Author's response to reviews

Title: Adherence to Brain Trauma Foundation guidelines for management of traumatic brain injury patients: study protocol for a systematic review and meta-analysis

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Version: 3
Date: 23 July 2015

Author's response to reviews: see over
Adherence to Brain Trauma Foundation guidelines for management of traumatic brain injury patients: study protocol for a systematic review and meta-analysis

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Adherence to Brain Trauma Foundation guidelines for management of traumatic brain injury patients: study protocol for a systematic review and meta-analysis

ABSTRACT

Background
Traumatic brain injury (TBI) is a leading cause of death and disability around the world. Management based on Brain Trauma Foundation (BTF) guidelines is widely accepted and thought to improve outcome. The objectives of this systematic review are to give an overview of adherence to the BTF guidelines, describe factors influencing adherence and study the effect of guideline-based management on outcome.

Methods/design
We will search electronic bibliographic databases: PROSPERO, Medline, EMBASE, SCOPUS, NHS, CINAHL, Cochrane Database, Proquest Dissertations and Theses Global. Two investigators will independently screen all titles, abstracts and articles and select, Randomized Controlled Trial (RCT), cohort studies, case-control studies and case series reporting the adherence rate, factors influencing adherence, and mortality or morbidity. These investigators will also independently extract data using a pre-designed and pilot-tested standardized electronic data extraction form and assess the risk of bias. We will exclude pediatric and military related TBI studies, studies that included fewer than ten patients or addressed adherence to pre-hospital guidelines. Narrative synthesis and if appropriate, quantitative meta-analysis clustered by type of recommendation will be reported.

Discussion:
This study is expected to demonstrate the current level of professionals’ adherence to BTF guidelines in patients with severe traumatic brain injury, it will describe the factors influencing adherence, which may provide valuable input for development of strategies to successfully increase adherence. In addition, if the studies are sufficiently homogenous it will describe the effect of these guidelines on patient outcome. This protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42015017794).

Keywords: Traumatic brain injuries, TBI, Brain injury guidelines, Brain Trauma Foundation guidelines.
Background:
Traumatic brain injury (TBI) is a leading cause of death and disability around the world (1,2). In the US, the prevalence of TBI is estimated to be 2% in the general population (3). The mortality rate was reported to be 18.4 per 100,000 persons with annual average of 53,014 deaths (4). A report from the Canadian Institute for Health Information (CIHI) report indicated that there were 16,811 hospitalizations annually for TBI with 1,368 (8%) related deaths (5). Among residents in a large Canadian health region, the annual incidence of severe TBI was 11.4 per 100,000 persons with a mortality rate of 5.1 per 100,000 persons per year (6).

Clinical practice guidelines are developed to improve quality of care, decrease discrepancy in practice and ensure that evidence is followed (7). Mostly, these guidelines are developed and distributed by well-recognized organizations. A guideline consists of systematically developed recommendations to guide practitioners in choosing the appropriate health care decision for specific clinical circumstances (8). A guideline recommendation is defined as “any statement that promotes or advocates a particular course of action in clinical care” (9). In the treatment of TBI, guidelines are proposed to be an important aspect of patient management.

There are several published guidelines in management of TBI from different countries. These guidelines target different aspects of TBI management including management during pre-hospital, at the emergency department, in-hospital and intensive care unit, indications for surgical management and computed tomography (CAT) scan of the head (10,11,12,13,14).

Internationally, BTF guidelines are widely disseminated. They have been translated into over 15 different languages and applied in Europe, South America, and some parts of China (15). The BTF maintains and revises several TBI Guidelines on an approximate 5-year cycles, including: Guidelines for Prehospital Management of Traumatic Brain Injury, Guidelines for the Management of Severe Traumatic Brain Injury, Guidelines for the Surgical Management of Traumatic Brain Injury, Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents, Guidelines for the Field Management of Combat Related Head Trauma and Early Indicators of Prognosis of Severe Traumatic Brain Injury. These guidelines are developed and maintained through a collaborative agreement with the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), and in collaboration with the AANS/CNS Joint Section on Neurotrauma and Critical Care, European Brain Injury Consortium and other stakeholders in TBI patient outcome (16).

