Intensive Care Med (2015) 41:701–704
DOI 10.1007/s00134-014-3573-4

Gordon S. Doig
Ian Roberts
Rinaldo Bellomo

The tens of thousands of lives saved by randomized clinical trials in critical care

Received: 17 November 2014
Accepted: 19 November 2014
Published online: 5 December 2014

G. S. Doig
Northern Clinical School Intensive Care Research Unit, University of Sydney, Sydney, Australia

I. Roberts
Clinical Trials Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK

R. Bellomo
School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

G. S. Doig (✉)
Level 6, Intensive Care Unit, Royal North Shore Hospital, Pacific Hwy, St Leonards, NSW 2065, Australia
e-mail: gdoig@med.usyd.edu.au
Tel.: +61 2 9463 2633

In the second half of 1952, a total of 2,722 patients with poliomyelitis were admitted to the Blegdam Hospital for communicable diseases in Copenhagen. With 12 % of all admissions requiring artificial respiratory support, resources were soon overwhelmed, and the initial case-fatality rate for patients with respiratory failure reached 90 %. Driven by necessity, a few dedicated professionals persisted with "therapeutic improvisations" and eventually refined the specific skills required to provide long-term manual positive pressure ventilation through a tracheostomy [1]. Because of excellent record keeping, subsequent publications demonstrated that manual positive pressure ventilation halved the case-fatality rate [2].

Since the polio pandemic of the 1950s, the practice of intensive care medicine has been built upon all types of objective research evidence: the well-conducted observational study [3] and the single-patient case report [4] have led to major improvements in patient outcomes. The main challenge faced by today's clinician is to fine tune an already well-established system of care. Fortunately, the randomized controlled trial (RCT) is uniquely suited for the efficient detection of modest treatment effects. The purpose of this short review is to highlight how RCTs complement other forms of research evidence, thus helping to advance the practice of modern intensive care medicine.

Mechanical ventilation: the hallmark of intensive care medicine

Lassen and Ibsen were prescient in their descriptions of long-term manual positive pressure ventilation during the Copenhagen polio epidemic, reporting that "when bag ventilation is administered correctly… it amounts to 20–30 cm. water" insufflation pressure, which "counteracts the development of oedema of the lungs" [1, 2]. Forty-eight years later, the most transformative RCT in our field confirmed their observations.

The Acute Respiratory Distress Syndrome Network (ARDS Net) lower tidal volume trial was conducted at ten university centres throughout the USA [5]. Within 36 h of the onset of ARDS, patients were randomized to receive a ventilation strategy that limited tidal volume (6 ml/kg predicted body weight) and plateau pressure (≤30 cm of

water) or a strategy based on a higher tidal volume (12 ml/kg predicted body weight) that also allowed higher plateau pressures (up to 50 cm of water). After 861 patients were enrolled, use of the lower tidal volume/lower plateau pressure strategy led to an 8.8 % absolute reduction in deaths [95 % confidence interval (CI) 2.4–15.3 %, $P = 0.007$].

General acceptance of the results of the ARDS Net lower tidal volume trial is demonstrated by the inclusion of strong recommendations for tidal volume and plateau pressure control in the surviving sepsis campaign guidelines, which were developed and endorsed by more than 28 clinical societies from around the world [6]. Furthermore, a landmark observational study enrolling 29,470 patients with sepsis demonstrated successful implementation of the recommendation for plateau pressure control was associated with a significant reduction in mortality (odds ratio 0.81, $P < 0.001$) [7].

Steroids: pluripotent panacea?

Corticosteroids have a direct and dramatic effect on almost every inflammatory process. Based on a thorough understanding of their physiological effects, steroids have been used in many conditions, including sepsis, acute spinal cord injury and head trauma. Despite widespread use for more than 30 years, objective evidence demonstrating that moderation of the inflammatory response improves patient outcomes remains controversial for sepsis and acute spinal injury, but not for head trauma.

