REMIFENTANIL-PROPOFOL VS DEXMEDETOMIDINE-PROPOFOL

- Anesthesia for Supratentorial Craniotomy -

NAMIGAR TURGUT*, AYGEN TURKMEN*, ACHMET ALI*, AND AYSEL ALTAN*

Abstract

The aim of the present study was to compare the perioperative hemodynamics, propofol consumption and recovery profiles of remifentanil and dexmedetomidine when used with air-oxygen and propofol, in order to evaluate a postoperative analgesia strategy and explore undesirable side-effects (nausea, vomiting, shivering).

In a prospective randomized double-blind study 50 ASAI-III patients scheduled for supratentorial craniotomy, were allocated into two equal Groups. Group D patients (n = 25), received i.v. dexmedetomidine 1 μg kg^{-1} as preinduction over a 15-min period and 0.2-1 μg $kg^{-1}hr^{-1}$ by continuous i.v. infusion during the operation period. Group R patients (n = 25), received remifentanil 1 μg kg^{-1} as induction i.v. over a 15-min period and 0.05-1 μg kg^{-1} min^{-1} as maintenance. The propofol infusion was started at a rate of 10 mg $kg^{-1}h^{-1}$ and titrated to maintain BIS in the range 40-50.

Propofol doses for induction and maintenance of anesthesia was lower with dexmedetomidine (respectively $p < 0.05$, $p < 0.01$). The time for BIS to reach 50 was significantly shorter in Group D ($p < 0.01$). Comparison of the parameters of recovery revealed; extubation time ($p < 0.01$); response to verbal commands ($p < 0.05$) and time for orientation ($p < 0.05$) were longer with Group D. With respect to Post Anesthesia Care Unit (PACU) discharge time, dexmedetomidine patients required longer time when compared to remifentanil patients to achieve their first normal neurological score (33 min *vs* 31 min). The earliest opioid administration was at 38 min. in the dexmedetomidine group and 33 min. in the remifentanil group. Propofol-remifentanil and propofol-dexmedetomidine are both suitable for elective supratentorial craniotomy and provide similar intraoperative hemodynamic responses and postoperative adverse events. Propofol-remifentanil allows earlier cognitive recovery; however, it leads to earlier demand for postoperative analgesics. Undesirable side-effects were similar in two Groups.

Keywords: Dexmedetomidine, remifentanil, propofol, neurosurgery.

* MD, Department of Anaesthesiology and Reanimation, S.B. Okmeydanı Teaching and Research Hospital, Istanbul, Turkey.
Corresponding author: Namigar Turgut Tasliçay Sok. Tepecik Yolu, Alta Palas, No. 3/3 Etiler Istanbul, Turkey. Tel: 00212 3515923, E-mail: drnamigar@yahoo.com.tr

Introduction

Because of its rapid onset of action and ultra-short duration, the effect of remifentanil hydrochloride does not increase with prolonged administration. Therefore, it is useful in settings, such as intracranial surgery, when rapid drug titration and recovery from anesthesia would be advantageous. Remifentanil may thus have benefits through enhancing timely and complete neurological assessments of patients shortly after the completion of surgery[1,2,3]. It is generally known that a good anesthetic agent provides hemodynamic stability without any side effects.

Dexmedetomidine on the other hand, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α_2-adrenoceptor agonism[4,5]. Activation of the receptors in the brain and spinal cord inhibits neuronal firing and causes hypotension, bradycardia, sedation, and analgesia[6,7,8,9]. Presynaptic activation of α_2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity, possibly leading to a decrease in blood pressure and heart rate[10,11].

The aims of the present study were:

(1) To compare the perioperative hemodynamics, propofol consumption, and recovery profiles of remifentanil and dexmedetomidine when used with air-oxygen and propofol

(2) To evaluate a postoperative analgesia strategy of administering *iv* tramadol in two groups at the time of craniotomy closure

(3) To assess undesirable side-effects: postoperative nausea and vomiting (PONV) and shivering.

Materials and Methods

The study was approved by the local Ethical Committee of the Ministry of Health, Okmeydani Research and Teaching Hospital and an informed consent was obtained from each patient.

