Review Article

Normal saline for intravenous fluid therapy in critically ill patients

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ABSTRACT

The efficacy and safety of normal saline (NS) for fluid therapy in critically ill patients remain controversy. In this review, we summarized the evidence of randomized controlled trials (RCTs) which compared NS with other solutions in critically ill patients. The results showed that when compared with 6% hydroxyethyl starch (HES), NS may reduce the onset of acute kidney injury (AKI). However, there is no significant different in mortality and incidence of AKI when compared with 10% HES, albumin and buffered crystalloid solution. Therefore, it is important to prescribe intravenous fluid for patients according to their individual condition.

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Introduction

Fluid resuscitation is a fundamental component of the management of acutely ill patients. The optimal dose and types of intravenous (IV) fluid for resuscitation remain undetermined. 0.9% sodium chloride, or the so-called “normal saline” (NS), is one of the most commonly used IV fluid for seriously ill or injured patients. Since NS has a totally different level of chloride from the plasma, its administration would be inevitably causes hyperchloremic metabolic acidosis. And the chloride has an important role in tubuloglomerular feedback mechanisms. As the chloride concentration in the distal tubule fluid rises, feedback occurs via the macula densa, the afferent arteriole constricts, and the glomerular filtration rate drops. However, whether this adverse event will affect mortality and the incidence of acute kidney injury (AKI) remains unknown. Meanwhile, whether the NS is the solution for crystalloid resuscitation or not the first choice for crystalloid resuscitation remains controversy.

Therefore, we summarized the evidence of randomized controlled trials (RCTs) which compared NS with other solutions in critically ill patients. The results were expected to lead to a better use of NS in critically ill patients, and may influence clinical outcomes positively.

NS for fluid resuscitation in critically ill patients

We selected RCTs comparing NS with other solutions in adult critically ill patients who required IV fluid therapy. The search strategy and inclusion criteria are listed in Table 1. The statistical analysis was performed using RevMan software (version 5.2; Cochrane Collaboration, Copenhagen, Denmark) for outcome measurements. The results of the risk ratio (RR) for dichotomous outcomes or the mean difference (MD) for continuous data were expressed as means and 95% confidence intervals (CI). A random-effects model was used regardless of heterogeneity. A p value less than 0.05 was considered to indicate a statistically significant difference. The outcomes reported across studies included mortality at 28 and 90 days, renal outcomes, and length of stay in intensive care units (ICU).

NS vs 6% hydroxyethyl starch (HES)

Seven RCTs investigated the efficacy and safety of 6% HES vs NS during the IV fluid therapy in critically ill patients. The results (Table 2) showed that more patients in the 6% HES group met the RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria for risk and injury (p < 0.05). Therefore, compared to NS, 6% HES may increase the risk of AKI when prescribed for critically ill patients. However, no significant differences were found between 6% HES and NS in all-cause mortality (at 28 days or at 90 days), renal replacement therapy, RBC transfusion and length of stay in ICU when used for fluid resuscitation in critically ill patients. No significant differences were found between 6% HES and NS in all-cause mortality (at 28 days or at 90 days), renal replacement therapy, RBC transfusion and length of stay in ICU when used for fluid resuscitation in critically ill patients. No significant differences were found between 6% HES and NS in all-cause mortality (at 28 days or at 90 days), renal replacement therapy, RBC transfusion and length of stay in ICU when used for fluid resuscitation in critically ill patients.
RCTS analysed the cost-effectiveness of the two fluid therapies. One cohort study did a pre-specified cost-effectiveness analysis from New South Wales enrolled in the Crystalloid vs HES trial (CHEST, NCT00935168),9 and found that the total hospital costs (including ICU costs) at 24 months were similar between the HES and saline groups ($62,196 vs $62,617; \ p = 0.83). This suggested that there may be no difference in hospital costs when these two fluids were prescribed for fluid resuscitation in critically ill patients.

