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Role of Propranolol and Clonidine in Sympathetic Hyperactivity After Severe Traumatic Brain Injury

Mohamed Mostafa Megahed[1, *], Tamer Nabil Habib[1], Zeyad Moqbel[2], Riyad Abdullah Almogahed[1], Islam El Sayed Mohamed Ahmed[3]

[1]Critical Care Medicine, Critical Care Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

[2]Radiodiagnosis Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

[3]Clinical Pharmacy Specialist, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt

Email address:

dr.muhammed.megahed@gmail.com (M. M. Megahed)

[*]Corresponding author

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Abstract: Sympathetic hyperactivity following severe traumatic brain injury (TBI) has compounding negative consequences on many body organs. Adrenergic blockade using beta blockers and alpha 2 agonists demonstrated positive effects in decreasing sympathetic hyperactivity and increasing survival. This study was conducted on 50 adult patients with severe TBI randomly assigned into two groups. Intervention group received propranolol 40 mg BID and clonidine 150 µg BID for 7 days. Control group didn't receive any beta blockers or alpha 2 agonists. The primary outcome was plasma norepinephrine level on day 8. Intervention group showed 20% reduction in plasma norepinephrine, while control group showed 10% reduction only. Glasgow coma score (GCS) and full outline of unresponsiveness (FOUR) score didn't show any significant differences (p = 0.554). Heart rate was significantly decreased in intervention group (p = 0.002), mean arterial pressure also decreased (p = 0.007), as well as respiratory rate (p = 0.001). Ventilator free days, coma free days, ICU length of stay, and mortality didn't differ significantly between the two groups. Propranolol and clonidine at the specified doses may decrease the sympathetic hyperactivity in patients suffering from severe traumatic brain injury.

Keywords: Critical, Neurology, Trauma, β-Blocker, α-Agonist

1. Introduction

Traumatic brain injury (TBI) could be defined as a non-congenital, non-degenerative damage to the intracranial tissue caused by an external kinetic force, probably leading to everlasting or short term deficiency of cognitive, psychosocial and physical functions, coupled with a decreased or changed level of consciousness. [1] Severe TBI is defined with a Glasgow coma score (GCS) of 8 or less within the first 48 hours following trauma. [2] Young age and males (15-30 years) are at bigger danger of severe TBI and road traffic accidents leads the list of causes in TBI related mortality. [3]

Trauma stands as a main public health crisis, blamable for over 6 million deaths and thrice as many disabled patients all over the globe yearly. TBI is an important factor in this area across all age strata. [4] There is a scientific evidence that even the mildest forms of head injuries can harmfully influence physical, cognitive and socioeconomic functioning. [5, 6] Official figures on economic and social impact of traumatic brain injury is lacking in Egypt, sketchy approximations or projections are provided by some overseas bodies which doesn't reflect the real status in Egypt.

Severe TBI is characterized by a dramatic increase in intracranial pressure (ICP) and heightened sympathetic nervous system (CNS) fluxes marked with spiking elevations in plasma catecholamine (epinephrine and norepinephrine) levels. The plasma levels of norepinephrine (NE) at 48 hours are directly correlated to the GCS in the 7th day. [7] Patients with multiple injuries and persistent coma have outstanding elevated plasma levels of catecholamine. [8]

A significant proportion of those patients show

paroxysmal attacks of sympathetic storms besides the basal hyperactivity, those sympathetic overshooting episodes manifest themselves with tachycardia, tachypnea, hypertension, hyperpyrexia, agitation, and dystonia, [9] there is not a formal nomenclature for those paroxysms, "autonomic storms", "paroxysms of sympathetic hyperactivity (PSH)", are suggested terms. [10, 11] Noteworthy, PSH are directly correlated with longer ICU stay, poorer neurologic outcome and cognitive fatigue. [12]

