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Original article

Hyperglycaemia on Admission-Related Mortality in Patients with Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis

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SUMMARY

Introduction: This present study focuses on the findings of clinical trials that have revealed unsatisfactory results and mortality escalation rates of patients suffering from serious traumatic brain injuries (TBI).
Aim: The main objective of this research was to investigate whether hyperglycaemia is a significant indicator of mortality in patients with the diagnosis of severe TBI.
Methods: The research was performed using meta-analysis. The research material was collected throughout PubMed, Cochrane, NCBI, and Google Scholar from 2010 to 2020.
Results: The research subjects were patients with TBI, proven to have hyperglycaemia on admission (random blood sugar evaluation > 200 mg/dl on arrival at the emergency department), with or without a history of DM (HbA1C evaluation ≥ 6.5%), a Glasgow Coma Scale score ≤ 8, and aged 0 – 100 years. The pooled risk ratio (RR) for mortality in severe TBI with hyperglycaemia on admission was 2.39. The evidence of mortality appeared significantly greater in patients with TBI with hyperglycaemia on admission than in those with normal blood glucose levels (RR = 2.39, p < 0.00001). The pooled RR had wide heterogeneity (I2 = 0.87), so the random-effect model was used.
Conclusion: Hyperglycaemia on admission is often associated with unsatisfactory clinical outcomes and greater mortality.

Keywords: **hyperglycaemia on admission, mortality, severe traumatic brain injury**

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INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of mortality and morbidity globally (1). More than 60,000 deaths and 250,000 hospitalizations due to TBI are reported annually in the USA (2). TBI is divided into three types of head injuries, and patients are classified based on their Glasgow Coma Scale (GCS) scores. The GCS score is a clinically objective standard of the severity of brain injury. GCS scores of 13 – 15 are categorized as "mild injury," those of 9 – 12 as "moderate injury," and of 8 or less as severe brain injury (3). In general, the consequences of this injury are classified as primary and secondary brain injuries. What differentiates both injuries is the complex process after the injury. Primary injury takes place during the initiation phase, resulting in a change of physical structures of the brain, and the process that occurs causing systemic complications afterward is defined as a secondary injury (4, 5).

Hyperglycaemia is one of the secondary complications and is considered to be a potential indicator of injury severity and treatment outcomes in TBI patients. Researchers have linked hyperglycaemia to unsatisfactory clinical outcomes and increased mortality in TBI patients. The pathological mechanisms that may contribute to the detrimental role of hyperglycaemia are hydroelectrolyte disturbances (such as lactic acidosis), vessel dysfunctions, inflammation, blood–brain barrier (BBB) rupture, and hyperpermeability (6).

With recent research highlighting hyperglycaemia's causative role in raising mortality and potentially creating unfavorable clinical outcomes in patients with TBI, we evaluate the potential string of events of hyperglycaemia in patients with severe TBI and further evaluate the risk of mortality in these patients to provide information for accurate prevention and treatment in the future. Furthermore, hyperglycaemia with severe and moderate TBI in children has a significant association with the mortality rate. The pathological mechanism is induced by catecholamine and cortisol release, as well as glucose intolerance (7 - 9). Using a meta-analysis approach, this research sought to determine whether hyperglycaemia at the time of admission became an indicator of the significant mortality experienced by patients with severe TBI.

MATERIALS AND METHODS

Research design

This research followed Preferred Reporting Items for Systematized Investigation and Meta-Analysis (PRISMA) protocols (10). The articles were retrieved using databases and sources such as PubMed,

