Using propranolol in traumatic brain injury to reduce sympathetic storm phenomenon: A prospective randomized clinical trial

ABSTRACT

Background: Traumatic brain injury (TBI) correlated with increased sympathetic activity on the expense of parasympathetic system due to loss of cortical control after brain injury. Manifestations of sympathetic storm include tachycardia, hypertension, tachypnea, and hyperthermia. The neuroprotective effects via reducing cerebral metabolism and lowering O₂ and glucose consumption are the targets early after trauma. Beta-blockers reduce sympathetic activity.

Objectives: We suppose that using propranolol blunts the sympathetic storming phenomenon as it is a nonselective β inhibitor and has a lipophilic property to steadily penetrate blood–brain barrier.

Patients and Methods: Sixty patients allocated randomly into two groups, each consisting of 30 patients. Group A started propranolol and Group B received placebo within first 24 h. Primary outcome was catecholamine levels on day 7, and the secondary outcomes were physiological measures (heart rate [HR], respiratory rate [RR], mean arterial blood pressure [MABP], temperature, random blood sugar, and follow-up Glasgow coma score [GCS] and sedation score).

Results: Analysis of outcomes demonstrated that Group A tended to have lower catecholamine levels in comparison to Group B in day 7 (norepinephrine 206.87 ± 44.44 vs. 529.33 ± 42.99 pg/ml, P < 0.001), epinephrine level (69.00 ± 8.66 vs. 190.73 ± 16.48 pg/ml, P < 0.001), and dopamine level (32.90 ± 4.57 vs. 78.00 ± 3.48 pg/ml P < 0.001). GCS of the patients in Group A improved and was statistically significant compared to Group B in day 7 (13 vs. 10, P = 0.006), with percent change interquartile range (20.0 vs. 8.33, P = 0.006). Regarding hemodynamic parameters between the two groups MABP, HR, RR, and temperature, there was no statistically significant difference on day 1, while on day 7, there is high statistical significance and significant percent change (P < 0.001).

Conclusion: Early usage of propranolol after TBI controls hemodynamics and blood sugar with decreased catecholamine levels correlated with the improvement of GCS.

Key words: Propranolol; sympathetic storm; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death. Severe TBI is correlated with an exaggerated stress response due to plasma catecholamine levels known as sympathetic storming. It is also autonomic dysfunction syndrome. This phenomenon is associated with brain tumors, severe hydrocephalus, and subarachnoid hemorrhage (SAH). Patients are presented with...
Pathophysiology
Sympathetic storming is due to increase in the activity of sympathetic nervous systems on expense of the parasympathetic nervous system; this autonomic balance dysregulation results from loss of cortical control due to the brain injury. The adrenergic receptors affected (alpha-1, alpha-2, beta-1, and beta-2) results in the specific response of target organs. The sympathetic storming events can be triggered by suctioning, repositioning, or environmental stimuli. To differentiate sympathetic storming from similar conditions, symptoms and signs have to occur in TBI patients a minimum of 1 cycle per day for 3 consecutive days (body temperature of 38.5°C or more, heart rate (HR) at least 120 beats/min, systolic blood pressure >140 mmHg, respiratory rate (RR) >20 breaths/min), in the presence of dystonia, diaphoresis, and agitation and laboratory investigations confirm elevated serum catecholamines. Beta-blockers have a cardioprotective effect via lowering HR, stroke volume, and mean arterial blood pressure (MABP), which limits myocardial O₂ consumptions and guards against myocardial infarction. They also have neuroprotective effects via reducing cerebral blood flow, thus lowering O₂ and glucose consumption, as cerebral metabolism is reduced. Propranolol, a nonselective B receptor antagonist, works on β1 receptors in brain, heart, and kidney and β2 receptors in lungs, liver, skeletal muscles, eye, and arterioles. We suppose that using beta-adrenergic receptor blockers as propranolol blunts the sympathetic storming phenomenon as it is a nonselective β inhibitor and has a lipophilic property which enables it to penetrate blood–brain barrier.

Patients and Methods
TBI patients were admitted to Demerdash Surgical and Traumatic ICU 42 beds.

