Effect of Enteral Propranolol in Acute Traumatic Brain Injury

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Abstract

Background: Severe traumatic brain injury (TBI) is the predominant cause of death and disability following trauma. Several studies have observed improved survival in TBI patients exposed to β-blockers.

Objectives: To evaluated effect of enteral propranolol on the outcomes of acute traumatic brain injury patients.

Patients and methods: Forty patients with acute TBI were enrolled and divided into two group: group I (20 patients) were received 20 mg of oral Propranolol in 10cc water every 12 h for 10 days through nasogastric ryle, the group II (20 patients) were received 10cc water (placebo group).

Results: Our results showed statistically significant (p-value < 0.001) increased percentage of neurological deficit in group II (20 patients, 100%) when compared with group I (0 patients, 0%), increased GCS after TTT in group I (12.3 ± 1.6) when compared with group II (7.85 ± 1.03). We also found statistically significant (p-value < 0.001) increased Karnofsky scale in group I (92 ± 6.2) when compared with group II (35.5 ± 5.1).

Conclusion: Early enteral propranolol can be used for longer survival and more functional recovery in cases with isolated severe traumatic brain damage.

Keywords: GCS; Propranolol; Traumatic Brain Injury.

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Introduction

Traumatic brain injury (TBI) is typically known as disturbances in brain function or signs of brain pathology brought on by blunt or severe head trauma. According to estimates, there are 50 million TBI instances worldwide each year, meaning that over half the population will experience one. TBI is the most common cause of morbidity and mortality in those under 40 in low- and middle-income nations**(Goda and Chandra, 2020).**

The mechanisms contributing to the secondary events after TBI are adrenergic-mediated cerebral vasospasm and cerebral edema. Cerebral vasospasm occurs in more than one third of TBI and denotes severe injury. The onset varies from 2 to 15 posttraumatic days; with hemodynamically significant vasospasm occurs in 50% of all patients developing vasospasm **(Schroeppel et al., 2014).** Conversely, people with modest levels of adrenergic stress, as shown by a normal heart rate, may have lower mortality after TBI. This hyperadrenergic state may lead to higher mortality following TBI **(Ley et al., 2010)**.

Propranolol may have beneficial effects over other beta blockers in patients with TBI as it has excellent penetration into central nervous system owing to its lipophilic properties. Also, it is found to be associated with improvement in cerebral perfusion and reduction in cerebral hypoxia. In addition, it decreases catabolism and oxygen consumption in hyperadrenergic states **(Ley et al., 2010).**

Due to its long-standing use in patients suffering from subarachnoid haemorrhage and stroke, where a decreased oxygen consumption, carbon dioxide production, and glucose intake have been measured, treatment with propranolol was utilised as the preferred beta-blocker therapy **(Ley et al., 2012).** Additionally, compared to certain other beta-blockers, propranolol's hydrophilic nature makes it easier for it to pass the blood-brain barrier. It has been hypothesised that the first week following a traumatic injury is when the hyperadrenergic state is most evident **(Murry et al., 2016).**

The fourth edition of the BTF's recommendations do not support the routine administration of beta-blockers as part of the recommended standard treatment plan for severe TBI. Numerous observational studies and the Lund concept guidelines, published by the Swedish Lund University Hospital, have shown the benefit of early beta-blockade on outcome**(Goda and Chandra, 2020).** The aim of our study was to determine the effect of enteral propranolol on the outcomes of acute traumatic brain injury patients.

Patients and methods

Forty TBI patients are divided into two group: group I (20 patients) were received 20 mg of oral Propranolol in 10cc water every 12 h for 10 days through nasogastric ryle, the group II(20 patients) were received 10cc water (placebo group) through nasogastric ryle.

The inclusion criteria included: Patients with ages ranging from 16 to 60 years who were proved as having severe acute TBI and requiring critical care admission.

Exclusion criteria Patients with pre-injury beta-blocker treatment, persistent shock (systemic blood pressure 100 mmHg, base deficit > 4, or oliguria) at 24 hours after arrival, bradycardic patients (pulse 60 beats per minute), and patients with previous cerebral dysfunction were all excluded from the study. Individuals who were contraindicated for the treatment with beta-blockers, such as asthmatic patients, were also excluded.

