In India, tuberculosis is treated mainly by private practitioners, many of whom are unqualified. This leads to inadequate management of TB patients as standard treatment guidelines are not adhered to. Moreover, the high cost of medications results in poor adherence to antitubercular therapy with the possible emergence of drug-resistant TB. To address this issue, one could draw lessons from the Brazilian Tuberculosis Control Programme where a single public sector agency is the sole drug dispensing agency for tuberculosis. Also, increased participation of the private sector could increase the coverage of childhood vaccination with special focus on the BCG vaccine.

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## REFERENCES


VINOOTH GNANA CHELLAIYAN
TIMIRESH KUMAR DAS
PALANIVEL C.
RAVI P. UPADHYAY
Department of Community Medicine
VMMC & Safdarjung Hospital, New Delhi
drchellaiyan@gmail.com

## Resuscitation in the intensive care unit: Choosing the right fluid

Myburgh JA, Finer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. (George Institute for Global Health, University of New South Wales, St George Hospital, University of Sydney, Royal North Shore Hospital, and Royal Prince Alfred Hospital, Sydney; University of Melbourne and Austin Hospital, Melbourne, Victoria, University of Queensland and Royal Brisbane and Women’s Hospital, Brisbane, Queensland, and University of Western Australia and Royal Perth Hospital, Perth, Western Australia, Australia; and Auckland City Hospital, Auckland, New Zealand.) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367:1901–11. Epub 2012 Oct 17.

**SUMMARY**

The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) aimed to determine whether normal saline or 6% hydroxyethyl starch (HES, 130/0.4) is the preferred solution to resuscitate patients admitted to intensive care units (ICUs). It was a multicentre, prospective, blinded, randomized, controlled trial that enrolled 7000 patients from 32 centres across Australia and New Zealand.

Patients were recruited on admission to the ICU if they were above 18 years of age and were considered to require bolus intravenous fluids beyond maintenance or replacement requirements by their treating physician. They were followed till death, discharge or 90 days from randomization. The rate and volume of resuscitation was determined by their physicians, who were blinded to the fluid that was administered; however, no patient was administered greater than the maximum acceptable dose of 50 ml/kg/day for HES. Patients were excluded from the trial if they were found to have established or impending dialysis-dependent renal failure, intracranial haemorrhage or if they had already received more than 1 litre of HES before admission to the ICU.

There was no difference in the 90-day mortality (HES 18% v. saline 17%; relative risk [RR] in the HES group 1.06; 95% CI 0.96–1.18, p=0.26), which was the primary end-point of the trial. Results were similar when analysed in six pre-defined subgroups to counter the effect of potential confounders such as pre-existing risk of renal injury, presence of sepsis, trauma or brain injury, APACHE score >25 and receipt of HES before randomization. Renal replacement therapy (RRT) was required more often in the HES group (7% v. 5.8%; RR 1.26; 95% CI 1.0–1.4, p=0.04). Renal injury as well as renal failure were more frequent in the HES group—38% v. 34.6% and 10.4% v. 9.2%, respectively (p=0.005 and p=0.12, respectively). HES was also associated with significantly more adverse effects (5.3% v. 2.8%, p<0.001).

**COMMENT**

The ideal fluid resuscitation protocol for ICUs remains elusive despite extensive ongoing research in this field. The nature of the fluid (colloid or crystalloid), triggers for resuscitation, the quantity and rate of infusion and end-points for resuscitation are still hotly debated notwithstanding a number of studies that have attempted to answer these questions.
This paper (CHEST study) attempts to clarify whether resuscitation is better with HES or crystalloids. Some early studies indicated that use of colloids was fluid-sparing and there might be particular benefit in the presence of sepsis. Animal studies demonstrated improved microcirculation and reduced tissue damage during endotoxaemia. However, the use of HES was associated with serious side-effects including coagulopathy and acute renal failure. The VISEP study, which used high molecular weight 10% HES (200/0.5), showed a significantly higher incidence of renal failure and an increased tendency towards 90-day mortality in those resuscitated using HES. A recent Cochrane review evaluated 21 trials with a total of 1385 patients and showed a slightly higher mortality with the use of HES for resuscitation (RR 1.10; 95% CI 0.9–1.3).

Concentrated HES solutions (10%) with a molecular weight of >200kD and molar substitution ratios (the number of hydroxethyl [HE] groups per glucose molecule) >0.5 are most likely to cause renal injury. The use of lower concentrations of HES with lower molecular weights and molar substitution ratios is under evaluation. 6% HES (130/0.4) was found to be fluid-sparing and safe for septic patients in the CRYSMAS trial. The FIRST trial showed that resuscitation with HES improves renal function and lactate clearance in penetrating trauma in a randomized controlled study in a smaller number of patients. However, both these studies were underpowered to arrive at strong conclusions. A review of 25 studies including 1608 patients using 6% HES (130/0.4) reported that these studies were of poor quality and data on acute kidney injury, red cell transfusion and coagulopathy were insufficient to permit meta-analysis.

The recently published Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial, which also used low molecular weight HES, demonstrated an increased risk of death at day 90 (51% v. 43%, p=0.03), greater likelihood of RRT (22% v. 16%, p=0.04), and greater risk of severe bleeding (10% v. 6%, p=0.09) in patients with severe sepsis assigned to fluid resuscitation with 6% HES (130/0.42), as compared to those receiving Ringer acetate. The results were supported by multivariate analysis, adjusting for risk factors for death or baseline acute kidney injury. The reason for the observed increased mortality has been variously ascribed to over resuscitation with HES resulting from lack of definition of resuscitation end-points and probably the use of ‘more harmful’ potato-derived starch fluids rather than maize-derived ones.

The CHEST study used low molecular weight, maize-based starch for resuscitation across a wide variety of indications. It was analysed across six subgroups to account for the potential effect of pre-existing risk for renal injury, background illness (sepsis, trauma, brain injury) and severity of Illness (APACHE score). It did not show any difference in 90-day mortality between the two groups (18% v. 17%). The estimated baseline mortality used to calculate sample size for the study was 26%. The lower mortality in both study groups due to the self-confessed exclusion of very high-risk patients and postoperative patients therefore makes the study slightly underpowered to detect differences in mortality. The criticism aimed at previous studies with regard to lack of defined end-points for resuscitation is applicable to this study as well. However, there is no discounting the fact that there was a 21% greater need for some form of RRT in the group using HES. Although the indication for RRT was not defined in the study and was left to the treating clinician, they were blinded to the nature of the resuscitation fluid and were therefore unlikely to be influenced by it.

The present study confirms the need for a significantly lower volume of fluid in the group resuscitated with HES, with a higher central venous pressure and significantly lower onset of new cardiovascular organ failure as well (36.5% v. 39.9%; RR 0.91; 95% CI 0.84–0.99; p=0.03). However, this was associated with a greater need for transfusion, a greater onset of new liver dysfunction and a greater incidence of adverse events including pruritis, fever and skin rash.

Data from these two well-conducted randomized trials demonstrate that the use of HES for fluid resuscitation is much more likely to cause renal injury than the use of crystalloids, irrespective of its maize or potato origin. There continues to be some ambiguity regarding whether or not HES resuscitation is associated with a higher mortality. Given the much higher cost of HES compared with normal saline and its potential for renal injury and adverse events, it cannot be recommended for resuscitation at present.

REFERENCES