Patients with isolated blunt TBI from (age 18–60 years) both sex, moderate Glasgow coma score (GCS) between 9 and 12, and not in need of mechanical ventilation included in the study and followed prospectively. Severity of trauma is evaluated by GCS, Rotterdam computed tomography score (CTS) care system with the help of our radiodiagnosis colleagues.

Inclusion in the study required GCS on admission between 9 and 12, Rotterdam CTS from 2 to 4 and normal procalcitonin test to exclude infection.

Exclusion criteria
Patients with preexisting heart disease, myocardial injury, craniotomy, preexisting cerebral dysfunction, spinal cord injury, diabetes mellitus, or severe liver or kidney disease and patients with sepsis were excluded.

After obtaining approval of the Ain Shams University Hospital ethics committee and obtaining informed consent from patients’ first-degree relatives, 60 patients were divided into two groups. Computer-generated randomization numbers were used to allocate patients into two groups using sealed opaque envelopes. Envelopes containing the information of the randomization were sealed and kept in the folder of patients until the end of the study.

Group A (n = 30): received IV propranolol 1 mg every 6 hours from day of admission and for 7 days, doses stopped for HR <60 bpm, MABP <60 mmHg. Group B (n = 30): received IV placebo (normal saline)6 hrs from day of admission and for 7 days.

In both groups, hyperthermia was managed according to our unit protocol included in physical tools, and antipyretic drugs included paracetamol and nonsteroidal anti-inflammatory drugs. Hyperglycemia was managed by insulin infusion. The current guidelines advise keeping blood glucose at 120–180 mg/dl.

Monitoring
• Vital data every 2 h (HR, RR, MABP, and temperature), random blood sugar every 4 h
• Catecholamine levels on admission and on day 7 of the study (sample withdrawn 1 h after enrollment in the study and after treatment on day 7).
Study outcomes

- Primary outcome was catecholamine level on day 7
- Secondary outcomes were vital data of the patient and daily physiological measures (HR, RR, MABP, temperature, random blood sugar and follow-up GCS and Richmond Agitation Sedation Scale on day 7.

Statistical method

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23 (Chicago, USA). The quantitative data were presented as mean, standard deviations, and ranges when their distribution found parametric and as median with interquartile range (IQR) when their distribution found nonparametric while the qualitative data were presented as number and percentages. The comparison between two independent groups with qualitative data was done by using Chi-square test. The comparison between two independent groups with quantitative data and parametric distribution was done using independent t-test while data with nonparametric distribution were compared using Mann–Whitney test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The confidence interval was set to 95% and the margin of error accepted was set to 5%. Hence, the P value was considered statistically significant at P < 0.05.

Results

From October 2016 to August 2017, we enrolled 60 patients with TBI. Patient’s enrollment, allocation, follow-up, and analysis are depicted in Figure 1.

Demographic data and Rotterdam CTs on admission showed no statistically significant difference between groups [Table 1].

As regards hemodynamic parameters between the two groups MABP, HR, and RR, there was no statistically significant difference in day 1 (P = 0.317, 0.690, and 0.182) respectively, while on day 7, there are high statistical significant and significant percent change (P < 0.001). Temperature on day 1 showed no statistically significant difference between the two groups (P = 0.065) while on day 7 decreased significantly (P < 0.001) with statistically significant difference in percent change between the two groups (P < 0.001). As regards, random blood sugar on day 1 was statistically significant between groups and on day 7 was no statistically significant difference between groups with statistically significant percent change [Table 2].

Analysis of outcomes demonstrated that Group A tended to have lower catecholamine levels in comparison to Group B on day 7 (NE 206.87 ± 44.44 vs. 529.33 ± 42.99 pg/ml P < 0.001), epinephrine (E) level (69.00 ± 8.66 vs. 190.73 ± 16.48 pg/ml, P < 0.001) and dopamine (D) level (32.90 ± 4.57 vs. 78.00 ± 3.48 pg/ml P < 0.001). GCS of the patient in Group A improved and there was statistically significant difference compared to group B on day 7 (13 vs. 10, P = 0.006), with percent change IQR (20.0 vs. 8.33, P = 0.006).

