National Essential Medicine List Adult Hospital Level
Medication Review Process
Component: Emergencies and injuries

Date of Review: October 2015

Medication: Ringer lactate

Indication: Resuscitation in patients with hypovolaemia

Executive summary: Normal Saline (NS) is recommended in the Adult Hospital Level EML 2012 for resuscitation in patients with hypovolaemia. The KwaZulu-Natal Pharmacy Therapeutics Committee (KZN PTC) commented that Ringer's Lactate (RL) should replace NS as the recommended fluid in these patients on the basis of "good evidence" suggesting RL has a favorable inflammatory profile compared with NS. Furthermore, KZN PTC stated that the use of NS was no longer supported by "current resuscitation council and critical care literature". A comparison between crystalloids, specifically normal saline vs so-called "balanced" solutions such as Ringer's Lactate was undertaken as debate centered around the potential of NS to cause hyperchloraemic metabolic acidosis.

Introduction:

Often referred to as 'normal saline', 0.9% saline contains sodium and chloride in supraphysiological concentrations. Balanced solutions, in contrast, contain significantly lower concentrations of sodium and chloride, making them closer in composition to plasma than 0.9 % saline. However, isotonic saline is often the preferred resuscitation fluid because of its nature and compatibility with blood transfusion. (Smith *et al*., 2015)

Despite its widespread use, isotonic saline has been linked to metabolic acidosis, immune suppression, and decreased renal perfusion. Isotonic saline has been shown to cause a metabolic acidosis in healthy volunteers and in patients undergoing elective surgical procedures. Relative to a balanced isotonic crystalloid, in which electrolyte composition is similar to plasma, isotonic saline infusion during resuscitation after trauma delays normalization of the pH and base deficit after injury. Furthermore, metabolic acidosis has been implicated in the development of coagulopathy, though its specific role has not been fully characterized. Consequently some guidelines recommend the use of balanced solutions as a default during resuscitation. (Smith *et al*., 2015)

A recent narrative review on the use of IV fluids in sepsis, published in 2013, showed that there is no strong evidence showing differences in the outcomes of using balanced or unbalanced crystalloids during resuscitation. The choice of intravenous fluid should be based on the underlying pathophysiology and should not be a 'one size fits all' approach. Given the available data, the authors recommended that balanced fluids should be considered in patients who have persistent hyperchloremic acidosis after receiving chloride-rich fluids. Furthermore, it was stated that type of crystalloids may not influence the clinical outcome. (Karakala *et al*., 2013)

Objective: To review the evidence comparing the use of NS with RL (and other crystalloids) in order to establish if RL should replace NS.

Results

One Cochrane Review was summarized: The Cochrane review undertaken by Burdett *et al*,. (2012) compared perioperative buffered versus non-buffered (normal saline) fluid administration for surgery in adults; in order to review the safety and efficacy of perioperative administration of buffered versus non-buffered (normal saline) fluids for plasma volume expansion or maintenance in adult patients undergoing surgery. Publications from Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 4), MEDLINE (1966 to May 2011), EMBASE (1980 to May 2011), and CINAHL (1982 to May 2011) were included. The reviewers also hand searched conference abstracts and where possible, contacted leaders in the field. Only RCTs of buffered versus non-buffered intravenous fluids for perioperative fluid resuscitation were included. The trials with other forms of comparisons such as crystalloids versus colloids and colloids versus different colloids were excluded. Trials using hypertonic fluids and dextrose-based fluids were excluded. Fourteen publications reporting 13 trials or comparisons with a total of 706 participants were included. The primary outcome of mortality at any time was reported in only three studies (n=267). The mortality rate was 2.9% for the buffered fluids group and 1.5% for the non-buffered fluids group but this difference was not statistically significant. Organ dysfunction was only presented for renal impairment. There was no difference in renal insufficiency leading to renal replacement therapy between the buffered and non-buffered groups (OR 0.61, 95% CI 0.23 to 1.63, P = 0.32, I^2 = 0%). Markers of organ system failure as assessed by urine output, creatinine and its variables (for renal function), $PaC0_2$ (respiratory function) and postoperative nausea and vomiting (gastro-intestinal function) showed a statistically significant difference only in $PaC0_2$ levels. The mean difference was 1.18 with lower $PaC0_2$ levels in the non-buffered fluid group (95% CI 0.09 to 2.28, P = 0.03, I^2 = 0%) compared to the buffered fluid group. There was no difference in intraoperative blood loss nor the volumes of intraoperative red cell or fresh frozen plasma transfused between groups. There was an increase in platelet transfusion in the non-buffered group which was statistically significant after analysing the transformed data (log transformation because the data were highly skewed). A number of metabolic differences were noted. There was a difference in postoperative pH of 0.06 units, lower in the non-buffered fluid group (95% CI 0.04 to 0.08, P < 0.00001, I2 = 74%). However, this difference was not maintained on postoperative day one. There was no difference demonstrated in length of hospital stay and no data were reported on cost or quality of life. ***The reviewers concluded that the administration of buffered fluids to adult patients during surgery is equally safe and effective as the administration of non-buffered saline-based fluids.*** The use of buffered fluids is associated with less metabolic derangement, in particular hyperchloraemia and metabolic acidosis. (Burdett *et al., 2012)*

