Improving outcomes in acute life threatening emergencies

Ph.D. thesis

Gergő Vilmos Szabó M.D.

Translational Medicine Program

Pharmaceutical Sciences and Health Technologies Division

SEMMELWEIS UNIVERSITY

Supervisor:	Zsolt Molnár, M.D., Ph.D., Prof.
Head of the Complex Examination Committee:	Gábor Varga Ph.D., D.Sc., Prof.
Members of the Complex Examination Committee:	Tamás Tényi M.D., Ph.D., D.Sc., Prof., Kinga Farkas, M.D., Ph.D., Péter Fehérvári Ph.D., Mitja Lainscak M.D., Ph.D., Prof
Opponents:	Tihamér Molnár M.D., Ph.D., Prof.
	Ivica Grgurević M.D., Ph.D., Prof.

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1.Introduction

1.1. What is the topic?

The focus of my research has been on how to improve outcomes in acute life-threatening emergencies, especially evaluating the utility of Point of Care Ultrasound (PoCUS) in patients treated with acute onset dyspnea and finding the best type of infusion in adult patients admitted with Diabetic ketoacidosis (DKA).

1.2. What is the problem to solve?

Patients with shortness of breath often do not have time to wait for conventional testing methods, and in patients hospitalised for DKA, inadequate fluid supplementation can cause serious side effects.

1.3. What is the importance of the topic?

1.3.1. Study I.

Acute-onset dyspnea is one of the most common symptoms for which patients visit the Emergency Department (ED). In addition to its high incidence, the 30-day mortality rate of these patients remains relatively high (8–13%). Therefore, rapid and appropriate diagnosis of

the underlying pathology is of utmost importance for prompt and adequate treatment. However, differential diagnosis is often challenging.

1.3.2. Study II.

DKA is an acute life-threatening condition. The classic clinical triad in DKA is hyperglycaemia, ketosis, and acidosis. Fluid therapy, in addition to the control of electrolyte balance and insulin therapy, is one of the cornerstones of DKA management. The most frequently applied crystalloid solution in DKA treatment is 0.9% sodium chloride (saline), however, the chloride and sodium content of 0.9% saline is 154 mEq/L, which is substantially higher than the physiologic concentrations in humans. In contrast, Balanced Electrolyte Solutions (BES) have more physiological properties. Hence, they may be a better alternative for fluid resuscitation in patients admitted with DKA.

1.4. What would be the impact of our research results?

1.4.1. Study I.

There is an increasing body of evidence demonstrating that the accuracy of PoCUS is comparable to the current imaging reference standard chest X-ray. PoCUS has other advantages, such as being free from ionizing radiation, and most importantly can be performed in real-time at the bedside. However, very few trials have examined meaningful clinical outcomes related to PoCUS usage to date and the results on outcome measurements were heterogeneous. Therefore, we conducted a high-quality, comprehensive systematic review and meta-analysis that included the most recent publications that reported clinical outcomes with the use of PoCUS in patients who developed acute onset dyspnea.

1.4.2. Study II.

It may be reasonably stated that although international guidelines still recommend 0.9% saline as the fluid of choice when treating DKA, this recommendation stands only because very few studies have been published comparing BES with 0.9% saline in adults admitted with DKA, and because 0.9% saline is the traditional choice. Therefore, our main aim was to evaluate the effects of

BES compared with 0.9% saline in adult patients admitted with DKA.

2. Objectives

2.1. Study I.: Investigating the clinical value of PoCUS in patients with acute onset dyspnea

The early, appropriate management of acute onset dyspnea is important but often challenging. The aim of this study was to investigate the effects of the use of PoCUS versus conventional management on clinical outcomes in patients with acute onset dyspnea.

2.2. Study II.: Investigating the efficacy of balanced electrolyte solutions in patients admitted with diabetic ketoacidosis

Fluid resuscitation is the cornerstone of early management in DKA. Guidelines recommend 0.9% saline as first line choice, although this infusion can cause hyperchloremic metabolic acidosis and impaired renal function. In contrast in BES electrolyte levels are more physiological thereby theoretically it can improve acid base balance. Evidence is still controversial on this topic, therefore in our systhematic review and meta-analysis we compared

the efficacy of 0.9 % saline versus Balanced Electrolyte Solutions in resolving diabetic ketoacidosis in adults.

