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Original Article

Effects of intravenous dexmedetomidine on hemodynamic stability, inflammatory factors, and brain injury biomarkers in patients with Moyamoya disease undergoing revascularization surgery

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Abstract: Objective: To evaluate the effects of dexmedetomidine (DEX) on perioperative hemodynamic stability, inflammatory response, and brain injury markers in patients with moyamoya disease (MMD) undergoing revascularization procedures. Methods: A total of 68 patients with confirmed MMD were enrolled in this single-institution, randomized, placebo-controlled, prospective trial and were randomized into either the DEX group or the placebo group (34 patients each). The DEX group received a loading dose of 1 μg/kg DEX and a continuous infusion at 0.4 μg/kg/h throughout the surgery. Instead, the control group was given the same volume of saline with the same dosing regimen. Hemodynamic parameters, including heart rate (HR), systolic blood pressure (SBP), mean blood pressure (MAP), and diastolic blood pressure (DBP), were recorded at six defined time points: before induction (T0), during tracheal intubation (T1), at the moment of surgical incision (T2), immediately after surgery (T3), before extubation (T4), and during extubation (T5). Additionally, fluctuation amplitudes for heart rate variability (HR-V), systolic blood pressure variability (SBP-V), and mean arterial pressure variability (MAP-V) were calculated from data collected during T0-T5. Plasma levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), the neural injury marker S100 beta protein (S100β) and neuron-specific enolase (NSE) were obtained at four different time points: prior to anesthesia induction, after reperfusion, immediately after surgery, and 24 hours postoperatively. Adverse events and neurological complications within 24 hours postoperatively were also documented. Results: Compared with control group, DEX group exhibited significantly lower SBP, MAP, and DBP at time points T1, T2, T4, and T5 (all $P < 0.05$) and significantly lower HR throughout T1 to T5 (all $P < 0.05$). The DEX-treated patients also demonstrated reduced HR variability (HR-V; 37.39 ± 12.29 vs. 45.15 ± 12.18, $P < 0.05$), SBP variability (SBP-V; 18.04 ± 6.60 vs. 21.41 ± 6.94, $P < 0.05$), and MAP variability (MAP-V; 23.12 ± 7.67 vs. 27.46 ± 9.68, $P < 0.05$). Additionally, serum levels of IL-6, TNF-α, and S100β were significantly lower in the DEX group at post-reperfusion, surgery completion, and 24-hour post-operation compared to the control group (all $P < 0.05$). The incidence of neurological complications in the DEX group was lower than that in the control group, although the difference did not reach statistical significance ($P = 0.099$). The overall incidence of adverse events was comparable between groups ($P > 0.05$). Conclusions: Intraoperative infusion of DEX enhances perioperative hemodynamic stability, mitigated postoperative inflammatory response, and lowers serum S100β levels associated with brain injury in MMD patients undergoing superficial temporal artery-middle cerebral artery (STA-MCA) bypass surgery.

Keywords: Dexmedetomidine, hemodynamics, inflammatory factors, brain injury biomarkers, direct revascularization surgery

Introduction

Moyamoya disease (MMD) is a progressive cerebrovascular disorder characterized by gradual stenosis or occlusion of the distal internal carotid arteries [1]. Surgical revascularization remains the preferred treatment, effectively reducing stroke recurrence and improving long-term neurological outcomes [2, 3]. However, due to impaired cerebral autoregulation in MMD patients, cerebral blood flow during anesthesia is highly dependent on systemic blood pressure

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[4, 5]. As a result, hemodynamic fluctuations during laryngoscopy, intubation, surgical stimulation, and extubation may trigger perioperative ischemic or hemorrhagic events [6, 7]. Given the essential role of cerebral perfusion in MMD patients, current anesthetic practices recommend maintaining mean arterial pressure (MAP) between 70-100 mmHg or systolic blood pressure (SBP) between 110-155 mmHg during surgery to avoid risks of hypoperfusion or hyperperfusion [6]. Moreover, temporary occlusion of cortical supply arteries during surgery can cause ischemic injury. Following reperfusion, this may further trigger stress responses, inflammation cascades, and ischemic-reperfusion injuries, all of which are potential causes of postoperative neurological complications in MMD patients undergoing direct revascularization.

Dexmedetomidine (DEX), a highly selective α2 receptor agonist, is commonly used as an anesthetic adjunct for its sedative, anxiolytic, and sympatholytic effects [8]. Previous clinical and experimental studies have shown that DEX can mitigate surgical and anesthetic stress, suppress inflammation, and exert neuroprotective effects [9-12]. Its mechanisms primarily involve suppressing central sympathetic activity and reducing norepinephrine release, thereby improving hemodynamic stability. Also, DEX may modulate systemic inflammatory responses by regulating cytokine levels. However, its overall effects on stress regulation, inflammation modulation, and neuroprotection during MMD revascularization surgery remain incompletely understood, necessitating further investigation of its clinical significance in this patient population.

