



Dexmedetomidine and remifentanil as adjuncts to total intravenous anesthesia with propofol

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ABSTRACT

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Received: 2 Feb 2017

Reviewed: Mar, 5 Mar 2017

Corrected & Accepted: 2 Sep 2017

Aim: The aim was to compare the effects of dexmedetomidine and remifentanyl in total intravenous anesthesia (TIVA) in laparoscopic cholecystectomy operations.

Methodology: Forty, 18-60 years old, elective laparoscopic cholecystectomy patients were included in the study. In Group D, TIVA was performed by 150 µg/kg/min propofol and 0.5 µg/kg/h dexmedetomidine infusions. In Group R patients, TIVA was performed with 150 µg/kg/min propofol and 0.5 µg/kg/min remifentanil infusions. Systolic blood pressure, heart rate, SpO₂, end tidal CO₂ were recorded. All infusions were terminated at the end of surgery. Adequate spontaneous respiration, extubation, and response to verbal commands; and Aldrete score ≥ 9 times, postoperative pain scores and vital parameters in the postoperative period were recorded. Patient-controlled analgesia pump was used in all postoperative patients. Total analgesic consumption, patients' first analgesic needs were recorded.

Results: Intraoperative Systolic blood pressure, diastolic blood pressure and heart rate values remained significantly lower in remifentanyl group compared to those in dexmedetomidine group (p < 0.05). First postoperative analgesia time was shorter and hemodynamic parameters were significantly higher in this group (p < 0.05). Postoperative recovery of dexmedetomidine group remained more stable in terms of VAS values (p < 0.05).

Conclusions: Remifentanil provides a potent intraoperative anesthesia compared with dexmedetomidine; however, dexmedetomidine may be considered in TIVA as an option for a stable postoperative recovery.

Key words: Dexmedetomidine; Remifentanyl; Total intravenous anesthesia; Hemodynamics; Recovery; Pain

Citation: Subasi H, Ozdemir Kol I, Duger C, Kaygusuz K, Isbir AC, Gursoy S, Mimaroglu C. Dexmedetomidine and remifentanil as adjuncts to total intravenous anesthesia with propofol. *Anaesth Pain & Intensive Care* 2017;21(3):328-334

This article was presented as a poster abstract at **Euroanaesthesia 2011 Congress, Amsterdam, Netherlands**

INTRODUCTION

Total intravenous anesthesia (TIVA) has been used more frequently in recent times as it is suggested to provide a cardiovascular stability better and a full and fast recovery compared with inhalation anesthesia.¹⁻³ Today, due to its short acting properties, propofol

is preferred as a hypnotic agent and remifentanil is preferred as an analgesic agent in TIVA.³ Remifentanyl provides intense analgesia, blocks somatic responses and thus reduces the autonomic system activity in balanced and total intravenous anesthesia techniques. High dose analgesia reduces

intravenous hypnotic requirements and adjusts the balance during anesthesia.³

During the recent years dexmedetomidine has been commonly used in anesthesia procedures.⁴ Dexmedetomidine is a highly selective specific and strong alpha 2 (α_2) adrenoreceptor agonist. Although there is strong evidence showing that α_2 receptor stimulation provides analgesia at spinal cord level, it is still under investigation whether the analgesic effects of dexmedetomidine are related primarily to an opioid sparing effect.⁴

Although there are many TIVA studies conducted using remifentanyl, the number of studies comparing total intravenous anesthesia with dexmedetomidine and remifentanyl comprehensively is limited.⁵

In the present study, our aim was to compare the effects of dexmedetomidine and remifentanyl on intraoperative hemodynamic responses, recovery profile, postoperative hemodynamic parameters, postoperative analgesic consumption and postoperative pain during total intravenous anesthesia in laparoscopic cholecystectomy operations.

METHODOLOGY

After obtaining approval from the ethical committee (No:2007/1/20) and written informed consents from the patients, 40 American Society of Anesthesiologists (ASA) risk classification I-II patients, aged between 18-60 years and scheduled to undergo elective laparoscopic cholecystectomy, were included in our controlled, randomized clinical study.

