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LETTER TO THE EDITOR Open Access

Is early goal-directed therapy associated with a higher risk of adverse events?

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Abstract

The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 suggested against the use of the early goal-directed therapy (EGDT) in patients with septic shock. This recommendation was based on the three large-scale trials (ProCESS, ARISE, and ProMISe). Although the three trials showed no difference in mortality between EGDT and usual care, the guidelines determined that the potential harms presented by EGDT likely outweigh its potential benefits. On the contrary, analysis of data from the three trials showed an approaching statistical significance lower risk of serious adverse events in the EGDT group compared to usual care (risk difference = − 1%, 95% confidence interval; − 2% to 0%, $P = 0.05$). EGDT may still be beneficial in patients with high disease severity and low central venous oxygen saturation, especially when managed by less experienced staff.

Keywords: Septic shock, Early-goal directed therapy, Usual care, Serious adverse events

Dear Editor,

I read with great interest the English edition of the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 published recently in the *Journal of Intensive Care* [1]. Although the guidelines are primarily tailored to the Japanese context, it represents an excellent summary of the current literature and thus it is of great interest to intensivists from around the globe. I would like to discuss a few points regarding section CQ7: Initial resuscitation/inotropes.

First, the guidelines suggested against the use of the early goal-directed therapy (EGDT) when performing initial resuscitation in patients with sepsis or septic shock. EGDT is a 6-h resuscitation protocol for the administration of intravenous fluids, vasopressors, inotropes, and red-cell transfusion to achieve pre-specified targets for central venous pressure, arterial blood pressure, urine output, and central venous oxygen saturation ($ScvO_2$) [2]. This recommendation was based on the three large-scale randomized controlled trials (RCTs); ProCESS [3], ARISE [4], and ProMISe [5] reported in 2014 and 2015. Although the three RCTs showed no significant difference in mortality between EGDT and usual care (i.e., equipoise), the guidelines determined that the potential harms presented by EGDT likely outweigh its potential benefits and explained their rationale as follows: "Dobutamine dosages and the quantity of blood transfused increased significantly in the EGDT group, and due to the increased frequency of arrhythmias associated with dobutamine, greater overall risk of side effects associated with transfusions, and increased time and quantity of work required of hospital staff, it is possible that compliance with EGDT may increase the risk of harm (burden) faced by patients" [1].

The notion that EGDT may increase the risk of harm to patients is rather speculative and not supported by clinical evidence or patients' data. On the contrary, pooled data from the three RCTs (Fig. 1) showed an approaching statistical significance lower risk of serious adverse events (SAEs) in the EGDT group compared to usual care (risk difference = − 1%, 95% confidence interval; − 2% to 0%, $P = 0.05$). SAEs were uniformly defined among the three RCTs as "any untoward medical occurrence that: (1) results in death, (2) is life-threatening, (3) requires in-patient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity, (5) is a congenital anomaly/birth defect, or (6) other adverse event considered serious by medical judgment" [3–5].

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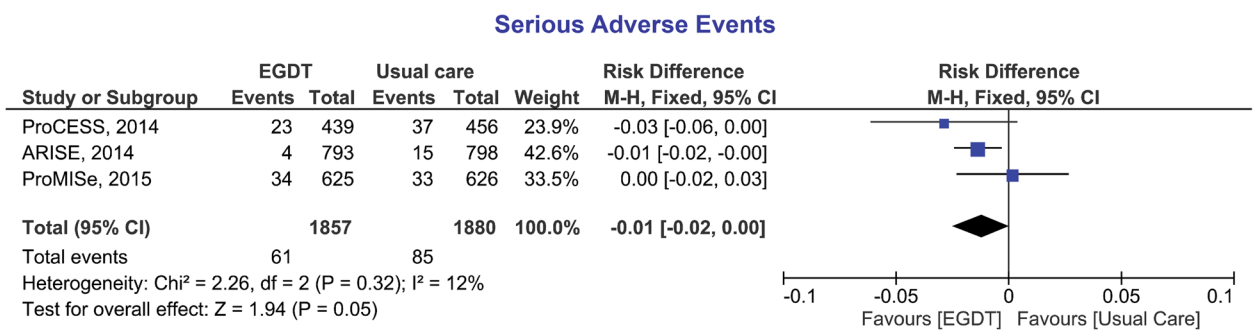

