Very Early Administration of Progesterone Does Not Improve Neuropsychological Outcomes in Subjects with Moderate to Severe Traumatic Brain Injury

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Abstract

A Phase III, double-blind, placebo-controlled trial (ProTECT III) found that administration of progesterone did not reduce mortality or improve functional outcome as measured by the Glasgow Outcome Scale Extended (GOSE) in subjects with moderate to severe traumatic brain injury. We conducted a secondary analysis of neuropsychological outcomes to evaluate whether progesterone is associated with improved recovery of cognitive and motor functioning. ProTECT III was conducted at 49 level I trauma centers in the United States. Adults with moderate to severe TBI were randomized to receive intravenous progesterone or placebo within 4 h of injury for a total of 4 days. At 6 months, subjects underwent evaluation of memory, attention, executive functioning, language, and fine motor coordination/dexterity. Chi-square analysis revealed no significant difference in the proportion of subjects (263/280 progesterone, 283/295 placebo) with Galveston Orientation and Amnesia Test scores ≥ 75 . Analyses of covariance did not reveal significant treatment effects for memory (Buschke immediate recall, $p = 0.53$; delayed recall, $p = 0.94$), attention (Trails A speed, $p = 0.81$ and errors, $p = 0.22$; Digit Span Forward length, $p = 0.66$), executive functioning (Trails B speed, $p = 0.97$ and errors, $p = 0.93$; Digit Span Backward length, $p = 0.60$), language (timed phonemic fluency, $p = 0.05$), and fine motor coordination/dexterity (Grooved Pegboard dominant hand time, $p = 0.75$ and peg drops, $p = 0.59$; nondominant hand time, $p = 0.74$ and peg drops, $p = 0.61$). Pearson Product Moment Correlations demonstrated significant ($p < 0.001$) associations between better neuropsychological performance and higher GOSE scores. Similar to the ProTECT III trial's results of the primary outcome, the secondary outcomes do not provide evidence of a neuroprotective effect of progesterone.

Keywords: adult brain injury; clinical trial; cognitive function; head trauma; prospective study

Introduction

PROGESTERONE IS A STEROID HORMONE that has been found to have neuroprotective effects in animal models of traumatic brain injury (TBI) via reductions in both cerebral edema and neuronal loss as well as increased remyelination.¹ An early Phase II clinical trial of subjects sustaining moderate to severe TBI conducted by our group² demonstrated a 50% reduced mortality at 30 days post-injury in subjects receiving progesterone versus placebo. Similar promising preliminary findings were also obtained by Xiao and colleagues³ who found reduced mortality out to 6 months post-injury and improved outcomes on the Glasgow Outcome Scale

(GOS)⁴ at both 3 and 6 months post-injury in patients treated with progesterone compared with controls.

Despite these encouraging results, two recent Phase III studies^{5,6} failed to demonstrate efficacy on their primary outcomes. Specifically, the NIH supported Progesterone for the Treatment of Traumatic Brain Injury, Experimental Clinical Treatment Trial (ProTECT III) did not find a significant difference in favorable outcome at 6 months post-injury on the Glasgow Outcome Scale-Extended (GOSE)⁴ in subjects with moderate to severe TBI.⁵ A concurrent industry (BHR Pharma) sponsored trial, Study of the Neuroprotective Activity of Progesterone in Severe Traumatic Brain Injuries (SyNAPSE), similarly did not observe a favorable

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outcome at 6 months on the GOS in a progesterone treated group versus a placebo control group of persons with severe TBI.⁶

The above-mentioned clinical trials assessed primary efficacy by using global measures of functional outcome. Investigators have noted, however, that studies should include more sensitive measures that are able to capture not only the complexity of neurologic outcomes after TBI, but ones that also evaluate the predicted effects of the pharmacologic agent.⁷

In planning the ProTECT III trial, we expected that progesterone, via its previously demonstrated benefits in reducing central nervous system damage in animal models of TBI, would yield neuroprotective effects on cognitive and motor functioning. We therefore administered sensitive neuropsychological outcome measures to test the hypothesis that subjects with moderate to severe TBI who were treated with progesterone would exhibit significantly better cognitive functioning and fine motor coordination at 6 months post-injury than subjects who received placebo.