Exclusion criteria were, a body weight over 100 kg, poor patient cooperation in terms of patient controlled analgesia (PCA) equipment, suffering from kidney and/or liver failure, cardiac failure, ischemic heart disease, rheumatic valve diseases, long-term drug treatment (beta blockers, analgesics, sedatives or tricyclic antidepressants), psychiatric disease and alcohol addiction, being a heavy smoker, enrolled in any drug research in the period of 30 days before this study, having any complication during the operation, pregnancy, respiratory problems and a history of convulsion and not using the study medication for any reason during operation.

Written consents were obtained by visiting the beds a day before the study and groups were determined by sealed envelope method. On the previous day and just before the surgery, PCA equipment (Hospira® ,Inc. Lake Forest, Illinois, USA) was introduced and visual analog scale (VAS) (0: no pain, 10: severe pain), to be used to evaluate postoperative pain, was explained to the patients.

Before surgery, 2 ml/kg ringer lactate solution was infused for fluid resuscitation. No premedication was given. Patients were grouped as dexmedetomidine group (Group D, n=20) and remifentanyl group (Group R, n=20) randomly. Randomization was performed by sealed envelope technique one day prior to operation. Propofol, remifentanyl and dexmedetomidine infusions were prepared just before the patients were taken to the surgery room. Patients taken to the surgery room were monitored (Drager Infinity Vista XL) for non-invasive systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate (HR), peripheral oxygen saturation (SpO_2), and end tidal carbon dioxide ($EtCO_2$). Then normal saline solution was started IV. In Group D (dexmedetomidine group), endotracheal intubation was performed after inducing anesthesia with 2.5 mg/kg propofol, 0.6 mg/kg rocuronium (Esmeron, Organon, Netherlands), 1 μ g/kg fentanyl (Fentanyl-citrate, Abbott, USA). During maintenance, 150 μ g/kg/min propofol and 0.5 μ g/kg/h dexmedetomidine infusions were pumped using two different pumps at each cannulation sites. After the 5th minute of infusion, dexmedetomidine infusion rate was lowered to 0.3 μ g/kg/h.

In Group R (remifentanyl group) patients, endotracheal intubation was performed after inducing anesthesia using 2.5 mg/kg propofol, 0.6 mg/kg rocuronium, 1 μ g/kg fentanyl. During maintenance, 150 μ g/kg/min propofol and 0.5 μ g/kg/min remifentanyl infusions were pumped using two different pumps at two different venous cannulation site. After the 5th minute of infusion, remifentanyl infusion was lowered to 0.3 μ g/kg/min.

In both groups, 0.15 mg/kg rocuronium was administered when deemed necessary. After intubation all patients were given 100% O_2 and $EtCO_2$ values were maintained between 25-35 mmHg.

SAP, DAP, HR, SpO_2 and $EtCO_2$ were recorded before intubation, after intubation and on the 1st, 5th, 15th, 25th, 35th and 45th min of the surgical incision. Medications administered to the patients when deemed necessary were recorded too. A decrease in SAP, more than 20% of the values before infusion, was regarded as hypotension and 10 mg ephedrine IV was given in case of no response to initial fluid replacement. A heart rate of less than 45 beat/min was regarded as bradycardia which was treated by 0.5 mg atropine IV.

Time to sufficient spontaneous respiration, time to extubation time, time to verbal commands and time to reach an Aldrete score ≥ 9 after the operation were

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Table 1. Demographic data

Variable	Group D (n=20)	Group R (n=20)	p-value
Age (year)	45.30 ± 9.01	43.25 ± 7.55	0.495
Gender (M/F)	3/17	3/17	1.000
Weight (kg)	70.30 ± 10.34	68.23 ± 8.69	0.406
Height (cm)	169.10 ± 8.91	167.20 ± 8.83	0.585
ASA (I/II)	4/16	5/15	0.864
Operation time (min)	54.25 ± 4.94	53.75 ± 3.93	0.904

Table 2: Comparison of intraoperative SAP (mmHg)

