Prospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(12) 1–11

DOI: 10.1177/03000605211062789
journals.sagepub.com/home/imr
SAGE

Effects of different sedatives/analgesics on stress responses in patients undergoing craniotomy and bone flap decompression

Qingduo Guo[1], Meina Ma[1], Qiuying Yang[2], Hong Yu[1], Xupeng Wang[1], Chunling Wu[1] and Rui Li[1]

Abstract

Objective: To explore the effects of sedation and analgesia with dexmedetomidine and other drugs on the stress response in patients with cerebral hemorrhage after craniotomy hematoma removal and bone flap decompression and insertion of an indwelling endotracheal catheter.

Methods: A total of 180 patients with cerebral hemorrhage with consciousness disturbance who underwent emergency surgery were included in this study. They were divided into six groups treated with propofol, dexmedetomidine, lidocaine, sufentanil, dezocine, and remifentanil, respectively. Intravenous medication was given after recovery of spontaneous respiration, and stress responses were compared among the group.

Results: Serum concentrations of norepinephrine, epinephrine, and cortisol and systolic blood pressure were significantly correlated with drug treatment. Serum norepinephrine concentrations differed significantly among the groups, except between the sufentanil and propofol groups. There were significant differences in serum epinephrine concentrations among all groups, and significant differences in serum cortisol concentrations among all groups, except the propofol, dexmedetomidine, and lidocaine groups.

Conclusion: Dexmedetomidine can reduce the stress response in patients with intracerebral hemorrhage undergoing emergency craniotomy and bone flap decompression, and can reduce adverse events from an indwelling endotracheal catheter 3 hours post-operation.

[1]Department of Anesthesiology, Cangzhou Central Hospital, No. 16 Xinhua Western Road, Cangzhou, Hebei Province, P.R. China
[2]Purchasing Department, Cangzhou Central Hospital, No. 16 Xinhua Western Road, Cangzhou, Hebei Province, P.R. China

Corresponding author:
Qingduo Guo, Department of anesthesiology, Cangzhou Central Hospital, No. 16 Xinhua Western Road, Cangzhou, Hebei Province 061000, P.R. China.
Email: qdg6662021@163.com

Keywords
Cerebral hemorrhage, intravenous endotracheal tube, stress response, hemodynamics, calm, analgesic, dexmedetomidine

Date received: 27 September 2021; accepted: 9 November 2021

Introduction

Intracerebral hemorrhage (ICH) is the most fatal subtype of stroke.[1,2] Patients with ICH who experience consciousness disorders may need adjuvant prophylactic tracheotomy and may require an indwelling endotracheal catheter after surgery.[1] However, the various anesthetic drugs used for postoperative sedation and analgesia have been reported to influence the perioperative stress response, thus affecting patient prognosis.[3] Dexmedetomidine is a new, highly selective α2-adrenergic receptor agonist that has been shown to significantly reduce the incidence of adverse events in patients.[4] The effects of dexmedetomidine are dose-dependent in terms of its intermediate analgesia, antisympathetic activity, sedation, and reduced development of stress in patients.[5,6] It can stabilize the patient's hemodynamics, and in the process of stabilizing the patient's respiratory system, it can also be combined with the effects of other general anesthetics, sedatives, and analgesics to reduce the doses of propofol and fentanyl used during surgery.[7]

Negative emotions prior to surgery, bleeding, and painful stimulation during surgery can lead to a neuroendocrine stress response, resulting in increased blood cortisol levels.[8] In addition, an enhanced stress response is associated with increased hypothalamus–cortex axis activity and increased glucocorticoid release. The appropriate use of suitable anesthetic agents can reduce the probability of a stress reaction in patients undergoing surgery, thus reducing cortisol secretion and helping to maintain homeostasis. Interleukin-6 levels are also related to the patient's status during surgery, and the duration and magnitude of interleukin-6 release are essentially consistent with the levels of anesthesia and trauma, and provide a sensitive marker of the tissue stress response.[9] However, the effects of sedation and analgesia using different drugs on the perioperative stress response in patients undergoing decompressive craniectomy have not been confirmed. This study therefore investigated the effects of postoperative sedation and analgesia with dexmedetomidine and other drugs on the perioperative stress response in patients with ICH and consciousness disorders who underwent emergency surgery, to provide a reference for clinical treatment.

