ORIGINAL ARTICLE

Evaluation of beta-blocker effects on patients with traumatic brain injury: interventional double-blinded randomized controlled trial

Mostafa Saieed Mansour[1]* , Nihal Shahat El Seidy[2] and Yasser Ibrahim Fathey[1]

Abstract

Background Traumatic brain injury (TBI) is a major cause of death and disability throughout the world. Traumatic injury is one of the most common causes of death in people under the age of 40 worldwide, and one-third of all trauma-related deaths are a result of intracranial insults. We aimed to conduct a randomized controlled trial examining the effect of beta-blockers on outcomes in TBI patients.

Result Regarding CT brain, 45% of cases in the beta-blocker group and 60% of cases in the control group had abnormal CT findings. Contusion and brain edema were still observed in the beta-blocker group (5% in each), while hemorrhage was still found in 35% of cases in the beta-blocker group and 55% of cases in the control group. Furthermore, a fractured skull was observed in 5% of cases in the beta-blocker group and 20% of cases in the control group. No significant differences were found between the two groups regarding CT brain findings (*p*-value was > 0.05).

Mortality was 15% in the beta-blocker group and 30% in the control group, while 95% of patients in the beta-blocker group and 90% of patients in the control group had ICU stay ≤ 14 days.

Conclusions Total hospital stay > 14 days showed a significant rise in the beta control group when compared to the blocker group while no significant differences between them in survival, ICU stay, total hospital stay, and total hospital length of stay for patients stayed ≤ 14. Patients in the beta-blocker group showed no significant differences in overall survival compared to patients in the control group.

Trial registration ClinicalTrials.gov ID: NCT05195996.

Keywords Traumatic brain injury (TBI), Beta antagonist, Propranolol

Background

Traumatic brain injury (TBI) is a principal root of casualty and frailty worldwide. Worldwide, TBI causes hospitalization or death in over 54 to 60 million people, each year (Hyder et al. 2007). Strategies to improve outcomes, therefore, have a central role in the acute care of individuals suffering from TBI (European brain injury society 2011). The highest incidence of TBI is in adolescents and young adults, and he is older than 75 years (Loane et al. 2015). There are a lot of ways to classify patients concerning severity, injury mechanism, and pathophysiology, and each of them can influence medical scenarios and deal with pathology. Idealistically, the most accurate prognostic models would include each of the aforementioned factors, in addition to oldness and medical comorbidity.

*Correspondence:
Mostafa Saieed Mansour
dr.mostafa_s_fahim@yahoo.com; mostafa.said@med.menofia.edu.eg
[1] Anesthesiology, Intensive Care and Pain Management, Faculty
of Medicine, Menoufia University, Shebin-El Kom, Egypt
[2] Critical Care Unit, Menouf Hospital, Menoufia, Egypt

Mansour *et al. Ain-Shams Journal of Anesthesiology*   (2023) 15:65

Page 2 of 8

Glasgow Coma Scale alone may misclassify the severity of TBI. For this reason, in clinical practice and research, further criteria are used. These include periods of changed mental status or losing consciousness and periods of post-traumatic amnesia. Imaging tests such as computed tomography (CT) scans can also be used to identify structural damage to help assess the severity of the damage (Jain and Iverson 2020).

In research studies, TBI can be classified using the Abbreviated Injury Scale (AIS) score of the neck and head region. AIS ranks an injury on a 6-point scale based on the risk of death. A "1" indicates a minor injury, and a "6" indicates a nonviable injury. However, like the GCS, each severity criterion has some limitations and may not predict TBI severity and outcome precisely when used alone (Brasure et al. 2013).

Beta-blockers have potential to exert a survival benefit by inducing protection against secondary brain injury after severe traumatic brain injury (decrease sympathetic outflow, brain edema, and agitation (Zangbar et al. 2016).

The study's primary outcome was to compare survival in patients receiving propranolol with patients who did not receive any beta-blocker, and the secondary outcomes were to determine whether the effect of beta-blocker on TBI is related to HR control or not and evaluate the effects of beta-blockers in TBI on ICU and total hospital stay.

Methods

This prospective interventional randomized double-blinded controlled study was conducted in our hospital's intensive care unit (ICU). Forty patients underwent the standard procedures of the protocol.

