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The effect of dexmedetomidine versus propofol in traumatic brain injury: evaluation of some hemodynamic and intracranial pressure changes

Mohammed Khallaf[1*], Ahmed Mostafa Thabet[2], Mahmoud Ali[2], Essam Sharkawy[2] and Sherif Abdel-rehim[2]

Abstract

Background: Cerebral edema and increased intracranial pressure are of the major consequences of traumatic brain injury that affects the outcome. The aim of this study is to assess the efficacy of dexmedetomidine as an adjunct to conventional sedative therapy (propofol) compared to conventional sedative therapy alone in patients with traumatic brain injury, as regards its effects on hemodynamics and intracranial pressure.

Methods: This prospective randomized controlled clinical trial with 60 agitated and restless traumatic brain-injured patients was performed between May 2013 and May 2017. Patients who required mechanical ventilation, Glasgow coma scale (GCS) < 8, or hemodynamically instable were excluded. Patients were randomized into three equal groups: dexmedetomidine was infused in a dose of 0.5 μg/kg/h for 48 h in the first group, propofol 1% was infused in a dose of 4 mg/kg/h for 48 h in the second group, and dexmedetomidine was infused in a dose of 0.2 μg/kg/h and propofol was infused in a dose of 2 mg/kg/h for 48 h in the third group. ICP and CPP excursions and complications were assessed in the first 48 h.

Results: The number of ICP and CPP excursions per day was not significantly different between the three groups. Tachycardia, bradycardia, and hypertension in the three groups were statistically insignificant. As regards hypotension, there was a statistically significant difference between the three studied groups.

Conclusion: Dexmedetomidine or its combination with propofol is as effective as propofol alone in TBI; all alternatives are equal as regards the degree of sedation, effect on intracranial pressure, and cerebral perfusion pressure. The incidence of complications does not vary greatly between all groups.

Trial registration: 17200257 registered 5/2013

Keywords: Traumatic brain injuries, Sedation, Dexmedetomidine, Propofol

Introduction

Main text

TBI is a significant public health problem worldwide and is predicted to surpass many diseases as a major cause of death and disability. Cerebral edema and associated increased intracranial pressure are the major immediate consequences of TBI that contribute to most early deaths. An increase in intracranial pressure (ICP) may impede cerebral blood flow (CBF) and lead to cerebral ischemia [1], and its degree and duration are associated with outcome after TBI [2–4]. So, the primary aim of the intensive care management of TBI is to prevent and treat secondary ischemic injury. Prevention and control of increased ICP and maintenance of cerebral perfusion pressure (CPP) are fundamental therapeutic goals after TBI [1]. Several different classes of drugs are used as sedatives, but there is limited evidence available to guide the choice of specific sedative agents in TBI [5].

Dexmedetomidine is a highly selective α2-adrenergic agonist that possesses sedative-, anxiolytic-, and analgesic-sparing properties. The mechanism beyond the reduction

* Correspondence: khallaf_1973@yahoo.com
[1]Department of Neurosurgery, Assiut University Hospital, Assiut, Egypt
Full list of author information is available at the end of the article

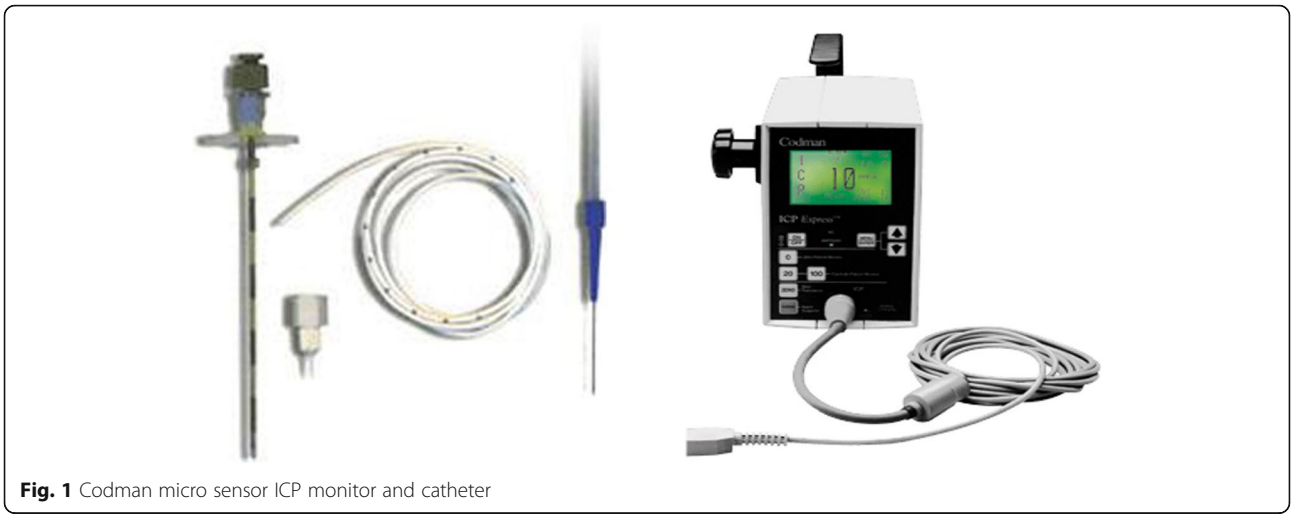

Fig. 1 Codman micro sensor ICP monitor and catheter

of ICP in trauma patients may be due to arterial vasoconstriction induced by α2 agonist activity which in turn leads to a decrease in the cerebral blood volume [2, 6]. It provides excellent sedation without respiratory depression, ease of arousability, and short-acting effects, has sympatholytic properties, and need not be stopped during weaning the patient from mechanical ventilation or for neurological assessment. It suits as an ideal sedative agent for patients with TBI [7].

