ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury

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Study objective: Laboratory evidence indicates that progesterone has potent neuroprotective effects. We conducted a pilot clinical trial to assess the safety and potential benefit of administering progesterone to patients with acute traumatic brain injury.

Methods: This phase II, randomized, double-blind, placebo-controlled trial was conducted at an urban Level I trauma center. One hundred adult trauma patients who arrived within 11 hours of injury with a postresuscitation Glasgow Coma Scale score of 4 to 12 were enrolled with proxy consent. Subjects were randomized on a 4:1 basis to receive either intravenous progesterone or placebo. Blinded observers assessed patients daily for the occurrence of adverse events and signs of recovery. Neurologic outcome was assessed 30 days postinjury. The primary safety measures were differences in adverse event rates and 30-day mortality. The primary measure of benefit was the dichotomized Glasgow Outcome Scale–Extended 30 days postinjury.

Results: Seventy-seven patients received progesterone; 23 received placebo. The groups had similar demographic and clinical characteristics. Laboratory and physiologic characteristics were similar at enrollment and throughout treatment. No serious adverse events were attributed to progesterone. Adverse and serious adverse event rates were similar in both groups, except that patients randomized to progesterone had a lower 30-day mortality rate than controls (rate ratio 0.43; 95% confidence interval 0.18 to 0.99). Thirty days postinjury, the majority of severe traumatic brain injury survivors in both groups had relatively poor Glasgow Outcome Scale–Extended and Disability Rating Scale scores. However, moderate traumatic brain injury survivors who received progesterone were more likely to have a moderate to good outcome than those randomized to placebo.

Conclusion: In this small study, progesterone caused no discernible harm and showed possible signs of benefit. [Ann Emerg Med. 2007;49:391-402.]

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Editor's Capsule Summary

What is already known on this topic

There are no proven neuroprotective agents for patients with traumatic brain injury. There have been animal studies in traumatic brain injury demonstrating neuroprotection for progesterone, but no human clinical trials to date.

What question this study addressed

This was a randomized, placebo-controlled, clinical trial in 100 patients to evaluate the safety and potential efficacy of progesterone in patients with traumatic brain injury.

What this study adds to our knowledge

The use of progesterone after traumatic brain injury in adults was well tolerated in terms of safety, and those receiving progesterone had a lower 30-day mortality rate. Patients in both groups had poor neurologic outcome; a small subcategory of patients with moderate initial traumatic brain injury and receiving progesterone were more likely to have better neurologic outcomes.

How this might change clinical practice

This pilot study will not change clinical practice but provides support for a phase III efficacy trial of progesterone for patients with traumatic brain injury.

INTRODUCTION

Background

No pharmacologic agent has been shown to improve outcomes of traumatic brain injury.[1] Methylprednisolone, once considered a mainstay of treatment, is harmful.[2-4] A recent large-scale trial of magnesium was disappointing.[5] Hypothermia produces variable effects and may be hazardous to brain-injured patients older than 45 years.[6-9]

During the past decade, progesterone has emerged as a promising therapeutic candidate. Although progesterone's nonneurologic effects are well known, the steroid also has neuroprotective properties.[10] Progesterone is present in the brains of men and women in small but roughly equal concentrations. Progesterone receptors are widely distributed throughout the central nervous system. A growing body of animal studies indicates that administering progesterone shortly after traumatic brain injury reduces cerebral edema, prevents neuronal loss, and improves functional outcomes.[10-35]

Importance

Traumatic brain injury is a massive public health problem worldwide. Approximately 1.5 to 2 million Americans sustain a traumatic brain injury each year.[36] In the United States, traumatic brain injuries annually cause 50,000 deaths, 235,000 hospitalizations, and 80,000 new cases of long-term disability.[37-45] The Centers for Disease Control and Prevention (CDC) estimates that 5.3 million Americans are disabled from a previous traumatic brain injury.[36] Aggregate lifetime costs exceed $56 billion per year.[37]

Goals of This Investigation

In light of promising preclinical evidence, we conducted a pilot clinical trial of intravenous progesterone to treat acute traumatic brain injury.