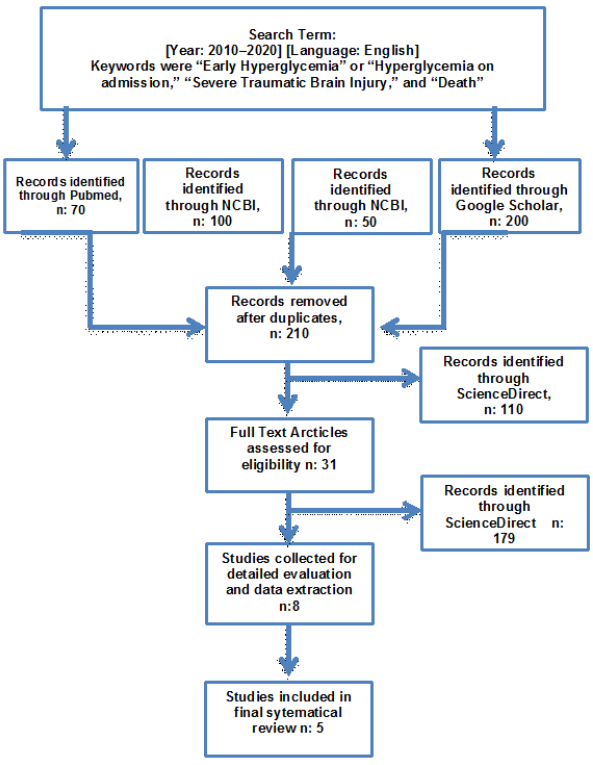

Figure 1. *Research flowchart*

Cochrane, NCBI, and Google Scholar, and they were written in English between 2010 and 2020. During the initial screening, all potentially relevant articles were selected and evaluated. Two indepen-dent investigators carried out this process autono-mously (PIDA and SQT) (Figure 1).

Eligibility criteria

This research had inclusion and exclusion criteria to ensure methodological consistency across the research included in the meta-analysis and to address potential research bias.

The following are the eligibility criteria for inclusion:

a) The existence of an abstract or complete manuscript in Indonesian or English, or one of the aforementioned in a language known to one of the authors.

b) A randomized control trial research or a full-text observational research.

c) Subjects in the research were proved to have hyperglycaemia on admission, based on the criterion of random blood sugar evaluation > 200 mg/dl on arrival at the emergency department.

d) Subjects with or without a history of diabetes mellitus (DM) (HbA1C evaluation ≥ 6.5%).

e) Subjects in the research had a GCS score ≤ 8.

f) Subjects were in the age range 0 – 100 years.

The exclusion criteria were as follows:

a) Articles that were not written in Bahasa or English.

b) Articles written before 2010.

Data extraction

Equal amounts of data were extracted separately by two independent investigators (PIDA and SQT). To reach an agreement, all differences were discussed. The two independent investigators compiled all the research. Simultaneously, both investigators eliminated researches that were duplicated. The full-text versions of the research collected were sought after. The independent investigators also assessed the risk of bias using a detection method based on the Cochrane Handbook for Systematized Investigations of Interventions (version 5.1.0).

Statistical analysis

The data was compiled and analyzed using Investigation Manager Version 5.3 analysis software and the random-effect model (REM). In this research, in which statistical heterogeneity value was required (I2 > 75%), REM was used. P ≤ 0.00001 (double-sided) was considered statistically significant. As a result, we assumed that the research we investigated was conducted under comparable situations with similar subjects. To assess the quality of the research, the Cochrane risk-bias tool was used (10). The sources of bias results were identified, including: random sequence generation (selection bias), participant and personnel blinding (performance bias and detection), allocation concealment (selection bias), incomplete finding data (friction bias), selective reporting (reporting bias), and other sources of bias.

RESULTS

PubMed, Cochrane, NCBI, and Google Scholar searches yielded 320 research from all keywords; we then checked for duplicates, yielding 201 research. After investigationing the abstracts and titles, 31 research were selected for full-text investigations. Eight research were thoroughly investigationed, and data from five of them (11 - 15) were extracted for meta-analysis. The primary outcome in patients with severe TBI was the mortality rate. This finding was assessed for all research for which a risk ratio (RR) could be computed. Table 1 shows the characteristics of each research.