Fig. 1 Forest plot of the risk difference of serious adverse events (SAEs) between early goal-directed therapy (EGDT) and usual care. The risk difference of individual studies is represented by a *square* through which runs a *horizontal line* (95% confidence interval). The *diamond* represents the pooled effect size. Data were extracted from the supplementary appendix of each trial and analyzed by RevMan 5. Events refer to number of SAEs not the number of patients (some patients might experience more than one SAE). *ProCESS* reported all SAEs occurring in the first 72 h post-randomization and after 72 h SAEs were limited to a specific list of events that could be related to the intervention at that point in time (e.g., central line infection, or arterial line complication), or events that the site principal investigator considered potentially related to the study intervention. *ARISE* reported SAEs up to 72 h post-randomization only. *ProMIse* reported SAEs within 30 days

Second, the guidelines provided some contradictory statements. Despite the recommendation against EGDT, the guidelines provided an expert consensus statement that either $ScvO_2$ or lactate clearance may be used as indicators of initial resuscitation (CQ7–8). And suggested that Dobutamine is used in septic shock when cardiac function remains diminished, and maintenance of hemodynamics is insufficient despite adequate fluid resuscitation and noradrenaline administration (CQ7–12) [1]. Both $ScvO_2$ monitoring and Dobutamine are cardinal components of the EGDT. $ScvO_2$ monitoring (with the subsequent use of Dobutamine and red-cell transfusion to correct $ScvO_2$) was the only intervention not allowed by study protocol in the usual care group in the three RCTs [3–5]. Thus, the only conclusion we could draw from the three RCTs is that catheter placement for continuous $ScvO_2$ monitoring is not necessary in every patient presented by septic shock. However, the three RCTs could not answer the question of whether targeting $ScvO_2$ of ≥ 70% is an effective intervention or not as the most of the patient were at target $ScvO_2$ on presentation (initial mean $ScvO_2$ was 71%, 72%, and 70% in the ProCESS [3], ARISE [4], and ProMISe [5], respectively). Until future trials focusing on the subgroup of patients with low $ScvO_2$ is conducted, the evidence from the original EGDT trial [2] which recruited patients with low $ScvO_2$ (mean 49%) is enough to consider the use of Dobutamine and red cell transfusion to correct $ScvO_2$ to decrease mortality.

Finally, I totally agree with the guidelines statement that "the treatment of sepsis can vary significantly depending on the level of care offered by a given facility and the level of knowledge and skills of the attending physician and staff". The Three RCTs [3–5] were primarily conducted in academic/tertiary care centers in high-income countries and included patients with low severity septic shock who rapidly responded to therapy. Even though, their usual care was associated with a trend toward higher risk of SAEs. The question here is, what would be the situation in less equipped facilities or with physicians with less expertise? In fact, multiple issues have been raised regarding the external validity of the three trials suggesting that EGDT may still be beneficial in patients with high disease severity and low $ScvO_2$, especially when managed by less experienced staff who may appreciate using simple protocols [6, 7].

Response to Dr. Saleh: "Is early goal-directed therapy associated with a higher risk of adverse events?"

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We read the letter to the editor from Dr. Saleh with great interest. For the assessment of the CQ7–1 "Is early goal-directed therapy (EGDT) recommended for initial resuscitation in patients with sepsis or septic shock?", three randomized controlled trials (RCTs) [3–5] were identified based on a search of the PubMed database and were used in the final analysis. Our analyses showed no significant difference in mortality between EGDT and the standard treatment (90-day mortality rate: risk ratio 0.98 [95% confidence interval {CI} 0.88–1.10]; 28-day mortality rate: risk ratio 0.98 [95% CI 0.84–1.13]) [1]. Regarding the benefit-risk balance, dobutamine dosages and the quantity of blood transfused were significantly increased in the EGDT group compared to the usual-care group [3, 4], and due to the increased frequency of arrhythmias associated with dobutamine and greater overall risk of side effects associated with transfusions, it is possible that compliance with EGDT may increase the risk of harm (burden) faced by patients. As Dr. Saleh suggested first, however, the pooled data from the three RCTs show an approaching statistical significance lower risk of serious adverse events (SAEs) in the EGDT group compared to the usual-care group (risk difference = − 1%, 95% CI − 2–0%, $P = 0.05$). We therefore examined the data on the SAEs and AEs of the three RCTs again in detail and obtained the following results: In the ProCESS trials, reports of potential SAEs (excluding death) were rare and did not differ significantly across groups, with 23 events (5.2%) reported in the EGDT group and 37 (8.1%) in the usual-care group [3]; in the ProMISe trials, there was no significant between-group difference in the number of SAEs, with 34 events (5.4%) reported in the EGDT group and 33 (5.3%) in the usual-care group and at least 1 SAE reported among 30 patients (4.8%) in the EGDT group and 26 patients (4.2%) in the usual-care group ($P = 0.58$) [5]; a significant difference in the number of SAEs was observed only in the ARISE trials, with 4 events (0.5%) reported in the EGDT group and 15 (1.9%) in the usual-care group, although there was no significant between-group difference in the number of patients with ≥ 1 AE (including SAEs) (56 patients [7.1%] in the EGDT group and 42 patients [5.3%] in the usual-care group; $P = 0.15$) [4]. Special precautions should be taken when interpreting the findings for SAEs in the ARISE trials, as (1) the number of SAEs in the ARISE trials was too small for a comparison with those of the other RCTs (ProCESS and ProMISe), and (2) the reason for the large difference between the number of SAEs and the number of AEs (including SAEs) in the ARISE trial was unclear. SAEs may develop less frequently in the EGDT group than in the usual-care group, as suggested by Dr. Saleh.