The pathophysiology of PSH was considered in origin to be epileptogenic, but electroencephalographic studies showed negative results and antiepileptic drugs were futile. [13-16] On the other hand one disconnection theory has been proposed in which brain stem excitatory centers are liberated from higher cortical and subcortical inhibitory control. [17] Another disconnection theory claims that brain stem centers are inhibitory in nature while sympathetic hyperactivity originates from spinal centers. [18] A neuroanatomical approach suggests that an injury to white matter tracts in a diffuse and extensive manner, causing disruption within the central autonomic network. One such disrupted pathway may be the fibers of the right insula via damage to the posterior limb of the ipsilateral internal capsule. [19]

Beta receptors blockade has been suggested as one pharmacological intervention to control sympathetic hyperactivity after severe TBI and has shown absolute mortality advantage, [20] another pharmacological measure is centrally acting sympatholytic drugs such as alpha 2 agonist clonidine, which decreases plasma catecholamine levels and cerebral vasoconstriction without changing cerebral blood flow in patients following severe TBI. [21] Combined adrenergic blockade namely nonselective beta blockade and central alpha 2 agonism has shown to be beneficial in terms of neurocognitive outcome and mortality. [22]

Both clonidine and propranolol are lipophilic in nature, enabling them to cross the blood brain barrier, clonidine reduces sympathetic outflow, decreases peripheral vascular resistance, heart rate, blood pressure, renal vascular resistance and prevents pain signal transmission to brain. Propranolol is a nonselective beta blocker which decreases heart rate and myocardial oxygen demand and blood pressure. Both of them have a wide spectrum of effects on memory, cognition and emotions, [23, 24] they also have safe profiles regarding cerebral perfusion pressure when used in a combination. [25]

2. Methods

After ethical approval for this clinical trial from the local committee of ethics in the faculty of medicine of Alexandria university and the department of critical care, Informed consent was taken from the next of kin. This prospective controlled study was conducted on adult patients admitted to the critical care department with the diagnosis of severe traumatic brain injury between the 1st of September 2016 and 2nd January of 2017. Alexandria Main University Hospital is the only tertiary referral trauma center serving a geographical area covering four governorates (Alexandria, Marsa Matrouh, El-Beheira, Kafr Elsheikh) with an estimated population of 14 million people.

Randomly selected patients were enrolled if they had an age from 18 to 64 years of both sexes (except pregnant females) and severe TBI, GCS of 8 or less within the first 48 hours after admission, with detected injury on Computed Tomography (CT) of the brain. But, we excluded all patients with heart diseases, cardiac dysrhythmia, allergy to study drugs, contraindication to enteral feeding, penetrating brain injuries, preexisting brain dysfunction, impending brain herniation, craniectomy or craniotomy, spinal cord injuries, myocardial injury, severe liver disease and current use of beta blocker and/or alpha 2 agonists. Any patient on intravenous vasopressors at any time of the study was also excluded.

All enrolled patients who completed the study (n = 50) were randomly (simple randomization technique) assigned into two groups 25 each. Intervention group received propranolol 40mg tablet BID and clonidine 150µg tablet BID in orogastric or nasogastric tube plus conventional treatment. Control group received conventional treatment only without any beta-blocker or alpha 2 agonists.

All enrolled patients were assessed within 24 hours of admission, the following was documented at enrollment: Personal data including, demographics, past medical and drug history; Complete clinical examination including GCS, full outline of unresponsiveness (FOUR score), blood pressure (BP) in mmHg, temperature (T) in degree Celsius, pulse in beats per minute, respiratory rate (RR) in cycles per minute. Computed tomography (CT) of the Brain without contrast, Marshall CT classification, and Rotterdam CT score were calculated accordingly by our radiology consultant.