Ethics of the study

The research ethics committee of our university approved the design of the study (IRB 2/2021ANESTH-4). Informed written consent was taken from the patient's first-degree relatives after clarification of welfare and dangers. Privacy of patient's data was settled. Registration of ClinicalTrial.gov was completed (ID NCT05195996).

Study population

The study was carried out on 40 patients admitted to Menoufia University Emergency Hospital from the 1st of October 2021 to the end of March 2022.

Inclusion criteria

Age between 18 and 50 years old of both sexes (below age of 18 is considered pediatrics and above 50 it is more likely to have other comorbidities) with head trauma, GCS preoperative > 10 (as GCS ≤ 10 is suspected to have poor outcome even with medical or surgical intervention), abbreviated Injury Scale (AIS) > 3, and length stay in *ICU* > 48 h.

Exclusion criteria

These are history of propranolol hypersensitivity, bronchial asthma, COPD, ongoing smoking, any cardiac diseases, e.g., heart failure or HB, pheochromocytoma, parturient, total time of stay in hospital < 48 h, declaration of death within 48 h of admission, patient medicated with a beta-blocker at home, and symptomatic bradycardia < 60 b/m (sick sinus syndrome). Also, patients with hemodynamics instability were excluded as this is a contraindication for beta-blocker.

This study included polytrauma patients who are admitted from the emergency room or postoperative with head trauma. Full history was taken from the patient or his/her relatives.

This included personal data (age, sex, weight).

Prehospital evaluation

These are time of trauma; mechanism of trauma; prehospital medication (if a patient took any medication before transfer); medication taken at ER; AMPLE history for allergies, especially from beta-blockers; current medication; previous illness; last meal; and situations related to the injury.

The patients were randomly split into two groups of equal size using the sealed envelope approach.

Group A administered propranolol 1 mg diluted with 10-ml distilled water intravenously every 6 h (Chen et al. 2017) for 48 h. Group B administered normal saline 10 ml every 6 h for 48 h. Caregivers and those who assessed the outcomes were blinded to the type of treatment given.

Parameter assessments

Duration of total hospital stay, duration of ICU stay, and functional status were assessed using the GCS, CT scan to exclude another intracranial hemorrhage or increase in hemorrhage, hemodynamic data (BlP/HR), a crystalloid volume that individuals took in 24h and mortality rate.

Statistical analysis

Data were gathered, aggregated, and statistically analyzed using an IBM-compatible personal computer with Statistical Package for Social Sciences (SPSS) version 28 (released by SPSS Inc. in 2020). IBM SPSS Statistics for Windows, Version 28.0, Armnock, NY: IBM Corp.). Cochran's test was used to evaluate multiple tests for paired categorical data measuring outcomes greater than 2×2. Overall survival is the duration between the date of histological diagnosis and the date of the last follow-up (for censored observation) or the date of death (for

Mansour *et al. Ain-Shams Journal of Anesthesiology*　　(2023) 15:65

Page 3 of 8

uncensored observation). Overall survival analysis and disease-free survival were performed using Kaplan–Meier statistics and log-rank tests and showed significance. Significant test results were given as two-sided probabilities. The significance of the results obtained was assessed at the 5% level ($p > 0.05$).

Results

As regards demographic characteristics among the two studied groups, the average age of the beta-blocker group and control group was 43.2 ± 11.04 years and 43.95 ± 11.7 years, respectively. No significant difference in age was found between the two groups (p-value was 0.836). There was a high prevalence of the male gender in both the beta-blocker group and control group (70% vs. 65%, respectively) with no significant differences found between them (p-value was 0.736). The mean BMI in the beta-blocker group and control group was respectively 27.6 ± 4.1 kg/m^2 and 27.9 ± 4.9 kg/m^2 with no significance in the difference found between them (p-value was 0.827).

Regarding medical history, 35% of cases in the beta-blocker group and 40% in the control group were hypertensive. DM was reported in 20% cases in beta-blocker group and 25% cases in control group. A total of 10% cases in beta-blocker group and 5% cases in control group had chronic liver diseases. No significant differences were found between the two groups regarding medical history (p-value was 0.744 for HTN and 1.000 for other disease).

RTA was the most frequent cause of trauma representing 70% of individuals in the beta-blocker group and 60% of individuals in a control group, and no significant difference was found between them (p-value was 0.508) (Table 1).