Materials and methods

General information

Patients with cerebral hemorrhage with consciousness disorders who underwent emergency surgery in our hospital from December 2018 to June 2020 were included in this study. The study was approved by the ethics committee of Cangzhou Central Hospital (CZCH2017056, 6 May 2017). The reporting of this study conforms to the CONSORT statements (Figure 1).[10]

The inclusion criteria were: (1) craniotomy hematoma removal under general anesthesia plus bone flap decompression, with a

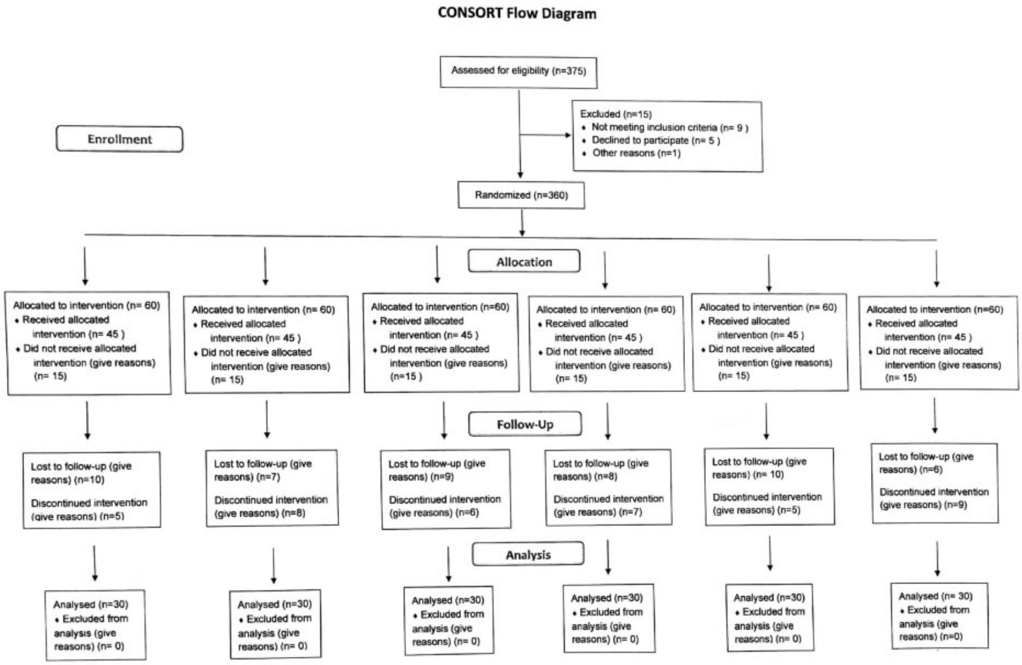

Figure 1. CONSORT flow diagram.

postoperative indwelling endotracheal catheter; (2) cerebral hemorrhage classified as grade I or primary grade according to the American Society of Anesthesiologists criteria; and (3) patients and their families signed consent for anesthesia and provided informed consent to participate in clinical research. The exclusion criteria were (1) serious heart or lung dysfunction or abnormal liver or kidney function; (2) severe hypovolemia, mean arterial depression of less than 50 mmHg, or uncontrolled hypertension; (3) patients who did not wish to participate or who were lost to follow-up; (4) pregnancy; and (5) steroid therapy or other immunosuppressant medications, or sympatholytics. The patients were divided into six groups using the random number table method and treated with propofol, dexmedetomidine, lidocaine, sufentanil, dezocine, and remifentanil, respectively.

Drug administration

Following recovery of spontaneous respiration after surgery, the drugs were administered in the following ways. Propofol (national medicine approval: H20030115; 0.2 g/20 mL; Sichuan Guorui Pharmaceutical Co., Ltd., China) was given as a single intravenous loading dose of 0.5 to 3 mg/kg followed by a continuous infusion of 0.5 to 4 mg/kg/hour using a minimal injection pump. Dexmedetomidine (national drug approval: H20163388; 0.1 mg/1 mL; Chenxin Pharmaceutical Co., Ltd., China) was administered at a loading dose of 0.6 to 1 g/kg/hour,[11] injected intravenously within 10 minutes, followed by a maintenance dose of 0.2 to 0.7 g/kg/hour by continuous infusion. Lidocaine (national drug approval: H20065388; 0.2 g/10 mL; China Otsuka Pharmaceutical Co., Ltd., China) was administered at a loading dose of 1 to 1.5 mg/kg, 2 mg/kg/hour for 4 hours, reduced to

