Dexmedetomidine Attenuates Hemodynamic and Proinflammatory Responses During Craniotomy for Traumatic Brain Injury: A Randomized Controlled Trial Study

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Abstract

Trauma to the brain not only directly injures cerebral tissues, but also results in secondary damage. Neuroanesthesia should not only provide optimal conditions during surgery and ensure stable cerebral hemodynamics, but also attenuate proinflammatory reactions. Dexmedetomidine is a powerful α2-agonist that has been shown to be neuroprotective in animal models of stroke. In this work 70 patients with craniocerebral trauma were randomized into 2 groups with each 35 cases. We tested the effect of dexmedetomidine on hemodynamic response and serum inflammatory markers when administered perioperatively. Our results show that dexmedetomidine attenuated the hemodynamic responses to tracheal intubation and surgical stimulation, the MAP in patients with dexmedetomidine was maintained between 90 mmHg to 100 mmHg, and the HR was kept at lower than 80 bpm during the operation. However, in the control group, both the BP and HR showed a significant increase at the time of intubation and skin scission. Dexmedetomidine attenuate immune reaction during operation. The plasma concentrations of TNFα, IL6 and neuron specific enolase (NSE) was significantly lower than control group ($P < 0.001$). In conclusion, dexmedetomidine in craniotomy not only attenuated hemodynamic responses in the surgical operation, but also depressed neuroinflammation in patients with TBI without serious adverse effects.

Trial registration: Chinese Clinical Trial Registry (ChiCTR), ChiCTR2000029501,28 Jan 2020□Retrospectively registered□http://www.chictr.org.cn

Introduction

Trauma to the brain not only directly injures cerebral tissues but also results in secondary damage due to conditions such as ischemia, cerebral hypoxia, cerebral edema (swelling of the brain), and an imbalance of neurotransmitters that lead to excitotoxicity and inflammatory reactions in the brain [1]. Therefore, neuroanesthesia should not only provide optimal conditions during surgery and ensure stable cerebral hemodynamics without sudden increases in intracranial pressure, but also attenuate or inhibit inflammatory reactions [2]. Inflammatory responses after acute traumatic brain injury (TBI) involve the activation of astrocytes and microglia, production of local cytokines, and recruitment and infiltration of inflammatory cells. These responses may contribute to neuronal injury and cell death. In particular, interleukin (IL)1β and IL6, and tumor necrosis factor (TNF)α are involved in acute inflammatory responses and may significantly contribute to secondary damage. In both patient and animal models of TBI, various pharmacological agents that are capable of attenuating proinflammatoy cytokine responses have been shown to improve histological and functional outcomes [3, 4].

Clonidine is an antihypertensive agent that reduces sympathetic outflow by stimulating α2-adrenergic receptors. These receptors are distributed widely within and outside the central nervous system, mostly in the pons and medulla, and regulate the transmission of the impulses from the sympathetic nervous system from the higher centers to the periphery. Activation of the presynaptic α2-receptors inhibits the release of norepinephrine. In contrast, stimulation of the postsynaptic α2-adrenoceptors situated in the

dorsal horn and the vascular smooth muscle prevents nociceptive signal transmission and causes vasoconstriction, respectively [5]. Stimulation of α2-receptors by clonidine in the central nervous system results in sedation; thus, clonidine is widely used as an adjunct to anesthesia and analgesia [6]. Clonidine reduces sympathetic tone and the release of norepinephrine from nerve terminals [7]. During general anesthesia, clonidine enhances intraoperative circulatory stability by reducing catecholamine levels [8]. Therefore, the use of clonidine during surgery has been proposed to improve hemodynamics, to decrease both the intracranial pressure as well as anesthetic requirements.

