Randomized Clinical Trials in Pediatric Critical Care

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Introduction

Evidence-based medicine (EBM) is the conscientious, explicit and judicious use of current best evidence in the care of individual patients [1]. To practice EBM requires the integration of clinical expertise with the integration of current best evidence from systematic research [1]. Randomized controlled trials (RCTs) are the strongest study design that can be used to answer a clinically important question about therapy or prevention [2]. There are numerous examples in the literature of the refutation of findings from observational studies by well-designed RCTs. One is the evaluation of extracranial-intracranial bypass where the superficial temporal artery is anastomized to the middle cerebral artery to prevent strokes in patients with symptomatic cerebrovascular disease who are not surgical candidates. This intervention was widely performed in the early 1980s based upon evidence from comparisons of outcomes among non-randomized 'cohorts' of patients who, for various reasons, did or did not undergo this operation. However, a large multicenter trial in which patients were allocated to surgical or medical treatment using a process analogous to flipping a coin (a RCT), demonstrated that the only effect of surgery was to increase adverse outcomes in the immediate post-surgical period [3]. Treatment effects found in observational studies are commonly overestimated in comparison to studies where treatments are assigned by random allocation [4] but underestimation also occurs [5].

Other surprises generated by RCTs that contradicted the results of less rigorous trials include the demonstration that early use of steroids does not improve the outcome of patients with acute respiratory distress syndrome (ARDS) [6] or sepsis [7], that steroids improve the respiratory outcomes of infants born prematurely [8], and that prophylactic lidocaine after myocardial infarction may increase the risk of death despite its ability to prevent arrhythmias [9]. Studies in which patient or physician preference determines whether a patient receives treatment or control (observational studies) often yield biased outcomes because morbidity and mortality result from many causes, the treatment under study being only one of them. Patient factors such as age, underlying severity of illness, and the presence of comorbid conditions can be prognostic factors or determinants of patient outcome. When patients are sicker in the control group, the treatment may appear more efficacious. The power of randomization is that treatment and control groups are far more likely to be balanced with respect to both the known and unknown determinants of outcome [2].

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One way to determine how strong the evidence-base is that underlies the practice of critical care medicine for infants and children, is to identify and critically appraise all published clinical RCTs trials of therapeutic and preventive interventions. This type of review has been done for the field of neonatal critical care by the Cochrane Neonatal Collaborative Review Group (http://www.nichd.nih.gov/cochrane/default.htm) but not for pediatric critical care. The rest of this chapter is focused on evaluating the state of the evidence supporting the pediatric critical care interventions.

Published Clinical RCTs in Critically Ill Infants and Children

To find published RCTs in pediatric critical care, a search of Medline from 1966–2000 was performed using the following search terms: Randomized controlled trial (publication type) or clinical trials or randomized, pediatric or child, and intensive care or intensive care units, pediatric or critical care. This yielded 557 potential citations and the abstracts were scanned to identify studies that met the criteria of having randomized or quasi-randomized allocation of patients in a pediatric population residing in a pediatric intensive care unit (ICU). In addition, the contents of the Pediatric Critical Care Evidence-Based Journal Club (http://PedsCCM.wustl.edu/EBJournal_club.html) were also reviewed to identify potential studies. Trials performed in newborns were excluded because many of these studies involved mainly neonatal intensive care units (ICUs) and the population of neonates with persistent pulmonary hypertension and congenital diaphragmatic hernia are often treated in neonatal ICUs. Trials where the intervention is performed outside of the pediatric ICU (PICU) (e.g., different cardiopulmonary bypass techniques) were also excluded. Other databases and references of references were not searched. Tables 1–5 list the references of the 42 trials identified and Table 6 lists the three meta-analyses identified.

Although the details of the studies are not listed, the topic areas of the trials as indicated by the titles do reveal some interesting points. There are only five trials eval-

Table 1. Published randomized controlled trials in pediatric critical care in sepsis, respiratory failure and traumatic brain injury

Sepsis

1. Levin M, et al. [10]
2. Reeves JH, et al. [11]
3. Barton P, et al. [12]
4. Slusher T, et al. [13]
5. Tassniyom S, et al. [14]

