Title: Fluid Resuscitation: 0.9% Normal Saline vs Lactated Ringer's vs Albumin

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PICO:
P: In patients requiring fluid resuscitation
I: Does the use of Lactated Ringer's Solution or Albumin
C: Compared with Normal Saline (0.9%)
O: Provide a better physiologic response to resuscitation?

Clinical Scenario:
A 55 year-old male presents to the ED hypotensive and tachycardiac. You immediately recognize the patient is in shock. The nurse asks what type of fluid you want to use to begin resuscitation. You think for a moment, does it matter which solution I pick? Does it matter what the etiology of his shock state is? How will initial resuscitation fluid impact long-term outcome?

Clinical background:
For over 100 years, there has been significant debate over the merits of various fluid compositions used in adult resuscitation. Traditional dogma has stated that medical physicians rely upon 0.9% Normal Saline while their surgical counterparts have declared Hartmann's Lactated Ringer's Solution to be the "only" physiologic compound available. The debate has expanded beyond the realm of crystalloid solutions to include colloids (Albumin, blood) to see if there is a better physiologic response with this class of fluid. Patients requiring acute resuscitation and critical care management are susceptible to metabolic changes induced during resuscitation, particularly with the parameters of morbidity (neurologic recovery, coagulation, response to therapeutic interventions, etc) and mortality, particularly during the acute phase of treatment. This literature review will explore the physiologic and metabolic changes associated with these various solutions.

Parameter	Human serum	0.9% NaCl	Lactated Ringer's	Albumin 5%
$[Na^+]$ (mmol/l)	135–145	154	131	140
$[K^+]$ (mmol/l)	3.5–5.3	-	5	-
$[Ca^{2+}]$ (mmol/l)	2.2–2.6	-	2	-
$[Cl^-]$ (mmol/l)	95–105	154	111	128
$[HCO_3^-]$ (mmol/l)	24–32	-	29	-
Albumin (g/L)	30 to 50	-	-	50 g/L
$[Na^+]/[Cl^-]$ ratio	1.28 : 1–1.45 : 1	1 : 1	1.18:1	1.09:1
pH	7.35–7.45	5.4	6.0	
Osmolality (mOsm/kg)	275–295	308	276	265

Search Outcome:

Authors, Date, and Country	Study populations	Study Type (Level of evidence)	Outcomes	Key Results	Study Limitations
SAFE Study 2004 Australia and New Zealand	6997 ICU patients receiving fluid resuscitation (3497 w/ albumin vs 3500 w/ NS)	Multicenter, randomized double-blind clinical trial	Mortality (death) after 28 days of ICU fluid resuscitation	No statistical difference between groups: no change in mortality, length of ICU stay, hospital stay, days on vent, or days of renal replacement therapy 726 deaths (Albumin) vs 729 (NS); RR= 0.99, 95% CI P= 0.87 Less fluid volume required in albumin group Subgroup analysis: Worse outcomes in trauma w/ albumin vs NS (RR 1.36, p=0.04); worse with NS vs albumin in severe sepsis (RR=0.87, p=0.06) and ARDS (RR= 0.93, p=0.74)	Low power for subgroup analysis
Bellomo, Rinaldo, Morimatso, Hiroshi, et al 2006 Australia	691 ICU patients receiving fluid resuscitation (339 w/albumin and 352 w/NS)	Prospective, randomized, double-blind clinical trial (nested cohort study) Subset of SAFE study	Measured chemistry changes (serum electrolytes, pH, albumin) over 4 day period of ICU resuscitation	No statistical difference in pH, or BE in NS vs albumin Slightly greater Cl levels with albumin during acute resuscitation on 1st day End points had greater influence by pt's age, illness severity, severe sepsis and amount of fluid given (on Multivariate analysis)	Pt's did not receive high volume resuscitation (small proportion to get > 3L per day) Used 4% Albumin (vs 5% or 25% available in US) No discussion of clinical outcomes
Reid, Fiona, Lobo Dileep, et al 2003 UK	9 healthy adult male volunteers	Prospective double blind crossover	Compare responses to 2-L infusions Extent and time course for changes in: body wt, serum Hct, Electrolytes, albumin, pH and urinary response	Higher fluid retention w/ NS (wt, ↓ Hct & alb) Expanded Blood Vol with NS (483mL vs 369; 24.1% volume expansion efficiency vs 18.8% LR) Decreased urine volume with NS	Small population Size Use of "young healthy adults"