Prior to being enrolled in this study, each patient signed a written informed permission form, and the trial was given the go-ahead by the institutional ethical committee of the Faculty of Medicine, Qena. Ethical approval code : SVU-MED-AIP029-1-21-2-136

All patients underwent the following:

All patients were subjected to the following:

I. History and Clinical Examination: Complete history taking, Full Clinical Examination, Vital data (HR, RR, MABP, and temperature), and random blood sugar every 6 h, Daily Follow‑up GCS.

II. Imaging study: - Study patients were submitted to brain computed tomography.

III. Drug administration: - TBI patients were randomize to either: group I (20 patients) will receive 20 mg of oral Propranolol every 12 h for 10 days, the group II (20 patients) no Propranolol,24 h after admission if hemodynamically stable (defined as systolic blood pressure over 100 mmHg), not requiring any vasopressor support. This dose was repeated every 12 h up to 10 days following injury.

IV. Assessment of Outcome: Functional recovery: Conscious level, and neurological deficit, by Glasgow coma scale (GCS), and Karnofsky scale **(Crooks et al., 1991)**.Hospital mortality. Cardiopulmonary side effects of beta-blockers include arrhythmia, clinically significant hypotension (systolic blood pressure 90 mm Hg, necessitating fluid resuscitation, discontinuation of the study drug, and/or an inotropic agent), clinically significant bradycardia (bradycardia necessitating a temporary pacemaker, a sympathomimetic agent, atropine, or discontinuation of the study drug).

Statistical analysis

The Statistical Software for Social Sciences (SPSS) version 26.0 was used to analyse the data. While qualitative data were presented as frequency and percentage number (percent), quantitative data were presented as mean standard deviation (M ± SD), and they were compared using the Student's t-test. Non-parametric data comparison was done using the chi-square test. It denotes significant results at $P < 0.05$.

Results

Baseline characteristics:

Our results shows that the mean age of all studied patients was 31.9 ± 13.9 years, there were 26 males (65%) and 14 females (35%) in the studied patients. The mean BMI of all studied patients was 27.6 ± 2.09 kg/m^2. The rest of demographic data were detailed in **Table (1).**

Table (2) shows statistically significant increased percentage of post-concussion in group I (6 patients, 30%) when compared with group II (0 patients, 0%), and increased percentage of epidural hematoma in group II (13 patients, 65%) when compared with group I (6 patients, 30%), but there is no statistically significant difference (p-value > 0.05) between both groups as regard brain contusion, SAH and depressed fracture.

Table (3) shows statistically significant **(p-value = 0.027)** increased percentage of operative procedure in group II (13 patients, 65%) when compared with group I (6 patients, 30%).

Our results showed statistically significant (p-value < 0.001) increased percentage of neurological deficit in group II (20 patients, 100%) when compared with group I (0 patients, 0%),increased GCS after TTT in group I (12.3 ± 1.6) when compared with group II (7.85 ± 1.03) as in **Table (4).**

We also found statistically significant (p-value < 0.001) increased Karnofsky scale in group I (92 ± 6.2) when compared with group II (35.5 ± 5.1) **Table (4).**

Table (5) shows Statistically significant (p-value = 0.028) increased MAP in group I (64.6 ± 4.3) when compared with group II (59.8 ± 7.3), Highly statistical significant (p-value < 0.001) decreased SBP in group I (122 ± 5.9) when compared with group II (139.5 ± 19.3), Statistically significant (p-value = 0.004) decreased DBP in group I (68.3 ± 8) when compared with group II (78 ± 12.8), Statistically significant (p-value = 0.002) decreased HR in group I (63.9 ± 8.4) when compared with group II (74 ± 10.5) and no statistical significant difference (p-value > 0.05) between studiedgroups as regard bronchospasm andcongestive heart failure.