Methods

Study design

Details of the PROTECT III study design have been described previously.⁵ Briefly, patients with nonpenetrating moderate to severe acute TBI (Glasgow Coma Scale [GCS]⁸ score 4–12) were randomized at level 1 trauma centers to receive intravenous progesterone or placebo initiated within 4 h of injury and administered for 96 total hours. Study site personnel trained in the administration of the neuropsychological battery collected secondary neuropsychological outcome measures at 6 months post-injury. The study protocol and procedures were approved by an Institutional Review Board at each site and met the exception from informed consent requirements for emergency medical research under Food and Drug Administration code of regulations 21 CFR 50.24.7.

Study subjects

Eligibility criteria to undergo neuropsychological testing included being seen for follow-up within a 6 month post-injury window (± 30 days) and receiving a score of ≥ 75 on the Galveston Orientation and Amnesia Test (GOAT).⁹ This cutoff score was used to ensure that subjects were not disoriented and confused, which would have affected their ability to complete the measures.

Study outcomes

Our study protocol, initiated in 2010, incorporated the recommendations of an expert TBI outcomes panel^{10,11} to include a brief yet sensitive neuropsychological battery to balance subject tolerance and completion with the ability to detect group differences. The 45-min battery was designed to evaluate the cognitive domains commonly affected in survivors of moderate to severe TBI including memory, attention, executive functioning, and language.

Episodic memory was assessed using the six trial Buschke Selective Reminding Memory Test¹² in which subjects were read a list of 12 words and were reminded on each subsequent trial only of those words not recalled on the previous trial. Total immediate word recall and 20 min delayed word recall were the dependent variables collected.

Attention was evaluated via the Wechsler Adult Intelligence Scale-III Digit Span¹³ Forward subtest, requiring repetition of increasingly longer number sequences, and the Trail Making Test,¹⁴ Part A, involving visual-motor sequencing of numbers under timed conditions. Dependent variables were the number of successful trials for Digit Span Forward, and the completion time and number of errors for the Trail Making Test Part A.

Executive functioning was measured by backward repetition of increasingly longer number sequences via the Digit Span Backward task, and alternating between sequencing numbers and letters under timed conditions on the Trail Making Test Part B. Dependent variables were the number of successful trials on Digit Span Backward, and completion time and number of errors on the Trail Making Test Part B. Language was examined using a phonemic fluency test, Controlled Oral Word Association,¹⁵ requiring the rapid generation of words beginning with specific letters. Total number of correct responses (excluding proper names and the same words with different endings) was the dependent variable. Fine motor coordination and dexterity were examined for the dominant and nondominant hands separately using the Grooved Pegboard Test¹⁶ requiring rapid placement of pegs under timed conditions. Dependent variables were the number of seconds to complete the task and the number of peg drops.

Study procedure

The neuropsychological battery was administered in a fixed order across sites by outcome examiners who were blinded to treatment versus placebo group assignment. Training to administer these measures and data collection were overseen by the ProTECT Central Neuropsychologists (AFC, FCG). All 6 month testing sessions were video recorded. The Central Neuropsychologists reviewed 100% of the first five evaluations completed by each site study examiner (including review of source documents and data entry) at a minimum. The Central Neuropsychologists were also blinded to treatment versus placebo group assignment.

Feedback after every evaluation regarding any administration issues and/or scoring errors was provided to the examiner. Administration and scoring errors were corrected on both the source documents and the online database by the site study examiner, and these corrections were verified by the assigned Central Neuropsychologist. Additional evaluations were reviewed if needed until the assigned Central Neuropsychologist was confident that the examiner was proficient. Review was then reduced to a random sample of 10% of the recorded evaluations.

