ORIGINAL ARTICLE

Comparison of dexmedetomidine or ondansetron with haloperidol for treatment of postoperative delirium in trauma patients admitted to intensive care unit: randomized controlled trial

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ABSTRACT

Objective: This study was designed to compare the effect of dexmedetomidine or ondansetron with haloperidol, as a control, for the treatment of postoperative delirium in trauma patients.

Methodology: A total of 96 adult trauma patients diagnosed with postoperative delirium were randomized into three equal groups. Patients were given either 1 μg/kg dexmedetomidine (Dexmed group) or 4 mg ondansetron (Ondan group) or 5 mg haloperidol (Halo group), administered twice daily for 3 consecutive days. Number of delirious patients, patients who needed "rescue haloperidol" and the total amount of "rescue haloperidol" during study period was calculated.

Results: At the end of the study, the number of remaining delirious patients was 3, 6, and 2 in Dexmed, Ondan, and Halo groups, respectively, without statistical significance. During the study period, there was no significant difference in the number of patients who needed "rescue haloperidol" between Dexmed and Halo groups (5 vs. 3; $p = 0.7$). However, the difference was significantly higher in Ondan group compared to Halo group (11 vs. 3; $p = 0.03$). The mean total "rescue haloperidol" dose was significantly higher in Ondan group compared to Halo group ($p < 0.001$), but there was no difference between Dexmed and Halo groups ($p = 0.07$). At the same time of delirium assessment, mean arterial blood pressure and mean score on Visual Analog Scale were not statistically different between Dexmed or Ondan group versus Halo group. No serious adverse events were reported.

Conclusion: Dexmedetomidine is a potential alternative treatment for postoperative delirium in trauma patients admitted to ICU.

Keywords: Delirium; Dexmedetomidine; Haloperidol; ICU; Ondansetron; Postoperative; Trauma

Citation: Bakri MH, Ismail EA, Ibrahim A. Comparison of dexmedetomidine or ondansetron with haloperidol for treatment of postoperative delirium in trauma patients admitted to intensive care unit: randomized controlled trial. Anaesth Pain & Intensive Care 2015;18(2):118-123

INTRODUCTION

The American Psychiatric Association defines delirium as "a disturbance of consciousness, attention, cognition, and perception which develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day".[1] Delirium is a serious complication in patients admitted to intensive care unit (ICU). It is associated with an increased morbidity, delayed functional recovery, prolonged ICU stay, and an increased overall health care cost.[2]

Daily screening of intensive care patients for delirium is important because delirium is not only limited to elderly patients, often under diagnosed and is associated with increased length of hospital stay and 6 month mortality.[3] The prevalence of delirium in ICU is high, and it ranges between 11 and 73% in different studies.[4,5] The management of ICU delirium should include preventive measures, identifying risk factors, early diagnosis, and treatment with nonpharmacologic and pharmacologic modalities.[6]

Studies show that dexmedetomidine has a role in the reduction of the incidence of delirium in the ICU setting.[7–10] Dexmedetomidine is a highly selective and potent α_2-adrenoreceptor agonist indicated for ICU sedation. It provides sedation and anxiolysis via receptors within the locus ceruleus and analgesia via receptors in the spinal cord with no significant respiratory depression.[11]

Moreover, it was suggested that ondansetron may have value in the treatment of delirium.[12,13] Ondansetron is a selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonist. It exerts its anti-delirium effect through central inhibition of 5-HT3 receptors, which has been implicated in the development of many anxiety disorders.

On the other hand, the new guidelines stated that robust evidence for haloperidol in the treatment of delirium in the adult ICU patients is lacking.[14] They stated that further research is needed before any recommendation about haloperidol is made. Haloperidol is a potent neuroleptic and psychotropic agent belonging to the group of butyrophenones. It mediates its action through blockade of dopaminergic receptors in the mesocortex and limbic system. Side effects of haloperidol include extrapyramidal ones such as dyskinesia, muscle stiffness, and tremors and prolongation of corrected QT (QTc) interval.

