



Preventive Intravenous Fluid Administration in Traumatic Rhabdomyolysis Patients at Risk of Acute Kidney Injury; a Systematic Review and Meta-analysis

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Abstract

Introduction: To determine the optimum volume of intravenous fluid administration in traumatic rhabdomyolysis patients to prevent acute kidney injury (AKI) and the need for dialysis.

Methods: Systematic search was done via the electronic databases Medline, Embase, Scopus, and Web of Science on January 21, 2024 using the query formed for keywords rhabdomyolysis, fluid therapy, and AKI. No filter was used. Citation searching was done, as well. Trials and observational studies reporting data on fluid therapy and AKI in traumatic rhabdomyolysis patients were included. Animal studies, case reports, reviews, and studies on non-traumatic causes were excluded. Risk of bias assessment was done using NHLBI tool for observational and cohort studies. The quality of evidence was assessed using the GRADE score. Analyses were carried out using STATA v.18 for outcomes AKI and dialysis by categorizing studies into three treatment volumes of ≤ 3 L/day, >3 L/day, and Better et al. protocols.

Results: Eight studies were included in the final analysis. The estimated prevalence of AKI and the need for dialysis in traumatic rhabdomyolysis patients were lowest when administering 3-8 L of IV fluid per 24 hours (AKI: 0.02 (95% CI: 0.00, 0.11) compared with 0.48 (95% CI: 0.0, 1.0), and 0.16 (95% CI: 0.01, 0.38) in studies administering ≤ 3 L/day, and those following Better et al. protocol, respectively; Dialysis: 0.01 (95% CI: 0.00, 0.03) compared with 0.05 (95% CI: 0.00, 0.18) in ≤ 3 , and 0.16 (95% CI: 0.01, 0.38) in Better protocol.). All studies were of non-low risk of bias and the quality of evidence is very low.

Conclusions: There is paucity of high quality data on fluid therapy in traumatic rhabdomyolysis, which warrants further studies. The scarce evidence is in favor of administering a volume of 3-8 L/day to prevent AKI and the need for dialysis in traumatic rhabdomyolysis patients, albeit with very low quality.

Keywords: Rhabdomyolysis; Fluid therapy; Acute kidney injury; Renal replacement therapy.

Introduction

Rhabdomyolysis denotes destruction of skeletal muscle cells and subsequent release of intracellular contents into the bloodstream. Traumatic and non-traumatic etiologies lead to this condition. Traumatic rhabdomyolysis can ensue natural or man-made disasters such as earthquakes and bombings, which

result in entrapment of the skeletal muscle mass under static physical pressure. It can also occur following blunt trauma with weapons like chains, whiplashes, or wooden objects. Medications, alcohol, toxic substances, and extreme muscle strain are among non-traumatic causes of rhabdomyolysis.^{1,2} Many densely populated

areas around the globe are subject to earthquakes and other natural disasters. Not only Homo sapiens is unable to prevent natural disasters, but also their wars and modern armaments leave more casualties than before.^{3,4} Rhabdomyolysis leads to electrolyte abnormalities including hypocalcemia and hyperkalemia, which can be rapidly fatal through cardiac arrhythmia. It also causes sequestration of large volumes of body water in the injured tissue leading to dehydration and decreased renal flow. Released myoglobin forms eosinophilic casts in the renal tubules. Acidic environment facilitates generation of free radicals and formation of pigmented casts. The decreased flow and vasoconstriction, tubular obstruction, and oxidant injury can eventually result in reduced glomerular filtration and acute kidney injury (AKI).⁵⁻⁸ AKI is an important, yet preventable complication of rhabdomyolysis. Prophylactic intravenous (IV) fluid therapy is the mainstay of preventing AKI in rhabdomyolysis patients, for which various approaches have been proposed but no integrated protocol and consensus exists.^{9,10}

Several reviews are done on treatment of rhabdomyolysis patients. Scharman et al. systematically reviewed 27 articles and proposed the administration of IV fluid at a rate targeting a urine output of 300mL/h, which equals >8L of fluid per day.¹¹ Chavez and Michelsen made no specific suggestion on volume of fluid,^{1,10} and Manspecker and Kodadek stated that an early IV replacement at 400mL/h followed by an adjusted volume between 200 and 1000 mL/h is usually indicated at clinical practice. However, this volume should be titrated according the urine output to prevent overload.^{6,12}

In mass disasters, limited medical resources are faced with huge number of victims; hence impracticability of liberal therapeutic approaches. Fluid therapy protocols requiring copious volumes of solution, like Better et al. protocol,¹³ cannot be implemented in such situations. This necessitates the quest for finding the optimum volume to be administered to victims to prevent AKI occurrence. We performed this systematic review and meta-analysis to provide an evidence-based answer to the following clinical question: what is the optimum volume of intravenous fluid administration in traumatic rhabdomyolysis patients to prevent AKI?

