ESMOLOL VERSUS DEXMEDETOMIDINE IN SCOLIOSIS SURGERY: STUDY ON INTRAOPERATIVE BLOOD LOSS AND HEMODYNAMIC CHANGES

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Abstract

Background: Surgical correction of scoliosis carries significant blood loss and needs for blood transfusion with its inherent risks and cost. The aim of this double-blind, randomized, controlled study was to compare the effects of esmolol or dexmedetomidine on intraoperative blood loss, anesthetics consumption, intra operative hemodynamic and effects on spinal cord monitoring in patients undergoing scoliosis surgery.

Methods: After obtaining institute review board approval and written informed consent, 60 adolescents (ASA physical status I–II), 14–18-year of age scheduled for posterior spinal fusion scoliosis surgery were enrolled in the study. Using computer generator software patients were randomly allocated to receive either saline as a control (group C), esmolol (Group E) or dexmedetomidine (Group D).

Results: There was a significant reduction in blood loss in patients who received esmolol and dexmeditomidine compared to control it was as follow; in control group 782±86.4ml ($P \leq 0.001$), esmolol group 667±145.2 ml ($P \leq 0.001$) and dexmeditomidine group 465±115.3ml ($P \leq 0.001$). Mean intraoperative total fentanyl and propofol consumption in the esmolol group was significantly higher than in the dexmedetomidine group, this was especially dramatic for the dexmedetomidine group where the propofol consumption was twice less $P \leq 0.001$. There was no significant effect seen in SSEPs (amplitude or latency) but there was isolated decrease in motor evoked potential (MEP) amplitude which was within acceptable range that was seen in 6 patients receiving dexmeditomidine at a dose of 0. 7 μg/Kg/H.

Conclusion: Both esmolol and dexmedetomidine, added to anesthetic regimen, provided an effective and well-tolerated method to reduce the amount of blood loss in patients undergoing scoliosis surgery. dexmedetomidine, was associated with plonoged extubation and recovery times.

Key words: Esmolol, Dexmedetomidine, Scoliosis, Blood loss.

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Introduction

Scoliosis surgery carries significant morbidity associated with intraoperative blood loss and the resultant transfusion therapy. Surgical stress plays an important role on the perioperative blood loss. We think that manipulating adrenergic receptors could attenuate this response and may thereby reduce intra operative blood loss. It has been suggested that esmolol and dexmedetomidine influence core components of an anesthetic regimen, such as analgesia, hypnosis, and memory function and have the ability to reduce both the anesthetic and opioid analgesic requirements during the perioperative period[1-2]. This study designed to compare the effects of esmolol versus dexmedetomidine on intraoperative blood loss, anesthetics consumption, intra operative hemodynamic changes and effects on spinal cord monitoring in patients undergoing scoliosis surgery.

Methods

After obtaining institute review board approval and written informed consent, 60 patients (ASA physical status I–II), 14–18-year of age, scheduled for posterior spinal fusion for scoliosis surgery were studied according to a randomized, double blind, placebo-controlled protocol. A block randomization software was used in order to keep equal the sizes of treatment while blindness of the studied drugs was achieved with the help of the hospital central pharmacy which provided coded identical intravenous bags containing either the dexmedetomidine, esmolol or saline as a control. The surgical and anesthesiologist team were blinded as to the type of solution. The author collecting the data was as well blinded to the type of studied drug delivered.Exclusion criteria included; patients with motor or sensory deficits in lower limbs, patients with neuromuscular scoliosis, allergy to or contraindication to drugs used in the study, severe cardiopulmonary disease, morbid obesity (BMI more than 40%) and underlying coagulation abnormalities.

Anesthesia Technique

On arrival to operating room patients were monitored with an electrocardiograph, pulse oximeter, and an automatic noninvasive arterial pressure monitor before induction of anesthesia.

Induction of anesthesia: Fentanyl 1µg/ kg, Propofol (2 -2.5 mg/kg), and a single dose of Rocuronium (0.6 mg/kg) to facilitate endotracheal intubation. Then arterial line and a urinary catheter were placed for invasive continuous measurement of arterial blood pressure and urine output. No additional muscle relaxants were given during the procedure. Temperature probe and bispectral index monitor (BIS) were used during the procedure to monitor temperature and maintain depth of anesthesia (BIS between 40 to 70). Mechanical ventilation was adjusted to maintain normocapnia (end-tidal CO2 35–40 mm Hg).

