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Effect of Progesterone Administration in Traumatic Subarachnoid Hemorrhage

Michael Lunney

EFFECT OF PROGESTERONE ADMINISTRATION IN TRAUMATIC SUBARACHNOID HEMORRHAGE

by

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ABSTRACT

INTRODUCTION: Traumatic brain injury (TBI) is a major public health problem, causing approximately 52,000 deaths from 1.7 million injuries in the United States annually, with a combined direct and indirect economic cost estimated at $60-75 billion per year. Traumatic subarachnoid hemorrhage (tSAH), a subtype of closed head injury, has a high prevalence within TBI—evident in up to two-thirds of moderately and severely brain injured patients. tSAH is also associated with poor clinical outcomes; some research suggests mortality and unfavorable outcome rates are two-to-three times higher in patients with tSAH, based on brain imaging, compared to those without. To date, no pharmacological treatment has been conclusively shown to improve outcomes in humans for either moderate or severe TBI or for specific tSAH injury. The aim of this study was to assess whether the effect of PROG was substantially different in study TBI patients with evidence of tSAH on initial brain imaging compared to those that did not have evidence of tSAH.

METHODS: ProTECT III clinical trial data was used for an exploratory, post hoc subgroup analysis to determine the effect of the hormone progesterone (PROG) on outcome. Study subjects with any abnormality on baseline brain imaging were included in the analysis and two subgroups, tSAH positive (+tSAH) and tSAH negative (–tSAH), were selected. The primary outcome evaluated was a favorable/unfavorable dichotomy derived from the 6-months post-injury Extended Glasgow Outcome Scale (GOSE) assessment, which evaluates both mortality and functional outcomes. Risk ratios (RRs) were calculated for the total sample and each of the two subgroups and used as statistical evidence for interaction between PROG and tSAH.

RESULTS: All subjects from the original ProTECT III trial cohort (N=882) with no abnormalities found on baseline computed tomography (CT) image (n=125) or missing image (n=1) were excluded from this analysis. Subjects with one or more abnormalities noted on CT (+CT, n=756) were then divided into subgroups based on presence (n=582) or absence (n=174) of tSAH. Subjects with +tSAH were more severely injured than –tSAH (mean Rotterdam CT score 3.3 vs. 2.2; 3.1 overall) and had a lesser proportion of favorable outcomes (47.4% vs. 74.3%; 53.6% overall). Compared to placebo, patients treated with progesterone had marginally better likelihood of favorable outcomes (risk ratio among +tSAH 1.06, 95% confidence interval [CI], 0.89 to 1.26; and RR among –tSAH 1.02, 95% CI 0.85 to 1.22). A multivariable model, adjusted for baseline differences in treatment group covariates did not yield substantially different results for the effect of progesterone on favorable outcomes (+tSAH 1.07; 95% confidence interval [CI], 0.84 to 1.36, –tSAH 1.08; 95% CI 0.75 to 1.56, +CT 1.06; 95% CI 0.87 to 1.29).

CONCLUSION: Our study demonstrated that progesterone did not result in different effects in patients with or without tSAH than those without based on initial brain imaging. This investigation supports previous research findings; tSAH is correlated with more severe injury and worsened outcomes. Concomitant injuries found in +tSAH group are likely worsening the outcomes over –tSAH, but this was not evaluated here. More complex statistical modeling should be used on this data to determine if it provides evidence that tSAH is an independent prognosticator of unfavorable outcome or merely associated with more severely injured patients.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

I. INTRODUCTION

Traumatic brain injury (TBI) is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (Menon, Schwab, Wright, & Maas, 2010, p. 1637). TBIs can range from minor (such as a mild concussion) to catastrophic and sometimes fatal injuries. As the magnitude of the brain injury increases, so does the cost of treatment and amount of future disability associated with the injury. Recent evidence shows staggering figures regarding the incidence and prevalence of TBI; each year, just in the United States, millions of individuals are affected by brain injury with billions of dollars of economic impact (Langlois, Rutland-Brown, & Wald, 2006).

In addition to the substantial cost of treatment and lost productivity, the burden of injury of TBI is massive. The most severe nonfatal cases cause permanent and profound morbidity, not only devastating the lives of the patients, but also those around them. The disruption suffered by the families and loved ones of these patients and the emotional impact of TBI will likely remain extremely difficult to quantify (Humphreys, Wood, Phillips, & Macey, 2013, p. 282). To further complicate their situation and prognosis, TBI patients are frequently at higher risk for a host of other harmful conditions, from depression and substance abuse to epilepsy and Alzheimer's disease (Langlois et al., 2006, p. 376).

Decades of research have been performed with the hope of alleviating some of this burden by improving diagnosis, clinical care, rehabilitation, and, consequently, the outcomes and quality of life attained by these patients. Although significant advances have been made in treatments throughout the course of the disease, from before the injury occurs to rehabilitation and care years later, much work remains to be done in virtually every area and at every stage of the trauma. Prevention and reduction of injury by safety devices (such as seat belts and helmets), behaviors (like geriatric fall risk assessments), and regulation (e.g. traffic safety measures) have undoubtedly saved countless lives and lessened the extent of many of the injuries suffered. No treatment will ever rival the avoidance of injury for the millions of TBIs sustained every year, so continued efforts in these endeavors is clearly warranted.

Clinical care has been greatly elevated as brain injury has become better understood. Diagnoses are made more rapidly with fast, high-resolution brain imaging technologies and refined, evidence-based clinical assessments. Advanced neurosurgical procedures and sophisticated monitoring devices are pushing our capabilities to new levels. Standardizing recommendations through the establishment of "best practice" guidelines has improved the quality and consistency of care (Carpenter et al., 2015). Specialized post-acute-phase facilities, such as Atlanta's Shepherd Center, have revolutionized not only the efficacy of the rehabilitation delivered to patients but have shifted our fundamental expectations for the extent of recovery that is possible after a TBI has been sustained (Kunik, Flowers, & Kazanjian, 2006).

Perhaps the area within TBI treatment that has the most potential for a significant breakthrough is the pharmacological treatment of brain injury. The acute-phase care of patients with moderate and severe brain injury is largely focused on supporting vital physiologic processes during the complex biochemical changes that occur within the brain and body as a result of TBI. Intervening in these injury cascades, repairing damage, or preventing further harm is the elusive "Holy Grail" of treatment for the more severely brain-injured patient. Neurosurgical procedures are indicated and effective in certain types of TBI, and physiologic mechanisms and measurements such as blood pressure or serum lab values can be manipulated through pharmacologic agents. But the search for medications that act directly on the injury and sequelae to improve the outcome of TBI patients has been a long, expensive, and unsuccessful one. Hundreds of millions of dollars have been spent and thousands of subjects enrolled in clinical trials without a single proven-effective pharmacological intervention that specifically treats acute traumatic brain injury (National Institutes of Health, 2015; Narayan et al., 2002).

The purpose of the present investigation is to evaluate the effect of the hormone progesterone in a specific subtype of TBI, called traumatic subarachnoid hemorrhage (tSAH), that is found in a large number of moderate and severe TBI cases and has been shown to be a negative prognostic factor. This analysis was performed using the primary data from a recent nationwide phase III randomized controlled trial evaluating progesterone administration on the outcomes in traumatic brain injury.

II. LITERATURE REVIEW

Overview

Traumatic brain injury is a major cause of death and disability, both in the United States and worldwide. Millions of individuals sustain TBIs every year and even more suffer from long-term effects from these injuries, costing tens of billions of dollars in care delivered and lost employment potential (Langlois et al., 2006). The specific type of TBI, traumatic subarachnoid hemorrhage, is both very common in more severe TBI (occurring in up to two-thirds of moderate and severe cases historically) and associated with poor outcome, with increased rates of mortality and unfavorable outcomes over patients without these injuries (Armin, Colohan, & Zhang, 2006, pp. 445–446).

Brain injury research is exceptionally challenging due to many reasons, such as the difficulty in classifying a heterogeneous injury and the paucity of objective and clinically relevant endpoints. Many pharmacological agents have been studied to treat TBI and even a few specifically for tSAH, but none have been shown definitively to improve outcomes or lower mortality (Maas, Stocchetti, & Bullock, 2008, p. 736; Armin et al., 2006, p. 445). Significant differences exist between the etiology and pathophysiology of tSAH and those of aneurysmal subarachnoid hemorrhage (aSAH, subarachnoid hemorrhage of non-traumatic origin), but there are also meaningful similarities. Basic science tests in animal subarachnoid hemorrhage (SAH) models have findings that may translate to human subjects with tSAH (Armin et al., 2006, p. 448).

The hormone progesterone, naturally occurring in both male and female bodies, has long held promise as a treatment for TBI, with extensive preclinical testing suggesting that it limits the detrimental secondary injuries sustained in TBI such as swelling and increased intracranial pressure. Subsequent research has supported the findings of two small human pilot trials investigating the efficacy of progesterone therapy for TBI (Espinoza & Wright, 2011). The Progesterone for Traumatic Brain Injury, Experimental Clinical Treatment (ProTECT III) trial, which began enrolling subjects in 2009, was the first phase III randomized controlled trial assessing the effect of progesterone in the setting of traumatic brain injury.

Existing literature provides theoretical reasoning that progesterone may have a different treatment effect in TBI patients with tSAH. This investigation analyzed ProTECT III trial data to evaluate if there is statistical interaction between progesterone and tSAH. An interaction would be suggested if there were a difference in the rates of favorable outcomes in the progesterone-treated subjects with tSAH over those without. This was assessed by measuring mortality and functional outcomes of patients and then performing a subgroup comparison based on treatment of progesterone or placebo.

Epidemiology and cost of traumatic brain injury

> Traumatic brain injury (TBI) is an important public health problem…TBI is frequently referred to as the 'silent epidemic' because the complications from TBI, such as changes affecting thinking, sensation, language, or emotions, may not be readily apparent. In addition, awareness about TBI among the general public is limited. (Faul, Xu, Wald, & Coronado, 2010, p. 5)

Over ten million traumatic brain injuries with the severity to cause death or hospitalization are estimated to occur worldwide every year (Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007). Considering that only a fraction of brain injuries are of the severity to necessitate hospitalization, the actual total global incidence of TBI is likely many times higher than this figure; no reliable point estimates of the worldwide prevalence of TBI could be found in a literature review. The World Health Organization estimates that "TBI is predicted to become the third leading cause of global mortality and disability by 2020" due to increasing rates of motor vehicle crashes ("The changing landscape of traumatic brain injury research," 2012, p. 651). Though data from developing countries is sparse and possibly inaccurate, it suggests that low- and middle-income regions have a higher relative burden of injury from TBI than high-income areas, thought to be in part due to lack of safety and health care infrastructure (Hyder et al., 2007, pp. 341–342). But even in the developed world, where subject literature is much more prevalent and reliable, it is clear that traumatic brain injury is a major public health problem.

Based on the Centers for Disease Control and Prevention's *Morbidity and Mortality Weekly Report*, of the estimated 1.7 million people who suffered a TBI each

year from 1997-2007 in the U.S., 1.4 million were seen and discharged from the emergency department (ED), 275,000 were hospitalized and survived, and 52,000 died (Coronado et al., 2011, pp. 1–2). Total prevalence is much higher—5.3 million Americans (~ 2% of the entire U.S. population or ~ 10% of those with any permanent disability) are estimated to be coping with long-term disability from a traumatic brain injury (Langlois et al., 2006, pp. 376–377). It is estimated that, in the U.S., someone suffers a TBI every 21 seconds (Hyder et al., 2007, p. 346).

Although anyone (regardless of age, socioeconomic status, comorbidities, or other factors that typically influence risk) can be susceptible to traumatic injury, population-level patterns certainly exist in TBI. Faul et al. (2010) synthesized the ED visitation, hospitalization, and mortality data of three national databases from 2002 to 2006 to compile the most comprehensive epidemiological analysis of TBI in the United States to date. They found those at highest risk for TBI are universally male (i.e. males are the majority of cases in all subgroups), making up 59% of all identified TBI cases (p.16). The gender disparity is much more lopsided in some subgroups, such as 20-34 year olds with fatal injuries, where greater than 80% of the victims are men (p. 38). As with many other diseases, the young and the old are especially vulnerable. Children aged 14 and younger make up almost 35% of all ED visits for TBI, and individuals 75 and older have the highest rates of hospitalization and death of all age groups (p. 7). Falls and motor vehicle collisions are the most likely causes of fatal injury, and TBI is estimated to contribute to one-third of all injury-related death (pp. 6-7). Importantly, this frequency data underestimates the actual burden of brain injury, as it does not include more than a half million patients. Anyone treated in medical settings outside of the hospital (e.g. primary care physician visits), any non-civilians (this report does not include data from federal, military, or VA hospitals), or any of the estimated 25% of TBI patients that seek no medical care at all, were not included in these figures (pp. 60-61).