Second, Dr. Saleh claimed that until future trials focusing on the subgroup of patients with a low $ScvO_2$ are conducted, the evidence from the original EGDT trial [2] that recruited patients with a low $ScvO_2$ (mean 49%) was sufficient to support the consideration of the use of dobutamine and red-cell transfusion to correct the $ScvO_2$ in order to reduce mortality [7]. Because the serum lactate levels and $ScvO_2$ are important for both assessing the oxygen transport capacity in tissues and as a marker of tissue hypoperfusion [8, 9], it is suggested that either factor ($ScvO_2$ or lactate clearance) may be used as an indicator of initial resuscitation [10]. Recently, a meta-analysis of individual patient data from the three recent trials (ProCESS, ARISE, ProMISe) was designed prospectively to improve the statistical power and explore the heterogeneity of the treatment effect of EGDT. The results showed that there was no evidence of a benefit associated with EGDT in the subgroups with the most severe septic shock, including those with a serum lactate level of ≥ 4.1 mmol/L (mean, 6.7 mmol/L), those who presented with both hypotension and hyperlactatemia (mean systolic blood pressure, 89 mmHg; mean serum lactate level, 6.7 mmol/L), those in the upper third of APACHE II scores (mean score, 24.6), and those in the upper third of predicted risk of death [11]. We therefore cannot conclusively say that EGDT is beneficial for the most severe septic shock patients with hyperlactatemia ($ScvO_2$ may be low).

Even if EGDT was associated with a lower incidence of SAEs than the usual-care and could be managed by less experienced staff who might appreciate using simple protocols, the recommendations for CQ7–1 in our guidelines remain unchanged. One of the most important principles to understand in the management of these complex patients is the need for a detailed initial assessment and ongoing reevaluation of the response to treatment. The use of CVP alone to guide fluid resuscitation, which is required by the EGDT protocol proposed by Rivers et al. [2], can no longer be justified [12] because the ability to predict a response to a fluid challenge when the CVP is within a relatively normal range (8–12 mmHg) is limited [13], and some patients treated with EGDT develop subsequent fluid overload, which may be associated with worse outcomes [14]. Dynamic measures of assessing whether or not a patient requires additional fluid have been proposed in an effort to improve fluid management and have demonstrated better diagnostic accuracy at predicting those patients who are likely to respond to a fluid challenge by increasing stroke volume. Furthermore, in recent years, the "hour-1 bundle" has been recommended, in which obtaining blood for measuring lactate and blood cultures, administering fluids and antibiotics, and in the case of life-threatening hypotension, initiating vasopressor therapy should all be begun immediately [15].

In their review, Nguyen et al. [6] stated that in this era of global reductions in sepsis mortality, clinicians should view EGDT as a verb (series of actions) rather than a noun. Thus, taking over the basic concept of EGDT to promptly improve the hypoperfusion of tissues but in keeping with the change in the new era, achieving the target value within 1 h (not 6 h) may require developing a new version of EGDT (modified EGDT) that not only selects dynamic indices instead of CVP to predict fluid responsiveness but also avoids the fluid overload following initial resuscitation.

Abbreviations

EGDT: Early goal-directed therapy; RCT: Randomized controlled trial; SAEs: Serious adverse events; $ScvO_2$: Central venous oxygen saturation

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Authors' contributions

AS drafted the manuscript, performed the data analysis and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The author declares that he has no competing interests.

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