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Research Article

Dexmedetomidine as a hypotensive agent: Efficacy and hemodynamic response during spinal surgery for idiopathic scoliosis in adolescents

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KEYWORDS

Controlled hypotension;
α2 Agonist;
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Abstract *Background:* This study was designed to evaluate the efficacy of dexmedetomidine as a hypotensive agent in comparison to sodium nitroprusside in scoliosis surgery.
Method: Forty patients ASA I or II aged (12–16) year scheduled for scoliosis surgery were randomly assigned to receive either dexmedetomidine 1 μg/kg over 10 min before induction of anesthesia followed by 0.2–0.5 μg/kg/h infusion during maintenance (DEX group) or sodium nitroprusside 1–10 μg/kg/min infusion after induction of anesthesia (SNP group) to maintain mean arterial blood pressure between (60–65 mmHg). Mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), systemic vascular resistance index (SVRI) and stroke index (SI) were recorded. The two groups were compared with reference to reversibility of hypotensive state, intraoperative blood loss and transfusion requirement.
Results: Dexmedetomidine administration resulted in significant reduction in MAP, HR and CI. During the steady state hypotension SNP group showed significant increase in HR and CI compared to baseline and to DEX group ($P < 0.05$). SVRI was significantly lower during controlled hypotension in SNP group compared to DEX group ($P < 0.001$). Time to restoration of baseline MAP was longer with DEX group (10.21 ± 1.52 min) than SNP group (4.87 ± 0.86 min) ($P < 0.001$). Blood loss and transfusion requirement were significantly lower in DEX group than

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SNP group [1095.62 ± 128.9 6 ml versus 1287.50 ± 182.54 ml, $P = 0.0013$] and [855.42 ± 140.23 versus 1006.00 ± 154.66 ml, $P = 0.0026$], respectively.

Conclusion: Dexmedetomidine is a safe and effective drug for controlled hypotension in scoliosis surgery. It may offer the significant advantage of reducing blood loss and transfusion requirement.

1. Introduction

Scoliosis surgery is an extensive operative procedure that is often accompanied by substantial blood loss which increases the risks for the patient [1]. Factors influencing amount of blood loss are the extent of dissection, the number of vertebrae exposed for fusion, duration of surgery and surgical technique [2].

Controlled hypotension is a commonly used technique to limit blood loss and improve visualization of the operative field during spinal fusion surgery [3]. The characteristics of an ideal hypotensive agent include easy administration, predictability with anesthetic agents, and lack of toxic side effect while maintaining adequate perfusion of the vital organs [4]. Many anesthetics and vasoactive drugs have been used successfully to produce deliberate hypotension, including volatile anesthetics [5], direct-acting vasodilators [6], autonomic ganglion-blockers, β-adrenergic receptor-blockers [7] and calcium channel blockers [8].

Sodium nitroprusside (SNP) is one of the popular vasodilators used to achieve induced hypotension because of its attractive pharmacodynamics; rapid onset, rapid offset and titrability. However, it may be associated with cyanide toxicity, reflex tachycardia, rebound hypertension and platelet dysfunction [9].

Dexmedetomidine (DEX) is a potent highly selective α_2 adrenergic agonist, possessing a differential specificity for the α_2:α_1 receptors of 1620:1 [10]. It has sedative, analgesic and anesthetic sparing effect, and sympatholytic properties [11]. The central and peripheral sympatholytic action of DEX is mediated by α_2 adrenergic receptors [12] and is manifested by dose-dependent decrease in arterial blood pressure, heart rate, cardiac output and norepinephrine release [11,13].

Despite several clinical trials that studied the effectiveness of dexmedetomidine in reducing intraoperative bleeding in adults [14–16], little is known about its effect as a sole hypotensive agent in children and adolescents [17].

The present work was designed as a prospective and andomized study to compare the efficacy and safety of dexmedetomidine versus sodium nitroprusside as a hypotensive agent in adolescents undergoing posterior spinal fusion surgery for repair of idiopathic scoliosis.

2. Methods

This study was conducted in Kasr El Aini teaching hospital from December 2006 to April 2009. After approval of the local ethical committee, written parental informed consents were obtained. Forty patients 12–16 years of age, ASA I or II physical status undergoing corrective spinal surgery for idiopathic scoliosis were enrolled in this prospective and randomized study. Exclusion criteria included; respiratory or cardiac dysfunction, renal insufficiency, liver impairment, and bleeding disorders.