From the acquired evidence, when 6% HES was prescribed for critically ill patients, we must take more attention on the change of renal function and give supportive treatment immediately. More studies are needed and should focus on long-term outcomes, clinical relative adverse events and the impact on coagulation.

**NS vs 10% HES**

Only two RCTs,18,19 with 86 patients were enrolled in the comparison of NS vs 10% HES (Table 3). The results show that there were no differences in all-cause mortality (at 28 days), renal failure and length of stay in ICU between the two groups. For the limited patient data, the conclusion has high risk of inconsistency and thus cannot be applied to guide the clinical practice. It is necessary to use 10% HES according to patients’ individual status.

**NS vs. albumin**

Five RCTs,10,11,15,18,20 evaluated the efficacy and safety of albumin vs NS during the IV fluid therapy in critically ill patients (Table 4). There were no differences in all-cause mortality (at 28 days or at 90 days), renal function, renal replacement therapy and length of stay in ICU between albumin and NS groups. Furthermore, two recent meta-analysis21,22 evaluated albumin vs other fluids for resuscitation in patients with sepsis and suggested that the present evidence did not demonstrate significant advantage of using human albumin solutions at reducing all-cause mortality. Meanwhile, Jiang et al21 reported that 4%—5% albumin may be relative safer than 20%—25% albumin for fluid resuscitation. However, the high cost of albumin may limit its wide applicability.23,24 Therefore, according to the current state of knowledge, we should carefully consider the hospital costs and the concentration when albumin was prescribed for critically ill patients.

### Table 1
Search strategy and inclusion criteria.

| Review eligibility structure | Population | Intervention | Control | Outcomes |
|-----------------------------|------------|--------------|---------|----------|
| Critically ill patients requiring acute volume replacement (e.g. resuscitation, but not maintenance fluid) | Normal saline | HES solutions, albumin, dextran, gelatin or buffered crystalloid solution | Primary outcome: incidence of mortality. Secondary outcomes: renal function, use of renal replacement therapy, lengths of stay in ICU, incidence of patients requiring of red cell transfusion. |

| Study design | Prospective randomized controlled trials |

| Review eligibility criteria | Inclusion criteria | Exclusion criteria |
|-----------------------------|--------------------|--------------------|
| 1. Randomized controlled trial; 2. Participants’ age ≥18 years; 3. Indication for acute volume resuscitation (e.g. hypovolemia, hypotension, inadequate indicators of pre-load or filling pressures); 4. Allocation to resuscitation with normal saline compared with HES, albumin, or buffered crystalloid solution. | 1. Fluids used as maintenance rather than resuscitation; 2. What control group used is whole blood, or blood products; 3. Use of normal saline for elective pre-operative volume loading; 4. Elective surgical procedures (e.g. cardiac surgery); 5. Observational study designs, quasi-randomized, cross-over, or cluster randomized trials. |