MATERIALS AND METHODS

Study Design

Our study was a phase II, randomized, placebo-controlled clinical trial. Its primary objective was to assess the safety of administering progesterone to patients with moderate to severe acute traumatic brain injury. We also hoped to detect possible signs of benefit. Except for our lead statistician, everyone involved was blinded to treatment group assignment for the duration of the trial.

In the United States, intravenous progesterone has been authorized for experimental administration in only 3 previous studies, none related to traumatic brain injury.[46-48] Therefore, it is necessary to produce preliminary data on the safety of intravenous progesterone before conducting a large-scale clinical trial. Because short-term administration of progesterone by other routes is generally safe and the 3 previous studies of intravenous progesterone reported no serious adverse effects, we hypothesized that the experimental treatment would not cause harm (ie, patients who received progesterone would not experience an increased rate of adverse or serious adverse events compared with those who received placebo).

The goal of this pilot study was to enroll 100 patients and randomly assign them 4:1 to receive either intravenous progesterone or placebo. With 3 interim and 1 final analyses planned after the enrollment of 20, 36, 48, and 100 patients, the study had 80% power to detect increased rates of the following adverse events, in which the placebo rate is based on historical data: pneumonia: placebo=5%, progesterone=32%; hypotension: placebo=10%, progesterone=40%; sepsis: placebo=23%, progesterone=57%; increased liver enzymes: placebo=43%, progesterone=77%. The power to detect potentially important signs of benefit was also limited, but we accepted this because our primary goal was to assess safety, not efficacy.

Setting

The study was conducted at Grady Memorial Hospital, a public teaching hospital in Atlanta, Georgia. The only Level I trauma center in north Georgia, Grady Memorial serves a population of more than 4 million people.

Selection of Participants

Adult blunt trauma victims who reached Grady Memorial Hospital within 11 hours of injury and had a postresuscitation,

or "index," Glasgow Coma Scale (GCS) score of 4 to 12 were eligible for enrollment. Emergency department (ED) personnel immediately screened patients on arrival. When a potential study candidate was identified, a member of the study team was summoned to confirm eligibility. Candidates were excluded if they had a blood alcohol concentration greater than 250 mg/dL, had penetrating brain injury, were younger than 18 years, had an index GCS score of less than 4 or greater than 12, had indeterminate time of injury, were pregnant, had a family-reported history of active cancer, had acute stroke or a family-reported history of older stroke with residual motor deficits, had acute or chronic spinal cord injury with neurologic deficits, or we were unable to identify the patient or secure proxy consent within 11 hours of injury (Table E1, available online at http://www.annemergmed.com).

Because the study candidates were cognitively impaired, legally authorized representatives were approached for proxy consent. Each proxy was informed of the study's rationale, design, anticipated benefits, and potential risks. Proxies were assured that participation was voluntary and nonparticipation would not affect the patient's care. To facilitate comprehension, our consent form was written at an 8th-grade reading level. A Spanish version was produced as well.

An investigational new drug authorization (IND 58, 986) to use progesterone to treat traumatic brain injury was secured from the US Food and Drug Administration (FDA). The National Institutes of Health appointed an independent data safety monitoring board to oversee the study. Emory University's institutional review board and Grady Memorial Hospital's Research Oversight Committee independently reviewed and approved the protocol. Before initiating enrollment, we consulted the leaders of several local patient and minority advocacy organizations. We also convened a community advisory board.

After proxy consent, each patient was assigned to one of 8 clinical subgroups defined by sex, race (black versus others), and traumatic brain injury severity (index GCS scores 4 to 8=severe; 9 to 12=moderate). Within each subgroup, permuted block randomization assigned 4 of every 5 consecutive patients to progesterone and the other to placebo. A 4:1 randomization scheme was used to increase the number of patients receiving progesterone while maintaining blinding. Drug kits were prepared and randomized off site by Emory's Investigational Drug Center. These kits were indistinguishable with respect to treatment assignment.

Interventions

The kits contained progesterone dissolved in 95% ethanol, filtered into sterile vials using a 0.2-μm filter. Aliquots were assayed to confirm uniform concentration and sterility. Each kit contained 6 vials of progesterone dissolved in ethanol (1.6 mL/vial) or ethanol alone (placebo). Vials were identical in appearance, clarity, odor, and physical properties.

