A Comprehensive Program for the Development of Intravenous Perfluorocarbon as a Treatment for Decompression Sickness

2011 ONR/NAVSEA
Undersea Medicine Research Program Review

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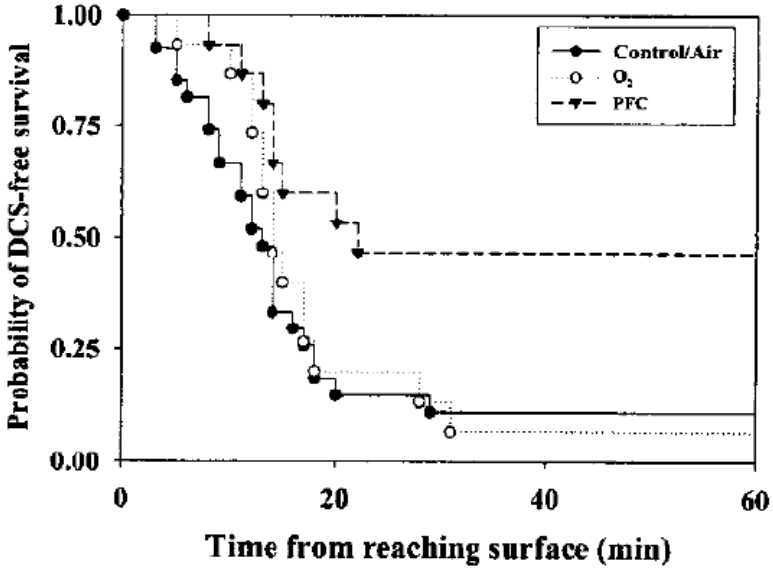
Perfluorocarbon Treatment for DCS



Oxycyte®

- Oxygen Biotherapeutics, Inc.
- 60% F-tert-butylcyclohexane (PTBCH)
- Egg yolk Phospholipid emulsion
- 200-250 nanometers particle size
- Blood half-life approximately 17 hours

Development Strategy

Background

- No existing FDA indication for treatment of DCS
- Severe DCS rare – Clinical trial not feasible
- Not ethical to induce severe DCS for purpose of testing PFC
- Not ethical to withhold recompression therapy
- "Animal Rule" (21 CFR Part 314, Subpart I)
  - 2 Species
  - Efficacy in animals
  - Safety in humans
  - All studies GLP

Development Strategy

Goal

FDA approval of Oxycyte® for treatment of severe DCS when recompression not available.

Objectives

Perform clinical trial of Oxycyte® for indication of severe DCS when recompression not available in timely manner – using "animal rule"

- Efficacy against DCS in swine & rats (per "animal rule").
- "General" safety (e.g., toxicity, teratogenicity, etc.) per manufacturer.
- "Specific" safety (e.g., used in conjunction with DCS +/- subsequent recompression)
  - pre-clinical studies in swine, rats,
  - clinical trial(s) of safety with recompression in humans.

Progress to Date

- **Good Laboratory Practices (GLP) at NMRC (2007-08)**
- **20 kg swine model developed (2008)**
- **Two different dose (5cc/kg, 3 cc/kg) efficacy trials in 20kg swine (2010-11)**
  - **200 fsw x 31 min, decompress @ 30 fsw/min**
  - **If cutis, O_2 and randomized to Oxycyte® or saline**
  - **Assessed at 24 hr: survival and stance/gait (modified Tarlov scale)**
  - **Spinal cord pathology (24 hr or 7d)**
- **Manuscript (5cc/kg dose, ASEM June 2010)**
- **Rodent DCS/PFC (96% complete)**
- **PFC toxicity (seizure) in Hyperbaric Oxygen (Complete)**

Progress to Date
(continued)

- **Decompression-recompression study (in progress)**
  - **Efficacy/Safety of Oxycyte® treatment plus delayed recompression**
  - **Temporary hiatus due to unavailability of Oyxcyte ®**
- **Pre-IND package to FDA with written FDA response/ recommendations (Fall, 2010)**
- **Written Response to FDA in preparation**
- **FDA-recommended hemodynamics study in preparation (IACUC, SOPS, training, etc.)**

FDA – Major Points

Applicability of the "animal rule"

- Likely to apply
- Additional information needed
  - Confirm that relevant clinical populations are not available to study severe DCS; response in preparation
  - Provide info regarding standard therapy and current practices for extraction of sailors from submerged submarines.
- Use of a single (vs. two) species
  - No, will need two species

