



Original article

Does early beta-blockade in isolated severe traumatic brain injury reduce the risk of post traumatic depression?



Rebecka Ahl^{a,c}, Gabriel Sjolin^b, Shahin Mohseni^{a,b,c,*}

^a Karolinska University Hospital, Division of Trauma and Emergency Surgery, Department of Surgery, 171 76, Stockholm, Sweden

^b Orebro University Hospital, Division of Trauma and Emergency Surgery, Department of Surgery, 701 85, Orebro, Sweden

^c School of Medical Sciences, Orebro University, Fakultetsgatan 1, 702 81, Orebro, Sweden

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ABSTRACT

Introduction: Depressive symptoms occur in approximately half of trauma patients, negatively impacting on functional outcome and quality of life following severe head injury. Pontine noradrenaline has been shown to increase upon trauma and associated β -adrenergic receptor activation appears to consolidate memory formation of traumatic events. Blocking adrenergic activity reduces physiological stress responses during recall of traumatic memories and impairs memory, implying a potential therapeutic role of β -blockers. This study examines the effect of pre-admission β -blockade on post-traumatic depression.

Methods: All adult trauma patients (≥ 18 years) with severe, isolated traumatic brain injury (intracranial Abbreviated Injury Scale score (AIS) ≥ 3 and extracranial AIS < 3) were recruited from the trauma registry of an urban university hospital between 2007 and 2011. Exclusion criteria were in-hospital deaths and prescription of antidepressants up to one year prior to admission. Pre- and post-admission β -blocker and antidepressant therapy data was requested from the national drugs registry. Post-traumatic depression was defined as the prescription of antidepressants within one year of trauma. Patients with and without pre-admission β -blockers were matched 1:1 by age, gender, Glasgow Coma Scale, Injury Severity Score and head AIS. Analysis was carried out using McNemar's and Student's *t*-test for categorical and continuous data, respectively.

Results: A total of 545 patients met the study criteria. Of these, 15% ($n = 80$) were prescribed β -blockers. After propensity matching, 80 matched pairs were analyzed. 33% ($n = 26$) of non β -blocked patients developed post-traumatic depression, compared to only 18% ($n = 14$) in the β -blocked group ($p = 0.04$). There were no significant differences in ICU (mean days: 5.8 (SD 10.5) vs. 5.6 (SD 7.2), $p = 0.85$) or hospital length of stay (mean days: 21 (SD 21) vs. 21 (SD 20), $p = 0.94$) between cohorts.

Conclusion: β -blockade appears to act prophylactically and significantly reduces the risk of post-traumatic depression in patients suffering from isolated severe traumatic brain injuries. Further prospective randomized studies are warranted to validate this finding.

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Introduction

Approximately one quarter of trauma patients develop post-traumatic stress disorder (PTSD) following a severe injury [1]. Depressive symptoms such as low mood and anxiety develop in up to half of all trauma patients and are a well-recognized impediment to functional recovery following traumatic brain

injury (TBI) [2,3]. In the context of trauma research, focus has been mostly directed towards precluding PTSD development, whereas the prevention of depression has been less explored. There is, however, an overlapping relationship between clinical depression and PTSD [4]. The development of PTSD is multifactorial but studies show that anxiety is an important maintenance factor. PTSD heightens the emotional response to recollection of traumatic memories and thereby aids the perpetuation of such memories [5,6]. Recollection of negative memories and the rumination of these are imperative elements in the consolidation of depression [7].

Patients who relive traumatic memories demonstrate an increase in adrenergic activation. Such physiological responses

* Corresponding author at: Department of Surgery, Orebro University Hospital, 701 85, Orebro, Sweden.

E-mail addresses: rebecka.ahl@cantab.net (R. Ahl), gabriel.sjolin@regionorebrolan.se (G. Sjolin), mohsenishahin@yahoo.com (S. Mohseni).

(e.g. heart rate and skin conductance) are significantly heightened in patients with PTSD [8]. Pontine noradrenaline levels increase in rodents at the time of trauma and the activation of β -adrenergic receptors appears to be involved in the formation of emotionally charged memories [9,10]. β -adrenergic receptors have, therefore, been suggested to play a central role in the consolidation of traumatic memories and subsequently in the early stages of trauma-induced depression. It has been demonstrated that the blocking of noradrenergic activity through the administration of β -blockers during the observation of a traumatic event results in blunted stress responses and impaired memory recall of the observed event itself [11–13].

The use of selective serotonin reuptake inhibitors (SSRIs) have demonstrated some efficacy in the treatment of PTSD but evidence suggests that this group of drugs is not able to prevent the diagnosis from initial manifest [14]. This fact is of great significance since depression is challenging to treat once fully established [15]. The lack of an established treatment to prevent the onset of depression thus represents a knowledge gap in the context of trauma care. β -blockers have, however, demonstrated promising effects on the reduction of depressive thoughts in patients following physiological stress caused by cancer and ischemic cardiac disease [16,17]. It is, therefore, reasonable to suggest a potential therapeutic role of β -blockers in the context of trauma care and the prevention of post-traumatic depression. If β -blockade protects against the TBI-induced catecholamine surge [18] and if the risk of anxiety and depression decreases with decreased adrenergic activity and physiological stress, it is possible that early administration of β -blockers could function as a depression prophylaxis. This study examines the effect of early and continuous β -blockade in patients with isolated, severe traumatic brain injury on the development of depression.