1 mg/kg/hour for 24 to 48 hours. Patients in the dezocine group (national drug approval: H20080329; 5 mg/mL; Yangzijiang Pharmaceutical Group Co., Ltd., China) received an intravenous injection of 0.1 mg/kg 10 to 20 minutes before the end of surgery, followed by a maintenance dose of 16 g/hour. Sufentanil (national drug approval: H20054172; 200 g/2 mL; Yichang Renfu Pharmaceutical Co., Ltd., China) was administered by intravenous injection of 10 g followed by a maintenance dose of 5 g/hour by continuous infusion. Patients in the remifentanil group (national drug approval: H20030199; 2 mg; Yichang Renfu Pharmaceutical Co., Ltd., China) received a loading dose of 0.5 to 1.0 g/kg followed by a maintenance dose of 0.25 to 4 g/kg/minute.[12,13]

Patient indicators

Blood samples (2 mL) were collected from the anterior cubital vein of patients at 3 hours post-surgery, and 1 mL serum samples were stored at low temperature. Serum samples were analyzed for norepinephrine, epinephrine, and cortisol using enzyme-linked immunosorbent assay kits (Nanjing Beiyu Biotechnology Co., Ltd., Nanjing, China) and an enzyme plate analyzer (Shanghai Xiyan Scientific Instrument Co., Ltd., Shanghai, China). Systolic (SBP) and diastolic blood pressure (DBP) were measured using a non-invasive blood pressure monitor and the occurrence of drug-related adverse events (tube agitation, respiratory depression, or choking) within 6 hours post-surgery were also recorded.

Statistical methods

Statistical analysis was carried out using SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) and graphs were drawn using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). Measured data were expressed as means ± standard deviation and numerical data were given as number and percentage. Comparisons between groups were made using *post hoc* Bonferroni, Tukey's, or Mann–Whitney U tests.

Results

Patients

A total of 180 patients with cerebral hemorrhage and consciousness disorders who underwent emergency surgery in our hospital from December 2018 to June 2020 were included in this study and divided equally among the six groups ($n = 30$ each). General data, such as sex, age, and body mass index (BMI) were compared among the groups at baseline (Table 1). There were no significant differences in the duration of surgery, stress response parameters, or hemodynamic indexes, including serum concentrations of norepinephrine, epinephrine, and cortisol, and SBP

Table 1. General patient data.

Group	Sex (male/female)	Age (years)	Body mass index (kg/m^2)	Operation time (h)
Propofol	20/10	60.50 ± 8.19	20.13 ± 0.25	6.83 ± 2.53
Dexmedetomidine	21/9	60.25 ± 10.14	20.40 ± 0.10	6.00 ± 2.69
Lidocaine	22/8	60.05 ± 10.10	21.93 ± 0.24	6.13 ± 1.79
Sufentanil	21/9	61.37 ± 9.61	21.90 ± 0.38	6.33 ± 2.91
Dezocine	20/10	61.07 ± 10.73	21.10 ± 0.32	6.37 ± 0.44
Remifentanil	20/10	59.73 ± 9.96	20.97 ± 0.15	6.17 ± 0.07
F/χ^2	1.410	2.16	1.98	1.83

and DBP prior to drug administration (Table 2).

Comparison of hemodynamic parameters

The hemodynamic parameters of the patients in the six groups at 3 hours post-surgery are shown in Table 3 and Figures 2–6. There were significant differences ($P < 0.05$) in serum norepinephrine levels among all groups, except between the sufentanil and propofol groups. Serum epinephrine levels also differed significantly among the groups ($P < 0.05$), and there were significant differences ($P < 0.05$) in serum cortisol concentrations among all the groups, except the propofol, dexmedetomidine, and lidocaine groups. There were no significant differences in SBP among the dexmedetomidine, lidocaine, dezocine, and remifentanil groups, or between the propofol and sufentanil groups, but the differences among the other groups were statistically significant ($P < 0.05$). There were no significant differences in DBP among the remifentanil, sufentanil, and lidocaine groups, the sufentanil, lidocaine, and dexmedetomidine groups, the propofol and dezocine groups; and the dezocine and remifentanil groups, but the differences among all the other groups were statistically significant ($P < 0.05$).

Drug complications

The incidences of tube agitation, respiratory depression, and choking in the six groups within 6 hours following drug

Table 2. Stress response parameters and hemodynamic indexes before administration.

