ORIGINAL PAPER

Acute Kidney Injury Following Mannitol Administration in Traumatic Brain Injury: a Meta-analysis

Athaya Febriantyo Purnomo[1], Khrisna Rangga Permana[2], Besut Daryanto[1]

[1]Department of Urology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

[2]Department of Neurosurgery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[3]Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

Corresponding author : Besut Daryanto, MD, Universitas Brawijaya, E-mail : urobes.fk@ub.ac.id ORCID ID : https://orcid.org/0000-0002-0776-1633

doi: 10.5455/aim.2021.29.270-274

ACTA INFORM MED. 2021 DEC 29(4): 270-274

Received: Oct 25, 2021

Accepted: Nov 30, 2021

ABSTRACT

Background: Acute kidney injury (AKI) is one of the most frequent but anticipated potential complications. The objective of this meta-analysis was to evaluate the AKI incidence following mannitol administration in traumatic brain injury (TBI) patients worldwide. **Objective:** So in this study, authors will discuss the incidence of AKI related to the provision of mannitol in TBI cases so it is expected to provide a better prevention of complications. **Methods:** We were using meta-analysis. Studies were searched throughout Pubmed, Cochrane, JNS in December 2017. Studies that were included ranged from 2009-2018. Keywords were "renal" or "kidney" and "traumatic brain injury". Inclusion criteria were full-text observational study or randomized control trial, subjects in study were newly diagnosed AKI after TBI, GCS < 13, with age range 15-100 years old, survived and followed at least for 30 days after discharge, and given mannitol at least 1g/kg BW/day for at least 3 days. From 648 studies, total 4 studies were eligible for this study. Statistical analysis was done by using Review Manager 5. **Results:** From those 4 studies, it is shown than the pooled risk ratio AKI incidence following mannitol administration in traumatic brain injury (TBI) was 1.57. The pooled risk ratio had wide heterogeneity (I^2 = 0.95 and 1, p< 0.05) so random effect model was used. **Conclusion:** AKI appeared more frequent in patient with TBI with mannitol administration. It still needs more multicentre and long term period researches in the future to get better understanding AKI in TBI following mannitol administration.

Keywords: Mannitol, Acute kidney injury, Traumatic brain injury.

1. BACKGROUND

Traumatic Brain Injury (TBI) is still a complex problem in the field of trauma, especially in developing countries (1). This is attributed to an increase in the number of motor vehicles as the greatest cause of TBI followed by falling and violence (1, 2). The incidence of TBI varies in each region based on the literature, ranging from 67 to 317 per 100,000 individuals (3). TBI mortality depends on the degree, in moderate TBI ranges from 4-7% and for severe TBI more than 50%.[3] In Indonesia alone there have not been many epidemiological studies on national incidence. TBI mortality in Dr. Soetomo General Hospital in Surabaya Indonesia from January 2002 to December 2013 ranged from 6.171 % to 11.22 % (4).

At the onset of TBI, an initial process called a primary brain injury results in mechanical damage in the form of impulsive forces, pulls or tears that cause cell damage (5). This process if left will develop into a secondary head injury which is a major cause of increased intracranial pressure (5). This increases in ICP is pushed to the surrounding area of the brain where the cranial space remains, this is associated with decreased consciousness and other clinical deterioration in TBI patients (6).

One of the common managements of ICP in TBI cases is the administration of mannitol fluid. Mannitol belongs to the osmotic diuretic fluid. Mannitol works by increasing the amount of fluid released by the kidneys and so is expected to help the body in reducing ICP pressure re-

sulting in improved clinical conditions in TBI patients (7). Urinary excretion is enhanced by mannitol preventing tubules from reabsorbing water and increasing osmotic pressure in glomerular filtration and tubules (7). However, the provision of mannitol is associated with the occurrence of acute kidney injury (AKI) (8). AKI alone in TBI has a prevalence of 1.5%–18.1% (8). AKI is one of the most frequent but often overlooked potential complications.

Patient	Patients with newly diagnosed AKI after TBI, GCS < 13, with age range 15-100 years old, survived and followed at least for 30 days after discharge.
Intervention	Given mannitol at least 1g/kg BW/day for at least 3 days
Comparison/ Control	Not given mannitol
Outcome	Acute Kidney Injury

Table 1. PICO table of the study.