The efficacy of dexmedetomidine for sedation in intubated ICU patients is well established; however, its use in patients with traumatic brain injury (TBI) has not been comprehensively described. The aim of this study is to assess the efficacy of dexmedetomidine as an adjunct to conventional sedative therapy (propofol) compared to conventional sedative therapy alone in patients with traumatic brain injury, as regards its effects on hemodynamics and intracranial pressure.

Patients and methods

This prospective randomized controlled clinical trial included 60 head-injured patients and was performed in the Trauma Intensive Care Units, Department of Anesthesia, and Intensive Care and Department of Neurosurgery, Assiut University Hospital (single Tertiary Hospital) between May 2013 and May 2017.

Inclusion criteria for the patients in this study were as follows: ASA I–III, patient between 18 and 80 years, Glasgow coma scale (GCS) ≥ 8, agitated and restless patients in need for sedation and close follow-up, diagnosis of TBI by CT or abnormal posturing, and placement of an intracranial pressure monitor at the discretion of the neurosurgical staff as a part of the standard of care. Exclusion criteria were as follows: patients who need mechanical ventilation on admission, AV block with HR < 45/min, and severe preadmission hemodynamic instability. For each patient, the following demographic data were collected from the trauma registry: sex, age, weight (kg), height (cm), BMI, Trauma Severity Score, and GCS on admission.

Allocated patients were randomized, using a program-generated random number table, into three groups; allocation concealment was done using opaque well-sealed envelopes which were opened sequentially for each allocated

Table 1 Patient characteristics

Parameter	Propofol group ($n = 20$)	DEX group ($n = 20$)	Mixed group ($n = 20$)	p value
Age (years)	38.7 ± 11	39.3 ± 8.5	39.3 ± 10.2	0.972
Gender (male/female)	16/4	19/1	18/2	0.322
Weight (kg)	85.4 ± 10.7	85.2 ± 13.3	84 ± 10.9	0.920
Height (centimeters)	171.7 ± 8.4	173.6 ± 8.6	171.5 ± 9	0.688
BMI	30 ± 3.3	29.6 ± 3.2	30.1 ± 3.1	0.890
Trauma Severity Score	30.95 ± 5.7	28.95 ± 4.2	30.85 ± 6.4	0.437
Time relapsed before ICU admission (hours)	4.3 ± 1.2	4.2 ± 1.1	3.8 ± 0.9	0.360
GCS on admission • Mild; GCS > 12 • Moderate; GCS = 8–11	14 6	16 4	15 5	0.766

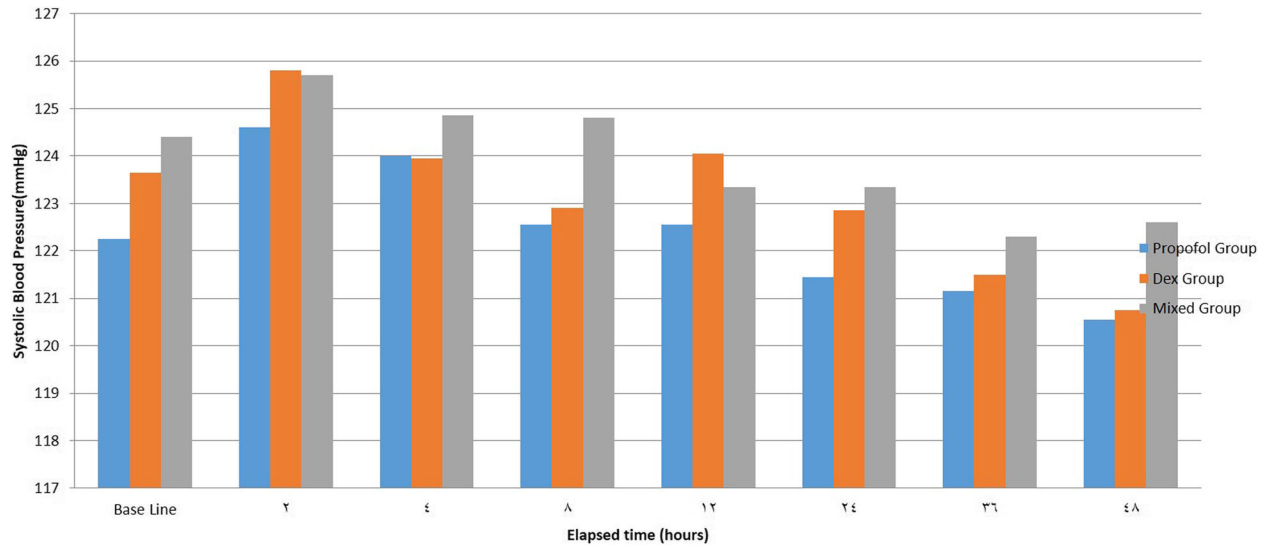

Fig. 2 Systolic blood pressure changes in the studied groups

patient. Groups are based on the type of sedation used in the ICU; patients were randomized into three groups; dexmedetomidine group ($n = 20$): dexmedetomidine (Precedex® Dexmedetomidine HCl vial, HOSPIRA, INC) was infused in a loading dose of 1 μk/kg followed by I.V infusion of 0.4–1 μk/kg/h. The dexmedetomidine is supplied in a 2-ml vial of 100 μg/ml; each vial was diluted in 48 mL of normal saline in a syringe pump to yield a final concentration of 4 μg/ml and infused for 48 h.

