



Postoperative Delirium in Elderly Patients Undergoing Elective Orthopedic Surgeries: A Comparative Study between Dexmedetomidine and Haloperidol

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Abstract

Background and aim: Delirium in surgical patients has a profound impact on postoperative outcomes. The main target of this study to compares the effect of Dexmedetomidine versus haloperidol in the incidence and severity of postoperative delirium in elderly patients undergoing elective orthopedic surgery under general anesthesia.

Patients and methods: Sixty elderly patients scheduled for orthopedic surgery under general anesthesia were randomly allocated into three groups. In the control group, patients received normal saline. In the dexmedetomidine group, patients received dexmedetomidine 1 µg/kg over 20 minutes then continuous infusion at a rate of 0.5 µg/kg/h until the end of surgery. In the haloperidol group, patients received haloperidol 2.5 mg IV over 20 minutes, followed by continuous infusion of 1 mg/h until the end of surgery. The primary outcome of the number of patients developed delirium and the degree of severity of postoperative delirium. The secondary results were the duration of surgery, hemodynamic variables, and Visual analogue scale (VAS).

Results: Hemodynamic variables (MAP and HR) were significantly lower in the dexmedetomidine group when compared to haloperidol and control groups. In the dexmedetomidine group, VAS was considerably lower immediately postoperative and up to 4 hours. The incidence and the severity of postoperative delirium were significantly reduced in the dexmedetomidine group.

Conclusion: The prevalence and severity of postoperative delirium were decreased significantly with the intraoperative administration of dexmedetomidine infusion when compared with haloperidol.

Keywords: Postoperative delirium; Elderly patients; Dexmedetomidine; Haloperidol

Introduction

Delirium is defined as a condition characterized by an acute cognitive decline, a fluctuating mental status, disturbance of consciousness, inattention, or disorganized thinking [1]. Multiple risk factors have been involved in the development of postoperative delirium (POD) including, pre-existing cognitive impairment, advanced age and limited functional status, severity of illness, chronic comorbidities, and use of multiple pharmacological agents [2]. POD is usually associated with recurrent falls, fractures, incontinence, and bladder catheterization with higher risk for infections, increased hospital stays, and death [3]. Recent studies reported that POD is also associated with an increased incidence of impaired cognitive functions, negatively affecting the whole quality of life of the patient [4].

Orthopedic patients are more susceptible to the experience of the delirium than those undergoing general surgery. Incidence of delirium was 44% to 55% in hip surgery patients versus 10% to 14% of general surgery patients [5]. Food and Drug Administration (FDA) has not been approved of the treatment or prevention of delirium in any population, but several studies have tested the impact of many medication classes [6-8]. The Folstein test or Mini-Mental State Examination (MMSE) is a 30-point questionnaire that was initially introduced by Folstein et al. to differentiate functional from organic psychiatric patients [9]. This test used to make a judgment the severity and progression of cognitive impairment and also to follow the changes of cognitive in an individual over time; so making it an effective way to document an individual's response to treatment. When applied, this test takes between 5 and 10 minutes and examines functions including registration, attention and calculation, recall, language, ability to follow orientation and simple commands [10].

Dexmedetomidine has high and specific receptor selectivity; the sedative effect of the dexmedetomidine by blocking a single neurotransmitter, norepinephrine, *via* α₂-adrenoceptor binding without disturbing other neurotransmitter systems, especially the cholinergic system [11]. The cholinergic neurotransmitter system is related to cognitive functions. So, a strong relationship has been documented between drugs with anticholinergic potential and an increased risk of delirium [12]. Moreover, Sanders et al. have hypothesized that gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, has the primary role in the pathogenesis of delirium [13]. Dexmedetomidine decreases the risk of developing delirium by reducing the use of other GABAergic agents like benzodiazepines and opiates [14]. Moreover, the analgesic effect of Dexmedetomidine could decrease the opioid use, which may lessen the incidence of delirium like opioids have been implicated in the development of delirium [15,16].

