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Intraoperative Dexmedetomidine Versus Midazolam in Patients Undergoing Peripheral Surgery With Mild Traumatic Brain Injuries: A Retrospective Cohort Analysis

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Abstract

Background: The intra- and postoperative effects of dexmedetomidine are not completely consistent and midazolam/fentanyl is most widely used in peripheral surgeries. The objectives of the study were to evaluate the sedative, analgesic, hemodynamic, anti-inflammatory, and antioxidant effects of dexmedetomidine against midazolam in patients undergoing peripheral surgeries with mild traumatic brain injuries.

Methods: Medical records of patients who underwent peripheral surgeries with mild traumatic brain injury were included in the analysis. Patients received intraoperative midazolam (MDZ cohort, n = 225) or dexmedetomidine (DEX cohort, n = 231). Pre-, intra-, and postoperative characteristics of patients were collected and analyzed.

Results: After administration of anesthesia, up to 40 minutes, patients of the MDZ group had lower modified observer's assessment of alertness/sedation score than those of the DEX group ($P = .041$), but after 40 minutes, patients of the MDZ group had a higher score than those of the DEX group throughout surgeries ($P = 0.048$). The DEX group has less requirements of postoperative morphine/equivalent doses than the MDZ group (4 ± 1 vs 5 ± 1, $P < .0001$, $q = 18.451$).

Conclusions: Intraoperative DEX offers better sedation, postoperative analgesia, and clinical recovery for peripheral surgeries and suppresses inflammatory response.

Level of Evidence: III.

Keywords

analgesia, anesthesia, dexmedetomidine, inflammatory response, midazolam, sedation

Introduction

Hemodynamic stability, weaker stimuli, and intracranial homeostasis are needed to achieve during surgeries.[1] Disordered hemodynamics enables neuroendocrine response or immune response, which leads to the onset of stress hormones and inflammatory response.[2] Inflammatory cascade emerged by neuroendocrine hormones and pro-inflammatory mediators contributes to the pathology of traumatic brain injuries.[3] During the major surgeries, these adverse physiological responses can be observed due to lower perfusion pressure, increased intracranial pressure, surgery-related damage, and/or pain stimuli.[4] Sometimes secondary traumatic brain injuries, for example, cerebral hemorrhage or cerebral edema, may damage brain

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tissue, which is affected by the recovery from anesthesia and postoperative cognition.[5] Therefore, to alter the balance of inflammation and neuroendocrine responses, to reduce incidences of postoperative complications, and to prevent traumatic brain injuries, it is necessary to consider anesthesia management.[1] Anesthesia and surgery often for causes unrelated to the early phase after mild traumatic brain injuries.[6] A stage in which the brain is vulnerable to the secondary insults could be caused or exacerbated by the procedure. Systemic inflammation and oxidative stress are postulated to have a role in such secondary injuries, and they seem to increase following a surgical procedure.[7]

Midazolam (MDZ) is a γ-aminobutyric acid receptor agonist type of benzodiazepine.[8] It is a commonly used anesthetic agent and does not affect neuronal growth.[9] It may protect against necroptosis and neuronal degeneration, which is induced by oxidative and physiological stress.[8] It exhibits dose-dependent respiratory depression.[10] Dexmedetomidine (DEX) has neuroprotective action by inhibiting neuroendocrine and inflammatory responses[1] and has a lack of respiratory depression.[10] However, the sedative, analgesic, and hemodynamic action of DEX is not completely consistent and MDZ with fentanyl is most widely used in peripheral surgeries. Anesthetics need a drug in peripheral surgeries that can be used safely with less severe adverse effects.[11] Therefore, there is a need for retrospective analysis to estimate the sedative, analgesic, hemodynamic, anti-inflammatory, and antioxidant role of DEX and MDZ before nonrandomized, single-blind, controlled trial.

The objectives of the retrospective analysis of prospectively collected data were to evaluate the sedative, analgesic, hemodynamic, anti-inflammatory, and antioxidant effects of DEX against MDZ in patients undergoing peripheral surgeries with mild traumatic brain injuries.

Materials and Methods

Ethics Approval and Consent to Participate

The designed protocol (GPPH/CL/15/19 dated January 12, 2019) of the established study had been approved by the Guizhou Provincial People's Hospital review board. The study had adhered to the law of China, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, and the Declaration of Helsinki (V2008). An informed consent form was signed by all participating patients regarding anesthesia, surgeries, pathology, and publication of the study during hospitalization.

Inclusion Criteria

Patients available at trauma care center due to sports injuries (eg, football, basketball, table tennis, and badminton), assaults, and falls (slipping, falling from a staircase, and falling from the ceiling) and underwent anesthesia and the surgical procedure (surgeon and emergency department physicians' decision) with mild traumatic brain injury (Glasgow Coma Scale 13-15 and the abnormal computed tomography scan like epidural hematoma, contusion, parenchymal hematoma, subarachnoid hemorrhage, subdural hematoma, and/or a skull fracture) were included in the study. Patients who had an American Society of Anesthesiology (ASA) status II or III were only included in the study.

Exclusion Criteria

Patients who faced motor vehicle accidents (automobile, boating, or motorcycle due to major brain injuries), a penetrating head injury (Glasgow Coma Scale less than 13), and duplicate anesthetic records were excluded from the study. Patients younger than 18 years of age and those who had ASA status I (no brain injuries), IV (a constant threat to life), or V (not expected to live 24 hours) were excluded from the study.