Then, blood samples were drawn for plasma catecholamine measuring, within 1 hour of enrollment and on day 8. The measured catecholamine is norepinephrine in pmol/Liter. All routine laboratory investigations were collected including complete blood count (CBC), serum sodium in milliequivalent per liter (mEq/L), serum potassium (mEq/L), serum creatinine in milligram per deciliter (mg/dl), serum urea (mg/dl), random blood sugar (mg/dl), alanine aminotransferase in unit per liter "U/L", aspartate aminotransferase (U/L), total bilirubin (mg/dl). Also, a standard 12 lead electrocardiogram "ECG" was done for all enrolled patients

The intervention group started study drugs (propranolol and clonidine) within 48 hours of injury after plasma catecholamine sample was drawn. Both drugs were administered for 7 days. Propranolol was held for heart rates below 60 beats per minute. Both study drugs were held for mean arterial pressure below 80 mmHg. Conventional treatment included standard sedative regimens which was midazolam or Propofol. Sedation interruption was done twice daily according to our hospital protocol. Analgesics as opioids were allowed as prescribed by attending senior resident.

For both groups, GCS and FOUR score were measured every 12 hours, CT brain was repeated when needed. Vital signs including MAP, pulse rate, respiratory rate and

temperature were measured every 4 hours.

The targeted primary outcome of this study is plasma norepinephrine level reduction on day 8. Secondary outcomes include twice daily measurement of Glasgow coma score and FOUR score, coma free days, ventilator free days, Intensive care unit length of stay "ICU LOS", and in ICU mortality.

3. Results

During this study period a total of 61 patients were approached as they fulfilled the inclusion criteria, 3 patients' kin withdrew from consent, 8 patients were excluded due to death before drawing the second plasma norepinephrine sample on day 8. A total of 41 men and 9 women were completed the study (n = 50), 21 men and 4 women in the control group, 20 men and 5 women in the intervention group, the youngest patient was 19 years old while the oldest 60 years with a mean age 31 for control group and 28 for intervention group (p = 0.064). Road traffic accidents (RTA) was the chief culprit with 80% of control cases and 52% in intervention cases. Routine laboratory values on admission for both study groups didn't show any significant differences. (Table 1)

Table 1. *Comparison between the two studied groups according to demographic data.*

	Control (n = 25)		Intervention (n = 25)		Test of sig.	p
	No.	%	No.	%		
Sex						
Male	21	84.0	20	80.0	χ^2= 0.136	^{FE}p = 1.000
Female	4	16.0	5	20.0		
Age (years)						
Min. – Max.	20.0 – 60.0		19.0 – 55.0			
Mean ± SD.	33.68 ± 10.36		28.48 ± 8.95		t = 1.899	0.064
Median	31.0		28.0			

χ^2, p: χ^2 and p values for Chi square test for comparing between the two groups
FE: Fisher Exact for Chi square test for comparing between the two groups
t, p: t and p values for Student t-test for comparing between the two groups

The CT brain Marshall classification of the 2 study groups were comparable, in the control group 9 patients classified (II), 16 patients classified (III) and the same in intervention group, by the Rotterdam CT brain score the control group. 7 patients scored (2), 15 scored (3). 3 scored (4); while in the intervention group 7 patients scored (2), 12 scored (3) and 6 scored (4). For both groups the mean Marshall classification (p = 1.000) and mean Rotterdam score (p = 0.537) didn't show any significant differences. (Table 2) Regarding Laboratory data between the 2 studies groups, there were no any significant differences. (Table 3)

Table 2. *Comparison between the two studied groups according to CT brain.*

CT brain	Control (n = 25)		Intervention (n = 25)		Test of sig.	p
	No.	%	No.	%		
Marshall CT classification						
2	9	36.0	9	36.0	χ^2=0.000	^{FE}p = 1.000
3	16	64.0	16	64.0		
Min. – Max.	2.0 – 3.0		2.0 – 3.0			
Mean ± SD.	2.64 ± 0.49		2.64 ± 0.49		t = 0.000	1.000
Median	3.0		3.0			
Rotterdam CT score						
2	7	28.0	7	28.0		
3	15	60.0	12	48.0	χ^2= 1.333	^{MC}p = 0.555
4	3	12.0	6	24.0		
Min. – Max.	2.0 – 4.0		2.0 – 4.0			
Mean ± SD.	2.84 ± 0.62		2.96 ± 0.73		t = 0.622	0.537
Median	3.0		3.0			