Propofol group ($n = 20$): propofol 1% (Fresenius Kabi AB) in 20-ml ampoule was administrated as a loading dose of 1 mg/kg followed by maintenance dose of 1.5–4.5 mg/kg/h titrated to the desired effect. Propofol was infused in a 50-ml syringe pump for 48 h. Dexmedetomidine + propofol group ($n = 20$): dexmedetomidine were infused in a dose of 0.2 μg/kg/h and propofol were infused in a dose of 2 mg/kg/h for 48 h. Sedative agents were titrated to reach a goal of ICP< 20 mmHg and CPP> 60 mmHg with calm patients (controlling agitation, restlessness, and anxiety). After starting the infusion, strict and vigil monitoring of hemodynamic and respiratory parameters at regular intervals of 2 h for 48 h was done. Patients fulfilling the inclusion criteria were admitted to the Trauma Intensive Care Unit and were treated according to our standard protocol for treatment of TBI.

At ICU, to describe physiological changes, baseline parameters were observed and recorded, which included heart rate (HR), systolic, diastolic, and mean arterial blood pressures, respiratory rate, and pulse oximetry (SpO2). Intracranial pressure (ICP) was monitored by an intraparenchymal

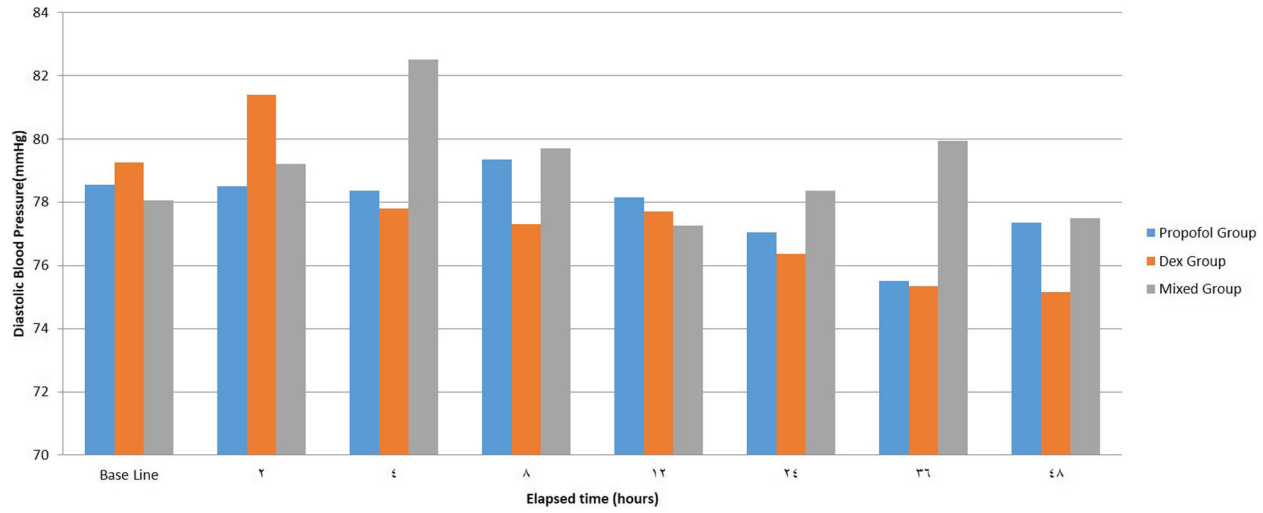

Fig. 3 Diastolic blood pressure changes in the studied groups

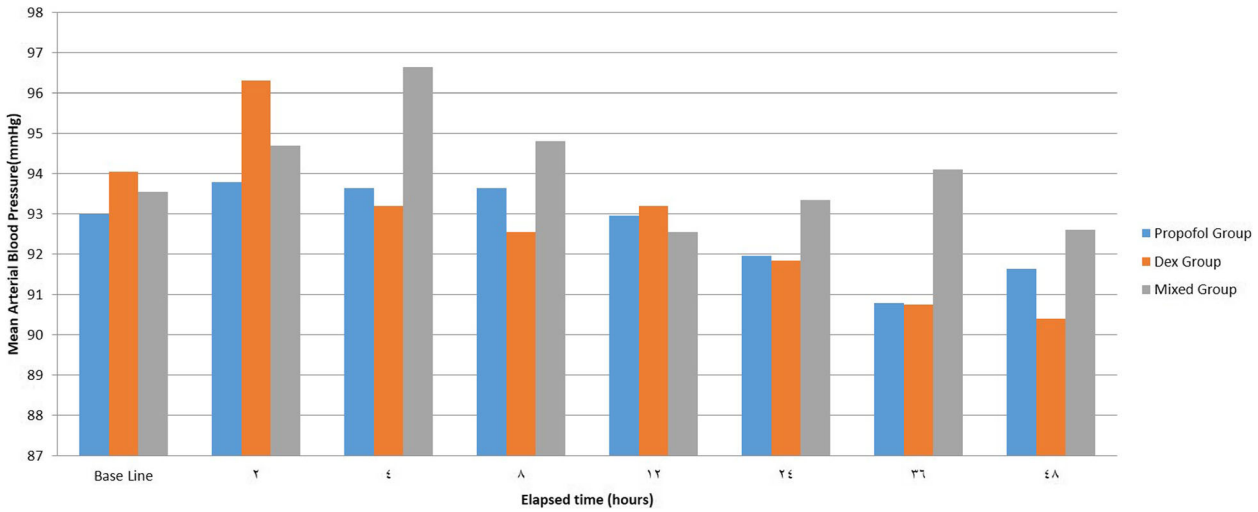

Fig. 4 Mean arterial blood pressure changes in the studied groups

Table 2 Blood pressure changes in the studied groups

	Propofol group ($n = 20$)	DEX group ($n = 20$)	Mixed group ($n = 20$)	p value
Systolic blood pressure				
Baseline	122.25 ± 3.57	123.65 ± 5.11	124.4 ± 4.74	0.319
After 2 h	124.6 ± 3.83	125.8 ± 4.7	125.7 ± 5.01	0.652
After 4 h	124 ± 4.47	123.95 ± 5.38	124.85 ± 6	0.835
After 8 h	122.55 ± 6.3	122.9 ± 7.72	124.8 ± 6.91	0.553
After 12 h	122.55 ± 3.82	124.05 ± 4.45	123.35 ± 6.7	0.655
After 24 h	121.45 ± 6.97	122.85 ± 5.14	123.35 ± 7.8	0.654
After 36 h	121.15 ± 6.56	121.5 ± 7.04	122.3 ± 9.66	0.894