Data Collection

For each enrolled patient, the demographic characteristics, preoperative and postoperative pain conditions, type of surgeries, anesthesia used, intraoperative conditions, postoperative parameters, adverse effects, and clinical outcomes during the follow-up period were collected from medical records of institutes after written permission from the competing authorities.

Cohorts

Patients who received 49.9 μG/kg MDZ (Hospira, Inc, Lake Forest, Illinois) and 1 μG/kg fentanyl (Siegfried Hameln, Hameln, GmbH, Germany) in 25 mL of normal saline (Baxter Healthcare Corporation, Deerfield, Illinois) infused over 12 minutes, followed by a continuous infusion of 50 μG/kg/h MDZ in normal saline till the end of the surgery, were included in the MDZ cohort. Patients who received 0.999 μG/kg DEX (Precedex; Hospira, Inc) and 1 μG/kg fentanyl in 25 mL of normal saline infused over 12 minutes and then a continuous infusion of 1.0 μG/kg DEX in normal saline till the end of the surgery were included in the DEX cohort. A total of 100 mL intraoperative paracetamol (10 mg/mL; Accord Healthcare Ltd, North Harrow, United Kingdom) was injected to all patients. The decision of interventions (MDZ or DEX) in the predesign of the study was made based on the age of patients, necessities of sedation and analgesia, availabilities of medications, and the other demographical and clinical condition(s) of patients by anesthesiologists (a minimum of 3 years' experience) of institute in consultation with surgeons (a minimum of 3 years' experience) of institute who performed surgeries.

Anesthesia Method

Intravenous access was opened, internal jugular vein and radial artery puncture were performed under local lidocaine (Xylocaine Spray; AstraZeneca UK Limited, Macclesfield, Cheshire, United Kingdom), and a catheter (Roche, Basel, Switzerland) was inserted and central venous pressure and arterial venous pressure were monitored; 2 mg/kg propofol (Diprivan;

AstraZeneca, Cambridge, United Kingdom), 0.1 mg/kg vecuronium (Flexivec; Bharat Serums and Vaccines Limited, Thane, India), and 4 mg/kg ketamine (Hospira, Pfizer Inc, Richmond, Virginia) were injected.[7] Anesthesia procedure was performed by anesthesiologists (minimum 3 years' experience) of the institute. Bispectral index values were targeted 45 to 70 during operation. For recovery of anesthesia, the infusion of normal saline with DEX or MDZ was titrated until the end of surgery.[12]

Sedative Effects

The sedation was measured using a modified observer's assessment of alertness/sedation score. The scores are as follows: 5: response readily to name spoken; 4: lethargic response; 3: response after name called loudly; 2: response after mild to moderate shaking; 1: response to trapezius squeeze.[13] Observer's assessment of alertness/sedation score was evaluated by anesthesiologists (a minimum of 3 years' experience) of the institute in consultation with surgeons (a minimum of 3 years' experience) of the institute who performed surgeries. Bispectral index values and recovery criteria were recorded by anesthesiologists (a minimum of 3 years' experience) of the institute at various stages of operation.

Postoperative Pain Assessment

Postoperative pain was evaluated using visual analog scale (VAS) 24 hours after surgeries. 0: no pain and 10: the maximum possible pain.[14] Visual analog scale was administered to the patients by nursing staff (a minimum of 3 years' experience) of the institute who was not involved in surgeries.

Laboratory Parameters

Blood samples were collected from all participants by pathologists (a minimum of 3 years' experience) of the institute 24 hours before surgery and 24 hours after surgery and serum was isolated from samples. Serum interleukin 6, superoxide dismutase, S100β (S100 calcium-binding protein β), tumor necrosis factor α, neuron-specific enolase enzyme, and malondialdehyde were evaluated using enzyme-linked immunosorbent assay.[7] All assays were performed by pathologists (a minimum of 3 years' experience) of the institute.

Hemodynamic Parameters

Mean arterial pressure and heart rate were evaluated before anesthesia induction and 5 minutes after tracheal intubation.

Postoperative Pain Management

A total of 100 mL/d postoperative paracetamol (10 mg/mL) for 3 consecutive days was injected to all patients. Postoperative morphine (Duramorph; Baxter Healthcare Corporation, Deerfield, Illinois) or equivalent was administered as and when required (when VAS $\geq$3; the decision of surgeon(s)). The nursing staff (a minimum of 3 years' experience) of the institute in consultation with surgeons (who performed surgeries) were involved in postoperative pain management.

Clinical Outcome Measures

During the follow-up period, clinical outcomes of patients were reported at institutes that were used for analysis.

Statistical Analysis

SPSS version 25 (IBM Corporation, Armonk, New York) was used for the purpose of statistical analyses. The Fisher exact test was performed for ordinal data, and Mann-Whitney U test was performed for numerical data[6] between the groups. A 1-way repeated measures analysis of variance was performed for numerical data within a group. Tukey test (considering critical value $[q] > 3.314$ as significant) was performed for post hoc analysis. All results were considered significant at a 95% confidence level.

Results

Enrollment

From January 1, 2014, to December 12, 2018, medical records of 627 patients with mild brain injuries undergoing anesthesia and peripheral surgeries available at the trauma care center of the Guizhou Provincial People's Hospital, Guiyang, Guizhou, China, and the referring hospitals were reviewed. Among the available records, 62 patients had faced automobile accidents (major brain injuries), 13 patients had faced boating accidents (major brain injuries), 91 patients had faced motorcycle accidents (major brain injuries), and 5 patients had penetrating head injuries. Therefore, these patients were not included in the analysis because they had major brain injuries. A total of 456 patients were included in the analysis. Patients who received MDZ were included in the MDZ cohort (n = 225) and those who received DEX were included in the DEX cohort (n = 231). The flowchart of the analysis is presented in Figure 1.