				Shorter time to urination with LR (↓ADH with lower Osmol?) Sustained hypercholemeia with NS	
O'Malley, Catherine M.N., Frumento, Robert J., et al. 2005 NY, USA	51 patients undergoing intraoperative fluid replacement during kidney transplantation	Prospective, randomized, double-blind clinical trial	Effect of fluid on transplant function (Cr) Effect on serum K+ and pH Safety of LR in renal transplants	No statistical difference in Cr levels 19% had elevated K+ with NS vs 0% with LR (p=0.05) 31% required Rx for acidosis with NS vs 0% w/ LR (p=0.004)	Relevance to acute (ED) resuscitation Small study size Baseline abn serum chemistries
Waters, Jonathan H., Gottlieb, Alexandru, et al. 2001 OH, USA	66 patients undergoing fluid management during AAA repair	Prospective, randomized, double-blind clinical trial	Evaluation of clinical outcomes (i.e. requirement for additional medical intervention such as Bicarb or blood products) Differences in serum electrolytes, BE	No differences seen in death, post-op complications, time on vent, ICU time, hospital stay ↑ UOP w/ NS vs LR (1200 mL vs 975 mL) intraoperative ↑↑ Bicarb use w/ NS vs LR for acidosis intraoperatively (3.8± 15.5 mL vs 40.2± 64.0 mL) → difference resolved in post-op period More fluid needed in pt's with NS Higher use of blood products (FFP) w/ NS	Intra-operative (relevance to ED care) Statistics do not provide p values for most end-points reported
Baker, Andrew J, Park, Eugene, et al. 2008 Toronto, Canada	Lab rats with produced TBI and hemorrhage	Prospective animal model; four groups (NS vs hypertonic saline vs albumin vs blood)	Neurophysiologic outcomes as determined by regional blood flow, co-oximetry, and hippocampal neurotransmission	Immediate ↑ in MAP w/ NS, but eventual decline vs Immediate & sustained ↑ in MAP w/ albumin ↑ Hippocampal response w/ albumin than NS Best results w/ blood & albumin vs NS & 3%NS (EPS, MAP, O2)	Animal Study No effect studied on survival or clinical neurologic recovery

Healy, Mark, Davis, Richard, et al. 1998 Saskatchewan, Canada	Animal Model (Swine; n=31) to reproduce moderate and severe hemorrhage	Prospective animal model; four groups (LR-B v NS-B); moderate vs severe hemorrhage	Serum Hct and biochemistries (electrolytes & pH) Survival Outcomes	100% survival in ModHR; MAP/BP restored quicker and w/ less fluid in NS vs LR; no change in serum lytes MHR had lower survival with NS-B vs LR-B; rates of BP resuscitation were equal; ↑ acidosis, base deficit , and Cl with NS-B ↑acidosis in non-survivors (only difference in chemistries)	Animal Study Small study sizes
Kiraley, Laszlo, Differding, Jerome A., et al 2006 Oregon, USA	Animal model (Swine, n=20) with reproduced uncontrolled hemorrhage	Prospective, blinded, animal model	R value (reaction time to clot formation), PT, PTT, and fibrinogen levels s/p grade V liver lac and resuscitation (NS vs LR)	Blood loss ↑ in NS vs LR ($p=0.009$) Decreased R value, CoAgs with LR vs NS w/ increasing difference from NS over time (i.e. ↑'ed hypercoaguability; no hypocoaguablitiy in NS; $p<0.05$) NS group required greater fluid volume to maintain MAP (10.9 vs 5.2 L) NS > acidosis than LR with greater change over time	Animal Study Small study sizes Fluid Amount was variable, w/ target of baseline MAP vs set value (traditionally 60 mmHg in such models)
Todd, S. Rob, Malinoski, Darren, et al. 2007 TX, USA	Animal model (Swine, n=20) with reproduced uncontrolled hemorrhage	Prospective randomized, controlled, blinded	Serum chemistries, ABG, lactate, and CoAgs s/p induced hemorrhage and resuscitation	Significantly more NS needed than LR to maintain MAPs (256.3± 145.4 mL/kg vs 125.7± 67.3; $p=0.04$) Greater UOP w/ NS vs LR (46.6± 39.5 mL/kg vs 18.9± 12.9, $p=0.04$) Hyperchloremia (119± 1.9 vs 105± 2.9 $p<0.01$) and acidosis (7.28± 0.12 vs 7.45± 0.06, $p<0.01$) seen w/ NS vs LR; however, elevated lactate levels w/ LR ↑ PT and ↓ Plt's and fibrinogen levels in NS vs LR	Animal Study Small study sizes