This study aims to investigate whether intraoperative DEX administration could help improve hemodynamic stability, suppress inflammation, and mitigate neuronal damage in MMD patients undergoing vascular reconstruction surgeries.

Materials and methods

General information

This is a prospective, randomized clinical trial conducted at Punan Hospital, Pudong New Area, Shanghai, from July 2023 through December 2024. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR), Registration No.: ChiCTR2500114022; URL: https://www.chictr.org.cn/hvshowproject.html?id=289617&v=1.0. Ethical approval for this trial was granted by the Institutional Ethics Committee of Punan Hospital. All patients or their legal guardians provided written informed consent. Randomization was done using the random number generator in SPSS 29.0 (IBM Corp., Armonk, NY, USA), and the grouping information was concealed through numbered sealed envelopes. A total of 68 patients were randomly assigned into either a DEX group (observation group) or a control group, each consisting of 34 participants. Both the patients and the personnel evaluating treatment efficacy and biomarkers were blinded to patients' group assignments.

Inclusion criteria: (i) Confirmed MMD via digital subtraction angiography (DSA), superficial temporal artery-middle cerebral artery (STA-MCA), and indirect bypass surgery; (ii) American Society of Anesthesiologists (ASA) physical status classification of I through III; (iii) Age ≥ 18 years; and (iv) ability and willingness to fully participate in the post-operative process and cooperate with evaluations. Exclusion criteria: (i) Severe functional impairment of major organs such as respiratory, cardiovascular, hepatobiliary, or renal systems; (ii) Hospitalization within two weeks prior to surgery due to acute respiratory infection; (iii) Documented history of DEX allergy or other adverse events (e.g., transient hypertension or post-operative vomiting); (iv) Presence of sinus bradycardia, pre-operative hypotension, or myocardial contraction abnormalities; and (v) History of any neurological-psychiatric or altered mental status.

Outcome measures

The primary outcomes were changes and fluctuations in intraoperative hemodynamics, including MAP, heart rate (HR), and SBP. Secondary outcomes included plasma concentrations of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), S100 beta protein (S100β), and neuron-specific enolase (NSE). Additionally, the incidence of postoperative neurological events and other adverse events within post-operative 24 hours were also evaluated.

Sample size

Sample size calculation was based on preliminary observational data from 20 patients at the same institution. In this dataset, the mean

difference in MAP during extubation was approximately 8 mmHg, with a pooled standard deviation of about 11 mmHg. The formal sample size was calculated using these pilot-derived parameters ($\delta \approx 8$ mmHg and $\sigma \approx 11$ mmHg) according to the formula: $N = [(Z\alpha/2 + Z\beta)^2 \times \sigma^2/\delta^2] \times (1/Q_1 + 1/Q_2)$, where $Z\alpha/2 = 1.96$ ($\alpha = 0.05$), $Z\beta = 0.84$ ($\beta = 0.20$), and $Q1 = Q2 = 0.5$ for equal allocation. Based on these assumptions, the estimated sample size was approximately 31 participants per group. Accounting for an anticipated 10% dropout rate, the final enrollment was increased to 34 participants per group, yielding a total of 68 patients. Since sample size was determined solely by the primary endpoint (MAP), no formal power calculations were performed for IL-6 and S100β. These secondary biomarkers were analyzed as exploratory and hypothesis-generating outcomes.

Anesthesia protocol

Patients in the DEX group received intravenous infusion of DEX (1 μg/kg) (H20130027, Chenxin Pharmaceutical Co., Ltd., China) diluted in 50 mL saline 15 minutes prior to anesthesia induction, followed by continuous infusion at 0.4 μg/kg/h until the end of surgery. This regimen has been proven to promote smooth emergence and improve recovery quality in nasal surgeries [13]. The control group received an equal volume of saline.

All patients underwent overnight fasting and received no preoperative sedation. Intravenous access was established and routine monitoring initiated upon arrival in the operating room.

The induction regimen included midazolam (0.05 mg/kg; Hangzhou Zhongtai Pharmaceutical Co., Ltd., Hangzhou, China, TMB25B07), propofol (2-3 mg/kg; Chenxin Pharmaceutical Co., Ltd., China, H20234180), sufentanil (0.3-0.5 μg/kg, Yichang Renfu Pharmaceutical Co., Ltd., China, H20054171), and rocuronium (0.6 mg/kg, Zhejiang Xianju Pharmaceutical Co., Ltd., China, H20093186), with dosages adjusted according to patient condition to attain adequate anesthetic depth and neuromuscular blockade. Following full neuromuscular blockade, tracheal intubation was performed by an expert anesthesiologist using video-assisted laryngoscopy. Anesthesia was maintained with propofol (4-6 mg/kg/h) combined with remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., China, H20030197; 0.05-0.15 μg/kg/min), and low-dose isoflurane (0.3 MAC; Shanghai Hengrui Pharmaceutical Co., Ltd., China, H20213735). Rocuronium was administered as needed intraoperatively to sustain neuromuscular blockade.

