

The efficacy and hemodynamic response to Dexmedetomidine as a hypotensive agent in posterior fixation surgery following traumatic spine injury

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Abstract

Aim: This study was designed to evaluate the efficacy of dexmedetomidine (DEX) as a hypotensive agent in comparison to nitroglycerin (NTG) in posterior fixation surgery for traumatic spine injury.

Materials and Methods: Forty patients ASA I or II aged 18-65 years scheduled for posterior fixation surgery were randomly assigned to receive either DEX 1 µg/kg over 10 min before induction of anesthesia followed by 0.2-0.7 µg/kg/h infusion during maintenance in DEX group or NTG 3-5 µg/kg/min infusion after induction of anesthesia in NTG group to maintain mean arterial blood pressure (MAP) between 65 and 70 mmHg. The two groups were compared for achievement of target MAP, intraoperative blood loss, and reversibility of hypotensive state. Student's *t*-test was used for continuous variables and chi-square test for categorical variables. *P*-value < 0.05 was considered significant.

Results: Patients in DEX group achieved the target MAP with better heart rate (HR) control, as compared to NTG group during the period of observation. The blood loss was significantly lesser in the DEX group (422.11 ± 149.34 ml) than the NTG group (564.51 ± 160.88 ml), *P* = 0.01. The time to hypotension reversal in NTG group (5.63 ± 1.93 min) was lesser compared to DEX group (9.15 ± 2.16 min), *P* = 0.65.

Conclusion: DEX is an effective and safe agent in achieving controlled hypotension in adults undergoing posterior fixation spine surgery.

Key words: α₂-agonist, controlled hypotension, dexmedetomidine, spine surgery

Introduction

Spinal surgeries, during its inception and early days, for traumatic spine fractures were infamous for the tremendous blood losses during the course of surgery. This could result in severe patient complications during and after surgery and also make the surgical visualization in blood filled field difficult. With the advent of newer anesthetic agents, drugs,

and monitoring techniques; this problem has been addressed. Controlled hypotension is a commonly used technique to limit blood loss and improve visualization of the operative field during spinal fusion surgery.^[1,2]

Many anesthetics and vasoactive drugs have been used successfully to produce deliberate hypotension, including volatile anesthetics, direct-acting vasodilators, autonomic ganglion-blockers, β-adrenergic receptor blockers, α-adrenergic blocking agents, prostaglandin E₁, and calcium channel blockers. Drugs used to produce controlled hypotension must be easy to administer, have a short onset time, a quick offset time on discontinuation, a rapid elimination without toxic metabolites, negligible effects on vital organs, and a predictable and dose-dependent effects.^[3]

Nitroglycerin (NTG) a directly acting vasodilator has been used to achieve induced hypotension because of its rapid onset, rapid offset, and titrability. However, it causes reflex tachycardia and venous congestion in and around the surgical site hence causing increased blood loss.^[4]

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Dexmedetomidine (DEX) is a potent and highly selective α_2 -adrenergic agonist, with a differential affinity for the $\alpha_2:\alpha_1$ receptors in a ratio 1,620:1. It is a sedative, analgesic, and possesses anesthetic sparing effect and sympatholytic properties too. The central and peripheral sympatholytic action of DEX by binding to α_2 adrenergic receptors brings about dose-dependent decrease in mean arterial blood pressure (MAP), heart rate (HR), cardiac output, and norepinephrine release.^{15,61}

Despite several clinical trials that studied the effectiveness of DEX in reducing intraoperative bleeding in adults, little is known about its effect as a sole hypotensive agent in posterior fixation surgery for spine injuries. This prospective, randomized study was done to compare the efficacy and safety of DEX versus NTG as a hypotensive agent in adult patients undergoing posterior fixation for traumatic spine fractures.

Materials and Methods

After obtaining ethical committee approval from institutional ethics committee, 40 patients aged between 18 and 65 years who were candidates for posterior fixation surgery after traumatic spine fractures were included in the study after obtaining written informed consent. The patients were randomized into two groups using the equal group random allocation method, that is, DEX and NTG groups. Patients who had respiratory or cardiac dysfunction, renal insufficiency, liver impairment, or bleeding disorders were excluded from the study. Patients were prepared by securing two 18 gauge intravenous (IV) cannulae, applying basic monitoring like plethysmography, standard 5-lead electrocardiography (ECG), noninvasive blood pressure (Datex-Ohmeda Avance S/5 Anesthesia Workstation™, GE Healthcare, Helsinki, Finland). Patients in the DEX group received 1 $\mu\text{g}/\text{kg}$ infusion (diluted in 50 ml of 0.9% normal saline) over a period of 10 min before premedication.

