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Original Research Article

Analgesic effect and safety of postoperative low-dose ketamine/midazolam combination vis-à-vis dexmedetomidine in non-cardiac surgery

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Abstract

Purpose: *To compare the analgesic efficacy and safety of use of postoperative low-dose parenteral ketamine/midazolam combination, and postoperative parenteral dexmedetomidine in major non-cardiac surgeries.*
Methods: *Major non-cardiac surgeries were performed in patients under propofol/morphine anesthesia. After the surgeries, patients received low-dose of ketamine with midazolam (KM cohort, n = 115), dexmedetomidine (DEX cohort, n = 112), or paracetamol infusion (PL cohort, n = 148). When visual analog scale score was > 4 in a resting condition, 3 mg bolus intravenous morphine was administered. Data for total morphine requirements and treatment-emergent adverse effects (within 2 days of post-operative treatment) were collected and analyzed.*
Results: *Thirty-eight patients from KM cohort, 55 patients from DEX cohort, and 109 patients from PL cohort required 3 mg bolus intravenous morphine for postoperative pain management. Patients from KM cohort had nausea, vomiting, blurred vision, dizziness, and hallucinations, while patients in DEX cohort experienced headache and bradycardia post-surgery. Patients in PL cohort reported drossiness, constipation, urinary retention, and dry mouth.*
Conclusion: *Postoperative low doses of ketamine + midazolam and dexmedetomidine are effective for postoperative pain management, and they produce low adverse effects.*

Keywords: *Bradycardia, Dexmedetomidine, Hallucinations, Ketamine, Midazolam, Postoperative pain*

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INTRODUCTION

Postoperative pain in patients is due to damage to soft tissues during surgery [1]. Inadequate pain recovery may lead to prolonged hospital stay, poor outcomes, and delayed recovery [2]. Therefore, pain management is required during postoperative care. The procedures generally used for postoperative pain management are neuraxial blocks with local anesthetics [3], oral or parenteral opioids, and non-steroidal anti-inflammatory drugs [4]. However, these methods result in some adverse effects. An example is the use of opioids which is linked to respiratory depression, nausea, urinary retention, constipation and vomiting [1].

It has been reported that low-dose ketamine produces analgesic action with manageable adverse effects in spinal fusion surgeries [1,5,6]. This is due to the fact that ketamine blocks N-methyl-D-aspartate (NMDA) receptors in the central and peripheral nervous system, and it has opioid-sparing effects due to central anti-hyperalgesic action [1].

Dexmedetomidine is a selective *α*-2 receptor agonist. It does not produce respiratory depression [7], and it has opioid-sparing effects in spinal fusion surgery [1]. Dexmedetomidine is more beneficial than clonidine [8], although it is associated with a risk of bradycardia (arterial hypotension) [8,9]. There is dearth of information as to the extent to which postoperative systemic dexmedetomidine reduces opioid consumption and severity of postoperative pain. Moreover, it is not clear whether it has additional beneficial effects such as reduction in incidents of opioid-related adverse effects, including respiratory depression and hyperalgesia [8].

The objectives of this retrospective study were to determine the efficacy and safety of postoperative low-doses of parenteral ketamine and midazolam vis-a vis postoperative parenteral dexmedetomidine as analgesia in major non-cardiac surgeries.

METHODS

Ethical approval and consent to participate

The study protocol was approved by the Anesthesiology Review Board of The three Gorges University (approval no. CTGU/CL/11/20 dated April 9, 2020) and adhered to the laws of China, as stipulated in V2008 of Helsinki Declarations [10], and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Cohort study. Prior to the commencement of the study, each participant signed an informed consent form with respect to anesthesia, surgery, and the publication of the results.

Study population

From January 3, 2019 to December 16, 2019, a total of 382 patients were subjected to major non-cardiac surgery at the Department of Surgery of the National Medicine Gezhouba Central Hospital, The Third Clinical Medical College of Three Gorges University, Yichang, China and the referring hospitals, under general anesthesia. Three patients were less than 18 years, two patients had American Society of Anesthesiologists status III (patients with severe systemic disease), one patient had American Society of Anesthesiologists status IV (constant threat to life) [11], while one patient died during surgery. The data of these patients were excluded from the analysis.

