The pros and cons of multicentre studies

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Summary. Clinical trials are carefully designed experiments involving human subjects and aimed at improving patient care. They are of crucial importance in critical care medicine and their results can change clinical practice; however, methodological problems often exist and can compromise the validity of the study. Differences between single-centre and multicentre study design include variations in sample size, time of patient recruitment, costs, presence of bias, validity, centre and investigator characteristics. We reviewed methodological issues related to clinical studies, both single- and multi-centre, with special emphasis on the recent literature covering therapeutic interventions in critically ill patients.

Multicentre collaboration can result in higher rates of patient enrolment than single-centre trials, thereby generating larger studies of shorter duration. Multicentre studies have rigorous study protocols to ensure uniform data collection among centres; however, heterogeneity in clinical practice among centres may be a major confounding factor in interpreting the results of these studies. The discrepancy between the results of single- and multi-centre studies may also be explained by variations in study protocols, inclusion and exclusion criteria, and adherence to study protocol. Factors related to timing of therapy, characteristics of the control group, and dosing of the study drugs may also be important. The results of multicentre studies should be interpreted with careful attention to their pros and cons.

Introduction

Clinical trials are carefully designed experiments involving human subjects and aimed at improving patient care [1]. They are devoted to answering scientific questions and generate evidence-based guidelines for medical practice [2,3]. The high morbidity and mortality associated with critical illness has stimulated a wealth of studies in the last few decades [4]. Issues of epidemiology, diagnosis, prognosis, prevention, treatment, and process of care in critically ill patients have been addressed in numerous multicentre studies.

Clinical studies can be observational or randomized; observational studies are essential in advancing our understanding of aetiology, pathophysiology, diagnosis, natural history, and the biological and human impact of complex critical diseases and disorders [5]. They play a critical role in establishing definitions, incidence, risk factors, prognosis, and the clinical and economic importance of the target outcomes for a future randomized clinical trial (RCT). RCTs have evolved to become the “gold-standard” research design used to distinguish the risks and benefits of therapeutic interventions [6]. The ideal RCT establishes whether therapeutic interventions work, and determines the overall benefits and risks of each alternative in predefined patient populations. This is accomplished by minimizing the influence of chance, bias, and confounding through appropriate methodology. Multicentre collaboration can result in higher rates of patient enrolment than single-centre trials, thereby generating larger studies of shorter duration. Enrolment of patients in several sites also enhances the generalizability of study results to similar patients in similar settings [4]. However, the wide variation in intensive care unit (ICU) organizational issues among sites may influence patient outcome [7,8], limiting the extrapolation of the results of multicentre RCTs to other ICU patients with different case mixes. Various methodological aspects may additionally limit the value of RCT-derived results in everyday practice.

We reviewed methodological issues related to clinical studies, whether single- or multi-centre, with special emphasis on the recent literature investigating therapeutic interventions in critically ill patients.

Sample size

Several methodological issues differentiate between single- and multi-centre studies (Table 1). Multicentre studies generally allow inclusion of larger sample sizes and can be conducted over a relatively shorter period of time; however, single-centre studies have better internal validity compared with multicentre studies, because of the enrolment of a specific population in a relatively homogenous experimental setting [4,9]. Several RCTs have investigated the possible effect of selenium supplementation on outcome. The interventional studies, eight of them single-centre [10-17] and two multicentre [18,19], differ in many aspects. However, a key factor is that most of these studies were performed on relatively small patient populations presenting with trauma, burns, sepsis, or acute pancreatitis and thus were underpowered to detect a treatment effect on clinically important outcomes. In a recent prospective, multicentre RCT by Angstwurm and colleagues [18], 249 patients with severe systemic inflammatory response syndrome (SIRS), sepsis, and septic shock were randomized to receive selenium or placebo. The primary end point of 28-day mortality was significantly reduced to 42.4% in the treatment group compared to 56.7% in the placebo group. The initial sample size of the study was determined based on the aim of achieving 80% power to detect a 20% reduction in 28-day mortality. However,
because of excessive losses to follow-up and because the observed reduction in mortality was less than predicted, the study’s per-protocol analysis may be associated with significant errors that could invalidate the results [18].

### Heterogeneity

In multicentre studies, a rigorous protocol is used to ensure uniform data collection; however, heterogeneity in clinical practice among different centres may be a major confounding factor in interpreting the results of these studies. For example, Pronovost et al. [8], showed that lack of daily rounds by an ICU physician was associated with a 3-fold increase in in-hospital mortality and significant morbidity in patients undergoing abdominal aortic surgery. Lack of daily rounds by an ICU physician, an ICU nurse-patient ratio of less than 1:2, no monthly review of morbidity and mortality, and extubating patients in the operating room were associated with increased resource use. Likewise, Dimick et al. [7] found that lack of daily rounds by an ICU physician after oesophageal resection was associated with a 73% increase in hospital length of stay, 62% increase in total hospital cost, pulmonary insufficiency, renal failure, aspiration, and reintubation, but there was no association with in-hospital mortality rates.