### Table 2
Comparison of 6% HES and NS on fluid resuscitation.

| Parameters | No. of patients | RR (95% CI) | Heterogeneity I² (p value) | Test for effect (p value) |
|------------|----------------|-------------|---------------------------|-------------------------|
| All-cause mortality (90 days) | 828/4089 958/4497 | 0.97 (0.81, 1.16) | 51% (0.07) | 0.73 |
| All-cause mortality (28 days) | 647/4073 746/4476 | 0.99 (0.86, 1.13) | Not applicable | 0.17 |
| All-cause mortality (28 days)—trauma | 12/56 6/53 | 1.89 (0.77—4.68) | Not applicable | 0.5 |
| All-cause mortality (28 days)—sepsis | 136/475 181/652 | 1.03 (0.85, 1.25) | 0% (0.41) | 0.05 |
| AKI- RIFLE—risk | 1809/3465 1935/3483 | 0.94 (0.90, 0.98) | 0% (0.36) | 0.006 |
| AKI-RIFLE—risk—trauma | 8/56 12/53 | 0.63 (0.28, 1.42) | Not applicable | 0.27 |
| AKI-RIFLE—risk—sepsis | 13/100 11/95 | 1.12 (0.53, 2.38) | Not applicable | 0.76 |
| AKI-RIFLE—injury | 1138/3421 1266/3488 | 0.91 (0.85, 0.97) | 0% (0.51) | 0.004 |
| AKI-RIFLE-injury—trauma | 4/56 8/53 | 0.47 (0.15, 1.48) | Not applicable | 0.2 |
| AKI-RIFLE-injury—sepsis | 4/100 5/95 | 0.76 (0.21, 2.75) | Not applicable | 0.68 |
| AKI- RIFLE—failure | 341/3343 308/3470 | 1.15 (0.99, 1.33) | 0% (0.35) | 0.06 |
| AKI-RIFLE—failure—trauma | 5/100 7/95 | 0.68 (0.22, 2.06) | Not applicable | 0.49 |
| Renal replacement therapy | 237/3408 199/3428 | 1.20 (1.00, 1.44) | 0% (0.47) | 0.05 |
| Use of renal replacement therapy—trauma | 2/56 3/53 | 0.63 (0.11, 3.63) | Not applicable | 0.61 |
| RBC transfusion | 29/100 20/96 | 1.38 (0.84, 2.26) | Not applicable | 0.21 |

| Length of stay | MD (95% CI) | Heterogeneity I² (p value) | Test for effect (p value) |
|----------------|-------------|---------------------------|-------------------------|
| HES | 15.4 ± 11.1 | 20.2 ± 22.2 | 76% (0.04) | 0.53 |
| NS | 7.3 ± 0.2 | 6.9 ± 0.2 | 5.83 (0.77, 7.67) | 0.65 |

AKI: acute kidney injury; CI: confidence interval; HES: hydroxyethyl starch; MD: mean difference; NS: normal saline; RIFLE: risk, injury, failure, loss, end-stage kidney disease; RR: relative risk.
and signiﬁcantly higher mortality in higher-risk populations (Table 5). We concluded that compared with NS, the buffered crystalloid solution cannot reduce mortality or the risk of AKI. One cluster randomized trials indicated that there was no signiﬁcant different between NS and Ringer’s lactate solution. Another cost-minimization analysis results suggested that the use of Plasma-Lyte A was associated with a relatively higher in-hospital cost but a reduced need for magnesium replacement in critically injured trauma patients. Therefore, further large scale RCTs are needed to assess the efﬁcacy in higher-risk populations and signiﬁcant adverse events.

### NS vs buffered crystalloid solution

Buffered crystalloid solution with electrolyte composition closely mimics human plasma in its content of electrolytes, osmolality, and pH. And it has been considered as a good alternative to NS for critically ill patients with AKI. However, from two RCTs results (Table 5), we concluded that when compared with NS, the buffered crystalloid solution cannot reduce mortality or the risk of AKI. One cluster randomized trials indicated that there was no signiﬁcant different between NS and Ringer’s lactate solution. Another cost-minimization analysis results suggested that the use of Plasma-Lyte A was associated with a relatively higher ﬂuid acquisition cost but a reduced need for magnesium replacement in critically injured trauma patients. Therefore, further large scale RCTs are needed to assess the efﬁcacy in higher-risk populations and signiﬁcant adverse events.

In this review, we compared NS vs other ﬂuids for IV ﬂuid therapy in critically ill patients. There is little doubt that excess exogenous chloride administration has been shown to induce renal artery vasoconstriction, AKI, hyperchloremic metabolic acidosis, gastrointestinal dysfunction, and the secretion of inﬂammatory cytokines. Although some observational studies have reported an increased mortality risk associated with the use of NS, our results and some recent meta-analysis results showed that patients mortality and the risk of AKI were not changed with the excess exogenous chloride administration.