Sample size calculation

The sample size was calculated on the basis of 80 % of power and a 5 % level of confidence. The minimum patients required in each cohort was 110.

Anesthesia procedure

All patients received propofol (Diprivan®, Aspen Pharma Trading Limited, Dublin, Ireland) at a dose of 2 mg/kg, morphine (Hameln Pharmaceuticals Ltd., Nexus, Gloucester, UK) at a dose of 0.1 mg/ kg, and vecuronium (Hospira, Inc., Lake Forest, IL, USA; to facilitate tracheal intubation) at doses of 0.01 – 0.015 mg/ kg. Patients were maintained on oxygen and air mixture (70:30 v: v).

The bi-spectral index was maintained within the range of 40 to 60 [5]. Systolic blood pressure, diastolic blood pressure, and heart rate were monitored during surgery. If hemodynamic parameters were decreased to 20 % below baseline, norepinephrine (Levophed, Hospira, Inc., Lake Forest, IL, USA) was given at a dose of 25 µg/kg, and if hemodynamic parameters were increased to 20 % over baseline, 10 mg bolus esmolol (Miniblock, USV, Mumbai, Maharashtra, India) was given [1].

Cohorts

After surgeries, all patients were transferred to the surgical intensive care unit for 1 day. The patients received 0.5 mg/kg bolus ketamine (Ketalar®, Par Pharmaceutical Chestnut Ridge, NY, USA) and 12.5 µg/kg bolus midazolam (Hospira, Inc., Lake Forest, IL, USA), followed by infusion of ketamine (0.25 mg/kg/h) and midazolam (10 µg/kg/h) in normal saline (Baxter Healthcare Corporation, Deerfield, IL, USA) for 1 day (KM cohort, n = 115), or were given dexmedetomidine (0.5 µG/ kg) (Precedex, Hospira, Inc., Lake Forest, IL, USA) in normal saline for 9 – 11 min, extended to 1 day (DEX cohort, n = 112). A total of 148 patients did not receive ketamine, midazolam or dexmedetomidine, but they received 100 mL of 10 mg/ mL paracetamol infusion (Perfalgan, Bristol Myers Squibb, New York, NY, USA) at a maximum of two infusions per day for 3-days (PL cohort) [5].

Postoperative pain intensity

Postoperative pain was measured on a visual analog scale (VAS) score in the resting stage of patients when they become conscious, and at 4 h after administration of postoperative treatment intervention(s) by nursing staff of institute (with a minimum 3 years of experience). In VAS, 0 indicates absence of pain, while 10 indicates maximum possible pain [3].

Postoperative pain management

When the VAS score was more than 4 in a resting condition, 3 mg bolus intravenous morphine was administered by nursing staff with a minimum of 3 years of experience, in consultation with surgeon(s) of the institute [1].

Evaluation of treatment-emergent adverse effects

Any adverse effects noticed within 2 days of postoperative treatment were recorded and considered as treatment-emergent adverse effects. Nausea and vomiting were treated with 4 mg ondansetron injection (Zuplenz®, Midatech Pahrma US, Inc., Raleigh, NC, USA) [5].

Statistical analysis

Numerical and ordinal data are presented as numbers (percentage), while continuous data are presented as mean ± SD. Statistical analysis was done using SPSS 25.0 (IBM Corporation, Chicago, IL, USA). One-way analysis of variance (ANOVA) was used for continuous data [9]. Fischer exact test was used for numerical and ordinal data [5]. Tukey test (considering critical value [q] > 3.328 as significant) was used for *post hoc* analysis. Differences were considered significant at a 95 % confidence level.

RESULTS

Study population

Data regarding postoperative pain management and post-surgery adverse effects in 375 patients were collected and analyzed. There were no statistically significant differences in demographic characteristics, perioperative clinical parameters, and operative conditions amongst the enrolled patients (p > 0.05). The detailed demographic/clinical characteristics and operative conditions of the included patients are shown in Table 1 and Table 2.

