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REVIEW

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On the need for observational studies to design and interpret randomized trials in ICU patients: a case study in stress ulcer prophylaxis

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Introduction

The primacy of well designed randomized clinical trials (RCTs) for evaluating the effectiveness of preventive and therapeutic interventions is undeniable. However, observational studies are essential for advancing our understanding of aetiology pathophysiology, diagnosis, natural history, and the biological and human impact of complex critical diseases and disorders. Both observational studies and RCTs have made notable contributions to the biomedical clinical intensive care literature during the past two decades [1], and international contributions have been prominent [2]. Two issues central to the advancement of knowledge in critical care medicine are whether sufficient information from observational studies has been obtained in preparing for RCTs (particularly when initial RCT results are negative), and whether we learn all we can from analyses on RCT databases prior to subsequent RCTs.

This contribution illustrates how an integrated research programme was developed by observational studies conducted both before and after a RCT evaluating two drugs used for stress ulcer prophylaxis (Fig. 1). The rationale for the preparatory observational studies, the insights we obtained from them, and the way in which they influenced the design of the subsequent RCT are presented. We also describe how pre-planned analyses which followed the RCT generated additional observational studies that helped to interpret the RCT results.

Setting

The Canadian Critical Care Trials Group (CCCTG) is an organization of intensivists that promote investigator-initiated clinical research in intensive care medicine [3]. Our original prioritized research agenda created in 1989 included a proposal to test the effectiveness of two stress ulcer prophylaxis agents and to evaluate whether increased gastric pH is a risk factor for ventilator-associated pneumonia (VAP).

Firstly, we prepared two meta-analyses of RCTs on bleeding prevention. One showed that histamine-2 receptor antagonists are superior to no prophylaxis, and that sucralfate may be as effective as histamine-2 receptor antagonists at bleeding prevention [4]. Concern about whether increased gastric pH predisposes to intragastric gram negative bacilli and aspiration led to the second meta-analysis focusing on VAP, which suggested that histamine-2 receptor antagonists are associated with higher rates of VAP than sucralfate [5]. However, only a few of these RCTs were double-blind, had objective outcome definitions, and used an intention-to-treat analysis, rendering their conclusions tenden-