Ventilation was set to a target tidal volume of 6-8 mL/kg, PEEP of 5 cmH_2O, and $PaCO_2$ of 35-40 mmHg. Intraoperative hemoglobin level was kept at ≥ 10 g/dL. Bradycardia, defined as HR < 50, was corrected with atropine (0.005 mg/kg). MAP was maintained within approximately ± 20% of the preoperative values; hypotension was corrected with ephedrine (3-6 mg), whereas hypertension was controlled with nitroglycerin (50-100 μg). MAP was stabilized during STA-MCA bypass to prevent cerebral hypoperfusion.

Bispectral index (BIS) was used to monitor anesthetic depth. However, BIS readings are often affected by signal interference during the STA-MCA anastomosis, limiting their reliability. Postoperatively, all patients remained intubated and were transferred to the Intensive Care Unit (ICU). Tracheal extubation was performed only after patients regained consciousness, achieved hemodynamic stability, and demonstrated adequate spontaneous respiration. Comprehensive neurological assessments, including the National Institutes of Health Stroke Scale (NIHSS), were performed in the ICU at predetermined intervals.

Measurements

HR, SBP, diastolic blood pressure (DBP), and MAP were recorded at six predefined perioperative time points: before anesthesia induction (T0), at intubation (T1), at skin incision (T2), at the completion of surgery (T3), before extubation (T4), and at extubation (T5). These six time points were selected to optimally capture hemodynamic fluctuations and stress responses throughout the perioperative period. Hemodynamic stability was assessed using the percentage variability of MAP (MAP-V), SBP (SBP-V), and HR (HR-V), with the following formula: Variation (%) = (Maximum value - Minimum value)/Mean value × 100%. Higher values indicate greater hemodynamic instability and a

stronger stress response, whereas lower values reflect more stable hemodynamics.

Serum measurements

Arterial blood samples were collected via a radial arterial catheter at predetermined time points: before anesthesia induction, at 5 minutes after reperfusion during the STA-MCA bypass, upon the completion of surgery, and 24 hours post-operatively. Samples were drawn into heparinized tubes, centrifuged (3,000 rpm, 10 min, 4°C), and the separated plasma was stored at -80°C until analysis.

Plasma levels of IL-6, TNF-α, S100β, and NSE was quantified using enzyme-linked immunosorbent assay (ELISA). IL-6 and TNF-α kits were obtained from R&D Systems (Minneapolis, MN, USA; IL-6: VAL102C; TNF-α: VAL105G), and S100β and NSE kits were purchased from Elabscience (Wuhan, China; S100β: E-EL-H1297; NSE: E-EL-H1047). All assays were performed in duplicate according to the manufacturers' instructions.

Adverse events and neurological complications

Postoperative adverse events occurring within 24 hours were recorded, including vomiting, nausea, hypotension, bradycardia, and drowsiness. Neurological sequelae such as cerebral hyperperfusion syndrome (CHS), seizures, acute cerebral infarction, or hemorrhage, were evaluated using computed tomography (CT) or magnetic resonance imaging (MRI).

Statistical analysis

Statistical analyses were performed using SPSS 29.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9.0 (GraphPad Software). Normality was tested with the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD) and compared between groups using independent sample t-test. Non-normally distributed variables were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Multiple comparisons were conducted using repeated-measures analysis of variance (ANOVA), followed by Bonferroni-adjusted post hoc analyses. A P value of < 0.05 was considered statistically significant.

Results

Baseline information

No significant differences were observed between groups in terms of age, sex, body mass index (BMI), comorbidity of hypertension and diabetes, and surgical laterality ($P > 0.05$). However, significantly higher intraoperative urine output was observed in the DEX group compared with the control group ($P = 0.023$), despite equal volumes of fluid were administered during the operation (**Table 1**).

Hemodynamic status

Baseline hemodynamics did not differ significantly between groups ($P > 0.05$). However, at T1, T2, T4, and T5, SBP, MAP, and DBP were significantly lower in the DEX group than in the control group ($P < 0.05$); and HR was significantly lower in the DEX group throughout T1-T5 compared with the control group ($P < 0.05$) (**Table 2**; **Figure 1**). Analysis of variability in HR, MAP, and SBP revealed significantly reduced fluctuations in the DEX group compared to the control group (HR-V: 37.39 ± 12.29 vs. 45.15 ± 12.18, $P < 0.05$; SBP-V: 18.04 ± 6.60 vs. 21.41 ± 6.94, $P < 0.05$; MAP-V: 23.12 ± 7.67 vs. 27.46 ± 9.68, $P < 0.05$) (**Table 3**). These observations indicate that DEX improved intraoperative hemodynamic stability.