After 48 h	120.55 ± 8.29	120.75 ± 8.74	122.6 ± 10.48	0.741
Diastolic blood pressure				
Baseline	78.55 ± 6.86	79.25 ± 8.55	78.05 ± 5.92	0.869
After 2 h	78.5 ± 5.38	81.4 ± 6.08	79.2 ± 6.95	0.308
After 4 h	78.35 ± 7.24	77.8 ± 8.39	82.5 ± 7.72	0.123
After 8 h	79.35 ± 6.35	77.3 ± 7.98	79.7 ± 10.59	0.630
After 12 h	78.15 ± 6.85	77.7 ± 5.8	77.25 ± 8.11	0.920
After 24 h	77.05 ± 7.61	76.35 ± 6.02	78.35 ± 7.8	0.673
After 36 h	75.5 ± 9.25	75.35 ± 9.81	79.95 ± 10.04	0.243
After 48 h	77.35 ± 8.49	75.15 ± 8.41	77.5 ± 13.54	0.729
MAP				
Baseline	93 ± 5.38	94.05 ± 7.09	93.55 ± 5.19	0.856
After 2 h	93.8 ± 4.4	96.3 ± 5.37	94.7 ± 5.89	0.321
After 4 h	93.65 ± 6	93.2 ± 6.86	96.65 ± 6.82	0.205
After 8 h	93.65 ± 5.95	92.55 ± 7.65	94.8 ± 9.24	0.657
After 12 h	92.95 ± 5.5	93.2 ± 4.98	92.55 ± 7.3	0.942
After 24 h	91.95 ± 7.12	91.85 ± 5.23	93.35 ± 7.8	0.739
After 36 h	90.8 ± 8.19	90.75 ± 8.54	94.1 ± 9.6	0.392
After 48 h	91.65 ± 8.01	90.4 ± 8.18	92.6 ± 12.42	0.775

Table 3 Heart rate changes in the studied groups (bpm)

Heart rate	Propofol group ($n = 20$)	DEX group ($n = 20$)	Mixed group ($n = 20$)	p value
Baseline	114.15 ± 10.16	116.15 ± 8.62	117.15 ± 13.99	0.689
After 2 h	109.55 ± 10.36	106.15 ± 8.62	107.15 ± 13.99	0.618
After 4 h	104.35 ± 10.64	101.85 ± 8.7	101.8 ± 14.22	0.723
After 8 h	105.1 ± 10.94	96.55 ± 8.47*	97.15 ± 13.98*	0.035*
After 12 h	103.85 ± 13.79	97.25 ± 11.67	97.45 ± 15.85	0.240
After 24 h	95.1 ± 15.53	98.5 ± 13.3	101.05 ± 16.54	0.466
After 36 h	95.7 ± 15.35	89.1 ± 13.18	89.9 ± 15.85	0.315
After 48 h	95.9 ± 15.99	89.55 ± 14.52	89.65 ± 15.57	0.333

*p value for these results are significant as it is less than 0.01

catheter placed by author neurosurgeon using CODMAN® MICROSENSOR® ICP Transducer. The abovementioned parameters were measured at 2, 4, 8, 12, 24, 36, and 48 h from admission to the ICU. Neurological assessment was done for all patients by GCS and agitation scale by modified Richmond Agitation-Sedation Score (RASS) [3].