χ^2, p: χ^2 and p values for Chi square test for comparing between the two groups
MC: Monte Carlo for Chi square test for comparing between the two groups
FE: Fisher Exact for Chi square test for comparing between the two groups
t, p: t and p values for Student t-test for comparing between the two groups

Table 3. *Laboratory Data for the two studied groups.*

Parameter	Control (n = 25)	Intervention (n = 25)	Test	*P* value*
Hb (g/dl)				
Min. – Max.	8.3 – 15.10	9.0 – 17.50		
Mean ± SD.	11.54 ± 2.21	12.26 ± 2.11	t = 1.184	0.242
Median	11.50	12.0		
WBCs (×10³/µl)				
Min. – Max.	7.0 – 26.0	8.0 – 28.0	t = 0.584	0.562

Parameter	Control (n = 25)	Intervention (n = 25)	Test	*P* value*
Mean ± SD.	15.88 ± 5.55	14.88 ± 6.57		
Median	16.90	12.50		
PLT (×10³/µl)				
Min. – Max.	132.0 – 441.0	180.0 - 538.0		
Mean ± SD.	258.04 ± 100.5	292.44 ± 86.66	t = 1.296	0.201
Median	218.00	292.0		
Urea (mg/dl)				
Min. – Max.	15.0 – 48.0	14.0 – 31.0		
Mean ± SD.	25.64 ± 10.61	21.76 ± 4.20	t = 1.700	0.099
Median	21.0	22.0		
S. Cr (mg/dl)				
Min. – Max.	0.20 – 1.30	0.40 – 1.30		
Mean ± SD.	0.83 ± 0.29	0.83 ± 0.28	t = 0.054	0.957
Median	0.80	0.80		
Na+				
Min. – Max.	123.0 – 154.0	132.0 – 150.0		
Mean ± SD.	140.64 ± 8.83	141.84 ± 5.23	t = 0.585	0.562
Median	141.0	145.0		
K+				
Min. – Max.	3.40 – 5.0	3.30 – 5.30		
Mean ± SD.	4.04 ± 0.45	4.25 ± 0.53	t = 1.539	0.131
Median	3.90	4.10		
RBS				
Min. – Max.	80.0 – 281.0	78.0 – 198.0		
Mean ± SD.	155.92 ± 63.17	136.0 ± 35.44	t = 1.375	0.177
Median	143.0	140.0		
ALT (U/L)				
Min. – Max.	12.0 – 322.0	18.0 – 65.0		
Mean ± SD.	55.24 ± 65.51	33.36 ± 15.62	U = 265.00	0.356
Median	32.0	30.0		
AST (U/L)				
Min. – Max.	13.0 – 431.0	15.0 – 75.0		
Mean ± SD.	56.52 ± 81.83	30.72 ± 15.01	U = 246.00	0.196
Median	28.0	25.0		

t and p values for Student t-test for comparing between the two groups.
U and p values for Mann Whitney test for comparing between the two groups
*: Statistically significant at $p \leq 0.05$
Hb: Hemoglobin, S. Cr: Serum Creatinine, RBS: Random blood sugar level, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

Mean plasma norepinephrine levels on day 1 for control group was 9621.7 pmol/L and for intervention group was 10329 pmol/L ($p = 0.764$), the p value for the mean plasma levels of norepinephrine on day 8 for both groups was 0.554 but the significance resides in the reduction percentage, mean plasma norepinephrine levels decreased by 10.98% in control group and by 20.95% in intervention group. The plasma norepinephrine levels didn't show significant differences when comparing levels on day 1 for both groups and on day 8 for both groups, but the percentage of reduction in intervention group was twice as in control group. (Table 4).