After premedication with injection ondansetron 4 mg IV, injection glycopyrrolate 0.2 mg IV, injection midazolam 0.05 mg/kg and injection fentanyl 2 $\mu\text{g}/\text{kg}$ in both the groups, anesthesia induction was done with injection thiopentone sodium 5 mg/kg. Tracheal intubation was facilitated by injection vecuronium bromide 0.1 mg/kg. The temperature and end tidal carbon dioxide (ETCO₂) monitors applied. The patients were positioned prone on a Relton's frame. We had taken necessary precautions to protect pressure points and avoid nerve injury and limb ischemia. Patients in the DEX group patients received a continuous infusion of DEX at 0.2-0.7 $\mu\text{g}/\text{kg}/\text{h}$, whereas patients in the NTG group were infused a NTG drip (0.01%) at 3-5 $\mu\text{g}/\text{kg}/\text{min}$ after

positioning. Both the continuous infusions were titrated to achieve the target MAP of 65-70 mmHg prior to skin incision.

Anesthesia was maintained with isoflurane (Tec 7 vaporizer) and O₂:N₂O (50:50). Isoflurane was kept constant at 1% concentration throughout the period of observation (60 min postinduction). Adequate muscle relaxation was achieved with incremental doses of injection vecuronium bromide. Normocapnia, normothermia, and normovolemia were maintained throughout the surgery. The anesthesiologist was given the option of titrating the isoflurane concentration according to hemodynamic variables after 60 min of observation.

The same surgical team was chosen for each surgery to ensure consistency of surgical technique. The hematocrit value was obtained for each patient prior to induction and at 60th min post-induction to calculate blood loss. Patients who had more than 15% fall in hematocrit were transfused with blood components as required.

The maximum infusion rate in the DEX group was 0.7 $\mu\text{g}/\text{kg}/\text{h}$ and in the NTG group was 10 $\mu\text{g}/\text{kg}/\text{min}$. Patients who reached the maximum dose without attaining the target MAP were given added therapy with intravenous metoprolol.

During the induced hypotension phase, reflex tachycardia was defined as a persistent increase in HR of more than 120 beats per minute (bpm) for a period of 10 min or more. This was treated by injection esmolol 0.5 mg/kg. Bradycardia (HR < 60 bpm) was treated with injection atropine 0.6 mg IV. Hypotension, defined as MAP < 65 mmHg after stoppage of hypotensive agent for 12 min in the DEX group and 5 min in the NTG group, was treated with injection ephedrine 10 mg intravenously.

The hypotensive infusions were stopped immediately after successful placement of the implants and the time to reversibility of the hypotensive state was recorded which was defined as time taken to restoration of MAP to that of the baseline after stopping of hypotensive agent.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, ECG, temperature, plethysmography (SPO₂), ETCO₂, HR, and urine output were measured at the following time points: Baseline (T_b); at the start of the hypotensive agent (T_s); immediately after intubation (T_i); 15 (T₁₅), 30 (T₃₀), 45 (T₄₅), 60 (T₆₀), 75 (T₇₅), 90 (T₉₀), 105 (T₁₀₅), and 120 (T₁₂₀) min after induction; at the point of stoppage of administration of hypotensive agent T_t; and at extubation T_e.

A sample size of 20 patients per group was needed to detect an intergroup difference of at least 10% in blood pressure and HR with a power of 0.80 and a of 0.05. Statistical analysis was done using the Epi Info (version 3.5.3 CDC Atlanta 2011 for Windows) software. Numerical data is expressed as mean \pm standard deviation (SD). Student's *t*-test was used for normally distributed data. Nonparametric Kruskal-Wallis test was used for variables not normally distributed. For categorical data chi-square test was used. A *P*-value < 0.05 was considered as statistically significant.

Results

A total of 40 patients were included for statistical analysis. The two groups were similar with respect to age, sex, weight, and ASA physical status. Duration of anesthesia was comparable between both the groups. Baseline hemodynamic parameters that include HR, MAP and preoperative hematocrit were similar in the two groups [Table 1].

