Ethical Principles in Clinical Research

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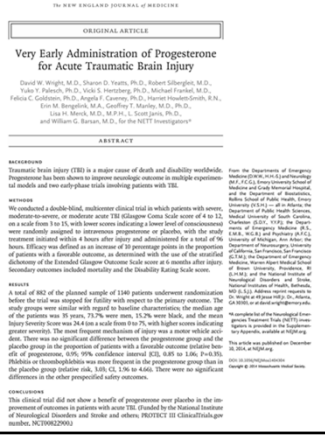
- *I have no conflicts of interest to disclose*



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ORIGINAL ARTICLE

Very Early Administration of Progesterone for Acute Traumatic Brain Injury

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ABSTRACT

BACKGROUND

Traumatic brain injury (TBI) is a major cause of death and disability worldwide. Progesterone has been shown to improve neurologic outcome in multiple experimental models and two early-phase trials involving patients with TBI.

METHODS

We conducted a double-blind, multicenter clinical trial in which patients with severe, moderate-to-severe, or moderate acute TBI (Glasgow Coma Scale score of 4 to 12, on a scale from 3 to 15, with lower scores indicating a lower level of consciousness) were randomly assigned to intravenous progesterone or placebo, with the study treatment initiated within 4 hours after injury and administered for a total of 96 hours. Efficacy was defined as an increase of 10 percentage points in the proportion of patients with a favorable outcome, as determined with the use of the stratified dichotomy of the Extended Glasgow Outcome Scale score at 6 months after injury. Secondary outcomes included mortality and the Disability Rating Scale score.

RESULTS

A total of 882 of the planned sample of 1140 patients underwent randomization before the trial was stopped for futility with respect to the primary outcome. The study groups were similar with regard to baseline characteristics; the median age of the patients was 35 years, 73.7% were men, 15.2% were black, and the mean Injury Severity Score was 24.4 (on a scale from 0 to 75, with higher scores indicating greater severity). The most frequent mechanism of injury was a motor vehicle accident. There was no significant difference between the progesterone group and the placebo group in the proportion of patients with a favorable outcome (relative benefit of progesterone, 0.95; 95% confidence interval [CI], 0.85 to 1.06; P=0.35). Phlebitis or thrombophlebitis was more frequent in the progesterone group than in the placebo group (relative risk, 3.03; CI, 1.96 to 4.66). There were no significant differences in the other prespecified safety outcomes.

CONCLUSIONS

This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI. (Funded by the National Institute of Neurological Disorders and Stroke and others. PROTECT III ClinicalTrials.gov number, NCT00822900.)

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*A complete list of the Neurological Emergencies Treatment Trials (NETT) investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux

The RIVUR Trial Investigators*

ABSTRACT

BACKGROUND

Children with febrile urinary tract infection commonly have vesicoureteral reflux. Because trial results have been limited and inconsistent, the use of antimicrobial prophylaxis to prevent recurrences in children with reflux remains controversial.

METHODS

In this 2-year, multisite, randomized, placebo-controlled trial involving 607 children with vesicoureteral reflux that was diagnosed after a first or second febrile or symptomatic urinary tract infection, we evaluated the efficacy of trimethoprim–sulfamethoxazole prophylaxis in preventing recurrences (primary outcome). Secondary outcomes were renal scarring, treatment failure (a composite of recurrences and scarring), and antimicrobial resistance.

RESULTS

Recurrent urinary tract infection developed in 39 of 302 children who received prophylaxis as compared with 72 of 305 children who received placebo (relative risk, 0.55; 95% confidence interval [CI], 0.38 to 0.78). Prophylaxis reduced the risk of recurrences by 50% (hazard ratio, 0.50; 95% CI, 0.34 to 0.74) and was particularly effective in children whose index infection was febrile (hazard ratio, 0.41; 95% CI, 0.26 to 0.64) and in those with baseline bladder and bowel dysfunction (hazard ratio, 0.21; 95% CI, 0.08 to 0.58). The occurrence of renal scarring did not differ significantly between the prophylaxis and placebo groups (11.9% and 10.2%, respectively). Among 87 children with a first recurrence caused by *Escherichia coli*, the proportion of isolates that were resistant to trimethoprim–sulfamethoxazole was 63% in the prophylaxis group and 19% in the placebo group.