Demographic Characters

There was no significant difference in anthropological, demographical, and clinical conditions of the patients, preoperative pain, heart rate, surgical characteristics, duration of surgery, and volume of propofol used during surgery between the 2 study groups ($P > .05$ for all) except age. Patients included in the MDZ group were younger than those of the DEX group ($P < .0001$). A higher percentage of patients with ASA status II ($P = .048$) and female patients ($P = .042$) were treated with MDZ (Table 1).

Sedative Effects

After administration of anesthesia, up to 40 minutes, patients of MDZ had lower modified observer's assessment of alertness/sedation score than those of the DEX group ($P = .041$), but

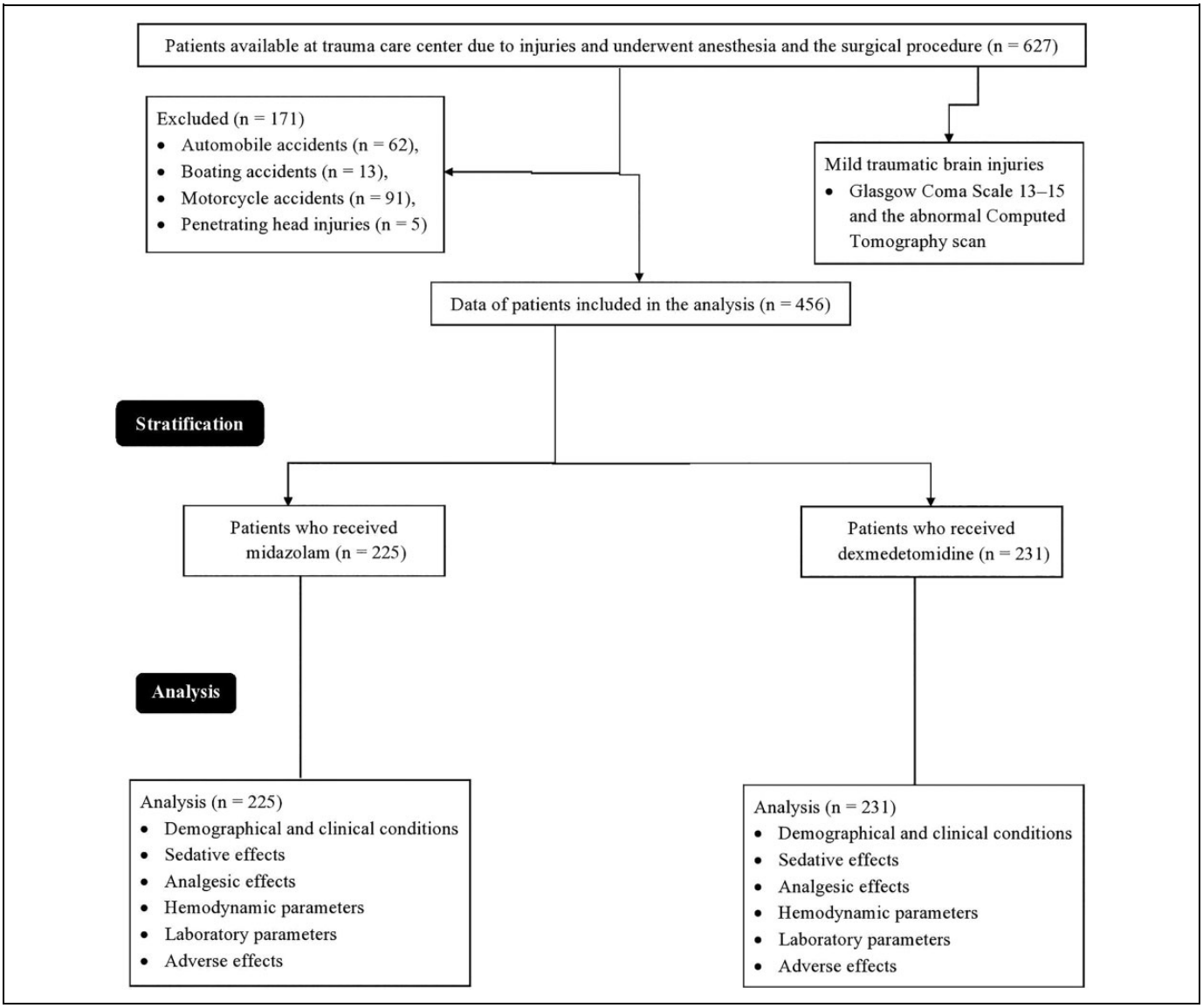

Figure 1. Flowchart of the study.

after 40 minutes, patients of the MDZ group had higher modified observer's assessment of alertness score than those of the DEX group throughout surgery ($P = .048$; Figure 2).

There were no significant changes for the bispectral index value between both groups at various stages of operation (Table 2). While eye-opening time and time required for the verbal response of patients were lesser for the DEX group than the MDZ group (Table 3).

Analgesic Effects

One day after surgeries, MDZ ($P < .0001$, $q = 21.278$) and DEX ($P < .0001$, $q = 27.899$) were successfully decreased postoperative pain but DEX decreased pain more strongly than MDZ ($P = .013$, $q = 3.552$; Figure 3). Also, the DEX group has less requirements of total morphine or equivalent doses administration than the MDZ group ($P < .0001$, $q = 18.451$; Figure 4).

Hemodynamic Parameters

Changes in mean arterial pressure and heart rate are reported in Table 4. Dexmedetomidine and MDZ both caused hypotension and decreased heart rate.