Dexmedetomidine is a newer, centrally acting α2 agonist with a more selective action on the α2-adrenoceptors and a shorter half-life than that of clonidine. It exerts neuroprotective effects in animal models of stroke. In addition to its sedative effects, dexmedetomidine has been shown to exert analgesic effects, demonstrating its efficacy as an adjunct to anesthesia [9]. It is well known that dexmedetomidine provides hemodynamic stability by suppressing sympathetic nervous system activity. In a retrospective clinical study, Aryan et al. [10] described an increase in the mean cerebral perfusion pressure and a decrease in intracranial pressure. Based on an *in vivo* study, Paris [11] indicated that dexmedetomidine could exert long-term effects on the brain, including neuroprotection against excitotoxic damage through α2 adrenergic receptors. In an *in vitro* study, Degos [12] showed that dexmedetomidine increased the astrocyte expression of brain-derived neurotrophic factor through an extracellular signal-regulated kinase-dependent pathway, subsequently inducing neuroprotective effects. Additionally, dexmedetomidine has been reported to reduce endotoxin induced systemic inflammatory responses and acute organ injuries in septic rats and critically ill patients with sepsis.

To test the effect of dexmedetomidine on hemodynamic changes and inflammatory responses in patients with TBI undergoing craniotomy, we monitored the hemodynamic parameter during surgery, measured the serum concentrations of pro-inflammatory cytokines and serum neuron-specific enolase (NSE), and statistically analyzed the prognosis of patients after surgery.

Materials And Methods

The study was approved by the Handan Center Hospital Research Ethics Committee (Ref. No. 2010-01-15-02). Written informed consent was obtained from patients and/or their immediate family members who had the required authorization letter. Eighty-six ASA status I-IV adult patients (18–70 years old), between Feb 2010 and Nov 2012, with craniocerebral trauma who required craniotomy within the next 24 h in Handan Center Hospital were enrolled in the study. Patients with multiple organ injury, spinal cord injury, heart disease, hepatic disease, kidney disease, dysrhythmia, mean arterial blood pressure (MAP) lower than 60 mm Hg, and those allergic to the study drugs were excluded from the study. No pregnant or lactating women were included in the study.

Sixteen patients were excluded from the study (Fig. 1). Using a random number table, 70 patients were randomized into two groups, with 35 patients per group. Patients were premedicated with 0.5 mg intramuscular injection of atropine and 15 mg dexamethasone, infused intravenously 30 min prior to

surgery. Upon arrival at the operating room, the heart rate (HR), invasive radial artery blood pressure (BP), and peripheral oxygen saturation (SpO2) were continuously monitored. Lactated Ringer's solution (10 mL/kg) was infused intravenously over 10 min before the initiation of anesthesia. Ten minutes before the induction of anesthesia, the patients in the study group (Group D) received 1 μg/kg of dexmedetomidine intravenously as a bolus, which was delivered over 10 min, followed by a maintenance dose of 0.4 μg/kg/h until the end of the surgery. Group C served as a control and the patients received a volume of saline that was similar to that of the drugs injected in the study group.

After 3 min of pre-oxygenation with 100% oxygen, anesthesia was induced using 2 μg/kg fentanyl and 1.5 mg/kg propofol. Cisatracurium at a dose of 0.15 mg/kg was used as a muscle relaxant to facilitate tracheal intubation. Patients were mechanically ventilated until tracheal extubation. Anesthesia was maintained with continuous infusion of propofol (5–10 mg/kg) and remifentanil (1–2 μg/kg). Bradycardia was defined as a HR lower than 60 bpm; if the heart rate was lower than 45 bpm, atropine (0.3–0.5 mg) was intravenously administered. If the systolic BP was 90 mmHg or when the decrease from baseline MAP was more than 30%, dopamine was administered. Relaxation was maintained with continuous infusion of cisatracurium at a rate of 0.25–0.5 mg/kg/h.

Venous blood samples were drawn before the induction of anesthesia (baseline, T1), 2 h after the beginning of the surgery (T2), after skin closure (T3), and at 24 h after surgery (T4). Blood samples were centrifuged at 350 × *g* for 15 min after 30 min at room temperature, and the serum was stored in 2-mL aliquots at − 80 °C until used to measure the concentrations of NSE, IL6, and TNFα using ELISA kits. NSE ELISA kits were purchased from Tianjin Haoyang Biological Products Technology Co., Ltd (Tianjin, China); IL6 and TNFα ELISA Kits were purchased from Wuhan BOSTER Biological Technology Co. Ltd. (Wuhan, Hubei, China).