In a prospective, randomized, bouble-blind study, 50 ASA I-III, 18-80 yrs patients (mean 55.04 ± 11.39), scheduled for supratentorial craniotomy with a maximum anticipated duration of 300 minutes, were allocated into two equal groups. Group D received Dexmedetomidine-Propofol and Group R received Reminfentanil-propofol. The allocation was done by a computer-generated codes based on a two-way randomization and which were kept in sequentially numbered envelops and opened 3 hours before operation.

Eligible patients had no incapacitating severe systemic disease, and only those in whom immediate postoperative extubation was planned, were included. Exclusion criteria consisted of body weight more than 130% of ideal body weight, uncontrolled hypertension with blood pressure higher than 140/90 mmHg, severe respiratory disease such as bronchial asthma, ischemic cardiac findings at ECG during preoperative visit or cardiac conducting defects (e.g., second-degree atrioventricular block, left bundle branch block). Patients were also excluded if they had any of the following neurological conditions: cerebral aneurysms, intracranial arteriovenous malformations, posterior fossa tumors, and symptoms of uncontrolled increased intracranial pressure (ICP), risk of impending cerebral herniation. Also excluded were patients requiring procedures performed in the sitting or prone position.

Before induction the routine monitoring of ECG and pulse oximetry (Datex-Ohmeda S/5™ Compact Critical Care Monitor) were started. The Bispectral Index (BIS) electrodes were placed on the forehead and were connected to an A-2000 BIS monitoring system (Aspect Medical Systems, BIS XP, Framingham, MA, USA).

Group D patients (25) received i.v. dexmedetomidine 1 μg kg^{-1} as preinduction over a 15-min period before induction of anesthesia and 0.2-1 μg kg^{-1} hr^{-1} by continuous i.v. infusion during the operative period. Group R patients (25) received remifentanil 1 μg kg^{-1} as induction iv over a 15-min period and 0.05-1 μg kg^{-1} min^{-1} as maintenance.

The infusion of dexmedetomidine or remifentanil was started before induction and adjusted to keep the mean arterial blood pressure at –20% to +10% from the preoperative value.

After preoxygenation for at least 2 min, anesthesia was induced with propofol in increments of 20 mg every 15s until the BIS reached a predetermined value of 50 (1-2.5 mg kg^{-1}). After induction with propofol, neuromuscular blockade was induced using cisatracurium in a bolus dose of 0.2 mg kg^{-1} followed by continuous intravenous infusion to maintain 90%

suppression of the single twitch response. Anesthesia was maintained with air (50%), oxygen (50%), and propofol. Depth of anesthesia was monitored by using a BIS-system, a range between 40 and 50 was thought to be adequate. Propofol maintenance doses were 50-150 μg kg^{-1} min^{-1}.

Patients were ventilated mechanically with an oxygen/air mixture to maintain an adequate oxygenation and a P_aCO_2 level between 30 and 35 mmHg (Datex-Ohmeda S/5 Avance). Approximately 30 min. before the end of the surgery, the cisatracurium infusion was discontinued. After that, the patients were allowed to recover spontaneously until the return of T1 = 25%. A combination of neostigmine 0.04 mg kg^{-1} and atropine 0.02 mg kg^{-1} were then administered to antagonize residual neuromuscular blockade. Tramadol of 1 mg kg^{-1} i.v. was given before the craniotomy closure.

At the end of surgery, the fresh gas inflow rate was changed to 6 L min^{-1} of oxygen and the following times were recorded:

1 – Time to extubation (spontaneous breathing with a minimum of 8 mL kg^{-1} body weight, ability to sustain a 5-s head lift, and adequate negative inspiratory force [-40 cm H_2O], sustained hand grip and, sustained arm lift).

2 – Time to response to verbal commands (starting from the time of discontinuation of anesthetic administration, a blinded investigator asked each patient at 1-min intervals, to open his or her eyes, squeeze the investigator's hand).

3 – Orientation time (for the patient to tell his name, birthday and the place he or she is in).