Study, Publication Year	Country	Study Design	Study Population	Other Demographic Data Included
Ahmed M. et al [11], 2015	Bangladesh	Cohort	95 patients	Type of injury; clinical, neurological, and systemic findings; laboratory reports; treatment received; important clinical events during the hospital stay; complications within the hospital; and the corresponding therapeutic interventions with special attention to ischemic and nephrotoxic factors.
Fang L. et al [12], 2010	China	Cohort	171 patients	Age, gender, and past history such as hypertension, diabetes, arteriosclerosis, dyslipidemia, hyperuricacidemia, coronary artery disease, chronic liver disease, chronic respiratory disorders, and tumor
Kim M. et al [13], 2011	South Korea	Cohort	153 patients	Age, sex, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and status at time of admission for all of the following conditions: diabetes mellitus, hypertension, liver disease, cerebrovascular accident, ischemic heart disease, Glasgow Coma Scale (GCS) score, and type of intracranial haemorrhage (ICH).
Zeng J. et al [14], 2013	Australia	Cohort	168 patients	Age, gender, GCS at admission

Table 2. Characteristics of the included studies.

2. OBJECTIVE

So in this study, authors will discuss the incidence of AKI related to the provision of mannitol in TBI cases so it is expected to provide a better prevention of complications.

3. METHODS

Information Sources and Search Strategy

This systematic review and meta-analysis was conducted based on PRISMA guidelines (9). Studies were obtained by searching electronic databases, Pubmed, Science Direct, Cochrane, Embase, and JNS in December 2017. Studies that were included ranged from 2009-2021. Only articles in Bahasa and English were included. Authors used the following search keywords to search all trials registers and databases: “renal” or “kidney” and “traumatic brain injury”. No ethical clearance is needed for this study.

Eligibility Criteria

Study used were full-text observational study or randomized control trial about AKI incidence following mannitol administration in TBI patients. Unpublished articles, abstracts, study not written in English or Bahasa were excluded from the study. Study characteristics were presented as PICO in Table 1.

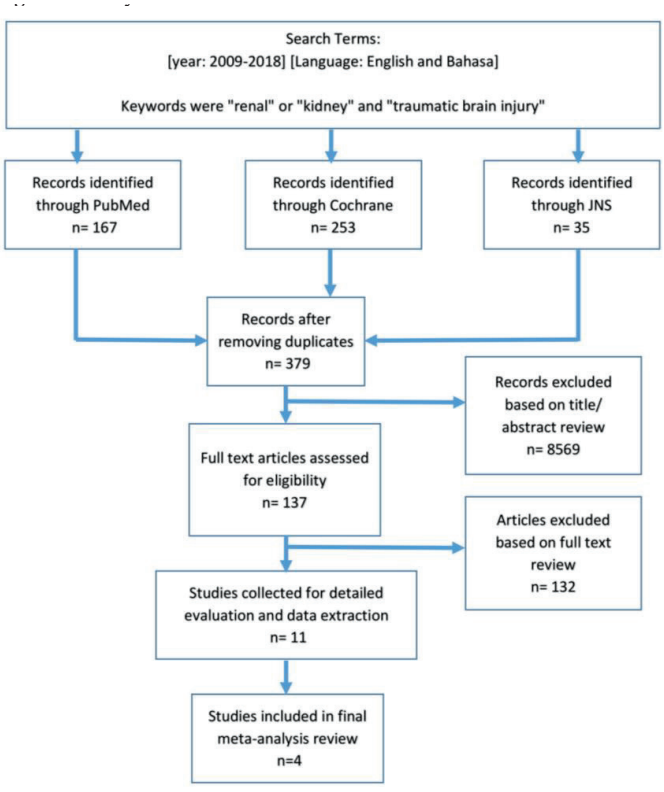

Figure 1. Study flow chart.

Quality Assessment

The methodological quality in each of these studies was assessed using the risk-of-bias assessment tool based on the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) by 2 reviewers (K.R.P. and A.F.P.).