The site study examiners assigned recorded reliability code values for every test to specify whether test administration was standard and reliable, highly irregular, or not done. If the code assigned was “highly irregular” or “not done,” the examiner recorded the reason(s), including whether the subject was too cognitively impaired, too physically impaired, or if there was a problem unrelated to the subject’s ability (e.g., examiner error). This coding allowed for a determination of whether tests were incomplete because of a neurologic reason associated with the brain injury.

Statistical analyses

The hypothesis of better outcomes for the progesterone group was evaluated in a number of ways. First, the groups were compared with respect to their ability to undergo neuropsychological testing at 6 months. Next, the groups were compared with respect to the mean differences in their test scores. Finally, each subject was classified as having a favorable or unfavorable outcome on a specific test as follows: the raw score of the subject on a test was converted to a z-score by using the demographically adjusted mean and standard deviation of nonhead injured subjects on that same test.^{17–22} Subjects with a z-score of ≥ -1 on a test were said to have a favorable outcome on that test, whereas subjects with a z-score of < -1 were said to have an unfavorable outcome on that test. We compared the groups with respect to the proportions of unfavorable outcomes on each test.

Analyses of covariance were used to compare groups with respect to continuous data (i.e., test scores) and chi-square tests to compare groups with respect to discrete outcomes (i.e., favorable

vs. unfavorable outcome). The threshold significance level using a false discovery rate approximation was adjusted ($\alpha(m+1)/2m$), where α is the original conventional threshold of 0.05, and m is the number of tests.²⁵ Therefore, with 13 dependent variables for each distinct set of analyses (continuous, dichotomous), a threshold significance level of 0.026 was used.

Tests that received a reliability code of “too cognitively impaired” were included in the analyses because they implied a poor outcome from the brain injury. In these cases, the worst score for the entire sample was substituted for missing data.⁷ Values coded as missing for noncognitive reasons were excluded from the analyses.

Results

Subject characteristics

Of 882 subjects randomized for treatment between April 5, 2010 and October 30, 2013, 263 subjects in the progesterone group and 283 subjects in the placebo group underwent neuropsychological testing at 6 months post-injury. Figure 1 shows the reasons for not being administered the neuropsychological measures. These included “not being seen” (i.e., death, consent withdrawn, lost to follow-up, other) and having GOAT scores that were “not available” (i.e., not scored in database, nonstandard, or unreliable administration) or were “out of range” (i.e., outside the 6 month window, GOAT score <75 points).

Table 1 shows their demographic characteristics and injury severity features. There were no significant differences in age and the distribution of sex, race, education, testing language, and severity of injury according to the Index GCS score. In addition, the groups were comparable in their self-reported pre-injury histories of alcohol use, illicit drug use, TBI necessitating hospitalization, and diagnosed learning disability. Both groups underwent a similar rate of nonstudy-related post-injury neuropsychological testing (e.g., at an inpatient facility or by a community neuropsychologist).

Ability to undergo neuropsychological testing as a function of performance on the GOAT

As shown in Figure 1 (see GOAT Scores Not Available/Out of Range’ section), 17 subjects in the progesterone group and 12 subjects in the placebo group were administered the GOAT but did not achieve scores of >75 points. We compared whether the proportion of subjects with GOAT scores <75 versus ≥75 points differed between the two groups and found that this difference was not significant ($p=0.27$). Of all the subjects who were administered the GOAT, 263/280 (93.9%) of those in the progesterone group and 283/295 (95.9%) of those in the placebo group achieved scores ≥75. In addition, there were no significant differences in the raw GOAT scores (out of 100 points) between the progesterone (mean=94.6 points, standard error [SE]=0.40) and placebo (mean=94.8 points, SE=0.40) groups ($p=0.74$).

Reliability codes of subjects receiving neuropsychological testing

We examined the percentage of subjects who, although eligible for testing by virtue of a GOAT score ≥75, subsequently received reliability codes indicating they were cognitively unable to complete a specific test. Chi-square analyses indicated that there were no significant differences between the progesterone and placebo

FIG. 1. Reasons neuropsychologic measures not administered.

groups in the proportion of subjects who received a “cognitively unable” reliability code for any of the measures (Table 2).