Patients were randomly assigned according to computer-generated randomization to receive either dexmedetomidine (DEX group: $n = 20$) or sodium nitroprusside (SNP group: $n = 20$) for controlled hypotension.

All patients were premedicated with IV midazolam 0.02 mg/kg after insertion of 22 G peripheral IV catheter. Upon arrival to the operating room, another 20 G peripheral IV catheter were inserted, one for administration of the study drug and the other was used for induction of anesthesia. Standard monitors (Infinity SC 8000, Dräger medical system, Avenue, Danvers, MA, USA) were applied and heart rate (HR), noninvasive blood pressure and oxygen saturation (SPO2) were continuously monitored. In addition, Cardiac Index (CI), systemic vascular resistance index (SVRI) and stroke volume index (SI) were evaluated using a non-invasive impedance cardiography (ICG) device (Bio.Z.Com, Cardiodynamics international corporation, USA).

Before induction of anesthesia, patients allocated to (DEX) group received loading dose of 1 μg/kg dexmedetomidine diluted in 10 ml 0.9% saline infused over 10 min followed by continuous IV infusion of 0.2 μg/kg/h.

All patients received standard anesthetic technique using 2 μg/kg fentanyl and propofol 1 mg/kg supplemented, if necessary by 0.2 mg/kg aliquots until loss of verbal response. The required induction dose of propofol was recorded. Endotracheal intubation was facilitated by the use of atracurium 0.5 mg/kg. Anesthesia was maintained with 0.5–1% end-tidal isoflurane in 100% oxygen and fentanyl infusion 1 μg/kg/h. Adequate muscle relaxation was maintained with incremental bolus doses of 0.2 mg/kg atracurium when indicated by peripheral nerve stimulation. Controlled ventilation was adjusted to maintain normocapnia (30–35 mmHg).

After induction of anesthesia, another large bore I.V catheter was inserted for fluids and blood transfusion. 22 G radial artery catheter was inserted for continuous measurement of arterial blood pressure. Esophageal temperature probe was applied and normothermia was maintained with a heating mattress and infusion of warm fluids. Foley's catheter was inserted to monitor urine output.

All patients were placed prone on a Relton frame with the abdomen hanging free where eyes, airway and pressure points were checked and protected.

After positioning patients allocated to (SNP) group received 1 μg/kg/min continuous sodium nitroprusside infusion (0.01%). The infusion rate of both studied drugs was gradually increased to achieve target mean arterial blood pressure (MAP) between 60–65 mmHg prior to skin incision.

The maximum allowed infusion rate was o.5 μg/kg/h in DEX group and 10 μg/kg/min in SNP group. Patient reached the maximum dose without obtaining the target MAP were excluded from the study and added therapy was given.

The same surgical team performed all operations to ensure consistency of surgical technique and duration of surgery.

During the course of induced hypotension, reflex tachycardia defined as persistent increase in HR exceeding 110 bpm for more than 10 min, was treated by a bolus dose of esmolol 0.5 mg/kg. If the MAP decreased below 60 mmHg, gradual decrease of the studied drug started together with ephedrine shots (10 mg) and fluid bolus, progressed to stopping the study drug if needed and those patients were excluded from the study. Bradycardia (HR <60 beat/min) was treated with 10 μg/kg atropine intravenously.

Fluid therapy included maintenance plus deficit fluids replaced over the first three to 4 h of the procedure and third space losses which were replaced by 6 ml/kg/h. Intraoperative blood transfusions were given to maintain the level of hemoglobin (Hb) equal to or greater than 10 g/dl.

Hypotensive infusions were stopped after placement of rods, and reversibility of the hypotensive state (time required to restore the MAP to baseline measurement after discontinuation of the study drug) was recorded. At the conclusion of surgery, fentanyl infusion was stopped and residual neuromuscular block was antagonized with neostigmine (0.05 mg/kg) and atropine (0.01 mg/kg). After extubation and full recovery, patients were transferred to the postanesthetic care unit (PACU) to be observed for 1 h where time to first analgesic rescue was recorded.

MAP, HR, CI, SI and SVRI were recorded at the following times: upon arrival to the operating room ($T0$), immediately before induction of anesthesia (after loading dose in DEX group) ($T1$), after induction of anesthesia ($T2$), 15 min after positioning (steady state hypotension) ($T3$), 5 min after stopping hypotensive drug ($T4$), 20 min after stopping hypotensive drug ($T5$).

