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Therapeutic effect of beta-blocker in patients with traumatic brain injury: A systematic review and meta-analysis

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ABSTRACT

Objective: β-Blocker exposure has been shown to reduce mortality in traumatic brain injury (TBI); however, the efficacy of β-blockers remains inconclusive. Therefore, a meta-analysis was conducted in this paper to evaluate the safety and efficacy of β-blocker therapy on patients with TBI.

Methods: The electronic databases were systemically retrieved from construction to February 2017. The odds ratio (OR), mean difference (MD) and 95% confidence intervals (CI) were determined.

Results: A total of 13 observational cohort studies involving 15,734 cases were enrolled. The results indicated that β-blocker therapy had remarkably reduced the in-hospital mortality (OR 0.33; 95% CI 0.27–0.40; $p < 0.001$). However, β-blocker therapy was also associated with increased infection rate (OR 2.01; 95% CI 1.50–2.69; $p < 0.001$), longer length of stay (MD = 7.40; 95% CI = 4.39, 10.41; $p < 0.001$) and ICU stay (MD = 3.52; 95% CI = 1.56, 5.47; $p < 0.001$). In addition, β-blocker therapy also led to longer period of ventilator support (MD = 2.70; 95% CI = 1.81, 3.59; $p < 0.001$).

Conclusion: The meta-analysis demonstrates that β-blockers are effective in lowering mortality in patients with TBI. However, β-blocker therapy has markedly increased the infection rate and requires a longer period of ventilator support, intensive care management as well as length of stay.

1. Introduction

Traumatic brain injury (TBI) has been recognized as a critical public health problem worldwide, which accounts for 1/3 of the total trauma-induced death cases [1,2]. TBI results in numerous death cases. However, those who survive are susceptible to secondary damage that may worsen the initial injury [3]. Therefore, treatment for TBI aims at reducing secondary damage in patients surviving the initial trauma [4,5]. Systemic hyperadrenergic state will emerge during secondary damage accompanied by increases in cardiac and cerebral oxygen demands [6,7]. In addition, the catecholamine level also has increased in this arousal phase [8]. This effect can be attributed to the blockade of the hyperadrenergic state, which is frequently observed after TBI [9]. Increase in catecholamine may cause vasoconstriction and subsequent ischemia [10]; alternatively, it may result in the development of extracranial organ dysfunction [11]. All these changes have worsened the secondary brain injury.

The crucial parts in the treatment protocols include limiting cerebral edema, maintaining adequate brain perfusion, and optimizing oxygen delivery [4]. Animal data have suggested the potential neuroprotective effects of β-blockers, which can be achieved through improving surrogate immunohistochemical markers of cerebral perfusion and decreasing cerebral oxygen demand, as can be observed with positron emission tomography [12,13]. In addition, multiple reports have revealed an association between survival and beta-blocker administration in patients with severe TBI [14-18]. These trials have demonstrated that β-blockers can impede the detrimental sympathetic hyperactivity and increase in catecholamine in severe TBI patients [19]. This can be attributed to the fact that β-blockers can not only reduce the systemic blood pressure, but can also protect β-receptor-rich brain cells by means of remarkably attenuating cerebral oxygen consumption and metabolism. These effects may contributed to alleviating secondary brain injury and ischemia in patients with head injury [20].

β-Blockers have been identified in animal studies, case series and historical control studies as the optimal therapy. However, their efficacy and safety after TBI remain to be further discussed. Therefore, a meta-analysis of the published trials was conducted in this paper, with an aim to evaluate the effect of β-blockers on mortality, safety and other clinical outcomes of patients with severe blunt traumatic brain injury.

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2. Methods

2.1. Retrieval strategy

The following electronic databases of Pubmed, Web of Science and the Cochrane database were retrieved from database foundation till February 2017. The terms of traumatic brain injury, subarachnoid haemorrhage, subdural haematoma, β-blockade, β-blocker, beta-blockade, Beta-Blocker, Beta-Adrenergic Blockade, randomized controlled trial, prospective cohort, observational study and clinical trial were set for retrieval. All pooled analyses were conducted by two investigators independently, and any disagreement was settled by mutual discussion. A flowchart of information identification, screening, eligibility, and the enrolled final studies was constructed according to "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) guidelines [21]. This systematic review was not registered, and no protocol was available. The meta-analysis was checked using terms in the PRISMA list (Table S1).

