



## Comparison of the Effects of Remifentanyl and Dexmedetomidine Infusions on Hemodynamic Parameters and Thyroid Hormones

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**Objective:** In this study, we compared the effects of remifentanyl and dexmedetomidine on hemodynamic parameters, inhalation agent consumption and thyroid hormone levels at the late postoperative period.

**Methods:** Forty-five euthyroid ASA I-II patients between 20 and 75 years of age were randomly assigned into three groups:

During induction,

- Group R received 1.0 mcg kg<sup>-1</sup> remifentanyl as slow bolus in two minutes,
- Group D received 1.0 mcg kg<sup>-1</sup> dexmedetomidine in 10 minutes as infusion,
- Group C received 1.0 mcg kg<sup>-1</sup> fentanyl as bolus. Afterwards, all patients received 2.0 mg kg<sup>-1</sup> propofol and 0.2 mg kg<sup>-1</sup> cisatracurium for induction.

For anaesthesia maintenance during and up to 15 minutes before the end of the surgery;

- Group R received 0.05 mcg kg<sup>-1</sup> min<sup>-1</sup> remifentanyl,
- Group D received 0.5 mcg kg<sup>-1</sup> h<sup>-1</sup> dexmedetomidine infusion.

During the surgery, heart rate, mean arterial pressure and end-tidal sevoflurane concentrations were recorded for every patient. Venous blood samples were taken after the operation, at postoperative 24<sup>th</sup> hour and postoperative 5<sup>th</sup> day and the variations in fT3, fT4, TSH levels were analyzed.

**Results:** Mean arterial pressure values and sevoflurane consumption were lower in Group R and Group D in comparison with the control group. In comparison between groups, the decrease in fT3 values at postoperative 24<sup>th</sup> hour was more significant in the control group than the other two groups.

**Conclusion:** We suggest that, both agents suppress the hemodynamic response, decrease the consumption of inhalation agents and cause less change in the levels of thyroid hormones, which can be considered as one of the indicators of endocrine response.

**Key Words:** Thyroid hormones, cholecystectomy, sevoflurane, dexmedetomidine, remifentanyl

### Introduction

The autonomic, endocrine, metabolic and immune responses directed against harmful stimuli to provide and maintain body homeostasis are known as stress responses. These responses may occur in conditions like major traumas, surgery, sepsis and hunger. One of the aims of modern general anaesthesia is to maintain the functions of vital organs and systems at physiological levels in patients undergoing surgical interventions.

Anaesthesia, anaesthetic agents and surgical intervention, are all stress factors for the body, and lead to the stimulation of the hypothalamic-pituitary-adrenal axis and enhance sympathoadrenal activity.

Pituitary gland is stimulated by the secretion of thyrotropic hormones from the hypothalamus. In response, pituitary gland secretes adrenocorticotrophic hormone, thyroid stimulating hormone, growth hormone, prolactin, follicle stimulating hormone, luteinizing hormone and antidiuretic hormone. While the levels of catabolic hormones such as cortisol, glucagon and catecholamines increase, anabolic hormones such as insulin and testosterone decrease by the stimulation of pituitary hormones. These changes support life by supplying the substances required for gluconeogenesis, glycogenolysis and protein synthesis (1-4).

At the present time, the opinion that endocrine response is a requisite for surgical stress is debatable. The benefit of catabolic endocrine response to the patient is controversial. Additionally, if metabolic, endocrine response is prolonged and be in excessive amounts, it may end up with some negative effects. Some complications such as thromboembolism, stress ulcers, cardiac failure due to the increase in

cardiac oxygen requirement and load, infarct and respiratory failure may occur (5, 6).

The functions of the thyroid gland, like all endocrine system, change under surgical stress, and the body creates the proper environment for itself. Thyroid hormones adapt to surgical stress by changes in the enzymes both in the thyroid gland and organs other than the thyroid gland (6).