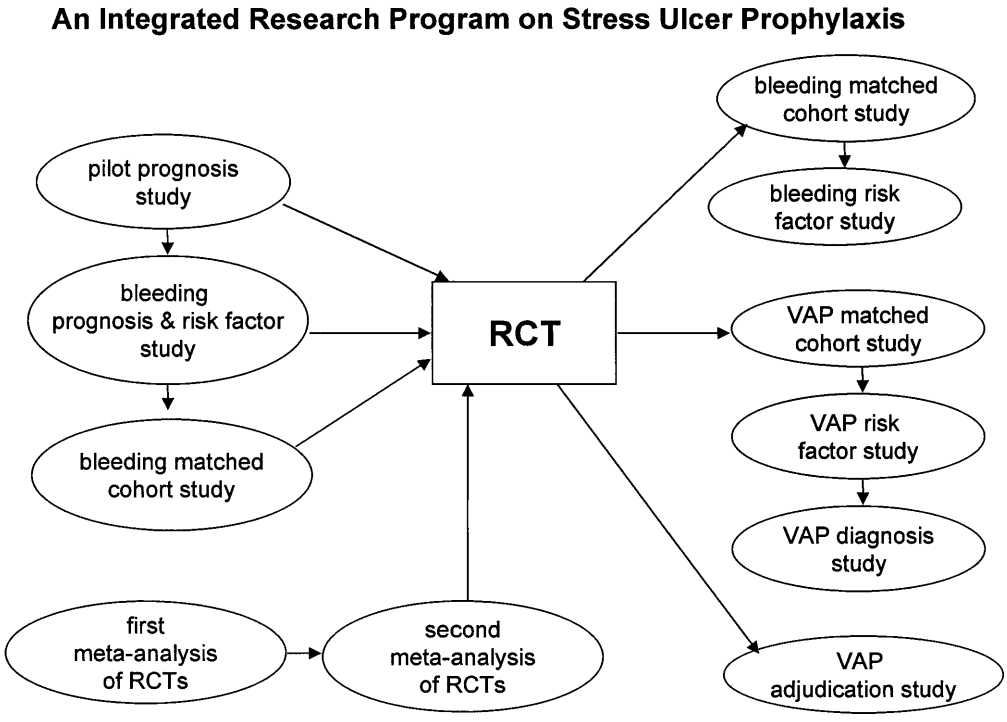

Fig. 1 Demonstration of the way in which observational studies helped with the design *(left)* and interpretation *(right)* of a randomized trial *(centre)* of stress ulcer prophylaxis

tious. Therefore we decided to build upon their strengths and address their weaknesses in a large multicentre RCT of stress ulcer prophylaxis.

Pre-trial observational studies

Initial discussions of the proposed RCT revealed that there was no consensus among our group, nor data from the literature, about what constituted clinically important gastrointestinal bleeding, nor about which ICU patients were at greatest risk of bleeding. Therefore we decided first to establish the most appropriate study population and the interventions and outcomes of interest.

What is clinically important gastrointestinal bleeding in ICU patients?

Rationale

The first step in this research programme was to estimate the magnitude and relevance of clinically important gastrointestinal bleeding. The objectives of this pilot study were to formulate bleeding definitions, estimate bleeding rates and obtain preliminary data about bleeding risk factors.

Results

We conducted a prospective prognosis study to estimate the gastrointestinal bleeding rate among 100 patients admitted to a medical-surgical ICU [6]. We utilized two definitions: overt bleeding manifest by haematemesis or frank blood from the nasogastric tube, and clinically important bleeding manifest as overt bleeding associated with hypotension and transfusion of 2 U red blood cells. The overt bleeding rate was 9.0% (95% CI 3.4–14.6%); the clinically important bleeding rate was 2.0% (95% CI 0–6.2%). Risk factors for overt bleeding by univariate analysis were coagulopathy [odds ratio (OR) 1.3, 95% CI 3.4–46.5], and 6 days of occult bleeding (OR 5.5, 95% CI 1.2–25.4).

What is the incidence of, and what are the risk factors for, clinically important bleeding?

Rationale

Assuming a bleeding rate of 2.0% from the pilot study, an RCT with 75% power to detect a 25% relative risk (RR) reduction in bleeding would have required approximately 19000 patients. Therefore one objective of this large prognosis study was to obtain a more precise estimate of the incidence of bleeding for the RCT sample size calculation; the secondary objective was to evaluate bleeding risk factors.

Results

We conducted a prospective multicentre cohort study of 2252 ICU patients in 4 centres [7]. Clinically important bleeding developed in 1.5% (95% CI 1.0–2.1%). Two independent risk factors were identified: mechanical ventilation for 48 h (OR 15.6, 95% CI 4.6–53.0) and coagulopathy (OR 4.3, 95% CI 2.0–9.4). Of 847 patients who had one or both risk factors, 3.7% bled, whereas 0.1% of 1405 patients without these risk factors bled. Therefore, the high-risk population that we targetted for the RCT comparing two stress ulcer prophylaxis strategies was patients who required at least 2 days of mechanical ventilation.

What is the attributable morbidity, mortality and cost of clinically important gastrointestinal bleeding?

Rationale

Not all ICU-acquired events are clinically or economically important enough to warrant prevention. Therefore our next objective was to determine whether there was an attributable length of ICU stay, mortality and cost associated with clinically important bleeding.

Results

We performed a matched cohort study, matching bleeding patients with controls based on age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, diagnosis, ventilator status, duration of ICU stay, and centre [8]. All direct costs were obtained from the ICU perspective. The ICU stay attributable to clinically important bleeding was 6.5 days (95% CI –12.3 to 25.3 days) and the increased RR of mortality was 12.5% (95% CI –38.0% to 63.0%). The attributable cost of bleeding was $12215 (1995, Canadian dollars). This observational study confirmed that clinically important bleeding has medical and monetary consequences, and that an RCT of preventive strategies was justified.