The length of ICU and hospital stay and adverse events were recorded daily for each studied patient and defined as hypotension (systolic blood pressure [SBP] < 90 mmHg or MAP < 65 mmHg), hypertension (SBP > 160 mmHg), bradycardia (heart rate [HR] < 40 bpm), and tachycardia (HR > 120 bpm). Assessment of delirium was performed every 12 h after cessation of sedation or as needed according to the patient's condition using the confusion assessment method (CAM) for ICU.

Informed consent according to the criteria set by the local research ethics committee in our center had to be obtained in writing before surgery. If consent could not be obtained because the patient was in a coma or dysphasic, consent was obtained from relatives. Through explanation, the purpose of the study and how data will be treated with respect and confidentiality were provided to the participants.

Statistical plan

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases), and percentages when appropriate. Comparison of quantitative variables between studied groups was done using the one-way ANOVA test. As for the samples for comparing categorical data, chi-square (χ^2) test was performed. A probability value of less than 0.05 was considered relative frequencies statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS 20 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows (Fig. 1).

Results

Patients' general characteristics and other admission data were summarized in (Table 1). Most of our patients were in

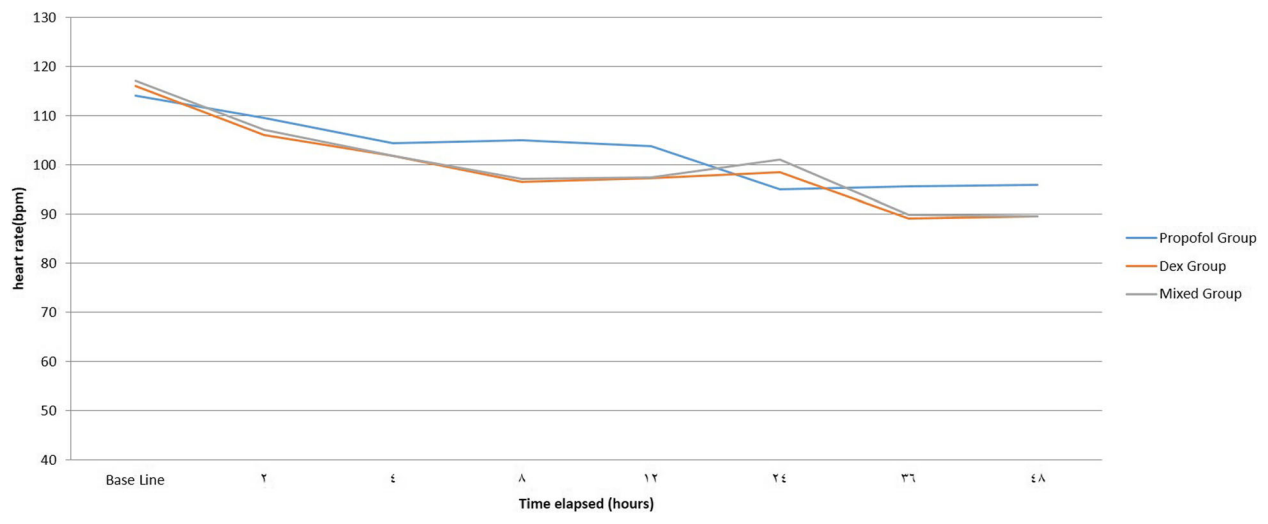

Fig. 5 Heart rate changes in the studied groups

Table 4 Intracranial and cerebral perfusion pressure changes and excursions in the studied groups (mmHg)

	Propofol group ($n = 20$)	DEX group ($n = 20$)	Mixed group ($n = 20$)	p value
ICP				
Baseline	15.4 ± 3.4	15.7 ± 2.9	15.8 ± 2.6	0.931
After 2 h	14.7 ± 2.9	14.4 ± 2.8	14.1 ± 2.3	0.787
After 4 h	13.4 ± 2.1	13.7 ± 3	13.1 ± 1.9	0.703
After 8 h	13 ± 2.6	12.6 ± 3.5	12.1 ± 2.7	0.673
After 12 h	12.3 ± 3.4	11.9 ± 4.2	11.5 ± 3.9	0.831
After 24 h	11.8 ± 4.5	11.1 ± 5.5	10.8 ± 5	0.811
After 36 h	12 ± 3.5	11.6 ± 4.4	11.2 ± 3.9	0.797
After 48 h	11.8 ± 4	11.2 ± 4.8	11 ± 4.5	0.842
CPP				
Baseline	86 ± 5.54	86.85 ± 6.25	87.3 ± 5.41	0.769
After 2 h	89.05 ± 4.85	90.3 ± 5.65	90.75 ± 6.93	0.640
After 4 h	89.35 ± 4.74	89.15 ± 6.16	90.95 ± 6.13	0.555
After 8 h	89.05 ± 6.92	89.1 ± 7.61	91.35 ± 6.93	0.514
After 12 h	89.55 ± 5.28	91.1 ± 5.56	90.8 ± 7	0.688
After 24 h	88.75 ± 7.74	90.6 ± 6.2	91.45 ± 7.73	0.489
After 36 h	88.1 ± 7.59	88.65 ± 6.44	90.1 ± 9.36	0.711
After 48 h	87.65 ± 9.73	88.8 ± 7.61	90.3 ± 10.15	0.663
Intracranial pressure excursions, number of patients (percentage)	6 (30%)	7 (35%)	5 (25%)	0.839
Cerebral perfusion pressure excursion, number of patients (percentages)	7 (35%)	5 (25%)	2 (10%)	0.192

ICP excursions > 20 mmHg. CPP excursion < 50 mmHg

the fourth decade of life; the mean age in the propofol group was 38.7 ± 11, in the DEX group, it was 39.3 ± 8.5, while it was 39.3 ± 10.2 in the mixed group, and there was no statistically significant difference between the means of all groups. Male patients were the majority in all groups. This finding is logical as males are more subjected to trauma due to their mobility; moreover, males are more likely than females to be involved in violent activities and motor vehicle crashes and often sustain more severe injuries compared to females.