In our study; euthyroid patients confirmed with anamnesis, physical examination and clinical findings, undergoing laparoscopic cholecystectomy with general anaesthesia were treated with remifentanyl, a short acting opioid, and dexmedetomidine, a specific alpha-2 agonist. The aim was to compare the hemodynamic parameters, sevoflurane consumption and changes in thyroid hormone levels in the late postoperative period.

## Methods

After approval was obtained from the ethics committee of the hospital (approval date and number: 26/5/2008, 145), the present study was performed in a total of 45 patients (American Society of Anaesthesiologist [ASA] physical status classification I-II), aged between 20 and 75 years of age, scheduled for elective laparoscopic cholecystectomy surgery.

Before the study, informed consents were obtained from each patient.

ASA I-II patients, who were determined to be euthyroid according to thyroid function tests, history, physical examination and clinical findings, without any endocrine problems and not using drugs affecting thyroid binding globulin levels, were included in the study.

Oral intake was prohibited 6 hours before surgery. The study was conducted on patients operated between 08:00 AM-12:00 AM. The patients who required blood transfusion were not included in the study.

The patients were randomly divided into three groups. Group R: Remifentanyl group, Group D: Dexmedetomidine group and Group C: Control group.

None of the patients were premedicated. When the patient was placed on the operating table, a 20 G venous cannula was placed in one of the superficial veins at the dorsum of the hand, and balanced electrolyte solution infusion was started. Datex-Ohmeda S500 monitor was used for standard DII derivation electrocardiography, end tidal CO<sub>2</sub>, pulse-oximeter and non-invasive blood pressure [systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP)] monitoring.

A-2000 Aspect Bispectral index (BIS) monitor was used to determine the depth of anaesthesia.

At the induction of anaesthesia,

1. Group D patients received dexmedetomidine at a dose of 1.0 mcg kg<sup>-1</sup> by 10 minutes infusion 10 minutes before induction,
2. Group R patients received remifentanyl at a dose of 1.0 mcg kg<sup>-1</sup> in 2 minutes as slow bolus,
3. Group C patients received bolus fentanyl at a dose of 1.0 mcg kg<sup>-1</sup>.

Thereafter, all patients were given 2.0 mg kg<sup>-1</sup> propofol and 0.2 mg kg<sup>-1</sup> cisatracurium. After induction, orotracheal intubation was performed.

Keeping the BIS value between 40 and 60, anaesthesia was maintained with sevoflurane in 50% O<sub>2</sub> and 50% air mixture.

For maintenance of anaesthesia, during and up to 15 minutes before the end of the surgery, Group R patients received remifentanyl at a dose of 0.05 mcg kg<sup>-1</sup> min<sup>-1</sup>, and Group D patients were given dexmedetomidine infusion at a rate of 0.5 mcg kg<sup>-1</sup> hr<sup>-1</sup>.

None of the patients received blood transfusion or colloids during surgery.

- Heart rate (HR), MAP and end tidal concentrations of sevoflurane used for each patient were recorded at 5 and 10 minutes of intubation, at 10-minute intervals in the first one hour and at 20 minute-intervals until the end of the surgery.
- Venous blood samples were obtained in the preoperative period, at postoperative 24 hours and 5 days.

Free T3 (fT3), fT4 and TSH were analyzed by radioimmunoassay method (Beckman-Coulter Unicel DXI 800 Access Immunoassay System) in the hormone laboratory.

The following ranges were considered normal;

fT3: 0.2-6.5 pg mL<sup>-1</sup>

fT4: 0.7-2.1 ng dL<sup>-1</sup>

TSH: 0.35-5.0 mIU mL<sup>-1</sup>

## Statistical analysis

SPSS 16.0 package program was used in the statistical analysis of data. Data was tested for normal distribution. Demographic variables (age, weight, gender) were presented as mean and standard deviation. Kruskal Wallis and One Way ANOVA tests were used in repeated measures analysis. Paired comparisons within groups were performed using the Tukey test. The results were evaluated within a 95% confidence interval and a p value <0.05 was considered to be significant.

