Comparison of Hemodynamics Recovery Profile and Costs of Remifentanil Versus Fentanyl-Based Sevoflurane Anesthesia

Remifentanil ve Fentanil Temelli Sevofluran Anestezisinin Hemodinami Derlenme Profili ve Maliyetlerinin Karşılaştırılması

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Geliş Tarihi/*Received:* 13.06.2011
Kabul Tarihi/*Accepted:* 06.01.2012

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ABSTRACT Objective: This trial was designed to compare the effects of fentanyl and remifentanil on hemodynamic parameters, postoperative recovery, sevoflurane consumption and the cost of anesthetics. **Material and Methods:** Cases that were scheduled to undergo elective laparoscopic cholecystectomy surgery were assigned to two groups with simple random sampling method, as Group F (Fentanyl) and Group R (Remifentanil), each including 30 patients. The anesthetic induction was initiated by administering 1-2 mg/kg propofol bolus based on the bispectral index (BIS) value followed by 2 μg/kg fentanyl in Group F patients and 1 μg/kg remifentanil in Group R patients administered in 60 seconds as iv bolus; subsequently, 0.5 mg/kg iv atracurium was administered. For maintenance of anesthesia, 50% oxygen in-air was administered at 4 L/min; the end-tidal sevoflurane concentration was adjusted to achieve a BIS value of 45 to 55. In Group R, remifentanil 0.25 μg/kg/min infusion was continued. The addition of 0.5 μg/kg fentanyl was planned as required in Group F. Sevoflurane end-tidal concentration and the changing times were recorded. For each case, the sevoflurane consumption was calculated using the Dion formula. **Results:** In Group R, the hemodynamic control, particularly the suppression of response to intubation was more successful than in Group F. The eye opening times and Post Anesthesia Care Unit (PACU) transfer times were shorter in Group R relative to Group F (p=0.001 and p=0.001, respectively). Sevoflurane consumption was lower in the Group R (7.18±3.45 mL) compared to Group F (16.45±7.15 mL) (p=0.001). The total anesthetic drug cost was similar between the groups. **Conclusion:** Compared to fentanyl, remifentanil provided a better intraoperative hemodynamic control, faster postoperative recovery and a favorable effect on anesthetic drug cost by decreasing sevoflurane consumption, eliminating the disadvantages of its price.

Key Words: Cost control; fentanyl; remifentanil; sevoflurane

ÖZET Amaç: Bu çalışma, fentanil ve remifentanilin hemodinamik parametreler, postoperatif derlenme, sevofluran tüketimi ve anestetik maliyeti üzerindeki etkilerini karşılaştırmak amacıyla tasarlandı. **Gereç ve Yöntemler:** Elektif laparoskopik kolesistektomi cerrahi yapılması planlanan olgular, basit tesadüfi örnekleme yöntemiyle her birinde 30 hasta bulunan, Grup F (Fentanil) ve Grup R (Remifentanil) olmak üzere iki gruba ayrıldı. Anestezi indüksiyonuna, BİS değerine göre bolus tarzında uygulanan 1-2 mg/kg propofol ve Grup F'de 2 μg/kg fentanil, Grup R'de de 1 μg/kg remifentanil verilerek başlandı; bunun ardından 0.5 mg/kg atraküryum uygulandı. Anestezi idamesi için, hava içinde %50 oksijen, 4 L/dk şeklinde uygulandı; "end-tidal" sevofluran konsantrasyonu BİS değeri 45-55 olacak şekilde ayarlandı. Grup R'de, 0,25 μg/kg/dak remifentanil infüzyonuna devam edildi. Grup F'de gerektiğinde 0,5 μg/kg fentanil eklenmesi planlandı. Sevofluran "end-tidal" konsantrasyonu ve değişme zamanları kaydedildi. Her olgu için Dion formülü kullanılarak sevofluran tüketimi hesaplandı. **Bulgular:** Grup R'de hemodinamik kontrolün, özellikle de entübasyona yanıtın baskılanmasının, Grup F'ye göre daha başarılı olduğu gözlendi. Göz açma zamanları ve Anestezi Sonrası Bakım Ünitesi (ASBÜ)'ne transfer zamanları Grup R'de Grup F'ye göre daha kısaydı (sırasıyla p=0,001 ve p=0,001). Sevofluran tüketimi Grup R'de (7,18±3,45 mL) Grup F'ye (16,45±7,15 mL) göre daha azdı (p=0,001). Toplam anestezik ilaç maliyeti gruplar arasında benzerdi. **Sonuç:** Fentanille karşılaştırıldığında remifentanilin, daha iyi intraoperatif hemodinamik kontrol ve daha hızlı postoperatif derlenme sağladığı ve sevofluran tüketimini azaltıp, kendi fiyat dezavantajını ortadan kaldırarak, anestezik ilaç maliyeti üzerinde olumlu etki yaptığı saptanmıştır.