Table 4. *Comparison between the two studied groups according to norepinephrine levels on day 1 and day 8.*

Norepinephrine	Control (n = 25)	Intervention (n = 25)	MW	p
Day 1				
Min. – Max.	1852 – 19478	5436 – 20798		
Mean ± SD.	9621.7 ± 4795.7	10329 ± 4984	U = 297.00	0.764
Median	7834	7950		
Day 8				
Min. – Max.	2878 – 18377	3468 – 17818		
Mean ± SD.	8374 ± 4260	8505 ± 5274	U = 282.0	0.554
Median	7451	5484		
% of change	*↓10.98 ± 18.77*	*↓20.95 ± 22.67*		

MW, p: U and p values for Mann Whitney test for comparing between the two groups

The mean Glasgow coma score (GCS) on day 1 in control group was 5.8 ≈ 6/15 and in intervention group 4.9 ≈ 5/15 ($p = 0.027$), on day 8 mean GCS in control group was 9.0 = 9/15 and in intervention group 9.9 ≈ 10/15 ($p = 0.506$). The intervention group scored slightly higher but the difference is insignificant (Figure 1). The FOUR score showed a similar pattern as in GCS, with mean FOUR score on day 1 for control group was 6.5 ≈ 7/16 and for intervention group 5.4 ≈ 5/16 ($p = 0.084$), on day 8 control group was 9.9 and intervention group 10.3 ($p = 0.722$) (Figure 2) (Table 5).

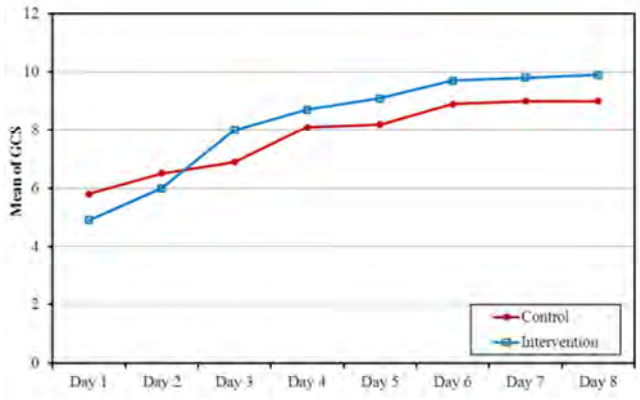

Figure 1. *The mean Glasgow coma score (GCS) of the 2 groups.*

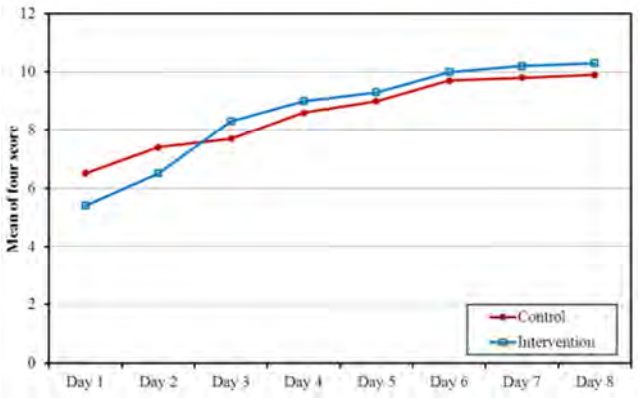

Figure 2. *The mean full outline of unresponsiveness (FOUR) score of the 2 groups.*

Table 5. *Comparison between the two studied groups according to different parameters.*

