Commentary

Recently published papers: Therapies failed, disputed, and beneficent

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Abstract

A recent meta-analysis puts another nail in the coffin of a therapy that held great promise for management of acute respiratory distress syndrome. Two papers further highlight the growing controversy surrounding the safety profile of drotrecogin alfa (activated) and increase the clamour for a new independent trial. Also covered are steroids and their role in preventing postoperative atrial fibrillation, and success in instituting hypothermia after cardiac arrest. Finally, which form of renal replacement therapy should we be using in the intensive care unit?

Nitric oxide: a promising therapy laid to rest?

In 1976, Ashbaugh first described acute lung injury/acute respiratory distress syndrome. Our subsequent understanding of the underlying pathophysiology has grown enormously and led to the development of many novel therapies. However, the high mortality rate has changed little in 40 years. Inhaled nitric oxide (NO) was one such therapy. It seemed perfect, being a selective pulmonary vasodilator resulting in reversal of pulmonary shunt, reduction in pulmonary artery pressure and improved right ventricular function, not to mention its inhibition of platelet aggregation and neutrophil adhesion. The clever money was on NO.

Sadly, all that sparkles is not gold. A multitude of studies have simply failed to demonstrate improved outcomes. Despite this, its clinical application has continued, albeit somewhat piecemeal.

In April the *British Medical Journal* published a systematic review and meta-analysis on the effect of NO in acute lung injury [1]. Outcomes included oxygenation, pulmonary artery pressure, duration of ventilation, mortality and adverse effects. Twelve randomized controlled trials ($n = 1,237$) were selected. The results and conclusions do not make for happy reading. NO was found not to improve mortality, duration of ventilation, or number of ventilator-free days. It bestowed a small oxygenation benefit in the first few days of use. It did not significantly reduce mean pulmonary arterial pressure. High-dose NO (80 ppm) was associated with methaemoglobinaemia and raised blood nitrogen dioxide levels. Finally, a statistically significant risk for renal dysfunction was identified in patients receiving NO, although the authors stressed cautious interpretation of this finding.

This was an assiduously conducted review and the results are in keeping with previous work [2]. It leaves one begrudgingly accepting the authors' conclusions that, 'given the best available evidence suggests no survival advantage and possible increased mortality and renal dysfunction with nitric oxide, we do not recommend its routine use'.

Drotrecogin alfa (activated): translating research into clinical practice

Hardly a day seems to pass without further drotrecogin alfa (activated; DAA) scandal and controversy. Concerns centre on the widespread implementation of this drug in the treatment of severe sepsis, based upon a single industry-sponsored trial and the applicability of this trial to 'real' patient populations. Many questions persist surrounding the indications for use and risk/benefit profile in patient subgroups. Bleeding risk is of particular concern.

Two recent publications are pertinent to this topic [3,4]. Bertolini and coworkers [3] reported a prospective pharmaco-surveillance programme monitoring the use of DAA in Italian ICUs between 2003 and 2006. The authors attempted to compare those who received DAA with a parallel nonrandomized untreated (control) group. The control group consisted of patients from a different study who were eligible for treatment with DAA but did not receive it. The authors reported a number of key observations. First, they

AF = atrial fibrillation; CRRT = continuous renal replacement therapy; DAA = drotrecogin alfa (activated); ICU = intensive care unit; IHD = intermittent haemodialysis; NO = nitric oxide; ROSC = return of spontaneous circulation.

identified a high incidence of off-license prescribing. This was largely attributable to administration commencing more than 48 hours after the onset of organ dysfunction. More worryingly, they report a higher incidence of both serious bleeding and other fatal and life-threatening events compared with the previous landmark studies [5,6]. The also observed that intensive care unit (ICU) mortality rates for treatment and control groups (46.5% and 54.9%, respectively) were much higher than the 28-day mortality in the aforementioned trials. This begs the question as to how well the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis) population was representative of the real target population. The second report is of a retrospective observational study of the use of DAA in Canada. Findings are strikingly similar to those of the study reported by Bertolini and coworkers. Both mortality rate and the incidence of serious bleeding were significantly greater than in PROWESS. However, early treatment with DAA (within 12 hours) was an independent predictor of survival.