Haloperidol is a potent psychotropic and neuroleptic agent belonging to the group of butyrophenones. It mediates its action by blockade of dopaminergic receptors in the mesocortex and limbic

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system. When Dopamine D2 receptor blockade leading to enhanced acetylcholine release. Delirium is highly related to cholinergic deficiency. So, it can be haloperidol may have an indirect beneficial effect on delirium [17]. When haloperidol is used with low-dose, it leads to lower delirium incidence in older postoperative intensive care unit (ICU) patients, and duration and severity in (mainly elective) hip-surgery patients [18]. The target of this study aimed to compare the effect of Dexmedetomidine versus haloperidol in the incidence and severity of postoperative delirium in elderly patients undergoing elective orthopedic surgery.

Patients and Methods

Our study was conducted at Benha university hospitals between December 2016 and April 2019 after local ethical committee approval and patient's informed written consent. This prospective, randomized, placebo-controlled, double-blind, clinical study was conducted on 60 patients, ASA I-III, more than 65 years old scheduled for orthopedic surgery. Patients refused to provide informed consent, patients with Mini-Mental State Examination <24, patients with diseases of the CNS, patients with history of consumption of tranquilizers or antidepressants, patients with severe visual or auditory handicap, patients currently diagnosed with alcoholism or drug dependence, patients of ASA grade IV (i.e., with coexisting severe cardiovascular, respiratory, renal or hepatic diseases), patients with severe infections, patients with anemia (hematocrit <30%), patients with fluid or electrolyte disturbance were excluded from the study. These patients were divided into three equal groups. An online randomization program was used to generate a random number list (<http://www.randomizer.org/>). Patient randomization numbers were concealed in opaque envelopes which were opened by the study investigator. In the control group (Group C), patients received normal saline. In the Dexmedetomidine (Group D), patients received dexmedetomidine 1 µg/kg over 20 minutes then continuous infusion at a rate of 0.5 µg/kg/h by a syringe pump maintained until the end of surgery. In the haloperidol (Group H) received haloperidol 2.5 mg IV bolus followed by continuous infusion of 1 mg/h by a syringe pump maintained until the end of surgery. In the operating room, patients were pre-oxygenated for 3 min and received fentanyl (1-2 µg/kg). Induction of anesthesia by given IV propofol (2 mg/kg) until loss of verbal response. Muscle relaxation was acquired with atracurium (0.5 mg/kg) and patients were ventilated with 100% oxygen *via* face mask for 3 minutes then cuffed endotracheal tube of appropriate size was inserted. Patients were subsequently maintained on isoflurane (1 MAC), with top-up doses of fentanyl and atracurium as required. At the end of the surgery, anesthesia was discontinued, and the patients were extubated following reversal of neuromuscular blockade with neostigmine (50-70 µg/kg) and atropine (0.01-0.02 mg/kg). Postoperative analgesia was maintained with IV paracetamol (1000 mg) every 6 hours along with diclofenac sodium (75 mg) intramuscularly twice-daily.

All patients were monitored by five-lead electrocardiograph, a peripheral pulse oximeter, and a noninvasive blood pressure device.

Mini-Mental State Examination (MMSE) was conducted to all patients before the operation (baseline) and in the following three postoperative days (postoperative days 1, 2, and 3). Any score of ≥ 24 points (out of 30) indicates a rational cognition. Below this, scores can show severe (≤9 points), moderate (10-18 points) or mild (19-23 points) cognitive impairment. The primary outcome of this study was detected the number of patients developed delirium in different postoperative days (MMSE <24) and the degree of severity of postoperative delirium. The secondary outcomes were demographic characteristics, duration

of surgery, hemodynamic variables (Mean Arterial Blood Pressure (MAP) and Heart Rate (HR) measured every 15 minutes intraoperative and every 30 minutes postoperative for 3 hours) and Visual analogue scale (VAS) assessed immediately postoperative and then at 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h.

Statistical Analysis

Analysis of data was done by using SPSS version 16. Quantitative parametric data were presented as mean ± Standard deviation and was analyzed by using a one-way ANOVA test, and the significant measures were detected by post-hoc analysis. Quantitative non-parametric data were presented as median and interquartile range and was analyzed by using the Kruskal Wallis test. Qualitative data were presented as numbers and percentages and was analyzed by using the Chi-square test and Fisher exact tests. When a p value <0.05 was considered statistically significant, and a p value <0.01 was considered statistically highly significant. Sample size based on the primary outcome (incidence of delirium) was calculated using a pilot study of the first 7 patients to detect the difference in proportions in relation to the control group using a power 80%, a error 0.05 and the allocation ratio=1. The calculated effect size was 0.4 (two-tailed). Twenty patients were considered in each group.