FDA – Major Points (continued)

Additional safety studies recommended in swine model of DCS + Oxycyte® with possible hyperoxic recompression therapy to follow

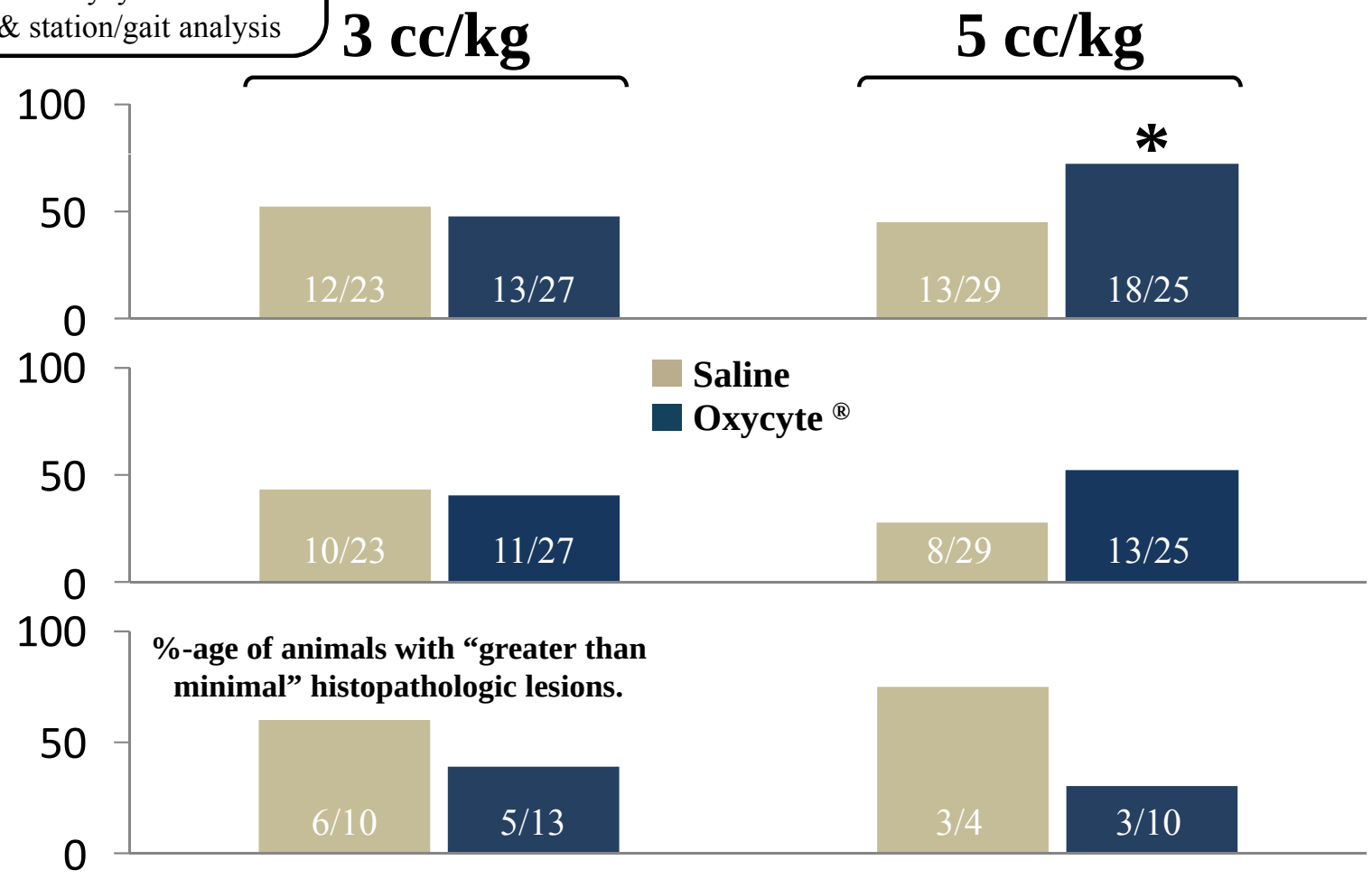
- **Platelets**
- **Opsonization and oxidative stress**
- **CNS Particulate embolism**
- **Hemodynamics (CO and PAP)**
- **Effectiveness of standard of care for treatment emergent seizures**