All patients in the DEX group achieved and maintained the target MAP during the period of observation. But in the NTG group all patients except two achieved the target MAP and these two patients required added therapy to maintain the target MAP. It was also observed that the mean HR in the NTG group was significantly higher compared to the DEX group at all time points during period of observation. The NTG group showed a mean rise in HR by 28.46% from baseline values during the period of observation as compared to the DEX group which showed a mean fall in HR by 21.7% [Figure 1].

The blood loss was significantly lesser ($P < 0.05$) in the DEX group (422.11 ± 149.34 ml) than the NTG group (564.51 ± 160.88 ml) during the period of observation [Table 2].

Four patients in the NTG group required blood transfusion, while none of the patients in the DEX group required blood transfusion. At the end of our observation period, we decided to transfuse packed cells when patients' blood loss level was 15% or more of his or her blood volume.

Time to reversibility of the hypotensive state was lesser in the NTG group when compared to the DEX group. The mean time to reversal of the hypotensive state was 5.63 ± 1.93 min in the NTG group ($n = 16$) and 9.15 ± 2.16 min in the DEX group ($n = 20$); $P = 0.65$ [Table 2].

It was also observed that at the time of extubation, the DEX group (HR = 92.5 ± 11.8076 bpm, MAP = 89.33 ± 8.08941 mmHg) maintained

Table 1: Demographic data were comparable among the two groups

	Test (n = 20)	Control (n = 20)	P-value
Age (in years)	38.3 \pm 8.21	38.75 \pm 9.82	0.92
Sex (male/female)	12/8	13/7	0.8
Weight (in kg)	64.85 \pm 8.12	65.75 \pm 9.11	0.88
Duration of surgery (min)	134.15 \pm 12.32	134.20 \pm 11.87	0.98

Table 2: Results showed a significantly lesser blood loss in the dexmedetomidine (DEX) group. The time to reversibility of hypotensive state was lesser in the nitroglycerin (NTG) group but statistically insignificant

Parameter	DEX	NTG	P-value
Blood loss (ml)	422.11 \pm 149.34	564.51 \pm 160.88	0.01
Reversibility of hypotensive state (min)	9.15 \pm 2.16	5.63 \pm 1.93	0.65

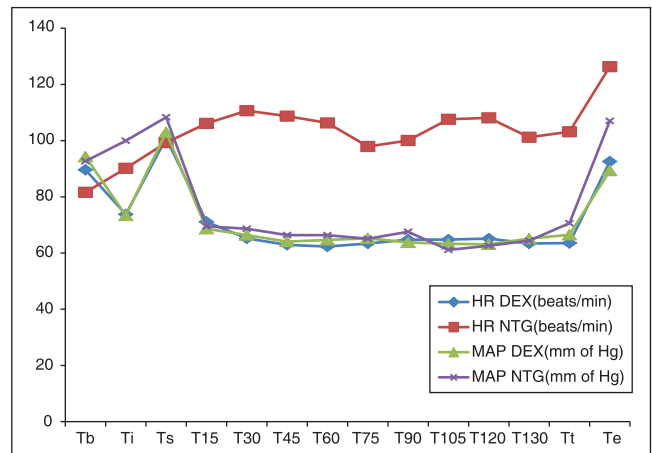


Figure 1: Mean arterial blood pressure (MAP) and heart rate (HR). Patients in dexmedetomidine (DEX) and nitroglycerin (NTG) groups achieved the target MAP. NTG group demonstrates a significantly higher HR during steady state hypotension. All the values depicted are means at the corresponding time points

a significantly superior hemodynamic profile than the NTG group (HR = 126.3 ± 10.4433 bpm, MAP = 107 ± 3.77124 mmHg); $P < 0.05$ [Figure 1].

Three patients in the DEX group experienced bradycardia between the 80th and 110th min of surgery, which was successfully treated with injection atropine. None of the patients in NTG group had bradycardia. None of the patients in the NTG and DEX groups had uncontrolled hypotension.

Discussion

The major observation in our study was that DEX was successfully used to achieve induced hypotension while exhibiting the desired hemodynamic profile. The efficacy of

the hypotensive technique was indicated with the estimation of intraoperative blood loss. Decreased blood loss in the DEX group indicates that the desired hypotension was effectively achieved.