When a patient was enrolled, the next kit in that clinical subgroup was used to prepare all study infusions. The first vial was mixed in Intralipid 20% (Fresenius Kabi, Clayton, NC) at a concentration designed to deliver a loading dose of 0.71 mg/kg of progesterone at 14 mL/hour for the first hour. Then, the infusion was reduced to 10 mL/hour to deliver 0.5 mg/kg per hour for the next 11 hours. Five additional 12-hour maintenance infusions were delivered at the standard rate of 10 mL/hour, for a total of 3 days of treatment.[49]

Surgical services at our hospital follow a consensus protocol for traumatic brain injury care based on the guidelines of the Brain Trauma Foundation.[50] It specifies a consistent, stepwise approach to treating episodes of increased intracranial pressure. This ensured that study patients received standard care for traumatic brain injury.

Methods of Measurement

One or more members of our team conducted rounds daily to examine patients, assess GCS, and record test results. Hourly vital signs (blood pressure, pulse rate, respiratory rate, temperature, and pulse oximetry), intracranial pressure readings, and other physiologic characteristics (eg, mean arterial pressure, cerebral perfusion pressure, and fluid balance) were abstracted from each patient's medical record, along with all administered medications and interventions. Laboratory values were obtained from the hospital's information system. To facilitate daily identification of adverse events, serious adverse events, and complications of intensive care, a safety checklist was developed (Table E2, available online at http://www.annemergmed.com).

Whenever a serious adverse event occurred, a senior neurosurgeon unassociated with the study team promptly assessed its potential relationship to administration of the experimental treatment. Because our internal safety monitor was blinded to treatment group assignment, he presumed that every patient was randomized to progesterone. All serious adverse event reports, regardless of the degree of attributed causality, were forwarded within 24 hours to Emory's institutional review board, our study's data safety monitoring board, and the FDA for external review. Adverse events of a less serious nature were reported weekly.

We planned to stop the infusion immediately if a patient experienced an anaphylactic reaction, a major thromboembolic event, an unexplained elevation of serum aspartate aminotransferase or alanine aminotransferase to a level exceeding 5,000 IU, or a serum bilirubin level greater than 10 mg/dL. We planned to halt enrollment if our data safety monitoring board advised us that any of 3 interim analyses revealed that one treatment group (coded A or B) experienced a significantly higher rate of serious adverse events, including mortality, than the other. These rules were based on O'Brien-Fleming boundaries,[51] constructed using an α spending approach.[52]

Outcome Measures

In hopes of detecting drug activity, several functional measures were collected, including duration of coma (hours from injury to awakening, GCS >8 or a motor score >5),[53]

duration of posttraumatic amnesia (number of days until a subject achieved 2 consecutive Galveston Orientation and Amnesia Test scores of 75 or better),[54] and mortality within 30 days of injury. To gauge progesterone's effects on cerebral edema, we noted hourly intracranial pressure measurements and calculated each patient's intracranial pressure therapeutic intensity level.[55]

Thirty days after each patient's injury, blinded outcome examiners used 2 highly validated tools, the Glasgow Outcome Score Extended[56,57] and the Disability Rating Scale,[58-61] to assess each survivor's functional status. Patients who remained hospitalized were evaluated in person. Those who were discharged were assessed by telephone with standard protocols. Severely impaired patients were classified as "not testable," a marker for poor outcome. Reliability codes were used to note reasons for nonadministration of a particular measure, such as physical impairment (eg, hemiparesis) or cognitive impairment (eg, could not understand instructions).

Primary Data Analysis

Data collection activities were guided by a formal data management plan and standard operating procedures manual. Clinical assessments and laboratory values were recorded on paper case report forms and double entered into a Web-based ORACLE database. Case report forms were not accepted as valid unless the double entries matched and all range checks were met. Special edit queries were constructed to generate transport files. These were imported into SAS version 9.1 for analysis (SAS Institute, Inc., Cary, NC).

