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ORIGINAL ARTICLE

Dexmedetomidine and remifentanil as adjuncts to total intravenous anesthesia with propofol

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ABSTRACT

Aim: The aim was to compare the effects of dexmedetomidine and remifentanyl in total intraveous 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, SpO_2, end tidal CO_2 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

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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 (α2) adrenoreceptor agonist. Although there is strong evidence showing that α2 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 remifentanil, the number of studies comparing total intravenous anesthesia with dexmedetomidine and remifantanil comprehensively is limited.[5]

In the present study, our aim was to compare the effects of dexmedetomidine and remifentanil on intraoperative hemodynamic responses, recovery profile, postoperative hemodynamic parameters, postoperative analgesic consumption and postoperative pain during total intraveous 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 antidepresants), 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 remifentanil group (Group R, n=20) randomly. Randomization was performed by selaed envelope technique one day prior to operation. Propofol, remifentanil 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 aterial 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), 1μg/ kg fentanyl (Fentanyl-citrate, Abbott, USA). During maintenance, 150 μg/kg/min propofol and 0.5 μg/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 μg/kg/h.

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

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 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 remifentanil group ($p < 0.05$) (Table 2). When DAP values of the groups were compared, DAP values of remifentanil at the 5th, 25th, 35th and 45th min of incision were significanty 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 remifentanil group ($p < 0.05$) (Table 4).

Postoperative SAP and DAP values at 1st and 2nd h, were found to be higher in remifentanil group ($p < 0.05$) (Tables 5 & 6). With higher postoperative HR values in remifentanil 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 significanly higher in remifentanil group at all times ($p < 0.05$) (Table 9).

Total morphine consumption was higher in remifentanil 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 remifentanil on peroperative hemodynamic parameters, postoperative recovery and analgesia requirement in TIVA were compared.

Many studies have shown that remifentanil offers hemodynamic stabilization during intraoperative period. In a study conducted in 1997 to compare remifentanil 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 ± 10.37	133.45 ± 6.80	*P=0.007
2nd hour	119.15 ± 11.07	127.00 ± 7.50	*P=0.020
4th hour	119.25 ± 8.92	121.00 ± 7.99	P=0.477
6th hour	117.15 ± 8.16	117.00 ± 9.37	P=0.955
8th hour	119.45 ± 7.19	114.75 ± 8.80	P=0.052
12th hour	119.85 ± 7.67	117.27 ± 7.85	P=0.278
24th hour	115.27 ± 5.95	117.00 ± 5.71	P=0.296

Data are mean ± 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 ± 7.48	81.30 ± 6.25	*P=0.001
2nd hour	71.50 ± 9.06	77.25 ± 4.43	*P=0.021
4th hour	73.00 ± 6.76	73.00 ± 5.93	P=0.955
6th hour	72.25 ± 6.17	73.00 ± 5.47	P=0.794
8th hour	70.75 ± 7.48	71.75 ± 6.74	P=0.547
12th hour	69.25 ± 6.12	72.00 ± 4.97	P=0.158
24th hour	67.25 ± 6.97	71.00 ± 4.75	P=0.052

Data are mean ± 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 ± 9.01	79.50 ± 6.81	*P=0.010
2nd hour	74.40 ± 8.51	79.45 ± 4.71	*P=0.049
4th hour	73.15 ± 7.47	79.35 ± 5.20	*P=0.004
6th hour	73.35 ± 7.40	79.70 ± 4.41	*P=0.001
8th hour	73.20 ± 8.22	79.00 ± 4.35	*P=0.015
12th hour	73.00 ± 8.56	77.90 ± 4.21	*P=0.049
24th hour	72.25 ± 6.38	77.10 ± 3.62	*P=0.009

Data are mean ± 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 ± 1.74	5.25 ± 0.71	P=0.415
Extubation time (min)	6.90 ± 1.37	6.10 ± 0.64	*P=0.025
Time to respond to verbal commands (min)	14.30 ± 3.71	8.05 ± 0.75	*P=0.001
Time to reach an Aldrete score of ≥ 9 (min)	16.45 ± 4.05	9.20 ± 1.00	*P=0.001
Time to first analgesic need (min)	43.75 ± 6.04	25.25 ± 4.43	*P=0.001

Data are mean ± SD; *$p < 0.05$

Table 9: Comparison of postoeprative 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

remifentanil offered superior hemodynamic stability when compared with alfentanil.[7] In a multi-center study conducted in 1997, Beverly et al. performed TIVA by administering remifentanil to 157 and alfentanil to 66 patients undergoing ambulatory laparoscopic surgery,[8] In patients receiving remifentanil, 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 remifantanil group.