Laboratory Parameters

One day after surgeries, MDZ ($P < .0001$, $q = 20.22$) and DEX ($P = .016$, $q = 4.081$) reduced superoxide dismutase level, but the intensity of MDZ to reduce superoxide dismutase level was higher than DEX ($P < .0001$, $q = 22.87$). Midazolam ($P = .0003$, $q = 5.137$) increased, but DEX ($P = .371$) had no effect on serum interleukin 6 level. Midazolam ($P < .0001$, $q = 12.584$) and DEX ($P = .012$, $q = 3.641$) increased tumor necrosis factor α level, but the intensity of MDZ to increase tumor necrosis factor α level was higher than DEX ($P < .0001$,

Table 1. Anthropological, Demographical, and Clinical Conditions of the Patients.[a]

Characteristics		Population: Cohort MDZ	Population: Cohort DEX	Comparison Between Cohorts
Medical Records of Patients Reviewed		225	231	*P* Value
[b]Age (years)	Minimum	18	28	<.0001
	Maximum	57	62	
	Mean ± SD	41.22 ± 11.45	47.54 ± 14.54	
[b]Gender	Male	135 (60)	160 (69)	.042
	Female	90 (40)	71 (31)	
Ethnicity	Han Chinese	209 (93)	218 (94)	.79
	Mongolian	14 (6)	11 (5)	
	Tibetan	2 (1)	2 (1)	
Body mass index (kg/m^2)		25.12 ± 2.45	24.68 ± 2.52	.059
[b]American Society of Anesthesiology status	II	111 (49)	92 (40)	.048
	III	114 (51)	139 (60)	
[c]Preoperative pain		5.12 ± 1.23	5.48 ± 2.55	.057
Heart rate (beats per minute)		71.19 ± 9.57	69.52 ± 10.61	.079
Intraoperative infusion type		Midazolam	Dexmedetomidine	N/A
Glasgow Coma Scale	13	87 (39)	81 (35)	429
	14	55 (24)	51 (22)	
	15	83 (37)	99 (43)	
Surgical/procedural type	Maxillofacial surgery	52 (23)	61 (27)	.77
	Dental surgery	63 (28)	58 (25)	
	Orthopedic surgery	81 (36)	79 (34)	
	Ophthalmological surgery	29 (13)	33 (14)	
Duration of surgery (hours)	Minimum	0.95	1	.064
	Maximum	6.5	7	
	Mean ± SD	5.12 ± 2.15	5.56 ± 2.85	
The volume of propofol used during surgery (mL)		75.42 ± 9.12	73.89 ± 8.15	.059
Serum interleukin 6 (pg/mL)		61 ± 11	63 ± 12	.064
Superoxide dismutase (U/L)		327±27	333 ± 41	.066
S100β (ng/L)		1.21 ± 0.21	1.25 ± 0.24	.059
Tumor necrosis factor α (pg/mL)		25 ± 8	26 ± 8	.183
Neuron-specific enolase enzyme		3.2 ± 0.6	3.1 ± 0.5	.054
Malondialdehyde (μM/L)		4.6 ± 1.1	4.8 ± 1.3	.077
Mean arterial pressure (mm Hg)		106.56 ± 17.81	105.96 ± 16.92	.712
The time lapse between traumatic brain injuries and surgery (days)		28 ± 5	29 ± 6	.054

Abbreviations: DEX, dexmedetomidine; MDZ, midazolam; N/A, not applicable.
[a]Ordinal data are presented as frequency (percentage) and numerical variables are represented as mean ± standard deviation. The Fisher exact test was performed for ordinal variables and the Mann-Whitney *U* test was performed for numerical variables for statistical analysis. A $P < .05$ was considered significant.
[b]Significant difference.
[c]0: no pain and 10: the worst pain.

$q = 6.956$). Midazolam ($P < .0001$, $q = 21.169$) and DEX ($P < .0001$, $q = 6.314$) increased level of malondialdehyde, but the intensity of MDZ to increase the level of malondialdehyde was higher than DEX ($P < .000$, $q = 14.789$). Midazolam ($P < .0001$, $q = 80.135$) and DEX ($P < .0001$, $q = 42.055$) increased level of S100β, but the intensity of MDZ to increase S100β was higher than DEX ($P < .0001$, $q = 35.545$). Midazolam ($P < .0001$, $q = 54.591$) and DEX ($P < .0001$, $q = 34.046$) increased serum level of neuron-specific enolase enzyme, but MDZ increased more strongly serum level of neuron-specific enolase enzyme than DEX ($P = .0002$, $q = 6.024$; Table 5).

Adverse Effects

Dexmedetomidine cause hypotension ($P = .033$) and bradycardia ($P = .019$) and MDZ leads to respiratory events ($P = .003$) as adverse effects during hospitalization (Table 6).