The FDA considers an "adverse event" any undesirable medical event occurring to a patient, whether or not it is attributed to the study drug, including events not seen at baseline or worse if present at baseline. "Serious adverse events" are defined as death, immediate risk of death, or suspicion that use or continued use of the study drug would result in the patient's death, prolongation of existing hospitalization, or persistent or significant disability or incapacity.[62]

We hypothesized that traumatic brain injury patients randomized to receive progesterone would achieve better clinical outcomes 30 days postinjury than those randomized to placebo. Our a priori primary measure of outcome was Glasgow Outcome Scale–Extended.[56] Other outcome measures, as noted above, included duration of coma,[53] duration of posttraumatic amnesia,[54] death within 30 days of injury, and the Disability Rating Scale.[61]

To assess the quality of randomization, treatment and placebo groups were compared with regard to demographic, historical, and clinical characteristics. To assess safety, rates of adverse and serious adverse events, including mortality, were compared using Fisher's exact test. Generalized linear model analysis using a negative binomial distribution was used to compare rates of events that occurred multiple times per patient.[63] To assess potential benefits, Fisher's exact test was used to analyze group Glasgow Outcome Scale–Extended scores, dichotomized into "good or moderate recovery" versus all other levels of recovery. Wilcoxon's rank sum test was used to compare group Disability Rating Scale scores. Mean and median durations of coma and posttraumatic amnesia were compared using Student's *t* test. Longitudinal mixed-effects models were used to analyze intracranial pressure–therapeutic intensity level scores, as well as other hourly and daily clinical measurements from the day of enrollment through treatment day 4. Because we anticipated, a priori, that clinical response might differ by traumatic brain injury severity, all outcome analyses were stratified into moderate (index GCS scores 9 to 12) versus severe (index GCS scores 4 to 8) injuries.

RESULTS

Two hundred eighty-one patients were screened between May 28, 2002, and September 17, 2004. Only 3 were missed. Common reasons for exclusion included GCS less than 4 or greater than 12 (17%), blood alcohol content 250 (13%), no next of kin (11%), unknown injury time (11%), unstable vital signs (9.2%), and unreliable GCS (9.2%). Six patients could not be enrolled because they presented during one of 3 study "holds." One was excluded postconsent but before randomization because the treating team determined that his injuries were nonsurvivable. Eleven proxies (10%) declined to consent (Figure). Nonparticipants resembled participants with respect to sex, race, and mechanism of injury.

Characteristics of Study Subjects

Seventy-one subjects were male patients; 34 were black. Mean age was 36 years. More than 80% were injured in a motor vehicle crash or a fall. Most patients reached the hospital within an hour of injury, 58% by helicopter. Seventy-two patients had an index GCS score of 4 to 8; the remainder had an index GCS score of 9 to 12. Because it often took hours to locate a proxy, mean time from injury to consent and initiation of infusion was 6.3 hours (95% confidence interval [CI] 5.9 to 6.8 hours) in the progesterone group and 6.2 hours (95% CI 5.9 to 6.6 hours) in the placebo group (Table 1).

Seventy-seven subjects were randomized to progesterone; 23, to placebo. Treatment groups were similar with respect to sex, age, race, index GCS score, mechanism of injury, revised trauma score, Injury Severity Score, time from injury to ED arrival, time from injury to initiation of study treatment, Marshal computed tomography (CT) score,[64] and ED disposition (Table 1).

Our pharmacokinetic findings are reported elsewhere.[49] Minor protocol violations, such as brief delays in changing intravenous bags, were common. Sufficient solution was provided to prevent most interruptions of infusion. Six major protocol violations occurred. Four involved prolonged interruptions (>2 hours) of infusion, 1 involved a dosing error (a 70-kg patient's initial 12-hour infusion was miscalculated for a 100-kg patient), and 1 involved inappropriate enrollment of a patient who should have been excluded because of an acute

Table 1. Characteristics by group: participants in ProTECT (N = 100).