From the five research chosen, the pooled RR for mortality from severe TBI with hyperglycaemia on admission was 2.39. The evidence of mortality appeared to be significantly greater in patients with TBI who had hyperglycaemia at the time of admission than in those who had normal blood glucose levels (RR = 2.39, p < 0.00001) (Figure 2). The pooled RR had wide heterogeneity (I2 = 0.87), so the REM was used.

Selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases were all assessed as biases (Figure 3). More than ten research used the funnel plot to calculate bias. All five research had insufficient random sequence generation (selection bias), allocation concealment (selection bias), and participant and personnel blinding

Table 1. *Characteristics of the included research*

Research, Publication year	Country	Research design	Overall population in research	Other demographic data included
Melo et al. (11)	France	Retrospective cohort	286	Age, PTS, GCS, SAP, SaO2. Multiple trauma. Body temperature, good outcome on hospital discharge, good outcome at 6 months
Smith et al. (12)	USA of America	Retrospective cohort	57	Sex, race, hypo/normothermia, age, exposure to insulin, Injury Severity Score (ISS) or Glasgow Coma Scale (GCS) score
Chong et al. (13)	Singapore	Retrospective cohort	59	Duration of mechanical ventilation, PICU, and hospital length of stay (LOS)
Bosarge et al. (14)	USA of America	Retrospective cohort	626	Age, sex, race, injury (injury mechanism, ISS), and clinical characteristics (lactic acid, hospital stay, ICU days, and days on ventilator support)
Ley et al. (15)	USA of America	Retrospective cohort	51,585	Age, sex, ISS, AIS, DM, and GCS) and outcomes (hospital length of stay)

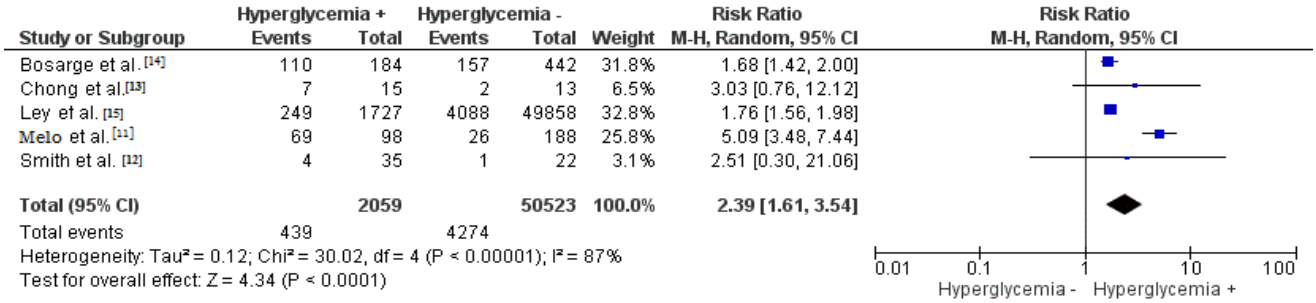

Figure 2. *Analysis of mortality in patients with severe TBI CVA with hyperglycaemia on admission compared to those without hyperglycaemia (forest plot)*

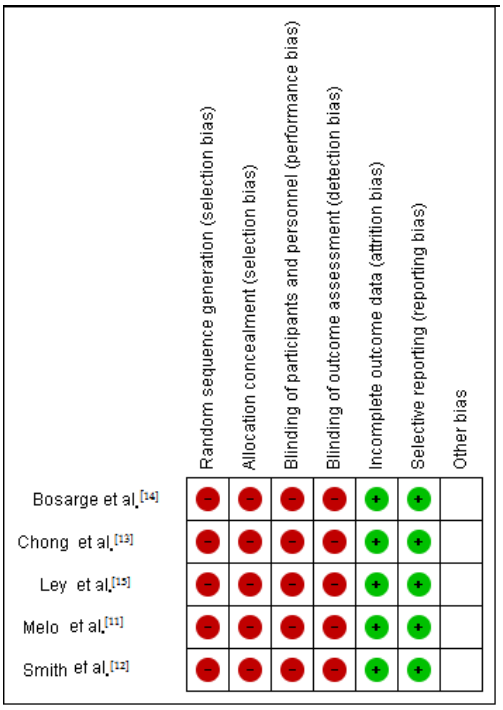

Figure 3. *The risk of bias*

(performance and detection bias). Other potential sources of bias were not adequately addressed. However, in terms of attrition bias and reporting bias, all research were of high quality.

