Prophylactic High Dose Methylprednisolone Fails to Treat Severe Decompression Sickness in Swine

David M. Dromsky, Paul K. Weathersby, and Andreas Fahlman

**Introduction:** Controlled decompression from saturation conditions is not always an option, particularly in a disabled submarine scenario. 

**Hypothesis:** Prophylactic high dose methylprednisolone (MP) would improve outcome in severe cases of decompression sickness (DCS).

**Methods:** Littermate pairs of male Yorkshire swine (n = 86, mean weight ± SE = 19.3 ± 0.2 kg) were randomized to one of three groups, then compressed on air to 4.3 ATA (33 msw) for 22 h and brought directly to surface pressure (1 ATA) at 0.9 ATA·min⁻¹. The MP-50 group received i.v. infusion of 50 mg·kg⁻¹ of MP dissolved in 60 cc normal saline (NS) immediately prior to the hyperbaric exposure. The NS group received 60 cc NS i.v. immediately prior to the hyperbaric exposure. The MP-10 group received i.v. infusion of 10 mg·kg⁻¹ MP dissolved in 60 cc NS during the hyperbaric exposure, 7 h before the decompression. **Results:** Outcomes of severe DCS and death were recorded. NS group: 14 DCS, 4 died; MP-50 group: 19 DCS, 12 died; MP-10 group: 19 DCS, 10 died. Compared with the NS group, logistic regression analysis suggested that animals in the MP-10 group were more likely to get severe DCS and to die (p < 0.01) and animals in the MP-50 group were more likely to die from their disease (p < 0.01).

**Discussion:** Prophylactic high dose MP exerts no protective effect against severe DCS and actually worsens mortality in this model. An earlier group of untreated controls (UC, n = 44, 30 DCS, 11 died, mean weight ± SE = 19.9 ± 0.3 kg) exposed to the same profile was also available for analysis. Comparison of the UC and NS animals suggested that presurge NS treatment may protect against severe DCS.

**Keywords:** diving, DCS, swine, saturation diving, methylprednisolone, steroids.

Despite the known dangers, there are plausible situations that may require humans to conduct a direct ascent from saturation conditions. United States Navy submarines almost never experience accidents that leave their ships disabled, but when they do, they pose a difficult rescue problem. Submarines are maintained at normal atmospheric pressure, but over time the pressure within a disabled submarine (DIS-SUB) is expected to rise due to a variety of factors. While awaiting rescue, the sailors' tissues will most likely become saturated with nitrogen from breathing air at elevated ambient pressure. Rescue efforts may not allow a proper, controlled decompression, and ready access to a recompression chamber cannot be guaranteed. Decompression sickness (DCS) sustained in this situation could potentially cause severe long-term morbidity and mortality. Accordingly, there is great interest in prophylactic or adjunctive treatments for severe DCS that can be used when recompressive treatment is delayed or unavailable.

In a previous effort we constructed a dose response curve using large animals to describe the natural history after such exposures and provide a platform for intervention testing (9). Corticosteroids have been advocated as adjunct treatment for DCS, presumably because their anti-inflammatory effects may moderate the immune activation that comes from mechanical and ischemic tissue damage (2,6,23,24). This trial was designed to assess the effect of prophylactic high-dose methylprednisolone (MP), a systemic anti-inflammatory agent, on severe DCS after rapid ascent from saturation conditions, a scenario resembling a possible DISSUB rescue situation.

**METHODS**

All procedures were conducted in accordance with National Research Council guidelines on laboratory animal use (26). Before commencing, the Institutional Animal Care and Use Committee reviewed and approved all aspects of this protocol. The institutional animal care facility is fully AAALAC accredited.

**Subjects**

Neutered male Yorkshire swine littermates (n = 86, mean weight ± SE = 19.3 ± 0.2 kg) were examined by a veterinarian on receipt, then fitted with an adjustable chest harness and housed in individual runs where water was freely available. Their daily feedings consisted of 2% by body weight of laboratory animal feed (Harlan Teklad, Madison, WI) and ad libitum access to water. Animals remained in the care facility for a min-

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SEVERE DCS PROPHYLAXIS FAILS—DROMSKY ET AL.

imum of 72 h adjusting to their new surroundings before experiments.