Table 1. Description of demographic data in all studied patients

Variables		Group I (N = 20)	Group II (N = 20)	Stat. test	P-value
Age (years)	Mean ±SD	28.2 11.3	35.7 15.3	MW = 132.5	0.068 NS
Sex	Male Female	1470% 6 30%	12 60% 8 40%	$X^2 = 0.44$	0.507 NS
BMI (kg/m²)	Mean ±SD	27.7 2.03	27.6 2.2	MW = 192	0.841 NS
Smoking	Non Smoker	1050% 1050%	1155% 9 45%	$X^2 = 0.1$	0.752 NS
Residence	Rural Urban	13 65% 7 35%	11 55% 9 45%	$X^2 = 0.41$	0.519 NS
Soscioeconomic status	Low Moderate	16 80% 4 20%	15 75% 5 25%	$X^2 = 0.14$	0.750 NS

This table shows no statistical significant difference (p-value = 0.968) between studied groups as regard demographic data (age, sex, BMI, smoking, residence and SES).

Table 2. Comparisons between studied groups as regard diagnosis

Variables	Group I (N = 20)		Group II (N = 20)		P-value
Brain contusion	7	35%	10	50%	0.337 NS
Post-concussion	6	30%	0	0%	0.008 S
SAH	1	5%	4	20%	0.151 NS
Epidural hematoma	6	30%	13	65%	0.027 S
Depressed fracture	6	30%	4	20%	1.465

This table shows: Statistically significant (p-value = 0.008) increased percentage of post-concussion in group I (6 patients, 30%) when compared with group II (0 patients, 0%). Statistically significant (p-value = 0.027) increased percentage of epidural hematoma in group II (13 patients, 65%) when

compared with group I (6 patients, 30%).No statistical significant difference (p-value > 0.05) between studied groups as regard brain contusion, SAH and depressed fracture.

Table 3.Comparison of operative procedure in studied groups

Variables		Group I (N = 20)		Group II (N = 20)		Stat. test	P-value
Operative procedure	No	14	70%	7	35%	$X^2 = 4.9$	0.027 S
	Yes	6	30%	13	65%		

This table shows statistically significant (p-value = 0.027) increased percentage of operative procedure in group II (13 patients, 65%) when compared with group I (6 patients, 30%).

Table 4. Comparison of primary outcome in studied groups

Variables			Group I (N = 20)		Group II (N = 20)		Stat. test	P-value
Functional recovery	**Neurological deficit**	**No**	20	100%	0	0%	**$X^2 = 40$**	**< 0.001 HS**
		Yes	0	0%	20	100%		
	GCS at admission	**Mean**	7.3		7.05		MW = 187	0.738 NS
		±SD	0.7		1.05			
	GCS after take TTT	**Mean**	12.3		7.85		**MW = 4**	**< 0.001 HS**
		±SD	1.6		1.03			
	karnofsky scale	**Mean**	92		35.5		**MW = 0.0**	**< 0.001 HS**
		±SD	6.2		5.1			
ICU mortality rate		**No**	18	80%	15	75%	$X^2 = 1.55$	0.211 NS
		Yes	2	20%	5	25%		

This table shows: Highly statistical significant (p-value < 0.001) increased neurological deficit in group II (20 patients, 100%) when compared with group I (0 patients, 0%).Highly statistical significant (p-value < 0.001) increased GCS after TTT in group I (14.1 ± 0.72) when compared with group II (7.05 ± 1.05). Highly statistical significant (p-value < 0.001) increased karnofsky scale in group I (92 ± 6.2) when compared with group II (35.5 ± 5.1).No statistical significant difference (p-value = 0.738) between studied groups as regard GCS at admission. It was 7.3 ± 0.7 in group I and 7.05 ± 1.5 in group II.No statistical significant difference (p-value = 0.211) between studied groups as regard ICU mortality rate. It was (2 patients, 20%) in group I and (5 patients, 25%) in group II.

Table 5. Comparison of Secondary outcome in studied groups.