Results

Eighty-two patients were assessed for eligibility; 66 patients met the inclusion/exclusion criteria, gave consents, and were randomized into the study where there were 22 patients in each group of general anesthesia. Three patients (2 in group C and 1 in group H) were lost to follow up. The intervention was discontinued in 3 patients (2 cases in group D and 1 case in group H) because of significant hypotension, significant bleeding, and prolonged intubation attempt (Figure 1).

Demographic characteristics and duration of surgery were comparable between groups (p>0.05) (Table 1).

Baseline measurements of mean arterial blood pressure (MAP) were comparable between groups. MAP was significantly lower after 15 min and 30 min in the dexmedetomidine group when compared to the control group. At 45 min till 120 min, MAP was significantly lower in the dexmedetomidine group when compared to haloperidol and control groups. At 135 min to 165 min, MAP was significantly lower in the dexmedetomidine group when compared to the control group. No statistically significant difference between groups at 180 min (Figure 2).

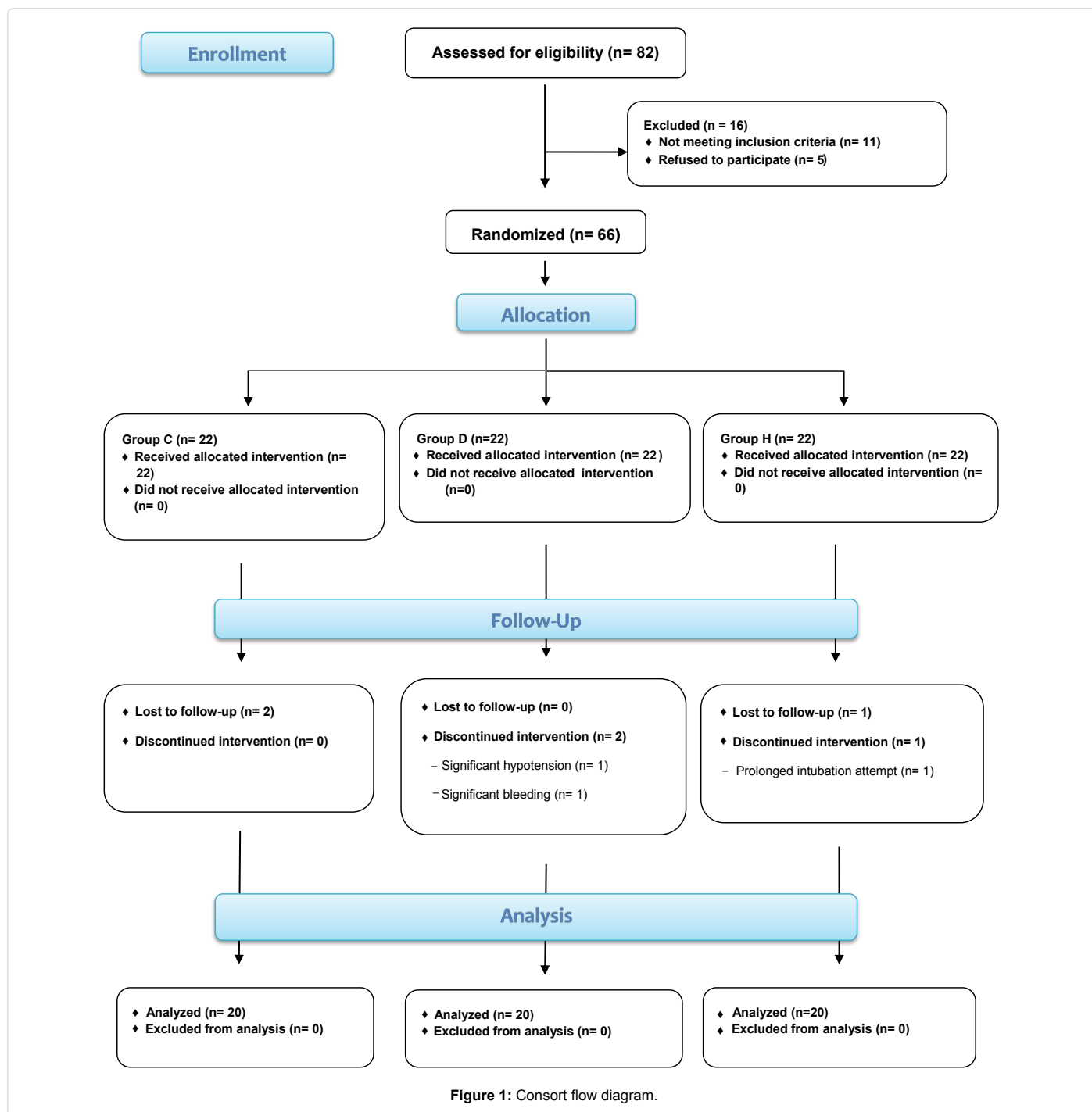
Regarding MAP postoperatively, there were no significant differences in measurements between the three groups (Figure 3).