Inflammatory factors

Baseline IL-6 and TNF-α levels showed no significant between-group differences. Both cytokines exhibited an upward trend after reperfusion, peaking at the end of operation before gradually declining. Nevertheless, compared with the control group, administration of DEX significantly alleviated the surges in IL-6 and TNF-α levels after reperfusion and at the end of operation ($P < 0.05$; **Figure 2A**, **2C**). These differences remained significant at 24 hours postoperatively (**Figure 2B**, **2D**), indicating that DEX attenuates inflammatory responses during the perioperative period and early recovery phase.

Brain injury biomarkers

At post-reperfusion, end of surgery, and 24 hours postoperatively, the increase in S100β

Table 1. Baseline profile of the two groups

Category	Observation group (n = 34)	Control group (n = 34)	t/χ^2	*P*
Sex (n, %)			0.249	0.618
Male	12 (35.29)	14 (41.18)		
Female	22 (64.70)	20 (58.82)		
Age (years)	49.24 ± 10.33	48.76 ± 10.85	0.183	0.855
BMI (kg/m^2)	23.92 ± 2.95	24.08 ± 2.35	-0.252	0.802
History of hypertension (n, %)			0.553	0.310
Yes	15 (44.11)	12 (35.30)		
No	19 (55.89)	22 (64.71)		
History of diabetes (n, %)			0.302	0.784
Yes	10 (29.41)	8 (23.53)		
No	24 (70.59)	26 (76.47)		
Operation side (n, %)			0.060	0.806
Left	19 (55.88)	20 (58.82)		
Right	15 (44.12)	14 (41.18)		
Intraoperative data				
Operation time (min)	295.50 ± 17.12	297.18 ± 16.23	-0.41	0.680
Administered fluid (mL)	2002.94 ± 219.48	2011.76 ± 303.28	-0.137	0.891
Estimated blood loss (mL)	266.18 ± 76.59	257.65 ± 78.93	0.653	0.452
Urine output (mL)	1144.12 ± 210.61	1027.94 ± 199.31	2.336	0.023

Note: BMI, body mass index.

Table 2. Comparison of perioperative hemodynamics between the two groups at various time points

	Observation group (N = 34)	Control group (N = 34)	t/χ^2	*P*
HR (bpm)				
T0	76.09 ± 8.60	78.35 ± 11.31	-0.929	0.356
T1	84 ± 7.92	96.15 ± 6.11	-5.35	0.000
T2	64.68 ± 6.11	69.56 ± 7.44	-2.956	0.004
T3	63.56 ± 5.90	68.76 ± 4.24	-4.182	0.000
T4	80.03 ± 8.77	90.56 ± 8.8	-4.932	0.000
T5	84.15 ± 9.04	91.24 ± 6.27	-3.758	0.000
SBP (mmHg)				
T0	137.32 ± 14.09	136.91 ± 13.77	0.122	0.903
T1	139.79 ± 11.90	151.68 ± 7.74	-4.878	< .001
T2	134.29 ± 10.10	140.91 ± 11.99	-2.462	0.016
T3	133.24 ± 9.32	136.56 ± 10.93	-1.349	0.182
T4	138.65 ± 12.36	150.06 ± 8.8	-4.383	< .001
T5	137.18 ± 10.25	145.97 ± 11.70	-3.298	0.002
MAP (mmHg)				
T0	92.59 ± 10.67	93.12 ± 10.32	-0.208	0.836
T1	99.62 ± 11.92	108.15 ± 7.30	-3.558	0.001
T2	95.24 ± 9.27	102.71 ± 8.95	-3.381	0.001
T3	95.35 ± 8.22	96.56 ± 10.93	-0.514	0.609
T4	100.41 ± 10.70	107.97 ± 6.88	-3.466	0.001
T5	98.26 ± 9.62	106.29 ± 10.55	-3.278	0.002

DBP (mmHg)				
T0	70.24 ± 10.58	71.26 ± 8.78	-0.437	0.664
T1	79.53 ± 12.06	85.18 ± 5.75	-2.465	0.016
T2	75.79 ± 12.06	83.62 ± 7.36	-3.781	< .001
T3	76.49 ± 10.11	76.56 ± 10.93	-0.029	0.977
T4	81.35 ± 12.70	86.94 ± 10.05	-2.012	0.048
T5	78.88 ± 11.94	90.59 ± 14.93	-3.57	< .001

Notes: HR, heart rate; SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure.