Time period	Group D (n=20)	Group R (n=20)	p-value
Pre induction	130.30 ± 11.08	134.80 ± 7.97	P=0.063
Intubation	148.40 ± 13.48	154.20 ± 7.87	P=0.176
Incision 1st min	126.85 ± 10.88	119.80 ± 12.35	P=0.110
Incision 5th min	126.70 ± 12.79	115.70 ± 13.05	*P=0.005
Incision 15th min	121.65 ± 16.57	110.90 ± 10.87	*P=0.015
Incision 25th min	115.55 ± 11.01	102.60 ± 7.53	*P=0.001
Incision 35th min	117.25 ± 9.85	97.85 ± 4.43	*P=0.001
Incision 45th min	117.15 ± 8.83	98.45 ± 5.79	*P=0.001

Data are mean ± SD; *p < 0.05

Table 3: Comparison of intraoperative DAP (mmHg)

Time period	Group D (n=20)	Group R (n=20)	p-value
Pre induction	78.50 ± 8.37	82.05 ± 7.49	P=0.104
Intubation	93.40 ± 7.80	94.00 ± 4.74	P=0.903
Incision 1st min	79.30 ± 9.62	73.40 ± 10.78	P=0.075
Incision 5th min	78.85 ± 10.09	71.45 ± 9.56	*P=0.015
Incision 15th min	75.50 ± 12.04	70.45 ± 9.12	P=0.101
Incision 25th min	73.10 ± 9.04	64.95 ± 7.90	*P=0.002
Incision 35th min	73.35 ± 8.46	62.00 ± 6.06	*P=0.001
Incision 45th min	70.50 ± 7.43	61.05 ± 7.69	*P=0.001

Data are mean ± SD; *p < 0.05

Table 4: Comparison of intraoperative HR (beats/min)

Time period	Group D (n=20)	Group R (n=20)	p-value
Pre induction	80.00 ± 10.12	80.75 ± 7.71	P=0.714
Intubation	96.05 ± 10.96	98.05 ± 4.33	P=0.957
Incision 1st min	78.45 ± 10.26	73.20 ± 4.34	*P=0.014
Incision 5th min	72.90 ± 9.66	72.20 ± 5.26	P=0.243
Incision 15th min	71.95 ± 9.12	71.35 ± 6.37	P=0.674
Incision 25th min	72.05 ± 9.09	71.40 ± 6.45	P=0.786
Incision 35th min	70.65 ± 7.49	70.00 ± 5.10	P=0.778
Incision 45th min	69.65 ± 8.88	68.75 ± 5.35	P=0.817

Data are mean ± SD; *p < 0.05

recorded. Those having an Aldrete recovery score ≥ 9 were taken to the recovery room. PCA was provided after assessing the pain scales and the time of first analgesia was recorded. For PCA, 60 mg morphine was diluted in 94 ml physiological saline. PCA was adjusted to a bolus dose of 1 mg with lockout intervals of 20 min. Patients were then reminded how to use PCA and encouraged to push the button of PCA in case of experiencing pain. Systolic arterial pressure, diastolic arterial pressure, heart rate, VAS, total morphine consumption and OAA/S (Observer Assessment of Alertness/Sedation) sedation scores were recorded at postoperative 1, 2, 4, 6, 8, 12 and 24 h. PCA were kept connected to the patients during postoperative 24 hours.

A power analysis was performed and with α error of 0.05 and power of 80%, the study needed 20 patients in each group. Mann-Whitney U test was used to evaluate the data loaded on SPSS (version 14) software. Data are expressed as arithmetical mean ± standard deviation with a significance level of 0.05.

RESULTS

Our study was conducted on a total of 40 patients who were all able to complete the study. In terms of demographic data, there was no difference between the groups (Table 1). Similarly, no difference was found when the groups were compared for the duration of surgery (Table 1).

The differences in term of SAP values before induction, during intubation and at the 1st min of incision were not significant; but the differences at the 5th, 15th, 25th, 35th and 45th min were significant with lower SAP values in remifentanal group (p < 0.05) (Table 2). When DAP values of the groups were compared, DAP values of remifentanal at the 5th, 25th, 35th and 45th min of incision were significantly lower (p < 0.05) (Table 3). When HR values of the groups were compared, HR values at 1st min of incision were significantly lower

in remifentanyl group ($p < 0.05$) (Table 4).