Pre-dive Preparation

Each experiment was done using three animals randomly assigned to one of three treatment groups as described below; normal saline (NS) or methylprednisolone (MP-50 or MP-10). Animals were brought to the laboratory in plastic transport kennels (22" x 32" x 22", Vari-Kennel, R.C. Steele, Brockport, NY), placed in a Panepinto sling (Charles River, Wilmington, MA), and anesthetized by intramuscular injection of 20 mg · kg\(^{-1}\) ketamine (Fort Dodge Laboratories, Inc., Fort Dodge, IA) and 1 mg · kg\(^{-1}\) xylazine (Rompun® 2 mg · kg\(^{-1}\), i.m.; Bayer Corp., Shawnee Mission, KS). Using sterile technique, 10 cm of a customized Micro-Renathane catheter (model #RPC-040, Braintree Scientific, Braintree, MA) was inserted into an ear vein and lightly tied in place. After closing the incision, the catheter was connected to an injection port. Animals then received 500 mg chloramphenicol (American Pharmaceutical Partners, Atlanta, GA) to reduce infection risk and 2 ml heparinized saline (2 U · ml\(^{-1}\)) to maintain catheter patency overnight. The catheter was sutured to the ear and taped down using waterproof surgical tape. After complete recovery from anesthesia, animals were returned to the care facility.

Hyperbaric Exposure Protocol

The morning after catheterization animals were brought to the laboratory and placed in a Panepinto sling where they received intravenous (i.v.) infusion of either 60 ml normal saline (NS group) or 50 mg · kg\(^{-1}\) methylprednisolone (MP, Pharmacia @ Upjohn Company, Kalamazoo, MI) dissolved in 60 ml NS (MP-50 group), both delivered over 30 min. The injections were followed by a bolus of 2 ml heparinized saline (2 U · ml\(^{-1}\)). The three animals were then weighed (establishing pre-dive weight), and put in a modified transport kennel that allowed direct visualization of the animal throughout the dive. The i.v. lines were connected through hull penetrators to pumps outside the chamber to allow administration of medications at depth. This allowed the third group to receive i.v. infusion of 10 mg · kg\(^{-1}\) MP in 60 cc NS delivered over 12 min at 7 h prior to decompression (MP-10 group).

Animals were placed in a hyperbaric chamber and compressed to 4.3 ATA using air. Compression progressed in phases, beginning with 0.15 ATA · min\(^{-1}\) to a depth of 2 ATA. If the animal showed no distress or other evidence of middle ear barotrauma, the descent rate was increased to 0.30 ATA · min\(^{-1}\). If the animal again showed no signs of discomfort the descent rate was increased to 0.45 ATA · min\(^{-1}\) beyond 4 ATA. Animal comfort was the limiting factor in all descent rates. Temperature was maintained between 26.7 and 29.4°C, humidity between 50 and 75%, and CO\(_2\) concentration below 0.3%. The animals were constantly monitored via closed-circuit television cameras through observation ports. After 22 h at depth the animals were returned to surface (1 ATA) at a nominal rate of 0.9 ATA · min\(^{-1}\) with no decompression stops. In practice that rate was closely followed until a depth of about 1.4 ATA. Due to piping restrictions, the remainder of the decompression required 60–70 s.

On reaching surface (1 ATA), the animals were fitted with individual oximeters that measured heart rate and arterial oxygen saturation (VetOx 4404, Heska, Ft. Collins, CO) and then transferred to individual 36" x 23" x 22" clear Plexiglas® observation pens. Average time into the observation pens was 4.5 min. Onset of severe DCS (neurological or cardiopulmonary dysfunction) was recorded to the nearest minute. Disease and symptom onset times are referenced to the time animals reached surface. Neurological DCS was defined as motor weakness (limb weakness, repeated inability to stand after being righted by the investigator), paralysis (complete limb dysfunction, areflexia, hypotonia), sensory compromise (lack of retraction from painful stimuli), or cranial nerve dysfunction. Cardiopulmonary DCS was defined as a visually observed respiratory rate >= 60 breaths · min\(^{-1}\) combined with respiratory distress, as evidenced by open-mouthed, labored breathing, central cyanosis, and inversion of the normal inspiratory/expiratory ratio, often accompanied by production of frothy white sputum. All subjects with signs of severe DCS were given 2.5 mg diazepam (Abbott Laboratories, North Chicago, IL) i.v. as necessary to alleviate their distress. Skin DCS and behavioral features indicative of milder DCS (e.g., limb lifting) were noted but not classified as positive cases for this study. After the 1 h observation period, subjects were weighed (post-dive weight). Close observation continued until 4 h post-surface, at which time they were returned to the care facility. Subjects were examined again 24 h later, anesthetized with i.v. injection of 20 mg · kg\(^{-1}\) ketamine and 1 mg · kg\(^{-1}\) xylazine, then euthanized by cardioplegia with bolus i.v. injection of 40 ml, 4-molar potassium chloride solution.