CONCLUSIONS

Among children with vesicoureteral reflux after urinary tract infection, antimicrobial prophylaxis was associated with a substantially reduced risk of recurrence but not of renal scarring. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; RIVUR ClinicalTrials.gov number, NCT00405704.)

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*A complete list of the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Antenatal Thyroid Screening and Childhood Cognitive Function

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ABSTRACT

BACKGROUND

Children born to women with low thyroid hormone levels have been reported to have decreased cognitive function.

METHODS

We conducted a randomized trial in which pregnant women at a gestation of 15 weeks 6 days or less provided blood samples for measurement of thyrotropin and free thyroxine (T_4). Women were assigned to a screening group (in which measurements were obtained immediately) or a control group (in which serum was stored and measurements were obtained shortly after delivery). Thyrotropin levels above the 97.5th percentile, free T_4 levels below the 2.5th percentile, or both were considered a positive screening result. Women with positive findings in the screening group were assigned to 150 μg of levothyroxine per day. The primary outcome was IQ at 3 years of age in children of women with positive results, as measured by psychologists who were unaware of the group assignments.

RESULTS

Of 21,846 women who provided blood samples (at a median gestational age of 12 weeks 3 days), 390 women in the screening group and 404 in the control group tested positive. The median gestational age at the start of levothyroxine treatment was 13 weeks 3 days; treatment was adjusted as needed to achieve a target thyrotropin level of 0.1 to 1.0 mIU per liter. Among the children of women with positive results, the mean IQ

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Ethical principles

- Are these studies ethical?
- How do we know?

Ethics of clinical research

- The goal of clinical research is to generate useful knowledge about human health and illness, and ways to prevent, diagnose and treat diseases.
- The goal is not benefit to the individuals who participate (although there is sometimes benefit)
- People are the *means* to developing useful knowledge; and are thus at risk of exploitation

Ethics of clinical research

- Promote benefits to society and future patients
- Protect and respect rights and welfare of participants

Ethics of Clinical Research: Lessons From History

- Few rules. Physicians experimenting to benefit individuals
- "Utilitarian era" emphasis on benefit to society, inclusion of vulnerable groups
- Examination of the scope and limitations
- Rules and Regulations. Protection of human subjects
- Participation in research as a benefit

Selected Codes and Guidelines

- Nuremberg Code (1949)
- Declaration Of Helsinki (1964- 2000, 2008?)
- The Belmont Report (1979)
- CIOMS/WHO International Guidelines (1993, 2002)
- ICH/GCP-International Conference on Harmonization- Good Clinical Practice

The Belmont Report

- Ethical principles underlying the conduct of research:
  - Respect for persons
  - Beneficence
  - Justice

http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

Distinction between clinical research and clinical practice

- Goals
- Methods
- Risks
  - The Belmont Report

U.S. Regulations and Guidelines

- The Common Rule (US 45CFR.46)
- FDA regulations (US 21CFR50 and 56, and others)
- NIH policy and guidelines

45CFR.46 Protection of Human Subjects

- Composition and function of a local institutional review board (IRB)
- Criteria for IRB approval of proposals
- Requirements regarding informed consent

45CFR 46

- Subpart B- Fetuses, pregnant women, and human *in vitro* fertilization
- Subpart C- Prisoners as subjects
- Subpart D- Children

FDA REGULATIONS

- 21CFR.50 Protection of Human Subjects (informed consent)
  - Subpart D on research with children
- 21CFR.56 IRB composition and function
- IND and IDE 21CFR.312 and 21CFR.812

Existing guidance

- Most developed in response to specific problems
- Some issues incompletely addressed, include divergent recommendations
- Need for a systematic, coherent, universally applicable framework

Ethical framework: 7 principles

- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit evaluation
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000, 283(20):2701-11; Oxford Textbook of Clinical Research Ethics 2008

Valuable Scientific Question

Ethical clinical research should answer a valuable question, i.e., one that will generate new knowledge or understanding about human health or illness, i.e. a socially, clinically, or scientifically useful question

Social Value

- Promote benefit to society
- Minimize exploitation
- Justify asking individuals to accept risk or burden
- Responsible use of resources

Valid Scientific Methodology

- Ethical clinical research should be designed in a methodologically rigorous manner (design, methods, statistical power and methods, etc.) that will yield valid, reliable, generalizable, and interpretable data, and that is feasible

Scientific validity, e.g.