Clinical Outcome Measures

Wound healing time was less in the DEX group than the MDZ group ($P < .0001$) and professional activity recovery was higher in the DEX group than in MDZ group ($P < .0001$). The

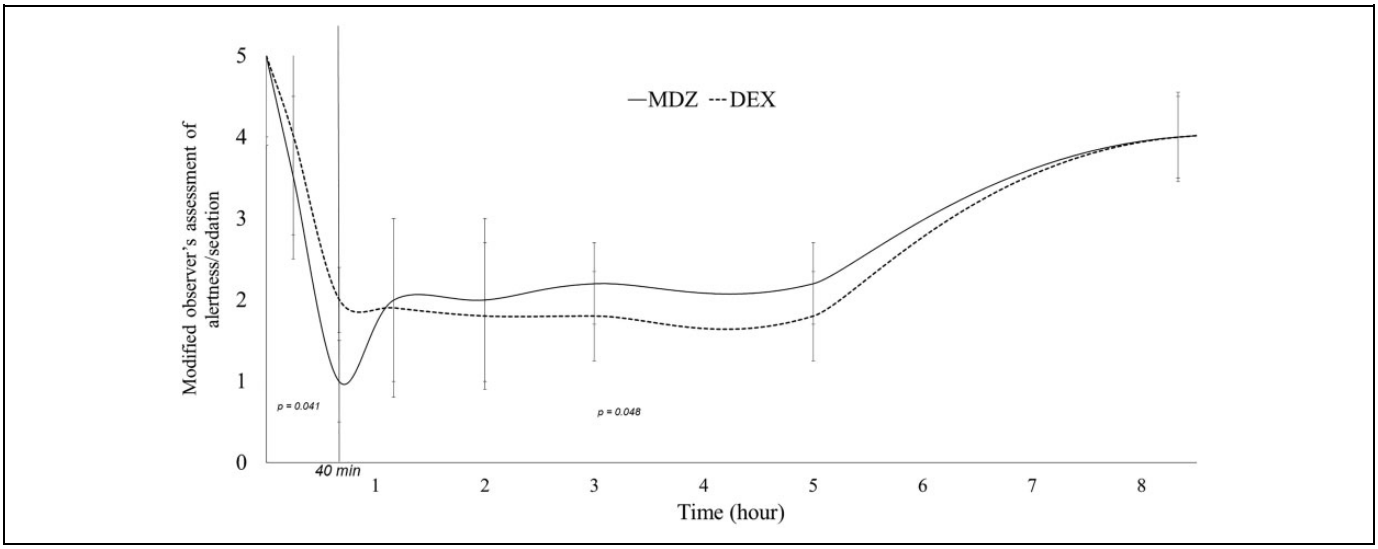

Figure 2. Modified observer's assessment of alertness/sedation score during operation. 5: Response readily to name spoken; 4: lethargic response; 3: response after name called loudly; 2: response after mild to moderate shaking; 1: response to trapezius squeeze. Observer's assessment of alertness/sedation score was evaluated by anesthesiologists (a minimum of 3 years' experience) of the institute in consultation with surgeons (a minimum of 3 years' experience) of the institute who performed surgeries.

Table 2. Comparisons of Bispectral Index Value.[a]

Characteristics	Population: Cohort MDZ	Population: Cohort DEX	Comparison Between Cohorts
Medical Records of Patients Reviewed	225	231	*P* Value
Before anesthesia induction	96.4 ± 1.2	96.2 ± 1.1	.064
At anesthesia induction	54.6 ± 1.7	54.3 ± 1.9	.077
Five minutes after tracheal intubation	44.2 ± 1.6	43.9 ± 1.7	.053
After skin closure	61.9 ± 1.3	62.1 ± 1.1	.077

Abbreviations: DEX, dexmedetomidine; MDZ, midazolam.
[a]Variables are presented as mean ± standard deviation. The Mann–Whitney *U* test was performed between groups. A $P < .05$ was considered significant.

Table 3. Anesthesia Recovery Criteria.[a]

Characters	Population: Cohort MDZ	Population: Cohort DEX	Comparison Between Cohorts
Medical Records of Patients Reviewed	225	231	*P* Value
Extubation time (minutes)	5.11 ± 0.11	5.01 ± 0.9	.099
Eye opening time (minutes)	6.02 ± 0.19	5.89 ± 0.11[b]	<.0001
Response to verbal (minutes)	7.03 ± 0.21	6.89 ± 0.18	<.0001

Abbreviations: DEX, dexmedetomidine; MDZ, midazolam.
[a]Variables are presented as mean ± standard deviation. The Mann-Whitney *U* test was performed between groups. A $P < .05$ was considered significant.
[b]Significantly lesser than the MDZ group.

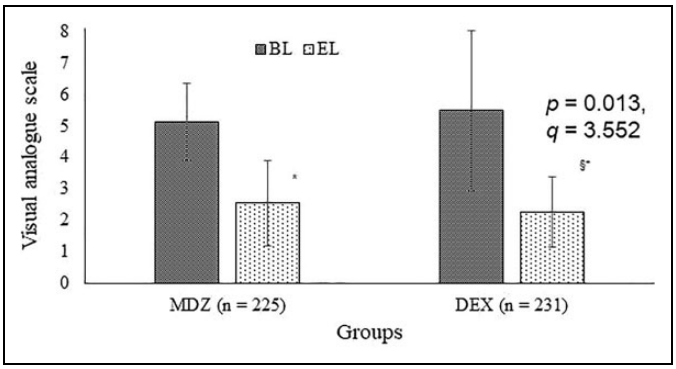

Figure 3. Analgesic effects of anesthetics. Variables are presented as mean ± SD. A 1-way repeated measures ANOVA was performed within a group. The Mann-Whitney *U* test was performed for statistical analysis between groups. Tukey test was used for post hoc analysis. A $P < .05$ and $q > 3.314$ were considered significant. *Significantly lower than BL. §Significantly lower than the MDZ group at EL. 0: no pain and 10: the worst pain; BL: 24 hours before surgery, EL: 24 hours after surgery. The visual analog scale was administered to the patients by nursing staff (a minimum of 3 years' experience) of the institute who was not involved in surgeries. ANOVA indicates analysis of variance; MDZ, midazolam; SD, standard deviation.

other clinical outcomes had no significant difference between both groups during the follow-up period (Table 7).