DISCUSSION

In this meta-analysis research, five research were eligible with the inclusion criteria. Hyperglycaemia is considered the primary cause behind unsatisfactory clinical outcomes and greater mortality among patients with TBI. It can be detected from higher blood glucose levels than those with moderate or mild TBI. Therefore, researchers try to determine the causes leading to hyperglycaemia on admission after TBI (6).

Numerous mechanisms can help elaborate on how hyperglycaemia developed following TBI. Following a TBI, stress hormone levels rise, activating the sympathetic autonomic nervous system and hypothalamic-pituitary-adrenal axis can lead to enhanced plasma levels of catecholamine, cortisol, glucagon, and growth hormone. These processes escalate glycogenolysis and hypermetabolism, resulting in an excess of glucose production (6, 14, 16). TBI is also followed by systemic inflammatory response syndrome. Throughout the response, release of cytokines (e.g., tumor necrosis factor-alpha [TNF-α]) may cause insulin resistance and hyperglycaemia (17, 18). Other observed responses that can lead to escalations in blood glucose, including an increase in corticotropin-releasing hormone levels and the release of adrenocorticotropic hormone (19). Children have a mechanism of hyperglycaemia induced by TBI that is not too different from that in adults. This mechanism seems to occur because it is mediated by an escalation in counter-regulatory hormones (epinephrine, norepinephrine, glucagon, cortisol, growth hormone) and pro-inflammatory cytokines (TNF-, interleukin-1, interleukin-6) (20, 21). Moreover, pro-inflammatory cytokines might very well directly inhibit pancreatic beta cell insulin secretion by trying to stimulate adrenergic receptors (22, 23). DM is also a comorbidity that plays a role in hyperglycaemia. In TBI patients with hyperglycaemia, the underlying insulin deficiency has the potential of promoting unsatisfactory clinical outcomes (15, 24).

The underlying pathology of what may be considered harmful in patients with TBI with hyperglycaemia are the complications that follow. Following severe TBI, a disruption in local blood flow (25) can cause ischemia and eventually causes hypoxia on the brain. Hyperglycaemia serves as an inhibitor of the tricarboxylic acid cycle and it causes anaerobic glycolysis which underlies the accumulation of lactic acid mechanism and impaired pH homeostasis (26, 27).

An increase in intracellular $Ca2^{+}$ is possible due to impaired energy metabolism and lactic acidosis, triggering cellular toxicity and accumulation that occurs in free fatty acids and glutamate (28, 29). Astrocytes act to absorb glutamate; excessive glutamate can lead to glutamate excitotoxicity in neurons (30). In addition to lactic acidosis, exceeding amount of lactic acid disrupts Na^{+}-K^{+}-ATPase, resulting in increased extracellular Na^{+} levels and cell edema. The aforementioned processes are what derived intracranial hypertension and cerebral hernia (31).

In the setting of injury, inflammation is a very common process. Hyperglycaemia in patients with severe TBI is connected to escalation of proinflammatory cytokines and proinflammatory transcription factors (32, 33). These cytokines are found in high concentrations in peripheral blood, brain tissue, and cerebrospinal fluid. (34). Following a TBI, inflammation can cause microglia activation and endothelial cell damage, which can lead to brain edema (35). Furthermore, hyperglycaemia can increase blood viscosity, which can lead to brain ischemia and hypoxia, possessing the potential of endothelial cells edema exacerbation and prompt BBB rupture (36 - 38). The aforementioned pathologies are the reasons why hyperglycaemia is said to have a detrimental role in increasing mortality and causing secondary complications in patients with severe TBI.