There was no significant difference between the three studied groups at all times of the study regarding systolic, diastolic, and mean arterial blood pressure (Figs. 2, 3, and 4) (Tables 2 and 3).

Heart rate decreased over time in all studied group in the first 48 h. There were no significant differences between the three studied groups as regards the heart rate except after 8 h; at this time, DEX and mixed groups showed significantly lower values compared to the propofol group (Fig. 5).

The mean baseline ICP was 15.4 ± 3.4 ml, 15.7 ± 2.9 ml, and 15.8 ± 2.6 mmHg for the three studied groups respectively. These means showed no statistically significant differences with each other. ICP measurement showed no significant differences between the three groups over the 48 h of the study. Baseline cerebral perfusion pressure differs insignificantly between the three studied groups and continued throughout the study period over the next 48 h. We recorded the number of ICP and CPP excursions for each patient during the infusion period and presented the median (range) per 24 h for each patient. The number of ICP and CPP excursions per day was also not significantly different between the three groups. When compared to each other, there was no difference in the median occurrence of ICP excursion (> 20 mmHg) and CPP excursion (< 50 mmHg), (Table 4) (Figs. 6 and 7).

Regarding tachycardia, bradycardia, and hypertension, there were no statistically significant differences between the three studied groups. As for hypotensive episodes, it occurred in 8 patients in the propofol group, in and 2 patients in the DEX group, and in 2 patients in the mixed group, with statistically significant differences between the three studied groups. Delirium was present in 3 out of 20 patients (15%) in the DEX and mixed groups, while it occurred in 7 out of 20 patients (35%) in the propofol group. There was a significant difference detected between the three studied groups regarding delirium duration. In patients in the DEX and mixed groups,

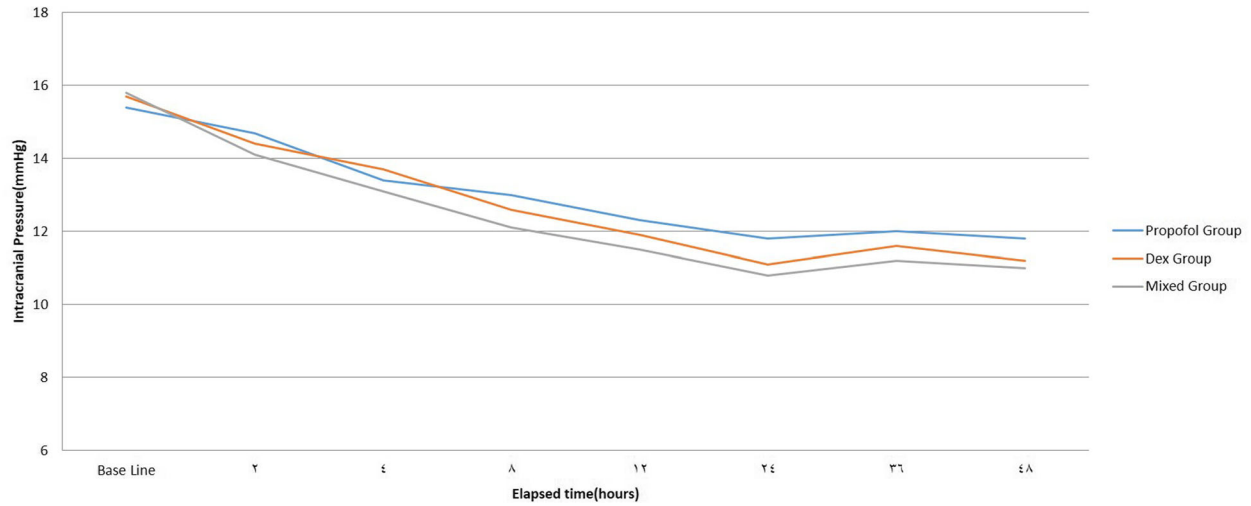

Fig. 6 Intracranial pressure changes in the studied groups

the median onset of delirium was delayed and the duration of delirium reduced, when compared to propofol group (Table 5) (Fig. 8).

Discussion

In TBI, there is a strong correlation between increased ICP and bad outcome [4–6]. The role of sedative agents in TBI extends from allowing mechanical ventilation which prevents hypoxia and hypercapnia and decreases $CMRO_2$ and hence ICP. These beneficial effects of sedation are opposed by the fact that these sedative agents may produce harmful episodes of hemodynamic instability; hypotensive episodes may greatly affect the outcome [8, 9].

The results of our study showed no statistically significant differences between the three groups as regards the values of ICP and CPP, mean arterial blood pressure, or the incidence of hypertensive or bradycardic episodes between the three studied groups.