All animals that died from their disease were immediately sent for necropsy. The viscera were removed and the heart was examined for patent foramen ovale. The heart, lungs, brain and spinal cord were removed and examined grossly. Tissues were preserved in formalin. Representative sections of cerebral, thoracic, lumbar and sacral spinal cord, brainstem, cerebellum, cerebrum and lung were embedded in paraffin. Sections were cut at 6 μm, stained with hematoxylin and eosin, and examined under light microscopy by a veterinary pathologist who was blinded to treatment group.

Analysis

- All mean values reported are ± 1 standard error (SE). Significant difference was set at the p < 0.05 level. Group differences in mean weight, pre-weight, and mean time of outcomes were analyzed by single factor ANOVA (Table I). A priori analysis, using a power of 70% and an expected difference of 30%, suggested that a sample size of 33 animals would be sufficient to detect a difference between two groups.

It was desired to determine if any additional variables had a significant effect on the outcome of DCS or death. Since the dependent variable (presence or ab-
sence of DCS or death) is dichotomous, and multiple candidate independent variables were involved, multivariate logistic regression techniques were used. This analysis determines the probability of DCS (P_{DCS}) or death (P_{death}), using the outcome as the dependent variable and up to four experimental variables (animal age, pre-dive weight, weight loss during the dive, a surrogate for fluid losses in this model, and treatment group were tested) as independent variables. Initially, a univariate analysis on each independent variable was performed; only those variables with a p-value < 0.20 (Wald test) were then included in a multivariate analysis. Exclusion of a variable from the multivariate analysis was based on the log-likelihood ratio test. Significance of specific independent variables was determined using logistic regression and likelihood ratio testing in the manner described by Hosmer and Lemeshow (17).

RESULTS

Except as noted below, the animals had DCS manifestations, case presentations, and histopathology similar to those previously described (9). Overall, 52/86 animals sustained severe DCS, and 26 animals succumbed to their disease. Table I presents descriptive statistics by group. Fig. 1A and B summarize outcomes by group. There was a significant increase in DCS incidence for the MP-10 group as compared with the NS and MP-50 groups (Fig. 1A). In addition, there was a significant increase in the death incidence in both the MP-10 and MP-50 group as compared with the NS group (Fig. 1B). Fig. 2 shows the DCS incidences by type, CNS or cardiopulmonary, and treatment.

MP-10 animals got severe DCS an average of 10.7 min sooner than the NS animals (p < 0.02, Mann-Whitney), and had faster onset than the MP-50 group by 7.5 min (p < 0.01, 2-tailed t-test). No significant differences in onset of severe DCS or death could be ascertained between the remaining groups.

Logistic regression was used to determine if there was a statistical correlation between the incidence of DCS or death in these animals, and one or more variables within the experiments. These variables included, animal age, pre-dive weight, weight loss during the dive, and treatment group as independent variables. Neither animal age nor weight loss during the hyperbaric exposure were significant predictors of DCS (p > 0.50; Table II). Pre-dive animal weight and treatment group passed the Wald test criteria (p < 0.20) for inclusion in a multivariate analysis. However, based on the log-likelihood ratio test the multivariate model did not significantly improve the prediction of P_{DCS} compared with the univariate models (p > 0.10, Table II). Still, both the univariate and the multivariate models suggested that the P_{DCS} increased with increasing weight, while injection of NS decreased the P_{DCS} as compared with injection of MP at pressure (MP-10).

Both treatment group and pre-dive weight were significant predictors of P_{death} (Table II). The parameters for this model suggested that increasing weight increased the P_{death}. However, both injection of MP prior to the hyperbaric exposure (MP-50) and at pressure (MP-10) increased the probability of DCS as compared with NS injection (Table II). Consequentially, prophylactic MP given at depth exerted no protective effect against DCS and actually increased mortality (Table II). The specific characteristics of the neurological and cardiopulmonary DCS cases and the pathological findings are reported in Appendix A.

As in previous trials, animals that died from DCS demonstrated profuse bubbles distributed throughout large blood vessels in the axillae, vena cava, large pulmonary vessels, chambers of the heart and, rarely, coronary arteries and superficial cerebral vessels. No arterial bubbles were noted. Hemorrhage within the CNS was limited to the cervical, mid-thoracic, and lumbar cord. The hemorrhage ranged from small petechiae with associated gliosis and perivascular cuffing to frank ecchymoses ("paintbrush hemorrhage"). In all cases, gross spinal cord hemorrhage was more pronounced on the dorsum of the cord, sometimes extending to the lateral aspect. Hemorrhages were subdural and did not extend deep into the parenchyma. The lungs ranged from normal to a mottled, edematous dark reddish purple color with a densely indurated, firm texture with marked perivascular cuffing. Frothy sputum was frequently noted in the trachea and bronchi. No statistically significant differences in histopathology could be demonstrated between groups. Subjects that survived their severe DCS were necropsied at 24 h. They showed similar gross changes, with only residual evidence of pulmonary edema and no observed intravascular bubbles.
SEVERE DCS PROPHYLAXIS FAILS—DROMSKY ET AL.