Study selection and data collection

Study selection and data collection were performed independently in an unblinded standardized manner by 2 reviewers (K.R.P. and A.F.P.) with the same portion. Discrepancies between the two authors were resolved by discussion. If no result could be reached, the third (B.D.) and the fourth (T.A.M.) author were consulted to decide. All studies were screened for duplicate together after being collected in a single folder. After that, the selected articles will be judged on their title and abstract using the

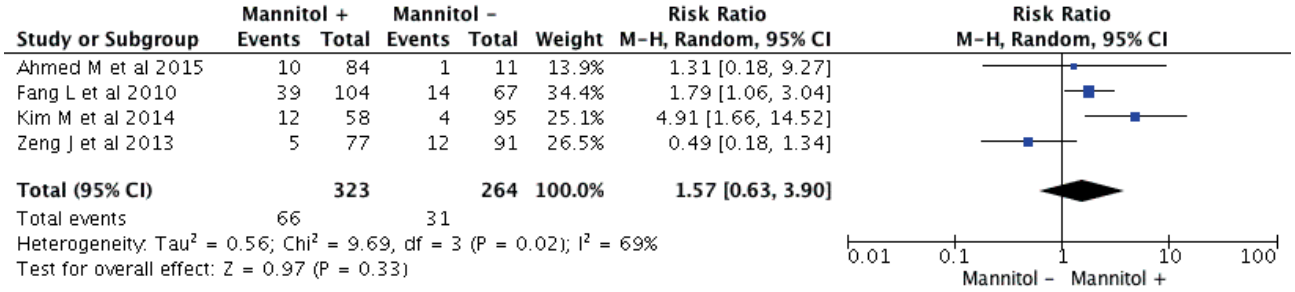

Figure 2. Forest plot comparing AKI incidence.

inclusion and exclusion criteria described earlier. Selected studies will be reviewed based on their full-text version. The incidence of AKI in patients with TBI from every eligible full text was extracted and analysed. Statistical analysis was done by Review Manager 5. From 648 studies, total 4 studies were eligible for this study.

Outcomes

The primary outcome was AKI incidence among TBI patients who received mannitol and those not. This outcome was evaluated for all studies for which an Risk Ratio (RR) could be calculated. The definition of AKI in each study was used as the basis for the analysis because the definition of AKI may differ in each study.

Assessment of bias and statistical methods

The quality of this study was assessed by K.R.P. and A.F.P with the same portion by using Cochrane-risk-of-bias tool (10). Bias assessed include random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias.

Effect size using Risk Ratio (RR) and 95% confidence interval (CI) for AKI, compared TBI patients who were given mannitol and those not. Homogeneity of study results is determined using Cochran Q test. Random Effect Model (REM) was used because statistical heterogeneity was found in the study (I^2> 75%). Otherwise, Fixed Effect Model (FEM) was used. P ≤ .05 (2-sided) was considered statistically significant.

4. RESULTS

Literature Search

A flow diagram of study selection is shown in Figure 1. After initially identifying 379 articles, 242 were excluded and the full texts of 137 were reviewed. Subsequently, 133 studies were excluded, and 4 studies were included in the systematic review and meta-analysis (Table 2).

From those 4 studies, it is shown that the pooled risk ratio AKI incidence following mannitol administration in traumatic brain injury (TBI) was 1.57. The pooled risk ratio had wide heterogeneity (I^2 = 0.95 and 1, p< 0.05) so random effect model was used.

Quality Assessment of the Included Studies

The quality assessment assessed included selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias (Figure 3). A funnel plot was planned to assess bias if including more than 10 studies.

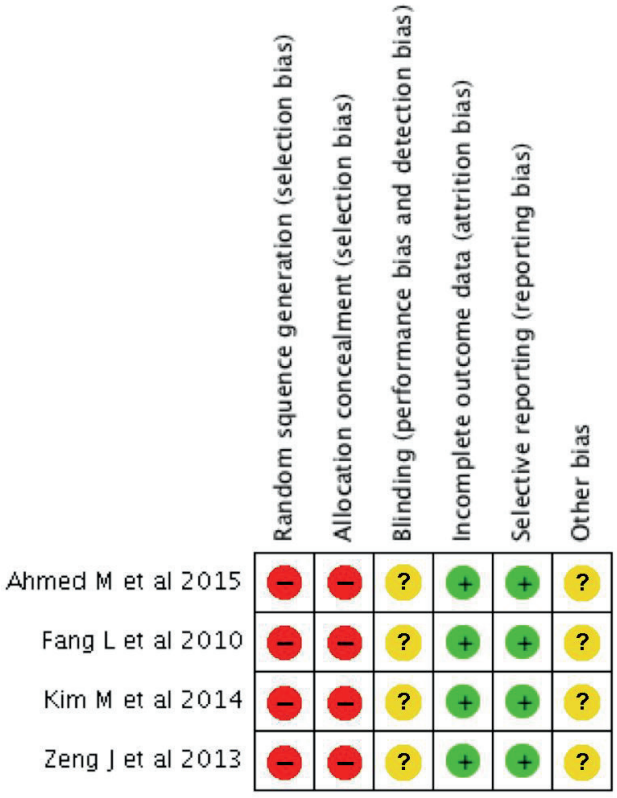

Figure 3: Risk of bias

In 4 studies, random sequence generation (selection bias) and allocation concealment (selection bias) weren't adequately generated. Blinding of participants and personnel (performance and detection bias) and other sources of bias weren't clearly addressed. But all studies had good quality in attrition bias and reporting bias.

