NICE National Institute for Health and Care Excellence

2020 exceptional surveillance of intravenous fluid therapy in adults in hospital (NICE guideline CG174)

Surveillance report

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Surveillance decision

We will not update the NICE guideline on intravenous fluid therapy in adults in hospital.

Reasons for the exceptional review

The purpose of this exceptional review was to examine any impact of 2 randomised controlled trials (RCTs) on NICE's guideline on intravenous fluid therapy in adults in hospital. The 2 trials compare balanced crystalloids with 0.9% sodium chloride for fluid resuscitation in adults:

- the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) (2018)
- the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial (2018).

Methods

The exceptional surveillance process assessed new evidence on balanced crystalloids versus 0.9% sodium chloride for fluid resuscitation and consisted of:

- Considering the evidence used to develop recommendation 1.3.1 of the NICE guideline in 2013.
- Considering the evidence in this area identified in the 2017 standard surveillance review of the guideline.
- Considering new or updated Cochrane reviews.
- Examining related NIHR signals.
- Feedback from topic experts.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline.

We decided that full updated literature searches were not needed because the information we had from the original guideline, routine surveillance, Cochrane reviews, NIHR signals and topic experts was enough to establish whether an update to the guideline was needed.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered in this exceptional surveillance review

We considered 2 RCTs comparing balanced crystalloids with normal saline for fluid resuscitation: SMART (2018) and SALT-ED (2018). We also considered 1 relevant new Cochrane review from 2019 on balanced crystalloids for fluid resuscitation, and 1 relevant RCT identified by the 2017 surveillance review of the guideline.

SMART trial

The SMART trial (n=15,802) was a pragmatic, unblinded, cluster-randomised, multiple-crossover trial comparing a balanced crystalloid (lactated Ringer's solution or Plasma-Lyte A) with saline (0.9% sodium chloride) for fluid resuscitation in critically ill adults admitted to 5 intensive care units (ICUs) at a single medical centre in the USA. The ICUs used saline in even-numbered months and balanced crystalloids in odd-numbered months, or vice versa. Patients, clinicians and investigators were aware of group assignments. The treating clinician could choose which of the 2 balanced crystalloids to use, and had the option to use any of the 3 fluids in the trial to ensure safe treatment of a patient. Off-protocol fluids were used in 4.9% of patients. The median volume administered of the fluid that the patient was assigned to was 1,000 ml for balanced crystalloids and 1,020 ml for saline.

The primary outcome of a major adverse kidney event within 30 days (a composite of death, new renal-replacement therapy, or persistent renal dysfunction, for example serum creatinine greater than or equal to 200% of baseline) occurred significantly less frequently in patients receiving balanced crystalloids (942 of 1,139; 14.3%) than in patients receiving saline (1,211 of 7,860; 15.4%; marginal odds ratio [OR] 0.91, 95% confidence interval [CI] 0.84 to 0.99; conditional OR 0.90, 95% CI 0.82 to 0.99; p=0.04). However, no significant differences were seen for the individual outcomes making up the composite: in-hospital mortality at 30 days (10.3% with balanced crystalloids versus 11.1% with saline, p=0.06); new renal-replacement therapy (2.5% versus 2.9% respectively, p=0.08); and persistent renal dysfunction (6.4% versus 6.6% respectively, p=0.60).

Most of the secondary outcomes (ICU-free days, ventilator-free days, vasopressor-free days) were not significantly different between groups, except the renal-replacement therapy-free days group which was slightly higher with balanced crystalloids than saline (mean 25.0 days versus 24.8 days,

p=0.01).

An NIHR signal also discusses the findings of the SMART trial: Balanced electrolyte solutions give marginal benefit over saline for very ill patients. The expert commentary for the signal suggested that balanced solutions may be an appropriate choice in ICU. However overall conclusions noted that the benefits of balanced crystalloids are small, the increased costs need consideration, and treatment decisions ultimately depend on the circumstances of each patient which should be viewed on an individual basis.

SALT-ED trial

The SALT-ED trial (n=13,347) was a pragmatic, unblinded, randomised, multiple-crossover trial comparing a balanced crystalloid (lactated Ringer's solution or Plasma-Lyte A) with saline (0.9% sodium chloride) for fluid resuscitation. Participants were non-critically ill adults treated in the emergency department before hospitalisation outside the ICU in a single medical centre in the USA. The protocol for use of fluids was the same as the SMART trial. Off-protocol fluids were used in 11.7% of patients. The median volume administered of the fluid that the patient was assigned to was 1,000 ml for both balanced crystalloids and saline.

There was no significant difference between groups for the primary outcome of hospital-free days to day 28 (a composite of in-hospital death and hospital length of stay defined as the number of days alive and out of the hospital between the index emergency department visit and 28 days later; median 25 days in each group; adjusted odds ratio 0.98, 95% CI 0.92 to 1.04; p=0.41).