Both groups were compared with reference to intraoperative blood loss, blood transfusion requirement and number of patients who required esmolol supplementation.

Based on the findings of a pilot study we had performed before conduct of the main study, we observed a standardized effect size (d) of 0.98 in blood loss which represented a between-group percentage difference of 16%. By adopting a statistical significance of 95%, a statistical power of 80% ($\alpha = 0.05$, $\beta = 0.20$) and a group allocation ratio of 1:1, sample size calculation determined that 18 subjects are required in each of both study groups to detect difference 16% or more in blood loss. Power calculations was performed using computer program G*Power 3 for Windows (Franz Faul, Universität Kiel, Germany).

3. Statistical methods

Data was analyzed using SPSSwin statistical package version 15. Numerical data was expressed as mean ± standard deviation. Comparison between the two groups was done using parametric or non-parametric t-test. Intragroup comparison relative to baseline were performed using repeated measure analysis of variance (ANOVA) with post hoc Dunnet's test if ANOVA results were significant. P-value <0.05 was considered significant.

4. Results

Fifty two patients were assessed for study eligibility, seven patients failed to meet the inclusion criteria and five patients, their parents refused to sign the consent form. The remaining forty patients who fulfilled the study criteria were enrolled in this study. All patients were able to complete the entire study and their data were included in the final analysis.

Patient demographic data, the number of levels fused and the duration of surgery were comparable between the two groups (Table 1).

The propofol dose required for induction of anesthesia was significantly lower in DEX group than in SNP group [(1.57 ± 0.27 mg/kg) versus (2.28 ± 0.44 mg/kg)], respectively ($P < 0.001$).

Baseline values of MAP and HR were comparable in both groups. Dexmedetomidine administration in DEX group resulted in significant reduction of MAP from T1 to T4 compared to baseline value. In SNP group, MAP was significantly lower than baseline only at T3 ($P < 0.05$). At T3 both groups reach the desired MAP (60–65 mmHg) with no intergroup significant difference while at T4 DEX group showed significantly lower MAP than SNP group ($P < 0.05$) (Fig. 1).

Heart rate decreased significantly relative to baseline after administration of loading dose ($T1$) in DEX group and remained so until $T4$. However, in the SNP group there was significant increase in HR compared to baseline only at $T3$. Compared to SNP group, HR in the DEX group was significantly lower at $T3$ and $T4$ ($P < 0.01$) (Fig. 2).

In DEX group CI was significantly lower compared to baseline from $T1$ till $T4$. Conversery, CI in the SNP group was comparable to baseline at all time intervals except at $T3$, where it was significantly higher ($P < 0.05$) (Fig. 3).

Table 1 Demographic and operative data [mean (SD) or ratio].

	SNP group ($n = 20$)	DEX group ($n = 20$)	P value
Age (year)	13.45 (1.47)	12.9 (1.15)	0.195
Weight (kg)	48.25 (5.61)	46.92 (7.60)	0.53
Height (cm)	143.25 (7.89)	146.11 (6.73)	0.225
Sex (M/F)	8/12	7/13	
Duration of surgery (h)	4.32 ± 0.50	4.11 (0.42)	0.159
Blood loss (ml)	1287.50 ± 182.54	1095.62 ± 168.96	0.0013
Blood transfusion (ml)	1006.00 ± 154.66	855.42 ± 140.23	0.0026
Levels fused	9.4 ± 1	10 ± 1.2	0.094

SNP group = sodium nitroprusside group, DEX group = dexmedetomidine group.

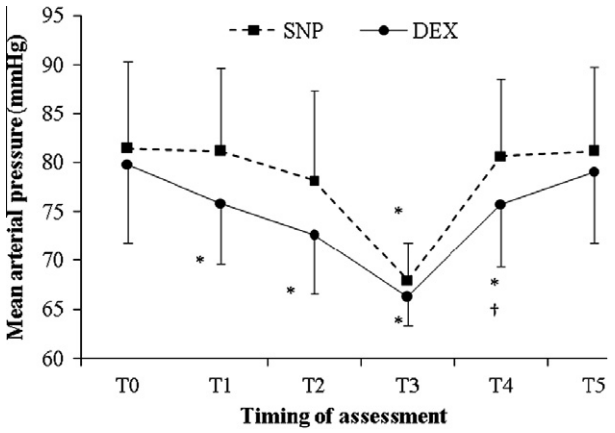

Figure 1 Perioperative mean arterial pressure. Data points are means and bars are SD. SNP group = sodium nitroprusside group, DEX group = dexmedetomidine group. *T*0 = upon arrival to the operating room, *T*1 = immediately before induction, *T*2 = after induction of anesthesia, *T*3 = during steady state hypotension, *T*4 = 5 min after stopping the hypotensive agent, *T*5 = 20 min after stopping the hypotensive agent. * = $P < 0.05$ relative to baseline value. † = $P < 0.05$ relative to the SNP group.