Complexity and heterogeneity of ICU patient population limits the availability of evidence from high quality randomized control trials. To date, there is no study comparing the effect of dexmedetomidine or ondansetron with haloperidol for the treatment of postoperative delirium in trauma patients. Therefore, the aim of this study was to compare the effect of intravenous injection of 1 μg/kg dexmedetomidine or 4 mg ondansetron with 5 mg haloperidol, as a control, for the treatment of postoperative delirium. Number of patients with delirium, number of patients requiring rescue haloperidol and dose of rescue haloperidol were calculated. All three drugs were given by infusion twice daily for three consecutive days. We chose 3 days because it was reported that the highest incidence of postoperative delirium occurred during the first 3 postoperative days.[15]

METHODOLOGY

The study was carried out in the ICU of King Fahd Hospital, Saudi Arabia. Our ICU includes 24 beds, mixed medical and surgical cases. However, the commonest ICU admissions are the trauma patients. During the first 3 days after ICU admission, adult postoperative trauma patients who screened delirium-positive, by using Intensive Care Delirium Screening Checklist (ICDSC),[17] were candidate for inclusion in this study. After local ethical committee approval and obtaining informed written consent from patients' next of kin or legal guardian, 96 consecutive patients were included in this study over 23-month period.

Patients were excluded if they had underlying neurological diseases, significant hearing loss, intracranial injury, ischemic/hemorrhagic strokes, or language barrier that would confound the evaluation of delirium. Similarly, severely injured, deeply comatose, or moribund patients were excluded.

Patients were randomly allocated into three equal groups (32 patients each) according to computer-generated random-number sequence. Patients were given either 1 μg/kg dexmedetomidine (Dexmed group) or 4 mg ondansetron (Ondan group) or 5 mg haloperidol (Halo group) administered as a continuous intravenous infusion over 20 min. Study medications were started after diagnosis of delirium and were given twice daily for 3 consecutive days (6 doses). The dose of ondansetron in the previous studies was 8 mg once a day.[12,16] We divided this dose into 2 equal doses per day. However, for dexmedetomidine, the recommended dose is 0.2-0.7 μg/kg/h. We used 1 μg/kg twice a day to maintain blinding of treatment arms.

The treating physicians were free to prescribe additional haloperidol as rescue when clinically needed in all the three groups "rescue haloperidol." The total amount of "rescue haloperidol" during the study period was recorded. The study medications were calculated and prepared by physicians who were not a part of the research team. Data were collected by researchers who were blinded to the study drugs. Patients were managed by the ICU staffs who were not included in the study.

The delirium was assessed by Intensive Care Delirium Screening Checklist (ICDSC) which requires little or no patient help.[17] The ICDSC includes eight items, based on the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* criteria and features of delirium, which includes altered level of consciousness, inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep–wake cycle disturbances, and symptom fluctuation according to a total score system from 0 to 8 points. Delirium-positive was

defined if the patient had a score of 4 points or more on the ICDSC scale.

Delirium-positive patients were assessed twice a day for 3 days after inclusion in the study. The ICDSC was assessed 1 h after study medications were given. Averages of the two scores were recorded every day. Baseline scores were recorded when patients were consented for the study after ICU admission and before starting study medications. The ICDSC scale is integrated in our daily nurse scoring assessment and carried out by our ICU bedside nurses regularly. By the end of study, the number of remaining delirious patients and patients who needed "rescue haloperidol" was calculated. At the same time of delirium assessment, the mean arterial blood pressure and Visual Analog Scale (VAS) of pain were measured. Medications side effects, such as prolonged QTc interval, hypotension, or bradycardia, were closely monitored during study period.

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were derived for the study population and are expressed as number, percentage, or mean ± standard deviation (SD) or standard error of mean (SEM) as indicated. Data were analyzed and compared using chi-square (χ^2) test for categorical variables and unpaired *t* test for continuous data. The effect of drugs on delirium was compared between dexmedetomidine versus haloperidol or between ondansetron versus haloperidol. . A $p<0.05$ was considered statistically significant.x

RESULTS

A total of 96 trauma patients who underwent different surgical procedures and were admitted to ICU for postoperative care were included in this study. Table 1 shows the patients' baseline characteristics for all the study groups.

There were no statistically significant differences between the study groups in terms of age, weight, gender, type of surgery, duration of surgery, mean Injury Severity Score (ISS) or number of patients on mechanical ventilation on ICU admission. No study patient had history of alcohol or drug abuse before admission. During study period (3 days), no study patient required renal replacement therapy or had sepsis as part of their admission diagnosis. We did not follow up patients after the end of the study period. The mean daily ICDSC scores were not significantly different between three groups (Table 2).