Anahtar Kelimeler: Maliyet kontrolü; fentanil; remifentanil; sevofluran

doi: 10.5336/medsci.2011-25271

Turkiye Klinikleri J Med Sci 2012;32(3):707-14

Cost-effectiveness studies conducted in the field of anesthesia are focused on developing safe, rapid, inexpensive techniques with a lower risk of complications. Inhaled anesthetics account for approximately 20% of the total drug costs of anesthesia departments.[1] The use of low fresh gas flow combined with opioid administration could decrease the consumption of the inhaled anesthetics.[2] Comparing remifentanil to other opioids may provide an advantage in achieving hemodynamic stability during the operation owing to its short half-life, organ-independent elimination, and convenient titration of efficacy. While it is advantageous over other opioids, it is more expensive than the other agents.[3-9]

This trial was designed to compare the effects of fentanyl and remifentanil on intraoperative hemodynamic parameters, postoperative recovery, sevoflurane consumption and the cost of anesthetics, and providing adequate anesthetic depth by bispectral index (BIS) control in laparoscopic cholecystectomy operations.

MATERIAL AND METHODS

This prospective trial included 60 American Society for Anesthesiology (ASA) I-II patients between 18 and 65 years of age, who were scheduled to undergo elective laparoscopic cholecystectomy surgery between June 2010 and October 2010. Konya University Meram Medical Faculty Ethical Committee approved the study protocole. Informed consent in accordance with the Helsinki Declaration was obtained from the patients. Patients with cardiac, renal, hepatic failure or respiratory disease, known hypersensitivity to the investigational drugs, alcohol and drug addicts and those who had used opioid analgesics within the previous days were excluded from the trial.

The cases were assigned to two groups with simple random sampling method, Group F (Fentanyl, n=30) and Group R (Remifentanil, n=30). Throughout the operation, electrocardiography (ECG), noninvasive blood pressure (NIBP), pulse oximeter (SpO_2), BIS, and neuromuscular transport (NMT) monitorization (Drager infinity kappa, Drager medical systems inc. Denver, USA) was run for each patient. The patients were pre-oxygenated for three minutes using 100% oxygen before induction. The anesthetic induction was initiated by 1-2 mg/kg propofol bolus administration based on the BIS value followed by 2 μg/kg fentanyl in Group F patients and 1 μg/kg remifentanil in Group R patients administered in 60 seconds as iv bolus; subsequently, 0.5 mg/kg iv atracurium was administered. After intubation, the patients were connected to the mechanical ventilator (Drager medical systems inc. Denvers USA) and were ventilated at a flow rate of 4 L/min with 50% oxygen in-air such that the end-tidal CO_2 partial pressure ($EtCO_2$) was 35±5 mmHg. Sevoflurane was initiated at an end-tidal concentration of 1%. In Group R, 0.25 μg/kg/min remifentanil infusion was continued. In Group F, an additional 0.5 μg/kg fentanyl was administered at 30 minutes intervals after the induction and throughout the rest of the surgery. Anesthetic depth was assessed by BIS monitoring. The end-tidal sevoflurane concentration was adjusted to achieve a BIS value between 45-55. Sevoflurane concentration and the changing times were recorded.

In both groups, patients were administered IV ondansetron 4 mg and tramadol 1 mg/kg for postoperative analgesia. After the gallbladder was removed, administration of sevoflurane and remifentanil was terminated and the time of anesthesia termination was recorded. When the BIS value was ≥80 and the train of four (TOF) value was 75%, the patients were extubated and the total amount of remifentanil and fentanyl were recorded. The time from the termination of anesthesia to spontaneous eye opening was recorded as the time of eye opening. Upon achieving a Modified Aldrete Score ≥8 (Table 1), the patients were transferred to the post anesthesia care unit (PACU) and this period was recorded as the PACU transfer time. In the PACU, when the Modified Aldrete Score was ≥9, the pain score was ≤3 as per the visual analogue scale (VAS) (Figure 1), and the patient was hemodynamically stable and had no vomiting or nausea, he/she was transferred to the ward, recording this period as the time of transfer from

TABLE 1: Modified aldrete score.