Methods

After approval from both the Regional Review Board (Stockholm County) and Institutional Review Board (IRB) the trauma registry of Karolinska University Hospital, an academic urban trauma center, was reviewed to identify all adult patients (≥ 18 years) from January 1, 2007 to December 31, 2011 admitted with isolated, severe TBI. Isolated, severe TBI was defined as a head Abbreviated Injury Scale (AIS) score of at least 3 with chest, abdomen, and extremity AIS scores of 2 or lower. Since the head AIS includes intracranial, skull, neck, and cervical spine injuries, all patient injuries were reviewed, and only patients with a head AIS score of 3 or greater attributed to their intracranial injury (International Classification of Diseases 10th Revision S06.1–S06.9) were included. Patients were excluded if they died within one-year of the traumatic event or were prescribed antidepressants up to one-year prior to the index admission. Additional IRB approval was obtained from The National Board of Health and Welfare for access to the national drugs registry. Unique national personal identity numbers, which are linked to all contacts with all healthcare providers as well as national electronic prescriptions, were used to obtain patients' home medication at the time of admission. Information was retrieved for β -blockers within twelve months of admission and antidepressant therapy (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors) one year either side of the hospital stay. Post-traumatic depression was ascribed to patients prescribed antidepressant therapy within one year of discharge. Patient data obtained from the hospital's trauma registry and patient electronic medical records included age, gender, Glasgow Coma Scale (GCS) score on admission, intracranial injury characteristics, β -blocker administration during admission, AIS score for all body regions, Injury Severity Score (ISS),

neurosurgical interventions, intensive care unit length of stay (ICU LOS), hospital length of stay (HLOS) and mortality.

Statistical analysis

The outcome of interest was depression and the primary variable of interest was pre-admission β -blocker therapy. For analysis purposes, several continuous variables were analyzed as dichotomous variables using clinically relevant cut-off points (GCS ≤ 8 vs. >9 , and ISS ≥ 16 vs. <15). Since the number of confounders was large in comparison with the number of events, cases of pre-admission β -blocker therapy were matched in a 1:1 ratio to control cases that were not receiving such therapy using propensity score matching. Patients naive to β -blockers pre-injury were allocated to the non β -blocked group. A minority of patients in this group was exposed to β -blockers either in a singular dose or a limited number of times during their admission. No patients in this group were prescribed continuous β -blockers either in hospital or at discharge. Where β -blockers were administered the indication was mostly to control for a temporary rise in intracranial pressure. It was deemed unlikely that such short and irregular use of β -blockers would have any long-term effects on the outcome measured. Variables included in the propensity score model were age, gender, ISS, GCS, and head AIS. Propensity scores (predicted probability of receiving β -blockers) were calculated for all patients using binary logistic regression [19]. Each patient receiving β -blockers was matched to a patient who was not subjected to β -blockers within a 0.0135 caliper of propensity without replacement. The caliper was equal to one-quarter of a standard deviation (SD) of the logit of the propensity score [20]. Demographics and clinical characteristics between the matched cohorts were compared using univariate analysis. The differences between the cohorts were tested for significance using McNemar's test for categorical variables and paired Student's *t*-test or Wilcoxon signed rank test for continuous variables when appropriate. Values are reported as percentages for categorical variables and mean (SD) for continuous variables. The risk for depression between the groups was analyzed and the odds ratio (OR) and 95% confidence interval (CI) were derived. The statistical analysis was performed using the Statistical Package for Social Science (SPSS Windows[®]) version 21.0 (SPSS Inc., Chicago, IL).

Results

During the five-year study period, 785 patients were admitted to Karolinska University Hospital with isolated, severe TBI. Of these, 69% ($n = 545$) met the inclusion criteria. A total of 80 patients (15%) were treated with regular β -blockers prior to their traumatic insult.

After propensity matching, 80 matched pairs were available for analysis. Subsequent outlined results refer to these matched pairs. The average age of patients was 68 (SD 13) years and 71% were male. At admission, 55% of patients had a GCS of ≤ 8 with a total severe injury burden of 60% (ISS ≥ 16) and 40% of patients had a highest AIS score of 5 (Table 1). A total of 41% patients underwent a neurosurgical intervention (evacuation surgery or monitoring surgery e.g. Codman intracranial pressure monitor). There was no difference in the rate of evacuation surgery between groups ($p = 0.50$). Twenty-five percent of the total cohort developed post-traumatic depression up to one year following discharge (Table 1).

Table 2 outlines the demographic and clinical characteristics of the β -blocked cases and their respective non β -blocked controls. After matching there were no statistically significant differences in any variables included in the analysis. No discrepancies were noted for head injury severity, GCS, or occurrence of specific intra-cranial injury type (Table 2). Mean ICU length of stay in the β -blocked

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