### Study protocol

The discrepancy between the results of single- and multi-centre studies may also be explained by variations in study protocols. Inclusion and exclusion criteria may vary widely among clinical trials investigating therapeutic interventions. Two large prospective, single-centre RCTs [20,21] demonstrated that maintenance of normoglycaemia with intensive insulin therapy substantially prevented morbidity and reduced mortality in critically ill patients. In surgical patients [20], ICU and hospital mortality and morbidity were substantially reduced in patients treated with tight glycaemic control compared with the control group. These findings were only reproducible in medical patients [21] who remained in the ICU for at least three days. More recently, two large prospective, multicentre RCTs [22,23] analyzed the tight glucose control approach: one in mixed ICU patients (Glucontrol) [22] and the other in mixed ICU patients with severe sepsis (VISEP) [23]. Both studies were prematurely terminated due to potential harm and lack of efficacy. The study populations were clearly different among trials, with medical [21], surgical [20], mixed ICU patients [22], or patients with severe sepsis [23]. The reported incidence of hypoglycaemia was higher in the medical population treated with tight glycaemic control [21] compared with the surgical population and in the multicentre studies compared with the single-centre ones.

Factors related to timing of therapy, characteristics of the control group, and dosing of the study drugs may also be important. In addition, adherence to protocol may limit inclusion of patients in multicentre studies. In a multicentre French study, Annane et al. [24] demonstrated that a 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with early septic shock and relative adrenal insufficiency without increasing adverse events. Likewise, Bollaert et al. [25] showed that administration of hydrocortisone in patients with septic shock for more than 48 hours had a beneficial effect on survival. These observations were, unfortunately, not reproducible in all single-centre studies and, in a recent multicentre study, Sprung et al. [26] showed that administration of hydrocortisone did not decrease 28-day mortality rates in patients with septic shock regardless of ACTH responsiveness. Timing of therapy varied markedly among studies with patients enrolled as early as 6 hours from the onset of shock [24] and from 24 to 72 hours in other studies [25-29].

Five clinical trials have investigated the value of ventilating patients with ALI/ARDS with a protective strategy using low tidal volumes. In a single-centre Brazilian study, Amato et al. [30] randomized 53 patients with ARDS into two groups: one ventilated with a tidal volume of 4.6 ml/kg (protective strategy) and a control group ventilated with 12 ml/kg. Mortality rate at 28 days was lower in the protective strategy group. Only one of the four multicentre trials showed a decrease in hospital mortality rate in patients ventilated with low tidal volumes [31]. The others showed similar mortality rates between the study groups and higher adverse events like barotrauma and multiple organ failure in patients ventilated with higher than in those ventilated with lower tidal volumes [32-34]. On the basis of a recent meta-analysis, a parabolic relationship between mortality rates and changes in tidal volumes and resultant plateau pressures could provide an explanation for the contradictory findings in these five trials [35]. Both high and low tidal volumes and airway pressures may be associated with increased mortality compared with usual clinical practice. The meta-analysis [35] concluded that the two beneficial trials failed to use control arms representing current practice and they could not, therefore, determine whether the therapy tested was actually superior.

### Outcome parameters

Multicentre studies are mostly designed to investigate possible differences in mortality rates as the primary outcome [36]. The current standard end-point for ICU-based clinical trials is 28-day all-cause mortality [36]; however, due to small sample sizes, single-centre studies are mostly statistically under-powered to draw a final conclusion regarding differences in mortality rates. Therefore, the use of morbidity as an outcome parameter is common in these trials.

### Conclusion

Multicentre collaboration can result in higher rates of patient enrolment than single-centre trials, thereby generating larger studies of shorter duration, investigating important diagnostic and therapeutic issues in critically ill patients. Multicentre studies have several advantages over single-centre studies including more rigorous study protocols to ensure uniform data collection; however, heterogeneity in clinical practice among centres may be a major

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**Table 1. Differences in the design of single- vs. multi-centre studies**

<table>
<thead>
<tr>
<th>Study type</th>
<th>Sample size</th>
<th>Duration of patient recruitment</th>
<th>Validity</th>
<th>Protocol</th>
<th>Personal Bias</th>
<th>Costs</th>
<th>Statistical Data Analysis</th>
<th>Centre Characteristics</th>
<th>Adherence to protocol by investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-centre study</td>
<td>Smaller</td>
<td>Longer</td>
<td>Internal</td>
<td>Simple</td>
<td>More</td>
<td>Lower</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
<td>Greater</td>
</tr>
<tr>
<td>Multi-centre study</td>
<td>Larger</td>
<td>Shorter</td>
<td>External</td>
<td>More complex</td>
<td>Less</td>
<td>Higher</td>
<td>Stronger</td>
<td>Homogeneous</td>
<td>Lesser</td>
</tr>
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confounding factor in interpreting the results of these studies. The discrepancy between the results of single- and multi-centre studies may also be explained by variations in study protocols, inclusion and exclusion criteria, and adherence to study protocols. Factors related to timing of therapy, characteristics of the control group, and dosing of the study drugs may also be important. The results of multicentre studies should be interpreted with care in view of their methodological limitations.

Reference