Different studies showed the favorable effect of propofol on brain hemodynamics when used as sedative agents [7, 10]. Aryan et al. also showed that there was a slight decrease in the mean for ICP and a small corresponding increase in CPP with DEX administration in 39 neurosurgical patients. They concluded that dexmedetomidine can be a safe and effective sedative agent for neurosurgical patients [11]. Pajoumand et al., in their study, found that DEX failed to decrease the maximum ICP in the first and second day of the trauma compared to propofol or a mixture of DEX and propofol. DEX reached its maximum effect on reduction of ICP on day 4 after the trauma. Moreover, it was

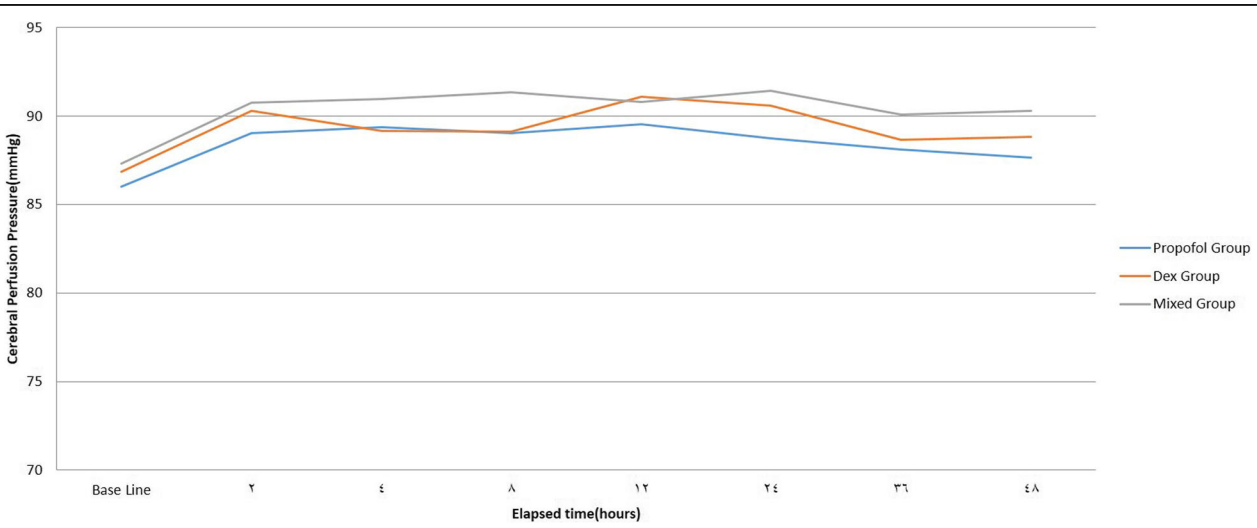

Fig. 7 Cerebral perfusion pressure changes in the studied groups

Table 5 Clinical outcome, length of stay, complications, and delirium in the studied groups

	Propofol group ($n = 20$)	DEX group ($n = 20$)	Mixed group ($n = 20$)	p value
GCS on discharge from ICU, median (range)	12 (8.75)	12 (7.5)	12 (5.75)	0.604
Length of ICU stay (days)	23.5 ± 3	24.1 ± 2.8	22.9 ± 3.1	0.428
Length of hospital stay (days)	46.6 ± 3.8	48 ± 3.1	46.4 ± 4.2	0.329
Complications				
Bradycardia	3 (15%)	6 (30%)	3 (15%)	0.392
Tachycardia	7 (35%)	5 (25%)	2 (10%)	0.170
Hypotension	8 (40%)	2 (10%)	2 (10%)	0.024*
Hypertension	6 (30%)	6 (30%)	4 (20%)	0.711
Vomiting	5 (25%)	3 (15%)	1 (5%)	0.208
Patients needed mechanical ventilation	4 (20%)	2 (10%)	1 (5%)	0.322
Death rate till ICU discharge	2 (10%)	1 (5%)	1 (5%)	0.765
Delirium				
Incidence	7 (35%)	3 (15%)	3 (15%)	0.208
Onset (days)	2 (1–5)	1 (2–4)	2 (2–4)	0.138
Duration (days)	3 (1–4)	2 (1–3)	2 (1–4)	0.034*

*p value for these results are significant as it is less than 0.01

significantly lesser in the DEX group compared to propofol or DEX-propofol mixture [12].

A recent retrospective cohort study conducted by Schomer et al. concluded that dexmedetomidine may avoid increases in the need for rescue therapy when used as an adjunctive treatment of refractory intracranial hypertension without compromising hemodynamics [13]. Also, Erdman et al. in their retrospective multicenter trial compared the hemodynamic effects of DEX and propofol in neurocritical patients; they found a similar incidence of hypotension between DEX and propofol and they recommended more trial on patients with TBI only [14].

