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Neuroprotective Effects of Intraoperative Dexmedetomidine Infusion Combined With Goal-directed Hemodynamic Therapy for Patients Undergoing Cranial Surgery: A Double-blinded Randomized Controlled Trial

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Abstract

Background

Despite dexmedetomidine may be neuroprotective in patients undergoing cranial surgery by inhibiting neuroinflammation; however, it reduces cardiac output and cerebral blood flow. We proposed that dexmedetomidine infusion combined with goal-directed hemodynamic therapy (GDHT) could improve cranial surgery neurological outcomes without hemodynamic perturbation.

Methods

A randomized, double-blind trial was conducted. One hundred sixty adult patients undergoing elective cranial surgery received either dexmedetomidine (0.5 μg kg^{-1} h^{-1}) or saline during surgery. The goal-directed hemodynamic therapy was used for stroke volume optimization. The proportion of patients who developed postoperative new neurological deficits was compared. The severities of new neurological deficit were assessed by using in-hospital Barthel index changes and the 30-day modified Rankin Scale (mRS). Postoperative delirium was identified using the Intensive Care Delirium Screening Checklist (ICSDC) criteria. The level of a perioperative serum neuroinflammatory mediator, high motility group box 1 protein (HMGB1), was compared.

Results

The dexmedetomidine group exhibited a lower cardiac index than did the control group (3.0 ± 0.8 vs. 3.4 ± 1.8 L min^{-1} m^{-2}; p = 0.0482) without lactate accumulation. Fewer patients in the dexmedetomidine group developed new postoperative deficits (26.3% versus 43.8%; p = 0.031) but numbers of patients remained symptomatic neurological deficit before discharge were comparable between the two groups (23.8% vs. 38.8%; p= 0.060). In addition, an attenuated Barthel index decline (−6.3 ± 20.4 vs. −13.6 ± 24.8; p = 0.043), a more favorable 30-day mRS profile (p = 0.013), and a higher incidence of postoperative delirium-free (ICDSC scored 0: 84.6% versus 64.2%; p = 0.012) were observed in the dexmedetomidine group. Furthermore, dexmedetomidine induced a significant decline in perioperative serum HMGB1 level (222.5 ± 408.3 vs. 152.2 ± 280.0 ng mL^{-1}; p = 0.0033).

Conclusions

Dexmedetomidine infusion combined with GDHT mitigates neuroinflammation during cranial surgery without hemodynamic perturbation, thus achieving neuroprotective effects.

Clinical Trial Registration

Prospectively registered at clinicaltrials.gov. (identifier NCT02878707, date of registration: August 25, 2016)

Introduction

Dexmedetomidine may have neuroprotective effects during cranial surgery. For instance, dexmedetomidine mitigates surgery-related neuroinflammatory cascade [1-3]. Numerous studies have revealed that dexmedetomidine inhibits potent initiators and amplifiers of neuroinflammation, namely high motility group box 1 protein (HMGB1), resulting in favorable neurological preservation in various neuronal injury models [2, 4]. In addition, intraoperative dexmedetomidine was reported to reduce postoperative delirium in nonneurosurgical populations [5]. Neurosurgical patients are also at high risk of developing postoperative delirium [6, 7]. However, these neuroprotective properties remain unexplored despite a growing body of clinical literature on the use of dexmedetomidine during cranial surgery [8, 9].

Notably, the literature in which dexmedetomidine use during cranial surgery has primarily focused on the arterial pressure stability [8, 9]. Because cranial surgery is associated with increased risk of cerebral ischemia [10] and dexmedetomidine infusion reduces cardiac output and cerebral blood flow [11], this hemodynamic concern may be clinically relevant. Regarding this aspect, the cumulative literature suggests that intraoperative goal-directed hemodynamic therapy (GDHT) for stroke volume optimization improves postcraniotomy outcomes [12-14]. Hence, considering that dexmedetomidine does not impede cardiac response to fluid infusion [15], intraoperative stroke volume optimization by using a GDHT protocol may be beneficial for patients receiving intraoperative dexmedetomidine infusion. Therefore, this study aims to test the hypothesis that intraoperative dexmedetomidine infusion combined with a GDHT may elicit neuroprotection in patients undergoing cranial surgery.

Methods

Study Design and Participants

This single-institution, double-blind, randomized controlled study was approved by the Research Ethics Committee of National Taiwan University Hospital and was registered at ClinicalTrials.gov with the identifier NCT02878707. We enrolled patients older than 20 years who had undergone elective cranial surgery for brain tumor resection, aneurysm clipping, intracranial bypass procedure, and microvascular decompression surgery between April 2017 and April 2020. Patients who met any of the following criteria were excluded: age > 80 years; metastatic brain tumor; revision surgery; history of arrhythmia or New York Heart Association Functional Classification class III or higher heart failure; liver cirrhosis > Child B class, renal insufficiency with an estimated creatinine clearance of <60 mL min^{-1} 1.73 m^{-2}.