Guidelines for Management of Severe Traumatic Brain Injury address key topics useful for in-hospital medical management of severe TBI in adult patients with a Glasgow Coma Scale (GCS) score of 3–8. These include: blood pressure and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, intracranial pressure monitoring, cerebral
perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics and sedatives, nutrition, antiseizure prophylaxis, hyperventilation through steroids use. In 2007, the third edition of these Guidelines was released following the first and second editions in 1995 and 2000. (17,18,19).

Guidelines for the Surgical Management of Traumatic Brain Injury address acute surgical management of TBI including acute epidural and subdural hematomas, parenchymal mass lesions, depressed skull fractures through posterior fossa lesions with focus on indications, technique and timing of surgery. These Guidelines were published in 2006. (20)

Studies suggest that implementation and strict adherence to BTF guidelines results in improvement in the neurological outcomes and reduction in mortality from severe traumatic brain injury (21,22). However, there is still significant variability and inconsistency in the management of traumatic brain injury patients (23,24). This review will be the first systematic review assessing the adherence with BTF guidelines and its effect on outcome.

Objectives
The first objective of this study is to present a systematic review of adherence by practitioners, mainly neurosurgeons and critical care physicians to the BTF guidelines for the management of severe TBI. The second objective is to explore the factors influencing adherence to the guidelines. Identification of these factors may provide valuable insight into the development of strategies to increase the adherence. Third objective is to study the outcome of guideline-based management in comparison to non-guideline based management to determine the effectiveness of these guidelines. The outcomes considered in this study include: mortality (ICU, in-hospital mortality) and morbidity (Glasgow Outcome Scale GOS, Modified Rankin Scale MRS, ventilation days, ICU stay and hospital stay).

Methods/Design
Protocol and study overview
Methods of this systematic review and meta-analysis have been developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (25) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE guidelines ) (26). We will begin by developing a comprehensive database containing all published literature that addresses adherence to BTF guidelines in the management of severe TBI. This protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42015017794).

Selection criteria
1- Population
The population of interest will include adult (≥18 years old) hospitalized patients with blunt TBI. Whenever outcome measures are available, the patients who were treated based on the BTF guideline will be compared to the patients who were not treated based on the BTF guideline. Additionally, the population of this study will include
the practitioners, mainly the neurosurgeons and critical care physicians, who will be assessed for adherences with guidelines.

2- Outcome
The main outcome will be the adherence rate with BTF guidelines. In addition, we will identify factors influence the adherence, morbidity and mortality of traumatic brain injury by comparing the patients who are managed according to the BTF guideline with patients who are not managed according to the BTF guideline.

3- Study design
RCT, cohort, case-control and case series.

4- Search strategy
The primary search strategy was developed by the primary investigator (YK) and in collaboration with an expert searcher/librarian (SC). We will search the following electronic bibliographic databases: PROSPERO, Medline (OVID), EMBASE (OVID), EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - ACP Journal Club, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Methodology Register, EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database, CINAHL Plus with Full Text, Proquest Dissertations and Theses Full-text, SCOPUS and Google Scholar using both controlled vocabulary (eg: EMTREE and MeSH) and keywords to retrieve concepts including: (Brain Trauma Foundation) or (brain injur* and guideline* and adhere*). Searches will be limited to adult patients in non-military settings. Animal studies will be excluded. No other exclusions will be applied. We will include gray literature as well as reviewing reference lists. We will also try to contact experts in the field.

