ICU TOPICS

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Introduction

In this era of evidence-based medicine, an enormous number of randomised controlled clinical trials (RCTs) are being done to improve the scientific foundation of daily intensive care patient management and ultimately to improve patient centred outcomes such as mortality. Data extracted from PubMed reveals a total of 168 published RCTs on sepsis, and 303 published RCTs on mechanical ventilation in 2011 alone. Unfortunately the majority of ICU studies demonstrate no beneficial effect of the intervention on the outcome, and interventions that do show a beneficial effect are often not implemented in clinical practice for a number of reasons.[1]

Recent Mostly-negative-but-possibly-practice-changing Trials

Disease Modifying Agents for Sepsis

The search for a disease-modifying agent that improves outcome in patients with sepsis has been on-going for many years. The list of initially promising agents that didn't live up to the expectations in clinical trials is becoming very long, and includes nitric oxide synthase inhibitors such as L-NMMA; anti-inflammatory agents such as corticosteroids and NSAIDs; anticoagulants such as anti-thrombin III and tissue pathway factor inhibitor.

The most promising and best-studied agent was recombinant human activated protein C, or drotrecogin alpha activated (DrotAA). Sufficient preclinical data and pathophysiological plausibility warranted a large RCT. In the PROWESS study (Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis), a phase 3 multicentre PRCT published in 2001, DrotAA administration was associated with a 6.1% absolute mortality reduction.[2] However, because of concerns with this trial (the trial was stopped early for efficacy; the study protocol was modified during the trial possibly influencing the outcome; the lack of confirmatory data from other PRCTs) the European Medicines Agency concluded in 2007 that sufficient doubt existed to warrant a new PRCT. In the multicentre randomised double-blind placebo-controlled PROWESS-SHOCK study, 1,697 patients with septic shock were randomised to receive DrotAA or placebo for 96 hours with 28-day mortality as primary outcome. The study failed to show a difference in overall mortality and in outcomes in any of the predefined subgroups.[3] On 25 October 2011 Eli Lilly and Co. announced a worldwide voluntary market withdrawal of Xigris, based on the results of PROWESS-SHOCK.

Fluid Management in Critically Ill Patients

Choice of Fluid

Resuscitation fluids administered to critically ill patients are not innocent bystanders, but may have an effect on morbidity and mortality. Some of these effects appear to be immune mediated and may depend on the type of fluid used as well as the timing of the fluids given.[4,5] Until recently, fluid choice and more specifically the crystalloid versus colloid debate in anaesthesia and intensive care has been to a great extent dependent on belief, dogma and local availability or practice and less so on sound evidence.[6]

The publication of the SAFE trial in 2004 (a comparison of 4% albumin and 0.9% saline for fluid resuscitation in the intensive care unit) confirmed that albumin resuscitation, although safe, does not have any significant benefit over saline resuscitation.[7] The SAFE study did suggest that patients with traumatic brain injury resuscitated with albumin had an increased mortality rate compared to saline. This was confirmed in a post hoc follow-up study of these patients.[8] Subgroup analysis of the SAFE study also showed a non-significant trend towards improved

outcome for patients with severe sepsis resuscitated with albumin. Following this interesting observation, three large-scale randomised studies were initiated to determine whether this potential benefit could be confirmed. The first of these studies, performed by the group of Dr Mira in France, has been presented at a major scientific meeting but not yet published. In this approximately 800 patients study, albumin resuscitation did not result in improved mortality or improvement of any of the secondary outcome measures. The second study by Dr Gattinoni et al in Italy is close to finishing recruitment of 1,800 patients, and the Canadian Critical Care Trials Group is conducting the third study.

With regards to modified starch solutions (hydroxyl-ethyl starch, HES), there has been much controversy regarding the safety and potential benefits of these solutions. Nonetheless, HES solutions are the most widely used colloids in the world, mainly because of widespread use in Europe. Studies investigating older HES preparations and hyperoncotic solutions found possible evidence of harm, but this was not confirmed in a large cross-sectional observational study.[9,10] In a recent meta-analysis of poor quality studies of a newer HES preparation (6% HES 130/0.4), and after exclusion of retracted fraudulent studies conducted by Dr Boldt, no harm or benefit of 6% HES 130/0.4 could be shown.[11] In a recent multicentre PRCT done by the Scandinavian Starch for Severe Sepsis / Septic Shock (6S) trial group, 804 patients with severe sepsis were randomly assigned to fluid resuscitation in ICU with either 6% HES 130/0.42 or Ringers' acetate.[12] The patients receiving HES had an increased risk of death at day 90 (51% vs 43%; RR 1.17; 95% CI 1.01-1.36; p=0.03), and were more likely to require renal-replacement therapy (22% vs 16%; RR 1.35; 95% CI 1.01-1.80; p=0.04).

Finally, in the recently completed Crystalloid Hydroxy-Ethyl Starch Trial (CHEST), 7,000 intensive care patients were randomised to receive fluid resuscitation with starch (6% hydroxyethyl starch 130/0.4) or saline (0.9% sodium chloride).[13] The results of this trial are still under embargo at the time this abstract was written, and will be publicly released September 2012.