Before starting this trial, stratified randomization was performed by an independent statistic expert using a block size of 4. At an inclusive 1:3 ratio, patients who underwent cerebrovascular and brain tumor surgeries were equally randomized to the dexmedetomidine and control groups. All patients provided written informed consent on the day before surgery to an investigator who was unaware of the randomization result. The masked drug was provided by an independent pharmacy, thereby concealing the allocation from investigators and clinicians.

Anesthesia

An infusion of dexmedetomidine (0.5 μg.kg^{-1}.h^{-1}) or equivalent dose of saline placebo was started immediately before the anesthesia induction and was maintained throughout the surgery. General anesthesia was performed and maintained through total intravenous anesthesia by using target-controlled infusion of propofol based on the Schnider model. Remifentanil and fentanyl were infused during the surgery per the attending anesthesiologist's discretion. Intraoperative opioid consumption was calculated in fentanyl equivalents for comparison [16]. Anesthesia was titrated to maintain the bispectral index (BIS; employed at the contralateral to the surgical side) between 40 and 60. The patients were ventilated with a tidal volume of 6–8 mL kg^{-1} and air:oxygen ratio of 1:1 and a positive end-expiratory pressure of 5 cmH_2O. For analgesia, each patient received a scalp nerve block containing 10 mL of 0.5% levobupivacaine with 1:200,000 epinephrine mixture for each side of the scalp before skin incision [17]. Neurophysiological monitoring techniques were used to enhance surgical safety.

Cardiac Output Monitoring and Goal-Directed Hemodynamic Therapy Protocol

After anesthesia induction, a 20-G radial arterial line was inserted and connected to the fourth-generation Vigileo/FloTrac system (Edwards Lifesciences, Irvine, CA, USA) to obtain the stroke volume index and cardiac index. A 16 or 14 G intravenous catheter was inserted in the forearm for the GDHT protocol. Details of the GDHT protocol and hemodynamic goals are provided in Appendix File 1. Briefly, the aim of the hemodynamic protocol was to optimize the stroke volume index while maintaining a cardiac index ≥ 2.2 L min^{-1} m^{-2} by repeatedly administrating 250 mL of colloid (Voluven; Fresenius Kabi, Uppsala, Sweden). The decision to administer the colloid was based on a stroke volume index increase of ≥5% after the mini-fluid challenge test of 100-mL crystalloid infusion within 1 min because this test remains valid during low tidal volume ventilation [18-20]. In addition, intraoperative blood pressure was maintained to mean arterial pressure ≥75 mm Hg and ≥85% of baseline state. The intraoperative parameters—including BIS, heart rate, mean arterial pressure, and cardiac index—were recorded every 15 min and were compared using the average values in the two study groups.

Postoperative Care

After surgery, all patients were immediately transferred to the same neurosurgical intensive care unit (ICU) and received identical postoperative care without using the study drug. If tracheal tube could not be extubated in the operating theatre, a weaning program was initiated to prevent prolonged mechanical ventilation (defined as the failure of extubation within 3 h of arrival in the ICU). Patients were considered to have delayed emergence if they did not either spontaneously open their eyes in response to speech or have motor response to command within 30 min after surgery. The hemodynamic protocol and criteria for discharge from the ICU and hospital are listed in Appendix File 2.

Postoperative Neurological Function and Outcome Assessment

This study's primary outcome was the proportion of patients who developed new neurological deficit. Nurses specializing in neurosurgical care and neurosurgeons oversaw the patients' assessment at least twice daily throughout the whole hospital stay. Diagnosis of neurological deficit was based on the criteria

of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision. The severity of disability of neurological deficit was evaluated by using in-hospital modified Barthel index change and perioperative modified Rankin Scale (mRS) [21-23]. In-hospital modified Barthel indices, assessed at admission and discharge, were obtained from institutional medical records, and the mRS scores were determined by an independent neurosurgeon who was unaware of the group allocation and other outcomes. The mRS, a 7-point scale in which 0 represents no disability, 1-2 represents slight disability, and 3-6 represents moderate to severe disability or death (mRS=6), was employed at preoperative baseline and 30 days after surgery. In addition, Postoperative change in mental state was assessed at least twice daily to document any delirium signs. One trained physician blinded to the group allocation reviewed these medical records and diagnosed the delirium sign using the criteria of the Intensive Care Delirium Screening Checklist (ICDSC) , a scale scored from 0 to 8 [6, 24]. The mRS and ICDSC scores were measured by another independent physician to determine interrater agreement.