Neuropsychological raw scores of subjects receiving neuropsychological testing

Table 3 displays the performance of the groups on the cognitive and fine motorcoordination/dexterity measures. As shown, there were no significant performance differences for any of the dependent measures.

Favorable versus unfavorable outcomes of subjects receiving neuropsychological testing

Table 4 shows the frequency of subjects obtaining unfavorable outcomes (i.e., z-score of < -1) on each measure as a function of treatment group. Chi-square analyses revealed no significant differences.

TABLE 1. BASELINE CHARACTERISTICS OF SUBJECTS WITH GALVESTON ORIENTATION AND AMNESIA TEST SCORES ≥ 75

	Progesterone (n=263)	Placebo (n=283)	Overall group summary
Age: median (min-max)	32 (18–77)	30 (17–84)	31 (17–84)
Male: N (%)	196 (74.5)	203 (71.7)	399 (73.1)
African American: N (%)	39 (14.8)	38 (13.4)	77 (14.1)
Hispanic or Latino*: N (%)	40 (16.3)	50 (18.9)	90 (17.7)
Index GCS (as randomized) ⁺			
Moderate	85 (32.3)	83 (29.3)	168 (30.8)
Moderate to severe	144 (54.8)	160 (56.5)	304 (55.7)
Most severe	34 (12.9)	40 (14.1)	74 (13.6)
Education level*			
Less than high school	53 (20.4)	63 (22.4)	116 (21.4)
High school/GED	127 (48.9)	141 (50.2)	268 (49.5)
2 year college/associates	38 (14.6)	44 (15.7)	82 (15.2)
4 year college/BA or BS	32 (12.3)	22 (7.8)	54 (10.0)
Graduate	10 (3.9)	11 (3.9)	21 (3.9)
Pre-injury alcohol use*: N (%)	76 (29.2)	74 (26.3)	150 (27.7)
Pre-injury drug use*: N (%)	75 (28.8)	86 (30.6)	161 (29.8)
History of TBI*: N (%)	33 (12.7)	28 (10.0)	61 (11.3)
History of NP testing since injury*: N (%)	85 (32.7)	98 (34.9)	183 (33.8)
Pre-injury learning disability*: N (%)	41 (15.8)	38 (13.5)	79 (14.6)
Tested in language other than English*: N (%)	7 (2.7)	17 (6.0)	24 (4.4)

GED, General Educational Development; BA, Bachelor of the Arts; BS, Bachelor of Science; TBI, traumatic brain injury; NP, neuropsychological.

*Denominator is the N noted in the column header unless marked with asterisk.

⁺Overall scores on the Glasgow Coma Scale (GCS) range 3–15, with lower scores indicating a lower level of consciousness. The overall GCS score is the sum of scores for the motor, verbal, and eye-opening components. Motor scores on the GCS range 1–6, with lower scores indicating a lower level of consciousness. At randomization, an index GCS score (the highest reliable GCS score documented before randomization) of 9–12 indicated moderate injury, an index GCS score of 6–8 (or an index GCS motor score of 4 or 5 if the patient was intubated) indicated moderate-to-severe injury, and an index GCS score of 4 or 5 (or an index GCS motor score of 2 or 3 if the patient was intubated) indicated severe injury.

Correlations between test scores and GOSE scores

Pearson Product Moment Correlations were performed to evaluate associations between neuropsychological measures and the GOSE outcome scores. As seen in Table 5, all correlations were highly significant at $p < 0.001$. Better cognitive performance was consistently associated with higher GOSE scores.

Discussion

A number of studies, primarily conducted in rats with experimentally induced TBI, have demonstrated beneficial effects of

progesterone on measures of working memory, spatial navigation, avoidance learning, and motor performance (see Deutsch and co-workers²⁴ for a review). Our investigation is the first to test the potential benefits of progesterone on neuropsychological outcomes in humans sustaining moderate to severe TBI.