Methods

This systematic review is conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and 2020 checklist.¹⁴

Eligibility criteria

Randomized clinical trials (RCT) and observational studies on traumatic rhabdomyolysis patients were considered eligible for inclusion if they reported the volume or protocol of their IV fluid therapy and the number of patients that developed acute kidney injury (AKI). Studies on rhabdomyolysis of non-traumatic etiologies, like intoxication, were excluded. Animal studies, case reports, and review articles were also excluded. No language restriction was applied.

Search strategy

The electronic databases Medline, Embase, Scopus, and Web of Science were systematically searched from commencement until January 21, 2024. The search query was formed by using multiple medical subject heading (Mesh) terms, Emtree terms, and keywords for rhabdomyolysis, fluid therapy, and AKI. No filter was applied.

We also searched the reference lists of primary eligible articles and reviews. Lastly, we consulted with several experts in nephrology. The full search queries are provided in the supplementary appendix (Supplementary table 1).

Study selection

Search results were combined and duplicates were removed using Endnote X9 (PA, USA). The remaining imported titles and abstracts were screened by two investigators, independently. The full texts of seemingly eligible articles were retrieved and reviewed independently by two reviewers. Disagreements were resolved during the screening and reviewing process through discussion with a third person and by consensus.

Data collection

Data was extracted independently by two investigators who had no affiliation to the included studies. Extracted data included the study design, details of the enrolled population (number of cases, age, and sex), characteristics of the fluid therapy protocol (volume, type, and added agents), and data regarding outcome (number of patients who developed AKI, and number who required dialysis). No data was imputed

and discrepancies in extracted data were resolved by discussion.

Risk of bias assessment

Two investigators, not affiliated with the included studies, separately assessed the risk of bias for each of the included studies using National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool for observational cohort and cross-sectional studies.¹⁵ Each of the 14 criterion was assessed by two expert investigators to decide whether to be considered as a potential cause of fatal bias. Disagreements were resolved by discussion with a third investigator and consensus.

Data analysis

STATA v18.0 (Stata Corporation, College Station, TX) was used to carry out statistical analyses. A volume cut-point of three liters was selected to categorize the studies into high- and low-volume groups based on the mean volume of administered fluid per day. This cut-point was determined according to the analysis of 'occurrence of AKI and dialysis in different mean IV fluid intake per 24 hours' in the study of Najafi et al.¹⁶

Studies were classified into three groups according to the infused volume: 1) Studies administering fluid based on Better et al. hydration protocol (a primary 1.5L/h solution at injury site, followed by vigorous mannitol-bicarbonate solution infusion at a total volume of up to 24L/day),¹³ 2) Studies administering ≤ 3 L per 24h, and 3) Studies administering more than 3L per 24h but not following Better et al. protocol. Forest plots of AKI and dialysis prevalence were drawn according to this classification. The effect size was reported as prevalence and 95% confidence interval (CI). Heterogeneity among studies was assessed by I² statistics and an I² higher than 50% was considered as significant heterogeneity. Publication bias was assessed by Egger's test.

Grading the quality of evidence

Grading of recommendations assessment, development, and evaluation (GRADE) approach was used to evaluate the overall quality of evidence for each outcome.

Study flow and characteristics

The systematic search in electronic databases yielded 2726 studies. Citation searching added another 10 studies to this number. Full texts of 61 studies were retrieved and finally, 8 studies were included in the review and analysis with a sum of 1128 patients.¹⁶⁻²³ Figure 1 depicts the flow diagram of this review. Studies found to be not-relevant, reviews, case reports, editorials, perspectives, and letter to editors were omitted. Table 1 shows the characteristics of the included studies.