Outcomes

Primary outcome

The primary outcome measure was inflammatory reaction and cerebral injury. Inflammatory responses in acute TBI involve the activation of astrocytes and microglia, local cytokine production, and recruitment and infiltration of inflammatory cells. IL6 and TNFα are involved in acute inflammatory responses and may significantly contribute to secondary damage. In this study, the inflammatory responses in acute TBI were assessed by measuring serum IL6 and TNFα levels. Cerebral injury was assessed by measuring the elevation in blood-NSE concentration. NSE is the only biomarker that can be directly used to assess functional damage to neurons.

Secondary outcomes

1. Circulatory stability. Neuroanesthesia should ensure stable cerebral hemodynamics without sudden increases in intracranial pressure or causing acute inflammation in the brain during surgery. MAP

and HR were monitored, and the hemodynamic responses to tracheal intubation and skin incision were recorded to determine whether dexmedetomidine could stabilize circulatory function.
2. Adverse effect. The main adverse effect of dexmedetomidine is a reduction of the HR. The safety of dexmedetomidine was assessed based on the incidence of bradycardia and hypotension during surgery; specifically, if there was the occurrence of atropine-resistant bradycardia.
3. Anesthesia control. In this study, dexmedetomidine was used as an adjuvant to general anesthesia. As the patients underwent cranial surgery, the depth of anesthesia could only be assessed based on the BP and HR, but not by using the bispectral index. The dosages of propofol and remifentanil were adjusted based on the MAP and HR during surgery. And intraoperative awareness was observed.

Statistical analysis

SPSS 21.0 was used for statistical analyses. Two-way repeated measures ANOVA was used to evaluate the interaction effects (time*group). The effect of groups was tested using one-way repeated measures ANOVA. The effect of time was analyzed using single factor repeated measurement variance analysis (MANOVA); normally distributed measurement data are presented as mean ± SD. The enumerationcounting data were analyzed using the χ^2 (chi-square) test. A *p* value less than 0.05 was considered to represent a statistically significant difference. Please see supplementary material (Table 3 supp.docx and Table 4 supp.docx) for detail information about statistical analysis.

Results

As shown in Fig. 1, 16 patients were excluded and 70 were included in the study. As shown in Table 1, no significant differences in the clinical and demographic characteristics were found between the groups. Low SpO2 was not observed in either group and no intraoperative awareness occurred. The incidence of bradycardia and hypotension were not significantly different between the two groups (Table 2) and no atropine-resistant bradycardia occurred. During surgery, transient low BP was observed in both groups, but no dopamine-resistant hypotension developed. The doses of dopamine and atropine showed no significant difference between the two groups (Table 2).

Dexmedetomidine attenuated hemodynamic responses to tracheal intubation and surgical stimulation. As shown in Table 3, the MAP in Group D was maintained between 90 and 100 mmHg, and the HR was maintained at < 80 bpm during surgery. However, in the control group, both BP and HR showed a significant increase at the time of intubation and skin incision.

As shown in Table 4, craniotomy resulted in high serum levels of NSE, TNFα, and IL6 in both groups, and the concentrations of the cytokines after tracheal intubation were significantly higher than those at baseline. The addition of dexmedetomidine effectively inhibited the secretion of pro-inflammatory cytokines. The serum concentrations of TNFα, IL6, and NSE in Group D were significantly lower than those in the control group.

Discussion

It is well known that dexmedetomidine provides hemodynamic stability by suppressing sympathetic nervous system activity. We aimed to evaluate the efficacy of dexmedetomidine as an adjuvant to general anesthesia during decompressive craniectomies in patients with TBI. Our results showed that this α2-adrenoreceptor agonist could not only benefit patients by maintaining hemodynamic stability, but also by reducing NSE, IL6, and TNFα levels during surgery.