Regarding CT brain, 100% of individuals in the beta-blocker group, and 90% of patients in the control group, had abnormal CT findings. Contusion was seen in 45% of patients in the beta-blocker group and 30% of patients in the control group, while hemorrhage was reported in 55% of patients in the beta-blocker group and 60% of patients in the control group. A total of 35% of patients in the beta-blocker group and 25% of patients in the control group had brain edema. In addition, a fractured skull was seen in 5% of patients in the beta-blocker group and 20% of patients in the control group. There was no significance in the difference found between the two groups regarding the CT brain (p-value was > 0.05). It was found that 15% of patients in the beta-blocker group and 5% of patients in the control group needed mechanical ventilation (for non-neurological causes, e.g., chest trauma, severe maxillofacial insult, or other causes affecting respiratory parameters), and no significance in the

differences was found between them (p-value was > 0.05) (Figs. 1 and 2).

Regarding CT brain 1–2-week post-admission, 45% of patients in the beta-blocker group and 60% of patients in the control group had abnormal CT findings. Contusion and brain edema were still seen in the beta-blocker group (5% in each), while hemorrhage was still found in 35% of patients in the beta-blocker group and 55% of patients in the control group. Furthermore, a fractured skull was seen in 5% of patients in the beta-blocker group and 20% of patients in the control group. No significant difference was found between both groups regarding CT brain findings (p-value was > 0.05) (Table 2).

The results show that the rate of mortality was 15% in the beta-blocker group and 30% in the control group. A total of 95% of patients in the beta-blocker group and 90% of patients in the control group had ICU stay ≤ 14 days with the mean ICU duration of stay for patients who stayed ≤ 14 days which was 10.26 ± 2.13 days and 11.50 ± 2.71 days in beta-blocker group and control group, respectively (Table 3).

Patients in the beta-blocker group showed no significant difference in overall survival compared to patients in the control group (log rank = 0.842, p-value = 0.359) (Table 3 and Fig. 3).

Discussion

Our results were supported by the study of Zangbar et al. (2016), as they reported that a total of 25,858 adults with blunt trauma injury were examined, of whom 914 met the criteria for inclusion. One-hundred eighty-nine individuals were administered beta-blockers, 178 of whom received metoprolol. The average age was 52 ± 22 years, 74% were males, and there were no significant differences between the beta-blocker and controls, although there is difference in the age group of the study population.

Similarly, Ahl et al. (2017) revealed that they included β-block (BB(+)) patients ($n = 76$) and respective controls (BB(−) ($n = 76$)). No significant differences were found for any of the parameters analyzed. No differences were found regarding patient characteristics. The average patient age was 58 ± 16 years, and 77.0% were males.

No significance in the difference was found between the two groups in the CT brain (p-value was > 0.05). No statistically significant difference was found between the two groups regarding the need for mechanical ventilation or intervention as well as deterioration (p-value was > 0.05).

Regarding the CT brain for the beta-blocker group, there was a significant steady decline throughout the follow-up period in abnormal CT findings (p-value < 0.001), contusion (p-value 0.003), hemorrhage (p-value 0.018), and brain edema (p-value 0.009). The need for

Table 1 Sociodemographic characteristics and medical history of the studied groups

	Beta-blocker group (*n* = 20)		Control group (*n* = 20)		Test of significance	*p*-value
	No	%	No	%		
Age (years)					t	
Mean ± SD	43.2 ± 11.04		43.95 ± 11.7		0.208	0.836
Range	22–61		22–61			
BMI					t	
Mean ± SD	27.6 ± 4.1		27.9 ± 4.9		0.219	0.827
Range	22.4–35.8		19.2–41.0			
Sex					χ^2	
Male	14	70.0	13	65.0	0.114	0.736
Female	6	30.0	7	35.0		
Medical history						
Hypertension					χ^2	
Yes	7	35.0	8	40.0	0.107	0.744
No	13	65.0	12	60.0		
DM					FE	
Yes	4	20.0	5	25.0	0.143	1.000
No	16	80.0	15	75.0		
CLD					FE	
Yes	2	10.0	1	5.0	0.360	1.000
No	18	90.0	19	95.0		
Cardiac					FE	
Yes	1	5.0	0	0.0	1.026	1.000
No	19	95.0	20	100.0		
Cause of trauma					χ^2	
RTA	14	70.0	12	60.0	1.354	0.508
FFH	3	15.0	6	30.0		
Fight	3	15.0	2	10.0		

Range (minimum–maximum)

SD Standard deviation, *BMI* Body mass index, *DM* Diabetes millitus, *CLD* Cirrhotic liver disease, *t* Student *t*-test, *FE* Fisher's exact test, *χ²* chi-square test

P > 0.05: non-significant

mechanical ventilation showed no significant difference throughout the follow-up period (*p*-value was > 0.05).