Postoperative pain intensity

Postoperative pain was lower in the KM cohort than in PL cohort (4.19 ± 0.98 *vs*. 5.45 ± 1.23, p < 0.0001, q = 12.326) and DEX cohort (4.19 ± 0.98 *vs*. 4.62 ± 1.23, p < 0.0001, q = 3.907). Postoperative pain was lower in the DEX cohort than in the PL cohort (p < 0.0001, q = 8.092, Figure 1).

Table 1: Demographical characteristics and perioperative clinical parameters of the enrolled patients

Parameter		Cohort			Comparison between cohorts (*P*-value)
		KM	***DEX***	***PL***	
Post-operative treatment		***Parenteral ketamine/ midazolam***	***Parenteral dexmedetomidine***	***Parenteral paracetamol***	
Patients included in the analysis		115	112	148	
Age (years)	Minimum	18	18	18	0.053
	Maximum	64	61	63	
	Mean ± SD	48.15±15.64	45.13±12.46	49.95±18.15	
Gender	Male	69 (60)	65 (58)	89 (60)	0.934
	Female	46 (40)	47 (42)	59 (40)	
Weight (kg)		58.44±10.92	60.12±11.14	57.44±9.45	0.123
Body mass index (kg/m^2)		24.29±2.23	24.89±1.88	24.91±2.52	0.055
American Society of Anesthesiologists status	I (normal healthy patient)	71(62)	60(54)	82(55)	0.421
	II (patient with mild systemic disease)	44(38)	52(46)	66(45)	
Ethnicity	Han Chinese	95(83)	99(88)	131(89)	0.563
	Mongolian	19(16)	12(11)	15(10)	
	Tibetan	1(1)	1(1)	2(1)	

Numerical data are presented as frequency (percentage), while continuous data are shown as mean ± SD. One-way ANOVA for constant data and the Fischer exact test for numerical were used for statistical analysis. A p < 0.05 was considered significant

Table 2: Operative conditions of the enrolled patients

Parameter		Cohort			Comparison between cohorts (*P*-value)
		KM	***DEX***	***PL***	
Post-operative treatment		***Parenteral ketamine/ midazolam***	***Parenteral dexmedetomidine***	***Parenteral paracetamol***	
Patients included in the analysis		115	112	148	
Type of surgery	Spinal fusion surgeries	40(35)	41(36)	63(43)	0.385
	Urinary bladder surgeries	12(10)	8(7)	17(11)	
	Abdominal surgeries	11(10)	12(11)	21(14)	
	Lower extremity surgeries	18(17)	13(12)	17(12)	
	Upper extremity surgeries	20(17)	18(16)	13(9)	
	Gynecological surgeries	9(7)	13(12)	14(9)	
	Obstetrics surgeries	5(4)	7(6)	3(2)	

Data are shown as mean ± SD. The Fischer exact test was performed for statistical analysis. A $p < 0.05$ was considered significant

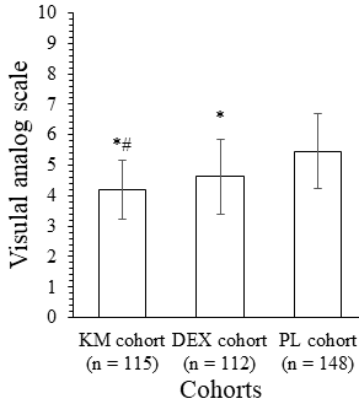

Figure 1: Intensities of postoperative pain. Data are expressed as mean ± SD. $^{*}p < 0.05$, vs PL cohort; $^{\#}p < 0.05$, vs DEX cohort

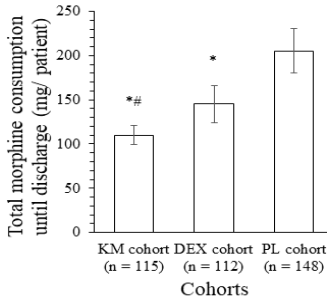

Figure 2: Total morphine used for postoperative pain management in the cohorts. Data are expressed as mean ± SD; $^{*}p < 0.05$, vs PL cohort; $^{\#}p < 0.05$, vs DEX cohort

