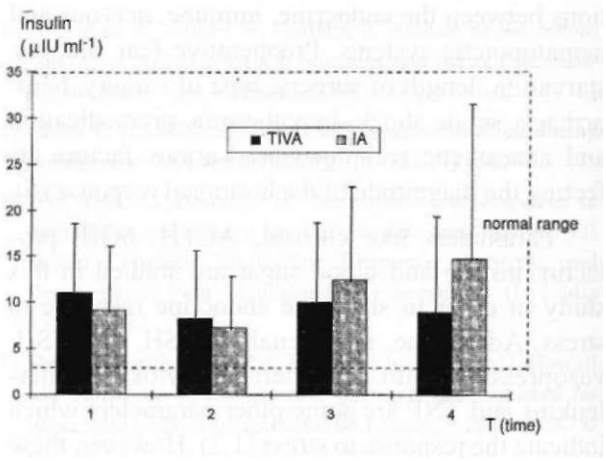

Figure 5. Serum insulin concentrations (mean±SD).
*: p < 0.05 (with T1), y : p < 0.05 (between TIVA and IA)

were higher than in TIVA group at T_3 ($p<0.05$) (Figure 2).

hGH. hGH concentrations did not change during the study period in group TIVA, whereas they increased at T_2, T_3 in IA group ($p<0.05$) and returned to initial level after the end of surgery (T_4). In IA group, hGH concentrations were higher than in TIVA group during the operation (T_2, T_3) (Figure 3).

Prolactin. In both groups, prolactin concentrations reached the maximum levels immediately after beginning of the surgery (T_2), remained elevated in the intraoperative period (T_3) and these increases started to decrease in the postoperative phase (T_4) ($p<0.05$). There was no significant difference in prolactin concentrations between IA group and TIVA group (Figure 4).

Insulin. Insulin concentrations did not change within time in both groups although there was a slight tendency to decrease (Figure 5).

Blood sugar. Blood sugar levels increased according to initial values and remained elevated during the study in both groups ($p<0.05$). There was no significant difference between the two groups (Figure 6).

Discussion

Endocrine response to stress is associated with perioperative morbidity or mortality (4,5). The response to stress is mediated by complex intcrac-

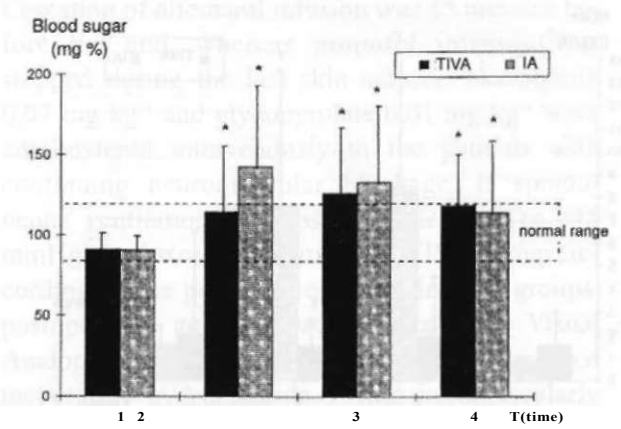

Figure 6. Serum blood sugar concentrations (mcan±SD).
***: p** < 0.05 (with **Ti),** *y* **: p** < 0.05 (between **TIVA** and **IA)**

tions between the endocrine, immune, nervous and hematopoietic systems. Preoperative fear, anxiety, starvation, length of surgery, type of surgery, hemorrhage, septic shock, hypothermia, premedication and anaesthetic technique are various factors affecting the magnitude of the hormonal response (6).

Parameters like Cortisol, ACTH, hGH, prolactin, insulin and blood sugar are studied in this study in order to show the endocrine response to stress. Adrenaline, noradrenaline, TSH, LH, FSH, vasopressin, renin, aldosterone, cytokines-interleukins and TNF are some other parameters which indicate the response to stress (1,2). However, these parameters are not investigated in this study due to our limited laboratory conditions and not to increase the cost of study.

The endocrine response to anaesthesia and surgery described in this study was characterized by increases in serum Cortisol, ACTH, prolactin and blood sugar concentrations, while insulin concentrations remained unchanged. ACTH and hGH responses were less pronounced by TIVA compared with IA. hGH and prolactin concentrations returned to the initial levels in the postoperative period.

The anesthesiologists must deal with the consequences of the body response to stress and must also be aware of the effects of anaesthetics on the response to stress (7). In recent years, many studies dealing with the endocrine response to surgical trauma and anaesthesia have been published (7-9). Inhalational agents, in general, are unable to suppress any of the response to stress (7,10). However, studies using high doses of opioids (11,12) and extradural anaesthesia have demonstrated marked suppression in the endocrine stress response (13). Recently it has been shown that Cortisol response to abdominal surgery is less with intravenous anaesthesia provided by propofol-alfentanil than with inhalational anaesthesia provided by isoflurane and prolactin increases in both groups (14). In our study, Cortisol and prolactin increased less in TIVA group than in IA group. This increase in the prolactin levels was higher during surgery than that in the postoperative period. Sassin and colleagues have reported that the prolactin levels were highest during the sleep period (15). It has also been demonstrated that the administration of opioid receptor agonists is one the factor increasing scrum prolactin levels (16) and that opioid regulation of prolactin secretion in human is unclear (17). According to our findings, the prolactin levels have been found to be lower in TIVA group receiving alfentanil which is an opioid. It was probably because of the low doses of alfentanil.

Hall and Desborough have emphasized that the normal feedback mechanisms which controlled hormonal secretion were less sensitivite in the perioperative period, for example, an increased circulating Cortisol was unable to suppress ACTH secretion and the hyperglycacmia was unable to stimulate insulin secretion (18). Recent data has suggested that anaesthesia may have a role in inhibiting insulin secretion (19). According to our findings, insulin levels did not change even though blood sugar increased and Cortisol secretion was unable to suppress the ACTH secretion as they were expected before.

In conclusion, our opinion is that; TIVA provided by propofol-alfentanil would better attenuate endocrine changes occuring in response to anaesthesia and surgical stress than the inhalation anaesthesia provided by halothane-N_2O. However, this conclusion should be correlated with patient outcome by further studies.

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