Progress to Date

Dose Finding

Methods

- Swine (20-30 kg)
- 200 fsw x 31 min, rapid ascent
- If cutis in ≤ 1 hr: 100% O_2 x 1 hr + randomization to Oxycyte® vs. Saline
- 24 hr survival & station/gait analysis



Details/Status

Data analysis nearing completion

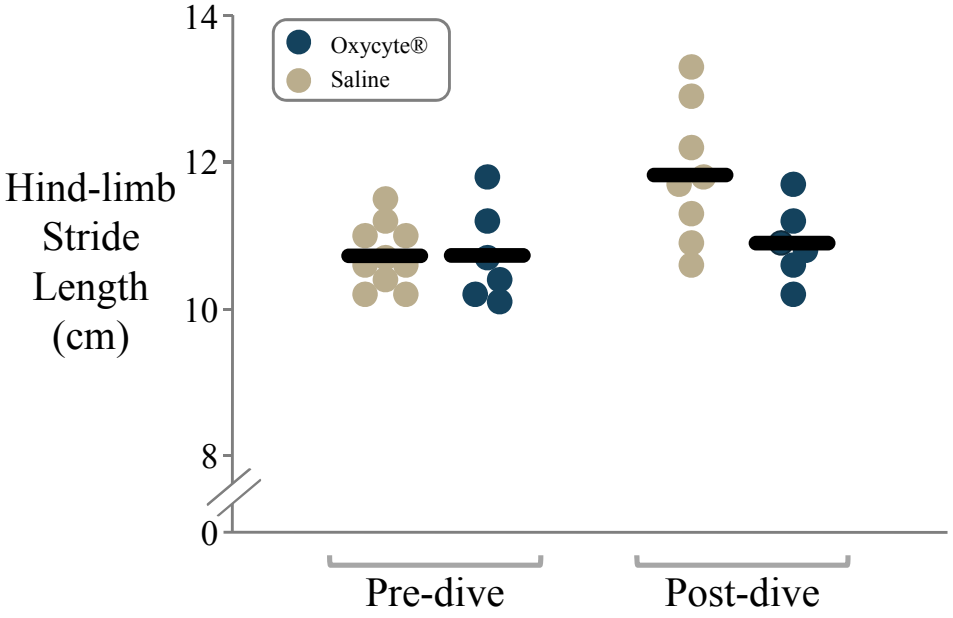
Mahon, et al., ASEM 81:555-9 (2010)