Regarding the CT brain of the control group, there was a significant steady decline throughout the follow-up period in abnormal CT findings (*p*-value was 0.012), contusion (*p*-value was 0.009), and brain edema (*p*-value was 0.008). No significant differences were found between the two groups regarding hemorrhage (*p*-value was > 0.05). The need for mechanical ventilation showed a significant increase throughout the follow-up period (*p*-value was 0.042).

Zangbar et al. (2016) conducted a cohort of three-hundred and six patients (178: metoprolol and 178: NBB). The average heart rate (89.9 13.9 vs. 89.9 15; *p* 0.99) and a standard deviation of (14.7 6.3 vs. 14.4 6.5; *p* 0.65) did not differ significantly between the two groups. There was no difference between the two groups in neurosurgical intervention (18% vs. 13%;

p 0.24). There were no differences in other matching cofactors in their patient cohort (e.g., SBP, GCS).

Also, Ley et al. (2018) demonstrated that there were no differences noted among BB users and the control group concerning admission hypotension (*SBP* < 90 mmHg) and intubation in the field.

In the study of Ko et al. (2016) over 29 months, a total of 440 sufferers with moderate-to-severe TBI met the inclusion criteria. Early propranolol after TBI (EPAT) changed and administered to 25% (109 of 440) of the sufferers. The EPAT cohort changed into younger (49.6 years vs. 60.4 years, *p* < 0.001), had decreased Glasgow Coma Scale (GCS) score (11.7 vs. 12.4, *p* = 0.003), had better admission coronary heart rate (95.8 beats/min vs 88.4 beats/min, *p* = 0.002), and required extra days at the ventilation (5.9 days vs. 2.6 days, *p* < 0.001). Resemblances were seen in sex and admission systolic blood pressure.

Mansour *et al. Ain-Shams Journal of Anesthesiology* (2023) 15:65
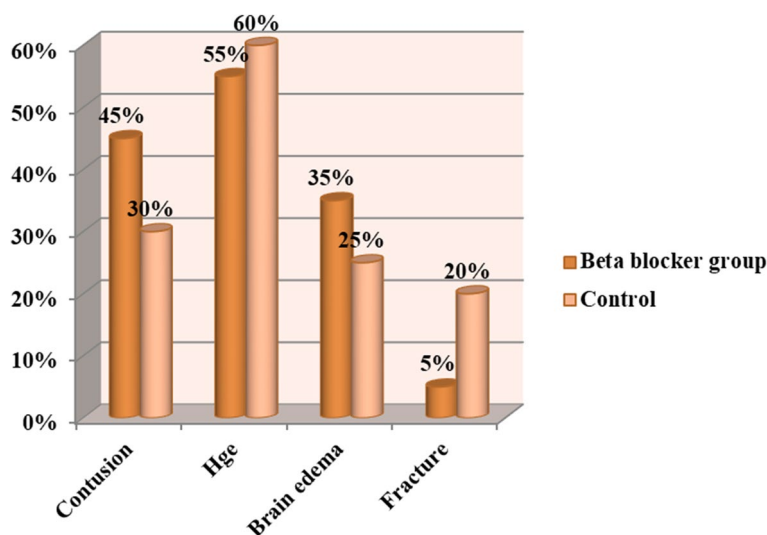
Page 5 of 8