Regarding the heart rate intraoperatively, there were no significant differences in baseline measurements among groups. Heart rate was significantly lower after 15 min till 135 min in dexmedetomidine group when compared to haloperidol and control groups. At 150 min and 1800 min, HR was comparable among groups (Figure 4).

Regarding heart rate postoperatively, there were no significant differences in measurements among groups (Figure 5).

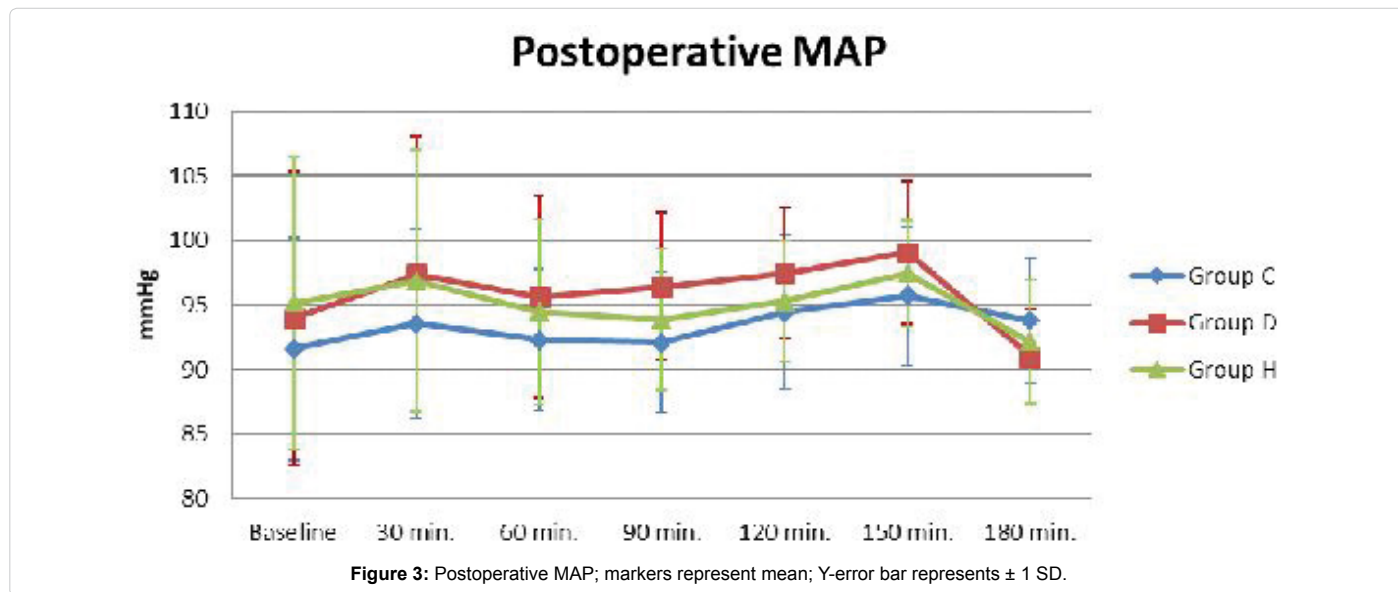
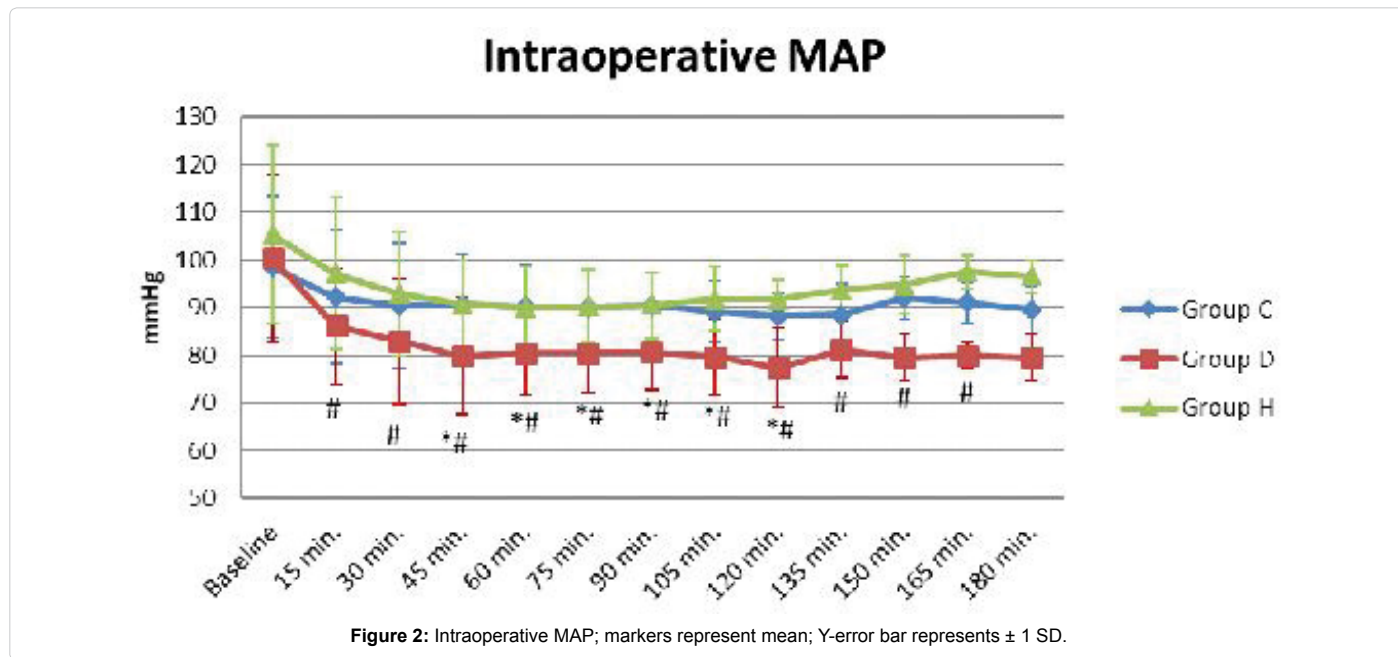
Regarding the visual analogue scale (VAS), VAS was significantly lower in the dexmedetomidine group immediately postoperative and up to 4 hours when compared to both control and haloperidol groups. After 8 hours, there was no significant difference among the groups (Figure 6).

Regarding the severity, there was a significant difference between the control group and both dexmedetomidine and haloperidol groups



	Group C	Group D	Group H	p value
Age (yrs)	70.95 ± 4.85	71.1 ± 5.43	71.3 ± 5.88	0.98
Weight (kg)	83.5 ± 7.91	78.65 ± 9.63	81.75 ± 9.80	0.24
Sex	M	13 (65%)	9 (45%)	8 (40%)
	F	7 (35%)	11 (55%)	12 (60%)
ASA	I	9 (45%)	7 (35%)	8 (40%)
	II	6 (30%)	8 (40%)	8 (40%)
	III	5 (25%)	5 (25%)	4 (20%)
Duration of surgery (min)	117 ± 28.62	117.75 ± 26.33	119.25 ± 27.73	0.96

Table 1: Demographic characteristics and duration of surgery.



where delirium was more severe in the control group according to Mini-Mental State Examination (MMSE) (Figure 7).

The occurrence of delirium was significantly lower in dexmedetomidine group 2 patients (10%) than haloperidol eight patients (40%) and control nine patients (45%) groups (Figure 8).