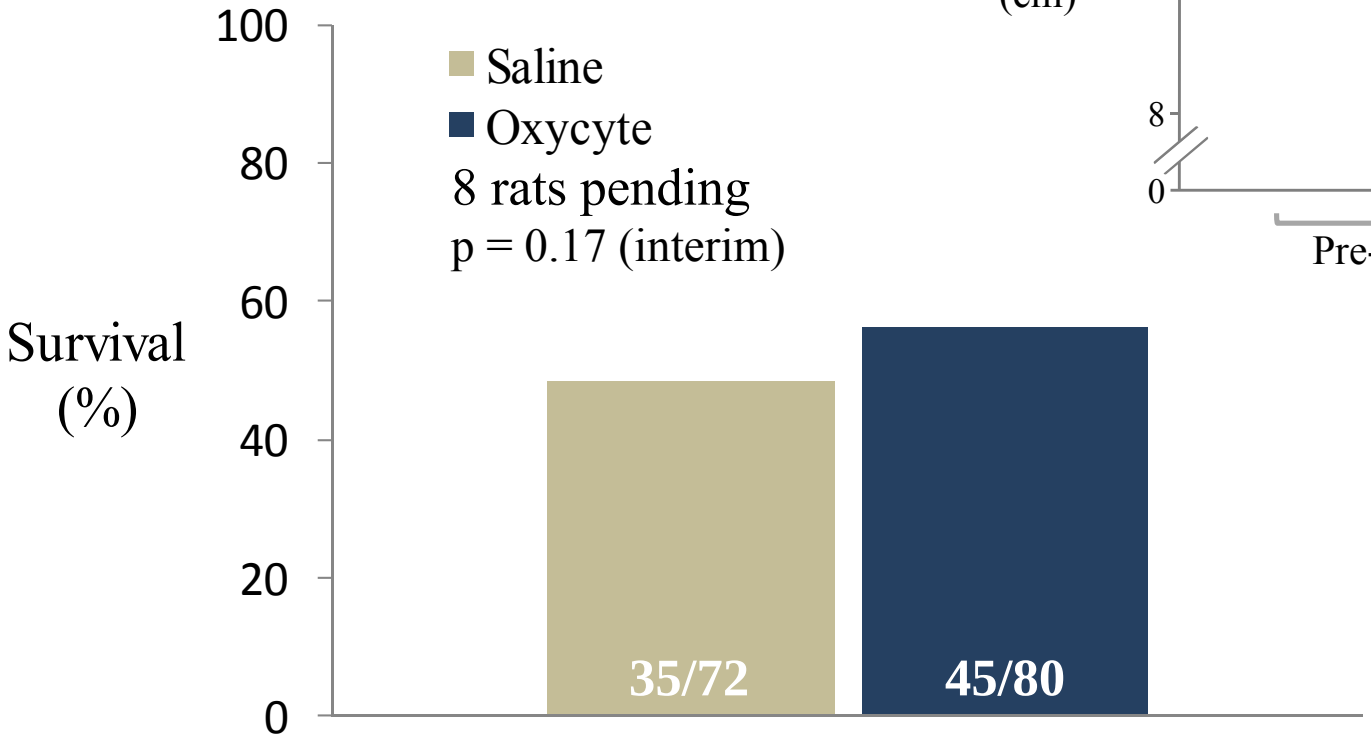
Progress to Date

Rat model

Methods

- Rats
- 210 fsw x 60 min, rapid ascent
- ≤30 min observation on rotating drum
- If DCS:
  - 100% O_2 (nose cone)
  - Oxycyte® vs. Saline (5cc/kg, tail vein)