Fig. 1 Positive CT findings (1st presentation). Contusion was seen in 45% of patients in the beta-blocker group, and 30% of patients in the control group, while hemorrhage was reported in 55% of patients in the beta-blocker group and 60% of patients in the control group. A total of 35% of patients in the beta-blocker group and 25% of patients in the control group had brain edema. In addition, a fractured skull was seen in 5% of patients in the beta-blocker group and 20% of patients in the control group
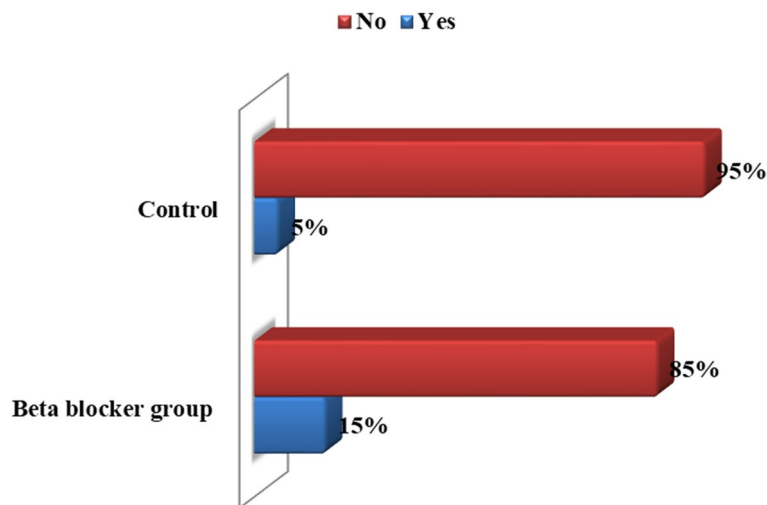

Fig. 2 Need for mechanical ventilation (1st presentation). It was found that 15% of patients in the beta-blocker group and 5% of patients in the control group needed mechanical ventilation, and no significance in the differences was found between them

However, in a meta-analysis conducted by Chen et al. (2017), 13 observational-cohort studies in total included 15,734 patients. β-blocker administration also resulted in a long time of ventilation ($MD = 2.70$; 95% $CI = 1.81, 3.59$; p 0.001).

Our results showed that as regards outcome. The results show that the rate of mortality was 15% in the beta-blocker group and 30% in the control group. A total of 95% of patients in the beta-blocker group and 90% of the patients in the control group had ICU stay ≤ 14 days with the mean ICU length of stay for patients who stayed ≤ 14 days was 10.26 ± 2.13 days and 11.50 ± 2.71 days in beta-blocker group and control group, respectively. A total of 95% of the patients in the beta-blocker group and 65% of patients in the control group had a total hospital stay ≤ 14 days with the mean total hospital length of stay for patients stayed ≤ 14 days being 11.16 ± 2.01 days and 11.38 ± 2.53 days in beta-blocker group and control group, respectively.

Mansour *et al. Ain-Shams Journal of Anesthesiology*   (2023) 15:65

Page 6 of 8

Table 2 Comparison between studied groups regarding post-1- to 2-week clinical evaluation and final outcome

	Beta-blocker group (*n* = 20)		Control group (*n* = 20)		Test of sig	*p*-value
	No	%	No	%		
GCS					**U**	
Mean ± SD	13.00 ± 4.12		10.5 ± 5.18		2.370	**0.018***
Range	3–15		3–15			
CT brain						
CT result					χ^2	
Abnormal finding	9	45.0	12	60.0	0.902	0.342
No finding	11	55.0	8	40.0		
Contusion					**FE**	
Yes	1	5.0	0	0.0	1.026	1.000
No	19	95.0	20	100.0		
HGE					χ^2	
Yes	7	35.0	11	55.0	1.616	0.204
No	13	65.0	9	45.0		
Brain edema					**FE**	
Yes	1	5.0	0	0.0	1.026	1.000
No	19	95.0	20	100.0		
Fracture					**FE**	
Yes	1	5.0	4	20.0	2.057	0.342
No	19	95.0	16	80.0		
Need for mechanical ventilation					**FE**	
Yes	3	15.0	6	30.0	1.290	0.451
No	17	85.0	14	70.0		

U Mann–Whitney test, *FE* Fisher's exact test, χ^2 chi-square test

* *P* < 0.05: significant

Table 3 Comparison between studied groups regarding final outcome

	Beta-blocker group (*n* = 20)		Control group (*n* = 20)		Test of sig	*p*-value
	No	%	No	%		
Survival					**FE**	
Died	3	15.0	6	30.0	1.290	0.451
Survived	17	85.0	14	70.0		
ICU stay					**FE**	
≤ 14 days	19	95.0	18	90.0	0.360	1.000
> 14 days	1	5.0	2	10.0		
ICU LOS for patients stayed ≤ 14 days					**t**	
Mean ± SD	10.26 ± 2.13		11.50 ± 2.71		1.549	0.130
Range	8–14		6–14			
Total hospital stay					**FE**	
≤ 14 days	19	95.0	13	65.0	5.625	**0.044***
> 14 days	1	5.0	7	35.0		
Total hospital LOS for patients stayed ≤ 14 days					**t**	
Mean ± SD	11.16 ± 2.01		11.38 ± 2.53		0.282	0.780
Range	8–14		6–14			

