

Impact of intraoperative fluid management on electrolyte and acid-base variables

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Title: Impact of intraoperative fluid management on electrolyte and acid-base variables

Investigators: David P. Martin, Renata Miketic, Ajay D'Mello, Joseph D. Tobias

Describe the background and rationale for this project. Reference to peer reviewed literature is desirable: During major surgical procedures, intravascular volume is maintained with the administration of isotonic fluids such as Lactated Ringers (LR), Normal Saline (NS) or Normosol-R. All three of these fluids are in common clinical use for this purpose. While all of these fluids have sodium concentrations that are close to physiologic levels, they contain varying amounts of chloride and different buffers (none in normal saline, acetate/gluconate in Normosol, and lactate in LR). Prospective trials have failed to show any significant differences in clinical outcomes among these 3 isotonic fluids, although there may be subtle differences in biochemical and electrolyte parameters (sodium and acid-base status). During the intraoperative care of patients undergoing major surgical procedures, acid-base status may be followed as an indirect measure of intravascular resuscitation and tissue perfusion. Inadequate resuscitation may result in a rising lactic acid, which will be reflected as an increasing base excess. However, an increasing base deficit may also occur merely due to the administration of a large volume of normal saline which results in a dilutional acidosis. This dilutional acidosis is not seen when LR or Normosol are used for intraoperative resuscitation. The difference is not easily discernible on standard arterial blood gas analysis and may require additional testing such as measurement of a serum lactate value.

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4. Williams EL, Hildebrand KL, McCormick SA, et al: The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg* 1999;88:999–1003.
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7. Neyra JA, Canepa-Escaro F, Li X, et al; Acute Kidney Injury in Critical Illness Study Group: Association of hyperchloremia with hospital mortality in critically ill septic patients. *Crit Care Med* 2015; 43:1938–1944.
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How will your study be funded (i.e., will you use departmental funds, submit a grant application, etc.): No funding is required.

Provide a potential start date for your study to be included in the IRB application: December 2016

Describe the significance of the proposed research: As large volumes of NS may result in a dilutional acidosis and an increasing base deficit, it may cloud clinical decision making when resuscitative efforts are guided by acid-base status on routine arterial blood gas analysis. The current study will evaluate changes in acid-base and electrolyte (sodium, potassium, calcium) status and lactate values, with the use of various isotonic fluids for intraoperative resuscitation. We hypothesize that the use of a fluid containing a buffer (LR or Normosol) will mitigate acid-base changes during intraoperative care and allow for the use of the base deficit as a surrogate measure of intravascular resuscitation.

State the primary and secondary objectives of the study:

1. The primary objective is to determine differences in acid-base status based on the fluid used for intraoperative status.
2. The second objectives are to determine the following based on the isotonic fluid used for intraoperative resuscitation:
 - a. Differences in electrolyte values (sodium, potassium and ionized calcium) and lactate values
 - b. Differences in intraoperative fluid requirements as judged by heart rate and blood pressure
 - c. Differences in intraoperative urine output

If this research is hypothesis driven, succinctly state the hypothesis:

The intraoperative administration of NS will result in an increase in the base deficit when compared to LR or Normosol-R resuscitation.

Outline the major steps and methodologies in the clinical protocol. If necessary, include a description of any procedures being performed already for diagnostic or treatment purposes.

Inclusion would be:

10-21 years of age

Major surgical procedure requiring arterial access

Exclusion criteria:

Comorbid disease process that contraindicates the use of any of the 3 crystalloid solutions.

The only variable that will be altered for the purpose of the study is the fluid used for intraoperative resuscitation. Although all 3 fluids are commonly used, the choice is based on the discretion of the attending anesthesiologist. For the purpose of this study, randomization will occur so that intraoperative fluid resuscitation/administration will include one of 3 isotonic fluids: NS, LR or Normosol-R.

The anesthetic technique will follow our routine standardized anesthetic for posterior spinal fusion. Premedication will include oral or intravenous midazolam following by anesthetic induction to including either inhalational or intravenous induction. As per our usual routine, two peripheral intravenous cannulas and an arterial cannula will be placed. Maintenance anesthesia will include desflurane (inspired concentration adjusted to maintain the bispectral index at 50-60) and a sufentanil or remifentanil (infusion up to 0.3 µg/kg/hour for sufentanil or 0.3 µg/kg/hour) to maintain the mean arterial pressure at 50-65 mmHg. Additional opioids such as morphine, hydromorphone or methadone may be administered according to the clinical plan per the attending anesthesiologist. Labetolol (0.1-0.15 mg/kg/dose) will be administered as needed to control the MAP if the sufentanil infusion is not effective. Fluid will be administered as clinically indicated based on clinical parameters including heart rate, blood pressure, and urine output. As clinically indicated, arterial blood gas and electrolytes will be analyzed using the point-of-care monitoring (I-stat). At this time, we will also run for lactate values. This is generally obtained 2-4 times during these cases. We will be recording the pre and post Cobb Angle, levels fused of spine, region of spinal fusion, and instrumentation.

Identify the variables to be measured and how they will be statistically evaluated: The primary outcome variable is base deficit. Secondary outcomes include electrolyte values, lactate values, intraoperative fluid requirements, and intraoperative urine output. The primary hypothesis of the study will be evaluated using measurements obtained after administration of fluid (NS, LR, or Normosol, according to randomized assignment) during each procedure. Specifically, the incidence of base deficit in excess of -2 mEq/L will be compared between NS and LR and between NS and Normosol using tests of proportions. In a pilot study enrolling 48 patients, we found that the incidence of base deficit in excess of -2 mEq/L was 15%. The study will be powered to detect an increase in incidence from 15% to 40% between NS and either LR or Normosol, with the overall Type I error set at 0.05 and the significance level of individual tests (NS vs. LR; NS vs. Normosol) adjusted for multiple comparisons using the Bonferroni correction. To attain 80% power for detecting this expected difference, two-

tailed tests of independent proportions will require 60 patients in each group. Therefore, we propose enrolling a total of 180 patients in the study, randomized equally among the 3 groups. For comparison, the proposed sample size will have >99% power to detect a -2 mEq/L difference in base deficit after fluid administration between NS and either LR or Normosol, using ANOVA with a Bonferroni correction for multiple comparisons, and assuming a standard deviation of 2.2 mEq/L based on our pilot data. Continuous data on the primary and secondary outcomes will be evaluated further using mixed effects linear models, to account for repeated measures (including any measures taken prior to fluid administration) and potential time-varying and time-invariant confounding characteristics.