After patients were turned to prone position, anesthesia was maintained with total intravenous anesthesia (TIVA) using propofol infusion at a rate of a rate of 80 –100 µg / kg/min, and fentanyl at rate of 1 to 3µg/kg/h in all patients. All patients received 10 ml/kg pentastarch (Pentaspan, Bristol-Myers Squibb, Montreal, Canada) plus intravenous fluid requirements were replaced with balanced crystalloid solutions Hemodynamic monitoring and total blood loss were estimated during whole procedure and after serial blood gas analysis patients received blood transfusion if a hemoglobin concentration of less than 8 gm/dl.

The administered drugs were prepared by the co investigator with the help of clinical pharmacist in identical intravenous bags each 100 ml saline contained either 400 µg (4 µg/ml) dexmedetomidine or 250 mg (2.5 mg/ml) esmolol, and normal saline bags as a control. Boluses and infusion rates were adjusted in a rate of 5 ml to 10 ml by co-investigator. Both the surgical and primary anesthetic investigator teams were blinded to the choice of the drug. Using computer generator software patients were randomly allocated to receive either saline as a control (group C), esmolol (Group E) or dexmedetomidine (Group D).

After obtaining baseline measurement of heart rate (HR) and mean arterial blood pressure (MAP), BIS and stabilization of the patients in prone position, patients were received fixed bolus dose of 10 ml and infusion of the 3 studied drugs in a dose as follow: 0.5 mg/kg esmolol was infused over 10 minutes, followed by maintenance rate of 0.25-0.50 mg/kg/h. In

dexmedetomidine group (D) loading dose was infused intravenously over 10 minutes at a rate of 0.5 to 1 µg/kg followed by a maintenance rate of 0.4-0.7 µg/kg/h, and normal saline as a control. All infusions were adjusted according to hemodynamic in a range of 5-10 ml/h.

Neurophysiologic monitoring of spinal cord integrity using somatosensory-evoked potentials and transcranial motor-evoked potentials were used. Patients were then monitored in the post operative care unit (PACU) and then transferred to a regular ward, where preordered morphine Patient control analgesia was started with the first report of pain.

Statistics

All continuous data were tested for normality using the Kolgomorov-Smirnov method. For data sets that followed a normal distribution, parametric tests were used. For all other data sets, the appropriate nonparametric tests were applied. Data were analyzed using SPSS V12.0.1 (SPSS Inc., Chicago, IL) and MedCalc - V 9.3.1 (MedCalc Software, Mariakerke, Belgium). A *P* value smaller than 0.05 was considered statistically significant. The size of our treatment groups was determined by a power calculation within statistical packages and software on internet sites.

Results

Patients in all groups did not vary significantly in age, weight, preoperative hemoglobin, duration of surgery or number of vertebrae fused (Table 1).

Effect on anesthetic consumption and recovery

Mean intraoperative total fentanyl and propofol consumption in the esmolol group was significantly higher than in the dexmedetomidine group this was especially dramatic for the dexmedetomidine group where the propofol consumption was twice less. In the control and esmolol group, the mean times to extubation and to recovery from anesthesia were significantly shorter than those of the dexmedetomidine group (17.0 ± 9.4, 19.1 ±11.7 versus 27.2± 13.4 minutes, respectively; (P = 0.001) (Table 1).