2.2. Selection criteria

Inclusion criteria were shown as follows: (i) comparative studies (randomized controlled trials (RCTs), cohorts, case-controls and observational studies); (ii) studies comparing the effects of β-blocker and placebo agent treatments in patients with TBI; and (iii) studies reporting the number of outcome events under different interventions. In addition, severe TBI was defined as a Glasgow Coma Score (GCS) of <8 points, or a head Abbreviated Injury Scale (AIS) score of at least 3 points. The inclusion criteria were set aiming to include randomized controlled trials specifically in the analysis. However, other intervention studies and observational studies were also included as a result of few quantities. Exclusion criteria were as below: (i) review articles, editorial comments, meta-analyses, duplicated studies and guidelines, (ii) studies lacking the availability of the numbers of patients who survived or information regarding other outcomes, and (iii) studies with no placebo agent control group.

2.3. Data extraction

Data were extracted by two reviewers independently; otherwise, data would be extracted by a third reviewer in the case of disagreement between the two reviewers. The following information was extracted from the trials: name of first author, country of origin, basic patient characteristics (mean age and gender), operational definitions and outcomes. For dichotomous outcomes, the number of participants experiencing the outcomes and that assessed in each treatment group were recorded.

2.4. Observational outcomes

The primary outcome of this review was in-hospital mortality. The secondary outcomes included incidence of infections and length of stay (LOS) in ICU and hospital. Major infection included wound infection, pneumonia, urinary infection and sepsis.

2.5. Quality assessment

The quality of each trial was assessed by two authors independently, so as to evaluate the risk of bias in the included studies. The quality of the non-randomized studies was evaluated using the Newcastle–Ottawa Scale (NOS), which was discriminated between case-control trials and cohort studies [22]. The NOS was a scale recommended by the Cochrane Non-Randomized Study Method Working Group. NOS could address three aspects, including selection, comparability and exposure when analyzing case-control trials, which included selection, comparability and outcome in cohort studies. A study could be awarded a

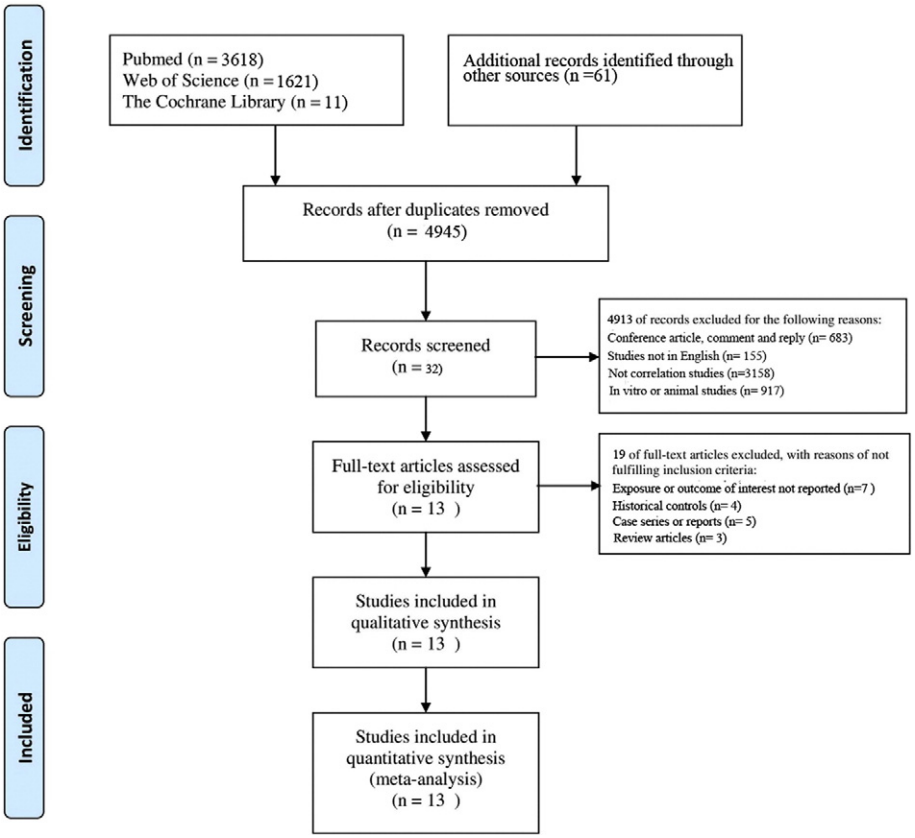

Fig. 1. The flow diagram shows the selection of studies for the meta-analysis.