The following three randomized control trails (one being an exploratory study within an RCT), one meta-analysis and one retrospective outcome study were submitted and reviewed. The Young et al study was published in October 2015 during the write up of this review.

Young *et al*., 2015 conducted a double-blind, cluster randomized, double-crossover trial conducted in 4 ICUs in New Zealand from April 2014 through October 2014 to determine the effect of a buffered crystalloid compared with saline on renal complications in patients. Three ICUs were general medical and surgical ICUs; 1 ICU had a predominance of cardiothoracic and vascular surgical patients. All patients admitted to the ICU requiring crystalloid fluid therapy were considered for inclusion. Patients with

established acute kidney injury (AKI) requiring renal replacement therapy (RRT) were excluded. All 2278 eligible patients were enrolled; 1152 of 1162 patients (99.1%) receiving buffered crystalloid and 1110 of 1116 patients (99.5%) receiving saline were analysed. Participating ICUs were assigned a masked study fluid, either saline or a buffered crystalloid, for alternating 7-week treatment blocks. Two ICUs commenced using 1 fluid and the other 2 commenced using the alternative fluid. Two crossovers occurred so that each ICU used each fluid twice over the 28 weeks of the study. The treating clinician determined the rate and frequency of fluid administration. The primary outcome was proportion of patients with AKI (defined as a rise in serum creatinine level of at least 2-fold or a serum creatinine level of≥3.96mg/dL with an increase of≥0.5mg/dL); main secondary outcomes were incidence of RRT use and in-hospital mortality. In the buffered crystalloid group, 102 of 1067 patients (9.6%) developed AKI within 90 days after enrollment compared with 94 of 1025 patients (9.2%) in the saline group (absolute difference, 0.4%[95%CI, −2.1%to 2.9%]; relative risk [RR], 1.04 [95%CI, 0.80 to 1.36]; P = .77). In the buffered crystalloid group, RRT was used in 38 of 1152 patients (3.3%) compared with 38 of 1110 patients (3.4%) in the saline group (absolute difference, −0.1% [95%CI, −1.6%to 1.4%]; RR, 0.96 [95%CI, 0.62 to 1.50]; P = .91). Overall, 87 of 1152 patients (7.6%) in the buffered crystalloid group and 95 of 1110 patients (8.6%) in the saline group died in the hospital (absolute difference, −1.0% [95%CI, −3.3%to 1.2%]; RR, 0.88 [95%CI, 0.67 to 1.17]; P = .40). ***Among patients receiving crystalloid fluid therapy in the ICU, use of a buffered crystalloid compared with saline did not reduce the risk of AKI.***

Smith *et al.,* (2015) conducted an exploratory analysis in a subset of participants from a larger RCT, comparing the effect of resuscitation with normal saline (NS) versus Plasma-Lyte A (PLA) on acidosis and electrolyte abnormalities. Since metabolic acidosis has been associated with coagulopathy, the study sought to explore whether resuscitation of injured patients with a balanced crystalloid solution affects coagulation, as measured by endogenous thrombin potential (ETP) and thromboelastography (TEG). Among 18 evaluated subjects, at 6 h, subjects receiving NS were more acidaemic. At 6 h, there were no differences in ETP parameters between groups; however, TEG results showed the time from initial clot formation to an amplitude of 20 mm (K) was shorter (3.8 ± 2.1 vs. 7.2 ± 2.8 s) and the rapidity of fibrin build-up and cross-linking (α angle) was significantly greater (41 ± 8 vs. 24 ± 15 deg) for the PLA group than in the isotonic saline group. ***The conclusion was that relative to PLA, NS does not alter thrombin generation, but isotonic saline and PLA may differentially impact clotting factor availability. "The results suggest that resuscitation with saline may impair the clotting process and perhaps contribute obliquely to post injury coagulopathy."***