5. DISCUSSION

In this meta-analysis study, there are 4 study included in terms of inclusion criteria. Each of study using criteria in order to recognize AKI, such as AKIN criteria, RIFLE criteria, and creatinin serum level in TBI patients following mannitol therapy compared to non-mannitol therapy. The mechanism mannitol in minimize or inducing acute kidney injury is still partially understood. However, physiologically body constantly excrete sodium after brain cells death due to sodium waste mechanism of the brain, which called sodium-wasting mechanism of brain. In some study showed there are proof of AKI incidence in TBI patients followed by mannitol therapy as already been showed by Ahmed et al, Fang et al, and Kim

et al. But one of the study found inversed, there is no significant difference between given mannitol therapy and without mannitol therapy as Zeng et al showed in terms of AKI complication (11-14).

Ahmed et al showed there was correlation between mannitol therapy with AKI incidence results among patients with cerebral injury with post surgical population following mannitol therapy in centers which intracranial pressure (ICP) was not routinely monitored, whereas cumulative dose of torsemide-mannitol impacted to AKI following TBI. Incidence of AKI increased risk of death until 6.17 times regardless of GCS. However this study realized the limitation about ICP-directed mannitol therapy has beneficial effect in AKI incidence, neurological, and physiological indicator.[11]

Fang et al study using RIFLE criteria, which identified independent risk factors of AKI such as sequential organ failure assessment, accumulative dose of torsamide and mannitol, then followed by adjustment for selection bias and confounding bias assessed by Propensity Score Match (PSM) in propensity analysis. This study described AKI was common complication of TBI with higher dose of mannitol. This could be explained by ischemia and hypoxia following cerebral trauma, indicated by hypovolemia, mediator inflammation, nephrotoxic drugs, and large dose of mannitol implicated to tubular edema, degeneration, and necrosis lead to AKI. Because mannitol is form of hexitol casually used to decrease ICP to prevent brain hernia which is nephrotoxic in large dose. Fang also explained that trauma and operation itself might lead to decreased effective blood volume and renal plasma flow lead to tubular ischemic injury and deteriorate Glomerular Filtration Rate (GFR). Large dose of infusion after blood loss might induce renal ischemia reperfusion injury and aggravated tubular injury (12).

Fang et al presented some of theories which tried to explained nephrotoxicity of mannitol, the first theory was about tubular injury indicated by swelling of proximal tubular cells and vacuolization, that was so-called osmotic nephrosis. The more exogen substance like mannitol accumulated, the more lysosome in proximal tubule aggregated inducing AKI even in patient with normal baseline renal function. Second theory was called pinocytosis. Substances comes to tbular cells by pinocytosis and vacuoles fused with each other and fused with lysosome to form the vacuole-containing substances and hydratase and injured kidney. It is confirmed mannitol takes effect through pinocytosis. The larger, the more, the quicker exogenous substance supply, the more vacuoles accumulation in tubular cells. This study showed daily dose recommendation as well, less than 300 gram of mannitol for patient with baseline renal disease and it was reported accumulative dose of mannitol inducing AKI was >1100 gram in patients with normal baseline renal function. Daily dose more than 200 gram made different osmotic pressure which lead to physiological changes of kidney. This study picturized its limitation in terms of individual differences in the timing of AKI after cerebral trauma, because renal function of every patient was not regularly monitored (12).

Kim et al explored the mannitol infusion rate in AKI more frequent for patients received at rate $\geq$ 1.34 gram/kgBW/day than it did in patients who received < 1.34 gram/kgBW/day. Higher mannitol infusion rate was associated with more severe AKI with GFR <60 mL/min/1.73 m^2. This study also showed accumulation of usual mannitol dose aggravated renal insufficiency in patient with or without underlying renal impairment. Kim also agreed on treatment of increasing ICP with administration <200gram / day or accumulated dosage of 1100 gram of mannitol.