Characteristic	Overall	Progesterone	Placebo
Number of subjects	100	77	23
Mean age, y (SD)	35.8 (15.0)	35.3 (14.3)	37.4 (17.4)
Male (%)	71	71	70
Black (%)	35	34	39
Mechanism of injury (%) (n=100)			
Motor vehicle	76	74	83
Pedestrian struck	3	4	0
Bicycle	3	3	4
Fall	7	6	9
Other	11	13	4
Index GCS (% severe)	72	73	70
24-h GCS (% severe)	61	70	50
Injury Severity Score (SD)	24.2 (9.2)	24.5 (9.9)	23.3 (6.4)
Revised Trauma Score (SD)	6.1 (0.6)	6.1 (0.6)	6.2 (0.7)
Probability of survival (SD)	0.9 (0.2)	0.9 (0.2)	0.8 (0.1)
Initial CT scan Marshall score[64] (1-5)	2.8 (1.6)	3.0 (0.2)	2.3 (0.3)
Time injury to arrival (SD), min	50.3 (30.3)	49.5 (32.3)	54.3 (32.3)
Time injury to infusion (SD), min	379.2 (118.0)	380.7 (125.6)	374.0 (91.2)

Table 2. Select serious adverse event and adverse event rates by treatment group.

Adverse Event	Progesterone (%), n = 77	Placebo (%), n = 23	Relative Risk (95% CI)
Acute respiratory distress syndrome	2.6	4.4	0.60 (0.06-6.29)
Central nervous system infection	1.3	0.0	—
Cardiac arrhythmia	5.2	17.4	0.30 (0.08-1.10)
Cholestatic jaundice	6.5	0.0	—
Death within 30 days	13.0	30.4	0.43 (0.18-0.99)
Fever	70.1	82.6	0.85 (0.67-1.08)
Gastrointestinal bleeding	5.2	0.0	—
Hyperglycemia, non-diabetes mellitus	27.3	30.4	0.90 (0.44-1.84)
Hypertension	11.7	8.7	1.34 (0.31-5.79)
Hypotension	9.1	21.7	0.42 (0.15-1.19)
Hypothermia	5.2	8.7	0.60 (0.12-3.06)
Hypoxemia	11.7	13.0	0.90 (0.26-3.04)
Increase liver enzyme	6.5	4.4	1.49 (0.18-12.15)
Phlebitis at injection site	1.3	0.0	—
Rash or hives	2.6	0.0	—
Syndrome of inappropriate antidiuretic hormone	1.3	0.0	—
Seizures	5.2	0.0	—
Sepsis	2.6	0.0	—
Shock	2.6	0.0	—
Suspected pneumonia	11.7	4.4	2.69 (0.46-20.12)
Tachycardia	24.7	13.0	1.89 (0.61-5.83)
Thromboembolic disease	3.9	4.4	0.89 (0.088-9.01)

ischemic stroke. When CT scanning on the second hospital day revealed the stroke, the study infusion was immediately stopped. Review of the pre-enrollment scan showed subtle but clear signs of the stroke, which was traced to a traumatic carotid artery dissection. Because the stroke preceded initiation of progesterone treatment, this incident was classified as a major protocol violation rather than a serious adverse event.

One patient who was randomized to progesterone died before the infusion could be started. This subject's data are retained in the analysis under the principle of "intention to treat." All other members of the treatment group and no member of the control group had elevated levels of progesterone in their sera.

With the exception of mortality, group rates of adverse and serious adverse events did not differ (Table 2) whether adverse events and serious adverse events were analyzed by any occurrence or mean episodes per subject. Laboratory values and physiologic variables (blood pressure, fluid balance, cerebral perfusion pressure, and intracranial pressure) were remarkably similar, whether analyzed by means or by the frequency that individual test values exceeded prespecified thresholds (Tables 3 and 4).

Table 3. Physiologic variables.