Postoperative SAP and DAP values at 1st and 2nd h, were found to be higher in remifentanyl group ($p < 0.05$) (Tables 5 & 6). With higher postoperative HR values in remifentanyl group, there was a significant difference when postoperative HR values were compared ($p < 0.05$) (Table 7).

There was no difference between the groups in terms of SpO_2 , $EtCO_2$ values.

The time to spontaneous respiration, time to extubation, time to verbal commands, time to reaching an Aldrete score of ≥ 9 and the time of the first analgesic were found to be longer in dexmedetomidine group ($p < 0.05$) (Table 8)

VAS scores were found to be significantly higher in remifentanyl group at all times ($p < 0.05$) (Table 9).

Total morphine consumption was higher in remifentanyl group at all times except the postoperative 1 hour ($p < 0.05$) (Table 10).

OAA/S scores of all the individuals in both groups were established as 5 at different time points.

DISCUSSION

Developments of intravenous anesthetic agents have led to an interest in nearly perfect agents. However, total intravenous anesthesia technique has not become widespread due to difficulties in its practice and some baseless fears of the performers.⁶ In the present study, the effects of dexmedetomidine and remifentanyl on perioperative hemodynamic parameters, postoperative recovery and analgesia requirement in TIVA were compared.

Many studies have shown that remifentanyl offers hemodynamic stabilization during intraoperative period. In a study conducted in 1997 to compare remifentanyl and alfentanil in patients undergoing major abdominal surgery. Shüttler et al. found that

Table 5: Comparison of postoperative SAP (mmHg)

Time period	Group D (n=20)	Group R (n=20)	p-value
1st hour	125.70 \pm 10.37	133.45 \pm 6.80	*P=0.007
2nd hour	119.15 \pm 11.07	127.00 \pm 7.50	*P=0.020
4th hour	119.25 \pm 8.92	121.00 \pm 7.99	P=0.477
6th hour	117.15 \pm 8.16	117.00 \pm 9.37	P=0.955
8th hour	119.45 \pm 7.19	114.75 \pm 8.80	P=0.052
12th hour	119.85 \pm 7.67	117.27 \pm 7.85	P=0.278
24th hour	115.27 \pm 5.95	117.00 \pm 5.71	P=0.296

Data are mean \pm SD; $p < 0.05$

Table 6: Comparison of postoperative DAP (mmHg)

Time period	Group D (n=20)	Group R (n=20)	p-value
1st hour	73.65 \pm 7.48	81.30 \pm 6.25	*P=0.001
2nd hour	71.50 \pm 9.06	77.25 \pm 4.43	*P=0.021
4th hour	73.00 \pm 6.76	73.00 \pm 5.93	P=0.955
6th hour	72.25 \pm 6.17	73.00 \pm 5.47	P=0.794
8th hour	70.75 \pm 7.48	71.75 \pm 6.74	P=0.547
12th hour	69.25 \pm 6.12	72.00 \pm 4.97	P=0.158
24th hour	67.25 \pm 6.97	71.00 \pm 4.75	P=0.052

Data are mean \pm SD; * $p < 0.05$

Table 7: Comparison of postoperative HR (beats/min)

Time period	Group D (n=20)	Group R (n=20)	p-value
1st hour	71.75 \pm 9.01	79.50 \pm 6.81	*P=0.010
2nd hour	74.40 \pm 8.51	79.45 \pm 4.71	*P=0.049
4th hour	73.15 \pm 7.47	79.35 \pm 5.20	*P=0.004
6th hour	73.35 \pm 7.40	79.70 \pm 4.41	*P=0.001
8th hour	73.20 \pm 8.22	79.00 \pm 4.35	*P=0.015
12th hour	73.00 \pm 8.56	77.90 \pm 4.21	*P=0.049
24th hour	72.25 \pm 6.38	77.10 \pm 3.62	*P=0.009