New and promising developments currently under investigation include hypertonic resuscitation fluids[14,15] and balanced fluids.[16]

Timing of Fluid Resuscitation

It has become more clear over the last seven years or so, that overly aggressive fluid resuscitation is associated with worse outcome.[17,18] It has been suggested that adequate initial fluid resuscitation combined with conservative post-resuscitation fluid management is associated with improved outcomes and mortality.[19] However, most of these data are observational and could potentially have been confounded by patient severity unbalance, where sicker patients receive more fluid and have worse outcomes. Three large studies evaluating early goal directed therapy are currently underway and are expected to answer some of these pertinent questions.

Conclusion

In conclusion, the choice, amount and timing of fluid resuscitation have an impact on patients' morbidity and mortality. Based on the results of recent large clinical studies, there is no clear benefit in using albumin or hydroxyl-ethyl starch over crystalloid solutions in critically ill patients. Based on the best available evidence and awaiting on-going clinical trials, early adequate fluid resuscitation followed by conservative post-resuscitation fluid management is recommended.

Beta-adrenergic Agonists for Treatment of Acute Respiratory Distress Syndrome (ARDS)

Beta-adrenergic agonists have several potential beneficial effects that might enhance the resolution of acute lung injury (ALI) and ARDS including up-regulation of alveolar fluid resorption, anti-inflammatory effects and endothelial and epithelial protective effects. Beta-agonists have been shown to reduce pulmonary oedema in preclinical models of acute lung injury. Retrospective data suggested that inhaled salbutamol was associated with a shorter duration and lower severity of ALI.[20] In the phase II beta-agonist lung injury trial (BALTI) intravenous salbutamol significantly reduced extra-vascular lung water and plateau pressures in patients with ARDS.[21]

Based on these encouraging findings two large-scale trials were conducted. In the BALTI-2 study, the same investigators planned to randomise 1,134 patients with ARDS to receive intravenous salbutamol (15 mcg/kg IBW/h) or placebo. The study was stopped after 326 patients for safety concerns, with an increased 28-day mortality in the treatment arm (35% vs 23%, RR 1.47, 95% CI 1.03-2.08).[22] In addition, the salbutamol group had fewer ventilator-free and organ failure-free days, and more frequent tachycardia, new arrhythmias and lactic

acidosis. In the other large randomised study undertaken by the National Heart Blood and Lung Institute's ARDS Clinical Trials Network, the efficacy of inhaled salbutamol (5 mg every 4 hours) was compared to placebo in patients with ALI / ARDS.[23] The study enrolled 282 of a planned 1,000 patients and was stopped for futility after the first planned interim analysis. No significant differences were found with regards to ventilator-free days or mortality.

In conclusion, despite strong preclinical data and good biological rationale, neither inhaled nor intravenous beta-adrenergic agonists are beneficial in patients with ALI and ARDS. Intravenous delivery of salbutamol was poorly tolerated in critically ill patients with adverse cardiovascular effects and an increased 28-day mortality.

Nutrition in Critically Ill Patients

Early Parenteral Nutrition

The timing and optimal route of nutrition in critically ill patients remain unclear. The use of early parenteral nutrition (PN) supplement to reach caloric goals is recommended in European guidelines (within 48 hours after ICU admission) but not in North American guidelines (recommended initiation after day eight). To address this question, a randomised multi-centre study in 4,640 patients was conducted to compare early versus late initiation of PN as supplement to enteral nutrition to achieve the daily caloric goal intake.[24] Patients in the late initiation group had a small (6.3%) reduction in ICU length of stay, fewer ICU infections (22.8% vs 26.2%, p=0.008), a reduction in the proportion of patients requiring more than two days of ventilation, a reduction in the duration of renal replacement therapy, and a reduction in healthcare costs. No differences were observed with respect to mortality.

Omega-3 Fatty Acids in ARDS

Preclinical studies and several small clinical trials have suggested a potential benefit for omega-3 fatty acid supplementation in patients with ALI / ARDS. Nutrition enriched with omega-3 fatty acids can reduce inflammatory eicosanoid production by altering membrane phospholipid composition and can provide substrate for anti-inflammatory mediators such as resolvins and protectins.

Two recent studies addressed this issue. In a multicentre phase II clinical trial, 90 mechanically ventilated patients with ALI / ARDS were randomised to receive 6-hourly fish oil or placebo.[25] There was no difference in bronchoalveolar lavage fluid levels of Il-8, organ failure, ventilator-free days, ICU-free days or mortality. The other study "OMEGA" was conducted by the National Heart Blood and Lung Institute's ARDS Clinical Trials Network and planned to randomise 1,000 patients to receive an enteral supplement enriched in omega-3 fatty acids, gamma-linolenic acid and antioxidants versus an isocaloric control feed.[26] The trial was stopped for futility after 272 patients were enrolled. Patients receiving the omega-3 supplement had significantly fewer ventilator-free days, fewer organ failure free days and a trend towards higher 60-day mortality (26.6% vs 16.3%, p=0.054).

Conclusion

In conclusion, there is no benefit to initiating very early parenteral nutrition as a supplement to enteral nutrition to achieve caloric goals in critically ill patients. Enteral supplementation of omega-3 fatty acids is not beneficial in ALI / ARDS and could potentially be harmful.

Conclusions

The past year in Intensive Care Medicine has again seen the publication of a number of large PRCTs that may aid us in our daily management of critically ill patients. Unfortunately most of these trials are "negative," in that they only tell us what we should not do; the evidence outlining or providing guidance towards what we should do remains limited.

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