Meta-analysis

As shown by figure 2, AKI prevalence was 0.48 (95% CI: 0.0, 1.0) and 0.16 (95% CI: 0.01, 0.38) in studies administering ≤ 3 L/day and those following Better et al. protocol, respectively. Meanwhile, AKI occurred in 0.02 (95% CI: 0.00, 0.11) of those who received a volume between the two mentioned groups. The maximum volume administered in this group did not exceed 8L/day.

Analysis of data on dialysis revealed the same group (>3 L/day and less than better) as having the lowest dialysis rate [0.01 (95% CI: 0.00, 0.03)]. An estimated rate of 0.05 (95% CI: 0.00, 0.18) of patients underwent dialysis in the ≤ 3 L/day group, while 0.16 (95% CI: 0.01, 0.38) of those treated by better et al. protocol required dialysis (fig. 3).

Risk of bias assessment

Questions 3, 4, 11, 13, and 14 on NHLBI quality assessment tool for observational cohort and cross-sectional studies were considered as key questions with potential of causing fatal bias. We rated seven studies as high risk (poor quality) since the studies had at least one fatal error (not reported or high risk in items 3, 4, 11, 13, and 14), and one as some concern (fair quality) (Supplementary table 2).

Certainty of evidence

There were serious risk of bias and considerable imprecision. In addition, we could not perform publication bias due to scarce number of included studies. Therefore, the level of evidence for both outcomes was rated as very low.