Krawjewski *et al*., (2014) conducted a meta-analysis on 21 studies (n= 6253) to assess the relationship between the chloride content of intravenous resuscitation fluids and patient outcomes in the perioperative or intensive care setting. The primary outcomes of interest were mortality, measures of kidney function, serum chloride, hyperchloraemia/metabolic acidosis, blood transfusion volume, mechanical ventilation time, and length of hospital and intensive care unit stay, high-chloride fluids did not affect mortality but were associated with a significantly higher risk of acute kidney injury (RR 1.64, 95 per cent c.i. 1.27 to 2.13; P <0.001) and hyperchloraemia/metabolic acidosis (RR 2.87, 1.95 to 4.21;P *<0.001).* High-chloride fluids were also associated with greater serum chloride (Mean Difference 3.70 (95 per cent c.i. 3.36 to 4.04) mmol/l; P <0.001), blood transfusion volume (Standardized Mean Difference 0.35, 0.07 to 0.63; P =0.014) and mechanical ventilation time (SMD 0.15, 0.08 to 0.23; P <0.001). ***The authors concluded that a weak but significant association between higher chloride content fluids and unfavorable outcomes was found, but mortality was unaffected by chloride content.***

Gunnerson et al., 2006 conducted a retrospective outcome evaluation of critically ill patients in an ICU environment (n=9799). They concluded that not all metabolic acidosis are the same. Through the cohort study, the researchers showed that each type of metabolic acidosis had a different mortality associated with it. There was increased mortality associated with lactate and unidentified anions (SIG). Metabolic acidosis (both lactic and non-lactic) was associated with high mortality and increased length of stay in hospital and in the ICU. This study did not compare specific IV fluids and its relation to metabolic acidosis. A total of 548 patients (64%) had a metabolic acidosis (standard base excess < -2 mEq/l) and these patients had a 45% mortality, compared with 25% for those with no metabolic acidosis ($p < 0.001$). Metabolic acidosis cases were sub classified on the basis of the predominant anion present (lactate, chloride, or all other anions). The mortality rate was highest for lactic acidosis (56%); for strong ion gap (SIG) acidosis it was 39% and for hyperchloremic acidosis 29% ($p < 0.001$). Of relevance was that hyperchloraemic acidosis was associated with mortality similar to that of the non-acidotic group (29% versus 26%; p = NS), despite many cases of hyperchloremic acidosis occurring in the NS group (that can mostly be avoided by resuscitating with a more balanced solution such as RL). ***This study was not a direct comparison of RL to NS but reviewed more the "condition" of metabolic acidosis and it's outcomes.***

Waters et al., (2001) sought to determine if metabolic acidosis and changes in serum osmolarity are consequences of 0.9% normal saline (NS) solution and if administration influences patient outcome. In a double blinded study patients undergoing aortic reconstructive surgery were randomly assigned to receive lactated Ringer's (LR) solution (n =33) or NS (n= 33). Anesthetic and fluid management were standardized. Multiple measures of outcome were monitored. ***The NS patients developed a hyperchloremic acidosis and received more bicarbonate therapy (30±62mLin the NS group versus 4±16mLin the LR group; mean±sd), which was given if the base deficit was greater than 5 mEq/L. The NS patients also received a larger volume of platelet transfusion (478 ± 302 mL in the NS group versus 223±24 mL in the LR group; mean ± sd). When all blood products were summed, the NS group received significantly more blood products (P=0.02). No difference in the postoperative complications nor death was seen. No difference was seen in the ventilator time (45.6 ± 147.2 h in the LR group versus 29.7 ± 61.8 h in the NS group), ICU time (4.1 ± 7.6 days in the LR group versus 2.8 ± 3.8 days in the NS group), nor hospital stay (10.1 ± 8.3 days in the LR group versus8.9 ± 4.7 h in the NS group). A significant difference in the volume of bicarbonate (3.8 ± 15.5 mL in the LR group versus 40.2 ± 64.0 mL in the NS group) used during the operative period was seen but there was no difference in the postoperative period. These changes should be considered when choosing fluids for surgical procedures involving extensive blood loss and requiring extensive fluid administration.***