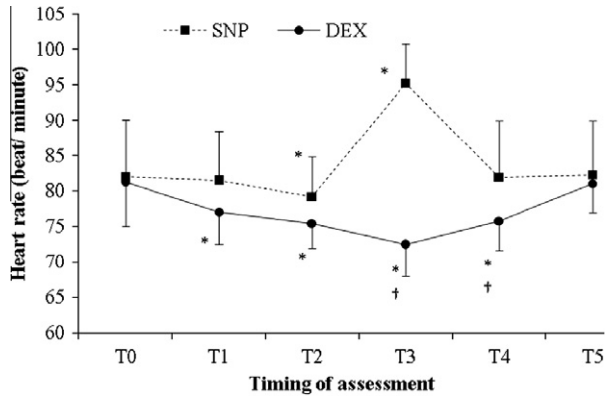

Figure 2 Perioperative heart rate. Data points are means and bars are SD. SNP group = sodium nitroprusside group, DEX group = dexmedetomidine group. *T*0 = upon arrival to the operating room, *T*1 = immediately before induction, *T*2 = after induction of anesthesia, *T*3 = during steady state hypotension, *T*4 = 5 min after stopping the hypotensive agent, *T*5 = 20 min after stopping the hypotensive agent. * = $P < 0.05$ relative to baseline value. † = $P < 0.01$ relative to the SNP group.

Both groups showed significantly lower SVRI relative to baseline at *T*2, *T*3, *T*4 ($P < 0.05$), however values in SNP group was significantly lower compared to DEX group during steady state hypotension ($P < 0.001$) (Fig. 4).

There were no significant intergroup or intragroup differences in stroke index values (Table 2).

Esmolol administration was necessary in 12 out of 20 (60%) patient in SNP group in comparison, no patient in DEX group received esmolol therapy. Withdrawal of the hypotensive agent was not associated with rebound hypertension in any of the patients included in the study.

Reversibility of hypotensive state as defined by the protocol was significantly shorter in SNP group compared to the DEX

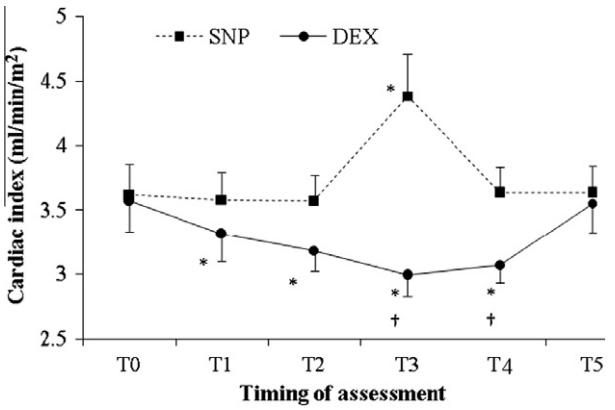

Figure 3 Perioperative cardiac index. Data points are means and bars are SD. SNP group = sodium nitroprusside group, DEX group = dexmedetomidine group. *T*0 = upon arrival to the operating room, *T*1 = immediately before induction, *T*2 = after induction of anesthesia, *T*3 = during steady state hypotension, *T*4 = 5 min after stopping the hypotensive agent, *T*5 = 20 min after stopping the hypotensive agent. * = $P < 0.05$ relative to baseline value. † = $P < 0.001$ relative to the SNP group.

