Biost 524: Design of Medical Studies

Discussion of HS Studies

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Outline

- Phase II study of hypertonic resuscitation following traumatic injury in the emergency (out of hospital) setting at a single clinical site
  - Discussion of design and results
- Follow-on phase III study conducted at multiple sites
  - Discussion of design
  - Discussion of results

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Question 1: Disease

- What is the targeted treatment indication?
  - Disease
  - Population
  - Treatment strategy
  - Outcome

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Question 1: Disease

- What is the targeted treatment indication?
  - Disease(s):
    - Severe traumatic injury leading to hypovolemic
    - Severe traumatic brain injury (TBI)
- Comments:
  - We consider the way the Phase III study was conducted to be the ultimate target
  - Although the investigators initially regarded that they were conducting a single trial of a single therapy in two “cohorts”, the FDA regarded that these were two separate indications

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Question 1: Population

- What is the targeted treatment indication?
  - Population
    - Patients experiencing severe traumatic injury and treated in the out of hospital setting by organized EMS
- Comments:
  - Trials were ultimately performed in adults, though there was no known contraindication to the treatment in kids
    - Performing an RCT like this with pregnancy, pediatrics, or prisoners is judged problematic,
      - Impact on definition of inclusion / exclusion criteria

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Question 1: Treatment Strategy

- What is the targeted treatment indication?
  - Treatment strategy
    - A single bolus of IV hypertonic fluids administered as soon as practical in the out of hospital setting
    - No restrictions on any other aspect of care
      - (Including monitoring of patients)
- Comments:
  - Patients were allowed additional treatments according to standard of care
    - Ultimate impact on Department of Defense interests

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Question 1: Outcome

- What is the targeted treatment indication?
  - Outcome
    - Hypovolemic shock: 28 day survival
    - TBI: Good neurologic functioning 6 months post injury
- Comments:
  - True clinical goal would be complete recovery from the traumatic injury
    - These surrogates are presumably based on the belief that the 1 month or 6 month data is representative of eventual status

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Question 2

- What was prior evidence that hypertonic resuscitation might be beneficial in severe trauma?
  - Epidemiologic
  - Laboratory
  - Animal
  - Clinical trials

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Question 2: Epidemiology

- What was prior evidence that hypertonic resuscitation might be beneficial in severe trauma?
  - Epidemiologic
    - Poor outcomes tend to be associated with
      - "Early mortality" due to the underlying injury
        - » Blood loss, cerebral edema (brain swelling)
      - "Late mortality" due to inflammatory cascade
        - » Reperfusion syndrome
        - » Major organ dysfunction
        - » Acute respiratory distress syndrome
        - » Infections due to immune suppression
    - Rationale
      - Osmotic pressure retains fluids in vessels
      - Hypertonicity may modulate infammatory cascade

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Question 2: Laboratory Evidence

- What was prior evidence that hypertonic resuscitation might be beneficial in severe trauma?
  - Laboratory
    - ? investigations of T cell reactivity in presence of hypertonicity
- Comments:
  - The preponderance of evidence comes from *in vivo* experiments

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Question 2: Animal Models

- What was prior evidence that hypertonic resuscitation might be beneficial in severe trauma?
  - Animal studies
    - Evidence for improved hemodynamic function
    - Evidence for effect on T cells
- Comments:
  - How good are the animal models?
    - Shock generally initiated through surgically precise bleeding
      - Traumatic injury in humans is generally much more diffuse with a lot of soft tissue damage

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Question 2: Clinical Trials

- What was prior evidence that hypertonic resuscitation might be beneficial in severe trauma?
  - Clinical trials
    - The paper describing the design of the phase III study presents a list of multiple clinical trials that vary in
      - Disease: Shock vs TBI
      - Patient population: Prehospital vs ED
      - Treatment: Hypertonic saline with vs without dextran
      - Outcomes: Neurologically intact, survival, ARDS, SBP
      - Results: "no difference", "trends toward", "improved"
      - Exploration: Subgroups