At the time of delirium assessment, there was no statistically significant difference in mean arterial

Table 1: Characteristics of the study population

Variable	Dexmed Group (n=32)	Ondan Group (n=32)	Halo Group (n=32)
Age (y) (Mean ± SD)	31 ± 4	32 ± 5	30 ± 7
Weight (kg) (Mean ± SD)	74 ± 9	72 ± 7	71 ± 10
Gender: (%)			
Male	29 (91%)	30 (94%)	28 (88%)
Female	3 (9%)	2 (6%)	4 (12%)
Surgery type (%)			
General Surgery	10 (31.3%)	8 (25%)	7 (21.8%)
Neurosurgery	8 (25%)	9 (28.1%)	10 (31.3%)
Maxillofacial	7 (21.8%)	8 (25%)	9 (28.1%)
Orthopedic	3 (9.4%)	1 (3.1%)	3 (9.4%)
Thoracic	1 (3.1%)	2 (6.3%)	0 (0.0%)
Vascular	1 (3.1%)	1 (3.1%)	2 (6.2%)
Mixed	2 (6.3%)	3 (9.4%)	1 (3.1%)
Mean duration of surgery (min) (Mean ± SD)	211 ± 27	219 ± 33	203 ± 42
Mean Injury Severity Score (ISS) (Mean ± SEM)	25.1 ± 2.2	23.9 ± 3.5	24.4 ± 2.9
Patients on mechanical ventilation on ICU admission (%)			
Yes	9 (28.1%)	7 (21.8%)	10 (31.3%)
No	23 (71.9%)	25 (78.1%)	22 (68.8%)

Table 2: The mean ICDSC score within 24 hours during 3-day observation

	Dexmed Group (n=32)	Ondan Group (n=32)	Halo Group (n=32)	p-value Dexmed vs. Halo	p-value Ondan vs. Halo
Baseline	6.7 ± 1.3	6.4 ± 1.5	6.5 ± 1.6	0.6	0.8
1st day	5.2 ± 1.6	5.9 ± 1.7	5.6 ± 1.4	0.3	0.4
2nd day	4.4 ± 1.3	4.8 ± 1.5	4.9 ± 1.2	0.1	0.7
3rd day	2.9 ± 1.2	3.5 ± 1.3	3.4 ± 1.1	0.08	0.7

blood pressure or mean VAS for pain between three groups (Tables 3 and 4). After the last dose of the study medications, the number of patients who remained delirious were 3 (9%), 6 (19%), and 2 (6%) in the Dexmed, Ondan, and Halo groups, respectively. In spite of more delirious patients in the Ondan group, there were no significant differences between the Dexmed group or the Ondan group compared to Halo group. Moreover, number of patients who needed "rescue haloperidol" during the study period was 5 (16%) in the Dexmed group versus 3 (9%) in the Halo group ($p = 0.7$). However, it was significantly higher in the Ondan group 11 (34%) compared with Halo group 3 (9%) ($p = 0.03$). In addition, mean total "rescue haloperidol" dose was significantly higher in the Ondan group compared to Halo group (2.1 ± 0.4 mg vs. 0.9 ± 0.6 mg, respectively; $p < 0.001$), however, it was not significantly different between Dexmed and Halo groups. (1.1 ± 0.2 mg vs. 0.9 ± 0.6 mg, respectively; $p = 0.07$). No patient in any study group had significant prolongation of QTc interval (compared with the baseline) during the study period. No serious adverse events were reported during study period.

DISCUSSION

The findings of this study showed that both dexmedetomidine and ondansetron were comparable to haloperidol in the treatment of postoperative delirium in trauma patients. We chose trauma patients because of high prevalence of delirium in surgical and trauma patients. [5]

Papadopoulos et al. examined the effect of postoperative administration of ondansetron for 5 consecutive days in patients undergoing femoral or hip fracture rehabilitation surgery.[13] They found that ondansetron was associated with reduction in the incidence and duration of delirium, regardless of patient age or history of stroke, and improved postoperative neuro-cognitive function.[13] However, the length of hospital stay in the ondansetron group was not statistically significant. Moreover, in patients who developed postoperative delirium after on-pump heart surgery, Tagarakis et al. found that both ondansetron and haloperidol have equal delirium-controlling effect .[12]

Meanwhile, dexmedetomidine was safe and effective for the treatment of delirium in ICU compared to haloperidol for the treatment of delirious,