Overall average	Control (n = 25)	Intervention (n = 25)	Test of sig.	*P**
MAP				
Min. – Max.	86.90 – 110.19	82.10 – 100.67		
Mean ± SD.	97.71 ± 6.53	93.14 ± 4.85	t = 2.807*	0.007*
Median	95.37	92.71		
HR				
Min. – Max.	85.52 – 125.69	76.92 – 121.92		
Mean ± SD.	107.63 ± 10.77	97.08 ± 11.82	t = 3.301*	0.002*
Median	108.50	93.33		
Temperature				
Min. – Max.	36.02 – 37.40	36.0 – 37.77		
Mean ± SD.	36.83 ± 0.26	36.89 ± 0.44	U = 279.500	0.522
Median	36.90	36.81		
RR				
Min. – Max.	17.63 – 35.27	17.10 – 26.33		
Mean ± SD.	24.82 ± 3.24	20.95 ± 2.90	t = 4.441*	<0.001*
Median	24.50	19.85		
GCS				
Min. – Max.	3.50 – 13.31	3.88 – 13.63		
Mean ± SD.	7.81 ± 2.80	8.26 ± 3.06	U = 294.0	0.719
Median	7.38	8.19		
RASS				
Min. – Max.	-5.0 – 1.13	-4.13 – 0.0		
Mean ± SD.	-2.78 ± 2.04	-2.16 ± 1.36	U = 243.0	0.177
Median	-3.19	-2.0		
Four score				
Min. – Max.	2.50 – 14.88	1.44 – 14.50		
Mean ± SD.	8.59 ± 3.40	8.64 ± 3.97	U = 309.500	0.954
Median	8.50	9.19		

t, p: t and p values for Student t-test for comparing between the two groups
U, p: U and p values for Mann Whitney test for comparing between the two groups
*: Statistically significant at $p \leq 0.05$
MAP: Mean arterial pressure, HR: Heart rate, RR: Respiratory rate, GCS: Glasgow coma scale, RASS: Richmond agitation sedation scale, FOUR: Full outline of unresponsiveness score

Mean arterial pressure showed a significant decrease in the intervention group, the MAP on day 1 in control group was 91.7 mmHg and in intervention group 98 mmHg (p = 0.06), on day 8 in control group 97.5 mmHg and in intervention group 91.7 mmHg (p = 0.017), the overall average of mean arterial pressure through the 8 days was 97.7 mmHg in control group and 93.14 mmHg in intervention group (p = 0.007) (Figure 3) Mean heart rate also showed a significant reduction in intervention group, the mean heart rate in control group on day 1 was 112.9 (b/min) and in intervention group 107.6 b/min (p = 0.166), on day 8 in control group mean heart rate was 99.6 b/min and in intervention group 91.3 b/min (p = 0.053), the overall average of mean heart rate all over the 8 days in control group was 107.63 b/min and in intervention group 97.08 b/min (p = 0.002). (Figure 4).