Table 1

Demographic data and operative parameters expressed as Mean ± SD

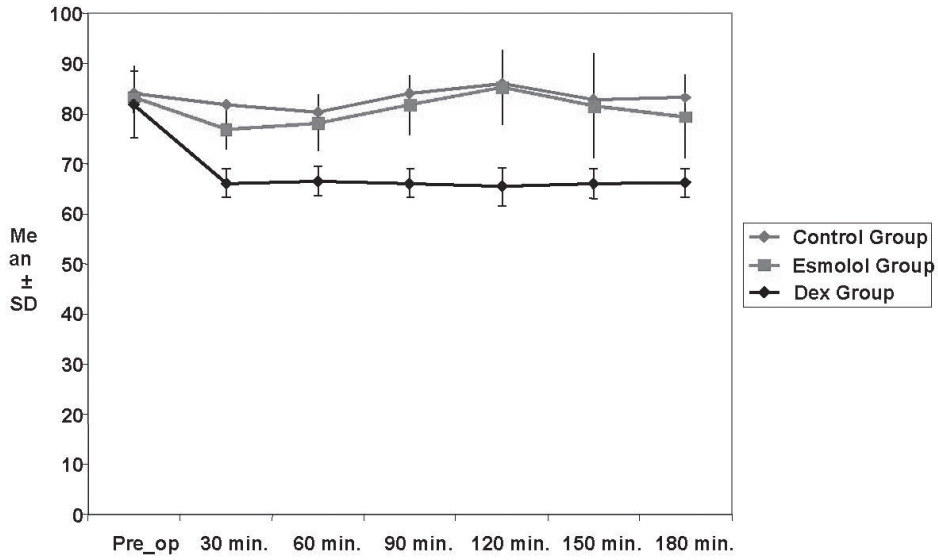
Group	Control group (C)	Esmolol group (E)	Dex group (D)
Number	20	20	20
Gender f/m	13/7	18/2	16/4
Age (yr)	13.63±1.64	14.4±1.64	14.85±3.065
Weight (kg)	41.15±4.717	41.10±5.919	42.15±4.89
Duration of surgery (hr)	4.72±46.3min	4.91±50.19min	4.966±36.31min
Numbers of vertebrae being fused	10.65±1.72	9.20±1.93	9.9±1.158
Intraoperative blood loss (ml)	782±86.4	667±145.2	465±115.3**
Preoperative Hb	13.03±1.009	13.35±.898	13.115±1.18
Post-operative Hb	8.8100±1.08	8.78±.637	9.945±.6533*
No. of patients received Blood	16	11**	5***
Total fentanyl consumption (mic)	511±90.43	441.5±65.79	384.5±50.62***
Total propofol consumption (mg)	1339.5±201.74	918.5±178.83	635.5±161.064***
Time to eye opening (min)	17.0 ± 9.4,	19.1 ±11.7	27.2± 13.4***

* Significance P less than 0.05.

** Moderate Significance P less than 0.01.

*** High Significance P less than 0.001.

Fig. 1
Mean Arterial Blood Pressure (Mean ± SD) in different times



Effects on Hemodynamic parameters and blood requirement

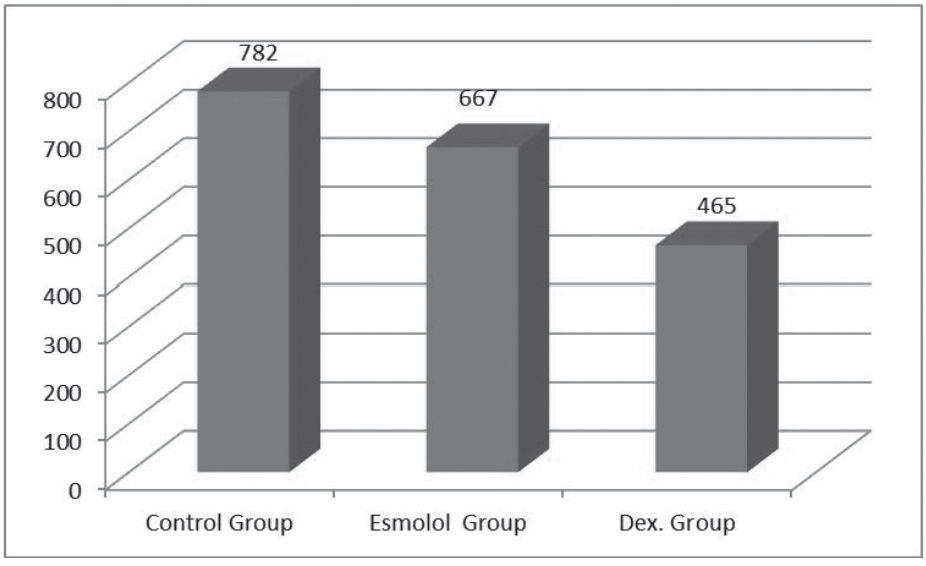
Blood loss was significantly reduced in patients who received esmolol and dexmeditomidine compared to control: as follow; in control group 782±86.4ml ($P \leq 0.001$), esmolol group 667±145.2 ml ($P \leq 0.001$) and dexmeditomidine group 465±115.3ml ($P \leq 0.001$).

The mean arterial blood pressure and heart rate were significantly low in the Dexmedetomidine group compared to control and esmolol groups; results were 86.05 ± 6.89 in control group, 85.3 ± 7.47 in esmolol group and 65.5 ± 3.79 mmHg in dexmedetomidine group. The mean arterial blood pressure was on average 20 mm of mercury less at 66 mmHg in the dexmedetomidine group constantly throughout the case once the induction period was passed (Figure 1).