The implications of the epidemiology data are profound. Treating significant TBI in modern medical facilities is very expensive; Farhad et al. (2013) found that the average hospitalization for brain injury costs more than $20,000 and acute-care hospital bills can easily rise above $100,000 for the most severe patients (p. 85-86). And these treatment costs have skyrocketed—the same literature notes a 200% increase in the cost

of TBI hospitalization between 1993-1994 and 2006-2007, after adjustment for inflation (Farhad et al., 2013, pp. 85–89). Even "mild" brain injury can have enduring, debilitating, and sometimes even fatal effects; a prospective cohort study in the United Kingdom found that around half of brain injury patients aged 14 and over had moderate or severe disabilities after one year, regardless of the severity of the index injury (Thornhill et al., 2000, pp. 1631–1633). The spectrum of increasingly-intensive rehabilitation cost between $50,000 to almost a half of a million dollars per year in 1991, and these figures are unadjusted for a subsequent quarter-century of inflation (Humphreys et al., 2013, p. 283).

Not only can TBI profoundly change lives through physical disability and personal and familial financial hardships, but brain injury also has major economic impacts at the societal level. Just in the United States, the cost of acute TBI care and rehabilitation paired with the indirect costs of the lost earning potential of patients and other collateral economic effects are estimated at $60 billion per year (Langlois et al., 2006, p. 377). More recently, the CDC approximates this figure to be $76.5 billion (Manley & Maas, 2013, p. 473). Though even rough estimates of the worldwide total cost of TBI are certainly very imprecise without more reliable epidemiologic data, extrapolating existing cost data to global frequency estimates likely puts the global economic impact of TBI in magnitude of hundreds of billions of dollars.

Classification and pathophysiology of TBI

Substantial research effort has gone into mitigating the immense burden of TBI, but it remains an exceedingly complex area of study and clinical trials are fraught with obstacles in the search for effective treatment (Saatman et al., 2008, p. 720). The term "traumatic brain injury" is actually a catchall phrase, representing a host of fundamentally distinct physical insults. There are several major phenotypes of brain injury, such as hematomas (collection of blood) and axonal injury (shearing of neuronal cells). These subtypes of TBI vary in the mechanical forces required to inflict them, the structural damage which occurs to the affected brain cells, the pathophysiological sequelae occurring as a result of the injury, and the prognosis of the patient (Saatman et al., 2008; Zhu, Wang, & Liu, 2009).

Most clinical trials to date have classified severity of brain injury by a mental status assessment called the Glasgow Coma Scale (GCS), which measures verbal response, eye opening, and motor response of the patient and compiles the three components into a score from 3 to 15 (Teasdale & Jennett, 1974). The GCS is performed soon after injury and a lower score represents a more depressed level of consciousness and, consequently, a more severe brain injury. "Mild," "moderate," and "severe" brain injury correspond to GCS assessments of 13-15, 9-12, and 3-8, respectively (Teasdale et al., 2014). According to a workshop described by Saatman et al. (2008), the use of the GCS has been prevalent due to "its high inter-observer reliability and generally good prognostic capabilities" (p.721). Despite being simple, fast, and therefore relatively easy for clinicians to use, the biggest problem with using the GCS to select patients for TBI research is that it does not discriminate between injuries that are classified differently using other methods, potentially confounding the assessment of treatments while other methods of classification "may be more relevant to the neuroprotectant action of a particular intervention" (Saatman et al., 2008, p. 721).

The literature by Saatman et al. (2008) reviews TBI classification systems for use in clinical trials, providing alternative methods of brain injury classification to the GCS include pathoanotomic, pathophysiologic, and prognostic models (p. 720). Pathoanotomic classification distinguishes between the type and location of injury. Primarily using imaging diagnostics such as computed tomography (CT) or magnetic resonance (MR), this method categorizes injuries into four basic types: hematomas (including epidural, subdural, and intraparenchymal—each are lesions in different structural areas of the brain), contusions (bruising of the brain tissue), diffuse axonal injury, or subarachnoid hemorrhage (pp. 722-724). Evidence suggests that mechanism of injury is correlated with the phenotype of injury sustained; linear and rotational forces damage the physical structures of the brain differently. "Impact loading," or contact forces, usually produce fractures, contusions, and epidural hematomas, while "inertial loading," or noncontact forces, are theoretically more likely to cause concussion, subdural hematomas, and axonal injury (p. 723).

Pathophysiologic classification, very simply put, distinguishes between "primary injury," or the direct insult to the brain from the index external force, and "secondary

injury," or damage occurring to the brain as a result of the complex injury cascades after the initial structural damage like swelling and vasospasm (constriction of blood vessels) (p.724). It is this "potentially avoidable damage that occurs at variable times after injury" that research efforts have attempted to target for pharmacological treatment (p.723).

Finally, prognostic classification uses complex multivariate statistical modeling to choose the factors with the strongest associations with outcomes to create a hybridized scoring system like the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) model, which uses data points from demographics, clinical assessments, brain imaging, and laboratory values to predict outcome in TBI (pp. 732-733).

Other obstacles in TBI research and past clinical trials

Leading neurotrauma researchers believe that historical and contemporary attempts to translate basic science findings into human clinical research have failed in part due to the inadequacy of prevalent classification systems and an inability to develop effective methodology to account for the heterogeneity of TBI (Yue et al., 2013). A multitude of other obstacles exist in clinical trials for brain injury. Randomized controlled trials (RCTs) are considered to be the "gold standard" in pharmacological efficacy trials, yet they are very expensive to conduct and research funding is limited (Roozenbeek, Lingsma, & Maas, 2012). Lack of standardization of data elements between trials limits the ability to combine data sets to achieve higher statistical power for post hoc analyses (Maas et al., 2011, p. 178). Typical outcome measures specific to TBI can be subjective and prone to bias and significant inter-rater variability. Other outcome assessments, such as neuropsychological tests, were not developed or validated for use in TBI patients. Outcomes measured at 6-months (the predominant follow-up time point in most TBI RCTs) are not taking into account long-term functional outcome, which have shown that many problems or improvements are still manifest up to three years from injury (van Baalen et al., 2003). Lastly, the Glasgow Outcome Scale (GOS) and its successor, the Extended Glasgow Outcome Scale (GOSE), the primary outcome measure used most frequently in brain injury clinical trials, may be inadequate in

assessing cognitive outcome and often are analyzed in ways that fail to maximize statistical power (Alali et al., 2014, pp. 1–2).

As a result of these factors along with inadequate preclinical testing, flawed study design, and insufficient evaluation of pharmacological biomechanics to target the complex cascade of secondary brain injury have lead to a veritable graveyard of experimental clinical trials in TBI (Kabadi & Faden, 2014, pp. 1216–1219). At least 33 phase III clinical trials have been performed for traumatic brain injury since 1980, the majority of which tested a pharmacological agent (Maas, Roozenbeek, & Manley, 2010, p. 116). In total, none of the more than 20 promising neuroprotective agents "have convincingly shown efficacy in the overall study population" for the treatment of TBI (Maas et al., 2008, p. 736). Several trials have evaluated efficacy of two drugs, milrinone and nimodipine, specifically in the subgroup of TBI with traumatic subarachnoid hemorrhage (tSAH), but conclusive benefit has not been shown for either agent in the treatment of tSAH (Lasry & Marcoux, 2014; Vergouwen, Vermeulen, & Roos, 2006). Despite the obvious negative of the inability to find a treatment for the injury that continues to kill and disable so many, the consistent failure of pharmacological TBI clinical trials seems to be hindering the further development of investigations despite promising new agents (Maas et al., 2010, p. 119).

Progesterone for the treatment of TBI

Long thought to be "a simple reproductive hormone" on account of its dramatic rise in females during gestation, the neurosteroid progesterone has been studied extensively in the context of TBI (Donald G. Stein & Wright, 2010, p. 849). Progesterone was first identified as having a potential effect in brain injured rats more than 20 years ago, after disparities in outcomes were seen relative to gender (Roof, Duvdevani, & Stein, 1992). Evidence suggests that progesterone acts in multiple ways to ameliorate sequelae of the complex biochemical chain of events that make up secondary brain injury. This pleiotropic effect of the hormone gave rise to the hope that it would succeed where many, more specifically-acting therapies had previously failed (Espinoza & Wright, 2011, pp. 497–498).

Briefly, progesterone has been shown in basic science tests to reduce cerebral edema, enhance neuronal survival, attenuate inflammatory pathways, reduce oxidative stress, and modulate receptor pathways, leading to improved functional outcome and limiting "behavioral, cognitive, and sensorimotor deficits" (Deutsch et al., 2013, pp. 88–89). The hormone was evaluated in over 180 preclinical brain injury trials and two phase II human trials (where it was deemed safe to continue with further testing) prior to the large clinical trials of ProTECT III and the Study of the Neuroprotective Activity of Progesterone in Severe Traumatic Brain Injuries, or SyNAPSE trial (D.G. Stein, 2011, pp. 104–105). Two other pilot trials of progesterone in humans with TBI were found in the literature, in addition to those mentioned by Stein (2011). Those trials also suggest that progesterone may improve outcomes in brain injured patients (Xiao et al., 2007; Shakeri et al., 2013).

ProTECT III and SyNAPSE trials

The ProTECT III study was a National Institute of Neurological Disorders and Stroke (NINDS)-funded clinical trial to determine if progesterone is effective in improving outcomes in moderate and severe TBI. Subjects included had an initial GCS between 4 and 12 while those with confounding events, such as significant hypoxia (low oxygen) or hypotension (low blood pressure) or signs such as two dilated and unreactive pupils (all of which are prognosticators of poor outcomes), were excluded. Because the ProTECT pilot trial suggested that subjects receiving progesterone most quickly might have the best response to the intervention, study treatment was delivered within four hours after the injury.

Subjects were monitored closely throughout their hospitalization, and treatment teams adhered (as closely as possible) to clinical care guidelines with the hopes of standardizing treatment and minimizing variability in the almost 50 sites nationwide that participated in the trial. The primary outcome for the trial was the 6-month GOSE assessment, and results were stratified to account for severity of initial injury. Enrollment for the trial was halted after randomizing 882 subjects, out of the planned sample of 1140, on account of futility to prove its primary hypothesis. Progesterone was not found to have a significant effect on the outcomes of moderate and severe traumatic

brain injury patients (Wright et al., 2014). Beginning enrollment one year after ProTECT III, the SyNAPSE trial was similarly structured except that it enrolled only severe TBI patients (those with a GCS ≤ 8). This research also did not show significant benefit for the intervention to improve outcomes in the study sample (Skolnick et al., 2014). Primary analyses for these trials were published together in the *New England Journal of Medicine* in December of 2014.

Traumatic subarachnoid hemorrhage

The arachnoid mater is one of the three meningeal layers of the brain, which lie underneath the skull and cover the brain cortex. Cerebrospinal fluid normally circulates in the space below the arachnoid mater. If there is hemorrhagic insult to the vasculature surrounding the brain, blood can collect there, hence the name of subarachnoid hemorrhage (SAH) (Bear, 2007, pp. 173–174). There are many different etiologies for SAH, but the two main causes are aneurysmal (as it is usually due to the rupture of an aneurysm), or as a result of trauma (aSAH and tSAH, respectively) (Suarez, Tarr, & Selman, 2006, p. 387). The medical community refers to and studies these two classifications of SAH as different diseases, though evidence suggests they have pathologic characteristics in common such as vasospasm and ischemia (decreased oxygen delivery to tissue) (Fukuda, Hasue, & Ito, 1998; Taneda, Kataoka, Akai, Asai, & Sakata, 1996). In previous studies, tSAH is seen on initial brain imaging between 33 and 67 percent of severe head injury patients (Kakarieka, Braakman, & Schakel, 1994, p. 2; Bobinski, Olivecrona, & Koskinen, 2012, p. 1072).

Though there is much variation in the literature of the prevalence of this specific finding, it is not the only inconsistency in tSAH-specific research. As with general study of TBI, assessments of the pathophysiology of tSAH are confounded on account of concomitant injuries and other covariates (Armin et al., 2006, p. 446). The correlation of tSAH and worsened outcomes, however, seems to be universal. A host of manuscripts exist supporting this association in brain-injured patients; one investigation saw a rise in mortality in severe TBI patients from 14% to 42% from those that did not have evidence of tSAH to those that did (Kakarieka et al., 1994, p. 3). But there is disagreement on whether this relationship is directly or indirectly caused by the tSAH itself (Mattioli et

al., 2003, p. 40). Conflicting data is responsible for this uncertainty, but two basic possibilities exist: tSAH is an independent prognosticator of outcome, or it is merely representative of a more severely injured patient and not responsible for increased morbidity and mortality outright (Armin et al., 2006, pp. 446-447).

