

Does the tonicity or rate of intravenous fluid infusion affect neurologic outcomes in children with diabetic ketoacidosis?

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Ratings: Methods – 4/5 Usefulness – 4/5

INTRODUCTION

Background

Prior guidelines for fluid management in pediatric diabetic ketoacidosis (DKA) were based on limited observational data. Rapid fluid administration was thought to cause cerebral injury due to sudden changes in serum osmolality.¹

Objective

To study the effect of different fluid regimens on neurologic outcomes in pediatric DKA.

METHODS

Design

Multicentre randomized, controlled trial (RCT) (2 x 2 factorial design).

Subjects

Children (0–18 years of age) with DKA.

Subjects were excluded if:

- Glasgow Coma Scale (GCS) \leq 11
- Pregnancy
- Treated DKA
- Condition impairing mental status
- Specific intravenous therapy required

Intervention

Fast rehydration with 0.45% or 0.9% NaCl (20 mL/kg bolus, replace half of 10% fluid deficit over 12 hours, remaining deficit over following 24 hours).

Comparison

Slow rehydration with 0.45% or 0.9% NaCl (10 mL/kg bolus, replace half of 5% fluid deficit over 48 hours).

Primary outcome

Neurologic decline (GCS < 14 twice consecutively within an hour of first 24 hours of treatment).

Secondary outcomes

Short-term memory loss in first 24 hours; clinically apparent brain injury; follow-up neurologic outcomes.

RESULTS

In total, 1,389 cases from 1,255 patients were included in the study. Ultimately, 1,361 cases were analysed for the primary outcome. No statistically significant differences were observed between groups for either the primary or secondary outcomes. Results are shown in [Tables 1](#) and [2](#).

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Table 1. Mental status change by treatment group

| Outcome | Fast administration groups | | Slow administration groups | |
|------------------------|----------------------------|-----------|----------------------------|-----------|
| | 0.45% NaCl | 0.9% NaCl | 0.45% NaCl | 0.9% NaCl |
| No. DKA episodes | 337 | 345 | 338 | 341 |
| Decline in GCS < 14* | 10 (3.0) | 11 (3.2) | 11 (3.3) | 16 (4.7) |
| No. DKA episodes | 344 | 351 | 345 | 349 |
| Clinical brain injury* | 2 (0.6) | 2 (0.6) | 5 (1.4) | 3 (0.9) |

*Reported as number of events and as a percentage; no statistically significant differences observed.

Table 2. Relative risk of mental status change by treatment group

| Outcome | Fast v. Slow | 0.45% v. 0.9% NaCl | Significance |
|-----------------------|----------------------------------|----------------------------------|-----------------------|
| Decline in GCS < 14 | RR = 0.76 (95% CI: 0.44–1.33) | RR = 0.80 (95% CI: 0.46–1.40) | NSS ($p > 0.05$) |
| Clinical brain injury | RR = 0.49 (95% CI: 0.15–1.64) | RR = 1.43 (95% CI: 0.46–4.40) | NSS ($p > 0.05$) |

CI = confidence interval; NSS = not statistically significant; RR = relative risk.

APPRAISAL

Strengths

- Consecutive patient recruitment
- Adequate participant randomization
- Baseline demographic and prognostic factors similar between study groups
- Analysis followed the intention-to-treat principle
- Between group therapy only varied based on treatment group assigned
- Successful follow-up for secondary outcome measures

Limitations

- Low primary outcome event rate predisposing the study to type II error
- Underpowered study due to an over-estimate of the incidence of the primary outcome
- Less than 50% of eligible patients included in the RCT
- 10% of patients were withdrawn by the treating physician
- The study design excluded the sickest DKA patients (GCS \leq 11)
- Physicians were not blinded to treatment group
- Total of 134 patients enrolled in the study more than once

CONTEXT

Increased rates of cerebral edema were not seen with rapid infusion of hypotonic fluids.² This should challenge the commonly cited “osmotic shift” theory which has long dictated DKA resuscitation guidelines. The fact that some trial results suggest better neurologic outcomes in the rapid infusion group [specifically, the highest rate of GCS decline [4.7%] was seen in the slow 0.9% NaCl arm] warrants re-evaluation of existing hospital treatment protocols, exploration of alternative hypotheses behind DKA-related cerebral edema, and replication of this study design in a sicker cohort of DKA patients.³

BOTTOM LINE

This was the first well-designed RCT to study the commonly held belief that rapid intravenous infusion can cause cerebral edema in DKA. Although both the lack of physician blinding and the inadequate power to detect between group interaction effects represent significant study limitations, the results of this study have already led to updated clinical practice guidelines.⁴ For pediatric rehydration, it is reasonable to use either 0.45% or 0.9% NaCl and to use a rapid or slow rate of intravenous rehydration (replacing 5%–10% of body weight over 24–48 hours) as detailed in the study protocol.

Keywords: Pediatrics, DKA, IV Fluid

Competing interests: None declared.

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