		Score
Level of consciousness Score	Awake and oriented	2
	Arousable with minimal stimulation	1
	Responsive only to tactile stimulation	0
Physical activity	Able to move all extremities on command	2
	Some weakness in movement of extremities	1
	Unable to voluntarily move extremities	0
Hemodynamic stability	Blood pressure, 15% of baseline MAP value	2
	Blood pressure 15%–30% of baseline MAP value	1
	Blood pressure 30% below baseline MAP value	0
Respiratory stability	Able to breathe deeply	2
	Tachypnea with good cough	1
	Dyspneic with weak cough	0
Oxygen saturation status	Maintains value 90% on room air	2
	Requires supplemental oxygen (nasal prongs)	1
	Saturation, 90% with supplemental oxygen	0

MAP: Mean arterial pressure.

PACU to the ward. The amount of Sevoflurane used during the operation was calculated using the formula (C=PxFxTxM/2412xD) described by Dion [C=the amount of inhaled anesthetic used (mL), P=Anesthetic Agent Concentration (%), F=Fresh gas flow (L/min), T=Time (min), M=Molecular weight (g) and D=Density (g/mL)].[10] Mean arterial pressure (MAP), heart rate (HR) and BIS values were recorded for baseline and following induction, at 1 and 5 minutes after the intubation and every 10 minutes thereafter. PACU admission and discharge times and the MAP, HR, pain, VAS at the PACU and the Modified Aldrete Scores for recovery were recorded.

An SPSS program was used for statistical analyses. The descriptive results were expressed as mean±standard deviation. Chi-square test was used for assessment of gender and ASA score. For all data, the analysis of compliance with the normal distribution regarding the groups was done using the One Sample Kolmogorov-Smirnov test. The Student's t Test and Mann Whitney U Test were used respectively for data that were compliant and incompliant with the normal distribution, respectively. Two-way analysis of variance was used for the intra-group comparisons that repeated measurements. Bonferroni corrected paired Student's t test was used as the *post hoc* test when this test was significant. The level of significance was set at $p<0.05$. For the intra-group HR and MAP measurements, the level of significance was set at $p<0.01$ after the Bonferroni Correction.

RESULTS

There was no statistically significant difference between the groups in the demographics and ASA classifications of the patients, the times of surgery or the anesthesia type ($p>0.05$) (Table 2).

Mean arterial pressure measurements revealed a statistically significant difference between the groups in the measurements of MAP 1 minute after the induction (MAPind) ($p=0.039$), MAP 1 minute after the intubation (MAPint) ($p<0.001$), MAP at 5 minutes (MAP5) ($p<0.001$), MAP at 10 minutes (MAP10) ($p<0.001$), MAP at 20 minutes (MAP20) ($p<0.001$), MAP at 30 minutes (MAP30) ($p=0.006$), and MAP at 40 minutes (MAP40) ($p=0.028$). The values were higher in Group F than those in Group R.

For Group F, the intra-group comparison of the basal mean arterial pressure (MAPb) values with the MAP measurements performed at other time points revealed significant differences for MAPind ($p<0.001$), MAPint ($p=0.002$), MAP5

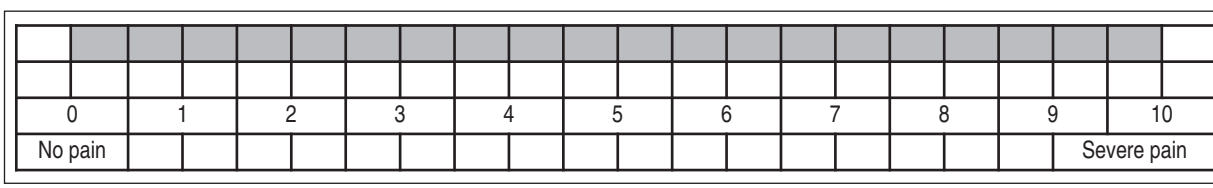

FIGURE 1: VAS Score.
VAS: Visual analogue scale.