Serum Biomarker Analysis

Serum lactate level was analyzed at baseline (after anesthesia induction) and at the end of surgery to assess the hemodynamic influence of dexmedetomidine. Plasma levels of biomarkers—including HMGB1, glial fibrillary acidic protein (GFAP), and S100β—were measured to assess the biochemical effects of dexmedetomidine on the attenuation of neuroinflammation. These serum biomarker levels at baseline (after anesthesia induction) and on the first postoperative day were compared. Serum concentrations of HMGB1 (Chondrex Inc., Redmond, WA, USA), GFAP (BioVendor LLC, Candler, NC, USA), and S100β (BioVendor LLC) were measured using enzyme-linked immunosorbent assay kits.

Statistical Analyses

According to previous studies, postoperative new neurological deficits can occur in 40% of cases [13, 21]. Accordingly, group sample sizes of 80 in each group achieves 80% power to detect a difference between the group proportions of 20% by using the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.05. Fisher's exact test or Chi-square test was performed to analyze dichotomous data, Student's *t*-test and the Mann–Whitney U test were used for normally distributed continuous data and nonparametric ordinal data respectively. The paired *t*-test was used to compare biomarker levels measured before and after surgery. Interrater agreement was analyzed by calculating the kappa coefficient. Logistic regression including all investigated preoperative and intraoperative variables was used to identify the risk factors of new postoperative neurological deficits and delirium. Preoperative and intraoperative variables were considered for the multivariate logistic regression model if $p < 0.05$ in the univariate analysis. Statistical analyses were performed using PASS Sample Size Software (NCSS, LLC, Kaysville, UT, USA) and MedCalc Statistical Software version 19.3.1 (MedCalc Software Ltd, Ostend, Belgium).

In our group sequential design, one interim analysis of severe adverse events was planned to investigate whether dexmedetomidine-induced cardiac output reduction resulted in lactate accumulation. Dexmedetomidine reportedly induces a heart rate reduction of 16.4 beats per min [9] which may comprise

an average cardiac index reduction of 0.5 $L \cdot min^{-1}$ m^2 given our previous report into patients receiving GDHT undergoing cranial surgery [13]. Accordingly, 24 patients in each group would enable detection of differences in intraoperative averaged cardiac index. Therefore, the planned interim analysis was performed once 50 patients had been enrolled, and the study safety board suggested termination of the trial once this cardiac index difference resulted in significant lactate accumulation ($p < 0.05$). Because the interim analysis did not assess the primary outcome, and thus, the significance level ($p < 0.05$) was not adjusted.

Results

The interim analysis of the first 50 patients revealed that dexmedetomidine resulted in marginal mean cardiac index reduction by 2.8 (0.7) and 3.2 (0.8) $L \cdot min^{-1} \cdot m^{-2}$ in the dexmedetomidine and control groups respectively ($p = 0.096$) without increasing serum lactate accumulation [mean change in serum lactate: 0.2 (0.8) vs. 0.2 (0.8) $mmol \cdot L^{-1}$ in the dexmedetomidine and control groups, respectively; $p = 0.981$].

Because the interim analysis revealed no serious adverse effect, 160 patients were ultimately enrolled in this study and completed the study protocol (n = 80 per group; Fig. 1). The patients in the two study groups exhibited comparable baseline characteristics (Table 1).

Perioperative Neurological Outcomes

The postoperative neurological outcomes are summarized in Table 2. Fewer patients in the dexmedetomidine group developed new neurological deficits (26.3% vs. 43.8% in the dexmedetomidine and control groups, respectively; $p = 0.031$; Table 2). However, numbers of patient remained symptomatic neurological deficit before discharge were comparable between the two groups (23.8% vs. 38.8% in the dexmedetomidine and control groups, respectively; p = 0.060; Table 2). The patients' baseline mRS profiles were comparable between the two groups, but the dexmedetomidine group had a significantly lower baseline mean (SD) modified Barthel index by 91.8 (17.9) than that of the control group by 96.8 (9.7) ($p = 0.029$). However, the dexmedetomidine group displayed an attenuated disability severity with a lower in-hospital median (IQR) Barthel index decline of 0 (−10-0) than that decline of -5 (-15-0) in control group ($p = 0.043$; Table 2) and a more favorable 30-day mRS profile ($p = 0.013$; Table 2). Regarding postoperative delirium profile, two patients from each group could not be assessed because of being comatose. The dexmedetomidine group had a more favorable ICDSC profile with fewer patients receiving an ICDSC score of 0 (84.6% vs. 64.2%; p = 0.012; Table 2). The details of neurological deficits and postoperative delirium are listed in Appendix File 3 and Appendix File 4 respectively. Table 3 displays the results of logistic regression, which revealed that dexmedetomidine was a protective factor in both new postoperative neurological deficits [odds ratio (OR), 0.457; 95% CI, 0.221–0.944; $p = 0.034$] and postoperative delirium (OR, 0.339; 95% CI, 0.147–0.785; $p = 0.012$).

