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Beta-Blocker Therapy in Severe Traumatic Brain Injury: A Prospective Randomized Controlled Trial.

Khalili H, Ahl R, Paydar S, and Sjolin G et al. Beta-Blocker Therapy in Severe Traumatic Brain Injury: A Prospective Randomized Controlled Trial. World J Surg. 2020;44:1844-1853.

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Context

One third of all trauma-related deaths are a result of traumatic brain injury (TBI). Secondary injury is caused by complications of the primary insult and is driven by hypoxia, cerebral edema and ischemia. Research is consequently focused on measures that can reduce secondary injury to improve survival and functional outcome after TBI. It is hypothesized that the adrenergic storm induced by the initial trauma may worsen secondary brain injury though cerebral vasoconstriction and subsequent ischemia. Treatment with beta-adrenergic receptor antagonists offers a protentional benefit by blunting this cascade of sympathetic activation. A systematic review found exposure to beta blocker after TBI was associated with a reduction in-hospital mortality (pooled OR 0.39, 95% CI 0.27-0.56, $p<0.00001$). They conditionally recommended the use of in-hospital beta blockers; however, the quality of evidence was low [1]. The aim of this study was to conduct a randomized controlled trial examining the effect of beta blockers on outcomes in TBI patients.

Methods

Khalili et al performed a single center (in Iran), non-blinded randomized control trial including adult patients with severe TBI (AIS >/= 3). Hemodynamically stable patients (SBP >100, not requiring vasopressor or transfusion) at 24 hrs after injury were randomized to receive either 20 mg propranolol orally every 12 hrs up to 10 days or until discharge or no propranolol. Patients who were on beta blockers pre-trauma and/or those with who developed bradycardia, hypotension or refused to continue treatment were excluded from analysis. Outcomes evaluated include in-hospital mortality and Glasgow Outcome Scale-Extended (GOS-E) score on discharge and at 6-month follow up.

Findings

- 219 patients met inclusion criteria and were randomized
- Of these, 154 patients suffered isolated severe TBI, and 68 (44%) patients received beta blockers
- The isolated TBI data was a sub-analysis of the TBI in the setting of polytrauma
- There were no demographic or clinical differences

- The beta blocker group had significantly lower mortality relative to no beta blocker (4.4% vs.18.6%, p=0.012)
- Propranolol had a significant protective effect on in-hospital mortality (Incidence rate ratio [IRR] 0.32, p=0.04) and functional outcome at 6-month follow up (GOS-E >/= 5, IRR 1.2, p=0.02)

Commentary

Several retrospective and prospective observational studies have demonstrated the safety and benefit of low dose beta blocker administration. These patients appear to have similar TBI severity to this study with AIS head >/=3 [1,2,3]. Propranolol was used here as the preferred beta blocker therapy due its hydrophilic profile that allows it to cross the blood brain barrier more readily and its longstanding use in subarachnoid hemorrhage and stroke patients. Although propranolol is a cheap, centrally acting agent with intravenous and oral formulations, consideration should also be given to determine the comparative effectiveness of other mixed-receptor agents or rapidly metabolized intravenous agents [1]. This was not evaluated in this study; however, a multi-institutional prospective, observational trial found propranolol was superior to other beta blockers (adjusted OR 0.51, p – 0.010) [2].

The strength of this study is the randomized design enrolling 154 patients with well-balanced baseline patient characteristics. Limitations of this study are its use of a single center, non-blinded structure without placebo, and insufficient study population to reach adequate power. The authors note the study was non-blinded and without placebo due to insufficient funding. This may have implications on participants' self-reported outcomes post-hospital because the patients were aware that they were in the treatment arm of the trial and actually received the drug. The individuals who did not receive the drug did not receive anything. This again could affect the participants' expectations and perceptions without a placebo. This study's power analysis calculated that 210 patients would provide 80% power at a significance level of 5% to detect at 65% relative risk reduction; however, only 154 patients had isolated TBI without concomitant injuries. Additionally, there was an unequal number of patients in the beta blocker exposed and beta blocker unexposed groups. Single doses of administered beta-blockade during the hospital stay were not controlled for, so it is possible that a minority of patients in the beta blocker group were given a single dose during the trial period. Another limitation is the lack of reporting of adverse effects, including hypotension and bradycardia.

Implications for practice

Prior to this study, no randomized controlled trial assessing the impact of beta blockers on mortality in the context of TBI had been performed. This randomized trial supports routine administration of beta blocker therapy as part of a standardized neurointensive care protocol. The present study population is derived from a sub-analysis of TBI in the setting of polytrauma. As it is common for severe TBI patients to present with multiple traumatic injuries, it is difficult to comment whether these data can be generalized to the greater polytrauma population. Nonetheless, a key component for patient inclusion is hemodynamic stability, as beta blocker therapy may blunt physiologic compensation in the setting of shock.

Currently, there is a paucity of data on standardized beta blocker dose-equivalents or time-varying adjustment to account for daily confounders of complex ICU care [1]. This study and others document beta blocker administration as binary, which does not allow for evaluation of titration to therapeutic effect or physiologic tolerance. Theoretically, titration to effect or blunting of the sympathetic response does follow an intuitive rationale allowing for personalized dosing. Another recent clinical trial attempted to investigate this concept. The beta blocker arm received propranolol dosage with up to 60 mg/day divided over three daily doses (or an additional 20 mg/dose) as necessary until the heart rate was less than 100. The maximum allowable daily dose for the treatment of hypertension was 640 mg. This clinical trial found all-cause mortality was reduced in the propranolol arm [3].

Once a defined therapeutic benefit has been achieved, tapering vs. discontinuation after a duration of treatment has not been rigorously detailed in the literature. Both pathways may be possible, though drug tapering may have the theoretical advantage of withdrawal avoidance with relapse prevention of the sympathetic phenotype. This issue is not addressed in the present trial or others, thus it is difficult to infer the most appropriate drug management strategy. As such, treatment approaches should be individualized to patients and by institutional guidelines. Future blinded, randomized, controlled trials with larger study populations will aide in verification of these findings and address additional questions.

References

1. Alali A, Mukherjee K, McCredie V, and Golan E et al. Beta-Blockers and Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Ann Surg. 2017;266(6):952.961.
2. Ley E, Leonard S, Barmparas G, and Dhillon N et al. 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. 2018;84(2):234-244.
3. National Library of Medicine (U.S.). (2016, January – 2018, May) Beta Blockade in Traumatic Brain Injury. Identifier: NCT02957331 https://clinicaltrials.gov/ct2/show/results/NCT02957331