TABLE 2: Age, weight, height, BMI, surgery and anesthesia times (mean ± SD), gender, ASA.

	Group F (n=30)	Group R (n=30)	p
Age (years)	47.10±12.94	48.33±14.71	0.732
Weight (kg)	72.13±8.13	70.47±10.31	0.490
Height (cm)	164.40±7.43	163.57±7.93	0.676
BMI (kg/m^2)	26.69±2.41	26.29±3.01	0.574
Anesthesia Time (min)	50.30±12.78	46.67±11.21	0.247
Surgery Time (min)	39.77±12.74	37.10±10.50	0.380
Gender (K/E)	9/21	6/24	0.371
ASA (I/II)	16/14	11/19	0.194

ASA: American Society of Anesthesiologists; BMI: Body mass index; F: Female; M: Male; SD: Standard deviation.

(p=0.002), MAP10 (p<0.001), MAP20 (p<0.001), MAP30 (p=0.001), MAP40 (p=0.004) and PACU admission mean arterial pressure (MAPpa) (p<0.001) times. As for the intra-group comparison for Group R, a significant difference was detected between the MAPb and MAPind (p<0.001), MAPint (p<0.001), MAPpa (p<0.001), and PACU discharge mean arterial pressure (MAPpd) (p=0.001) times (Figure 2).

Heart rate measurements revealed a significantly higher heart rate at 1 minute after the intubation (HRint) (p=0003) in Group F than in Group R.

The intra-group comparison of the basal HR values (HRb) with the HRs measured at other time poits for both groups showed a significant difference between the HRb and HRint (p=0.007); the HRint was higher in Group F than in Group R. As for Group R, there was a significant difference between HRb and PACU admission HR (HRpa) (p<0.001); the HRpa was higher (Figure 3).

The comparison of the BIS values between the groups revealed no significant difference (p>0.05). The eye opening time and PACU transfer time were significantly shorter in Group R than in Group F (Table 3).

The comparison of the Modified Aldrete and VAS scores between the groups revealed no significant difference in the PACU admission, PACU discharge Modified Aldrete Score and VAS values (p>0.05) (Table 4).

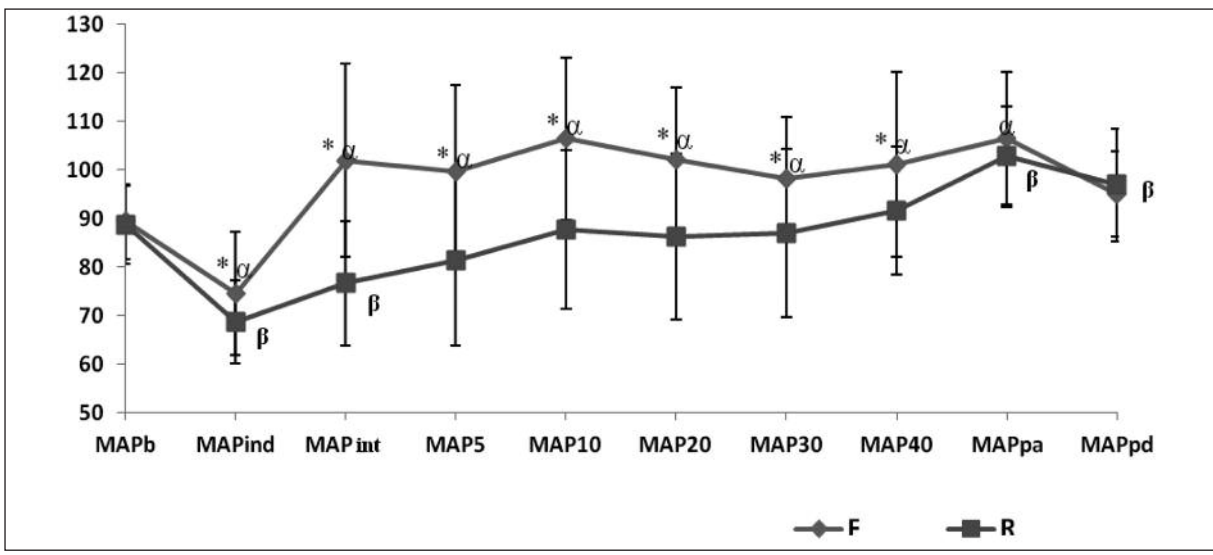

FIGURE 2: MAP data.