	Progesterone Group			Placebo Group		
Infusion Day	**n**	**Mean**	**95% CI**	**n**	**Mean**	**95% CI**
Intracranial pressure–therapeutic intensity level						
0	16	2.6	1.9-3.4	5	3.8	1.9-5.7
1	27	2.7	1.4-4.1	9	2.7	1.3-4.1
2	26	3.2	1.9-4.5	10	4.5	1.2-7.8
3	17	3.7	1.1-6.3	9	4.2	0.6-7.9
4	15	2.8	0.6-5.0	5	6.0	0-12.3
Intracranial pressure (mm Hg)						
0	17	16.0	12.3-19.7	5	13.13	8.1-18.2
1	36	17.1	12.6-21.5	12	14.69	10.1-19.3
2	34	15.4	13.2-17.5	12	17.32	12.1-22.6
3	34	16.0	13.8-18.2	12	18.27	13.3-23.2
4	25	17.7	14.8-20.7	12	19.95	13.8-26.1
Cerebral perfusion pressure (mm Hg)						
0	13	70.3	61.9-78.8	3	71.9	48.4-95.4
1	36	73.4	66.2-80.6	12	76.8	71.5-82.0
2	34	75.9	71.7-80.1	12	74.9	70.6-79.1
3	34	74.9	70.7-79.2	12	75.6	70.8-80.4
4	25	73.8	68.0-79.6	11	73.2	67.2-79.1
Systolic blood pressure (mm Hg)						
0	68	129.4	125.6-133.2	18	127.6	119.2-136.0
1	76	130.2	126.5-133.9	22	129.9	124.0-135.7
2	75	133.5	130.2-136.8	23	133.0	125.9-140.1
3	75	133.8	130.1-137.6	22	137.0	130.6-143.9
4	73	132.7	128.6-136.9	21	137.8	132.5-143.4
Diastolic blood pressure (mm Hg)						
0	68	69.5	66.6-72.5	18	66.6	60.3-72.9
1	76	67.4	65.1-69.8	22	66.4	62.6-70.1
2	75	67.2	64.8-69.7	23	65.7	60.7-70.8
3	75	67.5	65.3-69.6	22	66.4	62.2-70.6
4	73	67.3	65.2-69.4	21	67.3	63.6-71.1
Temperature (°C)						
0	35	37.0	36.6-37.4	11	36.9	36.3-37.6
1	76	37.4	37.3-37.6	22	37.4	37.1-37.7
2	75	37.4	37.3-37.6	23	37.7	37.4-38.0
3	75	37.4	37.3-37.5	22	37.7	37.4-37.9
4	73	37.5	37.3-37.6	21	37.7	37.4-38.0
Fluid balance (+mL)						
1	76	767.9	312.8-1223.0	23	834.7	0-1794.9
2	76	1189.5	645.9-1733.0	23	1282.2	583.4-1981.0
3	75	802.0	401.5-1202.5	22	1292.6	748.1-1837.0
4	75	818.7	386.3-1251.2	20	812.0	66.9-1557.2

Throughout the 3-day infusion interval, the progesterone group experienced a lower increase in mean temperature than controls, which was determined by analyzing a treatment-by-time interaction term for progesterone versus control patients, with the slope=−0.0055 (95% CI −0.010 to −0.001). This is important because endogenous release of progesterone is associated with a 1°F (0.55°C) increase in core temperature, and elevated temperatures have been posited to adversely affect neurologic outcome.

The only adverse event attributed to progesterone was a case of superficial phlebitis at the intravenous site. It resolved spontaneously. Three patients, all of whom received progesterone, developed deep venous thromboses 6 to 23 days after completing infusion. They were treated without incident.

Two patients had ischemic strokes. One, who was randomized to progesterone, sustained the stroke before enrollment and was classified as a major protocol violation. The other occurred in a patient who received placebo.

One patient sustained an acute myocardial infarction 2 days after his progesterone infusion was completed. At the time, high-dose phenylephrine hydrochloride was being administered to maintain cerebral perfusion pressure. Postmortem examination revealed no intracoronary thromboses.

During the first 3 days of treatment and for 1 day afterwards, the mean intracranial pressure level of treatment group subjects with monitors in place remained stable, whereas the mean intracranial pressure of control group subjects with monitors in place tended to increase. However, this trend was not

Table 4. Variables exceeding threshold values.