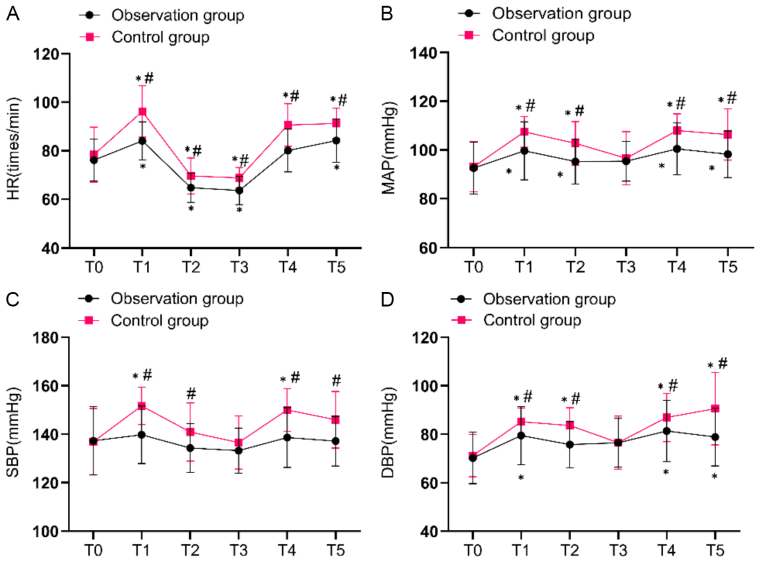

Figure 1. Perioperative changes in (A) HR, (B) MAP, (C) SBP, and (D) DBP, recorded at six time points: before anesthesia induction (T0), during intubation (T1), at skin incision (T2), at surgery completion (T3), prior to extubation (T4), and during extubation (T5). Patients in the DEX group (observation group) exhibited significantly reduced hemodynamic fluctuations compared with controls throughout the perioperative period. Data are presented as mean ± SD. *P < 0.05 vs. baseline; #P < 0.05 vs. control group. Notes: HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

levels in the DEX group was significantly lower than that in the control group (P < 0.05). However, NSE showed a slight increase at all these time points, yet no significant differences were observed between groups (P > 0.05; **Figure 3**).

Postoperative neurological complications and adverse events

Regarding postoperative neurological complications, two patients in the DEX group developed CHS events, compared with 5 patients in the control group. Although the incidence of neurological events was lower in the DEX group (17.6% vs. 35.3%), the difference did not reach statistical significance (P = 0.099; **Table 4**). The incidence of adverse events was similar between groups (P > 0.05; **Table 5**).

Discussion

In this clinical trial, it was observed that intraoperative infusion of DEX during STA-MCA bypass surgery for MMD patients improved hemodynamic stability, reduced inflammatory responses, and decreased the levels of brain injury markers, thereby confirming its potential neuroprotective effect.

Despite this, surgical revascularization remains the most effective treatment available for MMD, significantly lowering the risk of future ischemic or hemorrhagic attacks [13, 14]. Direct bypass between STA and MCA, often combined with indirect techniques such as encephalomyosynangiosis (EMS) or encephaloduroarteriosynangiosis (EDAS), improves local cerebral blood flow and is associated with favorable outcomes [15]. Most patients have a history of ischemic symptoms or infarction, leading to decreased regional perfusion and near-maximal dilation of the cerebral microvasculature [16]. The compromised cerebral autoregulation and blood-brain barrier (BBB) integrity in these patients diminish their ability to resist changes in cerebral perfusion pressures, making them highly sensitive to fluctuations in systemic blood pressure. Additionally, vascular reconstruction and bypass may lead to CHS, with a reported incidence of up to 50% following STA-MCA anastomosis. Abnormal brain pressures could potentially

Table 3. Comparison of the perioperative variability in HR, SBP, and MAP between the two groups

Group	n	HR-V	SBP-V	MAP-V
Observation group (n, %)	34	37.39 ± 12.29	18.04 ± 6.60	23.12 ± 7.67
Control group (n, %)	34	45.15 ± 12.18	21.41 ± 6.94	27.46 ± 9.68
t/χ^2	-	-2.612	-2.055	-2.048
P	-	0.011	0.044	0.045

Notes: HR-V, heart rate variability; SBP-V, systolic blood pressure variability; MAP-V, mean arterial pressure variability.