*p<0.05: compared to Group R

$^{\alpha}$P<0.01: relative to intra-Group F MAPb

$^{\beta}$P<0.01: relative to intra-Group R MAPb

MAP: Mean arterial pressure; MAPb: Basal MAP; MAPind: MAP at induction; MAPint: MAP at intubation; MAP5: MAP at 5 minutes after the intubation; MAP10: MAP at 10 minutes after the intubation; MAP20: MAP at 20 minutes after the intubation; MAP30: MAP at 30 minutes after the intubation; MAP40: MAP at 40 minutes after the intubation; MAPpa: MAP at postanesthesia care unit admission; MAPpd: MAP at discharge from postanesthesia care unit.

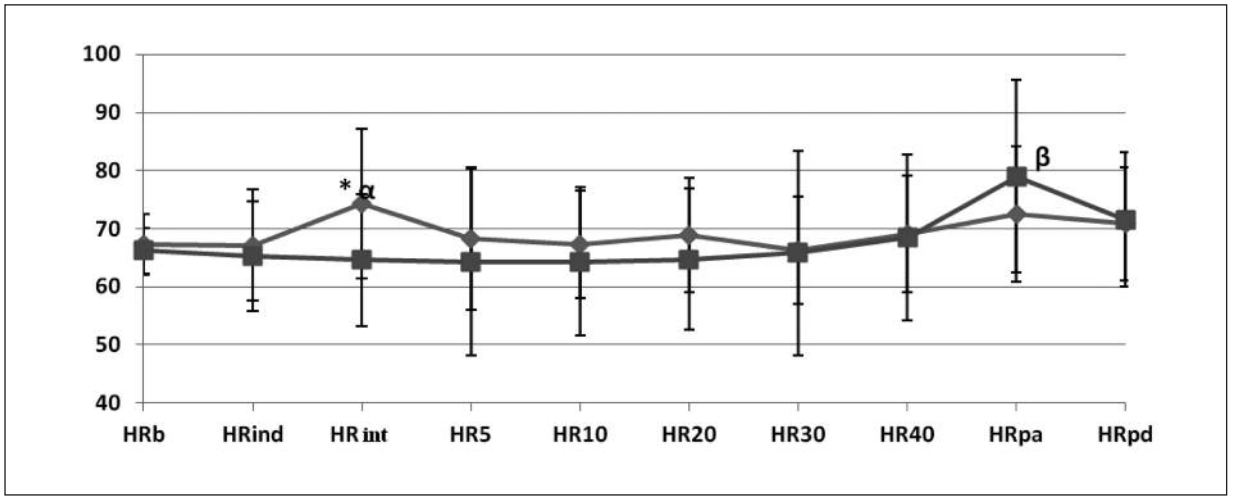

FIGURE 3: HR data

*p= 0.003 compared to Group R

$^{\alpha}$P= 0.007 relative to intra-Group F HRb

$^{\beta}$P< 0.001 relative to intra-Group R HRb

HR: Hear rate; HRb: Basal HR; Hrind: HR at induction; Hrint: HR at intubation; HR5: HR at 5 minutes after the intubation; HR10: HR at 10 minutes after the intubation; HR20: HR at 20 minutes after the intubation; HR30: HR at 30 minutes after the intubation; HR40: HR at 40 minutes after the intubation; Hrpa: HR at postanesthesia care unit admission; HRpd: HR at discharce from postanesthesia care unit.

The amount of sevoflurane consumption (ml) and sevoflurane cost per patient (Turkish Liras, TL) were higher in Group F than in Group R.

The cost of remifentanil per patient (TL) was significantly higher than the cost of fentanyl. There was no significant difference between the groups in the total anesthetic drug (AD) cost per patient, and AD cost per patient per minute (TL/min) (Table 5).

DISCUSSION

This trial looked at the effects of fentanyl and remifentanil, agents commonly used in anesthesia practice, on anesthetic drug cost and the intraoperative hemodynamic and the postoperative recovery characteristics of these agents, accompanied by BIS monitorization. Remifentanil seemed to exhibit a better perioperative hemodynamic control and a faster postoperative recovery with a lower sevoflurane consumption and similar total anesthetic drug cost.