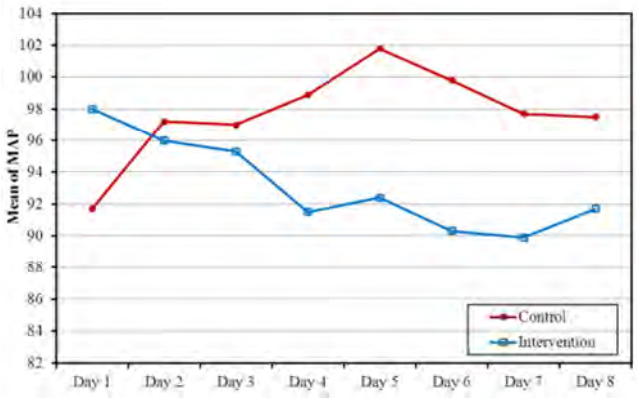

Figure 3. *The mean arterial pressure (MAP) of mmHg of the 2 groups.*

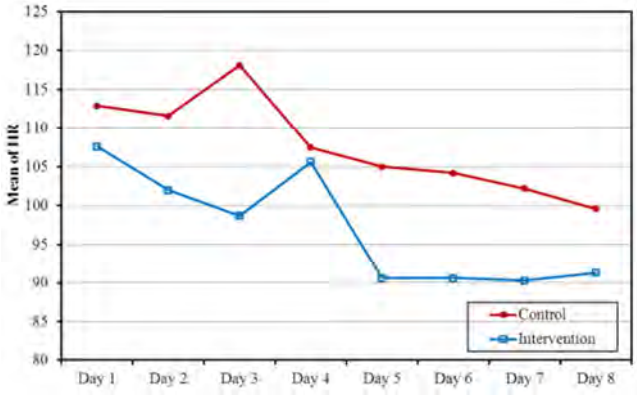

Figure 4. *The mean heart rate (HR) of beats/min of the 2 groups.*

Mean respiratory rate showed a significant reduction in intervention group, on day 1 in control group it was 25.6 cycle/min and in intervention group was 25.3 cycle/min (p = 0.858), on day 8 in control group it was 21.8 cycle/min and in intervention group 19.5 cycle/min (p = 0.042), the overall average of mean respiratory rate all through the 8 days in control group was 24.82 cycle/min and in intervention group 20.95 cycle/min (p = <0.001). (Figure 5) Mean temperature in degree Celsius didn't show any significant difference between the two groups, the overall average mean temperature of control group was 36.83 degree Celsius and on intervention group 36.89 degree Celsius (p = 0.522). (Figure 6)

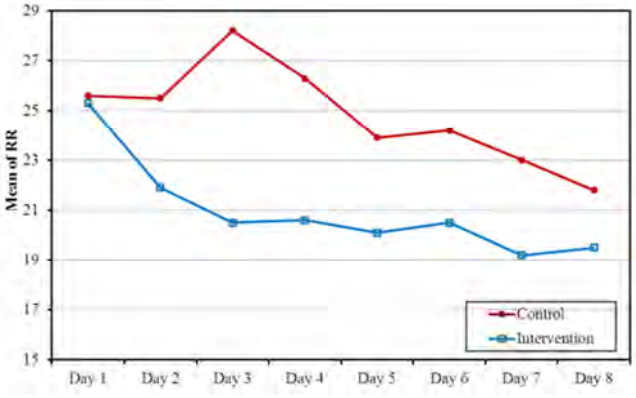

Figure 5. *The mean respiratory rate (RR) of cycle/min of the 2 groups.*

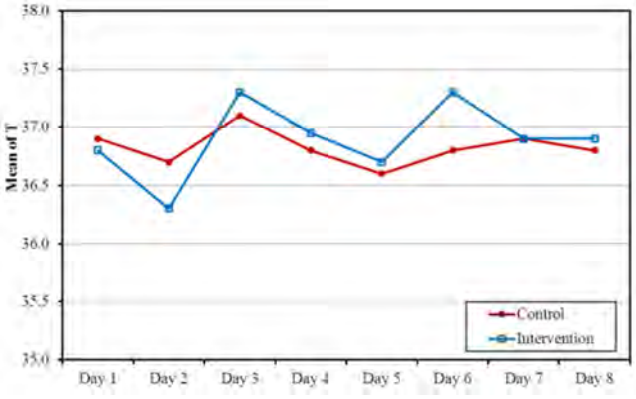

Figure 6. *The mean temperature (T) in degree Celsius of the 2 groups.*

Regarding mortality after 8 days in control group, 8 patients died while 7 patients died in intervention group. the mean values of Coma free days, ventilator free days, ICU length of stay and in ICU mortality didn't show any statistical differences between the two study groups. (Table 6)

Table 6. *Comparison between the two studied groups according to secondary outcomes.*