Devabhakthuni et al. compared the safety and clinical outcomes of prolonged infusions with standard-dose (≤ 0.7 μg/kg/h) dexmedetomidine (SDD) or high-dose (> 0.7 μg/kg/h) dexmedetomidine (HDD) to propofol in critically ill trauma patients. They concluded that higher doses of dexmedetomidine may result in higher

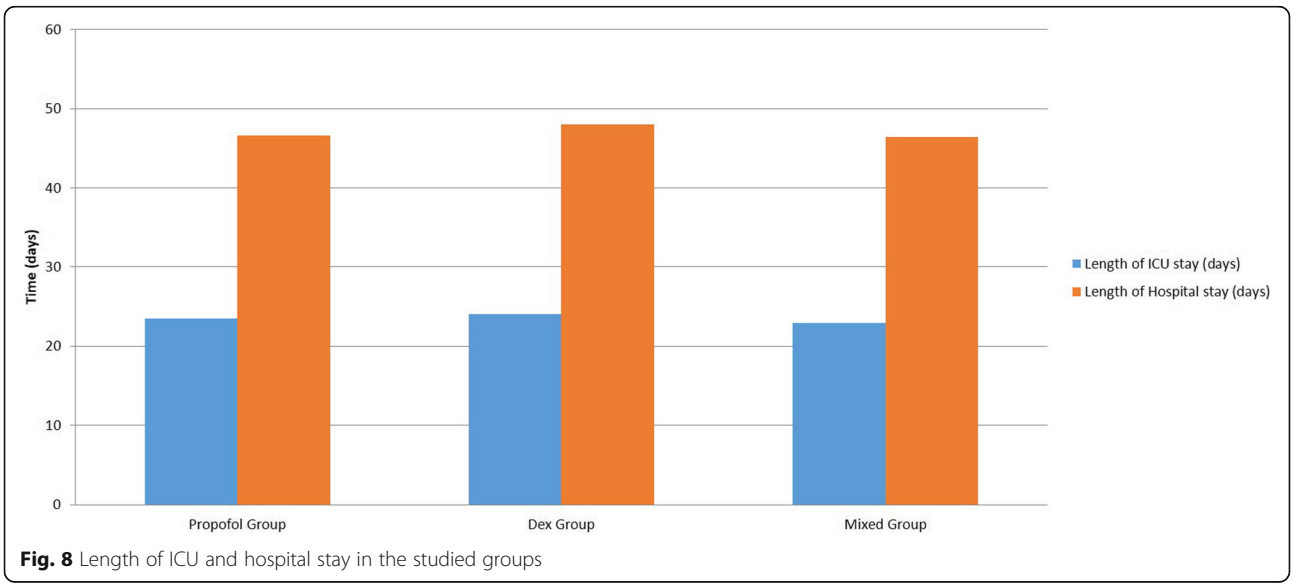

Fig. 8 Length of ICU and hospital stay in the studied groups

incidence of hypotension, longer LOS, and increased concomitant analgesic and sedative, requiring further evaluation in trauma patients [8].

Hypertension may also complicate critically ill head trauma patients. This may be due to inadequate sedation or due to paroxysmal sympathetic hyperactivity associated with head trauma. In our study, we find no differences in the incidence of hypertension between the three studied groups. Riker et al., in their double-blinded prospective study, found that patients sedated with DEX compared to midazolam have lesser ventilation hours and decreased incidence of hypertension and tachycardia [15]. Authors proposed that sympatholytic activity of DEX may be adventitious in the alleviation of these symptoms [9, 15–19].

In our study, we observed higher although non-significant increase in the incidence of delirium in the propofol group compared to other two groups. The only significant difference was observed in the duration of delirium which was longer on propofol compared to other groups. Djaiani et al. concluded that, when compared with propofol, dexmedetomidine sedation reduced the incidence, delayed the onset, and shortened the duration of delirium in ICU patients [20].

Propofol has been associated with rapid regain of consciousness upon discontinuation of sedation and better quality of sedation. Tang et al., in their study of non-intubated TBI patients, also showed that DEX allowed clinicians to conduct periodic neurologic examinations [17, 2]. Clinicians use propofol more commonly as the sedative for patients with TBI due to its extensively described neuroprotective effects [21, 22].

Limitations of our study may include the lack of generalizability as this is a single center study. We did not study the period after discontinuation of both sedative agent, and we did not study the opioid needs and opioid-sparing effect of both agents. We also evaluated the sedation level of patients by loss of agitation and being calm not by any scores like Richmond Agitation-Sedation Score (RASS).

Conclusion

From this study, we conclude that dexmedetomidine or combination of dexmedetomidine and propofol are as effective and safe as propofol alone in head trauma patients, and all alternatives are equal as regards the degree of sedation, the effect on intracranial pressure, and cerebral perfusion pressure. The incidence of complications and outcome do not vary significantly between all studied groups; although there are some results suggesting that dexmedetomidine might have better results regarding delirium "onset and duration", these findings need a larger sample size study. Therefore, although larger series are needed to confirm our results, we found that dexmedetomidine is an option to be taken into account in the integral management of patients with TBI.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors' contributions
MK is the main author who contributed to the study design and analysis of patients' data and is responsible for the neurosurgical procedure and writing of the publication. AM contributed to the data collection and followed up the patients at the ICU. MA, ES, and SA-r contributed to the analysis of the patients' data. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Research committee approval has been granted for this study by the Medical Ethics Committee, Faculty of Medicine, Assiut University. with ethics committee approval number 17200257 on May 2013. Informed consent according to the criteria set by the local research ethics committee in our centre had to be obtained in writing before surgery. If consent could not be obtained because the patient was in coma or dysphasic consent was obtained from relatives. Through explanation to the purpose of the study and how data will be treated with respect and confidentiality was provided to the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Author details
[1]Department of Neurosurgery, Assiut University Hospital, Assiut, Egypt. [2]Department of Anesthesia and Intensive Care, Assiut University Hospital, Assiut, Egypt.

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