Some of the early research in this area suggested that, as with aSAH, patients with tSAH are at risk for vasospasm and resultant cerebral ischemia—pathophysiology that would likely explain the worsened clinical outcomes in this population (Harders, Kakarieka, & Braakman, 1996, p. 82). Subsequent analysis has found associations between tSAH and more parenchymal damage, higher intracranial pressures, and inflammatory processes (such as swelling and edema), and concluded these sequelae are responsible for poorer outcomes in these patients rather than the tSAH or resultant vasospasm and ischemia itself (Servadei et al., 2002, p. 266). Recent review remains inconclusive exactly what role vasospasm plays in outcomes in tSAH patients (Kramer, Winer, Pease, Amar, & Mack, 2013, pp. 3–4). Even the most current literature acknowledges that the complex pathophysiology of secondary brain injury in tSAH remains incompletely understood, though relative certainty exists that tSAH is a prognosticator for poor outcomes (Servadei & Picetti, 2014 pp. e597-e598).

Theoretical basis for hypothesis

As previously mentioned, the literature supports beneficial effects of progesterone administration in the setting of brain injury as well as a host of other neurological conditions "including ischemia, spinal cord injury, peripheral nerve injury, motorneuron disease, demyelinating disease, and seizures" (Deutsch et al., 2013, p. 83). Though none of the six clinical trials studying progesterone in TBI found in the literature have specifically assessed tSAH until now, a number of studies have investigated progesterone's effect in SAH in animal models. Although these studies were designed to assess the affects of progesterone in aSAH, it is recognized that aSAH is not pathophysiologically identical to tSAH with clinically meaningful differences between the two conditions. It also cannot be assumed there is no translation of findings whatsoever from aSAH to tSAH. Furthermore, Armin et al. (2006) assert, "the traditional animal experiments that had originally sought to investigate vasospasm in

relation to aSAH may be considered to actually have been mimicking tSAH" (p. 448). Another review concluded that tSAH was the most reproducible of five different lesion types in multiple animal models of injury (Doppenberg, Choi, & Bullock, 2004, p. 87).

Although the exact characteristics and effects of vasospasm in tSAH require further evaluation, it is generally agreed that it does occur; one estimate of prevalence of vasospasm in tSAH to be between 25-30% of patients (Fukuda et al., 1998, p. 1044). Progesterone has been shown to significantly attenuate vasospasm in rats with induced aSAH (Chang et al., 2014). If vasospasm is contributing, at least in part, to worsened outcomes in tSAH, then it is possible that progesterone may benefit this population. But it is progesterone's varied and multiple mechanisms of neuroprotection that set it apart from most of the other experimental pharmacologic agents, which have more limited methods of action.

In addition to acting on vasospasm, progesterone ameliorates secondary injuries frequently found in tSAH. Wang et al. (2011) showed that, through complicated biochemical processes, progesterone affects the inflammatory response after the induction of SAH (p. 4). Thus this had important and clinically relevant effects on outcomes. Rats given progesterone showed statistically significant improvement on behavior function performance after SAH. Water content of the brains was significantly less in the progesterone-treated group, suggesting that cerebral edema (a common and potentially sinister finding in SAH and TBI in general) may be lessened by the intervention. Finally, this research demonstrated that progesterone significantly limits the permeability which develops in the blood-brain barrier (BBB) (pp. 6–8). The BBB is a specialization of the capillaries of the brain that regulate the passage of molecules from the blood into the brain, thus prohibiting the entry of bacteria and other blood borne substances (Bear, 2007, p. 71). In fact, cerebral edema and the disruption of the BBB are likely directly related (Unterberg, Stover, Kress, & Kiening, 2004). A more recent study confirmed the findings of the previous investigations into the effects of progesterone in the setting of SAH in the animal model, finding a reduction in cell apoptosis ("self destruction" of cells, put simply), edema, BBB disruption, and mortality, with improved neurological and functional outcomes in those that survived (Yan et al., 2013, pp. 165–167).

The preclinical evidence regarding progesterone in SAH shows promise for the intervention to improve functional outcomes and decrease mortality in TBI patients if these mechanisms translate to humans. If the theories of how progesterone acts to reduce secondary brain injury are correct, then perhaps progesterone will be effective in an analysis of the subgroup with tSAH findings on initial brain imaging in the ProTECT III clinical trial data, despite the negative findings of the drug in the total study sample.

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III. MANUSCRIPT

Background

Traumatic brain injury (TBI) is a major cause of death and disability; approximately 1.7 million people sustain a TBI every year in the United States—52,000 of these injuries are fatal.[1] Indirect and direct costs of TBI in America are estimated to be $60-75 billion per year.[2,3] Research of interventions for acute care of TBI is difficult, largely due to the heterogeneity of injury and complex pathophysiology of neurotrauma.[4] At least 20 pharmacological agents have been tested in phase III clinical trials over the last 30 years and none have shown convincing efficacy in treating TBI.[5]

Radiological findings of subarachnoid hemorrhage (SAH), or blood in the subarachnoid meningeal space, on initial computed tomography (CT) imaging are found in one- to two-thirds of more severely brain-injured patients.[6,7] The presence of subarachnoid hemorrhage caused by trauma (tSAH) is associated with increased mortality [6,8,9] and worsened functional outcome,[10–13] though there is still uncertainty if tSAH is an independent prognosticator (possibly through mechanisms such as vasospasm[14] or ischemia[15]) or an epiphenomenon.[16,17]

The endogenous hormone, progesterone (PROG), has been evaluated in over 180 preclinical brain injury studies showing neuroprotection.[18] Four human pilot trials[19–22] have showed that PROG may improve outcomes in TBI, but these trials were not powered for conclusive results. Evidence suggests that PROG is pleiotropic, acting through multiple neuroprotective mechanisms to attenuate several characteristics of secondary brain injury associated with both SAH and worsened clinical outcomes in animal models. PROG has been shown ameliorate several sequelae of tSAH in preclinical studies: reduction of vasospasm,[23] decreased inflammatory response, cerebral edema, and permeability of the blood-brain barrier,[24] and limitation of cell apoptosis,[25] all of which reduce mortality and improve functional and neurological outcomes after SAH.

Two recent phase III trials failed to show benefit of PROG over placebo for study subjects with a severe or moderate-to-severe TBI.[26,27] As of this writing, no published studies were found that investigate PROG specifically for the treatment of SAH of either traumatic or non-traumatic etiology in humans. This exploratory analysis of data collected in the Progesterone for Traumatic Brain Injury Experimental Clinical Treatment

(ProTECT III) study, a multicenter randomized controlled trial, is in response to this gap in the science. Since PROG may exert a different mechanism of action in TBI with tSAH due to changes in cellular pathophysiology and the blood-brain barrier, the objective of the present study is to determine if the effect of PROG administration in subjects with moderate and severe TBI is different in those with evidence of tSAH on baseline CT radiology compared to subjects without tSAH.

Methods

Design & participants

This analysis is a post hoc examination of trial data from the ProTECT III clinical trial.[26] Eight hundred eighty-two subjects, out of the planned sample of 1140, were enrolled in the study before recruitment was halted when a scheduled interim analysis determined it would not be able to show PROG efficacious for the treatment of study subjects with a moderate or severe TBI. See *Appendix 1* for the ProTECT III protocol summary.

Figure 1. **Glasgow Coma Scale (GCS)**

Eye Opening	
Spontaneously	4
To Command	3
To Pain	2
None	1
Verbal Response	
Oriented	5
Confused	4
Inappropriate	3
Incoherent	2
None	1
Motor Response	
Obeys Commands	6
Localizes Pain	5
Withdraws to Pain	4
Flexes to Pain	3
Extends to Pain	2
None	1
Total GCS	3-15

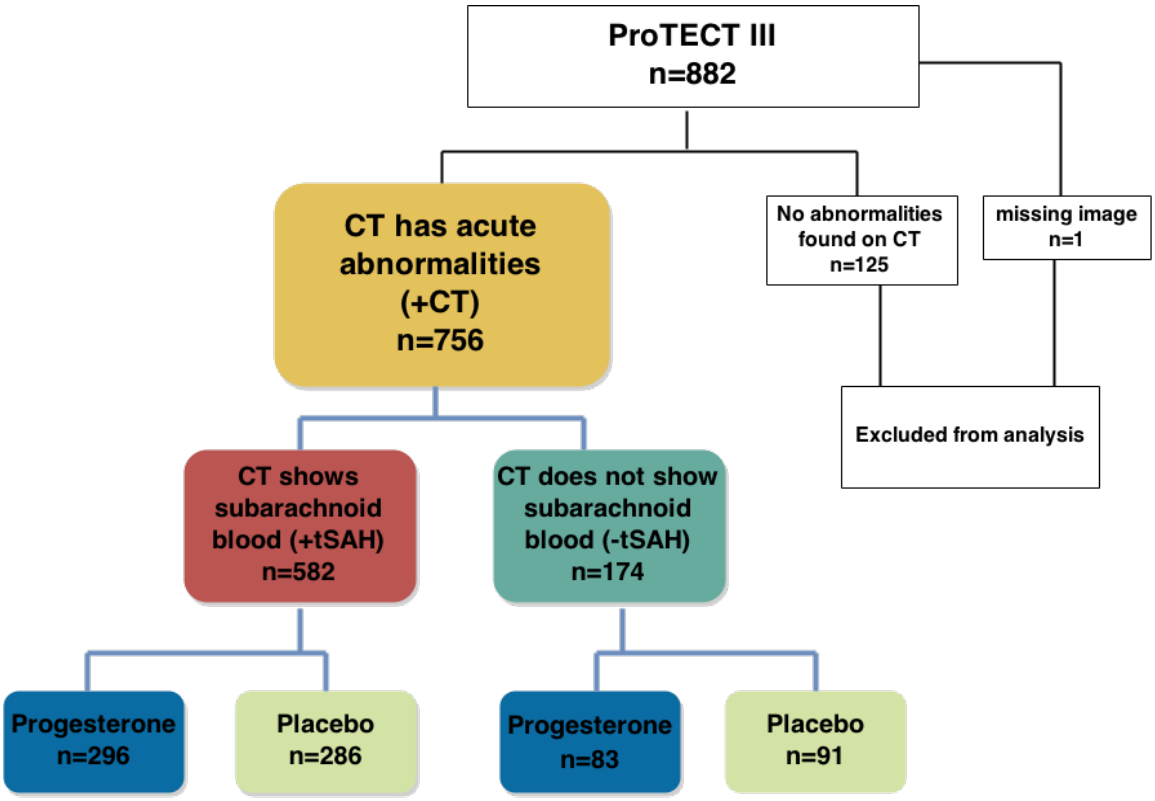
Subjects included in this analysis were adults with a blunt mechanism TBI and an initial Glasgow Coma Scale (GCS) of 4 to 12. The GCS is a mental status assessment that judges eye, verbal, and motor response—these 3 components are summed to reach the total GCS score, a composite number from 3 to 15. A lower score represents more severe brain injury (*Figure 1*). This scale was developed specifically to quantify TBI severity,[28] but its use has become common for all types of patients in emergency departments and intensive care units worldwide and has high predictive capabilities and inter-rater reliability.[29]

As is typical with trauma patients suspected of having a TBI, all of the subjects in this study received a CT scan as soon as possible after arrival at the enrolling trauma center. An independent neuroradiologist assessed all images and documented any findings indicative of acute brain injury in the study database (see *Supplement 1* for the radiology case report form from the trial). Major phenotypes of injury assessed (in addition to tSAH) were epidural, subdural, and intraparenchymal hematomas, brain contusions, diffuse axonal injury, and cranial fractures. Secondary injury characteristics

documented were signs of increased intracranial pressure, cerebral edema, or localized swelling.

All ProTECT III subjects with at least one abnormality noted on baseline CT were included in the present analysis. Those subjects in the parent trial that had no abnormalities on initial brain imaging or missing this scan altogether were excluded from the current study. The total sample, participants with abnormal radiological findings, was labeled CT positive (+CT). +CT subjects were then divided into two subgroups by presence or absence of the independent variable in question for this analysis, tSAH. Subjects were included in the tSAH positive (+tSAH) group if their radiology showed any evidence of subarachnoid blood defined as hemorrhage of any severity in one or more of the locations assessed (the suprasellar or basal cisterns; the Sylvian, interhemispheric, or lobar fissures; or the ventricular system). Subjects in the tSAH negative group (–tSAH) had no instance of any of the findings above. Any other abnormal CT findings had no bearing on subgroup allocation and +tSAH or –tSAH subjects could have any combination of concomitant injuries evident on baseline CT. Each subgroup was further divided upon which study treatment subjects received, PROG or placebo. *Figure 2* is a diagram detailing the sample selection in the study.

Figure 2. **Study Sample Diagram**



Intervention

Study medication was administered as soon as possible after enrollment, but within 4 hours. Progesterone and placebo were identical in appearance and packaging. Treatment infused for 96 hours, starting with a one-hour loading dose, then a 71-hour maintenance dose, and finally a 3-tiered taper with 8 hours at each step until the infusion was complete.