	Control (n = 25)		Intervention (n = 25)		Test of sig.	P*
	No.	%	No.	%		
Coma free days						
Min. – Max.	0.0 – 27.0		0.0 – 25.0			
Mean ± SD.	10.48 ± 8.46		9.48 ± 8.73		U = 285.50	0.593
Median	12.0		10.0			
Ventilator free days						
Min. – Max.	0.0 – 18.0		0.0 – 20.0			
Mean ± SD.	6.72 ± 5.88		7.60 ± 6.03		U = 287.00	0.615
Median	6.0		8.0			
ICU length of stay						
Min. – Max.	11.0 – 42.0		10.0 – 45.0			
Mean ± SD.	21.44 ± 7.71		22.68 ± 11.0		U = 309.50	0.954
Median	20.0		21.0			
Mortality in hospital						
No	17	68.0	18	72.0	χ^2 = 0.095	0.758
Yes	8	32.0	7	28.0		

χ^2, p: χ^2 and p values for Chi square test for comparing between the two groups
U, p: U and p values for Mann Whitney test for comparing between the two groups
*: Statistically significant at p ≤ 0.05

4. Discussion

This study aimed to evaluate the efficacy of adrenergic blockade through beta blockade and central alpha 2 agonist in reducing sympathetic hyperactivity which follows severe TBI. Propranolol and Clonidine were found to reduce plasma norepinephrine levels by day 8 and reduce heart rates, MAP, and respiratory rates significantly. But, both drugs didn't show any significant differences in terms of coma free days, ventilator free days, ICU LOS and in ICU mortality.

Changes in GCS throughout the 8 days of study didn't differ significantly between the two study groups despite the fact that mean GCS of intervention group was significantly lower at admission, a similar pattern was seen in FOUR score which is more convenient in assessing and following up level of consciousness in intubated patients.

Sympathetic hyperactivity in patients suffering from severe traumatic brain injury is usually multifactorial, pain from associated fractures, wounds, insertions, surgical sites, intubation, bed bath, anxiety in recovering patients, all contribute to the hyper-adrenergic state. In this study the attending ICU physicians were authorized to prescribe analgesia and sedation for enrolled patients, this heterogeneity in pain and anxiety management may have affected the primary outcome.

Ko et al. [26] reported in a recent prospective controlled study that early administration of propranolol in TBI was associated with improved survival but no increase in ventilator free days or decrease in ICU length of stay, their study didn't encompass evaluating propranolol's sympathetic blocking effects. Their study used similar propranolol dosages as this study but was continued as long as the patient stayed in the hospital.

Payen et al. [27] showed that intravenous administration of clonidine may decrease plasma levels of catecholamine significantly without affecting the cerebral blood flow. Payen et al. used a single intravenous dose of clonidine and measured plasma norepinephrine (NE) and epinephrine from arterial and jugular venous samples 3 times within 45 minutes. Their finding demonstrated the short half-life ($t_{1/2}$) of plasma NE making it a relevant and sensitive plasma marker of sympathetic activity, and it also shows the efficacy of clonidine in decreasing sympathetic hyperactivity.

Patel et al. [28] in 2012 published a protocol for a prospective controlled double blinded trial on decreasing sympathetic hyperactivity after severe TBI using propranolol and clonidine. they aimed to enroll 40 patients, and had plasma norepinephrine on day 8 as the primary end point. Patel et al. announced in April 2016 that the trial is halted due to futility at 50 percent accrual, shown by lack of significant increase of ventilator free days in intervention group. In this study propranolol and clonidine were able to decrease plasma norepinephrine, but didn't increase ventilator free days.

5. Conclusion

Propranolol and clonidine at the specified doses may decrease sympathetic hyperactivity in patients suffering from severe traumatic brain injury but without any benefits in terms of in ICU mortality. We recommend further studies on larger scale with more standardization of analgesia and sedation for all patients, or personalization of analgesic and sedative treatment to meet standard endpoints of pain control. We also recommend personalizing propranolol and clonidine dosages for every patient, this would enhance control of sympathetic hyperactivity and diminish side effects, this could be achieved by larger sample sizes and multiple cohorts receiving different dosages.

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