## Results

The distribution of the patients according to demographic characteristics is presented in Table 1. The groups were similar regarding age, weight and gender.

There was no significant difference between the groups regarding HR. In comparison of mean arterial pressure values, there was a significant difference between the groups in the values measured at 20, 30, 40, 50 and 60 minutes of surgery (p<0.001) (Figure 1).

There was a significant difference between the groups in terms of end-tidal sevoflurane concentrations at 40, 50 and 60 minutes of surgery (p<0.05) (Figure 2).

In paired comparisons, there was a significant difference between the fT3 values measured before the surgery and at postoperative 24 hours, and the values at postoperative 24 hours and at 5 days (p<0.01). The fT3 values at the postoperative 24<sup>th</sup> hour were significantly lower in the control group than that of the other groups (Figure 3).

There was no significant difference in time-dependent changes of Free T4 and TSH values between the groups (Figures 4 and 5).

**Discussion**

All functions of the human body are regulated by the nervous and endocrine systems. There are numerous interactions between the hormone system and the nervous system, and hypothalamus receives stimuli from almost all parts of the nervous system. A painful stimulus, even the presence of a fearful or an exciting thought may be sufficient to activate the hypothalamus.

General anaesthesia induces an unconscious state, in which functions of the central and peripheral nervous system are temporarily ceased. In an adequate depth of general anaesthesia, it is certain that painful stimuli are not perceived and no response is generated. However, our study along with the studies of many researchers show that under general anaesthesia, surgical stimuli, by activating the hormones secreted from the anterior lobe of the pituitary gland, lead to some endocrine and metabolic changes (7-12).

The appropriate use of hypnotic and analgesic agents is important in the regulation of the depth of anaesthesia and hemodynamic stability during surgery. Suppression of stress response and the related hemodynamic response is one of the aims of anaesthesia. Stress response increases surgery-related morbidity and mortality (13, 14).

Although the hypnotic effect of anaesthetic agents is at a sufficient level, patients may respond to surgical stimuli by an increase in arterial blood pressure and tachycardia. The reason for that is the increase in cardiac output and systemic vascular resistance by increased catecholamine secretion.

In balanced anaesthesia, opioids provide the required analgesia for blocking autonomic nervous system and suppressing somatic responses against surgical stimuli. Therefore, opioids, by decreasing surgical stress, help to maintain hemodynamic stability during surgery. Remifentanyl, a short and rapid-acting opioid, can

be titrated according to patient needs and can be used along with new methods and combinations in high-dose opioid anaesthesia (15-17).

In a multicenter study on 2438 patients, the effects of remifentanyl and fentanyl on hemodynamic responses against surgical stress were evaluated and lower blood pressure and heart rate values during induction and after intubation were achieved with remifentanyl (18). Remifentanyl provides a good hemodynamic stability during anaesthesia and surgery (19-21). There are reports stating that remifentanyl induces bradycardia and hypotension, and although the mean arterial pressure values of the group treated with remifentanyl infusion were significantly lower than the control group in our study, none of the patients experienced hypotension requiring discontinuation of infusion (17). In addition, although heart rates of remifentanyl group were lower in comparison to the control group, the difference between two groups was not significant.

Dexmedetomidine, a potent and selective alpha-2 agonist, leads to a dose dependent decrease in plasma norepinephrine concentrations, heart rate and blood pressure (22). Fragen et al. (23) in their study reported that while causing a dose dependent decrease in blood pressure and heart rate, dexmedetomidine provides hemodynamic stability by suppressing sympathetic nervous system activity and reduces anaesthetic agent requirement. However, it is known from many previous studies that dexmedetomidine decreases heart rate by postsynaptic alpha-2 adrenoceptor activity (22-27). Similarly, the mean arterial pressure values of dexmedetomidine group were significantly lower when compared with the control group in our study.