Table 1: Evidence table of RCTs identified for this review

Study (year)	Study design	Participants (studies) Follow up	Study comparators	Summary of findings					Quality of study	Risk of bias
				Study event rates (%)		Absolute risk reduction (95% CI)	NNT/NNH:	Relative risk: (95% CI)		
				Intervention	Comparator					
Smith et al., 2013	Prospectively planned exploratory sub study within an RCT	n=18	Isotonic saline vs. Plasma-Lyte A (PLA)	***Primary outcome:*** Endogenous thrombin potential (ETP) or thrombogram, which correlates with both hypercoagulable and hypocoagulable states. Thromboelastography (TEG), a whole blood-based examination of global hemostasis. "There were no significant differences between the isotonic saline and PLA groups for any of the ETP parameters (t-lag, t-max, C-max, or AUC) measured at 0 or 6 h. Baseline values on admission for R, K, α angle, maximum amplitude were similar between the isotonic saline and PLA groups. At 6 h, the α angle was significantly greater and there was a trend toward K being shorter in the PLA group vs. the isotonic saline group [41_8 vs. 24_15 degrees (P=0.008) and 3.7±2.1 vs. 7.2±2.8 s (p=0.06), respectively]."					Study groups were similar at baseline Small number of participants Patients were randomized in the parent study and parent study was powered to determine differences in acidosis and base deficit, however it was not designed to detect differences in coagulation parameters. TEG analysis performed on frozen plasma.	n/a

Krajewski et al., 2014	Systematic searches of PubMed/MEDLINE, Embase and Cochrane Library (CENTRAL) databases in accordance with PRISMA guidelines. RCTs and observational studies included	21 studies involving 6253 patients		***Primary outcome:*** Mortality, measures of kidney function, serum chloride, hyperchloraemia/metabolic acidosis, blood transfusion volume, mechanical ventilation time, and length of hospital and intensive care unit stay High-chloride fluids did not affect mortality but were associated with a significantly higher risk of acute kidney injury (RR 1.64, 95 per cent c.i. 1.27 to 2.13; P <0.001) and hyperchloraemia/metabolic acidosis (RR 2.87, 1.95 to 4.21;P <0.001). High-chloride fluids were also associated with greater serum chloride (MD 3.70 (95 per cent c.i. 3.36 to 4.04) mmol/l; P <0.001), blood transfusion volume (SMD 0.35, 0.07 to 0.63; P =0.014) and mechanical ventilation time (SMD 0.15, 0.08 to 0.23; P <0.001). MD = mean difference and SMD – standardized mean difference.	Conducted sensitivity analyses Risk of bias was assessed using for RCTs, the seven-category Review Manager risk of bias tool and for non-RCTs, the Newcastle–Ottawa Scale (NOS) was used	
Gunnerson et al., 2006	Retrospective outcome evaluation	Cohort of patients in which lactic acidosis was suspected but, other acid–base abnormalities might be present. Resulted in 9,799 ICU admissions being identified. 548 patients (64%) had a metabolic acidosis (standard base excess < -2 mEq/l)		***Primary outcome:*** Mortality in metabolic acidosis patients 45% mortality, compared with 25% for those with no metabolic acidosis (p < 0.001). Metabolic acidosis cases were sub classified on the basis of the predominant anion present (lactate, chloride, or all other anions). The mortality rate was highest for lactic acidosis (56%); for strong ion gap (SIG) acidosis it was 39% and for hyperchloremic acidosis 29% (p < 0.001).	Retrospective study which means some patients data might have not have been included if variables were missing. Unable to control for severity of illness between groups. The classification scheme used might have resulted in a combined lactic/SIG acidosis being misclassified as hyperchloremic. Hyperchloremic cases could have been misclassified as either SIG or lactic acidosis if pre-existing or concomitant metabolic alkalosis was also present, decreasing the apparent impact of chloride.	Attrition: 1 pt in each group lost to follow up.