However, a secondary outcome of major adverse kidney events within 30 days (a composite of death, new renal-replacement therapy, or persistent renal dysfunction, for example serum creatinine greater than or equal to 200% of baseline) occurred significantly less frequently in patients receiving balanced crystalloids (315 of 6,708; 4.7%) than in patients receiving saline (370 of 6,639; 5.6%; adjusted OR 0.82, 95% CI 0.70 to 0.95, p=0.01). Data were reported for the individual outcomes making up the composite, but the significance of differences between groups was not stated. No significant difference was seen between groups for the other secondary outcomes of acute kidney injury stage 2 or higher, or in-hospital death.

Cochrane review

The following Cochrane review was identified: Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Martin et al. 2019). It included 21 RCTs (20,213 participants) examining balanced crystalloids versus intravenous 0.9% sodium chloride in a critical care setting (resuscitation or maintenance). The 3 largest RCTs in the Cochrane review

(including the SMART trial and the SPLIT trial which are both discussed in this exceptional surveillance review) all examined fluid resuscitation in adults and contributed 19,054 participants (94.2%). Sixteen trials were in adults. Nine studies used Ringer's lactate, 5 used Plasma-Lyte A, 3 used Sterofundin, 2 used either Ringer's lactate or Plasma-Lyte A, 1 used both Ringer's lactate and Plasma-Lyte A, and 1 used Ringerfundin.

Meta-analyses found no significant effect of balanced crystalloids on the following outcomes:

- in-hospital mortality (OR 0.91, 95% CI 0.83 to 1.01, p=0.06; 19,664 participants; 14 studies; high-certainty evidence)
- acute renal injury (OR 0.92, 95% CI 0.84 to 1.00, p=0.06; 18,701 participants; 9 studies; low-certainty evidence)
- organ system dysfunction (OR 0.80, 95% CI 0.40 to 1.61, p=0.53; 266 participants; 5 studies; very low-certainty evidence).

Evidence from the 2017 surveillance of this guideline

A surveillance review in 2017 checked whether the guideline should be updated. Relevant evidence identified by the review included the SPLIT trial (2015) which compared a balanced crystalloid (Plasma-Lyte 148) with 0.9% sodium chloride for fluid resuscitation in 2,262 patients admitted to the ICU. Four ICUs were included (3 general medical and surgical ICUs, and 1 ICU with predominantly cardiothoracic and vascular surgical patients). The primary outcome of acute kidney injury (based on serum creatinine levels) within 90 days of enrollment was not significantly different between patients assigned to balanced crystalloids (9.6%) or saline (9.2%), (relative risk 1.04, 95% CI 0.80 to 1.36, p=0.77). Nor was there a difference in the secondary outcomes of use of renal-replacement therapy or in-hospital mortality.

The 2017 surveillance review concluded that there was no impact of the evidence on the guideline because none of the fluids demonstrated superiority. Topic experts involved with the 2017 review noted that this RCT would have been considered as indirect evidence during guideline development because of the ICU setting (the guideline was aimed more at hospital settings with fewer expert staff such as general wards, so evidence from ICU settings was deemed indirect, but was considered if no evidence in the target population was identified).

A topic expert also noted that based on a trend towards increased mortality with saline in this RCT, a larger study was set up (the PLUS trial) to compare the effect of 0.9% sodium chloride with balanced crystalloid (Plasma-Lyte 148) on 90-day mortality in 8,800 critically ill patients receiving

fluid resuscitation in the ICU. The expected trial end date is March 2021.

Information considered when developing the guideline

The guideline review question on the most clinically and cost-effective intravenous fluid for resuscitation of hospitalised patients included 12 RCTs, 1 Cochrane review (different from the Cochrane review identified for the current exceptional review) and 1 cost-effectiveness study. None of these studies compared balanced crystalloids with 0.9% sodium chloride. Very low-quality evidence from 3 RCTs of trauma and postoperative patients (including 1 based in ICUs) showed no difference in mortality between gelatin or balanced crystalloid (lactated Ringer's solution). Moderate quality evidence from 1 RCT of patients with severe sepsis undergoing fluid resuscitation in the ICU showed an increase in mortality at 90 days with tetrastarch versus balanced crystalloid (lactated Ringer's solution).