Fentanyl is 75 to 125 times and remifentanil is 250 times more potent than morphine.[11] Thus, the doses of fentanyl and remifentanil were determined accordingly and while fentanyl was administered as bolus, infusion was used for remifentanil.[12]

Twersky et al. investigated the impact of remifentanil and fentanyl on the hemodynamic responses to surgical stress in a multi-center trial involving 2438 patients.[13] Following induction and intubation, lower blood pressures and heart rates were achieved with remifentanil. The ability to achieve an appropriate anesthetic depth by dose titration with the pharmacokinetic and pharmacodynamic characteristics of remifentanil renders this agent superior over other opioid drugs.

Özcan et al. compared the effects of remifentanil and fentanyl on the hemodynamic response secondary to tracheal intubation.[14] In the trial, the first group received 1 μg/kg fentanyl and the second group received 1 μg/kg remifentanil. As a result, 1 μg/kg remifentanil was more effective hemodynamically in preventing the stress response secondary to intubation.

In this trial, while the hemodynamic values were stable in both groups, the hemodynamic response to orotracheal intubation and surgical stimuli were better suppressed in patients receiving remifentanil. During the operation, lower blood

TABLE 3: Eye opening time, PACU transfer time, PACU ward transfer times (Mean±SD).

	Group F (n=30)	Group R (n=30)	p
Eye Opening Time (min)	12.77±4.09*	9.03±1.84	0.001
PACU Transfer Time (min)	21.33±4.99*	17.80±4.06	0.004
PACU Ward Transfer Time (min)	49.87±9.56	45.87±9.45	0.109

PACU: Post-anesthesia care unit; SD: Standard deviation.
*p<0.05 Group F compared to Group R.

TABLE 4: Modified aldrete and VAS scores (Mean±SD).

	Group F (n=30)	Group R (n=30)	p
VAS (PACU admission)	4.23±1.16	3.93±1.20	0.276
VAS (PACU discharge)	2.83±0.46	2.97±0.49	0.460
Modified Aldrete Score (PACU admission)	8.97±0.80	9.20±1.37	0.064
Modified Aldrete Score (PACU discharge)	9.93±0.25	9.97±1.83	0.557

PACU: Post-anesthesia care unit; SD: Standard deviation; VAS: Visual analogue scale.

TABLE 5: The mean total anesthetic drug (AD) use and cost (mean±SD).

	Group F (n=30)	Group R (n=30)	p
Sevoflurane (mL)	16.45±7.15*	7.18±3.45	0.001
Sevoflurane cost per patient (TL)	13.01±5.66*	5.68±2.74	0.001
Fentanyl/remifentanil cost per patient (TL)	0.79±0.11*	5.79±1.75	0.001
Total AD cost per patient (TL)	13.81±5.69	11.48±3.59	0.063
AD cost per patient per minute (TL/min)	0.27±0.07	0.24±0.05	0.128

AD: Anesthetic drug; TL: Turkish lira.
*p<0.05 Group F compared to Group R.

pressure and heart rate values were obtained in the remifentanil group. In the postoperative group, the hemodynamic values at PACU admission and discharge were increased in both groups compared to the intraoperative and basal measurements; this was more marked in the remifentanil group. The more marked increase in Group R may be attributed to the pharmacokinetic characteristics of remifentanil that is rapidly eliminated right after anesthesia termination. Coşkun et al. used remifentanil and fentanyl as bolus injection for anesthesia induction in combination with propofol infusion and as infusion for maintenance.[15] In the remifentanil group, the spontaneous eye opening time, and extubation time was significantly shorter compared to the fentanyl group.

In a trial, Anthony et al. reported that the time of transfer to PACU was shorter in the remifentanil group relative to the fentanyl group while there was no difference between the groups in the time of transfer from PACU to the ward.[16] Twersky et al. compared the post-anesthesia recovery characteristics of remifentanil and fentanyl.[13] They observed an early response to verbal stimuli and a shorter time of transfer to PACU in the remifentanil group.

In this trial, the eye opening time of patients was shorter in the remifentanil group relative to the fentanyl group. A faster recovery from anesthesia was observed with remifentanil. The time of transfer from the operating room to PACU was also shorter in the remifentanil group. There was no difference in the time of transfer from the PACU to the ward.