The results do not provide support for a neuroprotective effect. The progesterone treated group did not exhibit an advantage, compared with the placebo group at 6 months post-injury, in their ability to undergo neuropsychological testing, their raw scores on the neuropsychological measures, or the attainment of favorable versus unfavorable outcomes.

The above conclusion is consistent with the ProTECT III Trial's conclusion regarding its primary outcome measure, the GOSE, in demonstrating no compelling evidence for a neuroprotective effect of progesterone at 6 months after injury. We had anticipated that the inclusion of sensitive neuropsychological measures as secondary outcomes in this clinical trial would demonstrate a benefit in specific cognitive domains such as memory and executive functioning beyond the more global abilities measured by the GOSE.

Similar to other studies^{25,26} in head injured subjects, we found significant correlations between performance on the neuropsychological measures and the GOSE, including some of the same domains and tests used in those studies evaluating memory (Selective Reminding), executive functioning (Trail Making), and fine motor coordination/dexterity (Grooved Pegboard). Whereas these positive correlations might suggest to some that the GOSE alone is sufficient as an outcome measure in Phase III clinical trials, we agree with the recommendations of The Traumatic Brain Injury Clinical Trials Network Outcomes Subcommittee that a single, global measure is unable to fully evaluate the multiple components of outcome from TBI, nor can it capture all the important aspects of

TABLE 2. FREQUENCY (%) OF INDIVIDUALS ELIGIBLE FOR TESTING BECAUSE OF GALVESTON ORIENTATION AND AMNESIA TEST SCORES ≥ 75 BUT WHO WERE "COGNITIVELY UNABLE" TO COMPLETE A TEST

	Progesterone n (%)	Placebo n (%)	p value
Buschke Selective Reminding Memory Test	8 (3.6)	10 (3.6)	0.74
Digit Span Forward	1 (0.4)	1 (0.4)	0.97
Digit Span Backward	1 (0.4)	2 (0.7)	0.60
Trail Making Part A	5 (2.0)	3 (1.1)	0.42
Trail Making Part B	6 (2.4)	8 (3.0)	0.66
Controlled Oral Word Association	4 (1.6)	6 (2.2)	0.59
Grooved Pegboard: dominant hand	3 (1.2)	5 (1.9)	0.54
Grooved Pegboard: nondominant hand	5 (2.1)	4 (1.6)	0.68

TABLE 3. ADJUSTED MEANS (STANDARD ERROR) OF TEST SCORES*

<i>Domains and dependent variables</i>	<i>Progesterone</i>	<i>Placebo</i>	<i>p value</i>
Memory			
Buschke Immediate Word Recall (Max = 72 words)	41.7 (0.7)	42.4 (0.7)	0.53
Buschke Delayed Word Recall (Max = 12 words)	5.7 (0.2)	5.7 (0.2)	0.94
Attention			
Trails A completion time (Max = 150 sec)	36.5 (1.2)	36.9 (1.1)	0.81
Trails A # of errors (Max = 25)	0.3 (0.1)	0.2 (0.0)	0.22
Digit Span Forward total score (Max = 16)	9.2 (0.1)	9.4 (0.1)	0.41
Span Length (Max = 9)	6.1 (0.1)	6.2 (0.1)	0.66
Executive functioning			
Trails B completion time (Max = 300 sec)	94.7 (3.6)	94.9 (3.5)	0.97
Trails B completion time- Trails A completion time	59.7 (3.1)	60.2 (3.0)	0.92
Trails B # of errors (Max = 25)	0.7 (0.1)	0.7 (0.1)	0.93
Digit Span Backward (Max = 14)	5.7 (0.1)	5.7 (0.1)	0.78
Span length (Max = 9)	4.2 (0.8)	4.3 (0.7)	0.60
Language			
Controlled Oral Word Association # of Words	31.8 (0.7)	30.0 (0.7)	0.05
Fine motor coordination/dexterity			
Grooved Pegboard: dominant hand # of sec (Max = 300 sec)	88.0 (2.2)	89.0 (2.2)	0.75
# of drops	0.6 (0.1)	0.5 (0.1)	0.59
Grooved Pegboard: nondominant hand # of sec (Max = 300 sec)	94.2 (2.2)	95.2 (2.2)	0.74
# of drops	0.6 (0.1)	0.6 (0.1)	0.61