The gold standard of neuroanesthesia includes the maintenance of anesthesia using isoflurane or propofol with fentanyl [13]. However, a combination of these drugs was not sufficient to inhibit stress responses to surgical stimulation, as shown in Table 3. intubation and skin incision elicited significant increases in arterial pressure and HR. It is known that an increase in BP may increase intracranial pressure and cause secondary damage in patients who have undergone craniocerebral trauma. To improve hemodynamic control, clonidine and dexmedetomidine have been used as anesthetic adjuvants in neurosurgery [14, 15]. Jan [16] and Wu [17] have reported that the addition of dexmedetomidine improved hemodynamic control in patients undergoing surgeries for the removal of intracranial tumors. Tang et al. [18] have reported that dexmedetomidine protects patients from secondary brain injury by preventing paroxysmal sympathetic hyperactivity. Our previous study and a few other studies have shown that premedication with dexmedetomidine can significantly reduce the levels of endogenous epinephrine and norepinephrine [19–21]. We found that dexmedetomidine significantly improved hemodynamic control in patients with craniocerebral trauma undergoing intubation and decompressive craniectomy.

Trauma to the brain not only directly injures cerebral tissues but also results in the rupture of the blood–brain barrier (BBB). This leads to the accumulation of leukocytes from the systemic circulation, which can release pro-inflammatory cytokines, cytotoxic proteases, and reactive oxygen species and, in turn, initiate the immune functions of the native glia. This phase of nonmechanical injury is progressive and can last from hours to days [3], significantly contributing to neurological disabilities. Dexmedetomidine is able to inhibit immune reaction in TBI and has shown promising results in animal experiments. In 2017, Shen [22] reported that dexmedetomidine inhibited TNFα, IFNγ, IL1β, and IL6 secretion by activating the PI3K/Akt/mTOR signaling pathway in rats suffering from TBI. In 2018, Wang [23] reported that dexmedetomidine attenuated early neurological dysfunction, reduced neutrophil infiltration, decreased microglial activation, decreased pro-inflammatory mediator secretion, and attenuated TBI-induced BBB damage and cellular apoptosis.

Consistent with the findings in previous studies, our results indicated that patients who underwent TBI in this study exhibited high serum levels of IL6, TNFα, and NSE. The surgery resulted in a further increase in the levels of these markers, even in patients receiving the “gold standard” of neuroanesthesia with propofol and remifentanil. However, the use of dexmedetomidine attenuated this enhancement. The end result indicated that the addition of dexmedetomidine improved the GCS score after surgery.

Dexmedetomidine has been reported to increase the risk of hypotension and bradycardia. These effects are often observed in healthy, young volunteers or after the rapid administration of a bolus dose [24–26].

In this work, there were no differences between the groups in the occurrence of bradycardia or hypotension. In these two groups, some patients received dopamine or atropine to prevent hypotension and bradycardia; however, the incidence of bradycardia or hypotension and the dose of the dopamine or atropine showed no significant difference between the two groups. No incidents of refractory hypotension or bradycardia were observed during surgery. Moreover, as dexmedetomidine does not cause respiratory depression, it did not prolong the tracheal extubation time in this study.

Limitation: This work was done 8 years ago, we did not published it promptly, this is one of limitation of our work, but our result is supported by recent animal experimental work reported by others. As the patients underwent cranial surgery, the depth of anesthesia was assessed based on the BP and HR, but not by using the bispectral index, this is another limitation of this work. Nevertheless the blood pressure and heart rate were controlled at a receivable level during operation and no intraoperative awareness was observed in either group, and our data demonstrated that addition of dexmedetomidine attenuated hemodynamic response to surgical stimulation.

In conclusion, dexmedetomidine, as an anesthetic adjuvant in decompressive craniectomies, not only attenuated the hemodynamic responses during surgery, but also alleviated neuroinflammation in patients with severe TBI, improving their conscious state after surgery without resulting in serious adverse effects.

Declarations

Ethics approval and consent to participate

The study was approved by the Handan Center Hospital Research Ethics Committee (Ref. No. 2010-01-15-02). Written informed consent was obtained from patients and/or their immediate family members who had the required authorization letter.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author (Yongxue Chen) on reasonable request.

Competing interests

The authors declare no competing financial interests.

