Mortality and Outcome Comparison Between Brain Tissue Oxygen Combined with Intracranial Pressure/Cerebral Perfusion Pressure–Guided Therapy and Intracranial Pressure/Cerebral Perfusion Pressure–Guided Therapy in Traumatic Brain Injury: A Meta-Analysis

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Key words
- Brain tissue oxygen monitoring
- Cerebral perfusion pressure
- Hypoxia, brain
- Intracranial pressure
- Meta-analysis
- Traumatic brain injury

Abbreviations and Acronyms
CI: Confidence interval
CPP: Cerebral perfusion pressure
GOS: Glasgow Outcome Scale
GOSE: Extended Glasgow Outcome Scale
ICP: Intracranial pressure
PbtO2: Brain tissue oxygen
RCT: Randomized controlled trial
RR: Risk ratio
SMD: Standardized mean difference
TBI: Traumatic brain injury

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BACKGROUND: **The combination of brain tissue oxygen and standard intracranial pressure (ICP)/cerebral perfusion pressure (CPP)–guided therapy is thought to improve traumatic brain injury (TBI) prognosis compared with standard ICP/CPP-guided therapy. However, related results of previous observational studies and recently published cohort studies and randomized controlled trials (RCTs) remain controversial. The objective of this study was to compare the effect of the combined therapy with that of standard ICP/CPP-guided therapy on mortality rate, favorable outcome, ICP/CPP, and length of stay (LOS).**

METHODS: **We systematically searched PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and Web of Science in July 2016 for studies comparing the combined therapy and standard ICP/CPP-guided therapy. Random-effect and fixed-effect models were used for pooled analyses.**

RESULTS: **After screening 362 studies, 8 cohort studies and 1 RCT were included. Primary outcomes were mortality and favorable outcome. The overall mortality risk ratio showed no obvious advantages between the 2 groups (risk ratio [RR], 0.76; 95% confidence interval [CI], 0.54–1.06) and discharge mortality (RR, 1.01; 95% CI, 0.80–1.26) and 3-month mortality (RR, 0.77; 95% CI, 0.53–1.12). Compared with the ICP/CPP group, the combined group was more likely to achieve better outcome during the 6 months after TBI (RR, 1.26; 95% CI, 1.04–1.52) or exactly at 6 months (RR, 1.34; 95% CI, 1.07–1.68), whereas ICP (standardized mean difference [SMD], −0.19; 95% CI, −0.43 to 0.05), CPP (SMD, 0.13; 95% CI, −0.09 to 0.35), and LOS (SMD, 0.13; 95% CI, −0.11 to 0.37) showed no obvious differences.**

CONCLUSIONS: **Compared with standard ICP/CPP-guided therapy, brain tissue oxygen combined with ICP/CPP-guided therapy improved long-term outcomes without any effects on mortality, ICP/CPP, or LOS.**

INTRODUCTION

Traumatic brain injury (TBI) is a major life-threatening condition worldwide; many survivors are left with devastating disabilities, resulting in a heavy burden for both family and society.[1,2] Improving the prognosis of patients with TBI is urgent and difficult because of the complexity of these lesions. The current therapy for TBI mainly focuses on preventing and reversing the aggressive pathologic process known as secondary brain injury. To achieve this purpose, an effective monitoring system to detect preclinical changes must be developed. Intracranial pressure (ICP) monitoring is the current standard of care. It involves the use of an invasive device that detects real-time ICP.[3] Many management strategies for TBI focus mainly on maintenance of ICP and cerebral perfusion pressure (CPP).[3,4] However, whether ICP/CPP-guided therapy plays a pivotal role in TBI management remains controversial.[5] Brain tissue oxygen (PbtO2) monitoring is a new monitoring system that detects PbtO2 tension. This parameter is assumed to be a more sensitive indicator because it changes at an earlier phase of injury than ICP,[6] but the underlying mechanism remains unclear. Thus, PbtO2 monitoring seems to provide some advantages over ICP monitoring for early detection and intervention in TBI. Meanwhile, some studies[7,8] showed that decreased PbtO2 (usually <20 mm Hg) is associated with worse outcome. To fully assess the effect of PbtO2 combined with ICP/CPP-guided therapy for TBI, we examined both cohort studies and randomized controlled trials (RCTs) and performed a meta-analysis comparing the combined therapy with standard ICP/CPP-guided therapy mainly on the basis of mortality rate and favorable outcome.