Different with other 3 studies, Zeng et al explained that mannitol itself has both side effects whether it could preserve brain and damaging kidney at the same time in the matter of dosage. Mannitol designed in hypertonic solution that make blood really viscous and can damage the kidney if it is not used wisely. Zeng explained ICP monitoring was the key of preserving both brain and kidney, and was used to eliminate bias due to casual observation and provide of mannitol and other osmotic agent. Recognized ICP as treatment variable rather than merely an indication of disease severity. ICP monitoring might lower incidence of AKI and had better neurological outcomes at 6 months post injury with mean mannitol dosage in ICP monitoring group was 443 $\pm$ 133 gram compared to non ICP monitored group with mean dosage of mannitol was 820 $\pm$ 412 gram. There was significant different between ICP monitored and control group (14).

6. CONCLUSION

Therefore we found studies as above with RR is 1.57 in 587 sample. Which means there is no significant difference between mannitol therapy and without mannitol in TBI patients. Authors recommend it is the matter of dosage and monitoring of ICP that mostly play role in acute kidney injury. If mannitol given in a wise manner of dosage, then there should not be any injury related to kidney. Recommendations and future directions still needed in further study and replication of the similar study is necessary in order to picturize the whole mechanism of acute kidney injury effect of mannitol therapy in TBI patients. AKI appeared more frequent in patient TBI with casual mannitol administration. It still needs more multicentre and long term period researches in the future to get better understanding AKI in TBI following mannitol administration.

- **Author's Contribution:** The investigation was arranged by AFP, KRP, and BD who also performed research, provided research materials, and collated and processed data. AFP and KRP were responsible for data analysis and interpretation. AFP, KRP, and BD contributed with the initial and final versions of the article as well as practical assistance. All authors were in control of the manuscript's substance after critically reviewing and approving the final text.
- **Conflicts of interest:** There are no conflicts of interest.
- **Financial support and sponsorship:** None.
- **Acknowledgment:** The completion of this paper could not have been possible without support Dr. dr. Sri Andarini, M.Kes, as dean of Faculty of medicine Brawijaya University and the participation and assistance of so many people whose names may not all be numerated.

REFERENCES

1. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation. 2007; 22(5): 341-353.
2. WHO. Global status report on road safety 2015. Geneva, Switzerland: World Health Organization, 2015.
3. Brun Jr J, Hauser WA. The epidemiology of traumatic brain injury: a review. Epilepsia. 2003; 44: 2e10.
4. Neurotrauma Team, Dr. Soetomo General Hospital Surabaya. Guideline in Management Traumatic Brain Injury. 2nd ed. Surabaya, Indonesia: Airlangga University Faculty of Medicine; 2014: 5-20.
5. Shawkat H, Westwood MM, Mortimer A. Mannitol: a review of its clinical uses. Continuing Education in Anaesthesia Critical Care & Pain, 2012; 12(2): 82–85.
6. Blyth BJ, Bazarian JJ. Traumatic Alterations in Consciousness: Traumatic Brain Injury. Emergency medicine clinics of North America. 2010; 28(3): 571-594.
7. Fandino W. Understanding the physiological changes induced by mannitol: From the theory to the clinical practice in neuroanaesthesia. Journal of Neuroanaesthesiology and Critical Care. 2017; 4(3): 138.
8. Fang L, You H, Chen B, Xu Z, Gao L, Liu J et al. Mannitol is an independent risk factor of acute kidney injury after cerebral trauma: a case–control study. Renal Failure. 2010; 32(6): 673-679.
9. Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Medicine. 2009; 6(7): e1000100.
10. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD. et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928.
11. Ahmed M, Sriganesh K, Vinay B, Umamaheswara Rao G. Acute kidney injury in survivors of surgery for severe traumatic brain injury: Incidence, risk factors, and outcome from a tertiary neuroscience center in India. British Journal of Neurosurgery. 2015; 29(4): 544-548.
12. Fang L, You H, Chen B, Xu Z, Gao L, Liu J et al. Mannitol is an independent risk factor of acute kidney injury after cerebral trauma: a case–control study. Renal Failure. 2010; 32(6): 673-679.
13. Kim M, Park J, Kang N, Jang H, Lee J, Huh W et al. Increased risk of acute kidney injury associated with higher infusion rate of mannitol in patients with intracranial hemorrhage. Journal of Neurosurgery. 2014; 120(6): 1340-1348.
14. Zeng J, Tong W, Zheng P. Decreased risk of acute kidney injury with intracranial pressure monitoring in patients with moderate or severe brain injury. Journal of Neurosurgery. 2013; 119(5): 1228-1232.