Acute Hypoxemic Respiratory Failure

1. Willson DF, et al. [15]
2. Dobyns EL, et al. [16]
3. Ream RS, et al. [17]
4. Arnold JH, et al. [18]

Traumatic Brain Injury

1. Simma B, et al. [19]
2. Chacon L [20]

uating therapies for sepsis (Table 1), one of the most common conditions causing excessive morbidity and mortality in PICU patients. Levin et al. [10] evaluated recombinant bactericidal/permeability-increasing protein (BPI) in severe meningococcal sepsis in 393 children across 22 international centers. Reeves et al. [11] evaluated continuous plasmafiltration in sepsis syndrome but only eight children were enrolled and 22 adults. Barton et al. [12] evaluated the use of i.v. milrinone lactate in septic shock but only 12 patients were enrolled and outcomes were alterations in hemodynamic parameters. Slusher et al. [13] evaluated corticosteroids for sepsis in Africa, and Tassniyom et al. [14] evaluated high-dose methylprednisolone for dengue shock syndrome in Thailand. As shown in Table 1, with the exception of the recent BPI for meningococcemia trial, there have been almost no rigorous evaluations of therapies for treating sepsis in chil-dren.

Another syndrome causing severe morbidity and mortality in critically ill children is acute lung injury (ALI) and ARDS. Unfortunately, there have been only four randomized trials evaluating therapies in this area (Table 1). Willson et al. [15] published a pilot study of calf lung surfactant for acute hypoxemic respiratory failure. These investigators are following this pilot study with a large multicenter RCT that is currently enrolling patients (personal communication, Doug Willson). Dobyns et al. [16] and Ream et al. [17] evaluated the effect of inhaled nitric oxide in acute hypoxemic respiratory failure. In both of these studies, intermediary outcomes related to oxygenation improvement were used. Only one trial evaluated a mechanical ventilation strategy (Table 1). Arnold et al. [18] compared high-frequency oscillatory ventilation and conventional mechanical ventilation in a crossover study of 70 patients with respiratory failure who had diffuse alveolar disease or airleak syndrome. The crossover design makes it difficult to evaluate the effect on mortality or length of ICU stay.

Severe traumatic brain injury (TBI) is another major cause of morbidity and mortality in critically ill children. Unfortunately, there have been only two trials of therapies aimed at improving outcome in these patients (Table 1). Simma et al. [19] evaluated two fluid management strategies, lactated Ringer's versus hypertonic saline, in 35 children. Chacon [20] evaluated the use of steroids in a group of children in Venezuela.

The pediatric disorder that has the most trials, eight in total, is bronchiolitis (Table 2). Ribavirin has been studied in three small trials [21–23] and an update of a meta-analysis of these studies (Table 6, [24]) shows a trend towards benefit but concludes that a large trial is needed. Critically ill children were one subgroup of patients in one trial of prednisolone for respiratory syncytial virus (RSV) bronchiolitis [25] and in another trial of RSV immune globulin [26]. In both of these trials, preliminary data showed that the intervention may have more of a positive effect in the critically ill population than in hospital ward patients but the numbers of patients were insufficient to reach a firm conclusion. Other interventions studied in RSV bronchiolitis patients are exogenous surfactant [27], Vitamin A [28] and helium-oxygen [29].

Status asthmaticus is a common reason for admission to the PICU. Only two trials have evaluated interventions for asthma in critically ill children (Table 2). Yung and South [30] evaluated the use of aminophylline for severe acute asthma. Papo et al. [31] evaluated use of continuous versus intermittent nebulized albuterol.

Table 2. Published randomized controlled trials in pediatric critical care of interventions for bronchiolitis and asthma

Bronchiolitis
1. Tibby SM, et al. [27]
2. Guerguerian AM, et al. [21]
3. Hollman G, et al. [29]
4. Rodriguez WJ, et al. [26]
5. van Woensel JB, et al. [25]
6. Quinlan KP and Hayani KC [28]
7. Meert KL [23]
8. Smith DW, et al. [22]
Asthma
1. Yung M and South M [30]
2. Papo MC, et al. [31]

Three trials evaluated prevention of post-extubation stridor with steroids ([32–34], Table 3). A meta-analysis of these studies by Markovitz and Randolph ([35], Table 6) concluded that steroids do prevent post-extubation stridor but their effect on reintubation rates requires a large RCT. One trial compared racemic isomers of nebulized epinephrine for post-extubation stridor [36]. Pain and sedation are important issues in the management of critically ill children but only two trials have been published in this area (Table 3). One study has evaluated the use of non-steroidal anti-inflammatory agents versus narcotics in post-operative patients [37] and one study evaluated whether it is beneficial to load patients with midazolam following open heart surgery before starting an infusion [38]. Fluid overload from congestive heart failure and capillary leak is a common problem in the PICU but only three trials have been performed in this area [39–41]. Klinge et al. [39] and Singh et al. [40] evaluated diuretic therapy using continuous versus intermittent furosemide. Pretzlaff et al. [41] evaluated aminophylline for fluid overload.