Bosarge et al. (14) reported that 184 severe TBI patients with hyperglycaemia on admission had a 50% greater risk of death than normoglycemic patients with TBI, with a total number of 110 deaths. Ley et al.'s (15) research of 1,727 patients with hyperglycaemia displayed that 14.4% of severe TBI patients with hyperglycaemia died, compared to 8.2% of normoglycemic patients, with a total number of 249 deaths. According to Chong et al.'s (13) research, there were seven deaths (50%) among 14 patients with TBI with hyperglycaemia on admission. Melo et al. (11) reported 69 death incidents (70%) among 98 patients with severe TBI with hyperglycaemia on admission. Lastly, Smith et al. (12) reported four deaths, with a mortality rate of 8.6% among 35 patients with severe TBI with hyperglycaemia on admission.

From the abovementioned research, we found that the RR is 2.39 (range, 1.61 – 3.54), meaning that there is a substantial increase in mortality among patients suffering from severe TBI with hyperglycaemia on admission. Hyperglycaemia suffered in patients with severe TBI as DM is unlikely to be associated with medical comorbidities, as Ley et al. (15) found an insignificant improvement with increasing age, given that with increasing age, patients with DM are more likely to have associated medical comorbidities. They also proposed that inflammatory cytokines TBI could interfere with glucose availability due to a relative insulin deficiency and that this was strengthened in DM. This can lead to an increasing number of deaths due to the inability of the brain's work to meet cellular energy needs (15, 39).

We discovered hyperglycaemia subsets on admission in patients with severe TBI, including acute stress-induced hyperglycaemia (SIH), diabetic hyperglycaemia (DH), and persistent hyperglycaemia during hospital stays. The researchers divided hyperglycaemia in the context of acute injury into SIH and DH (14). SIH was initially considered to be a protective mechanism, but research showed that it has a positive correlation value with increased morbidity and mortality (40, 42). This triggered a debate about whether hyperglycaemia is beneficial or harmful in patients with acute injuries. One of the mechanisms considered to benefit patients is SIH creating new glucose balance, causing a greater gradient in blood glucose difference, and further maximizing cellular glucose uptake in the maldistributed microvascular flow (43). Acute hyperglycaemia is also considered to promote antiapoptotic pathways and angiogenesis, both of which lead to an escalation in cell survival factors (44). Acute hyperglycaemia may protect against ischemic and hypoxic insults by increasing plasticity and cellular resistance (45). Severe stress-induced hyperglycemia can cause fluid changes because of its effect on serum osmolarity. In addition, severe hyperglycemia crosses the renal threshold, causing osmotic diuresis and volume depletion. However, it is not yet known at what level of stress hyperglycaemia becomes detrimental (46 - 48).

Bosarge et al. (14) demonstrated that patients with SIH and severe TBI have a significantly greater risk of death when compared to nondiabetic normoglycemic patients with TBI. Moreover, in DH patients, hyperglycaemia causes complications related to the wound-healing process (49). On the contrary, a research by Hill et al. (50) found that persistent hyperglycaemia in streptozotocin-induced diabetic mice caused a beneficial reduction of brain edema. Bosarge et al. (14) attempted to stratify SIH and DH based on HbA1C measurements, and they found no significance between the mortality rate and DH. It may be associated with patients' cellular adaptation to hyperglycaemia where there are physiological readjustments (51). However, other research mentioned that DM may cause exacerbation and that insulin deficiency may also play causative role behind greater mortality following TBI (50).

The pathological mechanism of TBI-induced hyperglycaemia in kids is not dissimilar to that in adults. Hyperglycaemia can usually be associated with increased mortality that occurs in children with severe and moderate levels of TBI (23). Hyperglycaemia can lead to adverse conditions on the effects of ischemia and hypoxia and produce worse discoveries (52, 53).