Postoperative pain

Thirty-eight (38) patients from the KM cohort, 55 patients from the DEX cohort, and 109 patients of the PL cohort required 3 mg bolus intravenous morphine for postoperative pain management. Patients in the KM cohort required lower amounts of total morphine doses before discharge than those in the PL cohort (110.12 ± 11.15 mg/patient *vs*. 205.25 ± 25.12 mg/patient, $p < 0.0001$, $q = 52.751$) and DEX cohort (110.12 ± 11.15 mg/patient *vs*. 145.21 ± 21.15 mg/ patient, $p < 0.0001$, $q = 18.219$). Patients in the DEX cohort required lower amount of total morphine before discharge than those in the PL cohort ($p < 0.0001$, $q = 33.045$, Figure 2).

Adverse effects

None of the patients reported tachycardia or hypertension after surgery. Patients in the KM cohort reported nausea, vomiting, blurred vision, dizziness and hallucinations, while patients in the DEX cohort presented with headache and bradycardia. Patients in the PL cohort reported sleepiness, constipation, urinary retention, and dry mouth. These results are shown in Table 3.

DISCUSSION

Postoperative pain was least in patients in the KM cohort. The results of the current study are consistent with the results of earlier randomized trials on spinal fusion surgery [1,5,6] and lumbar microdiscectomy surgery [12].

Table 3: Comparison of adverse effects

Parameter	Cohort			Comparison between cohorts			
	KM	***DEX***	***PL***				
Post-operative treatment	***Parenteral ketamine/ midazolam***	***Parenteral dexmedetomidine***	***Parenteral paracetamol***	***P*-value**	***q***		
Patients included in the analysis	115	112	148		***Between KM and DEX***	***Between KM and PL***	***Between DEX and PL***
Nausea	15 (13)*	2(2)	2(1)	< 0.0001	5.613	6.226	0.229
Vomiting	7 (6)*	1(1)	1(1)	0.008	3.648	4.059	0.162
Dizziness	11 (10)*	3(3)	1(1)	0.001	3.801	5.239	1.172
Hallucinations	12 (10)*	2(2)	1(1)	0.001	4.799	5.784	0.653
Nightmares	2(2)	1(1)	1(1)	0.693	N/A	N/A	N/A
¥Bradycardia	1(1)	7 (6)**	1(1)	0.017	3.004	0.756	3.935
Headache	5(4)	9(8)	7(5)	0.407	N/A	N/A	N/A
Blurred vision	8(7)*	1(1)	1(1)	0.003	4.058	4.489	0.154
Chest pain	3(3)	2(2)	1(1)	0.458	N/A	N/A	N/A
Drowsiness	2(2)	3(3)	8(5)	0.237	N/A	N/A	N/A
Dry mouth	2(2)	3(3)	15(10)***	0.004	0.451	4.299	3.789
Constipation	3(3)	4(4)	17(11)***	0.005	0.423	4.169	3.689
Urinary retention	2(2)	3(3)	16(11)***	0.002	0.441	4.548	4.047

Data are presented as frequency (percentage). One-way ANOVA, followed by Tukey *post hoc* test were used for statistical analysis; $p < 0.05$; $q > 3.328$. Adverse-effect was considered as 1 and the absence of effect was considered as 0; *$p < 0.05$, ketamine/midazolam-emergent adverse effects vs PL cohort adverse effects; **$p < 0.05$, dexmedetomidine-emergent adverse effects vs PL adverse effects; ***$p < 0.05$, vs adverse effect reported in PL cohort (due to excess of morphine consumption; this is prediction). N/A: not applicable. ¥Heart rate less than 60 beats/ min for more than 5min

Soft tissue injuries during surgery are due to pain activation mediated by the NMDA receptor which is inhibited by ketamine [1]. Postoperative pain is also influenced by the mood of patients [5]. Low dose of ketamine improves mood by increasing presynaptic glutamate release and up-regulating postsynaptic materials in the prefrontal cortex [13]. Studies have suggested the use of postoperative parenteral low dose ketamine with midazolam for postoperative pain management.