Results

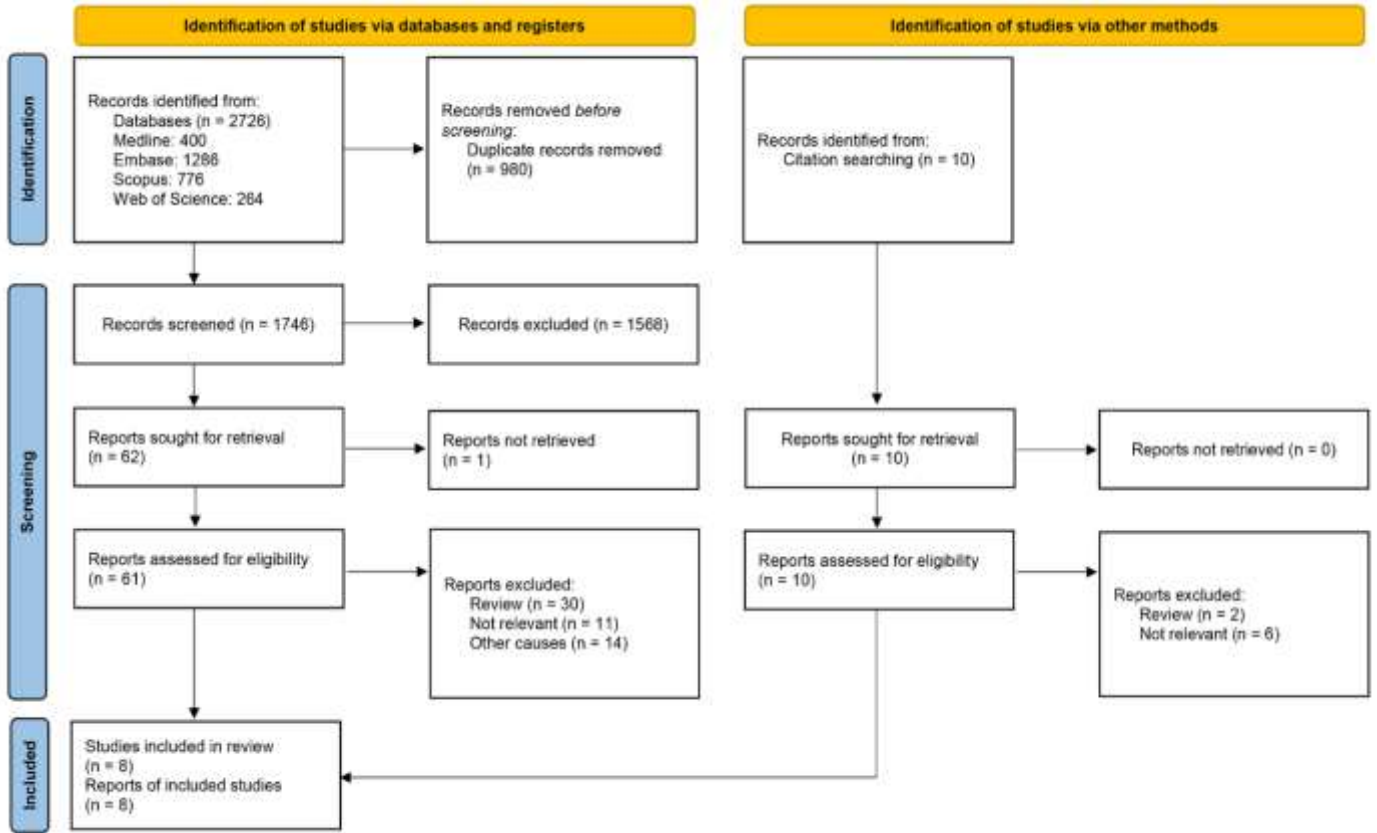


Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of results of search and reasons for exclusion of studies.