5- Study selection
Two investigators (YK and IG) will independently screen all titles, abstracts and articles to identify studies addressing the adherence to BTF guidelines for in-hospital management of adult civilian patients of ages 18 years or older with TBI. The assessed guidelines will be a) in-hospital guidelines regarding blood pressure and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, indications for intracranial pressure monitoring, intracranial pressure monitoring technology, intracranial pressure thresholds, cerebral perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics, and sedatives, nutrition, antiseizure prophylaxis, hyperventilation and steroids. b) Guidelines for surgical management for acute Epidural and subdural Hematomas, Parenchymal Lesions, Posterior Fossa Mass Lesions and Depress Cranial Fractures. Articles will be included if they meet the following criteria: 1) original research 2) RCT, cohort, case-control and case series 3) reported adherence rate, factors influencing adherence, point estimate and 95% confidence interval for mortality or morbidity of traumatic brain injury patients treated according to the BTF management guidelines in comparison to patients treated differently. We will exclude: 1) animal studies 2) studies with majority of pediatric patients 3) case reports 4) studies that included fewer than ten patients 5) studies addressed adherence to pre-hospital guidelines (the result from studies on pre-hospital management may not reflect the adherence because failure to achieve target recommendation may be an indicator of
severe injury) 6) studies focused on military/combat-related TBI, because the results would not be generalizable to the source population of civilian patients with TBI. Inclusion disagreement will be discussed and resolved by consensus or arbitration by other researcher (CO and DZ).

**Data extraction**

Two investigators (YK and IG) will independently extract data from eligible studies using a pre-designed and pilot-tested standardized electronic data extraction form. We will extract data on 1) Publication details (year and language of publication, name of the publishing journal and country in which the study was conducted) 2) Design: type of study (RCT, cohort, case-control, case series), study temporality (prospective, retrospective) 3) Study participant details: patient characteristics (age, sex, GCS, Injury severity score) 4) Data for percentage adherence to BTF guidelines, From each article, adherence percentages for each recommendation will be extracted. In case of a pre- and post-intervention design for evaluation of intervention (for example introducing a protocol or teaching program), only the post-intervention percentages will be extracted because our interest is in the current clinical practice. 5) Demographic and injury-related characteristics, which may influence adherence to the BTF guidelines: increase age, elevated blood alcohol level, normal CT scan and planned neurosurgical intervention or other factors reported in the study will be extracted when a statistically significant relationship between these factors and adherence is demonstrated 6) Outcomes including mortality or morbidity if they compared between patients treated according to the BTF guidelines and patients treated differently and 95% confidence interval are reported. Discrepancies will be discussed and resolved by consensus or arbitration by other researchers (CO and DZ).

**Quality assessment**

**Randomized Controlled Trials RCT:**
The quality will be assessed using the Cochrane Handbook ‘Risk of Bias’ assessment tool (27). We will assess the quality of reporting using a checklist, which will be based on the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) statement to assess the reporting of interventional studies.

**Observational studies:**
The quality will be assessed using the Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) (28), which evaluates the observational studies based on three domains: 1) Pre-intervention; evaluation of bias due to confounding and bias in selection of participants into the study. 2) At intervention: evaluation of bias in measurement of interventions. 3) Post-intervention: evaluation of biases due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported results. We will assess the quality of reporting of observational studies using a checklist, which will be based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Two researchers (YK and IG) will address quality assessment of the included studies independently. Differences of opinion will be resolved by a discussion with other researchers (CO and DZ).

**Data synthesis**
Narrative synthesis and, where appropriate, quantitative meta-analysis will be used. Synthesis will be based on clustering the selected studies based on type of recommendation. Adherence to BTF based protocol will be extracted as a separate category if the full description of the protocol and protocol adherence rate was reported. Data synthesis will include description of included studies. The median adherence and interquartile range for each recommendation will be calculated as well as for overall adherence. Additionally, factors influencing adherence will be examined based on type of recommendation.

