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**Article Appraisal**

**Article:   Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia: The SALSA Randomized Clinical Trial**

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**Background and Study Objective(s):**

Hyponatremia is the most common electrolyte imbalance. In the emergency department it is particularly important to recognize and treat symptomatic hyponatremia quickly, effectively, and safely. Under correction of hyponatremia increases risk of seizures, brain swelling, and may be insufficient to alleviate symptoms, whereas overcorrection puts people at risk of osmotic demyelinating syndrome (ODS). 3% hypertonic saline is the accepted treatment for symptomatic hyponatremia. There is some variability internationally in terms of the recommended method of delivering the hypertonic saline. Rapid boluses vs continuous infusion. North America and European guidelines recommend bolus therapy, whereas in South Korea, where this trial was done, most physicians use continuous infusion. The objective of the RCT is to examine two different ways of administering hypertonic saline for its efficacy and safety profile, namely, the incidence of overcorrection in each method.

Primary outcome was the incidence of overcorrection (> 12 mmol/L increase at 24 hours or >18 mmol/L increase at 48 hours). Secondary outcomes include symptom resolution at 24 and 48 hours; time to an increase in sNa of 5 mmol/L; time to achievement of >130 mmol/L; incidence of target correction rate, (5 to 9 mmol/L within 24 hours and 10 to 17 mmol/L within 48 hours); length of hospital stay; incidence of additional treatment; incidence of ODS; incidence of relowering treatment; and change in GCS.

**Study Design:**

The study is a prospective, open label, randomized controlled trial that took place in multiple hospitals in South Korea in a 3-year period ending in 2019. They recruited patients who were ≥ 18 years old with a glucose corrected initial Na of ≤ 125 mmol/L. There were many exclusion criteria, including primary polydipsia (urine osmolality ≤100 mOsm/kg), pregnancy, breastfeeding, anuria, hypotension, decompensated liver cirrhosis, or uncontrolled diabetes mellitus. Patients were also excluded if they had a history of cardiac surgery, ACS, sustained VT/VF, cerebral trauma, or increased intracranial pressure within the 3 months prior to randomization. They first stratified the patients based on symptom severity. Moderate symptoms include nausea, headache, drowsiness, general weakness, and malaise. Severe symptoms include vomiting, stupor, seizure, and GCS < 8. After stratifying 1:1, the patients are randomized in to either the rapid intermittent bolus (RIB) group or the slow continuous infusion (SCI) group in blocks of 2, 4, 6, and 8. Allocation sequence was blinded to the researchers but not the study coordinators, and treatment was blinded to the analysts but not blinded to the patients or MRP.

In the rapid intermittent bolus group, moderately symptomatic patients received 1 bolus of 3% saline at 2ml/kg, whereas severely symptomatic patietns received 2 such boluses up front, both over 20 minutes. After which, serum Na was remeasured at 1 hour, and Q6H until 48 hours. Further intervention or relowering therapy (with D5W or desmopressin) depended on the Na level found at each time point. See the flow chart at the bottom.

In the slow continuous infusion group, moderately symptomatic patients received 0.5ml/kg/hr of 3% saline, whereas severely symptomatic patients received 1ml/kg/hr of 3% saline. They also measured serum Na at 1 hour and Q6H until 48 hours. Rates of the infusion were either increased (if undercorrecting), stopped, or relowering therapy was initiated based on the serum Na level. See the flow chart attached.

Statistical analysis was as follows: Binary outcome were compared using χ2 and Fisher exact tests with absolute risk differences and 95% CIs calculated using a Poisson regression with robust error variance. These binary outcomes include the incidence of overcorrection (primary outcome), remaining symptoms, target correction rate, incidence of additional treatment, ODS, and relowering treatment. In contrast, the non-binary outcomes were analyzed using t test or Mann- Whitney U test. The mean difference was calculated using a linear regression. These non-binary secondary outcomes include differences in changes in GCS between pretreatment and 24 and 48 hours, time to achieved sNa 5 mmol/L or greater or sNa greater than 130 mmol/L for the first time, and length of hospital stay. Two-sided p values of less than 0.05 was considered statistically significant.

**Results:**

The 178 patients (mean age, 73.1 years; mean sNa concentrations, 118.2 mmol/L) were randomly assigned to the RIB group (n = 87) or the SCI group (n = 91). The causes of hyponatremia were use of thiazide diuretics (n = 53 [29.8%]), syndrome of inappropriate antidiuresis (n = 52 [29.2%]), adrenal insuffi- ciency (n = 29 [16.3%]), decreased extracellular cellular fluid volume due to nonrenal sodium loss (n = 25 [14.0%]), and in- creased extracellular fluid volume (n = 19 [10.7%]). Of all the patients, hypertonic saline was initiated in the emergency department and general ward in 74% and 26%, respectively.

Incidence of overcorrection were not statistically different between the two groups. Overcorrection occurred in 15 of 87 (17.2%) and 22 of 91 (24.2%) patients in the RIB and SCI groups, respectively (absolute risk difference, −6.9% [95% CI, −18.8% to 4.9%]; P = .26).

The RIB group showed lower incidence of relowering treatment than the SCI group (36 of 87 [41.4%] vs 52 of 91 [57.1%] patients, respectively; absolute risk difference, −15.8% [95% CI, −30.3% to −1.3%]; P = .04; number needed to treat, 6.3). RIB, when compared with SCI, showed better efficacy in achieving target correction rate within 1 hour (intention-to-treat analysis: 28 of 87 (32.2%) vs 16 of 91 (17.6%) patients, respectively; absolute risk difference, 14.6% [95% CI, 2%-27.2%]; P = .02

Groups did not differ in terms of efficacy in increasing sNa concentrations nor improving symptoms. No difference was noted in any other secondary outcome measures or post-hoc analyses. No patients developed ODS.

**Validity of Results:**

This study addressed a focused clinical question with objective, clinically relevant outcomes. It is specifically examining the efficacy and safety of RIB vs SCI of hypertonic saline in symptomatic hyponatremia. No competing interests or funding were identified, and the study contributors are clearly identified. The randomization methods were good, though the patients and MRP were not blinded to the treatment method.

One major comment is that there is a discrepancy between the definition of overcorrection (> 12 mmol/L correction within 24 hours or > 18 mmol/L within 48 hours) and their “target rate of correction”, which was 5 – 9 mmol/L in the first 24 hours. Their algorithm indicates that they relowered the patients if the target rate was overshot, so if patients corrected ≥ 10mmol/L in the first 24 hours. Therefore, their incidence of overcorrection taken at 24 and 48 hours may be an underestimation, as they were relowering people at ≥ 10mmol/L instead of 12mmol/L.

**Generalizability of Results:**

This study was conducted in South Korea, where physicians mostly use SCI for treatment of hyponatremia. This is not the case with our EDs. On a quick survey, most of our attendees at journal club used RIB and only 1 has used SCI. It is not practice changing information, though it is helpful for us to think of RIB as the continual “best choice” treatment.

Note also, that because of the numerous exclusion criteria (namely uncontrolled DM, cirrhosis, recent ACS), these results cannot be extrapolated to many of our population.

**The Bottom Line:**

Overall, this is a relatively well-done study though there are some questions of why the target correction rate is different from the definition of overcorrection. It shows that RIB may be marginally safer than SCI as it has a lower rate of using relowering treatment. It also shows that overcorrection incidence is quite high! (17 – 24%) Continue using RIB 3% saline to treat symptomatic hyponatremia and do frequent Na checks to watch for overcorrection.