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Authors' contributions

Yongxue Chen: conceived, designed and coordinated the study, and contributed to drafting the manuscript. Junde Hou, Hongfang Wei, Xiaowei Wang, Xiaohui Chi, Guangping Zhao: review the literature, and clinic anesthesia. Yanxing Cheng: statistic analysis, Senming Zhao: design the study and drafting the manuscript

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References

1. Yasir N, Jassam S, Izzy M, Whalen DB, McGavern. Joseph El Khoury. Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift. Neuron. 2017;95:1246–65. DOI:10.1016/j.neuron.2017.07.010.
2. Dennis W, Simon M, McGeachy H, Bayır, Robert SB, Clark DJ, Loane PM. Kochanek. Neuroinflammation in the Evolution of Secondary Injury, Repair, and Chronic Neurodegeneration after Traumatic Brain Injury. Nat Rev Neurol. 2017;13:171–91. DOI:10.1038/nrneurol.2017.13.
3. Si Yun Ng, Alan Yiu Wah Lee. Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. Front Cell Neurosci. 2019;13:528. DOI:10.3389/fncel.2019.00528.
4. Pan Z, Zhao Y, Huang W, Xiao Z, Li Z. Effect of progesterone administration on the prognosis of patients with severe traumatic brain injury: a meta-analysis of randomized clinical trials. Drug Des Devel Ther. 2019;13:265–73. DOI:10.2147/DDDT.S192633.
5. Kamibayashi T, Maze M. Clinical uses of alpha2 –adrenergic agonists. Anesthesiology. 2000;93:1345–9. DOI:10.1097/00000542-200011000-00030.
6. Costello T, Cormack J. Clonidine premedication decreases hemodynamic responses to pin head-holder application during craniotomy. Anesth Analg. 1998;86:1001–4. DOI:10.1097/00000539-199805000-00017.

7. Kim M, Hahn T. The effect of clonidine pretreatment on the perioperative proinflammatory cytokines, cortisol, and ACTH responses in patients undergoing total abdominal hysterectomy. Anesth Analg. 2000;90:1441–4. DOI:10.1097/00000539-200006000-00035.
8. Sanchez Munoz MC, De Kock M, Forget P. What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials. J Clin Anesth. 2017;38:140–53. DOI:10.1016/j.jclinane.2017.02.003.
9. Farag E, Kot M, Podolyak A, Argalious M, Deogaonkar M, Mascha EJ, et al. The relative effects of dexmedetomidine and propofol on cerebral blood flow velocity and regional brain oxygenation: A randomised noninferiority trial. Eur J Anaesthesiol. 2017;34:732–9. DOI:10.1097/EJA.0000000000000662.
10. Aryan H, Box K, Ibrahim D, Desiraju U, Ames C. Safety and efficacy of dexmedetomidine in neurosurgical patients. Brain Inj. 2006;20:791–8. DOI:10.1080/02699050600789447.
11. Paris A, Mantz J, Tonner P, Hein L, Brede M, Gressens P. The effects of dexmedetomidine on perinatal excitotoxic brain injury are mediated by the alpha2A-adrenoceptor subtype. Anesth Analg. 2006;102:456–61. DOI:10.1213/01.ane.0000194301.79118.e9.
12. Degos V, Charpentier T, Chhor V, Brissaud O, Lebon S, Schwendimann L, et al. Neuroprotective effects of dexmedetomidine against glutamate agonist-induced neuronal cell death are related to increased astrocyte brain-derived neurotrophic factor expression. Anesthesiology. 2013;118:1123–32. DOI:10.1097/ALN.0b013e318286cf36.
13. Todd M, Warner D, Sokoll M, Maktabi M, Hindman B, Scamman F, et al. A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/ nitrous oxide, and fentanyl/nitrous oxide. Anesthesiology. 1993;78:1005–20. DOI:10.1097/00000542-199306000-00002.
14. Jadhav N, Wasekar N, Wagaskar V, Kondwilkar B, Patil R. Use of Dexmedetomidine in Patients Undergoing Craniotomies. J Clin Diagn Res. 2017;11:UC01–8. DOI:10.7860/JCDR/2017/24002.9235.
15. Wang X, Ji J, Fen L, Wang A. Effects of dexmedetomidine on cerebral blood flow in critically ill patients with or without traumatic brain injury: a prospective controlled trial. Brain Inj. 2013;27:1617–22. DOI:10.3109/02699052.2013.831130.
16. Jan S, Ali Z, Nisar Y, Naqash I, Zahoor S, Langoo S, et al. A Comparison of Dexmedetomidine and Clonidine in Attenuating the Hemodynamic Responses at Various Surgical Stages in Patients Undergoing Elective Transnasal Transsphenoidal Resection of Pituitary Tumors. Anesth Essays Res. 2017;11:1079–83. DOI:10.4103/0259-1162.194575.
17. Wu H, Wang H, Jin J, Cui G, Zhou K, Chen Y, et al. Does dexmedetomidine as a neuraxial adjuvant facilitate better anesthesia and analgesia? A systematic review and meta-analysis. PLoS One. 2014;26:9:e93114. DOI:10.1371/journal.pone.0093114.
18. Tang Q, Wu X, Weng W, Li H, Feng J, Mao Q, et al. The preventive effect of dexmedetomidine on paroxysmal sympathetic hyperactivity in severe traumatic brain injury patients who have undergone