What are the benefits and harms of stress ulcer prophylaxis drugs?

Rationale

Since this research programme began, but before the RCT was launched, additional RCTs had been published. Our objective was to incorporate recent RCTs in an updated meta-analysis to determine the benefits and harms associated with prophylaxis, and to understand why prior meta-analyses yielded discordant results [9, 10, 11]. We also wanted assurance that the available evidence was not sufficiently robust that another RCT would be either unnecessary or unethical.

Results

Source of discrepancies between prior meta-analyses included variable definitions and statistical methods, and different approaches to non-randomized and non-English language articles [12]. The updated meta-analysis confirmed that prophylaxis with histamine-2 receptor antagonists significantly decreased clinically important bleeding compared to no prophylaxis (OR 0.4, 95% CI 0.2–0.9) but did not increase VAP risk (OR 1.1, 95% CI 0.7–1.8). Sucralfate appeared equivalent to histamine-2 receptor antagonists with respect to bleeding, although data were very sparse (OR 1.3, 95% CI 0.3–6.1). However, sucralfate was associated with a trend toward a lower incidence of VAP than histamine-2 receptor antagonists (OR 0.7, 95% CI 0.5–1.0). Since VAP is a potentially serious adverse effect of gastric pH-altering agents, and because most prior RCTs focused on bleeding outcomes, we calculated the RCT sample size to detect a clinically important difference in VAP. We assumed a 25% incidence of VAP associated with ranitidine, and a 25% RR reduction associated with sucralfate. This generated a sample size of 1200 patients for 75% power under a two-tailed significance test at the $p \leq 0.05$ level.

RCT of sucralfate versus ranitidine

Rationale

Because of concerns about the methodology of prior RCTs, we did not regard the meta-analysis as sufficient evidence to recommend sucralfate on the basis of its equivalence to histamine-2 receptor antagonists at bleeding prevention but its superiority with respect to VAP risk. Therefore the objective of this study was to compare histamine-2 receptor antagonists versus sucralfate with respect to clinically important bleeding and VAP in a large concealed, blinded RCT.

Results

In 16 centres, 1200 mechanically ventilated ICU patients were randomized to ranitidine or sucralfate [13]. Patients, caregivers, all research personnel and statisticians were blinded; the analysis was by intention-to-treat. Ranitidine was associated with a significantly lower bleeding rate than sucralfate (RR 0.4, 95% CI

0.2–0.9), but the VAP rate was similar (RR 1.2, 95% CI 0.9–1.5). There were no differences in mortality or duration of ICU stay. In light of the recognized discrepancies between meta-analyses of small RCTs and subsequent large RCTs [14], stress ulcer prophylaxis provides an interesting example of both discordance and concordance in one case study: the meta-analysis suggested that sucralfate and histamine-2 receptor antagonists were equivalent at bleeding prevention, but the RCT found a 50% lower bleeding rate with ranitidine (discordance). Conversely, the meta-analysis suggested a trend toward an increased risk of VAP associated with histamine-2 receptor antagonists, and the RCT demonstrated a very similar trend (concordance).

Posttrial observational studies

Pre-planned observational analyses of RCT databases can address important questions that help to interpret RCT results. Accordingly, we designed these observational studies to validate the length of ICU stay and mortality attributable to bleeding, to re-examine bleeding risk factors, to estimate the length of ICU stay and mortality attributable to VAP, to determine risk factors for VAP, to understand the impact of the VAP adjudication process on RCT outcome, and to evaluate the influence of VAP diagnostic approaches on patient management.

What is the length of ICU stay and mortality attributable to clinically important bleeding?

Rationale

Although we previously found that the incidence of bleeding in ventilated patients in Canada is approximately 4% [6], and that bleeding is associated with increased morbidity and mortality [8], reports of very low bleeding rates elsewhere [15] led us to re-appraise the burden of illness associated with this ICU-acquired event. The objective of the study was to obtain a more precise estimate of the length of ICU stay and mortality attributable to bleeding using 166 patients who were mechanically ventilated for less than 48 h from both the RCT [13] and our prognosis study [8]. We used a more rigorous matching procedure than previously by performing Cox' regression analysis using time to death as the dependent variable and the following as independent variables: age, APACHE II score, admitting diagnosis, duration of ventilation, duration of ICU stay, and Multiple Organ Dysfunction score [16] 3 days prior to the bleed. Bleeding patients were matched with non-bleeding patients based on β coefficients from the regression model.