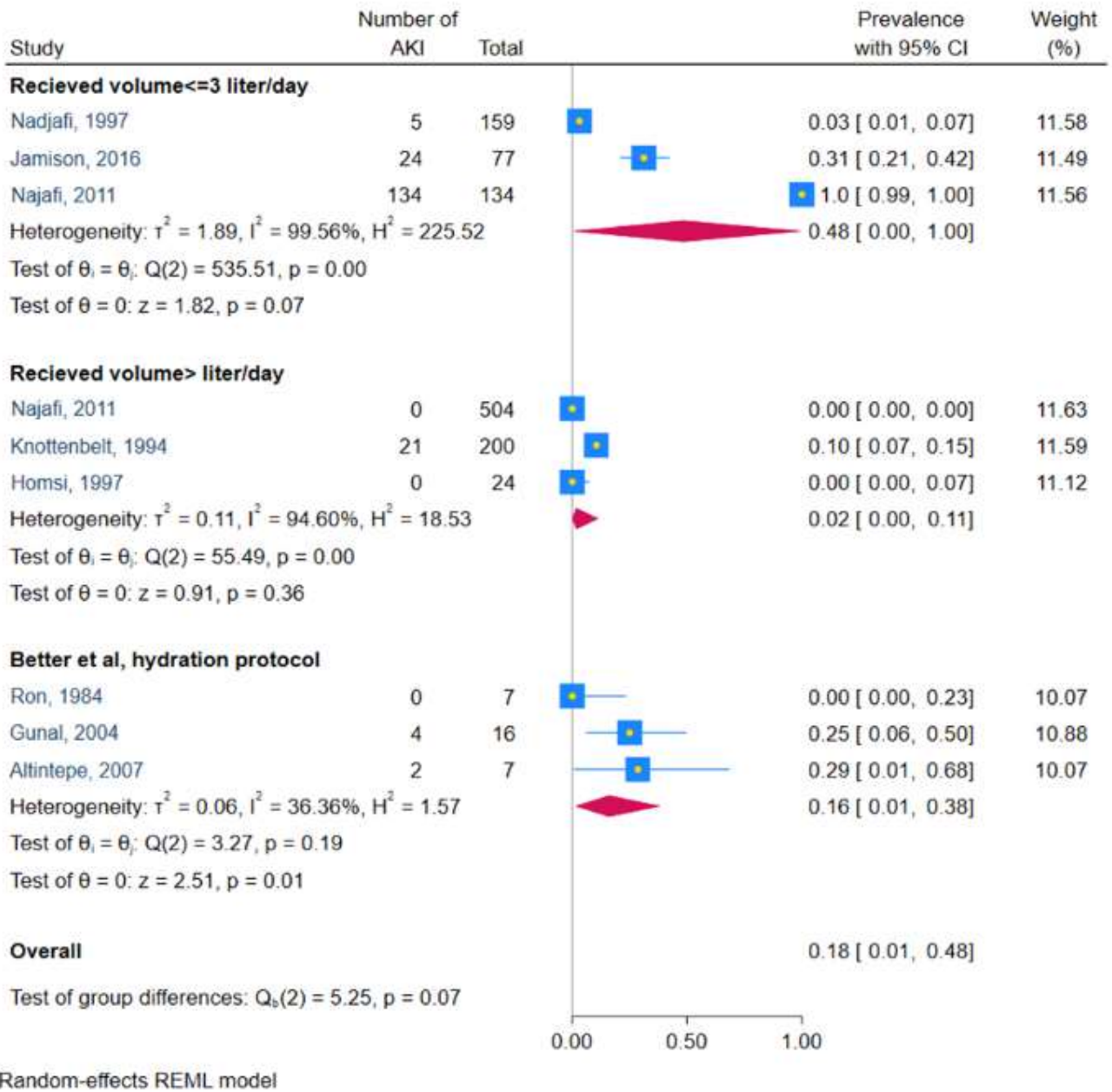


Figure 2: Forest Plot demonstrating the estimated prevalence of acute kidney injury (AKI) following three different intravenous fluid therapy protocols.

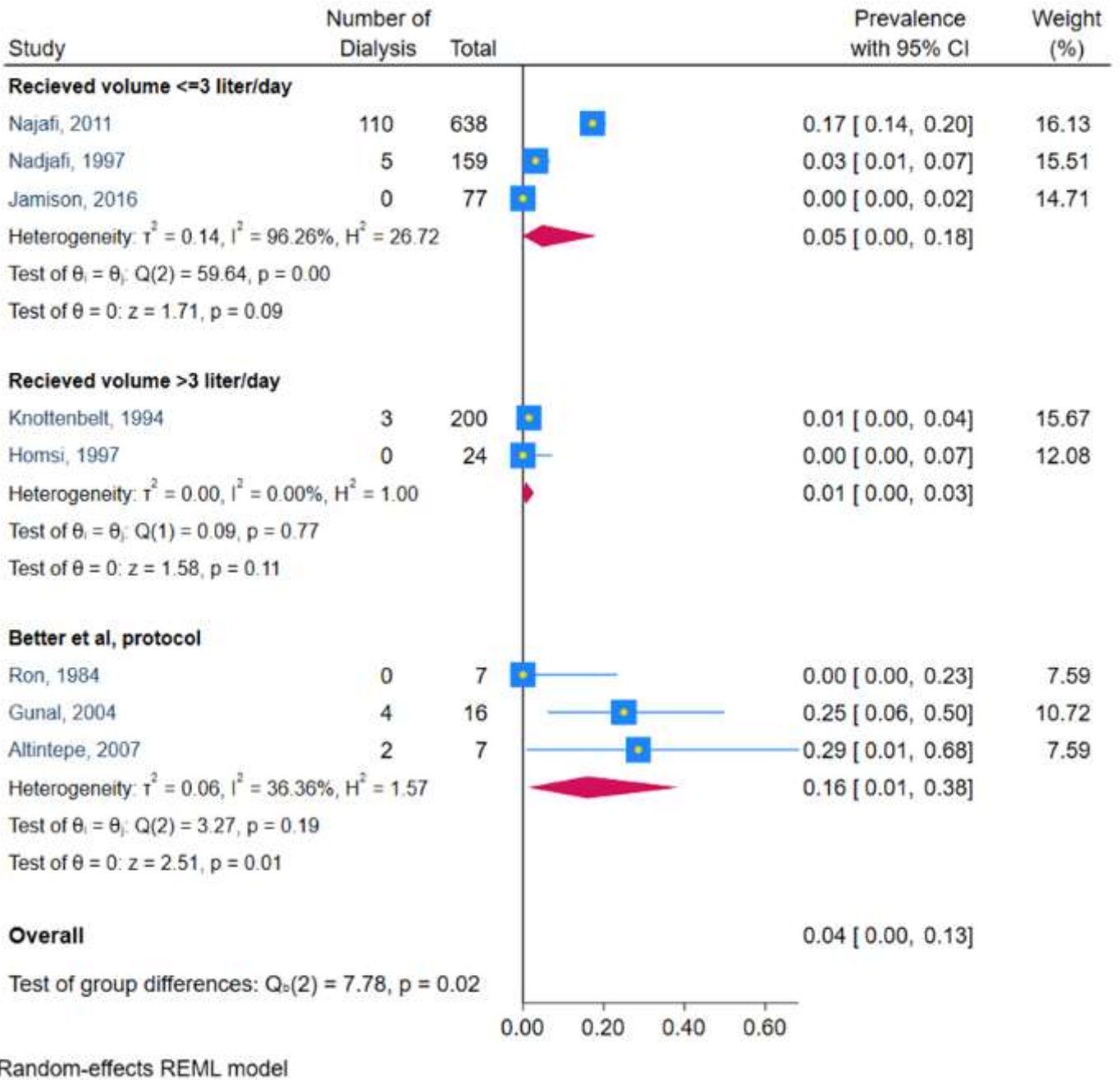


Figure 3: Forest Plot demonstrating the estimated prevalence of need for dialysis following three different intravenous fluid therapy protocols.