Hypotension occurred in 3 patients in the dexmedetomidine group with dose reduction by 40% from the current dose in 2 of them while hypotension occurred in 1 patient in both haloperidol and control groups. Bradycardia occurred significantly more in the dexmedetomidine group (5 patients) than in the haloperidol group (1 patient) and control group (0 patient). Two patients in the haloperidol group developed prolonged QTc-interval (>500 ms) (confirmed with 12 lead ECG) which improved with holding haloperidol for 1 h. Three patients developed vomiting in the haloperidol group compared to 2

patients in the control group and one patient in the dexmedetomidine group (Table 2).

Discussion

In our study, the main target to compare the effects of early prophylactic use of Dexmedetomidine or haloperidol on the incidence of delirium following elective orthopedic surgery. The incidence and severity of delirium were significantly reduced in the dexmedetomidine group than haloperidol and control groups. Haloperidol didn't lessen the impact of delirium when compared to dexmedetomidine and control group, but the severity of delirium was reduced.

Bakri and his colleagues compared the effect of ondansetron or Dexmedetomidine with haloperidol, as a control, for the management of postoperative delirium in trauma patients. They founded that

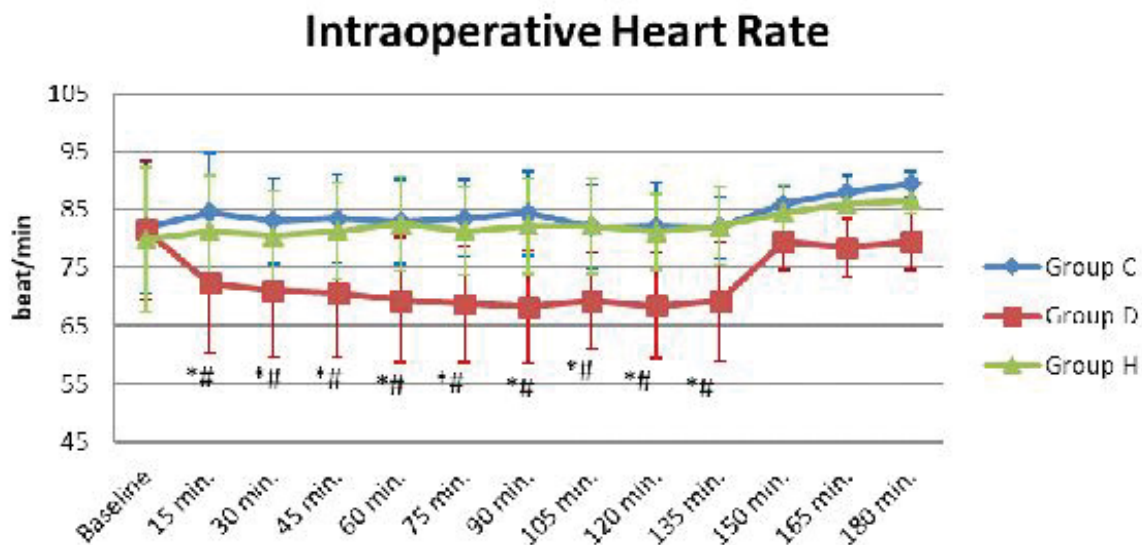


Figure 4: Intraoperative HR; markers represent mean; Y-error bar represents \pm 1SD.