Results

We found that the length of ICU stay attributable to clinically important bleeding was 6.7 days (95% CI 2.7–10.7 days), and that the mortality risk was significantly increased (RR 1.8, 95% CI 1.1–2.9; manuscript in preparation). These data confirmed that gastrointestinal bleeding had an important impact on morbidity and mortality.

What are the risk factors for clinically important gastrointestinal bleeding in mechanically ventilated patients?

Rationale

Although we enrolled patients in the RCT who were at highest risk for bleeding (those requiring mechanical ventilation for at least 48 h), we speculated that there may be subgroups of patients who, despite being ventilated, had such a low bleeding risk that prophylaxis might not be needed. The objective of this analysis was to examine additional factors associated with bleeding (both predisposing and protective) among highest risk patients.

Results

We found that the only independent predictor of bleeding was serum creatinine (RR 1.16, 95% CI 1.0–1.3), whereas ranitidine (RR 0.4, 95% CI 0.2–0.8) and enteral nutrition (RR 0.3, 95% CI 0.1–0.7) were associated with significantly lower bleeding rates [17]. Potential mechanisms by which renal insufficiency predispose to bleeding include gastric erosions such as angiodysplasia common in uraemic patients, or unmasking of previous erosive disease by thrombocytopathy; an alternative explanation for the association between bleeding and renal failure is that impaired perfusion is responsible for both ischaemic gastropathy and haemodynamically mediated renal failure.

The protective effect of ranitidine mirrored the overall RCT results [13]. In other non-randomized studies, enterally fed patients were found to have lower bleeding rates than patients who were not fed enterally [18]. Although a mucosal protective effect of feeds has been postulated, an alternate explanation is that patients with a lower intrinsic risk of bleeding are those who better tolerate feeds. This was supported by the consistent benefit of ranitidine in bleeding prevention whether patients had no enteral nutrition (RR 0.51), any enteral nutrition (RR 0.29), enteral nutrition for 3 days (RR 0.27), or in all 1200 patients in the RCT, 70% of whom had enteral nutrition (RR 0.44). In summary, this obser-

vational analysis shows that histamine-2 receptor antagonists lower bleeding rates regardless of enteral nutrition status. Whether a sufficiently powered RCT will be conducted to directly compare stress ulcer prophylaxis with ranitidine versus enteral nutrition on bleeding outcomes remains to be seen.

What is the length of ICU stay and mortality attributable to VAP?

Rationale

Although our RCT demonstrated that ranitidine is associated with a 50 % lower bleeding rate than sucralfate, ranitidine showed a trend toward an increased risk of VAP. The objective of this observational study was to evaluate the clinical consequences of VAP, given conflicting prior literature about whether VAP increases the risk of mortality [19, 20]. We estimated the length of ICU stay and mortality attributable to VAP using a matched cohort method, considering a hierarchy of the APACHE II score, medical or surgical status, duration of ICU stay, duration of ventilation, Multiple Organ Dysfunction score on the day prior to VAP, admitting diagnosis, age, centre and sex.

Results

Patients with VAP stayed in ICU 4.3 days (95 % CI 1.5–7.0) longer than matched patients without VAP and had a trend towards higher risk of death (absolute risk increase 5.8 %, 95 % CI –2.4 to 14.0; RR increase 32.3 %, 95 % CI –20.6 to 85.1 %) [21]. We concluded that VAP, as with clinically important gastrointestinal bleeding, confers substantial morbidity and a trend toward increased mortality.

What are the risk factors for VAP?