Commenced in April 1999, the Corticosteroid Randomisation After Significant Head Injury (MRC CRASH) trial enrolled patients in 239 hospitals from 49 countries [8]. Within 8 h of head injury, patients were randomized to receive 30 mg/kg methylprednisolone or placebo. After enrollment of 10,008 patients, the MRC CRASH trial demonstrated significant excess mortality attributed to steroid use: an absolute increase of 3.2 % more deaths at 2 weeks (relative risk 1.18, 95 % CI 1.09–1.27, $P = 0.0001$) [8]. This excess mortality persisted at 6 months ($P < 0.0001$), with no evidence of a difference in the quality of functional recovery between groups [9]. After more than 30 years of clinical use, the MRC CRASH trial brought clarity to the role of steroids in head trauma.

The future of intensive care: when is less more?

In 2006, the ARDS Network published the results of a 1,001-patient clinical trial comparing conservative fluid resuscitation targets to more liberal targets for patients with acute lung injury. During the first 7 days of study, patients randomized to the conservative targets achieved a net negative fluid balance, whereas patients with liberal targets achieved a net positive fluid balance (−136 vs. +6,992 ml, $P < 0.001$). Although the study groups did not differ with regards to mortality, patients in the conservative group experienced more days alive and free from mechanical ventilation (14.6 vs. 12.1 days, $P < 0.001$) and more days alive and discharged from ICU (13.4 vs. 11.2 days, $P < 0.001$) [10]. Benefits from less fluid resuscitation have also been demonstrated in critically ill patients who do not require mechanical ventilation.

The Fluid Expansion as Supportive Therapy (FEAST) trial was conducted in Africa and enrolled 3,141 children presenting to hospital triage with severe febrile illness and signs of impaired perfusion. Children were randomly assigned to maintenance fluids only or a conservative fluid bolus (40 ml/kg) for initial resuscitation. Bolus resuscitation was further randomized to be conducted with either saline or albumin. Patients randomized to receive maintenance fluids only were less likely to die than patients randomized to receive a bolus of saline (7.3 vs. 10.5 % mortality, $P = 0.01$) or a bolus of albumin (7.3 vs. 10.6 % mortality, $P = 0.008$) [11]. These potential survival benefits are also supported by the results of a well-conducted observational study.

The Randomized Evaluation of Normal Versus Augmented Level (RENAL) renal replacement therapy study enrolled 1,508 patients and compared a standard dose rate of continuous renal-replacement therapy to an augmented higher dose rate [12]. Because patient outcomes did not differ between randomized groups, the RENAL study database has been used to support a number of observational studies. One such observational study focused on the relationship between fluid balance and patient outcomes.

Approximately 50 % (748/1,508) of the patients enrolled into RENAL were able to maintain a negative mean daily fluid balance while they remained in intensive care [13]. Compared to patients with a positive mean daily fluid balance, patients who were able to maintain a negative balance were more likely to survive to study day 90 (57.2 vs. 32.3 % mortality, $P < 0.0001$). Complementary evidence from RCTs and observational studies conducted in diverse patient groups highlights an opportunity to improve outcomes for future patients by attempting to improve our understanding of how fluid resuscitation should be provided.

Summary

The total number of clinical trials conducted and published in the field of intensive care medicine has doubled