*Includes subjects with reliable tests and those who were cognitively unable to complete the tests. In these latter cases, the worse score was assigned. Adjustment is for index Glasgow Coma Scale.

recovery.⁷ The measures used in our trial captured an array of abilities impacted by TBI and critical for societal reintegration and quality of life. Many of the tests were also the same ones recommended by expert panels.^{7,10,11}

We do not believe the lack of a treatment effect of progesterone was related to study procedural shortcomings. We took great care to ensure adequate training of the neuropsychological evaluators at each site, and we monitored quality of test administration, scoring,

and data entry on an ongoing basis. We were also cognizant of the importance of noting the reasons why a particular test could not be administered. This was necessary to avoid the pitfall of only including data of persons who could perform the measure, which would have biased the results towards those with a better outcome. Finally, we analyzed performance not only in terms of mean group differences in raw scores but also using normative data from non-TBI persons to determine the degree of impairment.

TABLE 4. FREQUENCY (%) OF INDIVIDUALS WITH UNFAVORABLE OUTCOMES+

<i>Domains and dependent variables</i>	<i>Progesterone n (%)</i>	<i>Placebo n (%)</i>	<i>p value</i>
Memory			
Buschke Immediate Word Recall	166 (66.7)	168 (62.3)	0.30
Buschke Delayed Word Recall	217 (87.2)	235 (88.7)	0.59
Attention			
Trails A completion time (sec)	112 (45.3)	120 (46.0)	0.89
Digit Span Forward Length	58 (22.6)	66 (24.4)	0.63
Executive functioning			
Trails B completion time (sec)	115 (50.4)	122 (50.8)	0.93
Digit Span Backward Length	54 (21.1)	72 (26.7)	0.13
Language			
Controlled oral word association (# of words)	108 (43.2)	125 (47.0)	0.39
Fine Motor coordination/dexterity			
Grooved Pegboard: dominant hand	116 (47.9)	148 (57.4)	0.03
Grooved Pegboard: nondominant hand	112 (48.3)	128 (52.2)	0.39

Unfavorable outcomes = z-score values less than -1 standard deviation based on performance of nonhead injured subjects.

Conclusion

The more granular neuropsychological assessment of progesterone's purported neuroprotective properties did not reveal a

TABLE 5. CORRELATIONS BETWEEN NEUROPSYCHOLOGICAL TEST SCORES AND GLASGOW OUTCOME SCORE EXTENDED SCORE

<i>Measure</i>	<i>Correlation with GOSE</i>
Galveston Orientation and Amnesia Test	0.36*
Buschke Immediate Word Recall	0.40*
Buschke Delayed Word Recall	0.42*
Trails A completion time	-0.38*
Trails B completion time	-0.35*
Trails B- Trails A completion time	-0.29*
Digit Span Forward Length	0.18*
Digit Span Backward Length	0.24*
Controlled Oral Word Association Test (# Words)	0.33*
Grooved Pegboard: dominant hand completion time (sec)	-0.43*
Grooved Pegboard nondominant hand completion time (sec)	-0.38*

GOSE, Glasgow Outcome Score Extended.

* $p < 0.001$.

significant effect, and the findings were concordant with the GOSE primary outcome. The analysis neither supports nor invalidates the use of neuropsychological tests in TBI, but rather reflects the failure of progesterone to improve outcome in this cohort of subjects with moderate to severe TBI.

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Author Disclosure Statement

Dr. Wright reports receiving royalties from a patent related to progesterone for the treatment of patients with traumatic brain injury (U.S. patents 7,473,687, 7,915,244, and 8,455,468), which was licensed to BHR Pharma. For the remaining authors, no competing financial interests exist.

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