The current study demonstrated that low doses of postoperative ketamine/midazolam and dexmedetomidine decreased postoperative requirement for morphine. These results are in agreement with those obtained in randomized trials on spinal fusion surgery [1,5,6] and lumbar microdiscectomy surgery [12]. Ketamine, midazolam, and dexmedetomidine exert analgesic [1] and opioid-sparing [12] effects. In this study, low doses of ketamine and midazolam or dexmedetomidine decreased the requirements for postoperative morphine in the management of postoperative pain. Patients in the KM cohort reported dizziness and hallucinations. The results of the current study regarding adverse effects are not in agreement with those obtained in earlier randomized trials on spinal fusion surgery [1,5,6] and lumbar microdiscectomy surgery [12]. The reason for this contradiction was that the current study used low doses of ketamine and midazolam (because of major surgeries), while previous studies used very low doses of ketamine and midazolam or S (+)-ketamine. Ketamine [14] and midazolam [15] inhibit cholinergic pathways and excitation of the frontal lobe, leading to dizziness and hallucination. Esketamine [S (+)-ketamine] is recommended for reduction of emergent adverse effects due to ketamine.

Postoperative nausea and vomiting have been reported in patients in KM cohort, but not in patients in DEX cohort. The results of the current study are consistent with the results of randomized trials on spinal fusion surgery [1,5] and lumbar microdiscectomy surgery [12]. However, the results differ from those obtained in a randomized trial on spinal fusion surgery [6] because of use of a low dose of S (+)-ketamine. The use of ketamine and midazolam with propofol induces emesis [16]. Dexmedetomidine decreases the requirement for postoperative morphine, and it exerts an anti-emetic effect by decreasing catecholamine concentration (reduction in sympathetic tone) [17]. The use of postoperative dexmedetomidine for pain management resulted in manageable adverse effects.

Postoperative bradycardia has been reported in patients in DEX cohort, but not in patients in KM cohort. Dexmedetomidine causes direct vasoconstriction which leads to bradycardia [18]. The results of the current study are consistent with the results of a randomized trial on laryngoscopy [9] and uterine artery embolization [7]. However, the results are at variance with those of randomized trials on spinal fusion surgery [1] and prostatectomy [18]. The reason behind such contradiction may be due to the fact that the current study used a low dose of dexmedetomidine (because of major surgeries), whereas previous studies used very low dose of dexmedetomidine. Ketamine also causes direct vasoconstriction, but midazolam inhibits direct vasoconstriction [1]. Thus, this study reported bradycardia in the DEX cohort only.

Limitations of the study

This is a retrospective study. Moreover, it was not based on randomized trial. The study reported data only for the postoperative period, and only VAS and adverse effects were evaluated. There were no evaluations of outcome measures regarding physical/functional impairments and patients' satisfaction. Moreover, the follow-up period was very short.

CONCLUSION

These results suggest the use of postoperative low dose (0.5 mg/kg bolus followed by infusion of 0.25 mg/kg/h) of ketamine with midazolam, and 0.5 µg/kg dexmedetomidine for postoperative pain management in major non-cardiac surgeries. Postoperative low doses of ketamine and midazolam decrease postoperative morphine requirements, but are associated with risks of dizziness, hallucinations, nausea, and vomiting. Postoperative low dose of dexmedetomidine also decrease partial requirements of postoperative morphine, but produces adverse effect of bradycardia.

DECLARATIONS

Acknowledgement

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Availability of data and materials

The datasets used and analyzed during in this study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no conflicts of interest or any other competing interests with regard to this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. The authors read and approved the manuscript for publication. Weiwei Zhan and Yuanyuan Zheng contributed equally to resources, literature review, formal analysis, methodology, and supervision of the study, and they drafted, reviewed, and edited the manuscript for intellectual content. Chunmei Xu, the project administrator, contributed to formal analysis, methodology, data curation, resources, and literature review. Fang Wang contributed to the methodology, validation, literature review, software, and resources. Xiangyu Wang contributed to the investigation, methodology, resources, validation, and literature review.

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