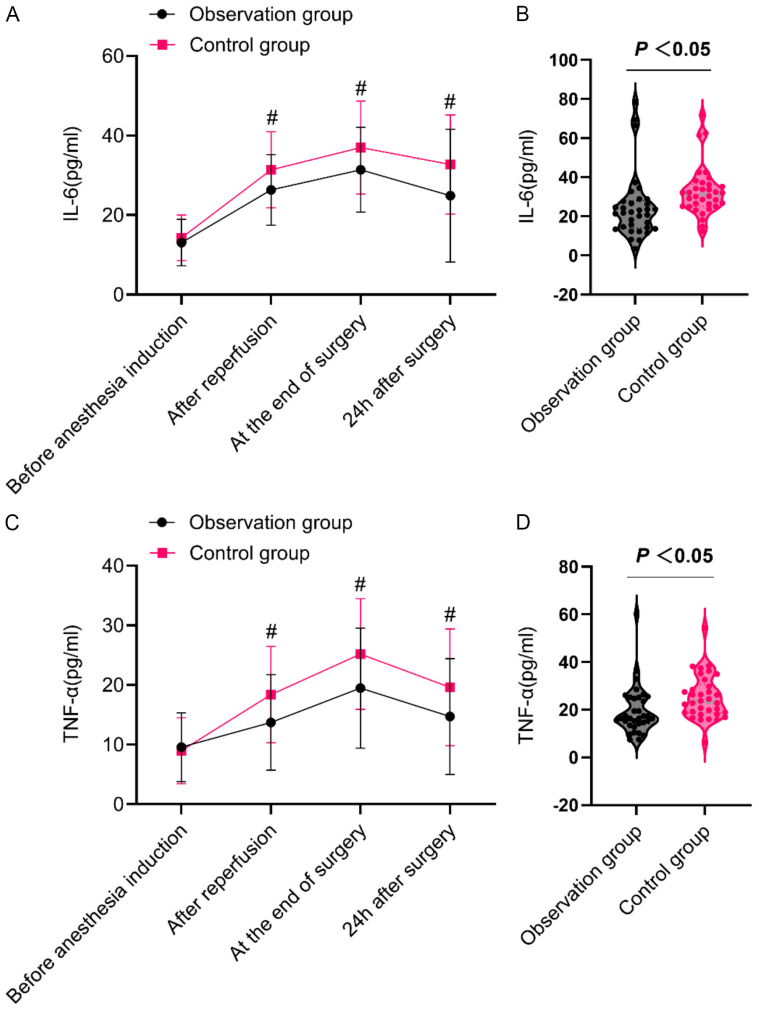

Figure 2. Perioperative serum concentrations of IL-6 and TNF-α in both groups. (A) IL-6 levels at various time points; (B) IL-6 levels at 24 h postoperatively; (C) TNF-α levels at various time points; (D) TNF-α levels at 24 h postoperatively. The DEX group had notably lower IL-6 and TNF-α levels than the control group at all postoperative time points (#*P* < 0.05 vs. control group). Notes: IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.

lead to hemorrhagic stroke or ischemic infarction [17, 18]. Thus, perioperative anesthetic management for MMD predominantly focuses on maintaining stable systemic blood pressure and avoiding rapid fluctuations that could compromise cerebral perfusion [6, 19]. Moreover, potential pathways of cerebral inflammation and vasospasm may be triggered by both observed and postulated etiological factors, including ischemic-reperfusion injuries to microvessels following cerebral surgeries [20, 21].

In this study, the DEX group showed significantly lower intraoperative MAP and SBP at key time points (T1, T2, T4, and T5) compared with the control group. Similar findings have been reported, that continuous DEX infusion can reduce cardiovascular responses triggered by surgical stress, tracheal intubation, skin incision, and extubation. The enhanced hemodynamic stability may stem from its central sympatholytic properties, resulting in a reduction in circulating catecholamines, such as epinephrine, norepinephrine, and cortisol [22, 23]. Moreover, perioperative parameter fluctuations (HR-V, MAP-V, SBP-V) from T0 to T5 showed that the DEX group had milder fluctuations than the control group, further supporting the stabilizing effect of DEX. It is noteworthy that, despite discontinuing DEX infusion before ICU transfer, MAP and SBP remained stable during extubation and post-extubation. However, caution is warranted as bradycardia remains a well-known cardiovascular adverse effect of DEX [24]. At multiple time points (e.g., intubation, skin incision, postoperative time points, and pre-extubation),

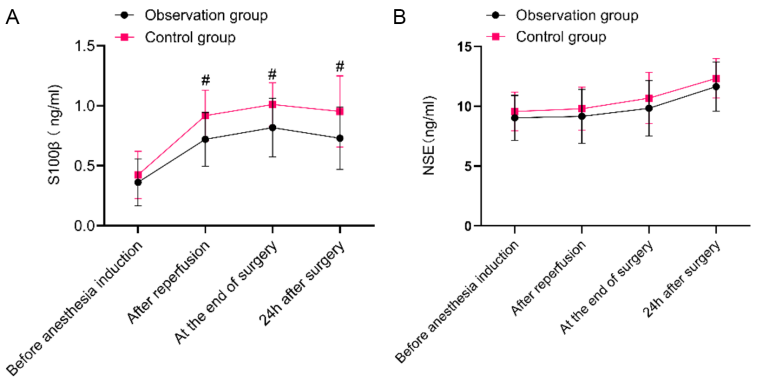

Figure 3. Serum concentrations of (A) S100β and (B) neuron-specific enolase (NSE) measured before anesthesia induction, after reperfusion, at surgery completion, and at 24 h postoperatively. The DEX group demonstrated significantly lower S100β levels compared to controls after reperfusion, at the conclusion of surgery, and at 24 h postoperatively (#$P < 0.05$ vs. control group). Notes: S100β, S100 beta protein; NSE, neuron-specific enolase.