Group	Plasma norepinephrine (pg/mL)	Plasma epinephrine (pg/mL)	Cortisol (ng/mL)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Propofol	306.77 ± 36.07	76.60 ± 8.56	204.13 ± 17.67	126.83 ± 12.53	74.30 ± 9.04
Dexmedetomidine	304.93 ± 20.60	74.36 ± 7.72	209.40 ± 27.69	126.00 ± 12.69	75.90 ± 8.71
Lidocaine	311.53 ± 29.59	71.97 ± 8.61	207.93 ± 19.24	125.13 ± 10.79	75.00 ± 8.62
Sufentanil	312.70 ± 34.68	70.37 ± 9.61	209.90 ± 24.57	127.33 ± 12.91	76.00 ± 9.18
Dezocine	307.70 ± 14.68	71.07 ± 8.73	203.10 ± 15.48	127.37 ± 10.44	75.83 ± 10.14
Remifentanil	305.70 ± 19.49	71.73 ± 7.96	208.97 ± 25.01	128.17 ± 11.07	74.67 ± 7.67
F value	1.76	1.69	0.55	1.84	0.25

Table 3. Stress response and hemodynamic parameters in patients treated with different drugs 3 hours after surgery.

Group	Plasma norepinephrine (pg/mL)	Plasma epinephrine (pg/mL)	Cortisol (ng/mL)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Propofol	350.77 ± 142.81	56.60 ± 14.71	284.13 ± 151.43	139.83 ± 13.86	95.90 ± 14.85
Dexmedetomidine	154.93 ± 58.06	34.37 ± 3.34	349.40 ± 151.71	120.00 ± 14.73	72.30 ± 11.15
Lidocaine	224.53 ± 52.50	41.37 ± 3.34	297.93 ± 149.18	158.13 ± 9.79	90.00 ± 14.38
Sufentanil	342.70 ± 25.62	50.37 ± 3.34	659.90 ± 25.61	146.33 ± 15.96	89.00 ± 11.93
Dezocine	437.70 ± 25.62	61.07 ± 3.99	613.10 ± 29.40	161.37 ± 18.86	75.83 ± 17.18
Remifentanil	524.70 ± 25.62	81.73 ± 5.25	710.97 ± 27.45	164.17 ± 16.84	83.67 ± 14.64
F value	115.442*	169.878*	97.970*	11.195*	12.117*

*$P < 0.05$.

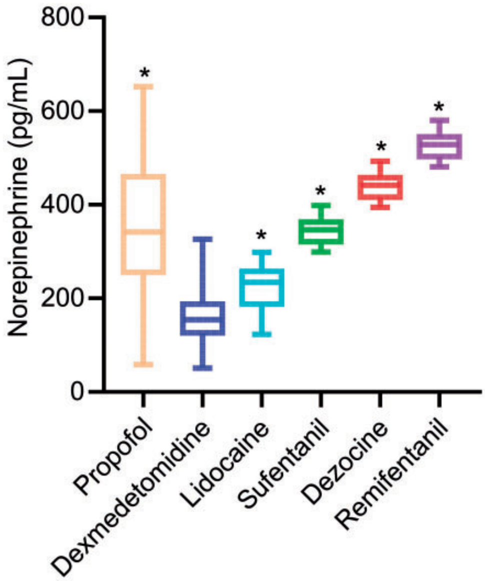

Figure 2. Serum norepinephrine levels in each group. Boxes and whiskers indicate median, interquartile range, maximum, minimum, and an outlier.

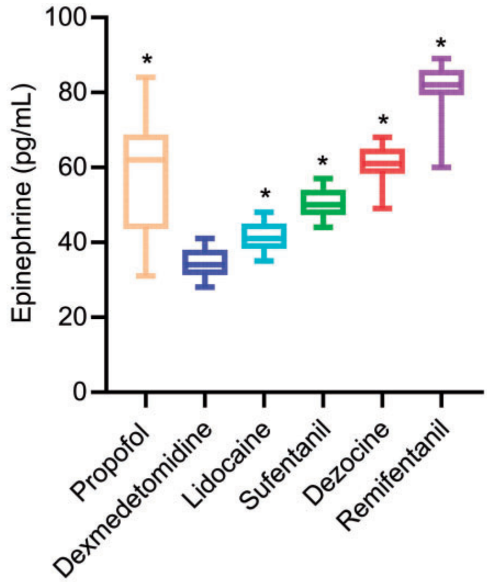

Figure 3. Serum epinephrine levels in each group. Boxes and whiskers indicate median, interquartile range, maximum, minimum, and an outlier.

administration are shown in Table 4. The incidences of tube agitation and cough differed significantly among the groups ($P < 0.01$).