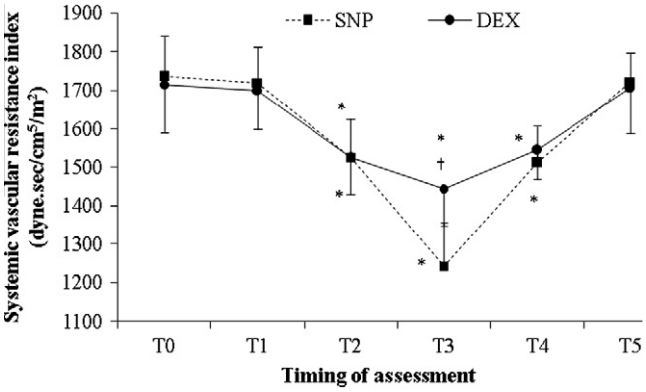

Figure 4 Perioperative systemic vascular resistance index. Data points are means and bars are SD. SNP group = sodium nitroprusside group, DEX group = dexmedetomidine group. *T*0 = upon arrival to the operating room, *T*1 = immediately before induction, *T*2 = after induction of anesthesia, *T*3 = during steady state hypotension, *T*4 = 5 min after stopping the hypotensive agent, *T*5 = 20 min after stopping the hypotensive agent. * = $P < 0.05$ relative to baseline value. † = $P < 0.001$ relative to the SNP group.

Table 2 Perioperative stroke index (ml/m^2) [mean (SD)].

	SNP group (n = 20)	DEX group (n = 20)
*T*0	39.85 ± 3.03	38.75 ± 2.53
*T*1	39.60 ± 3.07	38.50 ± 2.24
*T*2	39.40 ± 2.89	38.60 ± 2.35
*T*3	39.05 ± 2.76	38.35 ± 2.01
*T*4	39.45 ± 2.54	38.70 ± 1.95
*T*5	39.20 ± 2.33	38.80 ± 1.91

SNP group = sodium nitroprusside group, DEX group = dexmedetomidine group. *T*0 = upon arrival to the operating room, *T*1 = immediately before induction, *T*2 = after induction of anesthesia, *T*3 = during steady state hypotension, *T*4 = 5 min after stopping the hypotensive agent, *T*5 = 20 min after stopping the hypotensive agent.

group [(4.87 ± 0.86 min) versus (10.21 ± 1.52 min)], respectively ($P < 0.001$).

There was a statistically significant increase in the amount of blood loss and blood transfusion requirement in SNP group compared to DEX group ($P < 0.01$) (Table 1).

Time recorded to first analgesic requirement was significantly shorter in SNP group versus DEX group [(36.16 ± 7.20 min) versus (53.75 ± 6.15 min)], respectively ($P < 0.001$).

5. Discussion

Anesthesia for correction of scoliosis in children is a challenge because of the frequent co-morbidities of these patients and the extensive nature of the procedure itself [18]. Scoliosis correction may be associated with major blood loss (>50% of blood volume) and development of coagulopathy, which is both dilutional and consumptive [19].

In this prospective and randomized study, dexmedetomidine in comparison to sodium nitroprusside was successful at achieving deliberate hypotension. It provided less blood loss and blood transfusion requirement during spinal fusion surgery in adolescents with idiopathic scoliosis. In addition dexmedetomidine decreased the induction dose of propofol and prolonged the time to first analgesic rescue.

The hypnotic and sedative actions of dexmedetomidine are thought to be mediated primarily by postsynaptic α2-adrenrgic receptors [20]. In the current study, the induction dose of propofol was significantly lower in DEX group than in SNP group. This effect coinciding with the result of other investigators, Peden et al. found that dexmedetomidine caused a reduction in the overall concentration and dose of propofol required to produce loss of consciousness [21].

Controlled hypotension has been widely advocated to reduce blood loss, yet it may be associated with increased risk of neurological deficit because of reduced spinal cord perfusion, specially if this is compromised by distraction [22]. This is why we used a more conservative control of MAP (60–65 mmHg) which was effectively reached in both groups before skin incision. Patients who were treated with dexmedetomidine 10 min before induction of anesthesia had a significant decrease in MAP, HR and CI after administration the loading dose without significant changes in SVRI or SI.

This dexmedetomidine-induced haemodynamic profile can be attributed to the known sympatholytic effects of α2-agonists. The α2-receptors are involved in regulating the autonomic and cardiovascular systems. Alpha-2 receptors are located on blood vessels, where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release [23]. At lower doses, the dominant action of α2-agonist is sympatholysis [24].

There are several well-documented mechanisms for this activity including, the drug actions on several brain stem and medullary nuclei (nucleus tractus solitarus and the lateral reticular nucleus), and the hypothalamus to decrease sympathetic nervous system activity and inhibit norepinephrine release at neuroeffector junction [25]. The activation of central receptors leads to reduction of tonic level of sympathetic outflow, and an augmentation of cardiac vagal activity [26]. This can result in a decrease of HR and cardiac output (CO).