Table 1: Characteristics of the included studies.

First Author	Year	Study Type	Sample Size	Male Count	Age Mean (y)	Time Under the Rubble (Mean)	Type of Solution	Added Agents	AKI	Non AKI	Dialysis	Mass casualty	V Mean (L)
Gunal ¹⁷	2004	RCS	16	12	23	10.3	Better Protocol	Mann+Bicarb	4	12	4	No	>3
Altintepe ¹⁸	2007	RCS	7	N/R	23.5	11.1	Better Protocol	Mann+Bicarb	2	5	2	No	>3
Najafi ¹⁶	2011	RCS	638	371	>15	AKI: 6.3±3.1 NonAKI: 2.4±1.6	Normal Saline	None	134	504	110	Yes	<3
Knottenbelt ¹⁹	1994	RCS	200	148	28 (14-53)	N/R	Balanced Salt Solution	Bicarb	21	179	3	No	>3
Homsji ²⁰	1997	RCS	G1:15 G2:9	20	31±12	N/R	G1: NS G2: NS+B+M	G1:None G2: Mann+Bicarb	0	24	0	No	>3
Nadjafi ²¹	1997	RCS	159	N/R	N/R	AKI: 8 NonAKI: 3	1/3 2/3	Bicarb	5	154	5	Yes	<3
Ron ²²	1984	RCS	7	7	25 (18-47)	10.7 (1-28)	Better Protocol	Mann+Bicarb	0	7	0	No	>3
Jamison ²³	2016	RCS	77	N/R	N/R	N/R	See their article	See their article	24	53	0	No	<3

retrospective cohort study; G: group; N/R: not reported; AKI: acute kidney injury; NS: normal saline; B: Bicarb: Bicarbonate; M: Mann: Mannitol; y: year; L: liter.

Table 2: Certainty of evidence for the outcomes acute kidney injury and need for dialysis.

Estimated prevalence	Number of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence					Certainty of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
Acute kidney injury	8 studies (n = 1128)	Retrospective cohort study	Serious	Not serious	Not serious	serious	None	⊖⊖⊖⊖ Very low
Need for dialysis	8 studies (n = 1128)	Retrospective cohort study	Serious	Not serious	Not serious	serious	None	⊖⊖⊖⊖ Very low

Discussion

In this systematic review and meta-analysis, the estimated prevalence of AKI and need for dialysis in traumatic rhabdomyolysis patients were lowest when administering 3-8 L of IV fluid per 24 hours. AKI occurred more in volumes ≤3L/day or using Better et al.

protocol, and a higher proportion of patients required dialysis in these groups. All studies are of non-low risk of bias and the quality of evidence is very low. One well-recognized hydration protocol in traumatic rhabdomyolysis is of Better and colleagues, which suggests starting the isotonic saline infusion

immediately after extrication of the trapped limbs at the rate of 1.5 L/h followed by vigorous mannitol-bicarbonate solution infusion. The latter solution is prepared by adding 40 mEq NaHCO₃ and 50 ml of 20% mannitol to 1000 ml of 0.45% NaCl and 5% dextrose. The patient central venous pressure, blood gases, and urinary pH and output are monitored. This regimen is continued until the resolution of myoglobinuria.^{18,22} One major obstacle in implementing this protocol is the copious amount of solution needed. Better et al. reported that a young adult weighing 75 kg requires a relative volume of 12 L of IV fluid per day.¹³ Though this may be a well-measured approach in individual cases of rhabdomyolysis, the large number of victims in mass disasters impedes its utility.