The interrater agreement for baseline and 30-day mRS revealed good agreement, with weighted kappa coefficients of 0.79 [95% confidence interval (CI): 0.71–0.86] and 0.77 (95% CI: 0.71–0.83), respectively.

Furthermore, the interrater agreement in ICDSC score revealed excellent agreement with a weighted kappa coefficient of 0.88 (95% CI: 0.82–0.93). The incidence of mortality and delayed emergence, durations of ICU and hospital stay were comparable between the two groups (Table 2). Postoperative non-neurological outcomes were comparable between the two groups (Appendix File 5).

Perioperative Serum Neuroinflammatory Biomarkers

Figure 2 illustrates the perioperative changes in the serum levels of neuroinflammatory biomarkers. The dexmedetomidine group had a significant decline in serum HMGB1 level on the first postoperative day [baseline vs. first postoperative day: 222.5 (408.3) vs. 152.2 (280.0) $ng \cdot mL^{-1}$; $p = 0.003$], but this was not observed in the control group (Fig. 2A). Furthermore, the control group had a significant increase in serum GFAP level on the first postoperative day, but this was not observed in the dexmedetomidine group (Fig. 2B). The serum S100β level declined in both study groups (Fig. 2C).

Intraoperative Profiles

Table 4 summarizes the intraoperative profiles. The two groups had comparable operation time, blood loss, and transfusion profile. The dexmedetomidine group received a lower mean (SD) propofol dose of 2360 (839) than the dose of 2890 (1127) mg in the control group (p = 0.001) and lower fentanyl equivalent dose [509 (470) vs. 834 (864) mcg, respectively; p = 0.004]; the dexmedetomidine group's median (IQR) average BIS was significantly lower [41 (38-43) vs. 44 (41-47), respectively; p< 0.001]. The intraoperative mean arterial pressure and need for nicardipine, labetalol, atropine and changes in lactate level were comparable between the two study groups. Nevertheless, the dexmedetomidine group received a slightly higher dose of norepinephrine than the control group [6.9 (21.4) vs. 1.8 (5.5) μg; $p = 0.040$]. In addition, dexmedetomidine induced a significantly lower heart rate [71.1 (10.4) vs. 78.1 (11.0) beats per min in the dexmedetomidine and control groups, respectively; $p < 0.001$] and lower cardiac index [3.0 (0.8) vs. 3.4 (0.8) $L \cdot min^{-1} \cdot m^{-2}$ in the dexmedetomidine and control groups, respectively; $p = 0.048$]. Notably, these heart rate and cardiac index effects were both approximately 10% reductions. The iv fluid requirement were comparable between the two groups.

Discussion

This study obtained several findings. First, the intraoperative dexmedetomidine infusion combined with a GDHT protocol during cranial surgery was associated with fewer patients with new postoperative neurological deficits and fewer patients with postoperative delirium. Additionally, the severities of postoperative disability were attenuated. Second, dexmedetomidine infusion mitigated perioperative neuroinflammation with the resolution of serum HMGB1. Third, infusion resulted in a clinical irrelevant cardiac index reduction through its effects on heart rate.

We observed that dexmedetomidine may reduce the proportion of patients who developed postoperative new neurological deficits as well as the severity of neurological deficits after cranial surgery. Postoperative neurological deficits are highly related to patients' baseline neurological status as well as

surgical types. Therefore, numbers of patient remained symptomatic neurological deficit before discharge were comparable between the two study groups. Despite patients in the dexmedetomidine group revealed a lower baseline Barthel index, favorable postoperative neurological profiles were observed. In addition, the logistic regression model including analysis of baseline neurological status, type of surgery as well as intraoperative profiles revealed potential protective effects of dexmedetomidine. Dexmedetomidine has been reported to mitigate neuroinflammatory cascades, and inhibit catecholamine and glutamate release, thereby preventing regional cerebral ischemia [2, 11], which commonly occurs during cranial surgery [1, 10]. In addition, plausible mechanisms of neuroprotective effects of dexmedetomidine include the attenuation of neuronal necrosis, apoptosis, autophagy through the effects of an increase of focal adhesion kinase phosphorylation in hippocampus, inducing increases of brain derived neurotrophic factor expression [25] as well as inhibiting lipopolysaccharide-induced astrocyte pyroptosis [26]. The modified Barthel index was sensitive to in-hospital function changes [13, 23], and 30-day mRS may reflect longer-term disability recovery after cranial surgery [21]. The postoperative long-term beneficial effects of dexmedetomidine is compatible to those observed among elderly undergoing non-cardiac surgery [27]. However, both mRS and modified Barthel index have rarely been applied in previous studies of dexmedetomidine use during cranial surgery. Our results indicated the potential value of applying these assessment tools to investigate the effect of anesthetic management on postoperative neurological outcomes.