Calculation of pooled estimates of mortality among TBI patients managed based on BTF guidelines and patients managed differently.
In preliminary search, odds ratio was used as measure of association in several studies and we will also use the odds ratio as the summary measure of association in our study. If only the relative risk is reported in a selected study, we will transform the relative risk into an odds ratio using the method described by Deeks and Altman (29). The cohort studies and RCTs will be pooled separately. We will conduct stratified analyses of pooled estimate of mortality by type of recommendation and outcome (for example; in-hospital mortality, intensive care unit mortality, 30 days mortality or 6 months mortality). We will examine heterogeneity separately in the pooled estimates by study design (RCT, observational) using the Cochran Q and I² statistics [30]. In the presence of heterogeneity, random effects models will be used instead of fixed effects models to account for the expected variability beyond the chance and obtain pooled effect estimates across studies (31). The pooled estimates obtained from these calculations will be then compared to determine if the results are different between experimental and cohort study design. If the adjustment for confounding variables varies between studies, analysis will be stratified into two parts, one for studies adjusting for several confounding variables (e.g. age, GCS, injury severity score, pupillary response and CAT scan head finding), other one for studies adjusting for a few confounding variables.
If an adequate number of studies are chosen for the meta-analysis, we will conduct meta-regression considering the following covariates: year of publication, country of origin, and study period.
Publication bias will also be assessed using funnel plot and the methods described by Begg and Egger (32,33). Meta-analysis will be performed using Review Manager software (RevMan5.3.5, Cochrane Collaboration) and regression analysis will be conducted using Stata Statistical Software version 13.1. (StataCorp LP, College Station, TX, USA).

All data will be extracted by two independent investigators (YK, IG). To assess inter-rater reliability, the percent agreement will be calculated on adherence percentage for number of guidelines recommendations by third investigator (AS).

Discussion:
This systematic review and meta-analysis will be the first systematic review summarizing relevant literature on guidelines for management of severe traumatic brain injury. In this review, we will demonstrate the current level of professionals’ adherence to BTF guidelines in patients with severe traumatic brain injury. In addition, we will describe the factors influencing adherence, which may provide valuable input for development of strategies to successfully increase adherence.
Finally, we will describe the effect of these guidelines on patient outcome if data is sufficiently homogenous. Results of this review are expected to be available near the end of 2015.

The major strength of this systematic review will be the use of several electronic databases and other relevant sources based on established guideline for systematic review. An additional strength of the review will be the use of inter-rater reliability, standard protocol for reporting systematic reviews as well as quality assessment of the included studies. However, there are some limitations in this review. We may not be able to find the non-observational studies due to the nature of the measured effect. Furthermore, this review will be examining adherences with different recommendations at several locations using different clinical determinants. Therefore, a high level of heterogeneity will be expected and may limit our ability to perform meta-analysis.

**Abbreviations**

BTF: Brain Trauma Foundation; TBI: Traumatic brain injury; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CENTRAL: Cochrane Central Register of Controlled Trials; RCT: Randomized controlled trial; AANS: American Association of Neurological Surgeons; CNS: Congress of Neurological Surgeons; GCS: Glasgow Coma Scale; MOOSE: Meta-analysis of observational studies in epidemiology; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; EBM: Evidence Based Medicine; ACP: American College of Physicians; NOS: Newcastle-Ottawa Scale; STROBE: Strengthening the Reporting of Observational studies in Epidemiology; TREND: Transparent Reporting of Evaluations with Nonrandomized Designs.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

YK, DZ formulated the research question, YK, DZ and CO designed the study, YK developed the preliminary search strategy, and drafted the manuscript. SC refined and executed the search strategy and exported the results. YK, IG and AS designed the statistical analysis plan. YK, DZ, CO, AS, IG and SC critically reviewed the manuscript for content. All authors have approved the final version of the manuscript.

**Acknowledgements:**

YK is not funded, IG is financially supported by the Vice Deanship of Research Chair, King Saud University, Riyadh, Kingdom of Saudi Arabia., SC is not funded, AS is not funded. CO is not funded. DZ is not funded for this project specifically but is appointed to the Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta.
15. Brain trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS: Guidelines for the management of severe head
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