Only five patients in the dexmedetomidine group were transfused with homologous blood. The mean total number of units of blood required in Group C and E was 1.9 compared with 1.2 in Group D.

A comparable drop in haemoglobin concentration was observed in both groups after operation despite clinically adequate blood replacement (Figure 2).

Fig. 2
Mean Intraoperative blood loss (ml) expressed as Mean ± SD



Effects on Spinal cord monitoring

There was no significant effect seen in SSEPs (amplitude or latency) but there was isolated decrease in motor evoked potential (MEP) amplitude which was within acceptable range that was seen in 6 patients receiving dexmeditomidine at a dose of 0. 7 µg/Kg/H. We think this due to a synergistic effect of propofol and dexmedetomidine without downward adjustment of propofol produced a dose-dependent depression of MEPs. The MEP amplitude depression observed was overcome immediatly by multipulse and increase level of stimulation. There was no neurological deficits observed in all patients, we rely depression in MEP due to drug effects.

Discussion

The present study compared the effects of esmolol versus dexmedetomidine as an adjuvant to the total intravenous anesthesia using propofol and fentanyl in providing controlled hypotension and reducing need for transfusion during scoliosis surgery. Many techniques have been used to maintain dry surgical field, limit intraoperative blood loss and need for transfusion during spinal surgery 3,4**.** This study showed a significant and clinically relevant reduction in blood loss in patients who received esmolol or dexmedetomidine compared to control group. However, our results demonstrated that dexmedetomidine has more advantages, and its usage was associated with more stable haemodynamics and less fluctuation in MAP and HR than esmolol and control groups.

The anesthetic depth during the surgery was to maintain the values of bispectral index BIS between 50-70, that was used in previous studies during scoliosis surgery**5**. In the present study, the majority of patients in both groups esmolol and dexmedetomidine had a good depth of anesthesia condition and the surgical team did not complain of major issues during the surgical procedure such as bleeding or major neurological deficits as detected by neurophysiologic monitoring. In this study total blood loss was significantly reduced in the dexmedetomidine group as well as transfusion requirement was reduced by more than 40% compared to esmolol and control groups.

One of the consequences of surgical stress is the intense activation of the sympathetic nervous system that leads to cardiovascular fluctuations meanwhile, use of adrenergic antagonists can minimize this unwanted response and maintain hemodynamic stability during surgery[6].

Selection of used drugs in our study based on reports that, Esmolol is a moderate lipophilic drug with *B* receptor activity and could be involved in the modulation of central adrenergic activity[7], although some repots seem to argue whether it crosses the blood–brain barrier. Alpha 2 receptors are found in the peripheral and central nervous systems, the analgesic effects of dexmedetomidine are mediated through the activation of a2-adrenergic receptors in the dorsal horn of the spinal cord and inhibition of substance P release[8].

Based on assumption that esmolol has an opioid sparing effect, Collard and his colleges in 2007 enrolled Ninety (90) patients scheduled for laparoscopic cholecystectomy in a prospective randomized study to compare continuous infusion of esmolol versus intermittent fentanyl on postoperative oppioid sparing effect. The authors found that esmolol infusion significantly reduce opioid administration and allow early postoperative discharge[9].

Coloma et al have used esmolol as an alternative to ramifentanyl during desflurane anesthesia in patients undergoing outpatient gynecologic laparoscopic suergery[10]. The authers found that esmolol can be used instead of ramifentanyl to maintain hemodynamic stability. In our study, fentanyl and propofol consumption were significantly lower in the dexmedetomidine group compared with the esmolol and control groups. Bulow et al found that dexmedetomidine can also be used as an alternative to ramifentanyl in maintaining hemodynamic stability and reducing the stress response to surgery[11].

The same conclusion was reported by Unlugenc, who found that dexmedetomidine reduced postoperative morphine consumption with no effect on postoperative recovery time[12]. In the postoperative ICU setting, narcotic requirements were reduced by 50% when patients were receiving a dexmedetomidine drip compared with placebo[13].