An original cost analysis was also performed for the guideline comparing 0.9% sodium chloride, balanced crystalloids, gelatin, tetrastarch and albumin. The analysis used the following costs per litre for saline and balanced crystalloids: 0.9% sodium chloride £0.70; Hartmann's Solution £0.85; Plasma-Lyte M £0.92; Ringer's Lactate £2.50 (costs per litre of gelatin, tetrastarch and albumin were much higher, ranging from £3.80 to £68.12). The clinical review performed for the guideline had not clearly indicated the clinical benefit of any particular fluid, therefore because crystalloids (namely 0.9% sodium chloride and balanced crystalloids) were the lowest cost fluids and had no apparent clinical disadvantage, the guideline committee concluded that they appeared to be the most cost-effective fluid. The resulting recommendation (1.3.1) was to use crystalloids that contain sodium in the range 130 mmol/l to 154 mmol/l for intravenous fluid resuscitation, which allows for use of both 0.9% sodium chloride and balanced crystalloids.

The guideline committee also made the following research recommendation: Are balanced solutions superior to sodium chloride 0.9% for the resuscitation of patients presenting to the accident and emergency department with acute shock?

Topic expert feedback

We contacted topic experts who were recruited to the NICE Centre for Guidelines Panel of Expert Advisers. We asked the experts if they believed that the SMART and SALT-ED studies affected the current recommendations on fluid type, and whether balanced crystalloids are in routine clinical use for fluid resuscitation and/or maintenance in adults in hospital.

We received feedback from 4 topic experts (a clinical director for pulmonary and critical care

medicine, a professor of gastrointestinal surgery, a consultant nephrologist and a pharmacist). Three experts stated that the new evidence did not indicate a need to change the guideline. One of these 3 experts noted that although there appears to be a trend towards improved renal outcomes with balanced crystalloids, the decision to use a balanced crystalloid should be to increase the chance of a better outcome for the particular patient being treated. The same expert noted that in their trust, a balanced crystalloid is used for resuscitation in adult critical care, but not on general wards. A second expert commented that in their experience, hospitals almost always use saline, and the new evidence is unlikely to affect the guideline as the range of sodium concentration in the current guideline recommendation is very broad.

The one expert who felt there was an impact on the guideline suggested that recommendation 1.3.1 should more strongly support balanced crystalloids because the new evidence suggests a trend towards survival and improved renal outcomes, though acknowledging that for some outcomes the differences were not significant.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

New evidence from the SMART and SALT-ED trials was mixed. Both critically and non-critically ill patients receiving balanced crystalloids experienced fewer major adverse kidney events than with 0.9% sodium chloride, but this was a composite outcome – individual outcomes within the composite (including death) showed no difference in critically ill patients (data not reported for non-critically ill patients). Most secondary outcomes in these 2 RCTs (ICU-free days, ventilator-free days, vasopressor-free days, acute kidney injury stage 2 or higher, or in-hospital death) also showed no difference between balanced crystalloids and 0.9% sodium chloride. The SPLIT trial identified by the 2017 surveillance review also found no difference between balanced crystalloids and 0.9% sodium chloride for acute kidney injury, use of renal-replacement therapy or in-hospital mortality.

The RCTs examined by this exceptional review did not therefore consistently show benefits on the individual outcomes considered by the guideline committee to be critical (all-cause mortality) or important (morbidity and development of complications, acute kidney injury, and length of stay in the ICU and hospital). The Cochrane review also found no benefit of balanced crystalloids over 0.9% sodium chloride on mortality, renal injury or organ system dysfunction. Additionally, the ICU setting of 2 of the RCTs meant they would have been considered indirect evidence by the guideline committee because the guideline is aimed more at areas of hospitals with fewer expert staff such as

general wards.

Costs analysed for the original guideline indicated that balanced crystalloids are more expensive than 0.9% sodium chloride, and 3 of 4 topic experts stated that the new evidence did not affect the guideline. We therefore believe there is no impact on the guideline which currently allows for the use of both 0.9% sodium chloride and balanced crystalloids. Healthcare professionals can therefore use clinical judgement to select the most appropriate fluid. This position was emphasised by a topic expert who noted that choice of fluid should be individual to the particular patient being treated.

The SMART and SALT-ED studies were highlighted to us during consultation of the 2020 surveillance review of the NICE guideline on intravenous fluid therapy in children and young people in hospital. Stakeholders commented that use of balanced crystalloids is increasingly common in children in the UK, but large RCTs in children are lacking, so evidence in adults should be considered. As these studies are in adults, we conducted this exceptional surveillance review to examine any impact of the evidence on the NICE guideline on intravenous fluid therapy in adults in hospital, before considering any impact on the guideline for intravenous fluid therapy in children and young people in hospital. As there is no impact on the intravenous fluid therapy in adults guideline, there is no subsequent impact on the guideline for children and young people.

Results of the ongoing PLUS trial are awaited which has a primary outcome of 90-day mortality (mortality was considered by the guideline committee to be the critical outcome for decision making) and which may provide further insight to the most appropriate intravenous fluid for resuscitation. NICE will log this area as an issue for the guideline and will re-consider it at the next standard surveillance review of the guideline or if we become aware of any relevant new evidence that may impact the guideline.

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