Outcome and other measurements

The GOSE assessment was used as the primary outcome for this study. It ranks the functional outcome of brain injury patients into one of eight different categories[30] (*Figure 3*). There are different statistical models used to analyze this measurement,[31] but we chose a fixed dichotomy, which classifies a GOSE score of ≤ 4 as unfavorable and 5 or above as favorable, or more functionally capable. This method was chosen based on convention,[31] historical statistical distribution of outcomes,[5] improved generalizability of results,[32] and that covariate adjustment in well-balanced subgroups of RCTs is not likely to significantly change the results from an unadjusted model.[33]

Figure 3. **Extended Glasgow Outcome Scale (GOSE)**

	GOSE score	Category
	8	Upper good recovery
	7	Lower good recovery
	6	Upper moderate disability
Favorable ∧	5	Lower moderate disability
Unfavorable ∨	4	Upper severe disability
	3	Lower severe disability
	2	Vegetative state
	1	Death

Other classification systems used in this report are as follows. The Abbreviated Injury Scale (AIS) is an ordinal measurement from 1 to 6 for each of nine body regions.[34] It is based on severity and location of injury and a score of 1 represents minor injury while 6 is a fatal injury). The Injury Severity Score (ISS) is directly computed from the AIS, squaring the highest 3 values; a score of 75 is the maximum.[34] Finally, the Rotterdam CT classification is a prognostic assessment (also 1 to 6, with a higher score correlating with increased mortality) developed in part to account for the strong prognostic value of tSAH and improve the accuracy of previously-existing predictive models for outcome in TBI.[35,36] Other variables known to correlate with outcome in TBI that were considered in this analysis are age, GCS, pupil reactivity,[37] significant post-injury hypoxia or hypotension[38], and the presence of polytrauma (significant injuries in multiple body systems).[39]

Randomization

Subjects were randomized to treatment group either PROG or placebo, in a 1:1 ratio. Age and GCS were factored into randomization scheme in order to assure even population of initial risk stratifications and gross age distribution between treatment groups. Randomization assignment was double-blinded so that none of the clinicians or researchers, in addition to subjects or their friends and family, knew which treatment study participants were receiving. Blinding remained throughout the study

Statistical analysis

We compared patient characteristics by treatment assignment to assess the distribution of covariates; comparisons were performed for all eligible participants and by tSAH classification. Risk ratios (RRs) and 95% confidence intervals (CI) were calculated based on the number of subjects with a favorable outcome relative to PROG for each subsample. Subjects missing outcome data were excluded entirely from the analysis. For the primary analysis, we compared the effect of progesterone on risk of favorable outcome by tSAH classification to assess interaction. In secondary analyses, we used Poisson log regression to estimate an adjusted RR, controlling for covariates. Variables included in the regression analysis were chosen based on uneven treatment distribution at baseline regarding prognostic and clinical characteristics: age, race, mechanism of injury, and pre-randomization hypotension were included in the adjusted regression model.

Results

Of the 882 subjects enrolled in the ProTECT III trial, 756 had abnormalities present on baseline CT images; 125 were excluded from analysis because abnormalities were not present, and one subject did not have an image collected. Five hundred eighty-two subjects, or 66% of all of the subjects in the parent trial, had evidence of tSAH on CT. Treatment group prevalence within the +tSAH and –tSAH subgroups was even to within 5%. *Table 1* shows demographic distributions, causative mechanism for TBI, and mean times from injury across the subgroups (since receiving expedient care and timely

***Table 1.* Overall patient characteristics**

		+tSAH		-tSAH		Δ (+tSAH minus -tSAH)¶	+CT	
	n	582	(77.0%)	174	(23.0%)	+54.0%	756	
Age-mean		41.0	(±18.0)	35.4	(±16.6)	+5.6	39.7	(±17.9)
-median		39		30		+9	36	
-range		17-93		17-94		-	17-94	
Sex-male		429	(73.6%)	128	(73.6%)	0	557	(73.7%)
-female		153	(26.3%)	46	(26.4%)	-0.1%	199	(26.3%)
Race-white		433	(74.3%)	129	(74.1%)	-0.2%	562	(74.3%)
-black		86	(14.7%)	32	(18.4%)	-3.7%	118	(15.6%)
-other		63	(10.8%)	13	(7.5%)	+3.3%	76	(10.1%)
Ethnicity-Hispanic		80	(13.7%)	28	(16.1%)	-2.4%	108	(14.3%)
Mechanism-motor vehicle collision		190	(32.7%)	72	(41.4%)	-8.7%	262	(34.7%)
-Motorcycle collision/ all-terrain vehicle		114	(19.6%)	36	(20.7%)	-1.1%	150	(19.8%)
-person hit by auto		90	(15.5%)	16	(9.2%)	+6.3%	106	(14.0%)
-falls		98	(16.8%)	25	(14.4%)	+2.4%	123	(16.3%)
-bicycle crash		36	(6.2%)	7	(4.0%)	+2.2%	43	(5.7%)
-other		54	(9.3%)	18	(10.3%)	-1.0%	72	(9.5%)
Time¥-injury-to-emergency deptartment-mean		0:52	(±0:26)	0:53	(±0:28)	-0:01	0:52	(±0:27)
-injury-to-baseline image-mean		1:24	(±0:34)	1:26	(±0:33)	-0:02	1:24	(±0:34)
-injury-to-study treatment mean		3:41	(±0:55)	3:36	(±0:37)	+0:05	3:40	(±0:51)
Prehospital hypoxia		8	(1.4%)	0	(0.0%)	+1.4%	8	(1.1%)
Prehospital hypotension		11	(1.9%)	2	(1.1%)	+0.8%	13	(1.7%)
No pupillary response at time of randomization		27	(4.6%)	4	(2.3%)	+2.3%	31	(4.1%)

¶ Δ column absolute difference between subgroups
¥ All times h:mm

delivery to the hospital is beneficial to outcome for neurotrauma patients).[40]

The median age in the +tSAH group was 39 (range 17-93) compared to a median of 30 in the -tSAH group (range 17-94) and 36 among all enrolled participants (range 17-94). Gender distribution was almost exactly the same for all groups—males outnumbered females nearly 3 to 1. The largest variations were shown between treatment groups in the mechanisms of injury and in the smaller –tSAH group where age and race were substantially different (*Table 2*).

Injury severity was greater in the +tSAH group over the –tSAH group by all classification systems reported; absolute differences of +tSAH minus –tSAH were GCS, -0.6; AIS, +0.4; Rotterdam, +1.1; and mean ISS, +3.7 (*Table 3*). All subgroups and the entire sample had mean Injury Severity Scores (ISS) well above 15, typically

Table 2. Subgroup patient characteristics

	+tSAH				Δ (PROG minus placebo)¶	-tSAH				Δ (PROG minus placebo)¶
	PROG		placebo			PROG		placebo		
n	**296**	**(50.9%)**	**286**	**(49.1%)**	**+1.8%**	**83**	**(47.7%)**	**91**	**(52.3%)**	**-4.6%**
Age-mean	40.9	(±18.1)	41.1	(±18.0)	-0.2	39.1	(±19.0)	32.0	(±13.3)	+7.1
-median	38		39		-1	35		28		+7
-range	18-88		17-93		-	17-94		18-67		-
Sex-male	216	(73.0%)	213	(74.5%)	-1.5%	60	(72.3%)	68	(74.7%)	-2.4%
-female	80	(27.0%)	73	(25.5%)	+1.5%	23	(27.7%)	23	(25.3%)	+2.4%
Race-white	223	(75.3%)	210	(73.4%)	+1.9%	58	(69.9%)	71	(78.0%)	-8.1%
-black	43	(14.5%)	43	(15.0%)	-0.5%	21	(25.3%)	11	(12.1%)	+13.2%
-other	30	(10.1%)	33	(11.5%)	-1.4%	4	(4.8%)	9	(9.9%)	-5.1%
Ethnicity-Hispanic	42	(14.2%)	38	(13.2%)	+1.0%	10	(12.0%)	18	(19.8%)	-7.8%
Mechanism-motor vehicle collision	101	(34.1%)	89	(31.1%)	+3.0%	29	(34.9%)	43	(47.3%)	-12.4%
-Motorcycle collision/ all-terrain vehicle	53	(17.9%)	61	(21.3%)	-3.4%	14	(16.9%)	22	(24.2%)	-7.3%
-person hit by auto	47	(15.9%)	43	(15.0%)	+0.9%	7	(8.4%)	9	(9.9%)	-1.5%
-falls	52	(17.6%)	46	(16.1%)	+1.5%	21	(25.3%)	31	(34.1%)	-8.8%
-bicycle crash	17	(5.7%)	19	(6.6%)	-0.9%	3	(3.6%)	4	(4.4%)	-0.8%
-other	26	(8.7%)	28	(9.8%)	-1.1%	12	(14.5%)	6	(6.6%)	+7.9%
Time[ϒ]-injury-to-emergency deptartment-mean	0:52	(±0:27)	0:51	(±0:26)	+0:01	0:51	(±0:30)	0:54	(±0:25)	-0:03
-injury-to-baseline image-mean	1:23	(±0:36)	1:24	(±0:32)	-0:01	1:29	(±0:37)	1:24	(±0:28)	+0:05
-injury-to-study treatment mean	3:44	(±1:01)	3:37	(±0:48)	+0:07	3:37	(±0:43)	3:36	(±0:30)	+0:01
Prehospital hypoxia	4	(1.4%)	4	(1.4%)	0	0	(0.0%)	0	(0.0%)	0
Prehospital hypotension	2	(0.7%)	9	(3.1%)	-2.4%	1	(1.2%)	1	(1.1%)	+0.1%
No pupillary response at time of randomization	15	(5.1%)	12	(4.2%)	+0.9%	2	(2.4%)	2	(2.2%)	+0.2%

¶ Δ columns absolute difference between treatment groups

ϒ All times h:mm

Table 3. Overall severity and concomitant injuries*

	+tSAH		-tSAH		Δ (+tSAH minus -tSAH)¶	+CT	
	n=582		n=174		+408	n=756	
GCS-mean	7.7	(±2.4)	8.3	(±2.4)	-0.6	7.9	(±2.4)
AIS head-mean	4.0	(±0.9)	3.6	(±1.1)	+0.4	3.9	(±1.0)
Rotterdam score-mean	3.3	(±0.9)	2.2	(±0.8)	+1.1	3.1	(±1.0)
ISS-mean	26.9	(±10.8)	23.2	(±10.4)	+3.7	26.0	(±10.8)
ISS-median	26		22		+4	26	
Epidural hematoma	106	(18.2%)	24	(13.8%)	+4.4%	130	(17.2%)
Subdural hematoma	334	(57.4%)	85	(48.9%)	+8.5	419	(55.4%)
Intraparenchymal hematoma	42	(7.2%)	8	(4.6%)	+2.6%	50	(6.6%)
Brain contusion	284	(48.8%)	60	(34.5%)	+14.3%	344	(45.5%)
Diffuse axonal injury	187	(32.1%)	52	(29.9%)	+2.2%	239	(31.6%)
Skull fracture	322	(55.3%)	91	(52.3%)	+3.0%	413	(54.6%)
Increased ICP	213	(36.6%)	39	(22.4%)	+14.2%	252	(33.3%)
Generalized edema	166	(28.5%)	17	(9.8%)	+18.7%	183	(24.2%)
Focal swelling	47	(8.1%)	5	(2.9%)	+5.2%	52	(6.9%)

* GCS, Glascow Coma Scale; AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; ICP, intracranial pressure

¶ Δ column absolute difference between subgroups

considered the standard threshold for polytrauma.[39] Concomitant intracranial injuries were largely disparate in the two subgroups, with the +tSAH group having greater prevalence of all other main categories of abnormalities assessed on baseline CT. These findings ranged from a 2.2% increase of diffuse axonal injury in +tSAH over –tSAH to an almost 19% higher frequency of cerebral edema. Even in the –tSAH group, although less-severely injured as a whole, showed particularly high numbers of subdural hematomas (SDH) and skull fractures, occurring in approximately half of the subgroup sample.

Injury distributions between the treatment assignments were within 5% in the +tSAH group for all phenotypes. The PROG-treated subjects in the –tSAH group had 5.5% more skull fractures, 6% more brain contusions, and 12.6% more SDHs (*Table 4*). All severity classifications however, were nearly identical between treatment groups.