Discussion

Propofol is widely used to induce and maintain anesthesia and sedation. It has also demonstrated anti-emetic, anti-anxiety, and analgesic effects and can regulate immune activity,[14,15] and can be used as an effective neuroprotective agent.[16,17] In this study of patients with cerebral hemorrhage combined with consciousness disturbance who underwent emergency surgery, serum cortisol levels were lower in patients treated with propofol compared with the other groups, while SBP and DBP were also lower than all the other groups, except for the dexmedetomidine group. In terms of safety, the incidence of tube-intolerance agitation within 6 hours of

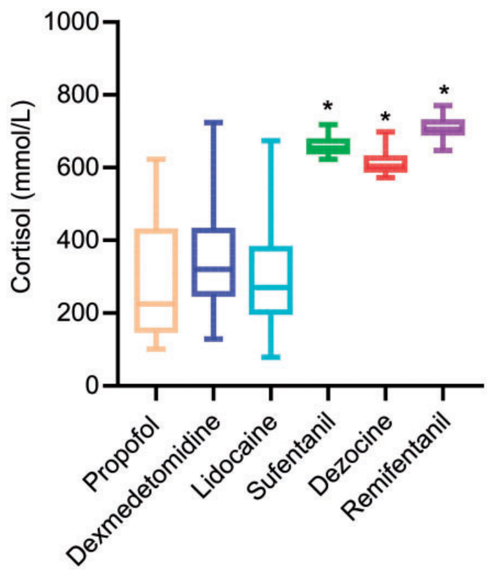

Figure 4. Serum cortisol levels in each group. Boxes and whiskers indicate median, interquartile range, maximum, minimum, and an outlier.

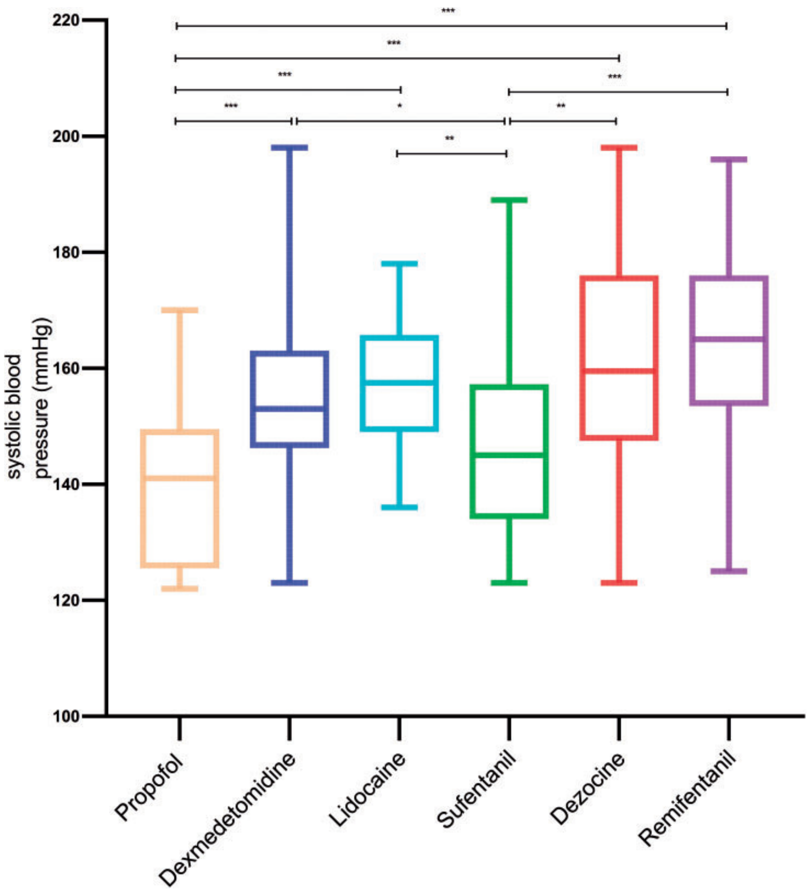

Figure 5. Systolic blood pressure levels in each group. Boxes and whiskers indicate median, interquartile range, maximum, and minimum. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

propofol administration was higher (63.3%) but the incidence of cough was lower (26.7%) than in the other groups, apart from the lidocaine and dexmedetomidine groups, respectively.