Rationale

Having established that VAP is a clinically important outcome, we then determined the influence of histamine-2 receptor antagonists as a potential VAP risk factor relative to other VAP risk factors. Although an early study identified cimetidine as an independent risk factor for VAP [22], subsequent multivariable analyses have reproducibly identified reintubation [23, 24, 25] and antibiotics [26, 27] as risk factors in more than one observational study. The objective of this study was to examine both baseline and time-dependent risk factors, including measures of illness severity, variables related to the gastropulmonary route of infection, and drug exposure.

Results

Independent predictors of VAP in the multivariable analysis were diagnosis of burns (RR 5.0, 95 % CI 1.6–16.2), trauma (RR 3.9, 1.5–10.0), central nervous system disease (RR 3.3, 1.3–8.4), respiratory disease (RR 2.8, 1.0–7.5), or cardiac disease (RR 2.7, 1.1–7.0), mechanical ventilation in the previous 24 h (RR 2.2, 1.1–4.5), witnessed aspiration (RR 3.1, 1.5–6.1), and paralytic agents (RR 2.0, 1.3–2.9), while antibiotic exposure conferred protection (RR 0.4, 0.3–0.5) which attenuated over time [28]. Histamine-2 receptor antagonists had no influence on the risk of VAP in the univariate or multivariate analysis; this was consistent with our RCT results. We concluded that stress ulcer prophylaxis with histamine-2 receptor antagonists is not an important VAP risk factor, alone or relative to other risk factors.

What is the influence of the VAP adjudication process on the RCT results?

Rationale

Diagnosing VAP is difficult because of the non-specific nature of the clinical and radiographic features. Given the absence of a reference standard, we used five different diagnostic methods (the first was used for the primary analysis): (a) by adjudication committee, (b) the bedside clinician's diagnosis, (c) the Centre for Disease Control definition (d) the Clinical Pulmonary Infection Score ≥7) [29], and (e) positive culture from either bronchoalveolar lavage (BAL; $> 10^4$ CFU/ml) or protected specimen brush (PSB; $> 10^3$ CFU/ml). The objective of this study was to evaluate the influence of the adjudication process on the RCT results. Each case of suspected VAP was examined by one of four pairs of adjudicators. All notes and laboratory data were allocated to adjudication pairs in groups of five patients. Each reader in the pair decided whether VAP was present, and differences were resolved by consensus.

Results

The proportion of charts adjudicated as VAP positive among the four pairs ranged from 50 % to 92 %; crude agreement between readers in each pair varied from 50 % to 82 % [30]. When adjudicators disagreed, in two of four pairs, the final decision reflected one dominant opinion. Given that adjudication teams had different thresholds for diagnosing VAP, dissimilar standards could theoretically have biased the overall RCT results. Therefore we compared the initial unadjusted RCT results for VAP (OR 0.82, $p = 0.21$) to results adjusted for adjudication pair (OR 0.85, $p = 0.27$). The RCT con-

clusion was unchanged; ranitidine was not associated with significantly higher VAP than was sucralfate.

We also concluded that to ensure rigorous adjudication of clinical outcomes without a standard definition adjudicators should be trained to use a reproducible process, and agreement should be monitored so remediation can occur if one adjudicator dominates decision-making. If independent adjudication teams exist, they should have similar thresholds and, all else being equal, judge a similar proportion of events as positive. To minimize the chance that interpretive differences might bias RCT results, charts should be block randomized to adjudication teams. More research on the effort-yield and cost-benefit ratios of adjudicating major morbid events in RCTs is warranted.

What is the influence of invasive versus noninvasive VAP diagnosis on VAP management?

Rationale

The objective of this study was to compare the effect of invasive versus non-invasive VAP diagnosis on physician decision-making (likelihood of the diagnosis and physician confidence), the process of care (antibiotics) and clinical outcomes.