Data are mean \pm SD; * $p < 0.05$

Table 8: Comparison of recovery profile

Time period	Group D (n=20)	Group R (n=20)	p-value
Time to adequate spontaneous respiration (min)	5.90 \pm 1.74	5.25 \pm 0.71	P=0.415
Extubation time (min)	6.90 \pm 1.37	6.10 \pm 0.64	*P=0.025
Time to respond to verbal commands (min)	14.30 \pm 3.71	8.05 \pm 0.75	*P=0.001
Time to reach an Aldrete score of ≥ 9 (min)	16.45 \pm 4.05	9.20 \pm 1.00	*P=0.001
Time to first analgesic need (min)	43.75 \pm 6.04	25.25 \pm 4.43	*P=0.001

Data are mean \pm SD; * $p < 0.05$

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Table 9: Comparison of postoperative VAS

Time period	Group D (n=20)	Group R (n=20)	p-value
1st hour	5.40 ± 1.23	6.45 ± 1.05	*P=0.007
2nd hour	4.25 ± 0.91	5.45 ± 0.95	*P=0.001
4th hour	3.75 ± 0.91	4.75 ± 0.96	*P=0.003
6th hour	3.20 ± 0.61	4.15 ± 0.67	*P=0.001
8th hour	2.60 ± 0.59	3.25 ± 0.63	*P=0.002
12th hour	2.05 ± 0.22	2.30 ± 0.47	*P=0.040
24th hour	1.00 ± 0.0	1.25 ± 0.44	*P=0.018

Data are mean ± SD; *p < 0.05

Table 10: Comparison of morphine consumption (mg)

Time period	Group D (n=20)	Group R (n=20)	p-value
1st hour	1.05 ± 0.22	1.00 ± 0.00	P=0.317
2nd hour	2.50 ± 0.60	2.95 ± 0.22	*P=0.003
6th hour	5.85 ± 0.56	6.85 ± 1.08	*P=0.017
12th hour	8.90 ± 2.22	11.80 ± 1.90	*P=0.001
24th hour	10.50 ± 2.66	14.20 ± 2.06	*P=0.001

Data are mean ± SD; *p < 0.05

remifentanyl offered superior hemodynamic stability when compared with alfentanil.⁷ In a multi-center study conducted in 1997, Beverly et al. performed TIVA by administering remifentanyl to 157 and alfentanil to 66 patients undergoing ambulatory laparoscopic surgery.⁸ In patients receiving remifentanyl, there was a significant decrease in somatic response to surgical incision and increase in SAP (P=0.029). Somatic response to trocar insertion and increased SAP response values were found statistically significant while repeated dose requirement was found to be statistically significant too. In our study, significantly less HR was found at the 2nd min of incision in remifentanyl group.

In a study conducted by Warner et al. in 1999, hemodynamic features of the patients receiving remifentanyl and fentanyl were close to each other except those in perioperative period.⁹ Most of the patient receiving remifentanyl between intubation and skin incision developed hypotension. This may be attributable to the remifentanyl induction dose of 1 µg/kg. Retrospective analysis of the overall remifentanyl experience performed after this study caused a revision in the recommended induction infusion rate from 1 to 0.5 µg/kg/min in patients > 65 y old. A higher incidence of hypotension was found during early recovery in patients receiving remifentanyl. The incidence of bradycardia was found to be higher with remifentanyl¹⁰. In our study, there was a significant difference between the groups in

terms of systolic and diastolic arterial pressures obtained at 5 min of incision, and the said values were significantly lower in remifentanyl group when compared with the dexmedetomidine group. With respect to heart rates, the heart rates of dexmedetomidine group were higher at the 1st minute of incision when compared with remifentanyl group with no difference at other time points.

In anesthesia practice, alpha 2 receptor agonists are used as anesthetic adjuvants producing analgesia and sedation, decreasing anesthetic requirements, reducing postanesthetic shivering and improving hemodynamic stability.^{11,12} Preoperative infusion of dexmedetomidine (0.4-0.5 µg/kg/h), which is an α2 receptor agonist, to support general anesthesia has been found to reduce the time to cooperation during recovery period and no apnea was observed after extubation.⁶ Hall et

al. showed that dexmedetomidine was an α2 receptor agonist having sedative and analgesic properties and that dexmedetomidine infusions resulted in reversible sedation and mild analgesia without causing cardiorespiratory compromise¹³. After a 10-min initial dose 6 µg/kg/h followed by 0.2 or 0.6 µg/kg/h dexmedetomidine infusion, heart rate, blood pressure, respiratory rate, ETCO₂, O₂ saturation, and processed electroencephalogram (bispectral analysis) were monitored and results of the groups were found to be similar.