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Question 3

- How well do the eligibility criteria for the phase II study address the target population?
  - Inclusion criteria
  - Exclusion criteria

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Question 3: Inclusion Criteria

- How well do the eligibility criteria for the phase II study address the target population?
  - Inclusion criteria
    - Hypovolemic shock vs low blood pressure (and high heart rate) in presence of presumed injury
    - Traumatic brain injury vs low level of consciousness in presence of presumed head injury
- Comments:
  - Our understanding of the investigators' intent
    - Age motivated by consent and vulnerable population issues ➔ exclusion criterion
  - Minimally injured patients will be included by accident

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Question 3: Exclusion Criteria

- How well do the eligibility criteria for the phase II study address the target population?
  - Exclusion criteria
    - Motivated by potential safety concerns when using an unproven therapy
      - Pregnancy, pediatrics
    - Motivated by thought of minimal efficacy
      - Isolated penetrating head injury, ongoing CPR, burns, asphyxia, excessive time since injury, excessive fluids
    - Motivated by logistics
      - Prisoners, unable to get IV access (but also feared safety issues in animals from intraosseous administration)

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Question 4

- What are the advantages of the randomized design?

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Question 4

- What are the advantages of the randomized design?
  - Ensures comparability of patient groups
    - Avoids investigator bias in treatment
      - "Indication bias"
    - Avoids time trends in treatments that might have been present with historical controls
  - Enables us to credibly establish cause and effect
    - Providing, of course, there is an effect
  - Facilitates generalizability
- Comments:
  - Blinding was extremely beneficial as well

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Question 5

- How well does the study intervention address the scientific question of hypertonic resuscitation in trauma?
  - Dose
  - Administration
  - Frequency
  - Duration
  - Ancillary treatments

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Question 5: Dose, …

- How well does the study intervention address the scientific question of hypertonic resuscitation in trauma?
  - Dose / Administration / Frequency / Duration
    - 250 mL of hypertonic solution is salt equivalent of two liters of fluid
      - Thus might mobilize 1- 1.5 liters of extravascular fluid
      - (And lower weight is goal of DoD)
    - A single administration is all that is likely feasible by EMS agencies prior to ED
    - Question remains whether more prolonged hypertonic resuscitation in hospital might also be desirable

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Question 5: Ancillary Treatments

- How well does the study intervention address the scientific question of hypertonic resuscitation in trauma?
  - Ancillary treatments
    - ED / hospital treatment primarily by standard medical care
      - In phase III study in particular, the treating physicians were likely only vaguely aware of the RCT conducted by EMS
    - Phase II study
      - Monitoring of sodium and chloride was restricted
    - Phase III study
      - FDA imposed monitoring of sodium

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Question 6

- What was the primary outcome for the phase II RCT?
- What were the important secondary outcomes?
- How were patient outcomes measured?

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Question 6: Primary, Secondary

- What was the primary outcome for the phase II RCT?
  - ARDS free survival during first 28 days
    - Note disclaimer about reason for including mortality
      - I would argue this is crucial
- What were the important secondary outcomes?
  - Multiple organ dysfunction, 28 day survival, nosocomial infection, ventilator free days, length of ICU, hospital stay
  - Subgroup analysis based on massive transfusion
    - Investigators: A surrogate for more severe injury
    - Me: A post-randomization variable potentially affected by treatment

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Question 6: Measurement Methods

- How were patient outcomes measured?
  - Pre-defined measures of efficacy
    - ARDS
    - MODS
    - Days alive without (bad event) during first 28 days
  - Pre-defined measures of safety
    - Serious adverse events (SAEs)
    - Adverse events
  - Monitoring for unexpected adverse events
    - Was this done?
    - Did it need to be/

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Question 7

- How were the safety and ethical issues addressed?