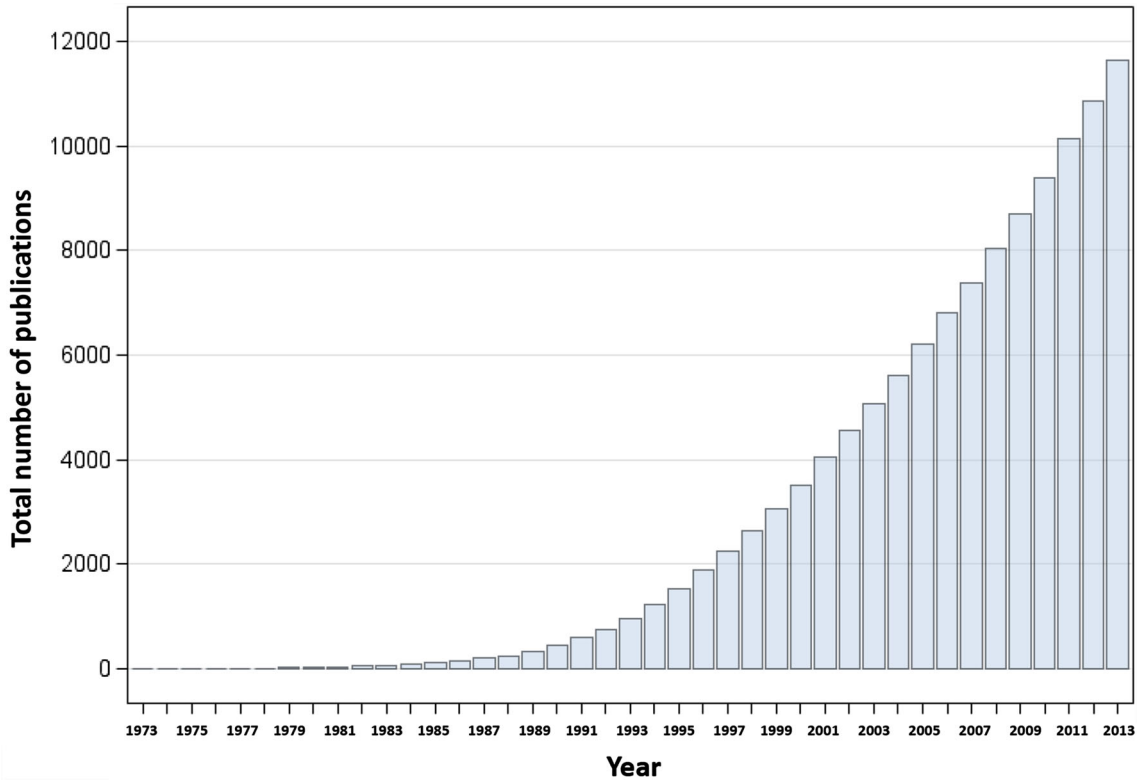

Fig. 1 Cumulative distribution of critical care RCTs indexed on PubMed. PubMed was searched using medical subject headings to identify randomized controlled trials published in the field of intensive care or critical care medicine. A total of 1,163 publications were indexed by Pubmed between 1971 and 2013 using the above terms

over the past 10 years (Fig. 1), but not because the RCT represents the only way forward. The well-conducted RCT represents one of many appropriate research tools at our disposal. In conjunction with the appropriate consideration of physiology, hard-earned bedside knowledge and information generated from well-conducted observational studies, we have little doubt that information generated by RCTs has helped to save tens of thousands of lives over the past 40 years. The appropriate use of objective research evidence will continue to play a major role in defining the future of intensive care.

Conflicts of interest None of the authors have any relevant commercial conflicts.

Ethical standard All appropriate ethical standards were followed during the writing of this review.

References

1. Ibsen B (1954) The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. Proc R Soc Med 47:72–74
2. Lassen HC (1953) A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. Lancet 1:37–41
3. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S et al (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34:1589–1596
4. Willoughby RE Jr, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ et al (2005) Survival after treatment of rabies with induction of coma. N Engl J Med 352:2508–2514
5. De Campos T (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 342:1301–1308
6. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM et al (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensiv Care Med 39:165–228

7. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R et al (2014) Surviving sepsis campaign: association between performance metrics and outcomes in a 7.5-year study. Intensiv Care Med 40:1623–1633
8. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G et al (2004) Effect of intravenous corticosteroids on death within 14 days in 10,008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 364:1321–1328
9. Edwards P, Arango M, Balica L, Cottingham R, El-Sayed H, Farrell B et al (2005) Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months. Lancet 365:1957–1959
10. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B et al (2006) Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354:2564–2575
11. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO et al (2011) Mortality after fluid bolus in African children with severe infection. N Engl J Med 364:2483–2495
12. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S et al (2009) Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 361:1627–1638
13. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J et al (2012) An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial. Crit Care Med 40:1753–1760