In dexmedetomidine infusion, bradycardia and hypotension can be observed during loading period. By reducing the initial dose, these cardiovascular adverse events can be brought down to a tolerable limit. Following termination of infusion, these values increase slowly and no respiratory depression is observed.¹⁴ In our study, we found no severe cardiovascular adverse events associated with dexmedetomidine and attributed this to not using a loading dose. It has been stated that dexmedetomidine causes no rebound hypertension and withdrawal syndrome and provides a comfortable extubation period.¹⁵

In studies comparing alfentanil and remifentanyl and alfentanil in patients undergoing major abdominal surgery and reported that extubation period was shorter in remifentanyl group when compared with alfentanil group.^{7,16}

Dexmedetomidine has no or minimal effect on the respiratory system, but in one study it caused obstructive apnea,¹⁷ perhaps due to loading dose in a short period of time.

In a study conducted in 1996 on patients undergoing ambulatory surgery, Cartwright et al. found that remifentanyl provided a deeper intraoperative analgesia and more rapid recovery¹⁸. In 2001, Wuesten et al. used remifentanyl and alfentanil combined with propofol and showed that time to sufficient respiration was shorter in remifentanyl group.¹⁹ Times to extubation, verbal response and an Aldrete score ≥ 9 were significantly longer in dexmedetomidine group when compared with remifentanyl group, in our study.

Strong opioids combined with inhalation anesthetics have safely been used for intraoperative analgesia and hemodynamic stability;²⁰ however, these may prolong recovery time and increase the incidence of postoperative nausea and vomiting. Remifentanyl has a half time independent of the duration of infusion and is metabolized by non-specific esterases and thus does not affect recovery.²¹ Also it does not lead to a significant increase in postoperative nausea-vomiting and residual sedation when compared with conventional opioids.²²

Postoperative pain, has the greatest effect during the first 24 hours, lessening gradually and ending by the tissue recovery. Once it starts, it is difficult to manage it. Especially in patients undergoing major abdominal surgery, moderate or severe postoperative pain may occur when the remifentanyl infusion is stopped, due to very short half-time of remifentanyl.² Vinik et al. claimed development of tolerance to analgesics, which was also seen in the case of remifentanyl.²⁴

Dexmedetomidine has been shown to have a mild analgesic effect.^{25,26} The studies have shown decreases by 20 to 30% in VAS pain scores showing

a mild to severe sedation depending on the dose of the drug administered.^{13,27} The combined usage of dexmedetomidine with fentanyl leads to a significant analgesic effect leading to reduced opioid requirement.²⁸

In 2007, Bulow et al. compared remifentanyl and dexmedetomidine in TIVA performed for laparoscopic interventions in gynecology and found that intraoperative blood pressure was significantly lower in remifentanyl group and there was a difference between extubation times although recovery times were equal.²⁹ Shukry et al. published a case series of children undergoing TIVA with dexmedetomidine and reported substantial results in terms of analgesia and sedation.³⁰ They showed that cardiovascular and respiratory stability could be achieved when dexmedetomidine was infused at a bolus dose of 2-5 $\mu\text{g}/\text{kg}$ during bronchoscopy and laryngoscopy. Wide range of conditions where dexmedetomidine can be used is given in a review on TIVA applications with dexmedetomidine in children and adults undergoing lumbar laminectomies.^{31,32}

CONCLUSION

In conclusion, we believe that remifentanyl provides a potent intraoperative analgesia compared with dexmedetomidine; however, it has rebound effects due to its short acting profile. Dexmedetomidine leads to more stable hemodynamic parameters during recovery period, has prolonged postoperative analgesic effects, results in less opioid consumption and provides a comfortable postoperative period.

Conflict of interest statement: None

Funding: No funding

Author contribution: All authors contributed equally in the concept, conduct of study, data acquisition, literature search and manuscript preparation

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