We found that dexmedetomidine promoted

controlled hypotension and reduced blood loss more than esmolol through its effects on cardiovascular system that include; decreased heart rate; decreased systemic vascular resistance; and indirectly decreased myocardial contractility, cardiac output, and systemic blood pressure. Tanskanen et al demonstrated that dexmedetomidine plasma target doses of 0.2 and 0.4 μg/mL decreased the haemodynamic responses caused by stimuli during anaesthesia[14]. Others noted that hypotension and bradycardia are the main side effects associated with dexmedetomidine, in our study lowest level of mean arterial pressure was 66 mmHg which was maintained by reducing and manipulating the infusion doses of propofol and fentanyl[15,16].

On the other hand Richa et al reported that dexmedetomidine, at the doses of 0.4-0.8 μg kg/h, was less effective than remifentanil in producing controlled hypotension, and good surgical field exposure during tympanoplasty[17].

Many studies have shown that concomitant administration of dexmedetomidine and prpofol has been found to reduce the anesthetic requirements for propofol as well as the inhalational anesthetic agents[18-19,20].

In the current study, patients received dexmedetomidine were associated with significantly longer recovery times, this effect was reported in previous studies[21-22] when they added dexmedetomidine to anesthetic regimen. Concerns regarding delayed recovery may related to development of significant hypothermia in spite of all warming measures. This may be explained by dexmedetomidine effect on the α2C-adrenoceptors subtype that has been shown to modulate dopaminergic neurotransmission, thermoregulation, hypothermia and a variety of behavioral responses[23-24].

We noted that six patients developed isolated decrease in motor evoked potential (MEP) amplitude when dexmedetomidine was administered without adjusting dose of propofol infusion rate. In that patient, there was a decrease in the BIS from 58 to 30. In the remaining patients, when the propofol infusion was decreased accordingly during the dexmedetomidine loading dose and maintenance, no interference with either SSEP or MEP monitoring noted.

It is likely that, if the anesthetic depth is not adjusted, adding dexmedetomidine may adversely affect MEPs due to either a drug effect of dexmedetomidine or related to the increased depth of anesthesia. Recently, Tobias et al reported that a dexmedetomidine infusion at a rate of 0.5 ug/kg/h) does not interfere with electrophysiologic monitoring or adversely affect SSEP or MEP monitoring[25]. Other studies reported that both SSEPs and MEPs were maintained within a clinically acceptable range during the scoliosis surgical procedure and concluded that dexmedetomidine did not interfere with intraoperative neurophysiologic monitoring the monitoring of either SSEPs or MEPs[26-27].

Conclusion

Both esmolol and dexmedetomidine, added to anesthetic regimen, provided an effective and well- tolerated method to reduce the amount of blood loss in patients undergoing scoliosis surgery. Dexmedetomidine, was associated with plonoged extubation and recovery times.