	Progesterone Group			Placebo Group			
Percentage of patients with clinical values exceeding the threshold	**n**	**Denominator**	**%**	**n**	**Denominator**	**%**	***P* Value**
MAP <70	22	76	29.0	10	23	43.5	0.21
CPP <60	18	37	48.7	5	12	41.7	0.75
ICP >25	12	37	32.4	5	12	41.7	0.73
Systolic BP <90	22	76	29.0	10	23	43.5	0.21
Mean duration of pressures exceeding threshold values, hours							
Duration, h	**n**	**Mean**	**Standard error**	**n**	**Mean**	**Standard error**	
MAP <70	76	2.5	0.7	23	3.4	1.40	0.24
CPP <60	37	6.9	2.9	12	2.4	1.18	0.56
ICP >25	37	5.0	2.5	12	11.3	7.88	0.46
Systolic BP <90	76	2.7	0.7	23	3.5	1.40	0.25
Mean frequency of pressures exceeding threshold values							
Event	**Occurrence**	**Consecutive readings, No.**	**Rate/1000 consecutive readings**	**Occurrence**	**Consecutive readings, No.**	**Rate/1000 consecutive readings**	
MAP <70	128	4334	29.5	61	1477	41.3	0.81
CPP <60	183	1969	92.9	23	816	28.2	0.41
ICP >25	145	2067	70.2	121	828	146.1	0.61
Systolic BP <90	132	4112	32.1	62	1365	45.4	0.81

BP, Blood pressure; *CPP*, cerebral perfusion pressure; *ICP*, intracranial pressure; *MAP*, mean arterial pressure.

significant. Mean intracranial pressure–therapeutic intensity level scores did not differ between groups (Table 3).

Severe traumatic brain injury patients (index GCS scores 4 to 8) randomized to progesterone remained in coma longer than those who received placebo (10.1 days [95% CI 7.7 to 12.5 days] versus 3.9 days [95% CI 2.5 to 5.4 days]). The duration of posttraumatic amnesia did not significantly differ between groups (Table 5).

Seven of 23 patients (30.4%) randomized to placebo died within 30 days of injury compared with 10 of 77 patients (13%) randomized to progesterone (relative risk [RR] 0.43; 95% CI 0.18 to 0.99). Excluding the subject who died before receiving progesterone strengthens this difference (RR 0.39; 95% CI 0.16 to 0.93). A strong trend toward fewer deaths from neurologic causes was noted in the treatment group compared with controls (RR 0.30; 95% CI 0.08 to 1.12). Mortality rates from non-central nervous system causes were similar in both groups (Table 5).

Mortality differed by traumatic brain injury severity. Fifteen patients with an index GCS score of 4 to 8 were randomized to placebo. Six (40%) died within 30 days of injury compared with 7 of 53 patients (13.2%) randomized to progesterone (RR 0.33; 95% CI 0.13 to 0.83). Seven patients with an index GCS score of 9 to 12 were randomized to placebo. One patient (14.3%) died. Three of 18 patients (16.7%) with an index GCS score of 9 to 12 and randomized to progesterone died (RR 1.17; 95% CI 0.14 to 9.41) (Table 5).

We were able to contact 92% of patients who survived 30 days postinjury to assess their functional status. Three fourths of patients enrolled with an index GCS score of 4 to 8 were functioning at a relatively poor level, regardless of treatment group. Only 4 of 15 placebo group patients (26.7%) had a Glasgow Outcome Scale–Extended score compatible with moderate or good recovery compared with 11 of 52 members (21.2%) of the progesterone group (RR for moderate or good recovery 0.79; 95% CI 0.29 to 2.13). Among patients enrolled with an index GCS score of 9 to 12, none of 7 (0%) randomized to placebo had moderate to good recovery compared with 10 of 18 (55.6%) randomized to progesterone (no RR estimate possible; $P=.0202$).

Disability Rating Scale scores revealed a similar relationship. Thirty days postinjury, severe traumatic brain injury survivors who received placebo were slightly less disabled than survivors treated with progesterone. But in the moderate traumatic brain injury stratum, patients treated with progesterone were significantly less disabled than those who received placebo (Table 5).

LIMITATIONS

Our study was limited to adults. Brain injury is an enormous problem in pediatric age groups, but progesterone's effects on brain-injured children are unknown. A separate trial will be needed to explore progesterone's safety and effectiveness as a treatment for brain-injured children.