Results

Physician knowledge of BAL or PSB results made VAP a less likely diagnosis than before bronchoscopy ($p < 0.001$) [31]. Confidence increased ($p = 0.03$), and physicians were more comfortable with the VAP management plan after BAL or PSB results ($p = 0.02$). Patients who underwent bronchoscopy received fewer antibiotics ($p = 0.05$) and more often had all antibiotics discontinued ($p = 0.04$) than in the control group. Duration of mechanical ventilation, ICU stay and hospital stay were similar. Mortality was significantly lower in the group undergoing BAL or PSB (18.5 versus 34.7 %, $p = 0.03$). We found that invasive diagnostic testing increased physician confidence in the diagnosis and management of VAP and resulted in more antibiotic discontinuation. Other comparative studies [32, 33] and regression analysis [34] have linked bronchoscopic diagnosis with more appropriate antibiotic treatment. Whether BAL or PSB results consistently affect clinically important outcomes requires further study. One RCT examining invasive methods and quantitative endotracheal aspirates versus quantitative endotracheal aspirates alone [35] found that 42 % versus 16 % of patients had antibiotic modification ($p < 0.05$), although mortality rates were not significantly different (46 % versus 26 %). A recent multicentre French RCT of 413 patients found that those diagnosed with an invasive strategy and treated with targetted antibiotics compared to patients diagnosed using clinical criteria and treated according to the American Thoracic Society guidelines had significantly lower antibiotic use ($p < 0.001$) and lower mortality (16 % versus 26 %, $p < 0.05$) [36]. Several research groups including ours are planning further RCTs in this area.

Conclusions

Observational studies play a critical role in establishing definitions, incidence, risk factors, prognosis, and the clinical and economic importance of the target outcomes for a future RCT. Observational analyses on RCT databases can re-examine risk factors, generate more precise estimates of the attributable morbidity and mortality of these outcomes, explore methodological issues such as outcome adjudication, and clarify questions best addressed by a subsequent RCT. Had we not capitalized on prior observational research to inform this RCT of stress ulcer prophylaxis, at least seven problems would have arisen: (a) non-reproducible outcome definitions, (b) inaccurate estimates of bleeding rates, (c) uncertainty about the clinical and economic importance of the target event, (d) enrolment of patients at trivial risk of bleeding rather than those at highest risk most likely to benefit from prophylaxis, (e) misunderstanding the risks and benefits of prophylaxis, (f) sample size calculations using an erroneous baseline risk of bleeding and an unrealistic expected difference between the two drugs, and (g) suboptimal expenditure of research funds. Instead, these potential problems were averted by data furnished in observational studies, rendering a pilot RCT unnecessary.

The merit of using an RCT database as the foundation for subsequent observational studies depends on the integrity and comprehensiveness of the database for the questions posed. Potential advantages include prospective and unbiased collection of data and their acquisition through resources already expended under the auspices of the RCT. We employed five observational analyses to conduct these post-RCT studies: concurrent comparisons, matched cohort methods, regression analysis, outcomes modelling, and before-after comparisons. Four of the five post-RCT observational studies described here were planned a priori while one analysis of risk factors for clinically important bleeding was planned following RCT completion. The consequence of this post hoc approach was that we were not able to validate our prior finding that coagulopathy was an independent bleeding risk factor [6]. This was because we did not collect in the RCT any international normalized ratio or partial thromboplastin time values. However, in the univariate analysis of the post-RCT observational study

thrombocytopenia was significantly associated with bleeding; considering this and other evidence [37, 38, 39], coagulopathy and mechanical ventilation remain the two major risk factors for gastrointestinal bleeding.

The goal of this paper was not to catalogue clinical research models in critical care or suggest a preferred archetype. However, integrating RCTs into a series of observational studies suits situations in which long-term research programmes are possible, when the goals of several investigators converge, when ongoing multidisciplinary collaboration is sought with epidemiologists, biostatisticians and economists, and for settings in which research funding is difficult to secure. Although the cost-effectiveness of funding basic science [40] and RCTs [41] has been examined from a resource allocation perspective, the return on investment for funding a research programme which is characterized by pre- and post-RCT observational analyses has not been appraised. In this model observational studies played a crucial role in the optimal design of, and adequate interpretation of, one RCT. Such an approach to a research programme is one of many fruitful alternative strategies, including those that (a) address broad issues in a field, (b) address a specific clinical syndrome or problem, (c) use one primary research design or (d) integrate basic sciences or health services research designs and perspectives.

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