Discussion

After administration of MDZ, up to 40 minutes, patients had lower modified observer's assessment of alertness/sedation score than those who received DEX, but after 40 minutes, patients who received MDZ had a higher score than those who received DEX throughout the surgery. Also, anesthesia

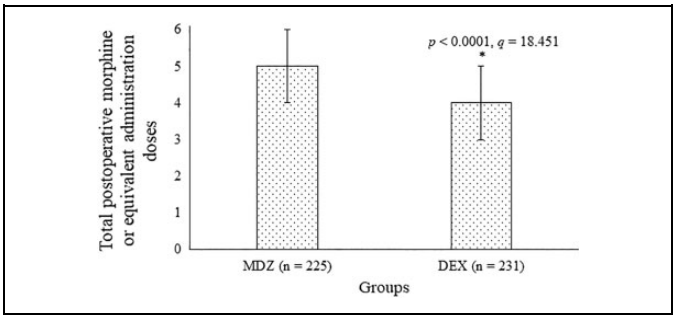

Figure 4. Total postoperative morphine or equivalent administration dose assessment. Variables are presented as mean ± SD. The Mann-Whitney *U* test following the Tukey test was used for statistical analysis. A $P < .05$ and $q > 3.314$ were considered significant. *Fewer requirements than MDZ group. MDZ indicates midazolam; SD, standard deviation.

recovery criteria were better for the DEX group than the MDZ group. The onset of action time for MDZ was 0.5 to 1 minutes, and it takes 5 minutes to reach peak plasma MDZ concentration, but the onset of action time for DEX is 10 to 15 minutes and it takes 25 to 30 minutes to reach peak plasma DEX concentration.[14] The results of the current study were in parallel with the results of prospective randomized study[12] and a randomized trial of patients who planned for total knee arthroplasty.[15] Dexmedetomidine could provide the desired level of sedation than MDZ without significant respiratory distress.

Dexmedetomidine had higher control over postoperative pain than MDZ. The results of the study were in parallel with the results of a randomized clinical trial of patients undergoing dental implant surgeries.[14] Midazolam has itself no analgesic property, but due to γ-aminobutyric acid agonist action, it assists the analgesic effect of fentanyl.[16] While DEX has an

Table 4. Hemodynamic Parameters.[a]

Characters	Population							
	Cohort							
	MDZ				DEX			Comparison Between Cohorts at EL
Level	BL	EL	Comparison Between BL and EL		BL	EL	Comparison Between BL and EL	
Medical Records of Patients Reviewed	225	225	*P* Value	*q* Value	231	231	*P* Value *q* Value	*P* Value
Mean arterial pressure (mm Hg)	106.56 ± 17.81	94.55 ± 12.11	<.0001	11.385	105.96 ± 16.92	96.52 ± 11.96	<.0001 9.106	.081
Heart rate (beats per minute)	71.19 ± 9.57	64.12 ± 8.16	<.0001	11.151	69.52 ± 10.61	63.69 ± 7.26	<.0001 9.579	.552

Abbreviations: DEX, dexmedetomidine; MDZ, midazolam.
[a]BL: Before anesthesia induction, EL: 5 minutes after tracheal intubation. Variables are presented as mean ± standard deviation. A 1-way repeated measures analysis of variance was performed within the group. The Mann-Whitney *U* test was performed between groups. Tukey test was used for post hoc analysis. A $P < .05$ and $q > 3.314$ were considered significant.

Table 5. Laboratory Parameters.[a]

Characters	Cohort								
	MDZ				DEX				Comparison Between Cohorts at EL
Level	BL	EL	Comparison Between BL and EL		BL	EL	Comparison Between BL and EL		
Medical Records of Patients Reviewed	225	225	*P* Value	*q* value	231	231	*P* Value	*q* Value	*P* Value *q* Value
Serum interleukin 6 (pg/mL)	61 ± 11	65 ± 12	.0003	5.137	63 ± 12	62 ± 12[b]	.371	N/A	.008 3.878
Superoxide dismutase (U/L)	327 ± 27	284 ± 25	<.0001	20.22	333 ± 41	325 ± 29	.016	4.081	<.0001 22.87
S100β (ng/L)	1.21 ± 0.21	3.3 ± 0.6	<.0001	80.135	1.25 ± 0.24	2.2 ± 0.5	<.0001	42.055	<.0001 35.545
Tumor necrosis factor α (pg/mL)	25 ± 8	32 ± 9	<.0001	12.584	26 ± 8	28 ± 9	.012	3.641	<.0001 6.956
Neuron-specific enolase enzyme (ng/L)	3.2 ± 0.6	6.2 ± 1.2	<.0001	54.591	3.1 ± 0.5	5.8 ± 1.1	<.0001	34.046	.0002 6.024
Malondialdehyde (μM/L)	4.6 ± 1.1	6.8 ± 2.1	<.0001	21.169	4.8 ± 1.3	5.3 ± 1.2	<.0001	6.314	<.0001 14.789

Abbreviations: DEX, dexmedetomidine; MDZ, midazolam; N/A, not applicable.
[a]BL: 24 hours before surgery, EL: 24 hours after surgery. Data are presented as mean ± standard deviation. A 1-way repeated measures analysis of variance was performed within the group. The Mann-Whitney *U* test was performed between groups. Tukey test was used for post hoc analysis. A $P < .05$ and $q > 3.314$ were considered significant.
[b]Not increased compared to BL.