Table 3. Published randomized controlled trials in pediatric critical care in prevention of post-extubation stridor, pain and sedation, and diuresis

Prevention of Post-Extubation Stridor
1. Harel Y, et al. [32]
2. Anene O, et al. [33]
3. Nutman J, et al. [36]
4. Tellez DW, et al. [34]
Pain and Sedation
1. Lieh-Lai MW, et al. [37]
2. Macnab AJ, et al. [38]
Diuresis
1. Pretzlaff RK, et al. [41]
2. Klinge JM, et al. [39]
3. Singh NC, et al. [40]

Table 4. Published randomized controlled trials in pediatric critical care in cardiovascular support, nutrition, and prevention of gastrointestinal bleeding

Cardiovascular
1. Morris K, et al. [42]
2. Laitinen P, et al. [43]
Nutrition
1. Maxvold NH, et al. [44]
2. Spalding HK, et al. [45]
3. Barbosa E, et al. [46]
4. Bindl L, et al. [47]
Prevention of Gastrointestinal Bleeding
1. Lacroix J, et al. [48]

Table 5. Published randomized controlled trials in pediatric critical care in transport, nosocomial infection prevention, intravascular access, and fluids and electrolytes

Transport
1. Dockery WK, et al. [49]
Nosocomial Infection Prevention
1. Ruza F, et al. [50]
Intravascular Access
1. Mudge B, et al. [51]
Fluids and Electrolytes
1. Bernardo LM, et al. [52]
2. Broner CW, et al. [53]

Tables 4 and 5 list the few trials that have been published in other areas: cardiovascular support, nutrition, prevention of gastrointestinal bleeding (Table 4) and transport, nosocomial infection prevention, intravascular access, and fluid and electrolyte management (Table 5). Although it is possible that some trials were missed because the references of references were not searched, the paucity of data supporting therapies in pediatric critical care is alarming. Few trials enrolled over 100 patients. Most studies were not sufficiently powered to show an effect. There are very few trials in disorders associated with high morbidity and mortality. No trials have evaluated the use of expensive therapies such as extracorporeal life support in pediatric patients.

Conclusion

Clinical practice should not change based upon the results of a single RCT. Even with a p value of 0.05, it is possible that 1/20 times the results will be spurious. Replication of results leads to robust interventions or to certainty that interventions are not efficacious. In the delivery of critical care to infants and children, practitioners are bas-

Table 6. Meta-analyses of randomized controlled trials in pediatric critical care

1. Randolph AG and Wang EE [24]
2. Markovitz BP and Randolph AG [35]
3. Ausejo M, et al. [54]

ing therapy on single trials or on weak or no evidence. It is possible that many commonly used interventions are harmful. Due to the influence of development, infants and children are physiologically different than adults and neonates. Extrapolation from studies in these populations to the care of critically ill children may lead to harm or to the use of expensive but ineffective interventions. In addition, there is some evidence [25, 26] that interventions found ineffective in children who are only mildly or moderately ill may be effective in children who are critically ill.

Why is it that there are so few trials in the field of pediatric critical care when investigators in the field of neonatal critical care have published over 3000 RCTs supporting or refuting many interventions (see Cochrane Neonatal Collaborative Review Group, http://www.nichd.nih.gov/cochrane/default.htm)? The number of pediatric ICUs is a fraction of the number of neonatal ICUs with a proportionate decrease in the number of trained clinician scientists. Neonatal units have a more homogeneous groups of patients so fewer centers are required to enroll a sufficient number of patients. Pediatric units accept children from birth through age 18 with a wide variety of underlying disorders. These challenges notwithstanding, the paucity of trials in pediatric critical care cannot be easily explained. The field of pediatric critical care is no longer in its infancy. For the sake of critically ill children, it is imperative that pediatric intensive care specialists collaborate to overcome the challenges to collecting the requisite evidence to answer important clinical questions. The lives of many children may be saved or improved.

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