Regarding sedation score, there was statistically significant difference on day 7 [Table 3]. When the GCS and catecholamine (NE, E, and D) levels were correlated, there was high statistically significant negative correlation on day 7 in Group A (−0.468, P < 0.009; −0.491, P < 0.006; and −0.567, P < 0.001) [Table 4 and Figure 2].

Table 4 shows that there was highly statistically significant negative correlation between GCS and catecholamine levels (NE, E, and D) in Group A on day 7.

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Manifestations of sympathetic storm include tachycardia, hypertension, tachypnea, hyperpyrexia, and agitation. Our study showed that early use of propranolol significantly reduced all these parameters, with better control of temperature which was resistant to decrease by conventional measures used in ICU. Using propranolol recorded better control of blood sugar and sedation score compared to the other group.

The current study investigated the empiric use of propranolol within 24 h of ICU admission to TBI patients. A randomized controlled trial discussed early adrenergic blockade in

### Table 2: Hemodynamics parameters measured in both groups on day 1 and day 7

| Parameter                  | Variable          | Group A (n=30)          | Group B (n=30)          | Test value | P       |
|----------------------------|-------------------|-------------------------|-------------------------|------------|---------|
| MABP (mmHg)                | Day 1             | Mean±SD: 109.70±6.35    | Mean±SD: 109.47±7.38   | 0.131*     | 0.896   |
|                            | Range: 96-120     | Range: 90-120           |                         |            |         |
|                            | Day 7             | Mean±SD: 80.83±4.04     | Mean±SD: 90.10±5.77    | -7.206*    | <0.001  |
|                            | Range: 75-90      | Range: 80-100           |                         |            |         |
| Percentage change          |                   | Median (IQR): -25.45 (-29.20—-23.81) | Median (IQR): -17.75 (-23.48—-13.04) | -5.477*    | <0.001  |
|                            | Range: -35—-14.29 | Range: -29.17—-4.76    |                         |            |         |
| HR (beats/min)             | Day 1             | Mean±SD: 106.2±7.74     | Mean±SD: 107.00±8.34   | 0.401*     | 0.690   |
|                            | Range: 90-121     | Range: 95-120           |                         |            |         |
|                            | Day 7             | Mean±SD: 69.53±1.43     | Mean±SD: 90.00±6.46    | -16.930*   | <0.001  |
|                            | Range: 66-72      | Range: 82-102           |                         |            |         |
| Percentage change          |                   | Median (IQR): -35.19 (-36.4—-32.7) | Median (IQR): -16.33 (-19.49—-12.63) | 6.656*     | <0.001  |
|                            | Range: -43.8—-22.2 | Range: -21.43—-6.25    |                         |            |         |
| Respiratory rate (breaths/min) | Day 1         | Mean±SD: 27.73±4.91     | Mean±SD: 26.33±2.84    | 1.352*     | 0.182   |
|                            | Range: 20-37      | Range: 20-30            |                         |            |         |
|                            | Day 7             | Mean±SD: 16.03±2.03     | Mean±SD: 18.20±1.45    | -4.766*    | <0.001  |
|                            | Range: 12-20      | Range: 16-21            |                         |            |         |
| Percentage change          |                   | Median (IQR): -41.64 (-52.94—-32) | Median (IQR): -30.77 (-35.71—-25) | -3.063*    | 0.002   |
|                            | Range: -62.5—-9.09 | Range: -46.67—-5       |                         |            |         |
| Temperature (°C)           | Day 1             | Mean±SD: 38.68±0.77     | Mean±SD: 38.36±0.54    | 1.879*     | 0.065   |
|                            | Range: 37.6-40.5  | Range: 37.6-40          |                         |            |         |
|                            | Day 7             | Mean±SD: 37.16±0.24     | Mean±SD: 38.25±0.68    | -8.244*    | <0.001  |
|                            | Range: 36.8-38    | Range: 37.5-40          |                         |            |         |
| Percentage change          |                   | Median (IQR): -3.38 (-5.13—-2.62) | Median (IQR): 0 (-1.32-0.0) | -6.017*    | <0.001  |
|                            | Range: -7.41—-1.32 | Range: -3.8-3.63       |                         |            |         |
| Random blood sugar (mg/dL) | Day 1             | Mean±SD: 222.13±14.78   | Mean±SD: 233.70±21.84  | -2.403*    | 0.019   |
|                            | Range: 199-246    | Range: 205-300          |                         |            |         |
|                            | Day 7             | Mean±SD: 148.73±24.65   | Mean±SD: 161.27±27.54  | 1.858*     | 0.068   |
|                            | Range: 125-160    | Range: 140-200          |                         |            |         |
| Percentage change          |                   | Median (IQR): -40.43 (-41.28—-37.8) | Median (IQR): -19.37 (-21.26—-9.52) | -4.308*    | <0.001  |
|                            | Range: -44.67—-33.5 | Range: -37.78-33.33   |                         |            |         |