HR was lower in the DEX group, consistent with previously documented dose-related reductions in HR following DEX administration [25]. Thus, close monitoring of HR during DEX infusion is imperative. Despite these observations, HR, MAP, and SBP were consistently maintained within acceptable ranges, suggesting that DEX can facilitate hemodynamic control during both anesthesia and recovery phases.

Inflammatory cytokines play an essential role in postoperative organ failure. During revascularization surgery, BBB disruptions and changes in cerebral perfusion parameters can potentially lead to inflammatory cytokines from the systemic circulation entering into the central nervous system, thereby increasing the risk of neuroinflammation and neuronal injuries [26, 27]. Furthermore, post-reperfusion levels of IL-6 and TNF-α were elevated, but the increase was significantly lower in the DEX group compared to the control group, both immediately after reperfusion and postoperatively. Experimental and clinical studies have documented that DEX exerts significant anti-inflammatory effects by suppressing cytokine secretion, particularly IL-6, IL-8, and TNF-α [9, 12]. These beneficial effects can be attributed to its inhibitory effects on both the sympathetic nervous system and the TLR4/NF-κB signaling pathways [28, 29]. Moreover, there were no significant between-group differences concerning the preoperative levels of IL-6 and TNF-α, consistent with previous studies indicating that cytokine levels were comparable between MMD and healthy subjects, except for IL-1β [30]. Given the variability in cytokine levels, IL-1β was excluded from this analysis to prevent interference with perioperative inflammation evaluation. Moreover, by inhibiting cytokine production, DEX reduces neuronal damage, improves postoperative outcomes, and ultimately promotes neural functional recovery.

Current studies on neuroanesthesia and neurosurgery emphasizes the growing importance of identifying effective biomarkers for neuronal damage. Among these, S100β and NSE have been established as biomarkers of neuronal damage associated with ischemic stroke, traumatic brain injury, or postoperative cognitive impairment [31, 32]. This study found that, DEX significantly decreased serum levels of S100β compared with controls, while NSE levels showed no changes. S100β is an astroglia cell protein that binds calcium and is mainly resident within the perivascular space. Upon BBB disruption, S100β is released into the bloodstream, making it a sensitive marker of BBB injury [33]. DEX may exert its protective effects by preventing or reducing ischemic-reperfusion injuries, thereby preserving BBB integrity and inhibiting S100β extravasation. Although S100β has been proven as a valid marker of BBB injury, its lack of specificity complicates clinical relevance, as it may be influenced by surgical stress and prolonged operative duration [31, 34, 35]. Conversely, NSE more specifically reflects neuronal injury, typically showing marked elevation only during severe cerebral ischemia or structural damage. The absence of significant NSE elevation may indicate milder cerebral injury during operation, suggesting a lower risk of cerebral damage associated with STA-MCA bypass under anesthesia.

Although the use of DEX during surgery appeared to reduce the incidence of neurological events, this trend did not reach statistical significance. This can be attributed to several factors. First, this clinical trial focused solely on intraoperative DEX infusion, whereas prior

Table 4. Comparison of postoperative neurological complications between the two groups [n (%)]

Group	n	CHS	TIA	Seizure	infarct	hemorrhage	RR (95% CI)	Total
Observation group	34	2 (5.89)	1 (2.94)	1 (2.94)	2 (5.89)	0 (0.00)	0.5 (0.21-1.18)	6 (17.65)
Control group	34	5 (14.70)	2 (5.89)	1 (2.94)	3 (8.82)	1 (2.94)	Reference	12 (35.29)
t/χ^2	-	-	-	-	-	-	-	2.72
P	-	-	-	-	-	-	-	0.099

Notes: CHS, cerebral hyperperfusion syndrome; TIA, transient ischemic attack; RR, relative risk; CI, confidence interval.