This agree with what was reported by Ebert et al. [27] who determined the response to increasing plasma concentration of dexmedetomidine in humans and stated that lower plasma dexmedetomidine concentration resulted in decreases in MAP, HR and CI without changes in stroke volume, pulmonary or systemic vascular resistance. Kallio et al. [28] reported a 23% decrease in CO after IV administration of 100 μg single-dose dexmedetomidine. Basar et al. [29] investigated the effect of a single dose of dexmedetomidine 0.5 μg/kg administered 10 min before induction of anesthesia and reported 27% decrease in CI, significant reduction in MAP and HR without changes in SVI.

Tobias and Berkenbosch [17] when used dexmedetomidine for controlled hypotension in a case of pediatric patient undergoing spinal fusion surgery, the target MAP (55–60) was successfully achieved with restoration of baseline values 7 min after discontinuation. The efficacy of dexmedetomidine in controlled hypotension was previously reported in adults [14–16].

The hypotensive effect of SNP is the result of both primary direct vasodilator effects on vascular smooth muscles, which tends to lower blood pressure and decrease systemic vascular resistance as well as compensatory homeostatic reflex [30]. This homeostatic reflex which includes tachycardia and increased CO is thought to be related to reflex sympathetic stimulation that result in the release of endogenous catecholamines and activation of renin angiotensin system [31]. This was evident in SNP group as significant increase in HR and CI during the period of steady sate hypotension with significant decrease in SVRI compared both to baseline and to the other group.

Sodium nitroprusside causes vascular relaxation via production of nitric oxide which has a half life of 0.1 s [32], while dexmedetomidine is highly specific alpha 2 agonist, removal of dexmedetomidine would not result in restoration of blood pressure until the drug diffused out of the receptor site [20]. This could explain the significant short time to restoration of MAP in SNP group compared to DEX group in the present study. Although rapid restoration of blood pressure in SNP group is beneficial both to patient and surgeon yet this gradual restoration could also have the advantage of limiting the occurrence of rebound hypertension and giving time for clot formation thus reducing immediate postoperative bleeding.

The key outcomes used to evaluate the efficacy of a technique for controlled hypotension are the estimated intraoperative blood loss and need for blood transfusion [33]. In the present work, intraoperative blood loss and blood transfusion requirement were significantly lower in DEX group than in SNP group. The efficacy of dexmedetomidine in providing better surgical field and less blood loss during controlled hypotension was previously reported in adult [14–16]. In consistency with our results, Hersey et al. [34] noted significant increase in blood loss in patients who received SNP compared to those who received nicardipinie for controlled hypotension during spinal fusion surgery for idiopathic scoliosis.

Blood loss in scoliosis is highly dependent on the degree of venous congestion. Sodium nitroprusside is a peripheral vasodilator agent with pronounced venous effect, dilatation of the venous plexus around the vertebral bodies may have contributed to increased blood loss when SNP used for controlled hypotension during scoliosis surgery [33]. The relationship between venous congestion and blood loss had been previously reported by Relton and Hall [35]. As the target MAP (60–65 mmHg) was achieved in both groups of the present study, it is conceivable that some degree of venous congestion occurred in the SNP group resulted in increased blood loss.

There are controversies whether MAP or CO determined blood loss during induced hypotensive anesthesia. Knight et al. [36] noted that; for scoliosis surgery, blood loss correlated with ventricular stroke work index calculated from SVR, CO and HR. However, Sivarajan et al. [37] when used SNP for controlled hypotension found that despite significant increase in CO and HR there was no significant increase in blood loss. In spite of the benefits of maintaining a constant CI in pediatric age group yet it may have contributed to increased blood loss in SNP group compared with that in DEX group in the present study.

Although the organic nitrate vasodilators inhibit platelet function via production of nitric oxide [38], it is unclear whether this is a contributing factor in the increased blood loss for SNP group in this study.

The prolonged postoperative analgesia demonstrated in DEX group in the present study is in accordance with Gurbet et al. [39] who stated that intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirement.

In conclusion, this study showed that dexmedetomidine is an effective and safe agent for controlled hypotension in adolescents undergoing spinal fusion surgery for idiopathic scoliosis. Compared with sodium nitroprusside, it offers the advantage of reduced blood loss. In addition, it posses inherent anesthetic and analgesic effect.

Further studies are required to evaluate the intraoperative analgesic effect of dexmedetomidine during scoliosis surgery.

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