SD: Standard deviation; IQR: Interquartile range; *Independent t-test; •: Mann-Whitney test; P<0.05, statistically significant difference. MABP: Mean arterial blood pressure; HR: Heart rate

### Discussion

The current study investigated the empiric use of propranolol within 24 h of ICU admission to TBI patients. A randomized controlled trial discussed early adrenergic blockade in...
patients with nontraumatic SAH showed that administration of propranolol and phentolamine within 48 h was associated with reduced mortality and a trend toward improved neurologic recovery. 

Persistent sympathetic hyperactivity is associated with increased ICU stay, lower cognitive ability, and higher cognitive fatigue. Pharmacologic intervention with propranolol a nonselective β-blockade, in preclinical mouse models, reduces brain edema, improves neurologic outcomes, increases cerebral perfusion, and decreases cerebral hypoxia. Furthermore, propranolol can reduce the maximum intensity of agitated episodes and even reduce aggressive behavior months after TBI. Beta-blockers

| Parameter | Variable | Group A | Group B | Test value | P |
|-----------|----------|---------|---------|------------|---|
| NE (pg/mL) | Day 1 | Mean±SD | 523.50±44.28 | 548.00±43.50 | −2.162* | 0.035 |
| Day 7 | Mean±SD | 268.67±44.44 | 529.33±42.99 | −25.568* | <0.001 |
| Percentage change | Median (IQR) | −20.83 (−51.81−−51.48) | −3.57 (−7.84−2.00) | 6.655* | <0.001 |
| E (pg/mL) | Day 1 | Mean±SD | 205.37±27.18 | 194.53±26.15 | 1.573* | 0.121 |
| Day 7 | Mean±SD | 69.00±8.66 | 190.73±16.48 | −35.821* | <0.001 |
| Percentage change | Median (IQR) | −67.04 (−72.5−58.29) | −0.63 (−7.32−5.26) | −6.659* | <0.001 |
| D (pg/mL) | Day 1 | Mean±SD | 81.63±8.61 | 80.13±7.59 | 0.716* | 0.477 |
| Day 7 | Mean±SD | 32.90±4.57 | 78.00±3.48 | −42.963* | <0.001 |
| Percentage change | Median (IQR) | −60.34 (−66.67−53.42) | −2.44 (−7.87−3.9) | −6.656* | <0.001 |
| GCS | Day 1 | Median (IQR) | 10 (9−11) | 9 (9−10) | 0.482* | 0.632 |
| Day 7 | Median (IQR) | 13 (11−13) | 10 (9−12) | 2.854* | 0.006 |
| Percentage change | Median (IQR) | 20.00 (0.00−44.44) | 8.33 (10.00−11.11) | 2.891* | 0.006 |
| Richmond Agitation Sedation Scale | Day 1 | Median (IQR) | 1 (−2−2) | 1 (−2−1) | −1.696* | 0.090 |
| Day 7 | Median (IQR) | 0 (−1−0) | 0 (0−1) | −2.613* | 0.009 |
| Percentage change | Median (IQR) | −100 (−100−−100) | −66.67 (−100−−50) | −2.825* | 0.005 |

SD: Standard deviation; IQR: Interquartile range; *Independent t-test; •: Mann-Whitney test; P<0.05, statistically significant difference; GCS: Glasgow coma score; NE: Norepinephrine; E: Epinephrine; D: Dopamine
that have neuroprotective effects may be mediated through decreased cerebral blood flow and decreased oxygen and glucose consumption, thus reducing cerebral metabolism.\textsuperscript{[20]} Schroeppel et al.\textsuperscript{[21]} demonstrated that propranolol was superior to other $\beta$-blockers in expressing a protective effect on patients with moderate-to-severe TBI (head Abbreviated Injury Scale score, 3–5).