3.Methods

3.1. Protocol registration and search strategy

Both studies' protocol was prospectively registered via the International Prospective Register of Systematic Reviews (PROSPERO). We report our results following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. We systematically searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) for eligible articles. We also scanned the reference lists of included studies and the cited articles in Google Scholar.

3.2. Selection process and data collection

Only randomized controlled trials (RCTs), and prospective and retrospective cohort studies were eligible for inclusion.

In **study I.** the selected studies had to match our previously defined PICO (Patients, Intervention, Control, Outcome) framework:

- P: Adults and children who were admitted to the ED or to the Intensive Care Unit (ICU), or to another inpatient setting because of acute onset or worsening dyspnea were eligible. We also included studies enrolling patients who developed shortness of breath from unknown etiologies and were already hospitalized.
- I: The examined intervention was PoCUS use on its own or in combination with conventional diagnostic measures.
- C: Control group included conventional diagnostic methods.
- O: For the primary outcomes, we defined time to diagnosis, time to treatment and length of stay (LOS). The secondary outcomes were the following: mortality, rate of appropriate treatment and 30-day re-admission rate.

In **study II.**:

- P: adults who were admitted with DKA
- I: patients who received BES. Infusions considered to be BES were Plasma-Lyte, Ringer's lactate, Isolyte, Sterofundin, Ringerfundin B Braun and Hartmann's solution (BES – group)
- C: in the control group everyone received 0.9% saline (Saline – group).
- O: Our primary outcome was time resolve diabetic ketoacidosis. The more relevant secondary outcomes were: post-resuscitation electrolyte and bicarbonate levels, duration of parenteral insulin administration, amount of total fluid administration and hyperkalaemia.

3.3. Risk of bias, and quality assessment

In both cases the authors independently assessed the risk of bias. In the case of randomized controlled trials, the Revised Cochrane Risk of Bias Tool for randomized trials (RoB 2) was used; in the case of observational studies, the Risk Of Bias In Nonrandomized Studies – of Interventions (ROBINS-I) was applied.

The quality assessment of the included studies was performed with GRADE-Pro (Grading of Recommendations, Assessment, Development and Evaluation–Pro) based on the recommendations of the Cochrane Collaboration.

3.4. Data analysis

In both sutideisFor continuous outcomes, pooled mean differences (MDs), and for dichotomous variables, pooled odds ratios (ORs) along with their 95% confidence interval (CI), were calculated to investigate the differences between the compared arms. Statistical heterogeneity across trials was assessed by means of the Cochrane Q test, and the *I2* values.

4.Results

4.1. Study I.

From 11,630 records finally 8 RCTs and 6 observational studies were processed for data collection. Altogether 5393 patients' data were gathered in this review. PoCUS use compared to controls resulted in a significant reduction in time to making the diagnosis (MD − 63 min;

95% CI − 115 to − 11 min). In the PoCUS group, patients also received treatment significantly earlier (MD − 27 min; 95% CI − 43 to − 11 min) compared to controls. Heterogeneity among these trials for both outcomes was considerable (*I2* = 100% and 88%). As far as in-hospital LOS is concerned, PoCUS use showed no significant effect (MD − 0.02 days; 95% CI − 0.43 to 0.39 days), with low heterogeneity (*I2* = 0%) . Regarding LOS in the ED, there was a mean of 35 min less waiting time to discharge or admission to a ward that proved not significant (MD − 35 min; 95% CI − 93 to 23 min), but heterogeneity was high (*I2* = 84%). Patients in the PoCUS group stayed for a significantly shorter time in the ICU than controls (MD − 1.27 days; 95% CI − 1.94 to − 0.61 days). Heterogeneity was moderate among these trials (*I2* = 46%).