- Choice of endpoints
  - e.g. infection, survival, viral load, tumor response, cardiac function
- Choice of design
  - RCT or not, blinded or not?
  - Choice of control?
  - Primary outcome
- Choice of procedures
  - Measures of outcome, length of follow- up
- Statistical methods
  - Power, methods, level of significance
- Feasibility

Scientific Validity

- Examples of design controversies
- Feasibility

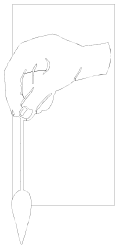
Fair subject selection

- Scientific objectives should guide inclusion criteria, recruitment strategies, and selection (not privilege or easy availability or vulnerability)
- Fairly distribute harms and benefits
- No exclusion without justification

Research as burden or benefit?

Research as 'burden'

Subjects need protection



Research as 'benefit'

Subjects need access

Favorable risk-benefit

- Are risks to subjects necessary and minimized?
- Are risks justified by benefit to individual subjects and/or the importance of the knowledge to society?
- Are benefits enhanced?

Non-maleficence and Beneficence

Risks in research

- Defining risks
  - Probability and magnitude
  - Types of risk
  - Uncertainty
- Minimizing risks
- Limiting risk

Benefits in research

- Defining benefits
  - Direct versus secondary benefits
- Maximizing benefits
- Balancing risks and benefits

Benefits and Risks in Research

[I]nterests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected.

The Belmont Report

Independent review

- To ensure ethical requirements have been fulfilled
- To check investigator biases and conflicts
- To assure the public that research is not exploiting individuals or groups

Criteria for IRB Review (45CFR.46.111 and 21CFR56.111)

- Risks … are minimized.
- Risks are justified by anticipated benefits, if any, to the subjects or the importance of the knowledge to be gained
- Subjects will be selected and treated fairly
- Informed consent is adequate

Challenges in Independent review

- Volume
- Conflicts
- Varied interpretations (inconsistency)
- NPRM proposals

Informed Consent

- The goal of informed consent is to ensure that individuals have the opportunity to decide whether they want to participate in research or continue participation and whether it is compatible with their goals, values and interests

Informed Consent

- The voluntary consent of the human subject is absolutely essential. Nuremberg Code
- For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject…or authorized representative. CIOMS guidelines

Informed Consent

- "To the degree subjects are capable, they should be given the opportunity to choose what shall or shall not happen to them". The Belmont Report
- Extra protections for those with limited capacity to consent

Informed consent

- Disclosure of information
- Understanding
- Voluntary decision making
- Authorization

IRB review of consent

Does the plan for informing participants about the objectives, risks, benefits, and alternatives of the study, assessing understanding, and seeking their voluntary agreement seem adequate?

Respect for enrolled subjects

- Ethical research requires continued respect for the rights and welfare of participants throughout research, including:
  - Protecting confidentiality
  - Monitoring welfare
  - Recognizing right to withdraw
  - Providing new information
  - Informing participants of findings
  - Post trial planning

Respect for enrolled subjects

- During the course of the experiment the human subject should be at liberty to bring the experiment to an end… Nuremberg Code
- …Every precaution should be taken to respect the privacy of the subject ,the confidentiality of the subject's information, and to minimize the impact of the study on … physical and mental integrity and on the personality of the subject. Helsinki 2000

7 principles

- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit evaluation
- Independent review
- Informed consent
- Respect for enrolled subjects

Framework

- Systematic and sequential
- Necessary
  - Procedural requirements may be waived
- Universal
  - Adapted and implemented according to context
- Require balancing, specifying

Balancing principles

- Example: Randomized Controlled Trials
- Balancing the need for a rigorous design with the obligation to maximize benefits and minimize harms

Ethical framework

In order to apply the principles, reconcile conflicts and make informed judgments about ethical research, need:

- Educated and informed investigators and research teams
- Educated IRBs with diverse members including investigators, statisticians, ethicists, and lay people.

Changing Landscape

- Multi-site and multinational studies
- Learning Health Care systems, Quality improvement
- Comparative effectiveness research and usual care research
- Research using databases or samples
- Genomic data and sharing

Links to more information

- http://www.hhs.gov/**ohrp**/
- http://ohsr.od.nih.gov
- http://www/fda.gov
- http://grants.nih.gov/grants/policy/hs/index.htm
- http://www.wma.net
- http://www.cioms.ch