Table 4*. Subgroup severity and concomitant injuries

	+tSAH					-tSAH				
	PROG		placebo		Δ (PROG minus placebo)¶	PROG		placebo		Δ (PROG minus placebo)¶
	n = 296		n = 286		+10	n = 83		n = 91		-8
GCS-mean	7.7	(±2.4)	7.7	(±2.3)	0	8.3	(±2.3)	8.3	(±2.5)	0
AIS head-mean	4.0	(±0.9)	4.0	(±0.9)	0	3.6	(±1.1)	3.7	(±1.1)	-0.1
Rotterdam score-mean	3.3	(±0.9)	3.3	(±0.9)	0	2.2	(±0.8)	2.2	(±0.7)	0
ISS-mean	27.0	(±11.2)	26.8	(±10.4)	+0.8	23.3	(±11.0)	23.1	(±9.8)	+0.2
ISS-median	26		27		-1	21.5		24		-2.5
Epidural hematoma	61	(20.6%)	45	(15.7%)	+4.9%	12	(14.5%)	12	(13.2%)	+1.3%
Subdural hematoma	167	(56.4%)	167	(58.4%)	-2.0%	46	(55.4%)	39	(42.9%)	+12.6%
Intraparenchymal hematoma	18	(6.1%)	24	(8.4%)	-2.3%	4	(4.8%)	4	(4.4%)	+0.4%
Brain contusion	149	(50.3%)	135	(47.2%)	+3.1%	31	(37.3%)	29	(31.9%)	+5.5%
Diffuse axonal injury	90	(30.4%)	97	(33.9%)	-3.5%	23	(27.7%)	29	(31.9%)	-4.2%
Skull fracture	161	(54.4%)	161	(56.3%)	-1.9%	46	(55.4%)	45	(49.5%)	+6.0%
Increased ICP	108	(36.5%)	105	(36.7%)	-0.2%	19	(22.9%)	20	(22.0%)	+0.9%
Generalized edema	82	(27.7%)	84	(29.4%)	-1.7%	8	(9.6%)	9	(9.9%)	-0.3%
Focal swelling	26	(8.8%)	21	(7.3%)	+1.4%	4	(4.8%)	1	(1.1%)	+3.7%

* GCS, Glascow Coma Scale; AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; ICP, intracranial pressure
¶ Δ columns absolute difference between treatment groups

+tSAH subjects did markedly worse than -tSAH, with an almost 27% shift from favorable to unfavorable outcome between the groups (*Table 5*). +tSAH subjects had a 10.3% higher mortality rate than –tSAH subjects, and 2.4% more than total sample. Although modest improvements in favorable outcomes were seen in the PROG treatment group between subgroups (1.4% increase in absolute rate of favorable outcome of +tSAH over –tSAH), mortality was also higher in the PROG-treated subjects regardless of grouping (+tSAH 2.7%, –tSAH 2.3%, +CT 2.1%; *Table 6* & *Figure 4*).

***Table 5*. Overall outcomes**

	+tSAH total		-tSAH total		Δ (+tSAH minus -tSAH)¶	+CT PROG		+CT placebo		Δ (PROG minus placebo)¶	+CT total	
	n = 582		n = 174			n = 379		n = 377			n = 756	
Missing outcome	23	(4.0%)	7	(4.0%)	0	14	(3.7%)	16	(4.2%)	-0.5%	30	(4.0%)
with outcome	**n = 559**	**(96.0%)**	**n = 167**	**(96.0%)**	**0**	**n = 365**	**(96.3%)**	**n = 361**	**(95.8%)**	**+0.5%**	**n = 726**	**(96.0%)**
Extended Glasgow Outcome Scale-mean	4.2	(±2.3)	5.4	(±2.1)	-1.2	4.5	(±2.4)	4.6	(±2.3)	-0.1	4.5	(±2.4)
Fixed dichotomy favorable§	265	(47.4%)	124	(74.3%)	-26.9%	199	(54.5%)	190	(52.6%)	+1.9%	389	(53.6%)
Fixed dichotomy unfavorable§	294	(52.6%)	43	(25.7%)	+26.9%	166	(45.5%)	171	(47.4%)	-1.9%	337	(46.4%)
Mortality§	128	(22.9%)	21	(12.6%)	+10.3%	80	(21.9%)	69	(19.1%)	+2.8%	149	(20.5%)
Death of non-neurological etiology⌘	37	(28.9%)	8	(38.1%)	-9.2%	25	(31.3%)	20	(29.0%)	+2.2%	45	(30.2%)

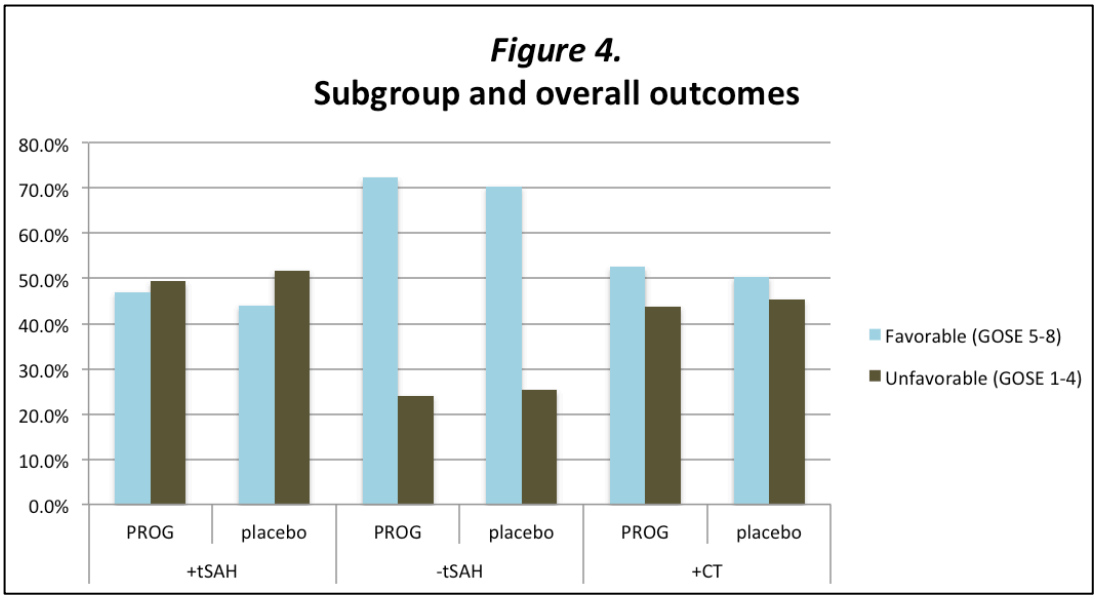
¶ Δ columns absolute difference between subgroups or treatment groups
§ All cases without outcomes excluded from analysis
⌘ "Mortality" used as denominator for all row percents (except Δ)

***Table 6*. Subgroup outcomes**

	+tSAH PROG		+tSAH placebo		Δ (PROG minus placebo)¶	-tSAH PROG		-tSAH placebo		Δ (PROG minus placebo)¶
	n = 296		n = 286			n = 83		n = 91		
Missing outcome	11	(3.7%)	12	(4.2%)	-0.5%	3	(3.6%)	4	(4.4%)	-0.8%
with outcome	**n = 285**	**(96.2%)**	**n = 274**	**(95.8%)**	**+0.4%**	**n = 80**	**(96.4%)**	**n = 87**	**(95.6%)**	**+0.8%**
Extended Glasgow Outcome Scale-mean	4.2	(±2.3)	4.3	(±2.4)	-0.1	5.4	(±2.2)	5.44	(±2.1)	0
Fixed dichotomy favorable§	139	(48.8%)	126	(46.0%)	+2.8%	60	(75.0%)	64	(73.6%)	+1.4%
Fixed dichotomy unfavorable§	146	(51.2%)	148	(54.0%)	-2.8%	20	(25.0%)	23	(26.4%)	-1.4%
Mortality§	69	(24.2%)	59	(21.5%)	+2.7%	11	(13.8%)	10	(11.5%)	+2.3%
Death of non-neurological etiology⌘	21	(30.4%)	16	(27.1%)	+3.3%	4	(36.4%)	4	(40.0%)	-3.6%

¶ Δ columns absolute difference between subgroups or treatment groups
§ All cases without outcomes excluded from analysis
⌘ "Mortality" used as denominator for all row percents (except Δ)

Figure 4.
Subgroup and overall outcomes



The RRs in *Table 7* show progesterone had a modest favorable effect in both the unadjusted and adjusted analyses. In the unadjusted analysis, the risk of a favorable outcome with PROG in the +tSAH group is 1.06 times that of subjects receiving placebo (95% CI 0.89 to 1.26). Risk for favorable outcome in the –tSAH group for PROG was 1.02 (95% CI 0.85 to 1.22) times that of subjects receiving placebo. After adjustment, RRs show that the risk of a favorable outcome of +tSAH patients treated with PROG to be 1.07 times that of placebo; PROG-treated subjects had 1.08 times the risk of a favorable outcome in the –tSAH group, but not +CT (and less absolute difference between all groups). However, these RRs were not statistically significant.

Table 7. **Risk ratios**

	Unadjusted	95% CI	Adjusted	95% CI
+tSAH	1.06	0.89 - 1.26	1.07	0.84 - 1.36
-tSAH	1.02	0.85 - 1.22	1.08	0.75 - 1.56
+CT	1.03	0.90 - 1.19	1.06	0.87 - 1.29

Discussion

Overall, we found +tSAH patients receiving progesterone therapy had a 2.8% greater likelihood of favorable outcome compared to +tSAH patients receiving placebo. Favorable outcome for PROG-treated subjects was 1.4% and 1.9% more likely in the –tSAH and +CT groups (respectively). Unadjusted estimates of relative benefit of PROG are 1.06 over placebo for +tSAH and 1.02 in the –tSAH sample. The small differences measured in treatment effect are not enough to suggest that tSAH changes the effect of progesterone in the treatment of TBI as postulated.

Mortality rates of subjects with tSAH on brain imaging in this analysis (23%) are comparable to those in a 2006 systematic review of nimodipine for the treatment of tSAH[39] (26%), although a smaller proportion of participants experienced an unfavorable outcome compared to what we report in the present study (40% vs. 53%). This discrepancy is likely due to differences in inclusion criteria between the studies, and the authors did not detail the characteristics that made patients eligible for enrollment. The review did not show a significant treatment effect of nimodipine in tSAH. Another investigation of milrinone specifically for vasospasm in tSAH[41] was not powered to draw any worthwhile conclusions. With 756 subjects, our study was the largest single analysis

found in the clinical trial literature evaluating an intervention specifically in the setting of tSAH (the next largest was the unpublished HIT 4 trial with 577 subjects[42]).

Some differences present in the distribution of baseline patient characteristics in this study could be meaningful. The –tSAH group was younger than the rest of the sample and, within this smaller subgroup, there was a large age difference between the treatment assignments. Age has been shown to be a specific and powerful measure for outcome in brain injury.[36] Additionally, given recent literature suggesting that tSAH patients in motor vehicle collisions may have poorer outcomes than those that fall from height (> 3 feet),[43] it is reasonable to adjust for the mechanism of injury in the multivariate analysis given variability in frequencies across treatment groups. Two related conclusions can be drawn from the evenness of subgroup and treatment groups with regards to most of the key prognosticators, injury patterns, and even subjects with missing outcome: randomization of the parent trial was very effective, and minimal (if any) adjustment should be necessary to answer the research question proposed.

If the unadjusted model is believed to be the most reliable computation (with even sample distribution as exhibited here), then it is possible that additional research, potentially in a prospective trial design, could be considered to further examine the possibility that PROG could improve outcome in patients with tSAH on baseline CT imaging. Of course the possibility that PROG may increase mortality should also be considered (although any adjustment for neurological vs. non-neurological [i.e. subject died from something else than TBI] was not factored into this analysis).

The basic prevalence of +tSAH and –tSAH in this analysis supports previously existing research findings that tSAH incidence is disproportionate among more-severely injured TBI patients.[6,7] However, the statistical models used here did not attempt to determine the underlying reason for this imbalance and no inferences can be made regarding why rates of favorable outcomes are lower in patients with evidence of tSAH on CT imaging from these data from those without signs of the injury. Obviously, it is expected that more severe TBI and higher prevalence of concomitant injuries will lead to poorer outcome. But it remains unanswered whether tSAH is an independent cause of worsened outcomes (possibly by associated secondary brain injury), or only correlated with other structural damages that are the responsible factors.

The present study has several important limitations worth noting. First, interpretation of subgroup analyses not specified in the original trial design should be critical due to a host of publicized issues such as low power, inappropriate statistical models, potential for type I error, and assumptive conclusions.[44,45] Nonetheless, TBI is a heterogeneous disease with multiple underlying pathologies and there was biologic plausibility for our research question in the context of exploratory analysis and hypothesis generation. We did not perform a statistical interaction test because it was likely to result in misleading results or misinterpretation of its *p*-value in this post hoc subgroup analysis.[33,46] Due to the fact that this study was exploratory with the intention of generating a hypothesis rather than testing one, clinical care recommendations or treatment guidelines should not be drawn from this analysis. Second, potentially important confounding covariates were not included in this analysis and, if there were large differences in treatment distribution, it is possible that our effect estimates were biased. For example, although the ProTECT III trial attempted to control treatment variability with clinical care guidelines for study subjects, significant differences have been found in previous studies between trial enrolling sites.[38] No consideration was made here to assess or account for discrepancies between hospitals that were unlikely to have occurred by chance, if they indeed exist in the parent trial data. Also, significant complications in the patients' hospital course can drastically effect outcome; although data regarding severe adverse events and deviations from treatment guidelines were collected, these data had not yet been properly processed at the time of the present analysis and thus could not be included herein. Third, subsequent imaging was also not included in this analysis, but could reveal important findings not visible on baseline CT such as diffuse axonal injury or hemorrhage expansion likely to be detrimental to the patient's condition.