The ICDSC was chosen in this study to detect postoperative delirium because that first, it was recently validated in neurosurgical and neurocritically ill patients [6, 7]. Second, it can be applied in patient inability to communicate, which is common in neurosurgical patients. Third, it can be used to identify subsyndromal delirium (scores of 1–3), which is common in surgical population [28]. Despite a recent meta-analysis indicating that dexmedetomidine reduces postoperative delirium [5], two randomized controlled trials, one on noncardiac surgery (most were spine and orthopedic surgeries)[29] and one on thoracic surgery [30], reported negative results. These findings imply that there may be an optimal target patient population for the therapeutic effects of dexmedetomidine. Patients undergoing cranial surgery are vulnerable to delirium because the breakdown of neural network frontoparietal connectivity, which is a major characteristic of delirium [31], can occur during surgery. Intraoperative dexmedetomidine infusion could preserve neuronal connectivity through its effect of inducing a sleep-like electroencephalographic pattern [32]. Moreover, Tanabe et al. recently reported that the changes to frontoparietal connectivity correlated with serum inflammatory cytokine levels in patients with postoperative delirium [31]. Therefore, the anti-inflammatory property of dexmedetomidine may also be beneficial.

The HMGB1 is a damage-associated molecular pattern molecule immediately released from cell nuclei after injury, and extracellular HMGB1 acts as a common biomarker in various neuroinflammatory conditions, such as traumatic brain injury, epilepsy, and cognitive dysfunction [4]. Because the half-life of serum HMGB1 was only 17 min [33], despite the postoperative serum HMGB1 level remained unchanged in the control group, an increase in intraoperative serum HMGB1 level may likely present otherwise the postoperative resolution should be observed. Dexmedetomidine inhibits the HMGB1/TLR4 pathway [2, 34], and its' cytoprotective effects may mitigate release of inflammatory mediators from injured cell [2].

Therefore, postoperative HGMB1 resolution was only observed in the dexmedetomidine group. This result is concordant with previous studies on cardiac surgery [35] and thoracic surgery [36]. In addition, we observed that the control group but not the dexmedetomidine group had significantly elevated postoperative GFAP. Conversely, change in serum S100β was comparable between the groups. Because GFAP is highly specific to glial cell of the nervous system whereas S100β is relatively unspecific to nervous system, our result was concordant with those of a previous report, which discovered that postoperative elevation of serum GFAP but not S100β was associated with postoperative cognitive decline [37].

Hypotension is one of the common adverse effects of dexmedetomidine [11], but we observed stable intraoperative arterial pressure among patients in both study groups with only a slightly higher intraoperative norepinephrine dose (5μg) administrated in patients in the dexmedetomidine group. This result is compatible to the literature that dexmedetomidine during cranial surgery may improve arterial pressure stability [8]. However, dexmedetomidine may elevate cerebrovascular resistance through activation of the alpha-2B receptor, resulting in a decrease of cerebral perfusion pressure regardless of arterial pressure stability [11, 38]. Furthermore, dexmedetomidine may impede cerebral autoregulation which dissociates arterial pressure and cerebral perfusion [39]. Hence, stable arterial pressure alone is insufficient to maintain cerebral perfusion in patients receiving dexmedetomidine infusion during cranial surgery. Nevertheless, cerebral perfusion correlates with cardiac output regardless of the change in autoregulation state [40]. Because it also reduces cerebral metabolic rate in similar proportion of heart rate reduction [41], intraoperative cerebral metabolism and blood flow coupling could be maintained satisfactorily when dexmedetomidine was combined with GDHT to optimize intraoperative stroke volume.

This study had limitations. First, this study was limited to a single center design. Second, this study was underpowered to differentiate durations of ICU and hospital stay because these outcomes were highly dependent on the postoperative care protocol. For instance, the withdrawal of postoperative vasodilator agent, a criteria for ICU discharge in this study, is unaffected by intraoperative dexmedetomidine infusion. Third, this study was limited in its resources for investigating other potential neuroinflammatory biomarkers, such as the tumor necrosis factor [1]. Forth, renal side effects are a concern regarding the use of starch colloids during GDHT. However, recent randomized trials revealed that starch did not cause acute or long-term renal toxicity [13, 42].