Unfortunately, inappropriate NS infusion management in hospitals may lead to clinical relative adverse events, prolong length of stay in ICU or increase the mortality. Many of the errors in NS infusion management are due to inadequate knowledge and clinician preparation, poor fluid balance monitoring and

### Table 3

Comparison of 10% hydroxyethyl starch (HES) and NS on fluid resuscitation.

| Parameters                                      | No. of patients | RR (95% CI)     | Heterogeneity | Test for effect |
|-------------------------------------------------|-----------------|-----------------|---------------|----------------|
| All-cause mortality (28 days)                  | 27/51           | 1.63 (0.92, 2.88) | Not applicable | 0.47           |
| All-cause mortality (28 days) — sepsis          | 9/21            | 1.36 (0.50, 3.10) | 0% (0.41)     | 0.75           |
| AKI - RIFLE - failure — sepsis                  | 3/21            | 2.71 (0.31, 23.93) | Not applicable | 0.37           |
| Length of stay                                 | MD (95% CI)     |                 |               |                |
| HES                                             |                 | 1.50 (−4.01, 7.01) | Not applicable | 0.59           |

### Table 4

Comparison of albumin and NS on fluid resuscitation.

| Parameters                                      | No. of patients | RR (95% CI)     | Heterogeneity | Test for effect |
|-------------------------------------------------|-----------------|-----------------|---------------|----------------|
| All-cause mortality (90 days)                   | 36/101          | 1.39 (0.48, 4.01) | 87% (0.0006) | 0.54           |
| All-cause mortality (28 days)                   | 759/3568        | 1.06 (0.87, 1.29) | 29% (0.25)    | 0.58           |
| All-cause mortality (28 days) — sepsis          | 81/396          | 1.36 (0.99, 1.86) | Not applicable | 0.06           |
| renal replacement therapy                        | 45/3473         | 1.09 (0.72, 1.67) | Not applicable | 0.68           |
| Length of stay                                  | MD (95% CI)     |                 |               |                |
| albumin                                         |                 | 0.30 (−0.00, 0.60) | Not applicable | 0.05           |

### Table 5

Comparison of buffered crystalloid and NS on fluid resuscitation.

| Parameters                                      | No. of patients | RR (95% CI)     | Heterogeneity | Test for effect |
|-------------------------------------------------|-----------------|-----------------|---------------|----------------|
| All-cause mortality (90 days)                   | 87/1112         | 1.05 (0.78, 1.40) | Not applicable | 0.75           |
| All-cause mortality (28 days)                   | 3/22            | 1.50 (0.40, 5.65) | Not applicable | 0.55           |
| AKI - RIFLE - failure                           | 123/1067        | 1.10 (0.86, 1.41) | Not applicable | 0.43           |
| AKI - RIFLE - injury                            | 46/1067         | 0.78 (0.53, 1.13) | Not applicable | 0.19           |
| renal replacement therapy                        | 54/1067         | 1.44 (0.95, 2.18) | Not applicable | 0.08           |
| Length of stay                                  | MD (95% CI)     |                 |               |                |
| Buffered crystalloid                             |                 | 0.96 (0.62, 1.50) | Not applicable | 0.87           |

### Table 6

Comparison of albumin and NS on fluid resuscitation.

| Parameters                                      | No. of patients | RR (95% CI)     | Heterogeneity | Test for effect |
|-------------------------------------------------|-----------------|-----------------|---------------|----------------|
| All-cause mortality (90 days)                   | 36/101          | 1.39 (0.48, 4.01) | 87% (0.0006) | 0.54           |
| All-cause mortality (28 days)                   | 759/3568        | 1.06 (0.87, 1.29) | 29% (0.25)    | 0.58           |
| All-cause mortality (28 days) — sepsis          | 81/396          | 1.36 (0.99, 1.86) | Not applicable | 0.06           |
| renal replacement therapy                        | 45/3473         | 1.09 (0.72, 1.67) | Not applicable | 0.68           |
| Length of stay                                  | MD (95% CI)     |                 |               |                |
| albumin                                         |                 | 0.30 (−0.00, 0.60) | Not applicable | 0.05           |