Hypotensive anesthesia was successfully used in traumatic spine fractures by Ullrich *et al.*, to reduce blood loss during posttraumatic spinal surgeries.^[7] It was deemed to be a safe and effective technique. In our study, the patients had spine fractures ranging from T10 to L5 and were operated upon within 48-72 h after trauma.

Though DEX is approved by the United States Food and Drug Administration only for sedation of intubated patients being mechanically ventilated in an intensive care unit and procedural sedation of nonintubated patients, the efficacy of DEX in controlled hypotension has previously been reported in adults in maxillofacial and ear surgeries by Durmus *et al.*, and Richa *et al.*, respectively.^[8,9] Consistent with their observations, our study showed that DEX can be effectively used to bring about controlled hypotension in posterior fixation spine surgeries. We demonstrated a 19.78% reduction in MAP in the DEX group similar to that achieved by Richa *et al.*^[9]

In our study, intraoperative blood loss and blood transfusion requirement were significantly lower in DEX group than in NTG group. Researchers in a study showed that the blood loss calculated using the modified Gross' formula is accurate, which we have adopted in our study.^[10] The efficacy of DEX in providing better surgical field and less blood loss during controlled hypotension was previously reported in adults.^[8,9] Contrary to Durmus *et al.*, and Richa *et al.*, who used a subjective scale to assess the efficacy of controlled hypotension, we have used an objective parameter, thus eliminating bias.

MAP was chosen as a parameter to quantify hypotension as it is the true measure of tissue perfusion.^[11] We adopted a conservative approach in terms of limiting the target MAP to 65-70 mm of Hg so as to minimize the risk of compromising the perfusion of spinal cord tissue resulting in neurological deficit. Chiesa *et al.*, showed that a perioperative hypotension with MAP < 70 mmHg was a risk factor for developing spinal cord ischemia.^[12]

NTG produces its hypotensive action by liberating nitric oxide (NO) which has a half-life of 0.1 s. DEX acts by selectively binding to α_2 receptors with great affinity.^[13,14] This could explain the higher time to restoration of baseline MAP in the DEX group compared to the NTG group even after the hypotensive drugs are stopped. The hypotension in DEX group can be reverted only when the drug diffused out of its

receptors. This is probably the reason for the hemodynamic stability observed during extubation in the DEX group in our study.

The favorable hemodynamic profile induced by DEX can be attributed to the well-established sympatholytic effects of α_2 -agonists.^[5] The α_2 -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.^[15] At lower doses, DEX is predominantly sympatholytic. DEX, on binding to α_2 receptors, reduces the sympathetic outflow and an augmented cardiac vagal activity resulting in decreased HR and cardiac output.^[16] Patients in the NTG group would have achieved the target MAP as NTG acts by liberating nitrite ions which get converted to nitric oxide which activates guanylyl cyclase to eventually cause vascular smooth muscle relaxation. This reduction in smooth muscle tone is more pronounced in the venous system, causing a decreased venous return to the heart and therefore reducing the stroke volume and hence reducing the cardiac output.^[4,17] NTG infusion causes activation of the renin-angiotensin system. This may be the cause for tachycardia in the patients in NTG group. NTG is also known to cause reflex tachycardia.^[18,19] Blood loss in spinal surgery is highly dependent on the degree of venous congestion around the vertebral bodies.^[2,20] NTG 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 NTG was used for controlled hypotension. The relationship between venous congestion and blood loss has already been demonstrated by Relton and Hall.^[20] As the target MAP (65-70 mmHg) was achieved in both groups of the present study, it is conceivable that some degree of venous congestion occurred in the NTG group, that resulted in increased blood loss. Although the organic nitrate vasodilators like NTG inhibit platelet function via production of nitric oxide, it is unclear whether this is a contributing factor in the increased blood loss in the NTG group in our study.^[21]

Cardiac output monitoring coupled with intra-arterial MAP recordings would have given a better understanding of the factors governing the blood loss and controlled hypotension. Transesophageal echocardiography could give us an accurate measurement of left ventricular end diastolic volume and cardiac output in real time.^[22] These parameters could not be assessed due to limited resources in our institute.

Thus the findings of our study conclude that a continuous infusion of DEX is an effective and safe method of producing controlled hypotension in posterior fixation spine surgeries

by achieving the target MAP, minimizing blood loss, and maintaining superior hemodynamics as compared to NTG.

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