Neither of these studies allows firm conclusions to be drawn as to the optimal indication for DAA and the precise risk/benefit profiles for various patient subgroups (for instance, surgical versus nonsurgical, or high versus low risk for death). However, they both cast further doubt as to the general applicability of PROWESS to the every day clinical setting and population. An accompanying editorial [7] emphasizes the urgent need for high quality, independent confirmatory research to identify those patients who are most likely to benefit from this therapy.

Matters cardiac

Atrial fibrillation (AF) is both common and troublesome. New-onset AF in the critically ill patient is related to the systemic inflammatory response, and is often refractory to treatments such as digoxin and amiodarone. A recent report published in the *Journal of the American Medical Association* [8] suggests that steroids are efficacious in prophylaxis against acute AF. A Finish group conducted a double blind randomized controlled trial, in which patients with no prior history of AF undergoing cardiac surgery were randomly assigned to preoperative and postoperative (3 days) hydrocortisone or placebo. The incidence of postoperative AF was significantly lower in the steroid group (30% versus 48%). No adverse effects were noted. The authors postulate an anti-inflammatory mechanism, although they also suggest that the antiemetic effect of steroids is also of benefit in terms of absorption of oral medications such as metoprolol, which all patients received. Clearly, this group of patients exhibits a high incidence of AF, higher than that in the general ICU population, and steroids have only been shown to be efficacious in preventing AF rather than treating established AF. As such, extrapolating this study to all ICU patients is probably flawed.

As alluded to above, translation of a therapeutic intervention from a clinical trial to reality is often fraught. This may be because of the study population not being representative of the target population, unrealistic/irreproducible protocols, or failure to capture the collective consciousness. In 2002, two papers were published in the *New England Journal of Medicine* that detailed evidence for improved outcomes following cardiac arrest with induced mild hypothermia [9,10]. August bodies such as the International Liaison Committee on Resuscitation have since recommended this therapeutic intervention, but is it happening on the shop floor? Arrich [11] decided to find out. In this observational study, data were collected from 19 European sites between 2003 and 2005. All patients presenting with return of spontaneous circulation (ROSC) after cardiac arrest were considered. Exclusions were similar to those in previous studies. The primary end-point was the cooling protocol, including the interval from arrest and ROSC to initiation of cooling, the cooling rate, cooling duration and re-warming rate. Secondary end-points were complications and neurological outcome. Results were very encouraging, with 79% of patients undergoing hypothermia. The median time from ROSC to cooling was 159 min, which was longer than that achieved in a recent clinical trial. However, the cooling rate of 1.1°C/hour was far superior to that in clinical trials. Cooling was maintained for an average of 24.3 hours. Rates of adverse events were lower than previously reported. Neurological outcome was better in the hypothermia group. This study demonstrates that therapeutic hypothermia is both feasible and safe in normal clinical practice, and that it benefits patients. No excuses then!

Intermittent haemodialysis versus continuous renal replacement therapy

Debate surrounding the pros and cons of intermittent haemodialysis (IHD) versus continuous renal replacement therapy (CRRT) in the ICU for the management of acute renal failure grumbles on. In the UK CRRT predominates, and serendipitously this appears to be the better choice. A Swedish group recently reported a large nationwide retrospective cohort study of renal outcome from acute renal failure following either IHD or CRRT ($n = 2,202$) [12]. Both groups were well matched before ICU admission, with an overall mortality of 50%. There was no difference in 90-day mortality between groups, which is in keeping with previous studies. However, patients treated with IHD were at significantly greater risk for chronic renal failure (need for renal replacement therapy at 3 months) and for being dialysis dependent, and unsurprisingly this group had the greatest long-term mortality. This was so despite data suggesting that patients in the CRRT group were sicker than those in the IHD group. Although clearly not a perfect study, this adds to the growing body of evidence indicating that CRRT is the renal replacement therapy of choice in the ICU. The authors suggest that a global re-evaluation of RRT in the ICU should now occur.

Competing interests

The author declares that they have no competing interests.

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