Apart from these, all patients were evaluated with the Aldrete Post Anesthesia Recovery Scoring System (PACU time).

Hemodynamics were monitored for 120 min. after surgery; at the time of postoperative first analgesic requirement, and undesirable side-effects (PONV), shivering, hypotension, and bradycardia were noted, whenever they occurred.

Statistical Analysis

For evaluation of the study findings, SPSS (Statistical Package for Social Sciences) for Windows 10.0 program was utilized for statistical analysis. Study data was evaluated according to Student t test for the comparison between groups. For the comparisons in groups, the paired sample t test was used. Chi-square test and Fisher's exact test were used for comparison of the qualification data. The results were taken into consideration in 95% confidence interval and the level of significance was set at $p < 0.05$.

Results

The two groups, D and R, were similar in terms of age, weight, height, duration of surgery ($p > 0.05$) Propofol doses for induction of anesthesia ($p < 0.05$) and the maintenance of anesthesia ($p < 0.01$) was lower with Dexmedetomidine (Table 1).

The time for BIS to reach 50 was significantly shorter in Group D ($p < 0.01$). At the end of anesthesia, recovery time for BIS to reach 80 was significantly shorter for Group R with respect to Group D ($p < 0.01$).

Table 1
Demographic Data

	Group D (n = 25)	Group R (n = 25)	*P value*
Age (years)	56.52 ± 12.54	53.56 ± 10.14	0.364
Height (cm)	165.12 ± 6.72	166.80 ± 4.83	0.315
Weight (kg)	71.00 ± 11.27	70.00 ± 6.45	0.702
Propofol doses for induction (mg kg^{-1})	1.65 ± 0.17	1.74 ± 0.08	0.020*
Propofol doses for maintenance (mg kg^{-1} h^{-1})	6.14 ± 0.71	7.51 ± 0.45	0.001**
Duration of surgery (min)	216.08 ± 52.01	229.40 ± 37.06	0.302
Perioperative Dexmedetomidine usage (μg kg^{-1} hr^{-1})	0.213 ± 0.0106		
Perioperative Remifentanil usage (μg kg^{-1} min^{-1})		0.052 ± 0.002	

Values are mean ± SD, number (%) or median (range).

When comparing the groups with respect to the parameters of recovery; extubation time ($p < 0.01$), response to verbal commands ($p < 0.05$) and the time for orientation ($p < 0.05$) were longer in Group D.

With respect to PACU discharge time; dexmedetomidine patients required a longer time compared to remifentanil patients to achieve their first normal neurological score (33 min *vs* 31 min).

Remifentanil patients required supplemental analgesia earlier than dexmedetomidine group, median time 33 *vs* 38 min (Table 2).

Table 2
Induction and recovery period for BIS

	Group D (n = 25)	Group R (n = 25)	*P value*
BIS < 50 (sec)	83.32 ± 13.17	114.80 ± 17.65	*0.001***
BIS > 80 (sec)	120.12 ± 15.93	108.88 ± 10.39	*0.005***
Extubation time (min)	12.72 ± 2.56	10.64 ± 1.68	*0.001***
Response to verbal commands (min)	6.48 ± 2.02	5.40 ± 1.19	*0.027**
Time for orientation (min)	12.52 ± 3.01	10.60 ± 2.18	*0.013**
PACU Discharge Time (min)	33.60 ± 4.44	31.32 ± 4.92	*0.046**
Time for postoperative analgesic requirement (min)	38.04 ± 3.98	33.68 ± 3.60	*0.0001****
PCA (Patient controlled analgesia) Tramadol Quantity (mg kg^{-1} sa^{-1})	0.27	0.28	*0.233*

Data are the mean (± SD) p values were determined by comparing dexmedetomidine and remifentanil groups. Significant difference within groups (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

The preoperative value of intraoperative MAP (prior to the administration of drug), was similar in both groups ($p > 0.05$). Nevertheless, comparing to the values before extubation; the MAP in Group D were significantly higher than those in Group R ($p < 0.01$) two hours later after extubation (Table 3). When each group was evaluated independently, MAP in two groups was observed to decrease significantly with respect to the values before and after infusion ($p < 0.01$). On the contrary, MAP was observed to increase significantly after intubation; after pinned head-holder; after skin incision; after dura opening and after extubation with respect to the values before ($p < 0.01$). The increases observed in MAP levels at 20^{th} min and at 2^{nd} hour postoperatively were not statistically significant with respect to those observed before extubation ($p > 0.05$), (Table 3).