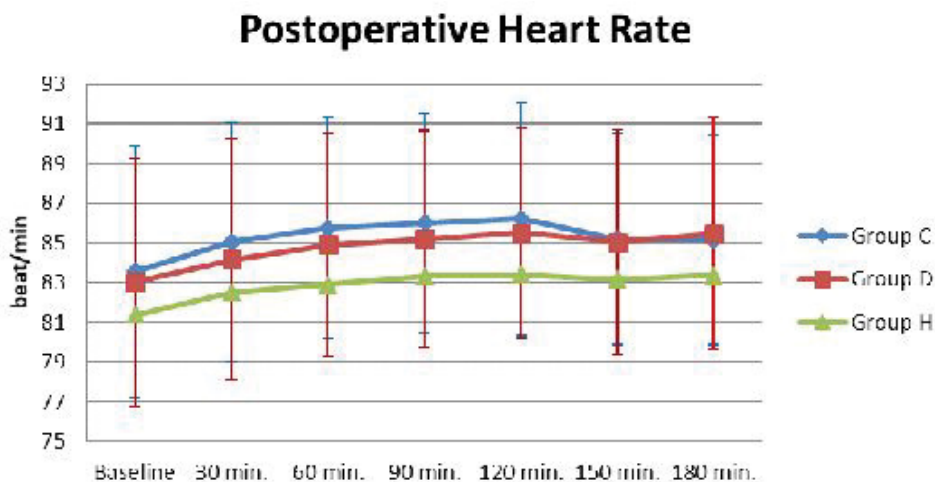


Figure 5: Postoperative HR; markers represent mean; Y-error bar represents \pm 1SD.

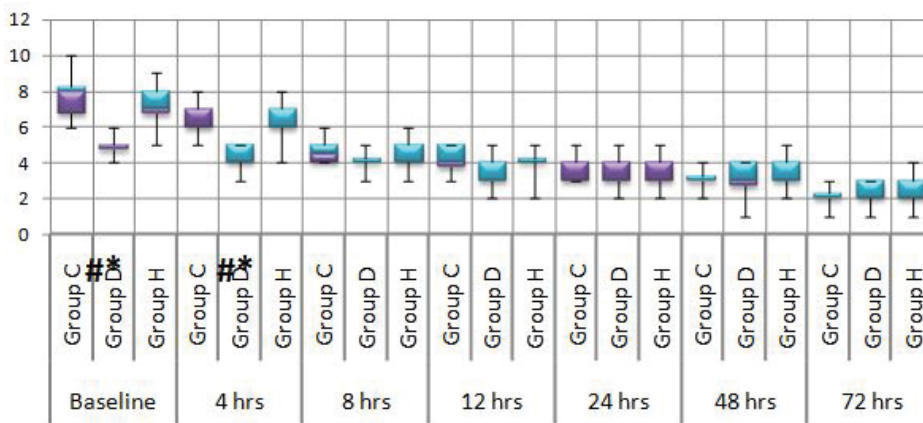


Figure 6: Visual Analogue Scale (VAS).

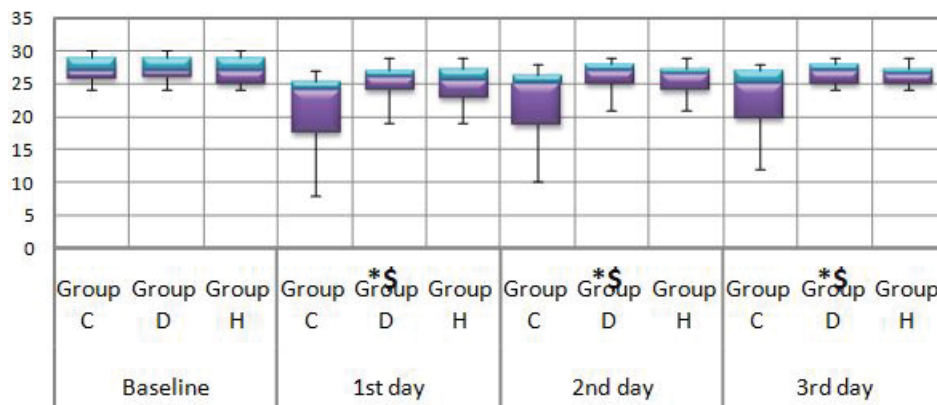


Figure 7: Severity of postoperative delirium.