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Question 7

- How were the safety and ethical issues addressed?
  - Exception to Informed Consent for Emergency Research
    - Community consultation
    - Community information
    - IRB approval based on 21 CFR 50.24 criteria
    - Patient notification of RCT and right to withdraw
  - Monitoring of patients for safety
    - Unexpected adverse events?
  - Monitoring of trial conduct
    - Data Safety Monitoring Board monitors interim data

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Question 8

- What were the results of the phase II study?
  - Primary endpoint
  - Secondary endpoints
  - Subgroup analyses
  - Safety endpoints

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Question 8: Preliminaries

- What were the results of the phase II study?
  - 209 of 261 eligible patients enrolled
  - 21 patients later found to be ineligible
    - As appropriate, still included in analysis
  - 3 LRS patients lost to follow-up after hospital d/c
  - Baseline comparability
    - Generally comparable on demographics, injury type
  - Injury severity (measured in ED but 2 LRS die in field)
    - Mean ISS comparable
    - Slightly higher very bad ISS in HSD
  - Blood transfusions
    - More massive transfusions in HSD

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Question 8: Primary Endpoint

- What were the results of the phase II study?
  - Primary endpoint
    - 28 day ARDS survival: 54% HSD vs 64% LRS
      - My crude analysis: two-sided P= 0.106
    - LRS : HSD hazard ratio: 0.75 (CI 0.49 – 1.15, two-sided P = 0.16, one-side P= 0.92)
    - Adjusted analyses in PH model
      - Age > 55, head AIS > 2, chest AIS . 3, ISS > 25, PRBC > 10
      - LRS : HSD HR: 1.01 (CI 0.63 – 1.60)

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Question 8: Secondary Endpoints

- What were the results of the phase II study?
  - Secondary endpoints
    - Prehospital fluids (L) : 2.3 HSD vs 1.8 LRS
    - SBP(mm Hg) at ED: 128 HSD vs 123 LRS
    - Hematocrit at ED: 0.30 HSD vs 0.34 LRS
    - 28 day mortality: 29% HSD vs 22% LRS
    - ICU days" 7.4 HSD vs 5.9 LRS
    - Ventilator free days: 14.8 HSD vs 17.4 LRS
    - Nosocomial infection: 18.2% HSD vs 15.2% LRS

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Question 8: Subgroup Analyses

- What were the results of the phase II study?
  - Subgroup analyses
    - Five total:
      - Baseline: Age > 55
      - Approx baseline: ISS > 25, head AIS > 2, chest AIS > 3
      - Post-randomization: PRBC > 10, Survival > 48 hours
    - Reported results in PRBC > 10
      - 28 day ARDS free survival: 13% HSD vs 0% LRS
      - LRS : HSD hazard ratio: 2.03 (CI 0.94 – 4.40)

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Question 8: Safety

- What were the results of the phase II study?
  - Safety endpoints
    - Higher rate of deep vein thrombosis in LRS (p=0.03)
    - "No AEs judged to be related to treatment"
      - SSE view: Treatment attribution by investigators is extremely prone to bias and error. We always ask, but do not treat as gospel.
  - Unreported safety issue
    - HR in all patients was 0.75
    - HR in 20% with PRBC > 10 was 2.03
    - Very crude calculation
      - HR in 80% with PRBC < 10 was 0.58
        - » Suggestive of harm of HSD in non-massively transfused

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Question 8: Futility

- What were the results of the phase II study?
  - Ultimately, the DSMB recommended termination of the RCT due to lack of important effect

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Question 9

- What are the major ways in which the phase III study design differs from the phase II design?
  - Data management
  - Disease
  - Patient population
  - Intervention
  - Endpoints

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Question 9: Data Management

- What are the major ways in which the phase III study design differs from the phase II design?
  - Data management
    - Phase II
      - Single center study
    - Phase III
      - Multicenter study, US and Canada
      - 100 EMS agencies (>8,000 providers)
      - Data abstraction of medical charts by staff with varying expertise
      - Web based data entry