References

1. Chiia YY, Chan MH, KO NH, Liu K: Role of β-blockade in anesthesia and postoperative pain management after hysterectomy. *Br J Anaesth*; 2004, 93:799-805.
2. davidson EM, doursout MF, szmuk P, chelly JE: Antinociceptive and cardiovascular properties of esmolol following formalin injection in rats. *Can J Anaesth*; 2001, 48:59-64.
3. Tobias JD: Controlled hypotension in children: A critical review of available agents. *Paediatr Drugs;* 2002, 4:439-453.
4. Degoute CS, Ray MJ, Manchon M, et al: Remifentanil and controlled hypotension; comparison with nitroprusside or esmolol during tympanoplasty. *Can J Anaesth;* 2001, 48:20-27.
5. Simpson P: Perioperative blood loss and its reduction: The role of the anaesthetist. *Br J Anaesth;* 1992, 69:498-507.
6. Koivusalo AM, Scheinin M, Tikkaen I, Yli-Suomu T, Ristkari S, Laakso J, Lindgren L: Effects of esmolol on haemodynamic response to CO2 pneumoperitoneum for laparoscopic surgery. *Acta Anaesthesiol Scand*; 1998, 42:510-7.
7. Gorczynski RI, Shaffer JE, Lee RJ: Pharmacology of ASL-8052, a novel beta-adrenergic receptor antagonist with ultrashort duration of action. *J Cardiovasc Pharmacol*; 1983, 5:668-77.
8. Collard V, Mistraletti G, Taqi A, Asenjo JF, Feldman LS, Fried GM, Carli F: Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. *Anesth Analg*; 2007, 105:1255-62.
9. Kuraishi Y, Hirota N, Sato Y, Kaneko S, Satoh M, Takagi H: Noradrenergic inhibition of the release of substance P from the primary afferents in the rabbit spinal dorsal horn. *Brain Res;* 1985, 359:177-182.
10. Coloma M, Chiu JW, White PF, Armbruster SC: The use of esmolol as an alternative to remifentanil during desfluraneanesthesia for fast track outpatient gynecologic laparoscopic surgery. *Anesth Analg*; 2001, 92:352-7.
11. Neusa Maria H, Bulow MD, Anilda Vargas Barbosa, Joao Batista Teixeira Rocha PHD: Opioid consumption in total intravenous anesthesia is reduced with dexmedetomidine: a comparative study with remifentanil in gynecologic videolaparoscopic surgery; *Journal of Clinical Anesthesia;* June 2007, volume 19, Issue 4, p. 280-285.
12. Unlugenc H, Gunduz M, Guler T, Yagmur O Isik G: The effect of pre-anaesthetic administration of intravenous dexmedetomidine on postoperative pain in patients receiving patient-controlled morphine, *European Journal of Anaesthesiology*; 2005, 22:386-391.
13. Venn RM, Bradshaw CJ, Spencer R, et al: Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia;* 1999, 54:1136-1142.
14. Tanskanene PE, Kytta JV, Randell TT, Aantta RE: Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: a double-blind, randomised and placebo-controlled study. *Br J Anaesth*; 2006, 5:658-665.
15. Lawrence CJ, De Lange S: Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative hemodynamic stability. *Anaesthesia;* 1997, 52:736-744.
16. Guler G, Akim A, Tosun Z, Eskitascoglu E, Mizrak A, Bovaci A: Single-dose dexmedetomidine attenuates airway and circulatory reflexes during extubation. *Acta Anaesthesiol Scand*; 2005, 49:1088-1091.
17. Richa F, Yazigi A, Sleilaty G and Yazbeck P: Comparison between dexmedetomidine and remifentanil for controlled hypotension during tympanoplasty. *European Journal of Anaesthesiology*; 2008, 25:369-374.
18. Tobias JD: Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. *Pediatr Crit Care Med*; 2007, 8:115-131.
19. Ngenyama NE, Anderson J, Hoemschemyer DG, et al: Effects of dexmedetomidine on propofol and remifentanil infusion rates during total intravenous anesthesia for spine surgery in adolescents. Pediatric Anesthesia; 2008, 18:1190-1195.
20. Thomton C, Lucas MA, Newton DEF, et al: Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 2: Auditory and somatosensory evoked responses. *Br J Anaesth*; 1999, 83:381-386.
21. Kol IO, Kaygusuz K, Yildirim A, Dogan M, Gursoy S, Yucel E and Mimaroglu C: Controlled Hypotension With Desflurane Combined With Esmolol or Dexmedetomidine During Tympanoplasty in Adults: A Double-Blind, Randomized, Controlled Trial; *Current Therapeutic Research*; June 2009, 70(3):197-208.
22. Makary L, Vomik V, Finn R, Lenkovsky F, MC Cllell and Al Thurmon J, Robertson B**:** Prolonged recovery associated with dexmedetomidine when used as a sole sedative agent in office-based oral and maxillofacial surgery procedures. *J Oral Maxillofac Surg*; 2010, 68(2):386-91.
23. Arcangeli A, D'al C and Gaspari R: dexmedetomidine use in general anaesthesia. *Current Drug Targets*; 2009, 10:687-695.
24. Quezado ZMN: Hypothermia-induced bradycardia in a neonate receiving dexmedetomidine. *Journal of Clinical Anesthesia*; Jun 2007, No. 4, 19:290-292.
25. Tobias JD, Timothy J, Goble TJ, Guy Bates G, John T and Hoernschemeyer D: Effects of dexmedetomidine on intraoperative motor and somatosensory evoked potential monitoring during spinal surgery in adolescents. *Pediatric Anesthesia*; 2008, 18:1082-1088.
26. Anschel DJ, Aheme A, Soto RG, et al: Successful intraoperative spinal cord monitoring during scoliosis surgery using a total intravenous anesthetic regimen including dexmedetomidine. *J Clin Neurophys*; 2008, 25:56-61.
27. Bala E, Sessler DI, Nair DR, Mclain R, Dalton JE, Farag E: Motor and somatosensory evoked potentials are well maintained in patients given dexmedetomidine during spine surgery. *Anesthesiology*; 2008, 109(3):417-425.