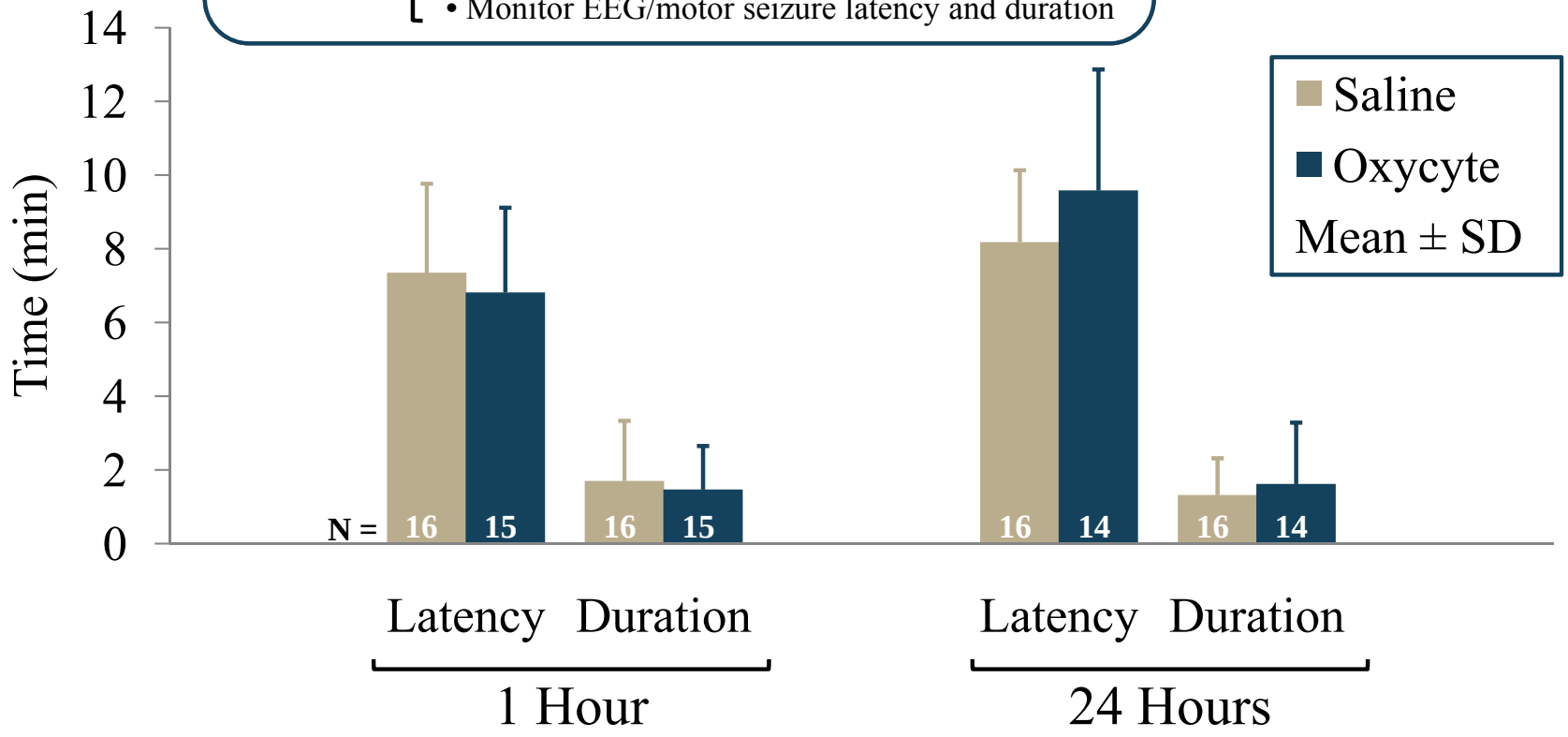


Tentative conclusion: Non-significant trend for improved survival.

Progress to Date
O_2 Seizure susceptibility

Methods

- Swine (20-30kg)
- Oxycyte® vs normal saline (5cc/kg)
- 2 HBO exposures – 165 fsw 100% O_2 until seizure
  - 1 hr post-injection
  - Repeat at 24 hr post-injection
- Monitor EEG/motor seizure latency and duration



Conclusion: No significant effect due to Oxycyte® ($p<0.05$).

Progress to date

Oxycyte® Therapy + Recompression

Methods

- Swine (25-30kg)
- 200 fsw x 31 min
- If cutis:
  - $100O_2$ (snout cone) x 1hr
  - Oxycyte® vs normal saline (4cc/kg)
- Survivors at 4 hrs →TT6
  - Monitor EEG and motor behavior for seizure
- 24-hr outcomes
  - Survival
  - Station/gait (Tarlov scale)
  - Motor activity - kinesthesia analysis of food foraging
  - Cognition (memory) – Delayed matching to sample test

- **Temporary hiatus due to unavailability of Oxycyte®**
- **Experiments were due to restart mid-May**
- **Anticipated completion: Summer 2011**
- **Treatment code unbroken**

Progress to Date

➢Regulatory

- **Pre-IND package submitted to FDA *18 May 2010***
- **Detailed written response received from FDA *06 Aug 2010***
  - **Pre-IND meeting deferred**
  - **"…animal rule likely would apply in this situation, additional information is needed to confirm that relevant clinical populations are not available to study severe DCS."**
    - **NMRC responses in preparation**
  - **Additional studies recommended**
    - **Hemodynamics**
    - **CBF**
    - **Platelets**
  - **IACUC protocol in preparation**

Progress to Date

Hemodynamics

- Response to FDA recommendations regarding additional safety studies
- IACUC in preparation
- Hypotheses
  - Primary hypothesis
    - Oxycyte® treatment of DCS does not alter CO or PAP
  - Secondary hypotheses
    - Oxycyte® treatment of DCS does not result in particulate emboli to brain
    - Oxycyte® treatment of DCS does not acutely alter platelet number or function
- Experimental Design
  - 20-30 kg swine
  - DCS (cutis) – randomize to Oxycyte® vs normal saline (5cc/kg)
  - 90 minute monitoring:
    - Hemodynamic monitoring (including S-G)
    - CBF monitoring and cerebral pathology
    - Platelet count, aggregometry
    - Other

Conclusions
(to date)

- 5cc/kg Oxycyte® reduces mortality from severe DCS by approximately 50%
- 3cc/kg not clinically effective
- Oxycyte® does not significantly alter HBO toxicity (seizure)
- Rat may not be best “second animal” (?)
- Completion of decompression-recompression study delayed

Plans for FY 11/12

- **Complete Decompression-Recompression study**
- **Hemodynamics study**
- **Submission of response(s) to FDA questions**
- **Oxygen Biotherapeutics/DoD-USAMRAA:**
  - **2-yr, $2.07M project**
  - **Address FDA questions regarding platelet function/distribution, and immunocompetence**
  - **Ricerca Biosciences, IIT Research Institute, Children's Hospital Boston**
- **Human safety testing deferred pending FDA-recommended pre-clinical safety studies**