Table 6. Adverse Events During Hospitalization.[a]

Events	Cohort		Comparison Between Cohorts
	MDZ	DEX	
Medical Records of Patients Reviewed	225	231	*P* Value
Nausea	2 (1)	9 (4)	.063
Vomiting	2 (1)	7 (3)	.176
Shivering	2 (1)	6 (3)	.285
Hypotension	3 (1)	12 (5)[b]	.033
Bradycardia	3 (1)	13 (6)[b]	.019
Headache	7 (3)	13 (6)	.253
Desaturations	13 (6)[c]	2 (1)	.003

Abbreviations: DEX, dexmedetomidine; MDZ, midazolam.
[a]Ordinal data are presented as frequency (percentage) and numerical data are presented as mean ± standard deviation. The Fisher exact test was performed for ordinal data and the Mann-Whitney *U* test was performed for numerical data. A $P < .05$ was considered as significant.
[b]Significant dexmedetomidine-emergent adverse effect.
[c]Significant midazolam-emergent adverse effect.

Table 7. The Intermediate- and Long-Term Sequela During the Follow-Up of Patients.[a]

Events	Cohort		Comparison Between Cohorts
	MDZ	DEX	
Medical Records of Patients Reviewed	225	231	*P* Value
Wound healing time (days)	10.45 ± 1.45	9.31 ± 1.85[b]	<.0001
Infections	9 (4)	8 (4)	.809
Rehospitalization	2 (1)	1 (1)	.619
Professional activity recovery	185 (82)	228 (99)[b]	<.0001
Mood disorder	42 (19)	33 (14)	.255
Sleep disorder	25 (11)	18 (8)	.263
Memory disorder	28 (12)	27 (12)	.886
Concentration disorder	21 (9)	15 (6)	.229
Head pain	27 (12)	26 (11)	.884
Meningitis	1 (1)	1 (1)	.999
Delirium	7 (3)	6 (3)	.785

Abbreviations: DEX, dexmedetomidine; MDZ, midazolam.
[a]Ordinal data are presented as frequency (percentage) and numerical data are presented as mean ± standard deviation. The Fisher exact test was performed for ordinal data and the Mann-Whitney *U* test was performed for numerical data. A $P < .05$ was considered as significant.
[b]Significant difference than the MDZ group.

analgesic effect because it has selective α-2 agonist action.[14] Dexmedetomidine offers better postoperative analgesia.

The study reported that hemodynamic parameters were not stable in patients who received DEX or MDZ. The results of the study were in parallel with the results of a randomized clinical trial on glioma patients undergoing craniotomy resections,[7] double-blind prospective clinical study in supratentorial craniotomies,[17] prospective randomized studies on elective surgery,[12,15] but were not consistent with the randomized clinical trial of patients undergoing dental implant surgeries.[14] In normal physiological conditions, there is self-regulation in the cerebral blood flow, but surgeries can disturb self-regulation in the cerebral blood flow; as a result, the perfusion of the brain decreases and intracranial pressure increases and therefore damages the brain.[7] Dexmedetomidine is a highly selective α-2 agonist and a selective α-1 agonist.[18] Dexmedetomidine acts on α-1 receptors of peripheral vascular smooth muscle, causes peripheral vasoconstriction, and transiently increases blood pressure when administered very quickly.[7] Dexmedetomidine and MDZ are not stabilized arterial pressure and heart rate.

The study reported that the intensity of DEX to increase tumor necrosis factor-α level was lower than MDZ ($P < .0001$). Also, DEX had no effect on serum interleukin 6 level. The results of the study were consistent with randomized clinical trials on craniotomy resections and dental surgeries.[7,14] Surgeries can cause local trauma, which can stimulate chemotaxis of monocyte, lymphocytes, and neutrophils that express inflammatory factors and induce the inflammatory cascade by direct or indirect pathways, which can lead to brain injury.[1] The expression levels of inflammatory cytokines induced by surgeries can effectively prevent DEX.

Dexmedetomidine had a weaker effect on contrasting malondialdehyde but had a stronger effect on increasing superoxide dismutase due to surgery when compared to MDZ. The results of the study were consistent with randomized clinical trials on craniotomy resections and dental surgeries.[7,14] Malondialdehyde and superoxide dismutase are antioxidants and protect the body from oxidative damage.[7] Midazolam recovers oxidative stress, hypoxia, and brain injuries.[8] Midazolam and DEX may be effective in the reduction of brain injuries.

The intensity of MDZ to reduce neuron-specific enolase enzyme level and S100β was lower than DEX. The results of the study were in parallel with the results of a randomized clinical trial on glioma patients undergoing craniotomy resections.[7] Neuron-specific enolase enzyme level and S100β are biomarkers of brain injuries and express the level of brain injuries.[7] Dexmedetomidine could have stronger neuroprotectant effects than MDZ.

The study reported hypotension and bradycardia due to DEX. The results of the study were in parallel with the results of randomized clinical trials on dental implant surgeries,[14] imaging performance study,[19] critically ill patients who require mechanical ventilation,[20] and patients during spinal anesthesia.[12] A detailed study is required for the use of DEX in hypertensive patients during peripheral surgeries.

There are several limitations to the study, for example, the study is a retrospective cohort study and lack a prospective, randomized trial. The placebo control group is required to ascertain the "naive" increase in biomarkers due to surgery,[7] but the lack of a control group. The other limitations are the single-center study, the lack of other medications to compare such as propofol, the lack of data on brain injury intensity, lack of brain monitoring. Age, sex, and clinical conditions have a significant impact on intraoperative and postoperative conditions of patients, for example, older patients may have more

hypotension and bradycardia and perhaps have a different inflammatory response than younger ones,[4] but the study did not evaluate the effects of demographical and clinical characters on outcome measures. The results did not clearly indicate the relationship for the betterment of surgical procedure, which provided only mechanistic clues. An in-depth study is required to elucidate the complete mechanism of DEX.