Philips, Charles R., Vinecore, Kevin, et al. 2009 OR, USA	20 swine undergoing grade V liver injury and bled for 30 minutes before resuscitation (10 w/ NS and 10 with LR)	Prospective, randomized, double-blind animal model	Evaluation of extravascular lung water index (EVLWI) and oxygenation (PaO2/FiO2) with resuscitation of LR vs NS	Both fluids ↑ EVLWI, but NS>LR at same amounts of vol. ($p=0.020$) with greatest impact earlier in resusc. BP response lower in NS (NS 56.9± 1.6 mmHg vs. LR 64.0± 2.0 mmHg; $p = 0.01$) despite requiring more total fluid over the entire study period (NS 330.8 ± 38.1 ml/kg vs. LR 148.4 ± 20.2 ml/kg; $p = 0.009$) No significant change in oxygenation w/ either solution (until levels of 250mL/kg)	Animal Study Small Sample Size
McIntyre, Lauralyn, Hébert, Paul, et al 2007 Ottawa, Canada	Canadian ICU physicians (Medicine, Anesthesia, Surgery); 232/355 responses (65.3%)	Survey- 5 point Likert Scale (always, often, sometimes, rarely, never)	Assess clinical practices for fluid selection and target endpoints of therapy for ICU resuscitation	Used "always" or "often": oxygen saturation (100%), foley catheters (100%), art-lines (96.6%), and CVP (89.2%) Clinical endpoints: UOP and BP (96.5% and 91.8%, respectively) Selection of fluids: NS, LR, and Albumin 5%= 84.5%, 52.2%, and 3.9%, respectively	Subjective Survey Response bias (desired response vs clinical practice)

Comments:

Animal models have been utilized for re-creation of massive hemorrhage and resuscitation due to challenges in low study numbers, urgency of patient care, and patient characteristic heterogeneity (age, co-morbidities, mechanism of injury, and pre-hospital time/therapy).

The L-lactate used in lactated Ringer's solution is thought to be through two different mechanisms:

1) gluconeogenesis
2) oxidation

Lethal triad of trauma: acidosis, coagulopathy, and hypothermia

Clinical bottom line

1. 0.9% NS causes a normal anion gap hyperchloremic acidosis as well as moderating coagulation in models of hemorrhage (elevated serum coagulation levels, decreased fibrinogen, and increased blood loss) compared with LR and 5% Albumin solutions.

2. There are conflicting results on the efficacy of NS on retained volume resuscitation, although most studies suggest LR and Albumin have better responses (in terms of MAP and BP) with less volume of solution administered. Normal saline appears to have greater response in urinary output (supported in all studies, except for study by Reid, F, Lobo, D., et al).

3. Limited subgroup analysis suggests that albumin may have a detrimental effect on patients with trauma (SAFE study); unclear if it may be advantageous for trauma associated with traumatic brain injury (Baker, A., Park, E, et al).

4. Limited studies for head-to-head-to-head comparison between NS, LR and 5% Albumin

5. Most recent data limited on human participants/clinical trials→ resultants effects based on bench/lab studies with theoretical clinical application

6. **No "magic bullet" resuscitation fluid. Further clinical studies may reveal use of each solution for particular clinical situations (shock due to trauma vs sepsis). LR appears to have greatest impact on volume replacement with fewest metabolic derangements and, therefore, may be the fluid of choice for acute ED resuscitation.**

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