### Table 7

Comparison of buffered crystalloid and NS on fluid resuscitation.

| Parameters                                      | No. of patients | RR (95% CI)     | Heterogeneity | Test for effect |
|-------------------------------------------------|-----------------|-----------------|---------------|----------------|
| All-cause mortality (90 days)                   | 87/1112         | 1.05 (0.78, 1.40) | Not applicable | 0.75           |
| All-cause mortality (28 days)                   | 3/22            | 1.50 (0.40, 5.65) | Not applicable | 0.55           |
| AKI - RIFLE - failure                           | 123/1067        | 1.10 (0.86, 1.41) | Not applicable | 0.43           |
| AKI - RIFLE - injury                            | 46/1067         | 0.78 (0.53, 1.13) | Not applicable | 0.19           |
| AKI - RIFLE - failure                            | 54/1067         | 1.44 (0.95, 2.18) | Not applicable | 0.08           |
| renal replacement therapy                        | 38/1112         | 0.96 (0.62, 1.50) | Not applicable | 0.87           |
| Length of stay                                  | MD (95% CI)     |                 |               |                |
| Buffered crystalloid                             |                 | 0.96 (0.62, 1.50) | Not applicable | 0.87           |

### Table 8

Comparison of albumin and NS on fluid resuscitation.

| Parameters                                      | No. of patients | RR (95% CI)     | Heterogeneity | Test for effect |
|-------------------------------------------------|-----------------|-----------------|---------------|----------------|
| All-cause mortality (90 days)                   | 36/101          | 1.39 (0.48, 4.01) | 87% (0.0006) | 0.54           |
| All-cause mortality (28 days)                   | 759/3568        | 1.06 (0.87, 1.29) | 29% (0.25)    | 0.58           |
| All-cause mortality (28 days) — sepsis          | 81/396          | 1.36 (0.99, 1.86) | Not applicable | 0.06           |
| renal replacement therapy                        | 45/3473         | 1.09 (0.72, 1.67) | Not applicable | 0.68           |
| Length of stay                                  | MD (95% CI)     |                 |               |                |
| albumin                                         |                 | 0.30 (−0.00, 0.60) | Not applicable | 0.05           |
inadequate knowledge are associated with increased clinical risk and harm. Meanwhile, improved knowledge led to improved confidence in NS infusion management. Therefore, it is necessary to use the present evidence to manage NS infusion, and we summarized some principles as follows.

1. Assess the fluid and electrolyte status of critically ill patients. Provide NS for patients whose demand cannot be met through oral or enteral routes, and stop as soon as possible.

2. A NS infusion management plan should be made, in which NS prescription over the next 24 h and monitoring program were indispensable.

3. The rate and volume of NS should be carefully considered; and the 4 Rs (resuscitation, routine maintenance, redistribution and reassessment) should be also remembered (Fig. 1).

4. Other sources of fluid and electrolyte intake should be taken into account, including any oral or enteral intake, and intake from drugs, IV nutrition, blood and blood products.

5. If possible, provide written information for patients and their family members.

In conclusion, NS as the most commonly used IV fluid for critically ill patients occupies a very important position in fluid resuscitation. A good understanding of its advantage and disadvantage when compared with other fluid prescribed for critically ill patients is conducive to make good clinical decision.

References

1. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369:1243–1251. https://doi.org/10.1056/NEJMra1208627.

2. Scales K, NICE CG, 174: intravenous fluid therapy in adults in hospital. Br J Nurs. 2014;23:36–58. https://doi.org/10.12968/hjon.2014.4.21.Supp8.56.