In a study by Luauté et al.,\textsuperscript{[22]} they analyzed 28 articles concerning 376 patients to set recommendation and guidelines for the management of agitation after TBI, and they recommended that the efficacy of beta-blocker and antiepileptic yields the most compelling evidence (Grade B for beta-blocker and Grade C for antiepileptic).

The American Society of Anesthesiologist 2016\textsuperscript{[13]} discussed the ICU management of central nervous system trauma and recommended that beta-blocker treatment following TBI is beneficial as sympathetic overstimulation may have a nonspecific detrimental effect on organ functions.

In the current study, propranolol group NE, E, and D on day 7 showed significant decrease in serum level as compared to Group B and GCS showed significant improvement.

In a study by Hamill et al.,\textsuperscript{[9]} they concluded that NE may have a prognostic value: among patients with GCS scores 3–4, those who improved to GCS score $>$11 at 1-week postinjury had only slightly elevated NE (544 ± 89 pg./ml); those who died or remained unchanged had markedly elevated NE (2176 ± 531 pg/ml). Another study\textsuperscript{[23]} found that plasma NE and E were significantly elevated compared with catecholamine values in healthy volunteers ($P < 0.001$).

The current study showed that there was highly statistically significant negative correlation between GCS and catecholamine level (NE, E, and D) in Group A on day 7 ($-0.468$, $P < 0.009$; $-0.491$, $P < 0.006$; and $0.567$, $P < 0.001$). With agreement of this, Woolf et al.\textsuperscript{[24]} concluded that the ICU management of central nervous system trauma and recommended that beta-blocker treatment following TBI is beneficial as sympathetic overstimulation may have a nonspecific detrimental effect on organ functions.

In the current study, propranolol group NE, E, and D on day 7 showed significant decrease in serum level as compared to Group B and GCS showed significant improvement.

### Table 4: Correlation between Glasgow coma score on day 7 with norepinephrine, epinephrine and dopamine in Group A

| Catecholamine level (day 7) | GCS (day 7) | $r$ | $P$ |
|----------------------------|-------------|-----|-----|
| NE                         | $-0.468^{**}$ | 0.009 |
| E                          | $-0.491^{**}$ | 0.006 |
| D                          | $-0.567^{**}$ | 0.001 |

Spearman correlation coefficients. **Highly significant. GCS: Glasgow coma score; NE: Norepinephrine; E: Epinephrine; D: Dopamine.
that GCS score was inversely proportional to degree of NE and E increase ($r = -0.41$, $P < 0.0001$ and $r = -0.37$, $P < 0.0002$). Another study by Rizoli et al.\textsuperscript{25} confirmed that higher admission levels of E were associated with a higher risk of unfavorable outcome which was assessed at 6 months by the extended Glasgow outcome scale score (odds ratio [OR], 2.04, 95% confidence interval [CI]: 1.31–3.18, $P = 0.002$) and that higher admission levels of NE were associated with higher risk of unfavorable outcome (OR, 1.59, 95% CI: 1.07–2.35, $P = 0.022$). Other investigators have not found such a correlation.\textsuperscript{26}

**Conclusion**

The ultimate goal is the rapid control of the signs and symptoms of excess activity of the sympathetic nervous system as tachycardia, tachypnea, hypertension, hyperthermia, and control of glucose level to prevent the secondary complications and improve consciousness level. Early usage of propranolol after TBI controls hemodynamics and blood sugar with decreased catecholamine level correlated with improvement of GCS.

**Limitations**

In our study, we did not follow the patient for long-term benefits or complications and we did not record either hospital stay or mortality rate. We only measured the effect of propranolol in the 1\textsuperscript{st} week after trauma.

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**Conflicts of interest**

There are no conflicts of interest.

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