Table 3: The mean arterial blood pressure at the time of delirium assessment

Assessment Time	Dexmed Group (n=32)	Ondan Group (n=32)	Halo Group (n=32)	p-value Dexmed vs. Halo	p-value Ondan vs. Halo
Baseline	90 ± 15	93 ± 12	91 ± 17	0.8	0.6
1st day	85 ± 12	90 ± 14	88 ± 13	0.3	0.5
2nd day	81 ± 18	88 ± 19	89 ± 16	0.06	0.8
3rd day	82 ± 16	89 ± 14	86 ± 15	0.3	0.4

Table 4: The mean Visual Analog Scale (VAS) of pain at the time of delirium assessment

Assessment Time	Dexmed Group (n=32)	Ondan Group (n=32)	Halo Group (n=32)	p-value Dexmed vs. Halo	p-value Ondan vs. Halo
Baseline	64 ± 11	65 ± 16	63 ± 13	0.7	0.6
1st day	54 ± 14	56 ± 18	58 ± 12	0.2	0.6
2nd day	41 ± 15	43 ± 12	46 ± 14	0.2	0.4
3rd day	33 ± 17	40 ± 15	37 ± 18	0.4	0.5

agitated, intubated patients.[9] In the DEXCOM trial, dexmedetomidine had a trend toward a lower incidence of postoperative delirium and significantly shorter duration of delirium compared to morphine.[18] However, subgroup analysis showed a significantly lower incidence of delirium in patients receiving dexmedetomidine. The SEDCOM study, which compared dexmedetomidine to midazolam for prolonged sedation showed that dexmedetomidine was associated with significantly less delirium and a shorter duration of intubation.[10] Moreover, Maldonado et al. demonstrated that the frequency of delirium after cardiac surgery was 3% in patients sedated postoperatively with dexmedetomidine and 50% in patients sedated with propofol or midazolam. The reduced incidence of delirium was associated with lower treatment costs.[7] In addition; a meta-analysis by Pasin et al. suggested a reduction of delirium in critically ill patients with dexmedetomidine.[19]

Different theories have been postulated to explain anti-delirium effects of dexmedetomidine. Dexmedetomidine has high and specific receptor selectivity; it causes sedation by blocking a single neurotransmitter, norepinephrine, via α_2-adrenoceptor binding without disturbing other neurotransmitter systems in particular the cholinergic system. [20] The cholinergic neurotransmitter system is linked to cognitive functions including memory, attention, concentration, and learning. Thus, a strong relationship has been documented between drugs with anticholinergic potential and an increased risk of delirium.[21] Moreover, Sanders et al. have hypothesized that gamma-amino butyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, plays a role in the pathogenesis of delirium.[22] Dexmedetomidine might attenuate the risk of developing delirium by reducing the use of other GABAergic agents such as benzodiazepines and opiates.[23] Midazolam and lorazepam are independent risk factors for transitioning to delirium in ICU patients.[5,24] Moreover, its analgesic effect could reduce the opioid use which may lessen the occurrence of delirium as opioids have been implicated in the development of delirium.[25] More importantly, dexmedetomidine promotes a more physiologic sleep–wake cycle which is very important in the ICU setting.[26] Sleep disruption and deprivation are the risk factors that may contribute to delirium and cognitive dysfunction in the ICU.[27]

The present study showed that both dexmedetomidine and ondansetron were comparable for the treatment of postoperative delirium in trauma patients. However, the unique mechanisms of dexmedetomidine make it superior to ondansetron and haloperidol in the treatment of postoperative delirium.[7] These mechanisms include GABA receptor-sparing activity, opioid-sparing effect, lack of anticholinergic activity, lack of extra pyramidal side effects, fewer interactions with other drugs, easily titrated, and more physiological sleep pattern. Therefore, in future, dexmedetomidine could have a major role in the treatment of postoperative delirium in trauma patients admitted to ICU.

LIMITATIONS

Sample size of this study was small because of difficulty to recruit patients with the above mentioned inclusion and exclusion criteria which can be managed by carrying a multi-center study. Some confounding factors which may contribute to the development of delirium such as the presence of nasogastric tube, bladder catheter or physical restraints, the appropriate light, and renal or hepatic dysfunction, were not measured. Finally, the dexmedetomidine dose was small compared to what was used in other studies. Further studies with larger sample size and using continuous infusion of dexmedetomidine are needed.

CONCLUSION

Dexmedetomidine is a potential alternative treatment for postoperative delirium in trauma patients admitted to ICU.

Acknowledgment: The authors would like to thank all ICU staff including nurses, technicians, and all medical staff for their cooperation.

Funding: This research was carried out without external funding.

Conflicts of interest: No conflicts of interest to be declared.

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