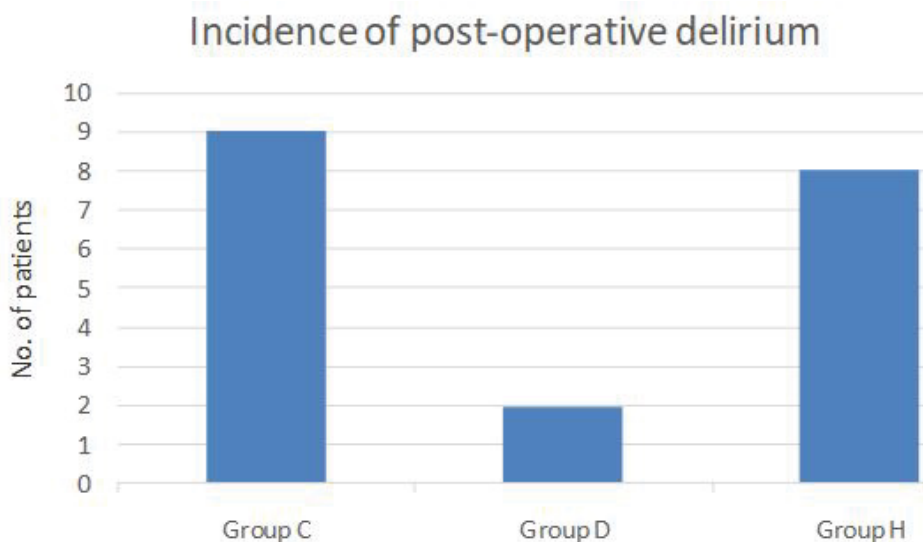


Figure 8: Incidence of post-operative delirium.

	Group C	Group D	Group H	p value
Hypotension	1 (5%)	3 (15%)	1 (5%)	0.41
Bradycardia	0	5 (25%)	1 (15%)	0.02
Prolonged QTc	0	0	2 (10%)	0.12
Vomiting	2 (10%)	1 (5%)	3 (15%)	0.57

Table 2: Incidence of complications.

ondansetron and Dexmedetomidine were comparable for the management of postoperative delirium in trauma patients. However, the solitary mechanisms of Dexmedetomidine make it superior to ondansetron and haloperidol in the management of postoperative delirium [15].

A systematic review from Pasin et al. including 14 randomized controlled clinical trials (RCTs) suggested a decrease of delirium in critically ill patients with Dexmedetomidine. The main results showed that the use of Dexmedetomidine was associated with significant reductions in the occurrence of delirium, agitation, and confusion [19].

Another meta-analysis by Duan et al. also suggested that

Dexmedetomidine can decrease the frequency of postoperative delirium for adult cardiac and non-cardiac surgical patients [20].

Also, a meta-analysis was conducted by Flükiger et al. to estimate the preventive and therapeutic effect of Dexmedetomidine on intensive care unit delirium. Administration of Dexmedetomidine was associated with the significantly lower overall incidence of delirium when compared to placebo. When used of Dexmedetomidine may lead to increase the risks of bradycardia and hypotension. This evidence of the side effects of Dexmedetomidine was limited as the treatment of ICU delirium [21].

Moreover, Maldonado et al. compared the effect of Dexmedetomidine with propofol and midazolam on postoperative delirium and demonstrated that Dexmedetomidine was associated with a significantly reduced incidence of postoperative delirium in patients submitting cardiac surgery with the use of CPB [10]. This study proposed two theories to explain the reduced rates of delirium associated with the sedative effect of Dexmedetomidine: The first theory explanation is based on the intrinsic delirium-simple property

decided by multiple characteristics of Dexmedetomidine [22]. The second theory is that the lower incidence of delirium associated with Dexmedetomidine is not because of its use, but because patients are not exposed to agents that participate in the development of delirium [13].

Deiner et al. studied the effect of Intraoperative Infusion of Dexmedetomidine for prevention of cognitive dysfunction and postoperative delirium in elderly patients submitting major elective noncardiac surgery and found that it didn't prevent postoperative delirium and that the reduction in delirium previously demonstrated in numerous (ICU) studies was not observed, which emphasizes the importance of timing when administering the drug to prevent delirium [23].

Reade et al. showed that Dexmedetomidine was safe and effective for the management of delirium in the surgical intensive care unit, when compared to haloperidol for the treatment of excited, agitated, intubated patients. It also significantly shortened the median time to extubation and decreased ICU length of stay [24].

In a study comparing haloperidol with placebo as prophylactic therapy for the prevention of postoperative delirium in elderly hip surgery patients, the severity and duration of delirium were reduced, but the incidence of delirium was not altered by haloperidol compared to placebo [17]. Another study also compared haloperidol with placebo for delirium prevention in acutely hospitalized older at-risk patients and found that prophylactic low-dose oral haloperidol did not reduce delirium incidence in those patients [25].

Conclusion

Intraoperative administration of dexmedetomidine infusion is associated with a decreased incidence and severity of postoperative delirium in elderly patients undergoing elective orthopedic surgeries when compared with haloperidol.

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