**Fig. 1.** A) Incidence of severe decompression sickness (% DCS with 95% confidence intervals in a binomial distribution) or B) death rate from pigs injected with normal saline (NS, n = 33) or with methylprednisolone before hyperbaric exposure (MP-50, n = 33), or injected with methylprednisolone at pressure (MP-10, n = 20). * Significantly different from the NS and MP-50 group (p < 0.05, 2-tailed chi-square test).

**DISCUSSION**

The United States Navy has not launched a major submarine rescue effort since the USS Squalus sank in 1939. However, as long as submarine operations continue, such situations remain possible, especially since the U.S. now maintains rescue assistance agreements with more than 20 countries. Many of these countries operate primarily in littoral waters, making the possibility of rescue operations even more likely. Rescue efforts may not allow a proper, controlled decompression, and ready access to a recompression chamber cannot be guaranteed. Decompression sickness (DCS) sustained in this situation could potentially cause severe long-term morbidity and mortality. Accordingly, there is great interest in prophylactic or adjunctive treatments for severe DCS that can be used when recompressive treatment is delayed or unavailable.

The swine was chosen as the animal model based on recent successful studies using this animal as a model for a variety of diving related conditions (5,9,29) and based on their well recognized anatomic and physiologic similarity to humans (21). In addition, the pathological findings after no-stop decompression are similar to results reported in previous experiments and in humans (4,7,8,15,32).

Prophylactic corticosteroid therapy has shown beneficial effects in animal models of sepsis and disseminated intravascular coagulation using 30–60 mg · kg⁻¹ doses (1,22). Post-injury corticosteroid treatment improves many parameters in animal models of ischemic spinal cord damage, including tissue edema, vascular permeability, polymorphonuclear cell infiltration, and gross neurological function with doses as high as 165 mg · kg⁻¹ (19,33). Post injury bolus doses of 30 mg · kg⁻¹ followed by maintenance infusions have been reported beneficial in human trials of spinal cord trauma (3), although some later reviews question these trial's design and conclusions (10,25).

Several case reports indicate that corticosteroids are beneficial for DCS when given alone or as adjuncts to recompression (16,18), but these are uncontrolled studies with very small sample sizes. Under more rigorous testing conditions, steroids have had less successful and sometimes contradictory results. Several cellular studies indicate that corticosteroids actually potentiate ischemic neuronal injury (27,30,31). In 1987 Francis et al., found no significant difference in collected physiologic data, somatosensory evoked potentials (SEP), or final outcome between animals treated with standard recompression and animals that received a 0.5 mg · kg⁻¹ dexamethasone bolus and recompression after the diagnosis of DCS was made (14). In a subsequent experiment using 20 mg · kg⁻¹ methylprednisolone (MP) as an adjuvant to recompression, the treated animals showed no difference in final outcome, but “if all the SEP recorded during the treatment period are compared, the MP-treated animals experienced a significantly worse outcome than the diluent-treated controls” (13). Similarly, Dutka et al. measured SEP after carotid air embolism and a brief period of arterial hypotension (11). Animals treated with 1 mg · kg⁻¹ dexamethasone 3–4 h pre-embolism showed a mild transitory benefit by SEP that was not considered statistically or clinically significant, and another group received dexamethasone after the embolism that exhibited no advantage over controls.

In this trial, MP was administered both prior to the hyperbaric exposure (MP-50) and at depth 7 h prior to decompression (MP-10), such that its anti-inflammatory effect should have been at its peak. There was no im-
provement in DCS outcome in the MP-50 group as compared with the NS group (Fig. 1A). For the MP-10 group, on the other hand, there was a significant increase in the DCS incidence as compared with the NS group (Fig. 1A). The benefit of MP for treatment of DCS was further refuted by the significantly higher death

![Graphs showing DCS incidence for CNS, CP, and Both for MP-50 and MP-10 groups](image)

**Table II. Logistic Regression Results.**

<table>
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<tr>
<th>Outcome</th>
<th>Intercept</th>
<th>Age (d)</th>
<th>Pre-Weight (kg)</th>
<th>Weight Loss (kg)</th>
<th>Group</th>
<th>LL</th>
<th>p-Value</th>
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<td>-0.005 ± 0.024</td>
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* Logistic regression results for animal age (df = 1), pre-dive weight (df = 1), weight loss during dive (df = 1), and treatment group (df = 2) for animals injected with normal saline (NS, n = 33), or with methylprednisolone before the hyperbaric exposure (MP-50, 50 mg·kg⁻¹, n = 33) as compared to animals injected with methylprednisolone at pressure (MP-10, n = 20). Parameter estimates (± SE), log likelihood (LL), and p-value for log likelihood ratio test compared to nested models (17).
that increase the risk of death in an emergency no-stop decompression situation.