Conclusion

In addition to the recent trials investigating PROG for TBI that showed no benefit in improving patient outcome, this study also suggests no significant treatment effect of PROG for tSAH. Although there was improvement shown in a dichotomous 6-month GOSE assessment to subjects given PROG in all groups in this analysis, this was not significant nor was an interaction effect noted between PROG and tSAH, as postulated in the objective for this study. Additional analyses should be performed using the full transgression and adverse event data, serial biomarker levels, and post-baseline imaging data to attempt to better determine why patients with tSAH have such poor outcomes when compared to those without the injury. Further research is needed to explore possible mitigators of secondary damage and other causes of worsened outcome in individuals suffering from acute brain injury as a result of trauma.

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ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

Form 03: Radiology Assessment– Central Reader (version 3)

1	Date of scan	__ __ - __ __ __ - __ __ __ __ (dd-mmm-yyyy)
2	Time of scan	__ __ : __ __ (24 hour clock hh:mm)
3	What type of scan was performed?	○ MRI ○ CT ○ CTA
4	Was the scan technically satisfactory?	○ No ○ Yes
5	**Were there any abnormal findings?** **If no, form is complete**	○ No ○ Yes
	Intracranial Bleeding	
6	**Were there any epidural hematoma findings?** **If no, skip to 12.**	○ No ○ Yes
	Epidural Hematoma—Frontal	
7A	Frontal - Left?	○ No ○ Yes
7B	Frontal - Left Depth	__ __ __ (mm)
7C	Frontal - Left Width	__ __ __ (mm)
7D	Frontal - Right?	○ No ○ Yes
7E	Frontal - Right Depth	__ __ __ (mm)
7F	Frontal - Right Width	__ __ __ (mm)
	Epidural Hematoma—Temporal	
8A	Temporal - Left?	○ No ○ Yes
8B	Temporal - Left Depth	__ __ __ (mm)
8C	Temporal - Left Width	__ __ __ (mm)
8D	Temporal - Right?	○ No ○ Yes
8E	Temporal - Right Depth	__ __ __ (mm)
8F	Temporal - Right Width	__ __ __ (mm)
	Epidural Hematoma—Parietal	
9A	Parietal - Left?	○ No ○ Yes
9B	Parietal - Left Depth	__ __ __ (mm)
9C	Parietal - Left Width	__ __ __ (mm)
9D	Parietal - Right?	○ No ○ Yes
9E	Parietal - Right Depth	__ __ __ (mm)
9F	Parietal - Right Width	__ __ __ (mm)
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

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Epidural Hematoma—Occipital		
10A	Occipital - Left?	○ No ○ Yes
10B	Occipital - Left Depth	__ __ __ (mm)
10C	Occipital - Left Width	__ __ __ (mm)
10D	Occipital - Right?	○ No ○ Yes
10E	Occipital - Right Depth	__ __ __ (mm)
10F	Occipital - Right Width	__ __ __ (mm)
Epidural Hematoma—Posterior fossa		
11A	Posterior fossa - Left?	○ No ○ Yes
11B	Posterior fossa - Left Depth	__ __ __ (mm)
11C	Posterior fossa - Left Width	__ __ __ (mm)
11D	Posterior fossa - Right?	○ No ○ Yes
11E	Posterior fossa - Right Depth	__ __ __ (mm)
11F	Posterior fossa - Right Width	__ __ __ (mm)
12	**Were there any subdural hematoma findings?** **If no, skip to 19**	○ No ○ Yes
Subdural Hematoma—Frontal		
13A	Frontal - Left?	○ No ○ Yes
13B	Frontal - Left Depth	__ __ __ (mm)
13C	Frontal - Left Width	__ __ __ (mm)
13D	Frontal - Right?	○ No ○ Yes
13E	Frontal - Right Depth	__ __ __ (mm)
13F	Frontal - Right Width	__ __ __ (mm)
Subdural Hematoma—Temporal		
14A	Temporal - Left?	○ No ○ Yes
14B	Temporal - Left Depth	__ __ __ (mm)
14C	Temporal - Left Width	__ __ __ (mm)
14D	Temporal - Right?	○ No ○ Yes
14E	Temporal - Right Depth	__ __ __ (mm)
14F	Temporal - Right Width	__ __ __ (mm)
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

Form 03: Radiology Assessment– Central Reader (version 3)

Subdural Hematoma—Parietal		
15A	Parietal - Left?	○ No ○ Yes
15B	Parietal - Left Depth	__ __ __ (mm)
15C	Parietal - Left Width	__ __ __ (mm)
15D	Parietal - Right?	○ No ○ Yes
15E	Parietal - Right Depth	__ __ __ (mm)
15F	Parietal - Right Width	__ __ __ (mm)
Subdural Hematoma—Occipital		
16A	Occipital - Left?	○ No ○ Yes
16B	Occipital - Left Depth	__ __ __ (mm)
16C	Occipital - Left Width	__ __ __ (mm)
16D	Occipital - Right?	○ No ○ Yes
16E	Occipital - Right Depth	__ __ __ (mm)
16F	Occipital - Right Width	__ __ __ (mm)
Subdural Hematoma—Posterior fossa		
17A	Posterior fossa - Left?	○ No ○ Yes
17B	Posterior fossa - Left Depth	__ __ __ (mm)
17C	Posterior fossa - Left Width	__ __ __ (mm)
17D	Posterior fossa - Right?	○ No ○ Yes
17E	Posterior fossa - Right Depth	__ __ __ (mm)
17F	Posterior fossa - Right Width	__ __ __ (mm)
Subdural Hematoma—Tentorial		
18	Tentorial	○ No ○ Yes
19	**Were there subarachnoid hemorrhage findings? If no skip to question 29.**	○ No ○ Yes
Subarachnoid Hemorrhage - Suprasellar		
20B	Suprasellar - Present?	○ No ○ Yes
20C	Suprasellar - Fisher Grade	○ (2) < 1 mm thick ○ (3) ≥ 1 mm thick
Subarachnoid Hemorrhage - Basal Cisterns		
21B	Basal Cisterns - Present?	○ No ○ Yes
21C	Basal Cisterns - Fisher Grade	○ (2) < 1 mm thick ○ (3) ≥ 1 mm thick
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

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Subarachnoid Hemorrhage - Sylvian fissure			
22B	Sylvian fissure - Left?	○ No	○ Yes
22C	Sylvian fissure - Left Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
22D	Sylvian fissure - Right?	○ No	○ Yes
22E	Sylvian fissure - Right Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
Subarachnoid Hemorrhage - Interhemispheric			
23B	Interhemispheric- Left?	○ No	○ Yes
23C	Interhemispheric- Left Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
23D	Interhemispheric- Right?	○ No	○ Yes
23E	Interhemispheric- Right Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
Subarachnoid Hemorrhage - Lobar - frontal			
24B	Lobar - frontal- Left?	○ No	○ Yes
24C	Lobar - frontal- Left Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
24D	Lobar - frontal- Right?	○ No	○ Yes
24E	Lobar - frontal- Right Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
Subarachnoid Hemorrhage - Lobar - parietal			
25B	Lobar - parietal- Left?	○ No	○ Yes
25C	Lobar - parietal- Left Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
25D	Lobar - parietal- Right?	○ No	○ Yes
25E	Lobar - parietal- Right Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
Subarachnoid Hemorrhage - Lobar - occipital			
26B	Lobar - occipital- Left?	○ No	○ Yes
26C	Lobar - occipital- Left Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
26D	Lobar - occipital- Right?	○ No	○ Yes
26E	Lobar - occipital- Right Fisher Grade	○ (2) < 1 mm thick	○ (3) ≥ 1 mm thick
General Comments:			
Name of person who collected this data (not for data entry):			

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

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Subarachnoid Hemorrhage - Lobar - temporal		
27B	Lobar - temporal- Left?	○ No ○ Yes
27C	Lobar - temporal- Left Fisher Grade	○ (2) < 1 mm thick ○ (3) ≥ 1 mm thick
27D	Lobar - temporal- Right?	○ No ○ Yes
27E	Lobar - temporal- Right Fisher Grade	○ (2) < 1 mm thick ○ (3) ≥ 1 mm thick
28	Were there intra-ventricular hemorrhage findings?	○ No ○ Yes, minimal layering ○ Yes, clot
29	**Were there any intraparenchymal hematoma findings? If no, skip to 37.**	○ No ○ Yes
Intraparenchymal Hematoma—Frontal		
30A	Frontal - Left?	○ No ○ Yes
30B	Frontal - Left Depth	__ __ __ (mm)
30C	Frontal - Left Width	__ __ __ (mm)
30D	Frontal - Right?	○ No ○ Yes
30E	Frontal - Right Depth	__ __ __ (mm)
30F	Frontal - Right Width	__ __ __ (mm)
Intraparenchymal Hematoma—Temporal		
31A	Temporal - Left?	○ No ○ Yes
31B	Temporal - Left Depth	__ __ __ (mm)
31C	Temporal - Left Width	__ __ __ (mm)
31D	Temporal - Right?	○ No ○ Yes
31E	Temporal - Right Depth	__ __ __ (mm)
31F	Temporal - Right Width	__ __ __ (mm)
Intraparenchymal Hematoma—Parietal		
32A	Parietal - Left?	○ No ○ Yes
32B	Parietal - Left Depth	__ __ __ (mm)
32C	Parietal - Left Width	__ __ __ (mm)
32D	Parietal - Right?	○ No ○ Yes
32E	Parietal - Right Depth	__ __ __ (mm)
32F	Parietal - Right Width	__ __ __ (mm)
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

Form 03: Radiology Assessment– Central Reader (version 3)

Intraparenchymal Hematoma—Occipital		
33A	Occipital - Left?	○ No ○ Yes
33B	Occipital - Left Depth	__ __ __ (mm)
33C	Occipital - Left Width	__ __ __ (mm)
33D	Occipital - Right?	○ No ○ Yes
33E	Occipital - Right Depth	__ __ __ (mm)
33F	Occipital - Right Width	__ __ __ (mm)
Intraparenchymal Hematoma—Basal ganglia		
34A	Basal ganglia- Left?	○ No ○ Yes
34B	Basal ganglia- Left Depth	__ __ __ (mm)
34C	Basal ganglia- Left Width	__ __ __ (mm)
34D	Basal ganglia- Right?	○ No ○ Yes
34E	Basal ganglia- Right Depth	__ __ __ (mm)
34F	Basal ganglia- Right Width	__ __ __ (mm)
Intraparenchymal Hematoma—Posterior fossa		
35A	Posterior fossa - Left?	○ No ○ Yes
35B	Posterior fossa - Left Depth	__ __ __ (mm)
35C	Posterior fossa - Left Width	__ __ __ (mm)
35D	Posterior fossa - Right?	○ No ○ Yes
35E	Posterior fossa - Right Depth	__ __ __ (mm)
35F	Posterior fossa - Right Width	__ __ __ (mm)
Intraparenchymal Hematoma—Midbrain/pons		
36	Midbrain/pons	○ No ○ Yes, 0-5 mm ○ Yes, >5 mm
37	**Evidence of surgical evacuation?**	○ No ○ Yes
38	**Were there any brain contusion findings?** **If no, skip to question 45.**	○ No ○ Yes
Brain Contusion—Frontal		
39A	Frontal - Left?	○ No ○ Yes
39B	Frontal - Left Depth	__ __ __ (mm)
39C	Frontal - Left Width	__ __ __ (mm)
39D	Frontal - Right?	○ No ○ Yes
39E	Frontal - Right Depth	__ __ __ (mm)
39F	Frontal - Right Width	__ __ __ (mm)
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

Form 03: Radiology Assessment– Central Reader (version 3)

Brain Contusion—Temporal		
40A	Temporal - Left?	○ No ○ Yes
40B	Temporal - Left Depth	__ __ __ (mm)
40C	Temporal - Left Width	__ __ __ (mm)
40D	Temporal - Right?	○ No ○ Yes
40E	Temporal - Right Depth	__ __ __ (mm)
40F	Temporal - Right Width	__ __ __ (mm)
Brain Contusion—Parietal		
41A	Parietal - Left?	○ No ○ Yes
41B	Parietal - Left Depth	__ __ __ (mm)
41C	Parietal - Left Width	__ __ __ (mm)
41D	Parietal - Right?	○ No ○ Yes
41E	Parietal - Right Depth	__ __ __ (mm)
41F	Parietal - Right Width	__ __ __ (mm)
Brain Contusion—Occipital		
42A	Occipital - Left?	○ No ○ Yes
42B	Occipital - Left Depth	__ __ __ (mm)
42C	Occipital - Left Width	__ __ __ (mm)
42D	Occipital - Right?	○ No ○ Yes
42E	Occipital - Right Depth	__ __ __ (mm)
42F	Occipital - Right Width	__ __ __ (mm)
Brain Contusion—Basal ganglia		
43A	Basal ganglia- Left?	○ No ○ Yes
43B	Basal ganglia- Left Depth	__ __ __ (mm)
43C	Basal ganglia- Left Width	__ __ __ (mm)
43D	Basal ganglia- Right?	○ No ○ Yes
43E	Basal ganglia- Right Depth	__ __ __ (mm)
43F	Basal ganglia- Right Width	__ __ __ (mm)
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

