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Interventions affecting mortality in critically ill and perioperative patients: A systematic review of contemporary trials

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ABSTRACT

Purpose: Confounders in randomized controlled trials (RCTs) reporting significant effects on mortality in critically ill patients using non-surgical techniques have not been systematically explored. We aimed to identify factors unrelated to the reported intervention that might have affected the findings and robustness of such trials.
Methods: We searched Pubmed/MEDLINE for all RCTs on any non-surgical interventions reporting an effect on unadjusted mortality in critically ill patients between 1/1/2000 and 1/12/2015. We assessed: the number needed to treat/harm (NNT or NNH), sample size, trial design (blinded/unblinded, single or multinational, single or multicenter (sRCT or mRCT)), intention to treat (ITT) analysis, and countries of origin.
Results: Almost half of RCTs were sRCTs. Median sample size was small, and 1/3 were not analyzed according to ITT principle. Lack of ITT analysis was associated with greater effect size ($p = 0.0028$). Harm was more likely in mRCTs ($p = 0.002$) and/or in blinded RCTs ($p = 0.003$). Blinded RCTs had double sample size ($p = 0.007$) and an increased NNT/NNH ($p = 0.002$). Finally, mRCTs had higher NNT ($p = 0.005$) and NNH ($p = 0.02$), and harm was only detected in studies from Western countries ($p = 0.007$).
Conclusions: These observations imply that major systematic biases exist and affect trial findings irrespective of the intervention being studied.

1. Introduction

Decreasing mortality in critically ill and postoperative patients is a public health goal. Thus, the primary outcome measure of multiple interventional trials [1]. Such patients are at high risk of death [2-6] and represent one of the main areas of health care expenditure in the western world [7]. Accordingly, any study reporting the effect of an intervention on mortality (either an increase or a decrease) has the potential to significantly change clinical practice worldwide, save thousands of lives, and reduce health-care costs [8].

According to Evidence Base Medicine (EBM) principles, randomized controlled trials (RCT) represent the most robust source of evidence to guide practice [9]. However, in the field of critical care and postoperative medicine, no assessment has been made of what confounding factors may affect the findings of such RCT beyond the intervention itself and whether any systematic biases exist, which may affect trial findings.

Accordingly, we systematically identified all contemporary RCTs of non-surgical intervention in critical care and postoperative medicine (all studies published since 2000) and reported in peer reviewed journals, which showed a statistically significant impact on mortality. The aim of our study was to identify whether there were confounding factors unrelated to the interventions, which might have systematically affected trial findings.

2. Methods

2.1. Systematic search and article selection

PubMed/MEDLINE were searched for all RCTs of any non-surgical intervention influencing unadjusted landmark mortality in critically ill and postoperative patients published between January 1st, 2000 and

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December 1st 2015 (see full PubMed search strategies in Supplementary Appendix). Additional articles were suggested by experts and obtained from a cross-check of references from primary papers.

Articles were then selected for further assessment if they met all the following criteria:

1) Publication in a peer-reviewed English-language journal;
2) Single-center or multicenter trial design;
3) Randomized controlled trial design;
4) Statistically significant reduction or increase in unadjusted landmark mortality;
5) Postoperative or critical care setting;
6) Publication date between January 2000 and November 2015.

Articles were excluded if they fulfilled at least one of these criteria: 1) Used a quasi-randomized or non-randomized methodology; 2) Dealt only with a pediatric population (<18 years); 3) Did not report mortality data.

We considered patients to be critically ill if, at randomization, they had at least one organ failure and/or were receiving intensive care treatment and/or emergency treatment, regardless of where they were treated (intensive care unit, emergency department, or general ward). Assessment of the eligibility of the identified studies was performed by two authors. Differences of opinion were discussed among authors until consensus was reached.

2.2. Data collection

For each RCT, we extracted details of the paper (title, first author, journal name, year of publication, impact factor of the journal in the year of publication), details of the RCT design (the intervention and its comparator, trial setting, blinding, intention to treat analysis, whether enrollment was interrupted after interim analysis, number of patients randomized to each group, number of patients who experienced an outcome in each group), details of the significant mortality outcome (follow-up time, whether mortality was the primary study outcome, type of statistical test used to assess the difference in mortality, and p-value reported).

2.3. Data analysis

We assessed and recorded the size effect of the intervention, the absolute risk reduction or increase, and the number needed to treat or number needed to harm (NNT/NNH) [10].