Table 5. Comparison of overall incidence of adverse events between the two groups [n (%)]

Group	n	Nausea and vomiting	Hypotension	Bradycardia	Drowsiness	Total
Observation group	34	1 (2.94)	1 (2.94)	2 (5.89)	1 (2.94)	4 (11.76)
Control group	34	2 (5.89)	1 (2.94)	0 (0.00)	0 (0.00)	5 (14.70)
t/χ^2	-	-	-	-	-	0.128
P	-	-	-	-	-	0.720

studies indicate that perioperative DEX infusion, from preoperatively through 72 hours postoperatively, significantly decreases the incidence of CHS following carotid artery stenting [36]. Compared with these studies, the more focused regimen of intraoperative DEX infusion alone may only reduce CHS episodes rather than the overall neurological events. Second, this trial only monitored CHS occurrence within the first 24 hours postoperatively, whereas CHS usually develops between 24 and 72 hours following MMD-revascularization surgeries, potentially leading to an underestimation of its occurrence [16]. All these observations suggest that larger-scale studies are warranted to comprehensively investigate and affirm the prolonged neuroprotective effects of DEX during MMD-revascularization surgeries.

In this study, DEX not only protected intraoperative hemodynamics but also decreased inflammatory cytokine levels and S100β, revealing its diverse and complementary neuroprotective effects. Stable intraoperative hemodynamics may help prevent cerebral blood flow irregularities, thereby reducing susceptibility to CHS, as blood pressure fluctuations play a critical role in preventing CHS [18, 37]. Moreover, DEX alleviates CHS by inhibiting systemic inflammation and preventing circulating mediators from penetrating the compromised BBB in MMD patients, and thereby reducing secondary neuronal injury [38-41]. Moreover, experimental studies have verified that DEX exerts diverse and complementary neuroprotective effects through multiple mechanisms, including anti-oxidation, protection against ischemia-reperfusion injury, and preservation of BBB integrity, providing comprehensive neuroprotection against CHS [42]. Through these comprehensive and diverse actions, DEX may facilitate neurological recovery and postoperative function improvement after revascularization. Although this clinical trial did not directly evaluate postoperative neurological improvement, multiple studies have proposed that postoperative DEX infusion significantly reduces postoperative delirium, shortens postoperative ICU stay, and facilitates early neurological recovery [43, 44]. Currently, available clinical guidelines do not include DEX in perioperative care protocols for MMD, nor do they recommend its clinical use in this population. However, based on its beneficial effects on blood pressure regulation and its anti-inflammatory properties observed in this study, DEX may serve as an adjuvant anesthetic and surgical care measure for other neurosurgical patient populations.

There are certain limitations of this study. First, neurological events were monitored only during the first 24 hours, while delayed CHS in MMD often emerges between postoperative 24 and 72 hours. This short observation window probably resulted in missed events and may partly explain why the DEX group had fewer complications without reaching statistical significance ($P = 0.099$). Future studies should extend postoperative neurological monitoring to at least 72 hours to detect delayed CHS and other neurological complications. Second, this study adopted a randomized controlled approach but with a small sample size, which may constitute a potential limitation as it may lack statistic

power and external validity, especially concerning rare neurological complications. Consequently, this could be one reason why there were no significant differences despite fewer neurological events in the DEX group. Furthermore, findings of inflammatory and neuronal biomarkers should be regarded as exploratory and warrant further investigation. Future research with larger sample sizes is needed to verify the positive effects of DEX on postoperative neurological recovery. Third, despite the efforts made, effective monitoring of BIS was not achieved due to artifactual changes induced during surgeries. Thus, anesthetic depth was primarily assessed based on dosing guidelines and hemodynamic parameters, and the effect of DEX on anesthetic depth and hemodynamics remains partially unaccounted for. Fourth, due to technical limitations and patient positioning issues, cerebral perfusion monitoring techniques such as transcranial Doppler (TCD) or near-infrared spectroscopy (NIRS) could not be employed, which would help verify whether stable hemodynamics directly improved cerebral oxygenation or perfusion. Finally, blood sampling was limited to 24 hours postoperatively, potentially overlooking delayed effects at the inflammatory or neuronal levels. Extending the sampling window is therefore warranted. Future studies should focus on determining whether the beneficial effects observed with intraoperative DEX, such as improvements in perioperative hemodynamics, inflammation, and S100β levels, can be translated into improved neurological and cognitive functions. Detailed cerebral perfusion studies, neurological assessments, along comprehensive analysis of neurological events, would help validate the translational potential of intraoperative DEX administration.

Conclusion

In summary, intraoperative DEX infusion played a crucial role in achieving hemodynamic stability, reducing inflammation, and lowering neuronal damage marker levels following direct revascularization in MMD patients. Although the incidence of neurological complication was lower in the DEX group, this difference did not reach statistical significance. Based on these preliminary clinical findings, it can be inferred that DEX possesses neuroprotective effects. However, larger-scale studies with broader geographic coverage are still required to validate its efficacy.

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Disclosure of conflict of interest

None.

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