Heart rate (HR) levels in Group D before incision were found statistically lower than those in Group R ($p < 0.05$). HR values in dexmedetomidine group were significantly lower than the values of the preoperative period at the 3^{rd} hour of the operation; during skin closure, after extubation ($p < 0.01$), and before extubation ($p < 0.05$).

When each group was evaluated independently, the decrease observed in HR level after infusion was found statistically highly significant when compared to the HR levels in the beginning in both Group D and Group R ($p < 0.01$). On the contrary, a highly significant increase was observed after intubation, after pinned head-holder, after skin incision and after dura opening with respect to the values before in both group ($p < 0.01$). The increase in HR levels observed in Group D after extubation compared to the HR level before extubation; at 20^{th} minute and at 2^{nd} hour postoperatively was found statistically highly significant ($p < 0.01$). Similarly, the increase in heart rate in Group R was found statistically highly significant ($p < 0.01$); the increase at postoperative 20^{th} min was also significant ($p < 0.05$). Nevertheless, there was no statistically significant change in heart rate at postoperative 2^{nd} hour when compared to the values before extubation ($p > 0.05$), (Table 4).

Table 3
Mean arterial blood pressure (mmHg)

		Group D (n = 25)	Group R (n = 25)	p value
Infusion	At the beginning	100.08 ± 9.48	95.44 ± 11.00	0.117
	After	88.68 ± 10.93	87.56 ± 9.52	0.701
	P	*0.001***	*0.001***	
Intubation	Before	79.52 ± 15.85	79.52 ± 14.14	1.000
	After	91.08 ± 15.16	96.64 ± 13.85	0.182
	P	*0.001***	*0.001***	
Pinned-head holder	Before	77.88 ± 12.52	76.95 ± 6.93	0.780
	After	90.70 ± 14.05	88.22 ± 6.83	0.508
	P	*0.001***	*0.001***	
Skin incision	Before	78.24 ± 9.05	76.76 ± 6.96	0.520
	After	84.96 ± 10.59	81.32 ± 7.16	0.161
	P	*0.001***	*0.001***	
Dura Opening	Before	76.52 ± 9.54	76.87 ± 6.68	0.889
	After	82.38 ± 7.81	80.61 ± 6.55	0.418
	P	*0.001***	*0.001***	
Intraoperative Period (120 min)		65.12 ± 5.13	67.36 ± 4.60	0.084
Intraoperative Period (180 min)		63.33 ± 4.37	67.52 ± 4.22	0.601
Skin closing		64.12 ± 5.81	70.84 ± 5.12	0.319
Before Extubation		87.56 ± 8.64	84.96 ± 7.07	0.250
After Extubation		97.12 ± 10.18	101.52 ± 10.61	0.141
P		*0.001*	*0.001*	
After Extubation (20 min)		89.08 ± 10.15	85.80 ± 7.09	0.192
P		*0.466*	*0.606*	
After Extubation (120 min)		92.04 ± 8.71	85.08 ± 7.88	0.005**
P		*0.087*	*0.942*	

Result are means ± SD p values were determined by comparing dexmedetomidine and remifentanil groups. Significant difference within groups (** $p < 0.01$).
When the *p* values groups evaluated as independent from each other (** $p < 0.01$).