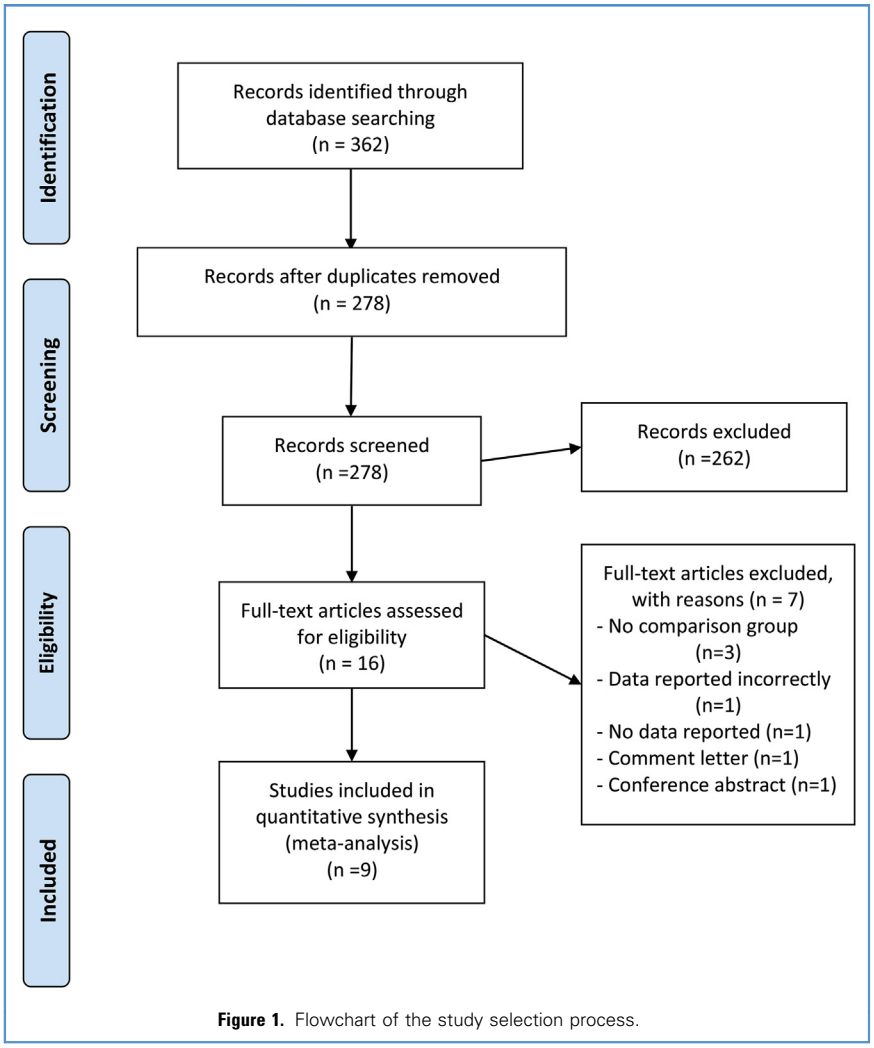

Figure 1. Flowchart of the study selection process.

METHODS

Statement and Search Strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines and was registered at the International prospective register of systematic reviews (registration number CRD42016043708).

Two reviewers separately searched PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov in July 2016. The search strategy focused on the intersection of the key words "traumatic brain injury" and "brain tissue oxygen," with all kinds of variations to include all potentially eligible studies. No language restrictions were applied. The PubMed search strategy details are stated at International prospective register of systematic reviews.

Study Selection, Data Extraction, and Quality Assessment

After the removal of duplicates, 2 independent investigators reviewed the titles and abstract of potentially eligible studies. Studies that satisfied the inclusion criteria were retrieved for full-text assessment. The 2 lists of included studies were then merged into a single list after discussing the inclusion of controversial studies among the group of investigators. The study inclusion criteria were as follows: 1) studies on patients diagnosed with TBI, 2) comparison of PbtO2 combined with ICP/CPP therapy with ICP/CPP therapy, 3) studies reporting mortality rate and/or favorable outcome, 4) studies with accessible full text, and 5) cohort studies or RCTs. The exclusion criteria were as follows: 1) reviews, conference abstracts, case reports, letters, editorials, and animal and in vitro studies; 2) studies on children; 3) studies without sufficient data; and 4) studies reporting data incorrectly (not appropriate for synthesis).

The following data were independently extracted by 2 investigators: first author, year of publication, study design, demographic data (age and sex), number of patients, admission Glasgow Coma Scale score, admission Injury Severity Score, mean daily ICP, mean daily CPP, mortality rate, and favorable outcome. A third reviewer checked the data and made corrections if necessary.

Two independent reviewers evaluated cohort studies using the Newcastle-Ottawa Scale and RCTs by the Cochrane Risk of Bias Tool.

Statistical Analysis

A standard meta-analysis was applied to evaluate the overall effect of PbtO2 combined with ICP/CPP-guided therapy on 5 outcomes: mortality rate (at discharge and 3 months), favorable outcome, daily mean ICP and CPP values, and length of stay. Risk ratio (RR) was used to synthesize dichotomous variables (Mantel-Haenszel method), whereas standardized mean difference (SMD) was used for continuous variables (inverse variance method). A random-effects model was applied when there was huge heterogeneity ($I^2 > 50\%$ or Q test P value <0.1). A fixed-effects model was used for homogeneous studies ($I^2 < 50\%$ or Q test P value >0.1).

Cochran Q test and Higgins I^2 test were used to investigate heterogeneity among studies. When $P < 0.1$ or $I^2 > 50\%$, substantial heterogeneity was detected. The leave-one-out procedure was applied to evaluate sensitivity. A subgroup analysis was adopted as an additional sensitivity test. We applied software Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and StataMP 13 (StataCorp LP, College Station, Texas, USA) for all statistical analysis.

RESULTS

Literature Search, Study Characteristics, and Quality Evaluation

The study selection process is shown in Figure 1. The initial search identified 362