Dexmedetomidine is widely used during the perioperative period to provide sedative, anti-anxiety, analgesic, and anti-sympathetic effects.[18,19] Compared with other sedatives, dexmedetomidine has the advantages of reduced respiratory depression, less effect on nervous system function, and maintaining airway patency and airway reflexes during wakefulness.[5,20] In this study, serum norepinephrine and epinephrine levels were lower in the dexmedetomidine group compared with the other groups, and the effect of dexmedetomidine on serum cortisol levels was similar to that of propofol. The incidence of tube intolerance agitation was lowest in the dexmedetomidine group (23.3%).

Intravenous lidocaine has anti-inflammatory, antimicrobial, and anti-tumor effects, and provides postoperative pain relief and inhibits thrombosis.[21,22] The clinical effect of intravenous lidocaine is particularly significant in abdominal surgery.[23] In the present study, intravenous lidocaine had a similar effect on

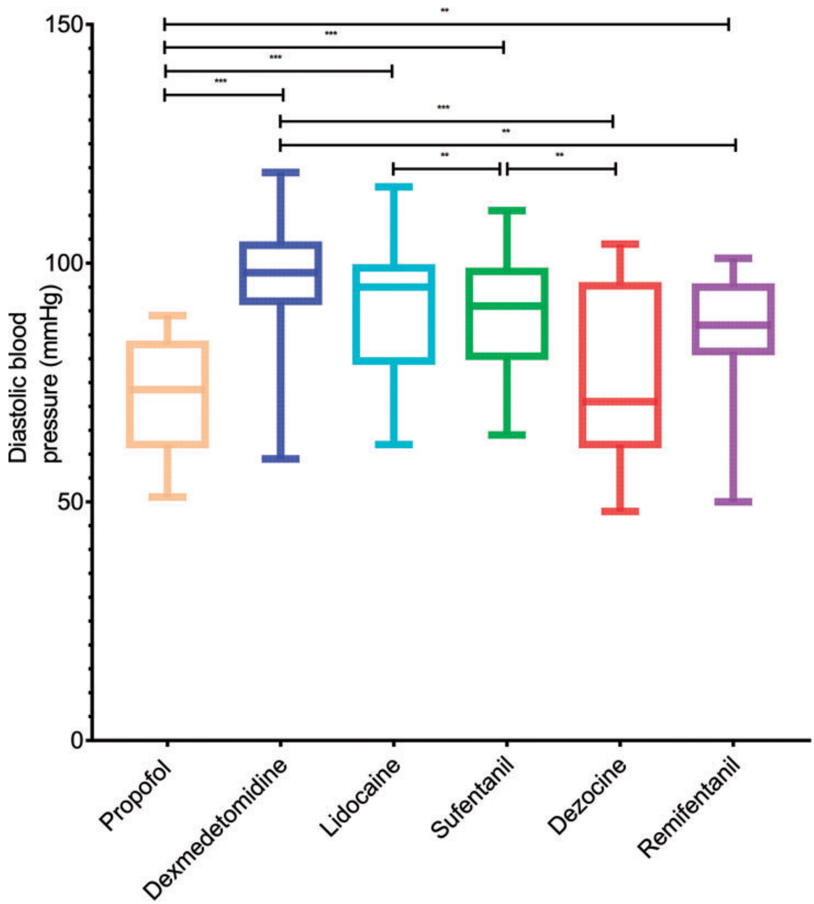

Figure 6. Diastolic blood pressure levels in each group. Boxes and whiskers indicate median, interquartile range, maximum, and minimum. $^{**}P < 0.01$; $^{***}P < 0.001$.

Table 4. Incidence of drug complications 6 hours after surgery in patients treated with different drugs.

Group	Anxiety of tube agitation (%)	Respiratory depression (%)	Choking cough (%)
Propofol	19 (63.3)	11 (36.7)	8 (26.7)
Dexmedetomidine	7 (23.3)	12 (40.0)	7 (23.3)
Lidocaine	22 (73.3)	10 (33.3)	13 (43.3)
Sufentanil	11 (36.7)	12 (40.0)	22 (73.3)
Dezocine	12 (40.0)	14 (46.7)	10 (33.3)
Remifentanil	9 (30.0)	11 (36.7)	10 (33.3)
χ^2	23.400**	1.309†	17.310**

$^{**}P < 0.01$; $^{\dagger}P > 0.05$.

hemodynamic parameters to dexmedetomidine. The incidences of respiratory depression (33.3%) and choking (43.3%) were lowest with intravenous lidocaine, while the incidence of tube intolerance agitation was the highest (73.3%).