Table 4
Heart Rate (Beat/min)

		Group D (n = 25)	Group R (n = 25)	p
Infusion	At the beginning	80.20 ± 5.76	77.32 ± 7.25	0.127
	After	71.92 ± 8.62	70.00 ± 6.36	0.375
	P	*0.001***	*0.001***	
Intubation	Before	67.44 ± 5.79	65.40 ± 5.95	0.225
	After	77.48 ± 6.12	81.32 ± 8.52	0.074
	P	*0.001***	*0.001***	
Pinned-head holder	Before	68.59 ± 5.07	71.84 ± 5.56	0.077
	After	82.82 ± 7.95	83.04 ± 5.96	0.921
	P	*0.001***	*0.001***	
Skin incision	Before	66.76 ± 6.42	70.60 ± 5.07	0.020*
	After	70.84 ± 5.93	75.40 ± 5.17	0.006**
	P	*0.001***	*0.001***	
Dura Opening	Before	67.62 ± 7.23	70.00 ± 4.22	0.185
	After	70.71 ± 8.12	73.30 ± 4.74	0.199
	P	*0.001***	*0.001***	
Intraoperative Period (120 min)		65.12 ± 5.13	67.36 ± 4.60	0.115
Intraoperative Period (180 min)		63.33 ± 4.37	67.52 ± 4.22	0.002**
Skin closing		64.12 ± 5.81	70.84 ± 5.12	0.001**
Before extubation		70.24 ± 5.82	74.72 ± 5.92	0.010*
After extubation		78.04 ± 5.94	91.84 ± 10.19	0.001**
P		*0.001***	*0.001***	
After Extubation (20 min)		78.68 ± 8.87	77.76 ± 4.46	0.645
P		*0.001***	*0.001***	
After Extubation (120 min)		77.84 ± 7.57	77.04 ± 5.12	0.664
P		*0.001***	*0.114*	

Result are means ± SD p values were determined by comparing dexmedetomidine and remifentanil groups. Significant difference within groups (** $p < 0.01$, * $p < 0.05$).
When the *p* values groups evaluated as independent from each other (* $p < 0.05$, ** $p < 0.01$).

There was no statistically significant difference for nausea, vomiting, shivering and bradycardia in Group D and Group R ($p > 0.05$) (Table 5).

Table 5
Adverse Events

	Group D (n = 25)	Group R (n = 25)	*p*
Nausea	3 (12.0%)	7 (28.0%)	*0.157*
Vomiting	1 (4.0%)	3 (12.0%)	*0.609*
Shivering	7 (28%)	13 (52.0%)	*0.083*
Bradycardia (atropine administered)	5 (20.0%)	1 (4.0%)	*0.189*

Discussion

In nonemergent intracranial surgery, fast recovery from anesthesia is especially important for detecting early complications and for performing the neurological examination[12]. The results of the current study demonstrate that an ultra-short acting opioid, such as remifentanil, is an effective and safe alternative to fentanyl. It is advantageous to the patient undergoing supratentorial craniotomy to emerge and recover from anesthesia quickly, as this allows prompt neurological assessment and determination of the need for urgent intervention[13].

Despite the potential advantages of total intravenous anesthesia in titratability, rapid return of consciousness and reduced respiratory complications, making it suitable for planned extubation at the end of neurosurgery, the postoperative complications of shivering, postoperative nausea and vomiting, and hypertension were still high[14].

The propofol-remifentanil regimen has been successfully used in various surgical settings, but a comprehensive comparison of propofol-dexmedetomidine and propofol-remifentanil anesthesia in patients undergoing craniotomy for supratentorial intracranial surgery, has not yet been done.

It has been reported that Dexmedetomidine has anesthetic and analgesic effects in addition to its sedative effects, appearing at i.v. 0.5-2 $\mu g\ kg^{-1}$ dose intervals[15]. Our study showed that when dexmedetomidine was used perioperatively for BIS 40-50, the doses of propofol for induction and maintenance were significantly reduced and the time for intubation was significantly shorter. It is predictable that the induction dose of propofol would be lower in Group D than in Group R, because dexmedetomidine is a sedative but remifentanil is not.

Because of the ventilatory depressing effects of fentanyl, Feld JM et al.[16] studied various alternative methods for analgesia in bariatric surgery. In their study comparing dexmedetomidine to fentanyl, they reported that dexmedetomidine provided both stable perioperative hemodynamics and postoperative analgesia, thus reducing the use of supplementary morphine. Similarly, Tanskenen PE et al.[17] reported that dexmedetomidine provided good perioperative hemodynamic stability compared to fentanyl in patients undergoing brain tumor surgery and that it also reduced intraoperative opioid requirements. Dexmedetomidine could be convenient as an adjuvant anesthetic in neurosurgical anesthesia. It prevents the tachycardic response to intubation and the hypertensive response to extubation.