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Question 9: Disease

- What are the major ways in which the phase III study design differs from the phase II design?
  - Disease
    - Phase II
      - Blunt trauma leading to hypovolemic shock
    - Phase III
      - Blunt or penetrating trauma leading to hypovolemic shock
        - » low SPB or moderate SBP with high HR
      - Traumatic brain injury

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Question 9: Patients

- What are the major ways in which the phase III study design differs from the phase II design?
  - Patient population
    - Phase II
      - Single clinical site
      - Well coordinated EMS agencies
      - All patients treated at 1 level 1 trauma hospital
    - Phase III
      - 12 clinical sites
      - Very diverse EMS structures
      - Patients treated at > 85 hospitals, level 1-3 trauma

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Question 9: Intervention

- What are the major ways in which the phase III study design differs from the phase II design?
  - Intervention
    - Phase II
      - Hypertonic saline with dextran vs Lactated Ringer's solution
      - No sodium monitoring by investigator
      - Standard medical care of one hospital
    - Phase III
      - Hypertonic saline with dextran vs Hypertonic saline vs Normal saline
        - » Hypothesized effect identical for HSD and HS
      - Protocolized sodium monitoring
      - Diverse standards of medical care

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Question 9: Endpoints

- What are the major ways in which the phase III study design differs from the phase II design?
  - Endpoints
    - Phase II
      - Primary endpoint
        - » ARDS free survival over 28 days
    - Phase III
      - Primary endpoint
        - » Shock: 28 day survival
        - » TBI: GOSE > 4 at 6 months
      - Safety
        - » Outcomes in low transfusion population

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Question 10: Phase II / Phase III

- For which of the two phase III clinical trial reports is the phase II study most directly relevant? Why?

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Question 10: Phase II / Phase III

- For which of the two phase III clinical trial reports is the phase II study most directly relevant? Why?
  - (Almost) same (shock) cohort
  - (Almost) same patient population
  - (Almost) same pre-hospital treatment
  - (Almost) same outcome measure

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Question 11: Confirm Phase II >>> III

- To what extent would you regard that the phase III study results confirm the findings of the phase II study?
- Would you have terminated the study early?

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Question 11: Confirm Phase II >>> III

- To what extent would you regard that the phase III study results confirm the findings of the phase II study?
  - Futility
  - Relative: Beneficial - Harmful
- Would you have terminated the study early?
  - ???

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Question 12: Current Medical Practice

- On the basis of these trial results, how would you change current medical practice using hypertonic saline?
- How do these trials affect future study of hypertonic saline for this indication?

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Question 12: Current Medical Practice

- On the basis of these trial results, how would you change current medical practice using hypertonic saline?
  - Used in 14 European countries
- How do these trials affect future study of hypertonic saline for this indication?
  - DoD question

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Other comments ?

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What's wrong with this?

- From abstract:
- "This paper proves that the placebo group (saline) displays a tendency, as indicated by two statistical tests, towards a significant increase in the red blood cells lost in the 24 hours after the operation."

Reference: Gray and Polakow, A study of Premarin intravenous and its influence on blood loss during transurethral prostatectomy, Journal of International Medical Research, 1979, 7(1) 96-99.

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Furthermore

- "… Once the patient had been operated upon and the exclusive pathology became known this disqualified the patient from the study retrospectively. The exclusions were:
  - Coagulation disorders.
  - Previous surgery to prostate.
  - …
  - Severe pre-operative anemia.
  - Admission hemoglobin less than 11 grams %.
  - History of salicylate, steroid or anti-inflammatory ingestion during the preceding six months.
  - Prostatic carcinoma."

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Furthermore

- Out of "47 consecutive patients undergoing transurethral prostatectomy between 03/09/75 and 12/05/77 were studied"….
- Guess how many were excluded due to the above criteria?

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Furthermore

Answer: 21 (leaving 26 for the analyses !)

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