With more research being conducted to determine the relationship that occurs between hyperglycaemia and severe TBI, questions are still being raised about current treatment protocols. The optimal glycemic target in glycemic control treatment is still uncertain and varies among patients. There is still no widespread agreement on glycemic control in patients with TBI; thus, further research are needed to define and focus on the underlying pathology of each type of hyperglycaemia, its effects on brain cell metabolism, and how it may affect clinical outcomes, especially the mortality rate in patients with severe TBI. This can facilitate a treatment base that is more critical than the one that can control blood glucose for additional treatment.

It was the first meta-analysis to function as a tool to examine the mortality of severe TBI patients with hyperglycaemia on admission. These findings are important implications for the evaluation and treatment of patients suffering from severe TBI. Hyperglycaemia on admission was found to be more common in patients with severe TBI and is linked to mortality. We recommend that the neurosurgery community considers hyperglycaemia on admission as an important determinant of mortality based on the discoveries of this research.

There were several limitations to this research. First, several potentially confounding factors, such as age, gender, ethnicity, nutritional status, underlying disease, family history, and environmental fac-

tors, are not included in this research. Second, because the research included in our analyses were non-randomized control trials, which means that they may have produced insufficient evidence. Third, false positive findings may have occurred as a finding of the small sample size, even when integrated. As a result, larger sample size number is needed to investigate the association in the future.

CONCLUSION

The findings of this research suggest that on - admission hyperglycaemia may be associated with mortality events occurring in individuals with severe TBI and it implies that on-admission hyperglycaemia is an important indicator of the prognosis of such patients. We believe that treating patients with severe TBI who have hyperglycaemia on admission requires a special strategy to minimize an unsatisfactory prognosis.

Authors' contribution

PIDA and SQT offered the concept of this work, data analysis, and manuscript preparation. PIDA collected data, wrote the manuscript, and is a guarantor. SQT corrected and guided the manuscript. All authors investigationed and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Mortalitet izazvan hiperglikemijom utvrđenom na prijemu kod pacijenata sa traumatskom povredom mozga

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SAŽETAK

Uvod. Ova studija fokusirana je na rezultate kliničkih ispitivanja koja su ukazala na nepovoljne rezultate i povećanu stopu mortaliteta kod bolesnika sa ozbiljnom traumatskom povredom mozga (engl. *TBI*).
Cilj. Studija je imala za cilj da utvrdi da li je hiperglikemija značajan indikator mortaliteta kod pacijenata sa dijagnozom ozbiljne TBI.
Metode. Istraživanje je sprovedeno primenom metaanalize. Materijal istraživanja prikupljen je u bazama *PubMed*, *Cochrane*, *NCBI* i *Google Scholar* u periodu od 2010. do 2020. godine.
Rezultati. Učesnici istraživanja bili su bolesnici sa TBI, sa potvrđenom hipeglikemijom na prijemu (nasumična provera šećera u krvi > 200 mg/dl po prijemu na odeljenje urgentne medicine), sa istorijom dijabetesa melitusa ili bez nje (procena HbA1C ≥ 6,5%), skorom Glasgovske skale kome ≤ 8 i godinama starosti 0 – 100 godina. Združeni relativni rizik od mortaliteta kod traumatske povrede mozga sa hiperglikemijom na prijemu iznosio je 2,39. Dokazi o mortalitetu bili su značajno veći kod bolesnika sa TBI sa hiperglikemijom na prijemu nego kod bolesnika sa normalnim nivoima šećera u krvi (RR = 2,39, p < 0,00001). Združeni relativni rizik bio je značajno heterogen (I2 = 0,87), tako da je primenjen model nasumičnog efekta.
Zaključak. Hiperglikemija na prijemu esto se čdovodi u vezu sa nepovoljnim kliničkim ishodima i većom stopom mortaliteta.

Ključne reči: **hiperglikemija na prijemu, mortalitet, ozbiljna traumatska povreda mozga**