In our study, remifentanil and dexmedetomidine were similar in overall efficacy. In the two groups, no hemodynamic and cardiovascular side effects were seen perioperatively. This finding is supported by a similar study by Bauer et al[12], though the time to extubation was about 4 times longer in the present study (10 *vs* 47 min).

The major reported problem with dexmedetomidine is its hemodynamic effects, as the drug often causes hypotension, hypertension, and bradycardia[18,19]. In our study, although bradycardia was seen more in Group D patients similar to other studies, this finding was not statistically significant[20,21,22]. Also hypotension and hypertension, was not observed in our groups. This could be attributed to the greater depth of anesthesia in the dexmedetomidine group either because the doses of the drug chosen were not exactly equipotent, or because they differ in their potentiation of propofol, or because remifentanil has a lower capability for causing hypotension.

Our study findings are similar to those of Djian et al[23]. Other studies of this type of surgery have also demonstrated a longer time to extubation than we found when remifentanil was used. In the study by Bauer et

al[12], the time period was 47 minutes, while it was 13 +/- 5 minutes in the study by Bilotta et al[24]. Gelb[25], however, recorded the time period as 8 minutes. In the study by Gerlach et al[26], patients in the remifentanil/ propofol group were extubated earlier (6.4 min). In our study, extubation time was longer and recovery was slower in Group D (12 *vs* 10 min). These differences possibly reflect differences in anesthetic protocols between the various studies.

The most commonly encountered complications in the early postoperative period in the recovery room in extubated patients after elective neurosurgical procedures using propofol-remifentanil anesthesia were, shivering, nausea, vomiting, and postoperative hypertension[14].

As for emergence characteristics, our study showed an advantage for remifentanil. With respect to PACU discharge time, dexmedetomidine patients required longer time compared to remifentanil patients to achieve their first normal neurological score (33 min *vs* 31 min). In the study by Gelb et al.[25] the remifentanil group PACU time was 26 minutes. Statistically significant differences between the groups were also found at times when the patients responded to verbal commands.

Previous studies with remifentanil identified pain and the need for early analgesia in the PACU, because of problems inherent in such an active drug[27]. In recent years, however, alpha$_2$ agonists have found wider applications, particularly in the fields of anesthesia and pain management. It has been noted that these agents can enhance the analgesia provided by traditional analgesics, such as opioids, and may result in opioid-sparing effects[28,29,30].

Another important aim of the present study was the evaluation of the use of tramadol 1 mg kg^{-1} i.v. at bone flap replacement for transitional analgesia. This proved to be effective in that early recovery but superior quality was still found in the dexmedetomidine group without early pain requiring urgent treatment.

Similar to the studies by Gelb et al.[25] and Gerlach et al[26], our study showed that remifentanil group required supplemental analgesia earlier than dexmedetomidine group (The earliest opioid administration was at 38 min. for the dexmedetomidine group and at 33 min for the remifentanil group).

Although respiratory depression due to opioids have been reported in different anesthetic combinations[31,32,33], dexmedetomidine, the highly selective alpha$_2$ adrenoreceptor agonist, has sedative and analgesic effects without causing postoperative respiratory depression[18,19]. 0.5 to 1.0 μg kg^{-1} dexmedetomidine over 20 minutes followed by an infusion at rates of 0.01 to 1.0 μg kg^{-1} h^{-1} was used in awake craniotomy and enabled the performance of the neurological examination[34,35].

The analgesic profile of dexmedetomidine has not been fully characterized in humans[36]. However, the anxiolysis, blood pressure stabilization, analgesia, anesthetic sparing effects, and sedation without respiratory depression or significant cognitive impairment effects of dexmedetomidine, are known. Cormack et al.[37] suggests that both of these alpha$_2$-agonists are useful adjuncts for the management of the neurosurgical patient during surgery and in the intensive care unit.