In a study conducted by Warner et al. in 1999, hemodynamic features of the patients receiving remifentanil and fentanyl were close to each other except those in perioperative period.[9] Most of the patient receiving remifentanil between intubation and skin incision developed hypotension. This may be attributable to the remifentanil induction dose of 1 μg/kg. Retrospective analysis of the overall remifentanil 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 receving remifentanil. The incidence of bradycardia was found to be higher with remifentanil[10]. 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 remifentanil 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 remifentanil 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 compromise[13]. 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, $ETCO_2$, O_2 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 atrributed 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 remifentanil and alfentanil in patients undergoing major abdominal surgery and reported that extubation period was shorter in remifentanil 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 remifentanil provided a deeper intraoperative analgesia and more rapid recovery[18]. In 2001, Wuesten et al. used remifentanil and alfentanil compined with propofol and showed that time to sufficient respiration was shorter in remifentanil group.[19] Times to extubation, verbal response and an Aldrete score $\geq$ 9 were significantly longer in dexmedetomidine group when compared with remifentanil group, in our study.

Strong opioids combined with inhalation anesthetics have safely been used for intraoperative analgesia and hemodynamic stability;[20] however, these my prolong recovery time and increae the incidence of postoperative nausea and vomiting. Remifentanil has a half time independent of the duration of infusion and is metabolized by non-spesific 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 my occur when the remifentanil infusion is stopped, due to very short half-time of remifentanil.[2] Vinik et al. claimed development of tolerance to analgesics, which was also seen in the case of remifentanil.[24]

Dexemdetomidine has been shown to hve 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 remifentanil and dexmedetomidine in TIVA performed for laparascopic interventions in gynecology and found that intraoperative blood pressure was significanly lower in remifentanil 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 μg/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 remifentanil 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 consumtions and provides a comfortable postoperative period.

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REFERENCES

1. Kayhan Z. Intravenöz Anestezi. Klinik Anestezi. Logos Publishing. 2nd Edition.1997; 82–85.
2. Aitkenhead AR, Smith G. Textbook of Anaesthesia. London Churchill Livingstone, 1998, 149.
3. Ozkose Z, Yalcin Cok O, Tuncer B, Tufekcioglu S, Yardim S. Comparison of hemodynamics, recovery profile, and early postoperative pain control and costs of remifentanil versus alfentanil-based total intravenous anesthesia (TIVA). J Clin Anesth. 2002 May;14(3):161-8. [PubMed]
4. Dogan Y, Alptekin A, Özkan D, Arık E, Gümüs H. Entübasyon sırasında oluşan hemodinamik yanıtlar üzerine deksmedetomidin'in etkisinin remifentanil ile karşılaştırılması. Anestezi Dergisi 2008; 16: 136-141.
5. Özcan AA, Özyurt Y, Saracoglu A, Erkal H, Süslü H, Arslan G, et al.. Dexmedetomidine versus remifentanil for controlled hypotensive anesthesia in functional endoscopic sinus surgery. Turk J Anesth Reanim 2012; 40: 257-261. [Free full text]
6. Kay B. Monographs in Anaesthesiology: Total Intravenous Anaesthesia. Elsevier Science Publishers B.V. Amsterdam, The Netherlands 1991; 159-163.
7. Schüttler J, Albrecht S, Breivik H, Osnes S, Prys-Roberts C, Holder K, et al. A comparison of remifentanil and alfentanyl in patients undergoing