Özköse et al. (28), in their study on patients operated in prone position gave dexmedetomidine infusion after the loading dose, and compared the hemodynamic changes, anaesthetic agent consumption and the duration of recovery with the placebo group. They concluded that continuous infusion of dexmedetomidine after the loading dose results in lower anaesthetic agent consumption, and provide a more rapid recovery. Yagmur et al. (29), in one of their studies, evaluated the effects of dexmedetomidine given intravenously on the minimum alveolar concentration (MAC) of desflurane by BIS monitor; at a BIS value of 40-50 they determined that dexmedetomidine excessively decreased the MAC value of desflurane. We also kept the BIS values between 40 and 60 in our study, and found that end-tidal sevoflurane concentrations of the group treated with dexmedetomidine infusion were significantly lower when compared to that of the control group.

A study on euthyroid sick syndrome is intriguing; Michalaki et al (30), in their study performed in 2001, evaluated the early changes

Table 1. Comparison of patient characteristics between the study groups

	Remifentanyl group (Group R) mean±SD	Dexmedetomidine group (Group D) mean±SD	Control (Group C) mean±SD	p
Age (years)	54.73±11.09	50.06±10.53	55.93±7.70	0.387
Weight (kg)	71.06±6.45	70.86±10.14	73.13±5.56	0.713
Gender (F/M)	10/5	8/7	7/8	0.301

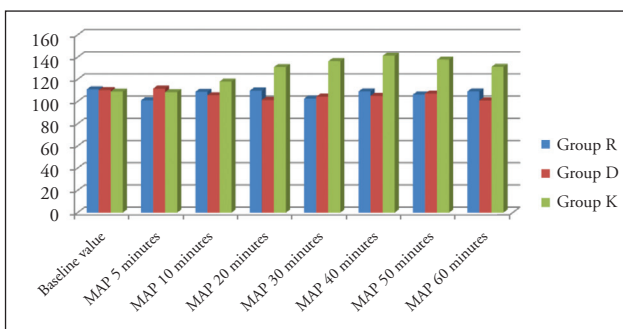


Figure 1. Comparison of mean arterial pressure values measured at different time points between the groups