Conclusion

In conclusion, propofol-remifentanil and propofol-dexmedetomidine are both suitable for elective supratentorial craniotomy and provide similar intraoperative hemodynamic responses and postoperative adverse events. Propofol-remifentanil allows earlier cognitive recovery; however, it leads to a higher demand for postoperative analgesics.

References

1. Mastronardi P, Dellacasa P: Observational study on the use of remifentanil in general anesthesia. Drug utilization research. *Minerva Anestesiol*; 2004, 70:605-616.
2. Tipps LB, Coplin WM, Murry KR, Rhoney DH: Safety and feasibility of continuous infusion of remifentanil in the neurosurgical intensive care unit. *Neurosurgery*; 2000, 46:596-601.
3. Del Gaudio A, Ciritella P, Perrotta F, Puopolo M, Lauta E, Mastronardi P, DE Vivo P: Remifentanil vs fentanyl with a target controlled propofol infusion in patients undergoing craniotomy for supratentorial lesions. *Minerva Anestesiol*; 2006, 72:309-319.
4. Ansah OB, Raekallio M, Vainio O: Comparison of three doses of dexmedetomidine with medetomidine in cats following intramuscular administration. *J V et Pharmacol Ther*; 1998, 21:380-387.
5. Coursin DB, Maccioli GA: Dexmedetomidine. *Curr Opin Crit Care*; 2001, 7:221-226.
6. Sakaguchi Y, Takahashi S: Dexmedetomidine. *Masui*; 2006, 55:856-863.
7. Smith H, Elliott: Alpha$_2$ receptors and agonists in pain management. *Curr Opin Anaesthesiol*; 2001, 14:513-518.
8. Furst S: Transmitters involved in antinociception in the spinal cord. *Brain Res Bull*; 1999, 48:129-141.
9. Ozkose Z, Demir FS, Pampal K, Yardim S: Hemodynamic and anesthetic advantages of dexmedetomidine, an alpha$_2$-agonist, for surgery in prone position. *Tohoku J Exp Med*; 2006, 210:153-160.
10. Gertler R, Brown HC, Mitchell DH, Silvius EN: Dexmedetomidine: a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)*; 2001, 14:13-21.
11. Prielipp RC, Wall MH, Tobin JR, Groban L, Cannon MA, Fahey FH, Gage HD, Stump DA, james RL, Bennett J, Butterworth: Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. *Anesth Analg*; 2002, 95:1052-1059.
12. Bauer C, Kreuer S, Ketter R, Grundmann U, Wilhelm W: Remifentanil-propofol vrsus fentanyl-midazolam combinations for intracranial surgery: Influence of anaesthesia technique and intensive sedation on ventilation times and duration of stay in the ICU. *Anaesthetist*; 2007, 56:128-132.
13. Viviand X, Garnier F: Opioid anesthetics (sufentanil and remifentanil) in neuro-anesthesia. *Ann Fr Anesth Reanim*; 2004, 23:383-388.
14. Wong AY, O'Regan AM, Irwin MG: Total intravenous anaesthesia with propofol and remifentanil for elective neurosurgical procedures: an audit of early postoperative complications. *Eur J Anaesthesiol*; 2006, 23:586-590.
15. Weinbroum A, Ben-Abraham R: Dextromethorphan and dexmedetomidine: new agents for the control of perioperative pain. *Eur J Surg*; 2001, 167:563-569.
16. Feld JM, Hoffman WE, Stechert MM, Hoffman IW, Ananda RC: Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. *J Clin Anesth*; 2006, 18:24-28.
17. Tanskanen PE, Kytta JV, Randell TT, Aantaa RE: Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: a double-blind, randomized and placebo-controlled study. *Br J Anaesth*; 2006, 97:658-665.
18. Sakaguchi Y, Takahashi S: Dexmedetomidine. *Masui*; 2006, 55:856-863.