Regarding secondary endpoints, patients in the PoCUS group had significantly higher odds (OR 2.31; 95% CI 1.61 to 3.32) of receiving appropriate therapy compared to controls, and studies showed low heterogeneity (*I2* = 0%). We found no significant effects on 30-day re-admission rate (OR, 0.81; 95% CI, 0.56 to 1.17), with low

heterogeneity (*I2* = 0%), 30-day mortality (OR, 0.82; 95% CI 0.31–2.18) and in-hospital mortality (OR 0.62; 95% CI 0.37 to 1.04), with moderate heterogeneity (*I2* = 50% and *I2* = 37%).

Based on the Cochrane proposal, the risk of bias assessment showed serious concern for only one article and moderate (some concern in cases of RCTs) or low risk for all others. For GRADE, the certainty of evidence in the studies was variable, only the rate of appropriate treatment fell into high certainty category.

4.2. Study II

The literature search yielded a total of 7096 articles, and two other articles were found from other sources: one from Google Scholar and one from manual web search. Ultimately, ten records (7 RCTs and 3 observational studies) were considered for data extraction in our meta-analysis. The total number of patients included in our systematic review and meta-analysis was 1006, with 472 receiving BES and 534 treated with 0.9% saline.

Regarding time to DKA resolution the difference in means between the intervention and control arms was significant (MD −5.36 hours; 95% CI −10.46 to −0.26 hours, *I2* = 0%).

Four studies reported on chloride levels, which were significantly lower (MD −4.26 mmoL/L, 95% CI −6.97 to −1.54 mmoL/L, *I2* = 95%) in the BES – group, similarly to serum sodium levels (MD −1.38 mmol/L; 95% CI −2.14 to −0.62 mmoL/L, *I2* = 0%). Potassium was numerically higher in the BES – group compared to the Saline – group (MD 0.18 mmol/L; 95% CI −0.16 to 0.53 mmoL/L, *I2* = 95%), but this difference did not reach statistical significance. Bicarbonate was significantly elevated in the BES – group (MD 1.82; 95% CI 0.75 to 2.89, *I2* = 1%). There was no statistically significant difference between the groups regarding the duration of parenteral insulin administration (MD 0.16 hours; 95% CI −3.03 to 3.35 hours, *I2* = 0%). We found three randomized and three observational studies reporting data about the amount of total fluid administration, but there were no significant differences between the two groups in any of

the cohorts (observational studies MD 181 ml; 95% CI −173 to 536 mL, *I2* = 32%; and randomized studies MD 86 ml; 95% CI −584 to 756 mL, *I2* = 0%). With regard to the dichotomous variables of randomized trials, there was no difference in hyperkalaemia between the groups (OR 1.07; 95% CI 0.21 to 5.32, *I2* = 58%).

Most of the randomized studies had low or some concerns of bias. Regarding the observational studies, all were considered at moderate risk of bias; only the study by Carrillo et al. showed a serious risk of bias.

The quality of evidence was low, as appraised by the GRADE criteria for the primary outcome of time to DKA resolution.

5. Conclusions

5.1. Study I.

The results of this systematic review and meta-analysis support the use of PoCUS to improve differential diagnosis, achieve early appropriate treatment and decrease LOS in the ICU compared to conventional

diagnostic modalities in patients admitted with acute onset dyspnea.

5.2. Study II.

Our systematic review and meta-analysis of the currently available data indicate that BES resolves DKA faster than 0.9% saline, although the level of evidence remains low, and more research on this topic should be encouraged. According to our results, DKA guidelines should consider BES instead of 0.9% saline as the first choice during fluid resuscitation. Furthermore, we found that resuscitation with BES results in lower serum sodium and chloride concentrations but higher bicarbonate concentrations after the DKA resolution compared to 0.9% saline; meanwhile, we acknowledge that the clinical importance of the observed differences is disputable.

6. Bibliography

Publications related to the thesis:

Szabó, G.V., Szigetváry, C., Szabó, L. et al. Point-of-care ultrasound improves clinical outcomes in patients with acute onset dyspnea: a systematic review and meta-

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Szabó GV, Szigetváry C, Turan C, et al. Fluid resuscitation with balanced electrolyte solutions results in faster resolution of diabetic ketoacidosis than with 0.9% saline in adults – A systematic review and meta-analysis. Diabetes Metab Res Rev. 2024;e3831. https://doi.org/10.1002/dmrr.3831 D1 IF: 4.6