Remifentanil is suitable for elderly patients because of its quick action, no retention in the body, no liver or kidney toxicity, and other characteristics; however, this drug can cause naloxone antagonism, producing restlessness, hypotension, bradycardia, and other stress reactions, thus aggravating patients' pain. In this study, patients treated with remifentanil had the highest serum norepinephrine, epinephrine, and cortisol levels, and the highest SBP among the six groups, indicating that remifentanil was associated with a greater stress response than the other drugs. However, the safety data were acceptable (tube agitation, 30%; respiratory depression, 36.7%; cough, 33.3%).

Sufentanil is an opioid receptor agonist that is about five to ten times more potent than remifentanil. The current results showed that patients in the sufentanil group had a better postoperative stress responses than those in the remifentanil group. Compared with the other groups, sufentanil had similar effects on serum norepinephrine and SBP to propofol. The incidences of tube agitation (36.7%) and respiratory depression (40%) were similar to those for remifentanil, but the incidence of cough was the highest among all six groups (73.3%).

Dezocine is widely used in postoperative pain management, but can cause adverse reactions common to other opioids, such as nausea, vomiting, dizziness, and drowsiness, as well as respiratory depression caused by improper drug application, especially when combined with other central nervous system sedative drugs.[24,25] In this study, the effects of dezocine on serum cortisol levels and SBP were similar to those of fentanyl-related drugs, and its effects on serum epinephrine and DBP were similar to those of propofol. Respiratory depression was the most frequent adverse event associated with dezocine (46.7%).

Dexmedetomidine has neuro-anti-inflammatory properties and can improve pain communication compared with midazolam and propofol.[26] Dexmedetomidine can therefore be used for mild sedation. The analgesic effects of dexmedetomidine and/or the reduction of other delirious sedatives may reduce agitation and delirium. Dexmedetomidine can suppress inflammatory reactions and protect organs in animals and humans.[27,28] Dexmedetomidine provides more comfort during procedures for both the patient and clinician.[11] It is currently widely used in surgical and non-surgical intensive care units, and has broad application prospects in neuroprotection, cardioprotection, and renal protection.[29]

This study had some limitations. First, the sample size was small and needs to be increased in further studies. Second, this was a single-center study, and further multicenter studies are needed to confirm the results.

In conclusion, different drugs had different effects on the stress response to an indwelling endotracheal catheter 3 hours post-surgery, and different adverse effects in patients with cerebral hemorrhage undergoing emergency craniotomy hematoma removal plus bone flap decompression. These results suggest that a combination of different drugs may help to reduce the stress response and complications in patients undergoing neurosurgery. This study provides useful information to guide the choice of perioperative sedative and analgesic use during neurosurgery.