19. Bekker A, Sturaitis MK: Dexmedetomidine for neurological surgery. *Neurosurgery*; 57:1-10, 2005.
20. Chrysostomou C, Di Filippo S, Manriqure AM, Schmitt CG, Orr RA, Casta A, Suchoza E, Janosky J, Davis PJ, Munoz R: Use of dexmedetomidine in children after cardiac and thoracic surgery. *Pediatr Crit Care Med*; 7:126-131, 2006.
21. Bhana N, GOA KL, MC Clellan KJ: Dexmedetomidine. *Drugs*; 2000, 59:263-268.
22. Lawrence CJ, DE Lange S: Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative haemodynamic stability. *Anaesthesia*; 1997, 52:736-744.
23. Djian MC, Blanchet B, Pesce F, Sermet A, Disdet M, Vazquez V, Gury C, Roux FX, Ragguenеau JL, Coste J, Joly LM: Comparison of the time to extubation after use of remifentanil or sufentanil in combination with propofol as anesthesia in adults undergoing nonemergency intracranial surgery: a prospective, randomized, double-blind trial. *Clin Ther*; 2006, 28:560-568.
24. Bilotta F, Caramia R, Paoloni FP, Favaro R, Araimo F, Pinto G, Rosa G: Early postoperative cognitive recovery aftr remifentanil-propofol or sufentanil-propofol anaesthesia for supratentorial craniotomy: a randomized trial. *Eur J Anaesthesiol*; 2007, 24:122-127.
25. Gelb AW, Salevsky F, Chung F, Ringaert K, MC Taggart-Cowan RM, Wongt T, Manninen PH: Remifentanil with morphine transitional analgesia shortens neurological recovery compared to fentanyl for supratentorial craniotomy. *Can J Anaesth*; 2003, 50:946-952.
26. Gerlach K, Uhlig T, Huppe M, Nowak G, Schmitz A, Saager L, Grasteit A, Schmucker P: Remifentanil-propofol versus sufentanil-propofol anaesthesia for supratentorial craniotomy: a randomized trial. *Eur J Anaesthesiol*; 2003, 20:813-820.
27. Burkle H, Dunbar S, Van Aken H: Remifentanil: a novel, short-acting, μ-opioid. *Anesth Analg*; 1996, 83:646-651.
28. Smith H, Elliott J: Alpha$_2$ receptors and agonists in pain management. *Curr Opin Anaesthesiol*; 2001, 14:513-518.
29. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B: Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. *Can J Anaesth*; 2006, 53:646-652.
30. Del Angel Garcia R, Castellanos Olivares A, Munguia Miranda C: Dexmedetomidine as preventive postoperative analgesia in inguinal hernioplasty. *Gac Med Mex*; 2006, 142:9-12.
31. Koo BN, Choi SH, Chun DH, Kil HK, Kim KJ, Min KT, Lee SJ: Respiratory depression caused by remifentnil infusion for postoperative pain control. *Anesth Analg*; 2006, 103:1627-1628.
32. Makita K, Ishikawa S: Remifentanil. *Masui*; 2006, 55:817-825.
33. Fourel D, Almanza L, Aubouin JP, Guiavarch M: Remifentanil: postoperative respiratory depression after purging of the infusion line. *Ann Fr Anesth Reanim*; 1999, 18:358-359.
34. ARD JL JR, Bekker AY, Doyle WK: Dexmedetomidine in awake craniotomy: a technical note. *Surg Neurol*; 2005, 63:114-116.
35. Mack PF, Perrine K, Kobylarz E, Schwartz TH, Lien CA: Dexmedetomidine and neurocognitive testing in awake craniotomy. *J Neurosurg Anesthesiol*; 2004, 16:20-25.
36. Cortinez LI, Hsu YW, Sum-Ping ST, Young C, Keifer JC, Macleod D, Robertson KM, Wright Dr, Moretti EW, Somma J: Dexmedetomidine pharmacodynamics: Part II: Crossover comparison of the analgesic effect of dexmedetomidine and remifentanil in healthy volunteers. *Anesthesiology*; 2004, 101:1077-1083.
37. Cormack JR, Orme RM, Costello TG: The role of alpha$_2$-agonists in neurosurgery. *J Clin Neurosci*; 2005, 12:375-378.