t Student *t*-test, *FE* Fisher's exact test, *LOS* Length of stay

* *P* < 0.05: significant

Mansour *et al. Ain-Shams Journal of Anesthesiology* (2023) 15:65
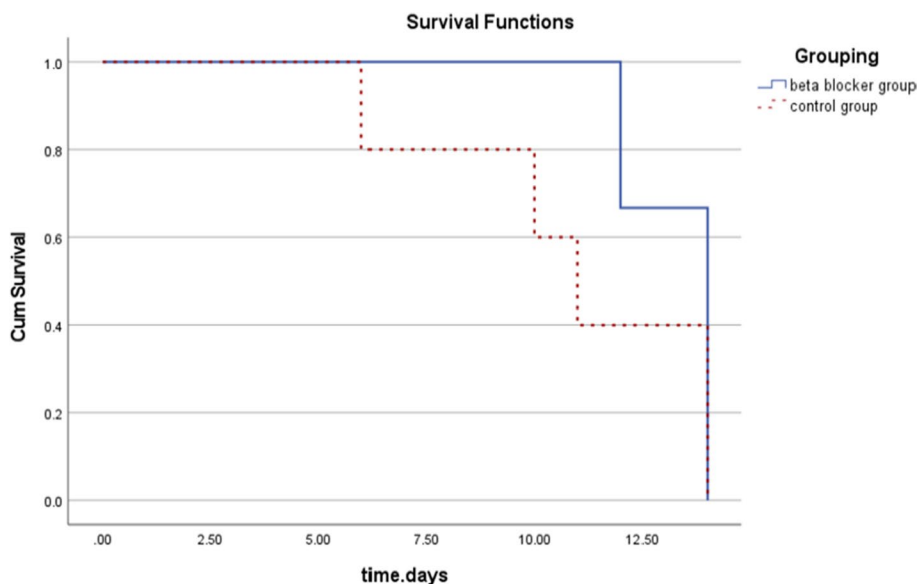
Page 7 of 8

Fig. 3 Kaplan–Meier curve for survival in beta-blocker and control groups. Patients in the beta-blocker group showed no significant difference in overall survival compared to patients in the control group

Whereas Ahl et al. (2017) found that the mean length of stay in the neonatal intensive care unit (NICU) in the study and control groups was 8.5 ± 11.7 vs. 10.8 ± 9.1 days ($p = 0.09$), the average length of hospital stay was shorter in her study group (18.0 days vs. 26.8 days, $p < 0.01$). Non-beta-blockers had more than double the risk of poor long-term functional outcomes (OR 2.44, 95% CI 1.01–6.03, $p = 0.03$). In a study by Chen et al. (2017), according to a meta-analysis, results showed that beta-blocker therapy significantly reduced the mortality rate for admitted patients (OR 0.33; 95% CI 0.27–0.40; p 0.001). Nevertheless, beta-blocker medication was associated with higher infection rates (OR 2.01; 95% CI 1.50–2.69; p 0.001), length of hospital stay ($MD = 7.40$; 95% $CI = 4, 39, 10.41$; p 0.001), and ICU stays ($MD = 3.52$; 95% $CI = 1.56, 5.47$; p 0.001). Ko et al. (2016) found similarities in his LOS in the hospital, his LOS in the ICU, and his rate of mortality. Multivariate regression revealed that EPAT correlated independently with a decreased rate of mortality (adjusted odds ratio, 0.25; $p = 0.012$). Similarly, Arbabi et al. (2007) stated that during hospitalization, individuals exposed to beta-blockers had higher survivability after traumatic brain injury. Even though these head trauma sufferers were older, more seriously wounded, and had a greater frequency of comorbidities than their non-blocker counterparts, the use of blockers was associated with improved outcomes. Inaba et al. (2008) reported a substantial decrease in mortality among elderly individuals with serious head injuries

($AIS \geq 4$). Beta-blockers were administered to patients throughout their ICU stay.