Conclusion

This study demonstrated that intraoperative dexmedetomidine infusion combined with a GDHT may elicit neuroprotection, thereby attenuating postoperative disability and prevention of delirium through mitigation of neuroinflammation during cranial surgery without hemodynamic perturbation.

Abbreviations

BIS: bispectral index; CI: confidence interval; GDHT: goal-directed hemodynamic therapy; GFAP: glial fibrillary acidic protein; HMGB1: high motility group box 1 protein; ICDSC: Intensive Care Delirium Screening Checklist; ICU: intensive care unit; IQR: interquartile range; mRS: modified Rankin Scale; OR: odds ratio; SD: standard deviation

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of National Taiwan University Hospital and was registered at ClinicalTrials.gov with the identifier NCT02878707. All Patients provided written informed consent before randomization.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PHC, YCY, CYW were involved in the design of this study. CYW performed the statistical analysis and interpretation of data. PHC, CTL, YCY, YJC, CYW were involved in manuscript preparation. PHC, FYT, CTL, HLC, TSL contributed to patient recruitment and data collection. YWC helped allocated patients. All authors read and approved the final manuscript.

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Tables

Table 1. Patient characteristics

	Dexmedetomidine (n = 80)	Control (n = 80)
Age (years)	59 (47 -66)	56 (43-65)
Male sex (n; %)	30 (37.5%)	33 (41.3%)
Body mass index (kg m^{-2})	24.4 (22.5-27.5)	24.2 (21.9-28.1)
Education level (years)	13 (9-16)	12 (11-16)
Surgery type (n; %)	19 (23.8%)	17 (21.3%)
Aneurysm or bypass	13 (16.2%)	16 (20.0%)
Intra-axial	32 (40.0%)	25 (31.2%)
Extra-axial supratentorial	16 (20.0%)	22 (27.5%)
Extra-axial infratentorial		
ASA classification (n; %)	5 (6.3%)	3 (3.8%)
I	48 (60%)	53 (66.3%)
II	27 (33.8%)	24 (30%)
III		
Comorbidity (n; %)	19 (23.8%)	27 (33.8%)
Hypertension	4 (5.0%)	3 (3.8%)
Coronary arterial disease	5 (6.3%)	4 (5.0%)
Pulmonary disease		
Diabetes	13 (16.3%)	11 (13.8%)
Other	16 (20.0%)	15 (18.8%)

ASA = American Society of Anesthesiologists; mRS= modified Rankin Scale. Continuous data are presented as mean (standard deviation), median (interquartile range) and categorical data are presented as n (%).

Table 2. Perioperative neurological outcomes

	Dexmedetomidine (n = 80)	Control (n = 80)	*p* Value
Patients with new neurological deficit (n; %)	21 (26.3%)	35 (43.8%)	p= 0.031
Total number	19 (23.8%)	31 (38.8%)	p= 0.060
Remained symptomatic before discharge			
Short-term disability severity	91.8 (17.9)	96.8 (9.7)	p= 0.029
Admission Barthel index	95 (75-100)	90 (80-100)	p= 0.5622
Discharge Barthel index	0 (-10-0)	-5 (-15-08)	p= 0.023
Barthel index changes	14 (17.5%)	14 (17.5%)	p= 0.191
Long-term disability severity	54 (67.5%)	61 (76.3%)	p= 0.013
Baseline mRS score (n; %)	12 (15.0%)	5 (6.2%)	
0	19 (23.8%)	7 (8.7%)	
1–2	29 (36.2%)	44 (55.0%)	
3–6	32 (40.0%)	29 (36.3%)	
30-day mRS score (n; %)			
0			
1–2			
3–6			
Delirium profile (n; %)	n= 78*	n= 78*	p= 0.012
ICDSC = 0	66 (84.6%)	50 (64.2%)	
ICDSC score 1–3	5 (6.4%)	14 (17.9%)	
ICDSC score ≥ 4	7 (9.0%)	14 (17.9%)	
Delayed emergence (n; %)	8 (10.0%)	10 (12.5%)	p= 0.803
Intensive care unit stay (days)	2.5 (5.9)	3.0 (4.0)	p= 0.519
Hospital stay (days)	11.5 (8.8]	10.8 (5.5)	p= 0.583
Mortality (n; %)	1 (1.3%)	1 (1.3%)	p= 1.000

mRS = modified Rankin Scale; ICDSC = Intensive Care Delirium Screening Checklist. Continuous data are presented as mean (standard deviation), median (interquartile range) and categorical data are presented as n (%).