Data availability

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

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Gross BA, Jankowitz BT and Friedlander RM. Cerebral intraparenchymal hemorrhage: A review. *JAMA* 2019; 321: 1295–1303. DOI: 10.1001/jama.2019.2413.
2. Stinear CM, Lang CE, Zeiler S, et al. Advances and challenges in stroke rehabilitation. *Lancet Neurol* 2020; 19: 348–360. DOI: 10.1016/S1474-4422(19)30415-6.
3. Zhu X. Efficacy of preemptive analgesia versus postoperative analgesia of celecoxib on postoperative pain, patients' global assessment and hip function recovery in femoroacetabular impingement patients underwent hip arthroscopy surgery. *Inflammopharmacology* 2020; 28: 131–137. DOI: 10.1007/s10787-019-00648-8.
4. Li A, Yuen VM, Goulay-Dufaÿ S, et al. Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. *Br J Anaesth* 2018; 120: 960–968.
5. Bao N and Tang B. Organ-protective effects and the underlying mechanism of dexmedetomidine. *Mediators Inflamm* 2020; 2020: 6136105. DOI: 10.1155/2020/6136105.
6. Xu Z, Wang D, Zhou Z, et al. Dexmedetomidine attenuates renal and myocardial ischemia/reperfusion injury in a dose-dependent manner by inhibiting inflammatory response. *Ann Clin Lab Sci* 2019; 49: 31–35.
7. Lee S. Dexmedetomidine: present and future directions. *Korean J Anesthesiol* 2019; 72: 323–330.
8. Scott AT and Howe JR. Evaluation and management of neuroendocrine tumors of the pancreas. *Surg Clin North Am* 2019; 99: 793–814.
9. McCann ME and Soriano SG. Does general anesthesia affect neurodevelopment in infants and children. *BMJ* 2019; 367: l6459.
10. Schulz KF, Altman DG and Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340: c332.
11. Barends CR, Absalom A, van Minnen B, et al. Dexmedetomidine versus midazolam in procedural sedation. A systematic review of efficacy and safety. *PLoS One* 2017; 12: e0169525.
12. Cohen J and Royston D. Remifentanil. *Curr Opin Crit Care* 2001; 7: 227–231.
13. Sridharan K and Sivaramakrishnan G. Comparison of fentanyl, remifentanil, sufentanil and alfentanil in combination with propofol for general anesthesia: A systematic review and meta-analysis of randomized controlled trials. *Curr Clin Pharmacol* 2019; 14: 116–124.
14. Cai X, Li Y, Zheng X, et al. Propofol suppresses microglial phagocytosis through the downregulation of MFG-E8. *J Neuroinflammation* 2021; 18: 18.
15. Stogiannou D, Protopapas A, Protopapas A and Tziomalos K. Is propofol the optimal sedative in gastrointestinal endoscopy? *Acta Gastroenterol Belg* 2018; 81: 520–524.
16. Sun W, Wang J, Cai D, et al. Neuroprotection of the developing brain by dexmedetomidine is mediated by attenuating single propofol-induced hippocampal apoptosis and synaptic plasticity deficits. *Exp Neurobiol* 2020; 29: 356–375. DOI: 10.5607/en20032.
17. Wang Y, Tian D, Wei C, et al. Propofol attenuates α-Synuclein aggregation and neuronal damage in a mouse model of ischemic stroke. *Neurosci Bull* 2020; 36: 289–298. DOI: 10.1007/s12264-019-00426-0.
18. Hashmi JA, Loggia ML, Khan S, et al. Dexmedetomidine disrupts the local and global efficiencies of large-scale brain networks. *Anesthesiology* 2017; 126: 419–430.
19. Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial

fibrillation and delirium after cardiac surgery (DECADE): A randomised placebo-controlled trial. *Lancet* 2020; 396: 177–185. DOI: 10.1016/S0140-6736(20)30631-0.
20. Zhao Y, He J, Yu N, et al. Mechanisms of dexmedetomidine in neuropathic pain. *Front Neurosci* 2020; 14: 330. DOI: 10.3389/fnins.2020.00330.
21. Beaussier M, Delbos A, Maurice-Szamburski A, et al. Perioperative use of intravenous lidocaine. *Drugs* 2018; 78: 1229–1246.
22. Yang SS, Wang NN, Postonogova T, et al. Intravenous lidocaine to prevent postoperative airway complications in adults: A systematic review and meta-analysis. *Br J Anaesth* 2020; 124: 314–323. DOI: 10.1016/j.bja.2019.11.033.
23. Liu J, Liu X, Peng LP, et al. Efficacy and safety of intravenous lidocaine in propofol-based sedation for ERCP procedures: A prospective, randomized, double-blinded, controlled trial. *Gastrointest Endosc* 2020; 92: 293–300. DOI: 10.1016/j.gie.2020.02.050.
24. Zhou J, Qi F, Hu Z, et al. Dezocine attenuates the remifentanil-induced postoperative hyperalgesia by inhibition of phosphorylation of CaMKIIα. *Eur J Pharmacol* 2020; 869: 172882. DOI: 10.1016/j.ejphar.2019.172882. 2020,869:172882.
25. Dong Y, Liang Z, Xu Z, et al. Effects of dezocine, morphine and nalbuphine on electropain threshold, temperature pain threshold and cardiac function in rats with myocardial ischemia. *Ann Palliat Med* 2020; 9: 1556–1563. DOI: 10.21037/apm-19-460.
26. Kawazoe Y, Miyamoto K, Morimoto T, et al. Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: A randomized clinical trial. *JAMA* 2017; 317: 1321–1328.
27. Shin AH, You JC, Ahn JH, et al. Anti-inflammatory effects of dexmedetomidine on human amnion-derived WISH cells. *Int J Med Sci* 2020; 17: 2496–2504.
28. Li B-Y, Liu Y, Li Z-H, et al. Dexmedetomidine promotes the recovery of renal function and reduces the inflammatory level in renal ischemia-reperfusion injury rats through PI3K/Akt/HIF-1α signaling pathway. *Eur Rev Med Pharmacol Sci* 2020; 24: 12400–12407.
29. Afonso J and Reis F. Dexmedetomidine: Current role in anesthesia and intensive care. *Rev Bras Anestesiol* 2012; 62: 118–133.