Waters *et al*., 2001	Double blinded study	Sixty-six patients (33 patients in the Ringers Lactate group, 33 patients in the NS group)	Ringers Lactate vs Normal Saline	***Primary outcome:*** Metabolic Acidosis NS resulted in significantly more acidosis on completion of surgery. This acidosis resulted in no apparent change in outcome but required larger amounts of bicarbonate to achieve predetermined measurements of base deficit and was associated with the use of larger amounts of blood products. ***Secondary outcome(s):*** Duration of mechanical ventilation, intensive care unit stay, hospital stay, and incidence of complications *No differences noted*	Sample size might not have been powered enough to find differences in the sub group analyses/multiple outcomes	
Young et al., 2015	Double-blind, cluster randomized, double-crossover trial	3 ICUs. All 2278 eligible patients were enrolled; 1152 of 1162 patients (99.1%) receiving buffered crystalloid and 1110 of 1116 patients (99.5%) receiving saline were analysed	Buffered crystalloid compared with saline on renal complications in patients	***Primary outcome:*** The primary outcome was proportion of patients with Acute Kidney Injury defined as a rise in serum creatinine level of at least 2-fold or a serum creatinine level of≥3.96mg/dL with an increase of≥0.5mg/dL); In the buffered crystalloid group, 102 of 1067 patients (9.6%) developed AKI within 90 days after enrollment compared with 94 of 1025 patients (9.2%) in the saline group (absolute difference, 0.4%[95%CI, −2.1%to 2.9%]; relative risk [RR], 1.04 [95%CI, 0.80 to 1.36]; P = .77). ***Secondary outcome(s):*** Incidence of RRT use and in-hospital mortality. In the buffered crystalloid group, RRT was used in 38 of 1152 patients (3.3%) compared with 38 of 1110 patients (3.4%) in the saline group (absolute difference, −0.1% [95%CI, −1.6%to 1.4%]; RR, 0.96 [95%CI, 0.62 to 1.50]; P = .91). Overall, 87 of 1152 patients (7.6%) in the buffered crystalloid group and 95 of 1110 patients (8.6%) in the saline group died in the hospital (absolute difference, −1.0% [95%CI, −3.3%to 1.2%]; RR, 0.88 [95%CI, 0.67 to 1.17]; P = .40).	Saline use is associated with the development of hyperchloremia and metabolic acidosis and the occurrence of these phenomena may have led clinicians to correctly deduce which fluid was which over the course of a block of treatment. Sample size calculations not performed 90% of patients might have recievd fluids before ICU admission.	n/a

Evidence Quality

Young et al.,(2015) did not perform sample size calculations. Dealing with a critically ill population more than 90% of patients were exposed to intravenous fluids before enrolment and the majority of pre-enrollment fluid was buffered crystalloid.

The Smith et al., (2015) study was limited by it being exploratory on a small sample size of RCT patients (n=18). Study groups were similar at baseline. The TEG analysis was conducted on frozen plasma and not on whole blood. Although groups were similar at baseline, the small number of participants limited the study's power to detect differences in coagulation parameters.

The Krawjewski et al., (2014) meta-analysis prompted caution with the intravenous administration of supraphysiological concentrations of chloride (above 111 mmol/l). However, most of the studies included in the meta analysis were small in size, thereby preventing firm conclusions from being drawn.

The Gunnerson et al., study (2006) has several limitations. The researchers conducted a retrospective study which means some patients data might have not have been included if variables were missing. Secondly, the researchers were unable to control for severity of illness between groups. The classification scheme used might have resulted in a combined lactic/SIG acidosis being misclassified as hyperchloremic. Conversely, some hyperchloremic cases could have been misclassified as either SIG or lactic acidosis if pre-existing or concomitant metabolic alkalosis was also present, decreasing the apparent impact of chloride.

A limitation of the Waters et al., study (2001) is that the sample size was not large enough to detect a meaningful difference on the various outcomes discussed.

Safety Information

In a review, Prough and Bidani (1999) indicated that most literature indicates that hyperchloraemic acidosis is not hazardous. However, correct treatment is dependent on differentiating between hyperchloraemic acidosis vs lactic acidosis.

Summary

No studies were found directly comparing NS and RL in haemorrhagic shock and in critically ill patients. However, the recent SPLIT Trial, conducted in critically ill patients, assessed effect of a buffered crystalloid compared with saline on renal complications in patients in New Zealand and concluded that use of a buffered crystalloid compared with saline did not reduce the risk of Acute Kidney Injury." (Young *et al*.,2015) . Other studies outlined above showed that that the administration of buffered fluids to adult patients during surgery is equally safe and effective as the administration of non-buffered saline-based fluids. One study did show that isotonic saline and PLA may differentially impact clotting

factor availability (Smith *et al*., 2015). Krawjewski *et al*. (2014) showed that there was a weak but significant association between higher chloride content fluids and unfavorable outcomes, but mortality was unaffected by chloride content. Waters *et al*. (2001) raise the point that because NS causes hyperchloremic acidosis and a significant difference in the volume of bicarbonate required during the operative period with NS was noted; such changes should be considered when choosing fluids for surgical procedures involving extensive blood loss and requiring extensive fluid administration.

Overall, the majority of current data might not be considered robust to select one treatment over the otehr, and limited to small RCTs and observational studies. The recent study in New Zealand did not show reduced risk in negative renal outcomes in using a buffered solution.

Further large randomized clinical trials are needed to assess efficacy in higher-risk populations and to measure clinical outcomes such as mortality. Evidence is limited regarding the effects of hyperchloraemic acidosis on hard clinical outcomes.

References

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