* Two patients from each group could not be assessed because of being comatose

Table 3. Risk factors of postoperative new neurological deficit and delirium

New neurological deficit			
Factor	**OR**	**95% CI of OR**	**p value**
Baseline modified Barthel index	1.002	0.977-1.027	0.895
Heart rate (beats per min)	1.002	0.971-1.035	0.885
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	0.887	0.653-1.204	0.442
Norepinephrine dose (µg)	0.995	0.970-1.021	0.705
Dexemedtomidine use	0.457	0.221-0.944	0.034
Postoperative delirium			
Factor	**OR**	**95% confidence interval**	**p value**
Baseline modified Barthel index	0.988	0.963-1.014	0.361
Heart rate (beats per min)	1.015	0.98-1.051	0.403
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	0.9	0.642-1.262	0.542
Norepinephrine dose (µg)	0.963	0.898-1.032	0.288
Dexmedetomidine use	0.339	0.147-0.785	0.012

OR= odds ratio; CI= confidence interval

Table 4. Intraoperative profiles

	Dexmedetomidine (n = 80)	Control (n = 80)	*p* Value
Surgical profile	234 (186-286)	246 (200-340)	p= 0.159
Operation time (min)	283 (336)	340 (531)	p= 0.412
Blood loss (mL)	14 (17.5%)	17 (21.3%)	p= 0.690
Patients needing transfusion (n; %)	0.4 (1.1)	0.6 (1.4)	p= 0.377
Red blood cell transfusion (unit)	none	0.1 (0.8)	NA
Plasma transfusion (unit)	0.3 (1.9)	0.6 (3.3)	p= 0.476
Platelet transfusion (unit)			
Anaesthetic profile	2360 (839)	2890 (1127)	p= 0.001
Propofol dose (mg)	509 (470)	834 (864)	p= 0.004
Fentanyl equivalent (mcg)	41 (38-43)	44 (41-47)	p< 0.001
Average BIS value			
Haemodynamic profile	85.0 (79.6-90.5)	85.2 (80.4-89.8)	p= 0.623
MAP (mmHg)	70.6 (64.7-78.3)	77.7 (69.7-86.4)	p< 0.001
Heart rate (bpm)	3.0 (0.8)	3.4 (1.8)	p= 0.048
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	-0.1 (-0.3-0.4)	0 (-0.2-0.4)	p= 0.223
Lactate change ($mmol \cdot L^{-1}$)	3.8 (4.9)	6.4 (12.6)	p= 0.080
Nicardipine dose (mg)	2.1 (7.7)	3.1 (8.3)	p= 0.417
Labetalol dose (mg)	4 (5.0%)	2 (2.5%)	p= 0.682
Patient needing atropine (n; %)	6.9 (21.4)	1.8 (5.5)	p= 0.040
Norepinephrine dose (µg)			
Fluid balance	1784 (1260-2260)	1921 (1358-2676)	p= 0.252
Crystalloid infused (mL)	664 (341)	868 (1083)	p= 0.109
Colloid infused (mL)	1200 (800-1875)	900 (550-1400)	p= 0.011
Urine output (mL)			

BIS = bispectral index; MAP = mean arterial pressure; bpm= beat per minute. Continuous data are presented as mean (standard deviation), median (interquartile range) and categorical data are presented as n (%).