Najafi et al. processed data from Bam earthquake victims and revealed that increase in volume of IV fluid received per day, decreases AKI prevalence. The volume increases up to 3 L/day results in prominent decrement in AKI prevalence, and almost no appreciable change is noted passed 5 L/day. The infused-volume and need-for-dialysis curve follows the same pattern. They concluded that in victims with severe rhabdomyolysis (creatinine phosphokinase (CPK) ≥ 15000), higher volumes (> 6 L) of IV fluid are required to prevent AKI, whereas in less severe cases, lower volumes (3-6 L) would suffice.¹⁶

Fluid therapy is not just inserting an intravenous catheter and running a solution to the circulation! It should be justified according to the severity of the injury, the clinical course of the patients, and their medical background. Previous studies have assessed the correlation of different factors to the severity of injury. Higher CPK level and longer time being trapped under the rubble (TUR) are indicators of more intense injury and subsequently higher chance of AKI and need for dialysis. It gets even more complex considering that the building architecture and the way of being entrapped changes the severity.^{16,24} For example, someone trapped for several days but protected against direct pressure by a concrete block may develop less severe injury than someone entrapped under direct pressure for several hours. Delay in initiation of fluid therapy is also shown to be associated with more risk of AKI. Several studies emphasize on early hydration therapy.^{4,10,17} However, even delayed hydration is shown to prevent AKI and need for dialysis.^{21,25} Overall, initiation of a conservative hydration therapy, as early as possible,

along with estimation of severity of injury based on objective laboratory markers like CPK, LDH (lactate dehydrogenase), and serum potassium and uric acid, seems an appropriate approach.^{17,26}

The type of the fluid and which items to add should be considered as well. Generally, crystalloids are preferred to colloids.¹⁰ Saline, normal or half, and lactated Ringer's solution are the two widely used fluids. A theoretical concern remains regarding the use of Ringer's as it contains potassium, which may worsen the hyperkalemia from rhabdomyolysis. Meanwhile, high volumes of normal saline can cause metabolic acidosis, which is in favor of rhabdomyolysis-induced AKI (RI-AKI) pathophysiology. Up to now, it remains the physician discretion to choose the fluid type.^{6,11,27} Mannitol reduces muscle compartment pressure and act as a free-radical scavenger and renal vasodilator. So, theoretically, it can well interfere with the RI-AKI pathogenesis; but, no study with strong evidence support its routine use.^{6,28} Studies on bicarbonate usually have coupled it with mannitol. So, it is hard to distinguish its role alone. A recent propensity score-matched cohort study indicated that the use of bicarbonate was associated with higher incidence of AKI and need for dialysis.²⁹ However, no RCT is available.

It is evident that catastrophic post-disaster situations call for simplest instructions and least use of material and resources. The results of this study, though with very low level of evidence, favors the recommendations of Najafi et al. in administering IV fluids to traumatic rhabdomyolysis victims. Volumes more than 3 L/day but not as liberal as Better et al. protocol seem most practical in disastrous circumstances. It is the authors' opinion that a rapid triage of victims using CPK and subsequent administration of a minimum of 3 and 6 Liters of IV saline per day, to non-severe and severe rhabdomyolysis patients respectively, may seem as a functional and easily-recalled formula to approach rhabdomyolysis. This study highlights an important point through its limitation; the fact that robust evidence is missing in this field and that high quality studies are warranted.

During preparation of the manuscript of this study, the catastrophic Turkey and Syria earthquake (Kahramanmaras) occurred. If enough attention was drawn by scientific community to this topic, invaluable data could be obtained with potential of producing

results that would save thousands of kidneys and lives!

Limitations

This study is limited by the fact that no RCT is available on this topic. The catastrophic situation in the aftermath of disasters can potentially cause poor documentation of therapeutic details and subsequent inaccurate reporting of data. Limited number of included studies and data prohibit the use of advanced analyses and providing robust results.

Conclusion

There is paucity of high quality data on fluid therapy in traumatic rhabdomyolysis. The scarce evidence is in favor of administering a volume of 3-8 L/day to prevent AKI and the need for dialysis in traumatic rhabdomyolysis patients, albeit with very low quality.

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Conflict of Interest Disclosures

The authors declare that they have no Conflict of Interest.

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None.

Authors' Contributions

All the authors meet the standard authorship criteria according to the recommendations of international committee of medical journal editors.

Ethical Statement

None.

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