Moreover, Khalili et al. (2020) stated that there were no significant differences in hospital mortality (adjusted IRR 0.6 [95% CI 0.3– 0.4], $p = 0.2$) or long-term functional outcomes ($p < 0.3$) between cohorts. A total of 154 cases experienced isolated severe TBI, of which 44% underwent BB. The BB + group was found to have a significantly lower mortality rate compared to the BB − group (18.6% vs 4.4%, $p = 0.012$).

Conclusions

Total hospital stay > 14 days showed a significant rise in the beta control group when compared to the blocker group while no significant differences between them in survival, ICU stay, total hospital stay, and total hospital length of stay for patients stayed ≤ 14. Patients in the beta-blocker group showed no significant differences in overall survival compared to patients in the control group.

Abbreviations

TBI	Traumatic brain injury
CT	Computerized topography
AIS	Abbreviated Injury Scale
GCS	Glasgow Coma Scale
BB	Beta-blocker
ER	Emergency room
RTA	Road traffic accident
HR	Heart rate
BLP	Blood pressure
SBP	Systolic blood pressure
ICU	Intensive care unit

Mansour *et al. Ain-Shams Journal of Anesthesiology*   (2023) 15:65

Page 8 of 8

Availability of data and materials
The data set used and analyzed in this study is available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from Menoufia Faculty of Medicine Ethical Committee to undertake research and publish the result, IRB 2/2021ANESTH-4. We attest that this research is in compliance with regulation of our institution and generally accepted guidelines governing such work in the country, Egypt. We obtain informed consent from each participant before the commencement of the research work.

Consent for publication
The participants were informed the result will not provide an identifiable individual or personal information; however, statistical descriptive data would be published.

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

References
Ahl R, Thelin EP, Sjölin G, Bellander BM, Riddez L, Talving P et al (2017) β-Blocker after severe traumatic brain injury is associated with better long-term functional outcome: a matched case control study. Eur J Trauma Emerg Surg 43(6):783–789

Arbabi S, Campion EM, Hemmila MR (2007) Beta-blocker use is associated with improved outcomes in adult trauma patients. J Trauma 62(1):56–61 61-2

Brasure M, Lamberty GJ, Sayer NA, Nelson NW, Macdonald R, Ouellette J et al (2013) Participation after multidisciplinary rehabilitation for moderate to severe traumatic brain injury in adults: a systematic review. Arch Phys Med Rehabil 94:1398–1420

Chen Z, Tang L, Xu X, Wei X, Wen L, Xie Q (2017) Therapeutic effect of beta-blocker in patients with traumatic brain injury: a systematic review and meta-analysis. J Crit Care 41:240–246

European brain injury society (2011) Available at: http://www.ebissociety.org/head-injury.html

Hyder AA, Wunderlich CA, Puvana Chandra P (2007) The impact of traumatic brain injuries: a global prospective. NeuroRehabilitation 22(5):341–531

Inaba K, Teixeira PG, David JS (2008) Beta-blockers in isolated blunt head injury. J Am Coll Surg 206(3):432–438. https://doi.org/10.1016/j.jamcollsurg.2007.10.005

Jain S, Iverson LM (2021) Glasgow coma scale. StatPearls. StatPearls Publishing, Treasure Island [Updated 23 Jun 2020]

Khalili H, Ahl R, Paydar S, Sjolin G, Cao Y, Abdolrahimzadeh FH et al (2020) Beta-blocker therapy in severe traumatic brain injury: a prospective randomized controlled trial. World J Surg 44(6):1844–1853

Ko A, Harada MY, Barmparas G, Thomsen GM, Alban RF, Bloom MB et al (2016) Early propranolol after traumatic brain injury is associated with lower mortality. J Trauma Acute Care Surg 80(4):637–642

Ley EJ, Leonard SD, Barmparas G, Dhillon NK, Inaba K, Salim A et al (2018) Beta blockers in critically ill patients with traumatic brain injury. J Trauma Acute Care Surg 84(2):234–244

Loane DJ, Stoica BA, Faden AL (2015) Neuroprotection for traumatic brain injury. Handb Clin Neurol 127:343–366

Zangbar B, Khalil M, Rhee P, Joseph B, Kulvatunyou N, Tang A et al (2016) Metoprolol improves survival in severe traumatic brain injury independent of heart rate control. J Surg Res 200(2):586–592

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.