surgery: a retrospective study. Peer J. 2017;5:e2986. DOI: 10.7717/peerj.2986. eCollection 2017.

19. Myoung H, Kim KY, Lee SJ, Bae M, Jo, Jin S, Cho. Intraoperative dexmedetomidine attenuates stress responses in patients undergoing major spine surgery. Minerva Anestesiol. 2019;85:468–77. DOI:10.23736/S0375-9393.18.12992-0.
20. Li Y, Wang B, Zhang L, He S, Hu X, Wong G, et al. Dexmedetomidine Combined with General Anesthesia Provides Similar Intraoperative Stress Response Reduction When Compared with a Combined General and Epidural Anesthetic Technique. Anesth Analg. 2016;122:1202–10. DOI:10.1213/ANE.0000000000001165.
21. Zhen S, LI J, Jin M, Chen Y. Effect of dexmedetomidine-ketamine combined anesthesia on stress response in chest surgery patients. China J Clinicans (Electronic Edition). 2013;7:5091–2. DOI:10.3877/cma.j.issn.1674-0785.2013.11.072.
22. Shen M, Wang S, Wen X, Han X, Wang Y, Zhou X, et al. Dexmedetomidine exerts neuroprotective effect via the activation of the PI3K/Akt/mTOR signaling pathway in rats with traumatic brain injury. Biomed Pharmacother. 2017;95:885–93. DOI:10.1016/j.biopha.2017.08.125.
23. Wang D, Xu X, Wu YG, Lyu L, Zhou ZW, Zhang JN. Dexmedetomidine attenuates traumatic brain injury: action pathway and mechanisms. Neural Regen Res. 2018;13:819–26. DOI:10.4103/1673-5374.232529.
24. Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and peroperative fentanyl. Br J Anaesth. 1992;68:126–31. DOI:10.1093/bja/68.2.126.
25. Salmenperä M, Szlam F, Hug CC Jr. Anesthetic and hemodynamic interactions of dexmedetomidine and fentanyl in dogs. Anesthesiology. 1994;80:837–46. DOI: 10.1097/00000542-199404000-00017.
26. Meert T, De Kock M. Potentiation of the analgesic properties of fentanyl-like opioids with alpha 2-adrenoceptor agonists in rats. Anesthesiology. 1994;81:677–88. DOI:10.1097/00000542-199409000-00022.

Tables

Table 1
Clinical characteristics of patients (n = 35 for each group)

	Age (years)	Weight (kg)	Sex (M/F, %/%)	GCS	Type of craniocerebral trauma		
					Extradural hematoma	Subdural hematoma	Ventricular hemmorhage
Group C	41.0 ± 6.8	66.0 ± 6.8	24/11, 68/32	5.7 ± 1.1	14 (40%)	15 (43%)	6 (17%)
Group D	43.4 ± 6.2	66.7 ± 5.7	27/8, 77/23	5.8 ± 1.3	16 (46%)	12 (34%)	7 (20%)

Body weight is expressed as mean ± SD, and sex is shown as the ratio of the absolute number and the ratio of percentage. The type of craniocerebral trauma is presented as the absolute number and the percentage. Quantitative data were analyzed using the independent samples t-test, and enumeration data were analyzed using the chi-square test.