Form 03: Radiology Assessment– Central Reader (version 3)

Brain Contusion—Posterior fossa		
44A	Posterior fossa - Left?	○ No ○ Yes
44B	Posterior fossa - Left Depth	__ __ __ (mm)
44C	Posterior fossa - Left Width	__ __ __ (mm)
44D	Posterior fossa - Right?	○ No ○ Yes
44E	Posterior fossa - Right Depth	__ __ __ (mm)
44F	Posterior fossa - Right Width	__ __ __ (mm)
45	**Were there any DAI findings? If no, skip to question 51.**	○ No ○ Yes
DAI—Frontal		
46A	Frontal - Left?	○ No ○ Yes
46B	Frontal - Left Depth	__ __ __ (mm)
46C	Frontal - Left Width	__ __ __ (mm)
46D	Frontal - Right?	○ No ○ Yes
46E	Frontal - Right Depth	__ __ __ (mm)
46F	Frontal - Right Width	__ __ __ (mm)
DAI—Parietal		
47A	Parietal - Left?	○ No ○ Yes
47B	Parietal - Left Depth	__ __ __ (mm)
47C	Parietal - Left Width	__ __ __ (mm)
47D	Parietal - Right?	○ No ○ Yes
47E	Parietal - Right Depth	__ __ __ (mm)
47F	Parietal - Right Width	__ __ __ (mm)
DAI—Basal ganglia		
48A	Basal ganglia- Left?	○ No ○ Yes
48B	Basal ganglia- Left Depth	__ __ __ (mm)
48C	Basal ganglia- Left Width	__ __ __ (mm)
48D	Basal ganglia- Right?	○ No ○ Yes
48E	Basal ganglia- Right Depth	__ __ __ (mm)
48F	Basal ganglia- Right Width	__ __ __ (mm)
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? ○ No ○ Yes

Form 03: Radiology Assessment– Central Reader (version 3)

DAI—Brainstem		
49A	Brainstem - Present?	○ No ○ Yes
49B	Brainstem - Depth	__ __ __ (mm)
49C	Brainstem - Width	__ __ __ (mm)
DAI—Corpus Callosum		
50A	Corpus Callosum - Present?	○ No ○ Yes
50B	Corpus Callosum - Depth	__ __ __ (mm)
50C	Corpus Callosum - Width	__ __ __ (mm)
DAI—Centrum Semiovale		
81A	Centrum Semiovale - Left?	○ No ○ Yes
81B	Centrum Semiovale - Left Severity	○ Mild ○ Moderate ○ Severe
81C	Centrum Semiovale - Right?	○ No ○ Yes
81D	Centrum Semiovale - Right Severity	○ Mild ○ Moderate ○ Severe
51	**Were there any generalized edema findings? If no, skip to question 53**	○ No ○ Yes
Generalized Edema - Hemisphere		
52A	Hemisphere - Left?	○ No ○ Yes
52B	Hemisphere - Left Severity	○ Mild ○ Moderate ○ Severe
52C	Hemisphere - Right?	○ No ○ Yes
52D	Hemisphere - Right Severity	○ Mild ○ Moderate ○ Severe
53	**Were there any focal swelling findings? If no, skip to question 59.**	○ No ○ Yes
Focal Swelling - Frontal		
54A	Frontal - Left?	○ No ○ Yes
54B	Frontal - Left Severity	○ Mild ○ Moderate ○ Severe
54C	Frontal - Right?	○ No ○ Yes
54D	Frontal - Right Severity	○ Mild ○ Moderate ○ Severe
Focal Swelling - Temporal		
55A	Temporal - Left?	○ No ○ Yes
55B	Temporal - Left Severity	○ Mild ○ Moderate ○ Severe
55C	Temporal - Right?	○ No ○ Yes
55D	Temporal - Right Severity	○ Mild ○ Moderate ○ Severe
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? O No O Yes

Form 03: Radiology Assessment– Central Reader (version 3)

Focal Swelling—Parietal		
56A	Parietal - Left?	O No O Yes
56B	Parietal - Left Severity	O Mild O Moderate O Severe
56C	Parietal - Right?	O No O Yes
56D	Parietal - Right Severity	O Mild O Moderate O Severe
Focal Swelling—Occipital		
57A	Occipital - Left?	O No O Yes
57B	Occipital - Left Severity	O Mild O Moderate O Severe
57C	Occipital - Right?	O No O Yes
57D	Occipital - Right Severity	O Mild O Moderate O Severe
Focal Swelling—Basal ganglia		
58A	Basal ganglia - Left?	O No O Yes
58B	Basal ganglia - Left Severity	O Mild O Moderate O Severe
58C	Basal ganglia - Right?	O No O Yes
58D	Basal ganglia - Right Severity	O Mild O Moderate O Severe
59	**Were there any radiological signs of increased ICP? If no, skip to question 71.**	O No O Yes
60	Sulcal obliteration	O Left O Right O Both O None
61	Lateral ventricle compression	O Left O Right O Both O None
62	Compression or obliteration of third ventricle and of basal cisterns	O No O Yes
63	Midline shift	O To the Left O To the Right O None
64	If 'midline shift, specify size	O 0-5mm O > 5mm
General Comments:		
Name of person who collected this data (not for data entry):		

Form 03: Radiology Assessment– Central Reader (version 3)

65	Transtentorial herniation present?	○ No ○ Yes
66	Uncal herniation present?	○ No ○ Yes
67	Tonsillar herniation present?	○ No ○ Yes
68	Upward herniation present?	○ No ○ Yes
69	Other radiologic sign of increased ICP present?	○ No ○ Yes
70	If 'other radiologic sign of increased ICP' specify:	
71	**Were there additional intracranial findings? If no, skip to question 75.**	○ No ○ Yes
Additional Intracranial Findings - Pseudoaneurysm		
72A	Pseudoaneurysm - Present?	○ No ○ Yes
72B	Pseudoaneurysm - If Yes, check all that apply	☐ Right ICA ☐ Right VA ☐ Left ICA ☐ Left VA
Additional Intracranial Findings - Dissection		
73A	Dissection - Present?	○ No ○ Yes
73B	Dissection - If Yes, check all that apply	☐ Right ICA ☐ Right VA ☐ Left ICA ☐ Left VA
Additional Intracranial Findings - Infarction		
74A	Infarction - Present?	○ No ○ Yes
74B	Infarction - If Yes, check all that apply	☐ Right ICA ☐ Right VA ☐ Left ICA ☐ Left VA
General Comments:		
Name of person who collected this data (not for data entry):		

ProTECT	Visit:	__ __ - __ __ Hub - Spoke Code	__ __ __ __ Subject ID		Scan received? O No O Yes

Form 03: Radiology Assessment– Central Reader (version 3)

75A	Was there a skull fracture - Left?	O No O Yes
75B	Was there a skull fracture - Right?	O No O Yes
76	Depressed skull fracture	O No O Yes
77	If [depressed skull fracture], is depression greater than the thickness of the skull?	O No O Yes
78	Basilar skull fracture	O No O Yes
79	Other skull fracture	O No O Yes
80	If [other skull fracture], specify:	

General Comments:

Name of person who collected this data (not for data entry):

Protocol Summary - ProTECT™ III

TITLE OF THE TRIAL

Progesterone for the Treatment of Traumatic Brain Injury

TRIAL OBJECTIVES

Primary Objective

Determine the efficacy of administering intravenous (IV) progesterone (initiated within 4 hours of injury and administered for 72 hours, followed by an additional 24 hour taper) versus placebo for treating victims of moderate to severe acute TBI (Glasgow coma scale score 12-4).

Primary Hypothesis

Progesterone will increase the proportion of patients with a favorable outcome by a 10% (absolute) difference, determined by the Glasgow Outcome Scale-Extended (GOSE) score at 6 months post injury when compared to placebo. Our primary outcome analysis of the GOSE will use a stratified dichotomy methodology for assessing improvement. This approach dichotomizes GOSE scores as “favorable” versus “not favorable”, based on the brain injury severity score measured at randomization (best pre-randomization GCS or iGCS). Patients with the most severe injury (iGCS 4-5) will have a favorable outcome if the GOSE is good to severe; patients with an intermediate severe injury (iGCS 6-8) will have a favorable outcome if the GOSE is good to moderate; and patients with a moderate injury (iGCS 9-12) will have a favorable outcome if the GOSE is good recovery. A maximum of 1140 patients will be randomized, adjusting for age, gender, injury severity and clinical site.

Secondary Endpoints

Examine the efficacy of IV progesterone vs. placebo for treating patients with moderate to severe acute TBI on additional 6 month outcomes: Mortality, Disability Rating Scale (DRS), cognitive, neurological and functional outcomes using a select battery of tests, and rates of adverse and serious adverse events.

Ancillary Study – BIO-ProTECT

The primary aim of this ancillary study is to determine whether elevated levels of serum biomarkers (including S100B, GFAP, UCH-L1, SBDP150), measured within 4 hours of TBI or at 24 and 48 hours after randomization, independently predict clinical outcome as measured by the Glasgow Outcome Scale Extended (GOS-E) at 6 months. The secondary aim is to determine, in progesterone treated subjects, if there a correlation between steady state serum progesterone levels and serum levels of S100B, GFAP, UCH-L1, SBDP150 at 24 and 48 hours after randomization, and whether progesterone levels predict those subjects with a favorable clinical response to the experimental treatment as determined by the primary outcome of the study.

METHODOLOGY

A double blind, randomized, placebo-controlled, multicenter clinical trial.

INFUSION PERIOD

Following a one hour loading dose, the study infusion (progesterone or placebo) will be administered as a continuous intravenous infusion for 71 hours, and then tapered over three additional 8-hour decrements to zero, for a total treatment duration of 96 hours.

NUMBER OF SUBJECTS (planned)

The total sample size is 1140 subjects, calculated for a 1:1 randomization scheme with 85% power (feasible in terms of number needed to enroll, and well within the accepted margins for error) to detect a 10% absolute difference in outcomes between treatment groups at the two-sided α of 0.05. With these assumptions, we will need 462 subjects per group (expected favorable outcome is 50% in those receiving placebo and 60% in those given treatment) after accounting for 3 analyses (2 interim after approximately 33% and 67% of enrollment and 1 final) and using O'Brien Fleming boundaries. Assuming a conservative non-adherence rate of 10% (due to withdrawal of consent during infusion and loss to follow-up), we will need a maximum of 1140 subjects to ensure sufficient power to achieve our study goals.

NUMBER OF SITES (planned)

The ProTECT™ III Clinical Trial will partner with The Neurological Emergencies Treatment Trials (NETT) network. The NETT is comprised of 17 Hubs, each consisting of several hospital complexes (Spokes).

INVESTIGATIONAL PRODUCT (dose, mode of administration)

Our current dose is 0.714 mg/kg bolus for 1 hour, followed by 0.5 mg/kg/hr for 71 hours, followed by a q 8 hour decrement taper (3 changes) to zero.

TRIAL DURATION PER SUBJECT

From trial entry until 6 months post injury.

MAIN OUTCOMES

Primary Outcome

Our *Primary Outcome will be GOSE 6 months post-injury*. GOSE is the primary measure of functional outcome and incorporates mortality in the primary outcome. A positive trial means that the treatment improves the proportion of patients having a "favorable" outcome by ≥10% absolute value. Favorable outcome is defined as described in the following table.

If the patient's iGCS is:	If the iMotor Score is:	Then the favorable outcome is:
4-5	2-3	6 mo GOSE = severe, moderate, or good
6-8	4-5	6 mo GOSE = moderate or good
9-12		6 mo GOSE = good recovery

Secondary Outcomes

Secondary outcomes of interest include the effects of progesterone vs. placebo in patients with moderate to severe TBI on 6 month mortality, Disability Rating Scale score, cognitive and neurological function outcomes and the rates of adverse and serious adverse events.

SAFETY MONITORING

Adverse events will be defined and severity graded according to the Common Terminology Criteria for Adverse Events (CTCAE). AEs will be submitted through the WebDCU™ and coded using MedDRA. Guidelines for report content and structure will be provided. All adverse events will be recorded for the first 7 days after enrollment (4 days of drug infusion and 3 days post infusion). Based on the reported potential risks of progesterone administration, several important risks were identified that could be associated with progesterone (serious thromboembolic events such as thrombotic myocardial infarction, pulmonary embolism, deep vein thrombosis, ischemic stroke; allergic reactions; marked liver function abnormalities; serious infections such as

pneumonia, sepsis, meningitis) and have labeled them as “potentially associate adverse events” (PAAE). Study personnel will evaluate subjects while in the hospital and at each telephone communication and follow-up for the presence of PAAEs or SAEs using a pre-constructed checklist. Sites will record and report PAAEs and SAEs within 24 hours of discovery throughout the course of the subject’s participation (6 months).

