Protective Effects of Propranolol in Adults Following Severe Burn Injury: A Safety and Efficacy Trial

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Agenda

I. The Propranolol Study

II. Data Management
Background

I. Severe Burn Injuries

• Burn Injuries Receiving Medical Treatment\textsuperscript{1}: 450,000

1. Sources: National Electric Injury Surveillance System-All Injury Project (NEISS-AIP); National Emergency Department Survey (HCUP-NEDS) (2010 Data); National Ambulatory Medical Care Survey.


II. Propranolol

- A non-selective beta blocker
- To treat hypertension, anxiety, and panic

Figure left: http://www.sigmaaldrich.com/catalog/product/sigma/p0884?lang=en&region=US
Figure right: http://marianuniversityscienceblog.wordpress.com/2010/10/15/beta-blockers-function-and-effects/
III. Beneficial Effects of Propranolol

In Children:

- Decrease infections
- Increase wound healing
- Improve cardiac work, hypermetabolism, and survival
The Role of Players

- **The sponsor**
- **American Burn Association (ABA)**
- **Data Coordinating Center (DCC)**
- **Data and Safety Monitoring Board (DSMB)**
- **The Propranolol Study**

- **Assist investigators**
- **Oversee the conduct of this trial**
The Study

Aim:
- To determine the safety and efficacy of propranolol relative to placebo in a cohort of severely burned adults

Design:
- A multi-center, phase 2a/b, investigator-initiated, randomized trial

Population:
- A group of 250 patients who are admitted to one of the participating burn centers within 72 hours of injury with a burn injury ≥ 20% total body surface area (TBSA)
Hypothesis:

- Propranolol will provide significant benefit to adults following severe burn injury at doses that are safe and do not increase risk of adverse infections and non-infectious outcomes.

Significance:

- A pilot study
- Safety and efficacy
- Subpopulations
- Dose levels
### Study Summary Timeline

<table>
<thead>
<tr>
<th>Burn Injury</th>
<th>Burn Center Admission</th>
<th>Randomization</th>
<th>First dose of drug</th>
<th>Burn Center Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt; 72 hrs</strong></td>
<td><strong>&lt; 96 hrs</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| Must be admitted to burn center within 72 hrs of injury (and meet all inclusion criteria and NO exclusions) | • Screening | • Alert pharmacy  
• Collect baseline specimens  
• Calculate dosing target heart rate and max dose  
• First dose of study drug with 96 hrs of injury | Dosing: dose every 8 hours (holding per protocol for MAP < 50 or HR < 55) |                      |

**Treatment day a:** Obtain peak and trough specimens around first dose of the day

**Treatment day b:** Obtain on-study specimens
Statistical Analysis Plan

**Efficacy**
Cardiac Rate Pressure Product (RPP aka. cardiovascular product/double product)
RPP = HR × SBP
- A piecewise linear random effects model
- Bonferroni correction

**Safety**
Mortality rates, infectious and non-infectious complications
- A mixed model negative binomial regression:
  - fixed treatment effects, log(follow-up time)
Two co-primary endpoints:
• A comparison of slopes over the first 2 weeks
• A comparison of means at 30 days
Overview of Statistical Issues

- Multi-center setting
- Loss to follow up

- A random center effect
- Inclusion of baseline covariates
Agenda

Data Management

1. Overview of data quality (DQ)
2. Data cleaning framework
3. Using SAS PROC SQL effectively
SCDM definition of DQ in clinical trials: “quality data is data that support conclusions and interpretations equivalent to those derived from error-free data” (Institute of Medicine, Roundtable Report, 1999)
Study Coordinating Sites
- Fill in data forms
- Determine if queries are resolvable

Studytrax Data Capture System
Built-in range and logic check

SAS Generates Spreadsheets for Errors

Was Error Previously Non-resolvable / Site?
- Yes and Keep
- Error

Spreadsheet Sent Back to Sites for Review

Further Analysis

Direct feedback

Error free

If Resolvable

If Non-resolvable

No
SQL (Structured Query Language) is the universally adopted language for querying a database

- Simple command structure for data definition, access, and manipulation
- Instead of specifying how to do, just say what you want to be done
Examples: SELECT and CREATE TABLE statements

```sql
/* Project Flow */
proc sql noprint;
create table work.flow1 as
    select ReferenceID, SiteName,
            'Participant Signed Consent but Consent Date is Missing' as problem,
            'Consent' as form, 'Consent-Inclusion-Exclusion' as Timeline
    from work.all_wide having SIGNCONS=1 and STARTDT = ;

create table work.flow2 as
    select ReferenceID, SiteName,
            'Study Termination Reason is "Other" and Missing Description' as problem,
            'Study Termination' as form
    from work.all_wide having TRMRFT =9 and TRMOIHSP='';

create table work.flow3 as
    select ReferenceID, SiteName,
            'Screening Date after Enrollment Date' as problem,
            '' as form, '' as Timeline,
            'Screening Date: ||put(ScreenDate, MMDDYY10.)||', Enrollment Date: ||put(EnrollDate, MMDDYY10.)||
    from work.baseline
    having .<EnrollDate<ScreenDate;

create table work.flow4 as
    select ReferenceID, Sitename,
            "Follow Up Visit Date is prior to Visit 1 Visit Date" as problem,
            'Visit Form' as form,
            'Visit 1 Date: ||put(VISITDT01, MMDDYY10.)||', Follow Up Date: ||put(VISITDT02, MMDDYY10.)||
    from work.all_wide having .<VISITDT02<VISITDT01;
```
References

1. Vadim Tantsyura, Olive Yuan, and Sergiy Sirichenko: Challenges and Opportunities in Clinical Trial Data Processing
2. Ranjit Singh and Dr. Kawaljeet Singh: A Descriptive Classification of Causes of Data Quality Problems in Data Warehousing
3. Clinical Trial Data Validation: Using SAS PROC SQL effectively, SFBC New Drug Services
4. Van den Broeck et al: Data Cleaning: Detecting, Diagnosing, and Editing Data Abnormalities
5. Propranolol Study Protocol, manual of operation, statistical plans and study training
6. Sources: National Electric Injury Surveillance System-All Injury Project (NEISS-AIP); National Emergency Department Survey (HCUP-NEDS) (2010 Data); National Ambulatory Medical Care Survey.
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