Figures

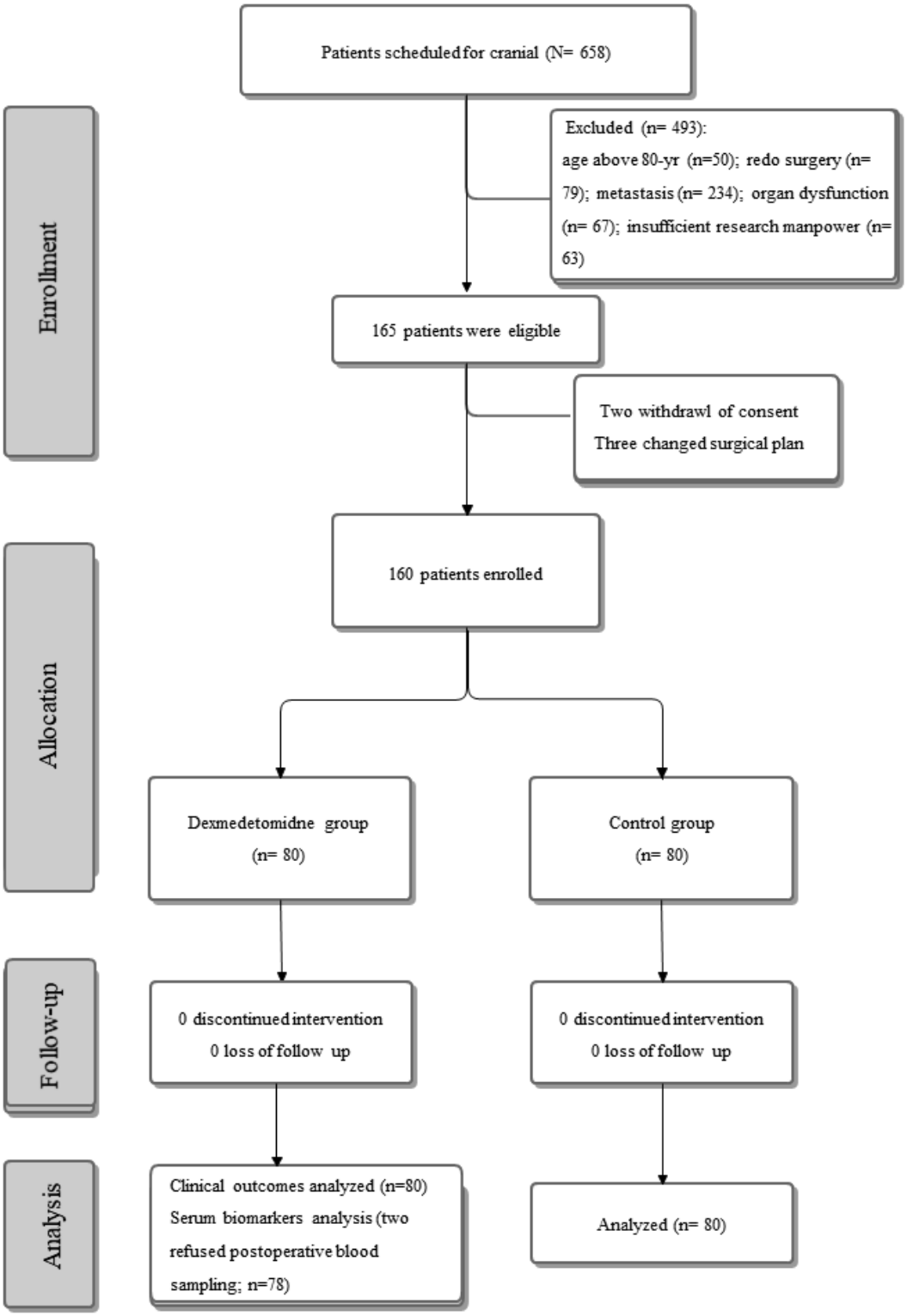

Figure 1

CONSORT flow diagram.

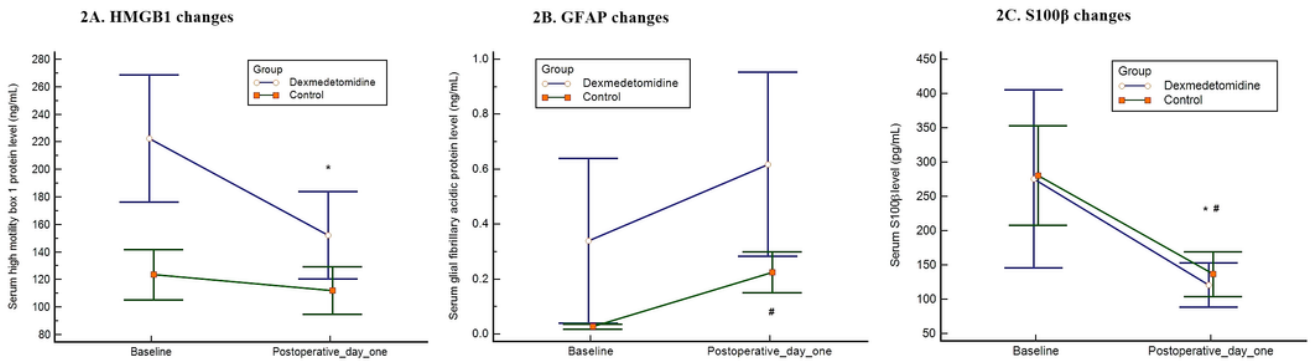

Figure 2

Perioperative changes in serum neuronal biomarker levels. The dot represents the mean value, whereas the error bar represents the standard error of the mean. A. Perioperative change in serum high motility box 1 protein level; B. Perioperative change in serum glial fibrillary acidic protein level; C. Perioperative change in serum S100β level. * indicates $p < 0.05$ between values at baseline and on the first postoperative day in the dexmedetomidine group; # indicates $p < 0.05$ between values at baseline and on the first postoperative day in the control group.

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