Variables		Group I(N = 20)		Group II (N = 20)		P-value
MAP	Mean	64.6		59.8		0.028 S
	±SD	4.3		7.3		
SBP	Mean	122.0		139.5		< 0.001 HS
	±SD	5.9		19.3		
DBP	Mean	68.3		78.0		0.004 S
	±SD	8.0		12.8		
HR	Mean	63.9		74.0		0.002 S
	±SD	8.4		10.5		
Bronchospasm	No	20	100%	20	100%	------
	Yes	0	0%	0	0%	
Congestive heart failure	No	20	100%	20	100%	------
	Yes	0	0%	0	0%	

This table shows: Statistically significant (p-value = 0.028) increased MAP in group I (64.6 ± 4.3) when compared with group II (59.8 ± 7.3).Highly statistical significant (p-value < 0.001) decreased SBP in group I (122 ± 5.9) when compared with group II (139.5 ± 19.3).Statistically significant (p-value = 0.004) decreased DBP in group I (68.3 ± 8) when compared with group II (78 ± 12.8).Statistically significant (p-value = 0.002) decreased HR in group I (63.9 ± 8.4) when compared with group II (74 ± 10.5).No statistical significant difference (p-value > 0.05) between studied groups as regard bronchospasm and congestive heart failure.

Discussion

Our results showed statistically significant (p-value < 0.001) increasedpercentage of neurological deficit in group II (20 patients, 100%) when compared with group I (0 patients, 0%),increased GCS after TTT in group I (12.3 ± 1.6) when compared with group II (7.85 ± 1.03). We also found statistical significant (p-value <0.001) increased Karnofsky scale in group I (92 ± 6.2) when compared with group II (35.5 ± 5.1).

According to the current study, 356 participants participated in a randomised controlled trial (RCT) that was published in 2020. In patients with isolated head injuries, the authors found that early propranolol administration enhanced survival and functional results at 6 months. This action of beta-blockers is based on the idea that an adrenal storm, also known as paroxysmal sympathetic hyperactivity, caused by a primary brain injury might exacerbate secondary brain damage from cerebral vasoconstriction and ischemia **(Khalili et al., 2020).**

Ahl et al. assessed 362 patients who had suffered a severe TBI. Of them, 76 (21.0%) patients received -blockers while being admitted to the hospital. After matching based on propensity, 76 matched

couples (n = 152) were examined. The patients were 77.0 percent male and had an average age of 58±16 years. They stated that the secondary outcome parameters were better in BB than non-BB group with significant statistical difference only in hospital LOS. These parameters were ICU LOS (8.5±11.7 vs. 10.8±9.1); hospital LOS (18±24.9 vs. 26.8±21.7); mortality rate (11.8% vs. 7.9%); and unfavorable GOS at discharge (88.2% vs. 89.5%) respectively (**Ahl et al., 2017**).

Similarly, **Attia et al.** conducted a recent study in Mansoura University Hospital that included 400 patients who were presented and admitted to surgical ICU with TBI. Included patients were randomly assigned to one of two groups: the Propranolol group, which included 200 patients who received IV propranolol, and the Control group, which included 200 patients who got only the conventional medical and surgical care. The study's clinical outcome was clearly superior in the propranolol group, as demonstrated by the authors (P<0.05). According to GCS, the neurologic test was improved by 34% as opposed to 27.5 %. According to the ECG in cardiac examination resulted that changes in 12% as opposite to 26.5% in propranolol and control groups. Additionally, the propranolol group performed better on secondary outcome assessment metrics such as ICU length of stay (LOS), ward LOS, mechanical ventilation, ventilation times, survival rate, and poor GOS (P< 0.05) **(Attia et al., 2021).**

874 participants from a retrospective, observational cohort of isolated severe TBI patients. Of these, 33% (n = 287) were given b-blockers while they were hospital patients. Patients who did not take b-blockers during their stay had a higher crude death rate (17% vs. 11%, p = 0.007). After adjusting for important confounders, the patients who weren't given b-blockers had a five fold higher probability of increase of mortality in the hospital **(Mohseni et al., 2015).**

Similar survival advantages were detected by **Alali et al** after conducting a meta-analysis on 9 studies encompassing 2005 unique TBI patients with β-blocker treatment and 6240 unique controls. Exposure to β-blockers after TBI was associated with a reduction of in-hospital mortality **(Alali et al., 2017)**.

