Systematic Review of Randomized Clinical Trials in Critical Care Medicine

Anand Gopal & Sydney Green
Mentor: Scott Halpern, MD, PhD
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Overview

• Study Question
• Define Critical Care Medicine and Randomized Clinical Trials
• State of RCTs in Critical Care
• Study Design
• Methods
• Findings
• Lessons Learned
Why do most published randomized clinical trials in Critical Care produce statistically negative results?
Significance of Critical Care Medicine

• About 5 million Americans are admitted to the ICU each year\(^1\)

• 1 in 5 Americans die during or after use of ICU services\(^2\)

• In 2005: over $80 billion was spent in critical care medicine, representing 13.4% of hospital costs, 4.1% of national health expenditures, and 0.66% of the GDP\(^3\)

\(^1\)Wunsch, H, et. al. Variation in critical care services across North America and Western Europe. Critical Care Medicine 2008.
Randomized Clinical Trials

Randomization allocates patients into groups which are similar in demographics and representative of the target population.

In theory, the design of an RCT reduces the complexity of statistical models used to analyze the data.

Assessed for eligibility N=2000

Excluded
N=880
Met exclusion criteria
Did not obtain consent

Randomized N=1120

Control N=560

Withdraw consent N=2

Lost to follow-up N=0

Analysis N=560

Intervention N=560

Discontinued N=8

Lost to follow-up N=0

Analysis N=560
State of RCTs in Critical Care

 Experts: Reduce emphasis on RCTs

 "Pendulum Effect" \(^5\)

 Strict Enrollment Requirements \(^5\)

 Ethical Issues \(^4\)

 High Rates of Statistically Negative Findings \(^5\)

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\(^5\)Vincent J-L. We should abandon randomized controlled trials in the intensive care unit. Critical Care Medicine 2010;38:S534-S8.
High Rates of Negative Findings

• Possible explanations:
  – Truly ineffective interventions
  – Treatment effect heterogeneity
  – Insufficient statistical power
  – Appreciable post-randomization losses
  – Inappropriate outcome measures
  – Improper statistical methods and considerations
Central Hypothesis

• Significant fraction of negative results in CC RCTs are due to:
  • Inferior statistical approaches and considerations
  • Inadequate statistical power to detect true effects in outcomes

• Overall Study Aim:
  – Provide evidence-base to understand current “state of the science” in CC with regard to design, analysis, and reporting of RCTs
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Trial Eligibility Criteria

• RCT design
  – Secondary, *post hoc* analyses excluded
• Adult patient population
• ICU setting
• Clinical or economic primary endpoint
  – Surrogate, intermediate, and physiologic outcomes ineligible
Study Methods

• Data abstraction instrument created using REDCap software

• Each article reviewed 2x independently, differences adjudicated by senior research team member

• Data elements of interest:
  – General information (country, funding source, target population, etc.)
  – Enrollment and retention data
  – Methods of informed consent
  – Reported outcomes
  – Statistical methods and power calculation
  – Trial results
  – Costs of care
Findings in Progress

• This study is currently in end stages of data abstraction

• Final database will be used to inform a number of future papers on the conduct, analysis, and reporting of CC RCTs

• What’s ahead:
  – ICU Length of Stay paper
  – Enrollment and Retention Issues paper
  – Statistical Considerations in Positive vs. Negative Trials paper
  – Maybe more
Lessons Learned

• Introduction to design and analysis of RCTs

• Better understanding of statistical methods and models

• What makes for a JAMA/NEJM-worthy article
  – Best practices and pitfalls to avoid

• Exposure to Critical Care Medicine and ICU setting
Lessons Learned

• Critical care medicine and Medical ICU

• Complexities of Statistical Analysis in RCTs

• Nuances of writing for major journals

• Exposure to health services research & new career goals
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