We have employed two independent medical safety monitors (IMSM) with extensive expertise to review the PAAEs and SAEs, and provide causality judgments. Together they will provide daily coverage for the ProTECT™ III trial. The IMSM will make a determination of causality and expectedness based on predetermined criteria. IMSM reports that are serious, unexpected, and study drug related (possibly, probably, or definitely) will immediately be sent to the ProTECT™ III PI and Project Manager, who will submit a MedWatch 3500A to the FDA. Reports will be routed to each institution’s IRB (via the CCC and institutional PIs). Other measures to safeguard the welfare of study subjects include a formal review of all deaths by the trauma outcomes review committee at each site and a regularly scheduled comprehensive review of all safety data and AB physiological measurements by an independent NIH appointed Data and Safety Monitoring Board (DSMB).

STATISTICAL METHODS TO ANALYZE THE PRIMARY OUTCOME

Outcome differences will be analyzed on the basis of intention-to-treat. To assess efficacy, the treatment groups will be compared with respect to the proportion of subjects with favorable outcome 6 months post randomization. The primary efficacy hypothesis is tested via generalized linear model relating the probability of a favorable outcome to the treatment, adjusting for three covariates - injury severity, gender, and age.

Appendix 2 - Master table 1

	+tSAH				-tSAH				+CT			
	PROG	placebo	total	Δ	PROG	placebo	total	Δ	PROG	placebo	total	Δ
N=	296 (50.9%)	286 (49.1%)	582	+1.8%	83 (47.70%)	91 (52.30%)	174	-4.6%	379 (50.1%)	377 (49.9%)	756	0.2%
Demographics												
Age-mean	40.86 (±18.1)	41.1 (±18.0)	41.0 (±18.2)	-0.2	39.1 (±19.0)	32.0 (±13.3)	35.4 (±16.6)	7.1	40.5 (±18.3)	38.9 (±17.4)	39.69 (±17.9)	1.6
-median	38	39	39	-1	35	28	30	+7	37	35	36	+2
-range	18-88	17-93	17-93	-	17-94	18-67	17-94	-	17-94	17-93	17-94	-
Sex-male	216 (73.0%)	213 (74.5%)	429 (73.6%)	-1.5%	60 (72.3%)	68 (74.7%)	128 (73.6%)	-2.4%	276 (72.8%)	281 (74.5%)	557 (73.7%)	-1.7%
-female	80 (27.0%)	73 (25.5%)	153 (26.3%)	+1.5%	23 (27.7%)	23 (25.3%)	46 (26.4%)	+2.4%	103 (27.2%)	96 (25.5%)	199 (26.3%)	+1.7%
Race-white	223 (75.3%)	210 (73.4%)	433 (74.3%)	+1.9%	58 (69.9%)	71 (78.0%)	129 (74.1%)	-8.1%	281 (74.1%)	281 (74.5%)	562 (74.3%)	-0.4%
-black	43 (14.5%)	43 (15.0%)	86 (14.7%)	-0.5%	21 (25.3%)	11 (12.1%)	32 (18.4%)	-13.2%	64 (16.9%)	54 (14.3%)	118 (15.6%)	2.6%
-other	30 (10.1%)	33 (11.5%)	63 (10.8%)	-1.4%	4 (4.8%)	9 (9.9%)	13 (7.5%)	-5.1%	34 (9.0%)	42 (11.1%)	76 (10.1%)	-2.2%
Ethnicity-hispanic	42 (14.2%)	38 (13.2%)	80 (13.7%)	+1.0%	10 (12.0%)	18 (19.8%)	28 (16.1%)	-7.8%	52 (13.7%)	56 (14.9%)	108 (14.3%)	-1.1%
Mechanism-MVC	101 (34.1%)	89 (31.1%)	190 (32.7%)	+3.0%	29 (34.9%)	43 (47.3%)	72 (41.4%)	-12.4%	130 (34.3%)	132 (35.0%)	262 (34.7%)	-0.7%
-MCC/ATV	53 (17.9%)	61 (21.3%)	114 (19.6%)	-3.4%	14 (16.9%)	22 (24.2%)	36 (20.7%)	-7.3%	67 (17.7%)	83 (22.0%)	150 (19.8%)	-4.3%
-person hit by auto	47 (15.9%)	43 (15.0%)	90 (15.5%)	+0.9%	7 (8.4%)	9 (9.9%)	16 (9.2%)	-1.5%	54 (14.2%)	52 (13.8%)	106 (14.0%)	0.5%
-falls	52 (17.6%)	46 (16.1%)	98 (16.8%)	+1.5%	21 (25.3%)	31 (34.1%)	52 (29.9%)	-8.8%	70 (18.5%)	53 (14.1%)	123 (16.3%)	4.4%
-bicycle crash	17 (5.7%)	19 (6.6%)	36 (6.2%)	-0.9%	3 (3.6%)	4 (4.4%)	7 (4.0%)	-0.8%	20 (5.3%)	23 (6.1%)	43 (5.7%)	-0.8%
-other	26 (8.7%)	28 (9.8%)	54 (9.3%)	-1.1%	12 (14.5%)	6 (6.6%)	18 (10.3%)	+7.9%	38 (10.0%)	34 (9.0%)	72 (9.5%)	1.0%
Time-injury to ED arrival mean	0:52 (±0:27)	0:51 (±0:26)	0:52 (±0:26)	0:01	0:51 (±0:30)	0:54 (±0:25)	0:53 (±0:28)	-0:03	0:52 (±0:28)	0:52 (±0:26)	0:52 (±0:27)	0:00
-injury to CT scan mean	1:23 (±0:36)	1:24 (±0:32)	1:24 (±0:34)	-0:01	1:29 (±0:37)	1:24 (±0:28)	1:26 (±0:33)	0:05	1:25 (±0:36)	1:24 (±0:31)	1:24 (±0:34)	0:01
-injury to study tx mean	3:44 (±1:01)	3:37 (±0:48)	3:41 (±0:55)	0:07	3:37 (±0:43)	3:36 (±0:30)	3:36 (±0:37)	0:01	3:42 (±0:58)	3:37 (±0:44)	3:40 (±0:51)	0:05
Prognosticators/covariates												
Significant hypoxia	4 (1.4%)	4 (1.4%)	8 (1.4%)	0.0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0%	4 (1.1%)	4 (1.1%)	8 (1.1%)	0
Significant hypotension	2 (0.7%)	9 (3.1%)	11 (1.9%)	-2.5%	1 (1.2%)	1 (1.1%)	2 (1.1%)	0.1%	3 (0.8%)	10 (2.7%)	13 (1.7%)	-1.9%
No pupillary response	15 (5.1%)	12 (4.2%)	27 (4.6%)	0.9%	2 (2.4%)	2 (2.2%)	4 (2.3%)	0.2%	17 (4.5%)	14 (3.7%)	31 (4.1%)	0.8%

Appendix 3 - Master table 2

	+tSAH					-tSAH				
	PROG		placebo		Δ	PROG		placebo		Δ
	n = 296		n = 286		+10	n = 83		n = 91		-8
Classifications										
GCS-mean	7.7	(±2.4)	7.7	(±2.3)	0	8.3	(±2.3)	8.3	(±2.5)	0
AIS head-mean	4.0	(±0.9)	4.0	(±0.9)	0	3.6	(±1.1)	3.7	(±1.1)	-1
Rotterdam score-mean	3.3	(±0.9)	3.3	(±0.9)	0	2.2	(±0.8)	2.2	(±0.7)	0
ISS-mean	27.0	(±11.2)	26.8	(±10.4)	+0.2	23.3	(±11.0)	23.1	(±9.8)	+0.2
ISS-median	26		27		-1	21.5		24		-2.5
Concomitant injuries										
Epidural hematoma	61	(20.6%)	45	(15.7%)	4.9%	12	(14.5%)	12	(13.2%)	1.3%
Subdural hematoma	167	(56.4%)	167	(58.4%)	-2.0%	46	(55.4%)	39	(42.9%)	12.6%
Intraparenchymal hematoma	18	(6.1%)	24	(8.4%)	-2.3%	4	(4.8%)	4	(4.4%)	0.4%
Brain contusion	149	(50.3%)	135	(47.2%)	3.1%	31	(37.3%)	29	(31.9%)	5.5%
Diffuse axonal injury	90	(30.4%)	97	(33.9%)	-3.5%	23	(27.7%)	29	(31.9%)	-4.2%
Skull fracture	161	(54.4%)	161	(56.3%)	-1.9%	46	(55.4%)	45	(49.5%)	6.0%
Increased ICP	108	(36.5%)	105	(36.7%)	-0.2%	19	(22.9%)	20	(22.0%)	0.9%
Generalized edema	82	(27.7%)	84	(29.4%)	-1.7%	8	(9.6%)	9	(9.9%)	-0.3%
Focal swelling	26	(8.8%)	21	(7.3%)	1.4%	4	(4.8%)	1	(1.1%)	3.7%

Appendix 4 - Master table 3

		+tSAH				-tSAH				+CT			
	N=	PROG 296	placebo 286	total 582	Δ +10	PROG 83	placebo 91	total 174	Δ -8	PROG 379	placebo 377	total 756	Δ 0.2%
Outcomes													
GOSE-mean		4.2 (±2.3)	4.3 (±2.4)	4.2 (±2.3)	-0.1	4.2 (±2.3)	4.3 (±2.4)	4.2 (±2.3)	-0.1	4.5 (±2.4)	4.6 (±2.3)	4.5 (±2.4)	-0.1
GOSE 1 (Mortality)		69 (24.2%)	59 (21.5%)	128 (22.9%)	+2.7%	11 (13.8%)	10 (11.5%)	21 (12.6%)	+2.3%	80 (21.9%)	69 (19.1%)	149 (20.5%)	+2.8%
GOSE 2		7 (2.5%)	4 (1.5%)	11 (2.0%)	+1.0%	0 (0.0%)	1 (1.1%)	1 (0.6%)	-1.1%	7 (1.9%)	5 (1.4%)	12 (1.7%)	+0.5%
GOSE 3		46 (16.1%)	56 (20.4%)	102 (18.2%)	-4.3%	5 (6.3%)	5 (5.7%)	10 (6.0%)	+0.5%	51 (14.0%)	61 (16.9%)	112 (15.4%)	-2.9%
GOSE 4		24 (8.4%)	29 (10.6%)	53 (9.5%)	-2.2%	4 (5.0%)	7 (8.0%)	11 (6.6%)	-3.0%	28 (7.7%)	36 (10.0%)	64 (8.8%)	-2.3%
GOSE 5		27 (9.5%)	18 (6.6%)	45 (8.1%)	+2.9%	8 (10.0%)	8 (9.2%)	16 (9.6%)	+0.8%	35 (9.6%)	26 (7.2%)	61 (8.4%)	+2.4%
GOSE 6		58 (20.4%)	47 (17.2%)	105 (18.8%)	+3.2%	23 (28.8%)	24 (27.6%)	47 (28.1%)	+1.2%	81 (22.2%)	71 (19.7%)	152 (20.9%)	+2.5%
GOSE 7		37 (13.0%)	35 (12.8%)	72 (12.9%)	+0.2%	19 (23.8%)	22 (25.3%)	41 (24.6%)	-1.5%	56 (15.3%)	57 (15.8%)	113 (15.6%)	-0.4%
GOSE 8		17 (6.0%)	26 (9.5%)	43 (7.7%)	-3.5%	10 (12.5%)	10 (11.5%)	20 (12.0%)	+1.0%	27 (7.4%)	36 (10.0%)	63 (8.7%)	-2.6%
Missing outcome		11 (3.7%)	12 (4.2%)	23 (4.0%)	-0.5%	3 (3.6%)	4 (4.4%)	7 (4.0%)	-0.8%	14 (3.7%)	16 (4.2%)	30 (4.0%)	-0.6%
Fixed dichotomy favorable		139 (48.8%)	126 (46.0%)	265 (47.4%)	+2.8%	60 (75.0%)	64 (73.6%)	124 (81.0%)	+1.4%	199 (54.5%)	190 (52.6%)	389 (53.6%)	+1.9%
Fixed dichotomy unfavorable		146 (51.2%)	148 (54.0%)	294 (52.6%)	-2.8%	20 (25.0%)	23 (26.4%)	43 (28.1%)	-1.4%	166 (45.5%)	171 (47.4%)	337 (46.4%)	-1.9%
Death of non-neurological etiology		21 (30.4%)	16 (27.1%)	37 (28.9%)	+3.3%	4 (36.4%)	4 (40.0%)	8 (38.1%)	-3.6%	25 (32.1%)	20 (29.0%)	45 (30.6%)	-3.1%