Our findings were corroborated by those of **Ley et al.,** who enrolled 1835 patients from 15 trauma centres in two nations, with beta blockers being prescribed to 46% of them. Propranolol predicted decreased mortality compared to all other beta blockers (AOR 0.53, p = 0.038), according to a multivariable model that found that beta blocker use was related with lower mortality (AOR 0.65; p = 0.012) **(Ley et al., 2018).**

In a recently published meta-analysis included 12 studies conducted by **Zagales et al.**, Severe TBI patients who were administered beta-blockers had a significantly reduced incidence of in-hospital mortality compared to the non-betablocker group (14.5% vs 19.2%). The authors concluded that beta-adrenergic blockade in severe TBI patients has the potential to significantly improve mortality rates and may have benefits in the overall management of patients with severe TBI **(Zagales et al., 2022).**

Beta-blocker-treated severe TBI patients showed a considerably lower incidence of in-hospital mortality compared to the non-betablocker group in a newly published meta-analysis that comprised 12 trials from Zagales et al (14.5 percent vs 19.2 percent). The authors ended that beta-adrenergic inhibition in patients with severe TBI has the potential to considerably lower mortality rates and may be advantageous for patients with severe TBI generally **(Zagales et al., 2022).**

Conclusion

Early enteral propranolol administration improved and enhanced functional outcome in patients with isolated traumatic brain injury.

Conflict of interest: None

References

- **Ahl R, Thelin E, Sjölin G (2017):** β-Blocker after severe traumatic brain injury is associated with better long-term functional outcome: a matched case control study. European Journal of Trauma and Emergency Surgery, 43(6), 783-789.
- **Alali AS, Mukherjee K, McCredie VA (2017):** Beta-blockers and traumatic brain injury: a systematic review, meta-analysis, and Eastern Association for the Surgery of Trauma Guidelines. Ann Surg 266(6):952–961
- **Attia SA, Nabeeh MM, Ahmed ME, Mohammed MAA (2021):**Role of Administration of Beta Receptor Blockers in the Management of Traumatic Brain Injury. The Egyptian Journal of Hospital Medicine. 83 (3); 455-460.
- **Crooks, V, Waller S (1991):** The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: M139-M144
- **Goda R, Chandra PS (2020):** Advances in traumatic brain injury research in 2020: A review article. Apollo Med.18:172-8.
- **Khalili H, Ahl R, Paydar S (2020):** Beta-blocker therapy in severe traumatic brain injury: a prospective randomized controlled trial. World Journal of Surgery, 44(6):1844-1853.
- **Ley E, Berry C, Mirocha J, Salim A (2010):** Mortality is reduced for heart rate 80 to 89 after traumatic brain injury. Journal of Surgical Research, 163(1): 142-145.
- **ley EJ, Clond MA, Bukur M (2012):** Beta-adrenergic receptor inhibition affects cerebral glucose metabolism, motor performance, and inflammatory response after traumatic brain injury. J Trauma. 73(1):33–40
- **Ley EJ, Leonard SD, Barmparas G (2018):** Beta blockers in critically ill patients with traumatic brain injury: Results from a multicenter, prospective, observational American Association for the Surgery of Trauma study. J Trauma Acute Care Surg. 84(2):234-244.
- **Mohseni, S, Talving, P, Thelin, EP, Wallin G, Ljungqvist O, Riddez L ,et al.(2015):** The Effect of β-blockade on Survival After Isolated Severe Traumatic Brain Injury. World Journal of Surgery. 39(8): 2076-2083.
- **Murry J, Hoang D, Barmparas G Harada, MY, Bukur, M, Bloom MB, et al. (2016):** Prospective evaluation of early propranolol after traumatic brain injury. Journal of Surgical Research, 200(1): 221-226.
- **Schroeppel T, Sharpe J, Magnotti L (2014):** Traumatic brain injury and β-blockers: not all drugs are created equal. Journal of Trauma and Acute Care Surgery, 76(2): 504-509.
- **Zagales I, Selvakumar S, Ngatuvai M (2022):** Beta-Blocker Therapy in Patients With Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis.The American Surgeon; 1-10.