For RCTs reporting a significant difference in mortality at more than one landmark time, we chose the longest follow-up time. For trials with more than one comparator treatment and where intervention affected mortality compared to more than one control group, we chose the comparison with the smallest p-value. We analyzed the differences in the NNT/NNH, sample size, number of multicenter randomized clinical trials (mRCTs) and single-center RCTs (sRCTs), number of blinded studies, median impact factor, median p-value of the studies, median number of centers and median number of nations, according to impact on mortality (harmful and beneficial studies), trial design (blinded versus unblinded, single nation versus multinational, and sRCTs versus mRCTs), countries (European and non-European, USA and non-USA, non-European, non-USA, non-Australia and New Zealand (ANZ), non-Canada vs. other countries), assessment of mortality as primary or secondary outcome, conflict of interest (none declared versus declared and not declared), setting (intensive care unit (ICU) and non-ICU); intervention type such non-invasive ventilation (NIV) versus all the other interventions.

2.4. Statistical analysis

The Dataset was created using Microsoft Excel 2010 for Windows (Microsoft Corporation, Redmond, WA, USA) and analyzed with the use of Stata software, version 13 (StataCorp). Continuous variables are reported as medians and interquartile range (IQR) and categorical variables as counts and percentage. Comparisons of dichotomous data were performed by Chi-squared test or Fisher's exact test as appropriate. Continuous measurements were compared with the use of the Wilcoxon – Mann Whitney test where appropriate. To adjust for multiple comparisons, a p-value < 0.01 was considered statistically significant.

3. Results

3.1. General study characteristics

The five search strategies initially returned >60 thousand RCTs. After excluding overlaps, our search identified 56,554 potential manuscripts published between January 2000 and December 2015. Of these, 139RCTs met the inclusion criteria (Fig. 1). The references and the PubMed links for all 139 abstracts are available in Supplementary Table 1.

Of the 139 papers identified, 119 (85.6%) reported interventions that decreased mortality, and 20 (14.4%) reported interventions that increased mortality. In addition, 73 studies (52.5%) were mRCTs, while 66 (47.5%) were sRCTs (Table 1). The country of origin for multinational studies was attributed to the affiliation of the corresponding author (25 RCTs 18.0%), but the majority of studies were single-nation in design (114 RCTs, 82.0%). Out of the 31 countries of origin, the three nations with most frequently published RCTs affecting mortality were the USA (eight sRCTs and 15 mRCTs) Spain (12 sRCTs and 11 mRCTs), and France (two sRCTs and nine mRCTs) (Supplementary Table 2).

3.2. Study size and analysis

Overall, the median sample size was 160 patients [79–341], and the overall number of centers involved was 3451 with a median value of 2 [1–10] centers per study. However, when excluding sRCTs, the median number of the centers involved was 9 [3–31].

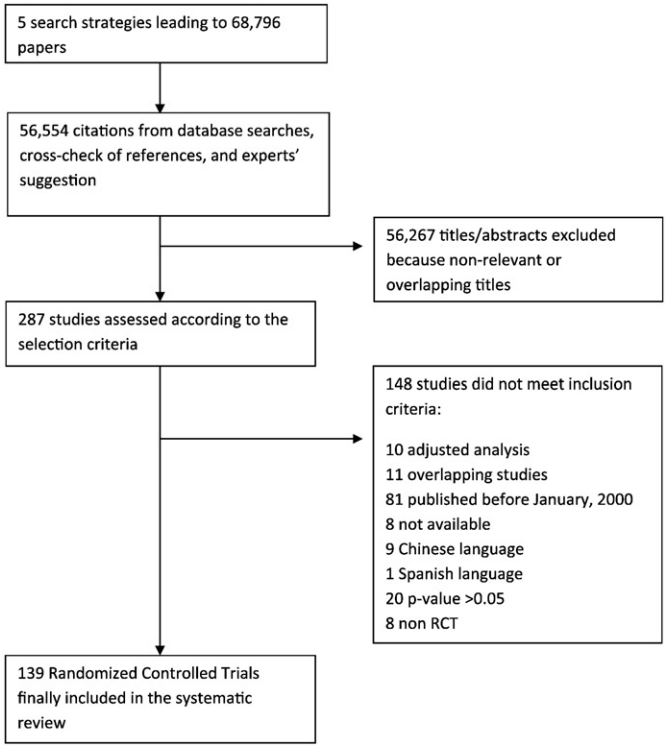

Fig. 1. Flowchart of the systematic review article selection process.