Table 2
The incidence of hypotension and bradycardia (n = 35 for each group)

	Hypotension	Bradycardia	Dopamine	Atropine
Group C	6 (17%)	7 (20%)	6 (17%)	3 (10%)
Group D	7 (20%)	5 (14%)	6 (17%)	1 (3%)

The incidence of hypotension and bradycardia and patients who received dopamine or atropine in the two groups were compared using the chi-square test. Data are presented as absolute values and percentages (in brackets). There was no significant difference between the two groups.

Table 3
MAP (mmHg) and HR (bpm) of patients (n = 35 for each group)

	Baseline	After induction	intubation	incision
MAP	104.2 ± 4.6	96.6 ± 4.3$^{\#}$	104.7 ± 4.0†	103.4 ± 4.2†
Group C				
Group D	102.8 ± 3.5	93.1 ± 3.6$^{*\#}$	96.8 ± 3.2$^{*\#}$	93.3 ± 3.3$^{*\#}$
HR	86.7 ± 6.3	84.2 ± 4.1	90.4 ± 5.8$^{\#\dagger}$	91.3 ± 5.3$^{\#\dagger}$
Group C				
Group D	88.1 ± 5.0	79.6 ± 2.8$^{*\#}$	77.1 ± 3.6$^{*\#\dagger}$	65.1 ± 3.8$^{*\#\dagger}$
group		$P < 0.001$		
time		$P < 0.001$		
time*group		$P < 0.001$		

The heart rate (HR) and invasive radial artery blood pressure (BP) before and during operation. Intra-group as well as inter-group comparison were done and data are expressed as mean ± SD. $^{*}p < 0.05$ *vs*. Group C; $^{\#}p < 0.05$ vs. baseline, $^{\dagger}p < 0.05$ vs. at induction. Please see supplemental material for absolute p value.

Table 4
Serum concentration of IL6, TNFα, and NSE (n = 35 for each group)

	Time			
	T1	T2	T3	T4
IL6 (ng/L)				
Group C	57.4 ± 5.7	72.8 ± 4.9$^{\#}$	82.4 ± 3.8$^{\#}$	60.2 ± 4.2$^{\#}$
Group D	58.8 ± 2.6	62.0 ± 5.7*	65.3 ± 4.4$^{*\#}$	52.9 ± 4.4$^{*\#}$
Time		F = 75.16	$p < 0.001$	
Group		F = 166.51	$p < 0.001$	
Time*group		F = 223.68	$p < 0.001$	
TNFα (ng/L)				
Group C	140.4 ± 7.1	153.8 ± 6.6$^{\#}$	169.1 ± 8.1$^{\#}$	120.3 ± 7.0$^{\#}$
Group D	141.1 ± 4.5	140.2 ± 4.2*	148.1 ± 4.6$^{*\#}$	112.8 ± 6.2$^{*\#}$
Time		F = 1721.4	$p < 0.001$	
Group		F = 81.82	$p < 0.001$	
Time*group		F = 110.68	$p < 0.001$	
NSE (μg/L)				
Group C	26.9 ± 2.5	39.1 ± 5.7$^{\#}$	40.7 ± 4.7$^{\#}$	29.8 ± 2.8
Group D	27.2 ± 2.5	30.6 ± 2.7$^{*\#}$	31.0 ± 2.6$^{*\#}$	21.5 ± 2.4$^{*\#}$
Time		F = 459.62	$p < 0.001$	
Group		F = 117.83	$p < 0.001$	
Time*group		F = 66.22	$p < 0.001$	

Serum concentration of IL6, NSE and TNF at different time intervals. Intra-group as well as inter-group comparison was done and data are expressed as mean ± SD.

* $p < 0.05$ *vs.* Group C; $^{\#}$ $p < 0.05$ vs. baseline. Please see supplementary material for absolute *p* value.