Conclusions

Midazolam offers rapid intraoperative sedation and suppresses oxidation responses. Dexmedetomidine offers better intraoperative sedation, postoperative analgesia, and better clinical recovery with manageable adverse effects and suppresses oxidative and inflammatory response during major peripheral surgeries. Dexmedetomidine may be an alternative sedative to MDZ in peripheral surgeries. The hypothesis is required to test for other surgeries.

Authors' Note

Jing Peng and Fujuan He contributed to this work equally. All authors read and approved the manuscript for publication. J.P. and F.H. both were equally contributed to the project administration, conceptualization, and literature review of the study and drafted, reviewed, and edited the manuscript for intellectual content. C.Q. contributed to software, formal analysis, validation, and literature review of the study. Y.Q. contributed to resources, data curation, investigation, and literature review of the study. R.F. contributed to software, data curation, validation, and literature review of the study. B.Q. contributed to data curation, software, formal analysis, and literature review of the study. The authors agree to be accountable for all aspects of work, ensuring integrity and accuracy. The data sets used and analyzed during this study are available from the corresponding author on reasonable request.

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References

1. Jiang L, Hu M, Lu Y, Cao Y, Chang Y, Dai Z. The protective effects of dexmedetomidine on ischemic brain injury: a meta-analysis. *J Clin Anesth*. 2017;40:25-32.
2. del Zoppo GJ. Acute anti-inflammatory approaches to ischemic stroke. *Ann N Y Acad Sci*. 2010;1207:143-148.
3. Zihl J, Almeida OF. Neuropsychology of neuroendocrine dysregulation after traumatic brain injury. *J Clin Med* 2015;4(5): 1051-1062.
4. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology*. 2009;110(2):231-238.
5. Goldfarb Y, Sorski L, Benish M, Levi B, Melamed R, Ben-Eliyahu S. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. *Ann Surg*. 2011;253(4):798-810.
6. Abcejo AS, Savica R, Lanier WL, Pasternak JJ. Exposure to surgery and anesthesia after concussion due to mild traumatic brain injury. *Mayo Clin Proc*. 2017;92(7):1042-1052.
7. Luo X, Zheng X, Huang H. Protective effects of dexmedetomidine on brain function of glioma patients undergoing craniotomy resection and its underlying mechanism. *Clin Neurol Neurosurg*. 2016;146:105-108.
8. Liu JY, Guo F, Wu HL, Wang Y, Liu JS. Midazolam anesthesia protects neuronal cells from oxidative stress-induced death via activation of the JNK-ERK pathway. *Mol Med Rep*. 2017;15(1): 169-179.
9. Barends CR, Absalom A, van Minnen B, Vissink A, Visser A. Dexmedetomidine versus midazolam in procedural sedation. A systematic review of efficacy and safety. *PLoS One*. 2017; 12(1):e0169525.
10. Silva-Jr JM, Katayama HT, Nogueira FA, Moura TB, Alves TL, de Oliveira BW. Comparison of dexmedetomidine and benzodiazepine for intraoperative sedation in elderly patients: a randomized clinical trial. *Reg Anesth Pain Med*. 2019;44(3): 319-324.
11. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY. Monitored anesthesia care with dexmedetomidine: a prospective, randomized, double-blind, multicenter trial. *Anesth Analg*. 2010;110(1):47-56.
12. Jo YY, Lee D, Jung WS, Cho NR, Kwak HJ. Comparison of intravenous dexmedetomidine and midazolam for bispectral index-guided sedation during spinal anesthesia. *Med Sci Monit*. 2016. 22:3544-3551.
13. Kim TK, Niklewski PJ, Martin JF, Obara S, Egan TD. Enhancing a sedation score to include truly noxious stimulation: the extended observer's assessment of alertness and sedation (EOAA/S). *Br J Anaesth*. 2015;115(4):569-577.
14. Li S, Yang Y, Yu C, et al. Dexmedetomidine analgesia effects in patients undergoing dental implant surgery and its impact on postoperative inflammatory and oxidative stress. *Oxid Med Cell Longev*. 2015. doi:10.1155/2015/186736.
15. Park SW, Choi JH, Kim HT, Cho YH. Replacement of dexmedetomidine loading with midazolam for sedation in elderly patients with spinal anesthesia. *Medicine*. 2018;97(39):e12565.
16. Kashefi P, Montazeri K, Honarmand A, Safavi M, Hosseini HM. The analgesic effect of midazolam when added to lidocaine for intravenous regional anaesthesia. *J Res Med Sci*. 2011;16(9): 1139-1148.

17. Ilhan O, Koruk S, Serin G, Erkutlu I, Oner U. Dexmedetomidine in the supratentorial craniotomy. *Eurasian J Med*. 2010;42(2):61-65.
18. Giovannitti JA Jr, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesth Prog*. 2015;62(1):31-39.
19. Koroglu A, Teksan H, Sagir O, Yucel A, Toprak HI, Ersoy OM. A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. *Anesth Analg*. 2006;103(1):63-67.
20. MacLaren R, Preslaski CR, Mueller SW, et al. A randomized, double-blind pilot study of dexmedetomidine versus midazolam for intensive care unit sedation: patient recall of their experiences and short-term psychological outcomes. *J Intensive Care Med*. 2015;30(3):167-175.