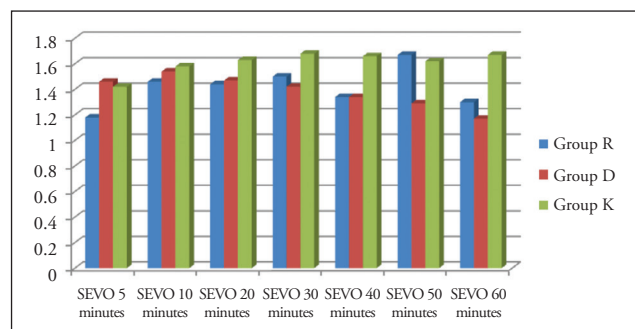


Figure 2. Comparison of end-tidal sevoflurane concentrations between the groups

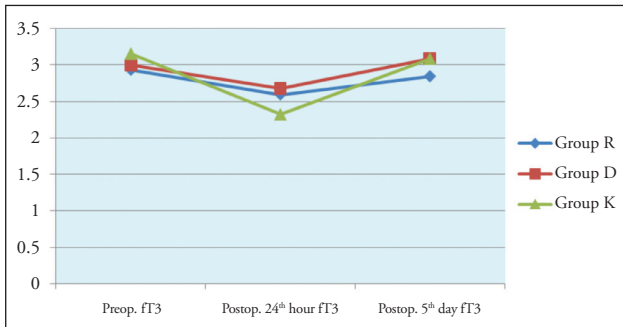


Figure 3. Inter-group comparison of fT3 values

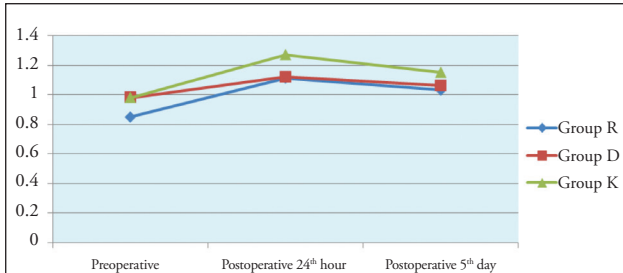


Figure 4. Inter-group comparison of fT4 values

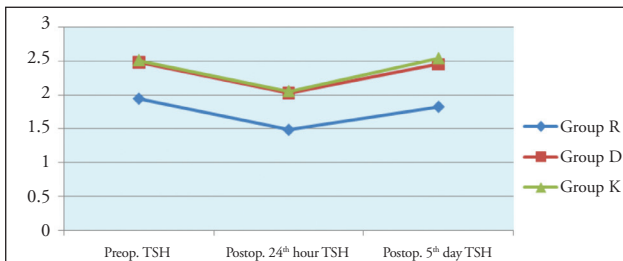


Figure 5. Inter-group comparison of TSH values

in  $tT3$ ,  $tT4$ ,  $fT3$ ,  $fT4$ , TSH,  $rT3$ , Interleukin-6 and cortisol values before, during and after surgery in relation with euthyroid sick syndrome in 19 patients undergoing elective abdominal surgery (open cholecystectomy and morbid obesity surgery). In that study, values measured 24 hours before the surgery were considered as baseline values and the difference between baseline values and the values measured at -1, 0, 0.5, 1, 2, 3, 4, 5, and 6 hours of skin incision were evaluated. That study, although was performed in a limited number of patients, is significant as it shows the changes in thyroid hormone levels during extrathyroid surgery. With regard to free  $T4$ ; when all patients are considered, values started to increase at 30 minutes of surgery and reached to a statistically significant value at the first hour. When the changes in free  $T3$  levels were considered, it was found that a significant decrease was found in the second hour of surgery. With regards to thyroid stimulating hormone (TSH) changes, a statistically significant increase was observed at 30 minutes of surgery. Among these hormones, the elevation in TSH and  $fT4$  levels is considered to be associated with surgical stress.

In our study; a better hemodynamic stability was provided in patients who received remifentanyl and dexmedetomidine during surgery compared to the control group. Blood pressure values and sevoflurane consumption during surgery were lower in both groups in comparison to the control group. In comparison to baseline val-

ues, some changes were observed in  $fT3$ ,  $fT4$  and TSH values measured at postoperative Day 1 and Day 5 in all three groups. While TSH and free  $T3$  values measured at postoperative Day 1 were lower than the baseline values in all groups, postoperative Day 5 values approached the baseline values.  $fT3$  changes at postoperative 24 hours in patients treated with remifentanyl and dexmedetomidine, was less than the changes observed in the control group, however, there was no difference between Group R and Group D. In all three groups,  $fT4$  values at postoperative day 1 was found to be higher than that of baseline values, and postoperative day 1 values were close to the baseline levels. Although  $fT4$  levels at postoperative 24 hours increased to levels higher than that in the control group, no significant difference could be detected. The changes in TSH levels were similar in all groups.

### Conclusion

Both agents, even with low dose infusion, suppress the hemodynamic response caused by surgical stress, decrease the consumption of inhalation agents and lead to small changes in the levels of thyroid hormones, especially  $fT3$ , which is one of the indicators of endocrine response.

### Conflict of Interest

No conflict of interest was declared by the authors.

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### Peer-review: Externally peer-reviewed.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Ministry Health Okmeydanı Trainin and Research Hospital.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

### Author Contributions

Concept - B.Ö., A.E.; Design - B.Ö., A.E.; Supervision - A.E. Materials - A.A.; Data Collection and/or Processing - B.Ö., M.L.U.; Literature Review - B.Ö., A.E.; Writer - B.Ö.; Critical Review - A.A.

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