3. Ke L, Calzavacca P, Bailey M, et al. Systemic and renal haemodynamic effects of fluid bolus therapy: sodium chloride versus sodium octanoate-balanced solution. Crit Care Resusc. 2014;16:29–33.

4. Chowdhury AH, Cox EF, Francis ST, et al. A randomized, controlled, double-blind crossover study on the effects of 2-l: infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012;256:18–24. https://doi.org/10.1097/SLA.0b013e31825b6e72.

5. Yunos NM, Bellomo R, Story D, et al. Bench-to-bedside review: chloride in critical illness. Crit Care. 2010;14:226. https://doi.org/10.1186/cc9052.

6. Young P. Saline is the solution for crystallloid resuscitation. Crit Care Med. 2016;44:1538–1540. https://doi.org/10.1097/CCM.0000000000002844.

7. Morsing P, Velazquez H, Ellison D, et al. Resetting of tubuloglomerular feedback by interrupting early distal flow. Acta Physiol Scand. 1993;148:63–68. https://doi.org/10.1111/j.1748-1716.1993.tb09532.x.

8. Semler MW, Rice TW. Saline is not the first choice for crystallloid resuscitation fluids. Crit Care Med. 2016;44:1541–1544. https://doi.org/10.1097/CCM.000000000000194.

9. Taylor C, Thompson K, Finfer S, et al. Hydroxyethyl starch versus saline for resuscitation of patients in intensive care: long-term outcomes and cost-effectiveness analysis of a cohort from CHEST, Lancet Respir Med. 2016;4:418–425. https://doi.org/10.1016/S2213-2600(16)30120-5.

10. Rackow EC, Fark J, Fein IA, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med. 1983;11:839–850.

11. van der Heijden M, Verheij L, van Nieuw Amerongen GP, et al. Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia. Crit Care Med. 2009;37:1275–1281. https://doi.org/10.1097/CCM.0b013e31819ceedd.

12. Dubin A, Pozo MO, Casabella CA, et al. Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. J Crit Care. 2010;25:655.e1–e8. https://doi.org/10.1016/j.jcc.2010.04.007.

13. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSMAS study. Crit Care. 2012;16:894. https://doi.org/10.1186/cc11358.

14. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–1911. https://doi.org/10.1056/NEJMoa1206759.

15. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs. crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310:1809–1817. https://doi.org/10.1001/jama.2013.280502.

16. Li F, Sun H, Han XD. [The effect of different fluids on early fluid resuscitation in septic shock], Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2008;20:472–475.

17. James MF, Michel WL, Joubert IA, et al. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth. 2011;107:693–702. https://doi.org/10.1093/bja/aer229.

18. Veneman TF, Oudeij Hjoue J, Woutieres AJ. Human albumin and starch administration in critically ill patients: a prospective randomized clinical trial. Wien Klin Wochenschr. 2004;116:305–309.

19. McIntyre LA, Ferguson D, Cook DJ, et al. Fluid resuscitation in the management of early septic shock (FINES5): a randomized controlled feasibility trial. Can J Anaesth. 2008;55:819–826. https://doi.org/10.1016/S0008-4955.

20. Finfer S, Bellomo R, Boyce N, et al. Comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–2256. https://doi.org/10.1056/NEJMoa040232.

21. Jiang L, Jiang S, Zhang M, et al. Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. PLoS One. 2014;9, e114666. https://doi.org/10.1371/journal.pone.0114666.

22. Patel A, Laffan MA, Waheed U, et al. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. BMJ. 2014;349:g4561. https://doi.org/10.1136/ bmj.g4561.

23. Latour-Perez J. New recommendations for the use of serum albumin in patients with severe sepsis and septic shock. Crit Care Med. 2013;41:e289. https://doi.org/10.1097/CCM.0b013e3182b8ed28.

24. Lyu PF, Murphy DJ. Economics of fluid therapy in critically ill patients. Curr Opin Crit Care. 2014;20:402–407. https://doi.org/10.1097/MCC.0000000000000117.