Yıldız et al. compared remifentanil and alfentanil in laparoscopic cholecystectomy operations they performed using total intravenous anesthesia (TIVA) and detected that 20% and 50% of the patients in the alfentanil and remifentanil groups respectively needed analgesic administration in the PACU and that analgesic requirement occurred earlier in the remifentanil group.[17]

In our trial, intraoperative tramadol 1 mg/kg was administered for postoperative analgesia; this may account for the lack of a difference between the groups in the PACU admission VAS values. The comparison of the VAS scores between the groups revealed no significant difference between the groups in PACU admission and discharge values. In both groups, the mean PACU admission VAS value was below 5 and the mean PACU discharge value was below 3. Postoperative pain treatment should not be considered a disadvantage for remifentanil, an agent that enables rapid recovery by rapid elimination provided that the necessary measures are taken.

In trials comparing the quality of anesthesia and costs, anesthesia of equal depth is administered, enabling more reliable results to be obtained. BIS enables an objective assessment of the anesthesia depth by quantitatively measuring the effect of the anesthetic agent on the central nervous system.[18] Thus, it avoids excessive or inadequate anesthetic consumption. The opioids used as an adjunct in general anesthesia are reported to have no effect on the BIS. In a trial investigating the effect of different concentrations of remifentanil on the BIS between the periods with no painful stimulus below the constant level of propofol infusion and the intubation period, remifentanil did not affect the BIS values, however, it did prevent the BIS increase associated with laryngoscopy and orotracheal intubation in a dose dependent manner.[19]

In our trial, the sevoflurane doses were titrated by using BIS monitoring to achieve an equal-depth anesthesia between the groups. Starting from induction, the BIS values were kept at between 45-55 in both groups. Thus, we could compare the effect of fentanyl and remifentanil on sevoflurane consumption by achieving an adequate anesthesia depth in both groups. In our trial, sevoflurane consumption was significantly decreased in the remifentanil group compared to the fentanyl group.

In a trial investigating sevoflurane consumption accompanied by BIS monitoring, the consumption was 17.16 mL/hour and 22.08 mL/hour in the remifentanil group and control group respectively.[20] In another trial investigating the effect of remifentanil on sevoflurane consumption by entropy monitoring, remifentanil was used at a dose of 1 μg/kg in the study group; for maintenance, one group was administered 0.1 μg/kg/min remifentanil while the other received 0.002 mL/kg/min saline infusion and the investigators administering saline infusion reported a significantly lower end-tidal sevoflurane value in the remifentanil group.[21]

Beers et al. compared the cost-effectiveness of remifentanil and fentanyl and used 3μg/kg fentanyl in one group and 0.5 μg/kg remifentanil in the other group for induction, and for the maintenance of anesthesia; the second group was administered 0.2 μg/kg/min of remifentanil as infusion.[22] Sevoflurane consumption was 12 mL in the fentanyl group and 6.7 mL in the remifentanil group.

In our trial, there was a significant difference between the groups in sevoflurane consumption and sevoflurane cost per patient. In our hospital, the cost of 250 mL sevoflurane is 197.97 TL as of October 2010. The comparison of the opioid costs revealed that the cost was lower in Group F than in Group R. This is an expected finding, due to the 30-fold higher cost of remifentanil compared to fentanyl. In our hospital, 1 ampoule of fentanyl was purchased (100 μg/2 mL) at 0.450 TL and one vial of 2 mg remifentanil was purchased at 13.71 TL as of October 2010, while the anesthetic agent cost per patient was 13.81±5.69 TL and 11.48±3.59 TL in Group F and Group R respectively with no significant difference detected. Thus, the cost difference resulting from the low sevoflurane consumption in the remifentanil group was not reflected in the anesthetic drug cost to the same extent.

In our trial comparing the cost-related and anesthetic characteristics of sevoflurane-fentanyl and sevoflurane-remifentanil anesthesia during laparoscopy operations, remifentanil was shown to provide better hemodynamic control, a faster postoperative recovery and in particular a favorable effect on cost by reducing the sevoflurane consumption. In conclusion, the addition of remifentanil to sevoflurane can be safely used in the anesthetic practice for good intraoperative hemodynamic control and early post-operative recovery without resulting in an increase in cost.

Acknowledgements

We thank Dr. Kemal Tahir Şahin for the statistical analyses of the study.

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