major abdominal surgery. Anaesthesia 1997; 52: 307-317. [PubMed] [Free full text]
8. Philip BK, Scuderi PE, Chung F, Conahan TJ, Maurer W, Angel JJ, et al. Remifentanil compared with alfentanil for ambulatory surgery using total intravenous anesthesia. The Remifentanil/Alfentanil Outpatient TIVA Group. Anesth Analg 1997; 84: 515-521. [PubMed]
9. Warner DS. Experience with remifentanil in neurosurgical patients. Anesth Analg 1999; 89: 33-39. [PubMed]
10. Chinachoti T, Werawatganon T, Suksompong S, Techanivate A, Kitsampanwong W, Tansui R, et al. A multicenter randomized double-blind comparison of remifentanil and alfentanil during total intravenous anaesthesia for out-patient laparoscopic gynaecological procedures. J Med Assoc. Thai 2000; 83: 1324-1332.
11. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs 2000; 59: 263-294. [PubMed]
12. Farber NE, Samso E, Staunton M, Schwabe D, Schmeling WT. Dexmedetomidine modulates cardiovascular responses to stimulation of central nervous system pressor sites. Anesth Analg 1999; 88: 617-624. [PubMed]
13. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic and analgesic properties of small dose dexmedetomidin infusions. Anesth Analg 2000; 90: 699-705. [PubMed]
14. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. Br J Anaesth 2002; 88: 669-675. [Free full text]
15. Walker J, Maccallum M, Fischer C, Kopcha R, Saylors R, McCall J. Sedation using dexmedetomidine in pediatric burn patients. Journal of Burn Care Research 2006; 27: 206-210. [PubMed]
16. Sanjay SP,Spencer CM. Remifentanil. Drugs 1996; 52: 417-427. [PubMed]
17. Belleville JP, Wards DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. Anesthesiology 1992; 77: 1125-1133. [PubMed] [Free full text]
18. Cartwright DP, Kvalsvik O, Cassuto J, Jansen JP, Wall C, Remy B, et al. A randomized, blind comparison of remifentanil and alfentanil during anesthesia for outpatient surgery. Anaesth Analg 1997; 85: 1014-1019. [PubMed] [Free full text]
19. Wuesten R, Van Aken H, Glass PS, Buerkle H. Assessment of depth of anesthesia and postoperative respiratory recovery after remifentanil- versus alfentanil-based total intravenous anesthesia in patients undergoing ear-nose-throat surgery. Anesthesiology 2001; 94: 211-217. [PubMed] [Free full text]
20. Gesztesi Z, Mootz BL, White PF. The use of a remifentanil infusion for hemodynamic control during intracranial surgery. Anesth Analg 1999; 89:1282-1287. [PubMed]
21. O'Hare RA, Mirakhur RK, Reid JE, Breslin DS, Hayes A. Recovery from propofol anaesthesia supplemented with remifentanil.BrJAnaesth, 2001, 86: 361-365. [Free full text]
22. Pinsker MC, Carroll NV. Quality of emergence from anesthesia and incidence of vomiting with remifentanil in a pediatric population. Anesth Analg 1999; 89: 71-74. [PubMed]
23. Albrecht S, Schuttler J, Yarmush J. Postoperative pain management after intraoperative remifentanil. Anaesth Analg 1999; 89: 40-45.
24. Vinik HR, Kisin I. Rapid development of tolerance to analgesia during remifentanil infusion in humans. Anesth Analg 1998; 86: 1307-1311. [PubMed] [Free full text]
25. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine – a novel □2 adrenoceptor agonist – in healty volunteers. Pain 1991; 46: 281-285. [PubMed]
26. Cortinez LI, Hsu YW, Sum-Ping ST, Young C, Keifer JC, Macleod D, et al. Dexmedetomidine pharmacodynamics: part II. Crossover comparison of the analgesic effect of dexmedetomidine and remifentanil in healty volunteers. Anesthesiology 2004; 101: 1077-1083. [PubMed] [Free full text]
27. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93: 382-394. [PubMed] [Free full text]
28. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 2004; 98: 153-158. [PubMed]
29. Bulow NM, Barbosa NV, Rocha JB. Opioid consumption in total intravenous anesthesia is reduced with dexmedetomidine: a comparative study with remifentanil in gynecologic videolaparoscopic surgery. J Clin Anesth. 2007; 19: 280-285. [PubMed]
30. Shukry M, Kennedy K. Dexmedetomidine as a total intravenous anesthetic in infants. Pediatric anesthesia 2007; 17: 581-583. [PubMed]
31. Mani V, Morton NS. Overview of total intravenous anesthesia in children. Paediatr Anaesth. 2010 Mar;20(3):211-22. doi: 10.1111/j.1460-9592.2009.03112.x.[PubMed]
32. Turgut N, Turkmen A, Gökkaya S, Altan A, Hatiboglu MA. Dexmedetomidine-based versus fentanyl-based total intravenous anesthesia for lumbar laminectomy, Minerva Anestesiologica 2008; 74: 469-474. [PubMed] [Free full text]

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