The animals injected with NS prior to the hyperbaric exposure had a lower death rate than the other groups and we hypothesized pre-hydration could potentially reduce the DCS incidence. Consequently, the NS animals were compared with an earlier group of 44 un-
treated controls exposed to the same compression and decompression sequence (9). There was both a significantly increased DCS incidence and death rate in the historical control animals as compared with the NS group (Fig. 3A and B). The mean time of onset for the various symptoms for the historical control group was 21.3 ± 2.8, 21.1 ± 3.1, 25.2 ± 2.9, and 31.2 ± 3.1 min for severe, CNS, and CP DCS, and death, respectively. These were not different from the mean times of the NS treated animals (p > 0.3, 2-tailed t-test and Mann-Whitney).

Logistic regression analysis suggested that only treatment group was a significant predictor for DCS, and that pre-injection of NS decreased the PoCS (p < 0.05, Table III). There was also a trend for pre-weight as a significant predictor of PoCS (p < 0.1, Table III). Since weight correlates positively with PoCS (20), the final model should be considered to be the one with both pre-dive weight and treatment. For death, on the other hand, both age and pre-dive weight were significant predictors of the outcome (Table III). Interestingly, treatment group was not a significant predictor of Pdeath (p > 0.1, Table III). Consequently, in this sample size, pre-dive injection of NS is only protective against severe DCS symptoms while the death rate is similar as compared with historical control animals. One plausible reason for this could be the subjective classification of DCS, while death is unambiguous. Nevertheless, the rigorous compression and decompression sequence used throughout this study caused signs of DCS that were in most cases severe enough to leave no ambiguity. Still, the possibility of a significant effect with pre-
hydration is intriguing and warrants further investigation. If pre-hydration has a beneficial effect, this would be an easy preventive measure prior to any hyperbaric exposure.

In conclusion, this trial adds further evidence that steroids do not acutely improve DCS outcome. Further, this trial suggests that steroids should not be considered a benign intervention and that, in larger doses, steroids may in fact have some adverse effects that potentiate death in the setting of cardiopulmonary DCS.

**APPENDIX A**

**Neurological DCS**

Neurological DCS occurred in 34/86 animals. It usually appeared < 1 h after surfacing and developed rapidly over the course of a few minutes. It manifested as progressive weakness of one or more limbs, most commonly the hind limbs, but occasional cases of rystagmus or cranial nerve dysfunction were also noted. Most animals with evidence of neurological DCS began to show recovery within the 4-h observation period. All that survived 1 h after decompression were deficit-free and normal to examination at the 24-h check. No significant differences in onset of CNS signs could be ascertained between the groups.
TABLE III. LOGISTIC REGRESSION RESULTS (HISTORICAL CONTROLS)*.

<table>
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<tr>
<th>Outcome</th>
<th>Intercept</th>
<th>Age (d)</th>
<th>Pre-Weight (kg)</th>
<th>Weight Loss (kg)</th>
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* Logistic regression results for animal age (df = 1), pre-dive weight (df = 1), weight loss during dive (df = 1), and treatment group (df = 2) for animals injected with normal saline (NS, n = 33) compared to historical control animals exposed to the same compression and decompression sequence (AIR, n = 77). Parameter estimates (± SE), log likelihood (LL), and p-value for log likelihood ratio test compared to nested models (17).

Cardiopulmonary DCS
Cardiopulmonary DCS occurred in 47/86 animals. Cases presented as progressive tachypnea and tachycardia, with respiratory rates exceeding 100 breaths - min⁻¹ (>500% of baseline) and sustained heart rates near 200 bpm (200% of baseline), combined with declining hemoglobin saturation and often accompanied by production of frothy white sputum. Twenty-five animals with cardiopulmonary DCS recovered (40%). If the animal did not recover, it manifested central cyanosis, increasing respiratory distress, eventually declined into agonal respiration, and then died. On average, MP-10 animals got cardiopulmonary DCS 10.1 min sooner than the NS animals (p < 0.01, 2-tailed t-test). No significant differences in cardiopulmonary DCS onset time could be ascertained between the remaining groups.

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