Table 5. Outcome variables 30 days postinjury.

	Progesterone Group n=77			Placebo Group n=23		
Outcome Variables	**n**	**Mean**	**95% CI**	**n**	**Mean**	**95% CI**
Duration of coma, days						
Severe (iGCS 4-8)	55	10.11	7.7-12.5	16	3.9	2.5-5.4
Moderate (iGCS 9-12)	20	4.1	1.4-6.8	7	6.1	0-13.2
Duration of posttraumatic amnesia, days						
Severe (iGCS 4-8)	37	18.6	15.2-22.0	9	12.8	5.2-20.4
Moderate (iGCS 9-12)	15	10.7	6.2-15.3	3	18.3	0-46.9
Mortality						
Severe (iGCS 4-8)	7	13.2%		6	40.0%	RR 0.33 (0.13-0.830)
Moderate (iGCS 9-12)	3	16.7%		1	14.3%	RR 1.11 (0.14-9.41)
All-cause mortality	10	13.0%		7	30.4%	RR 0.43 (0.18-0.99)
Neurologic deaths	4	5.3%		4	17.4%	
Nonneurologic deaths	5	6.6%		3	13.0%	
Disability Rating Score (DRS)						
Severe (iGCS 4-8)						
Employ	46	2.7	2.5-2.9	9	2.4	1.9-2.9
Function	46	2.9	2.9-3.5	9	1.8	0.54-3.1
Total DRS	45	10.7	8.3-13.1	9	4.4	0.0-9.8
Moderate (iGCS 9-12)						
Employ	15	1.8	1.2-2.4	6	3.0	2.0-3.96
Function	15	1.5	0.6-2.4	6	3.8	2.4-5.2
Total DRS	15	5.0	1.8-6.2	6	12.7	7.6-17.78
Dichotomized Glasgow Outcome Score–Extended (GOS-E)						
Severe (iGCS 4-8)						
Dead/vegetative/severe	41	78.9%		11	73.3%	RR 0.79 (0.29, 2.13)
Moderate/good	11	21.2%		4	26.7%	
Moderate (iGCS 9-12)						
Dead/vegetative/severe	8	44.4%		7	100%	*
Moderate/good	10	55.6%		0	0.00%	

iGCS, Index GCS score; *RR*, relative risk.
*No relative risk estimate, because of 0 cell; however, $P=.0202$.

No discernible harms were noted in the 77 patients who were randomized to progesterone. However, small studies like ours are prone to type II error. Disproportionate allocation of subjects to the treatment group enhanced our ability to assess dosing and drug-related adverse events but diminished our power to detect group differences in outcome.

Because progesterone has not been previously used to treat traumatic brain injury, we elected to enroll patients with proxy consent rather than exception to informed consent. The need to identify and contact a legally authorized representative for each patient imposed unavoidable delays to treatment.

We assessed several measures of outcome to determine their suitability for a subsequent large-scale trial. This practice can produce statistical errors. We chose to depict 95% CIs rather than adjusting for multiple comparisons because this is an exploratory analysis.

Two validated measures, Glasgow Outcome Scale–Extended and Disability Rating Scale, were used to assess functional status 30 days postinjury. A National Institutes of Health expert consensus panel has noted that Glasgow Outcome Scale–Extended and Disability Rating Scale scores can miss clinically important findings that may be detectable by more sophisticated neuropsychological tests.[65]

We used postresuscitation, or index GCS, to screen patients and assign them to clinical subgroups for randomization. We also stratified our outcome analysis by index GCS score. Clinicians know that a patient's GCS can fluctuate during the first few hours after a traumatic brain injury. It is possible, if not likely, that some patients classified as having a "moderate" traumatic brain injury according to index GCS score actually had a more severe injury, and some patients classified as "severe" on the basis of their index GCS score of 4 to 8 had a more moderate injury. If such misclassifications occurred, they should be randomly distributed. To address this possibility, we conducted a multivariate analysis of progesterone's effect on mortality using 24-hour GCS. It did not change our findings.

DISCUSSION

Progesterone offers a number of advantages over other experimental treatments for traumatic brain injury. Because it is

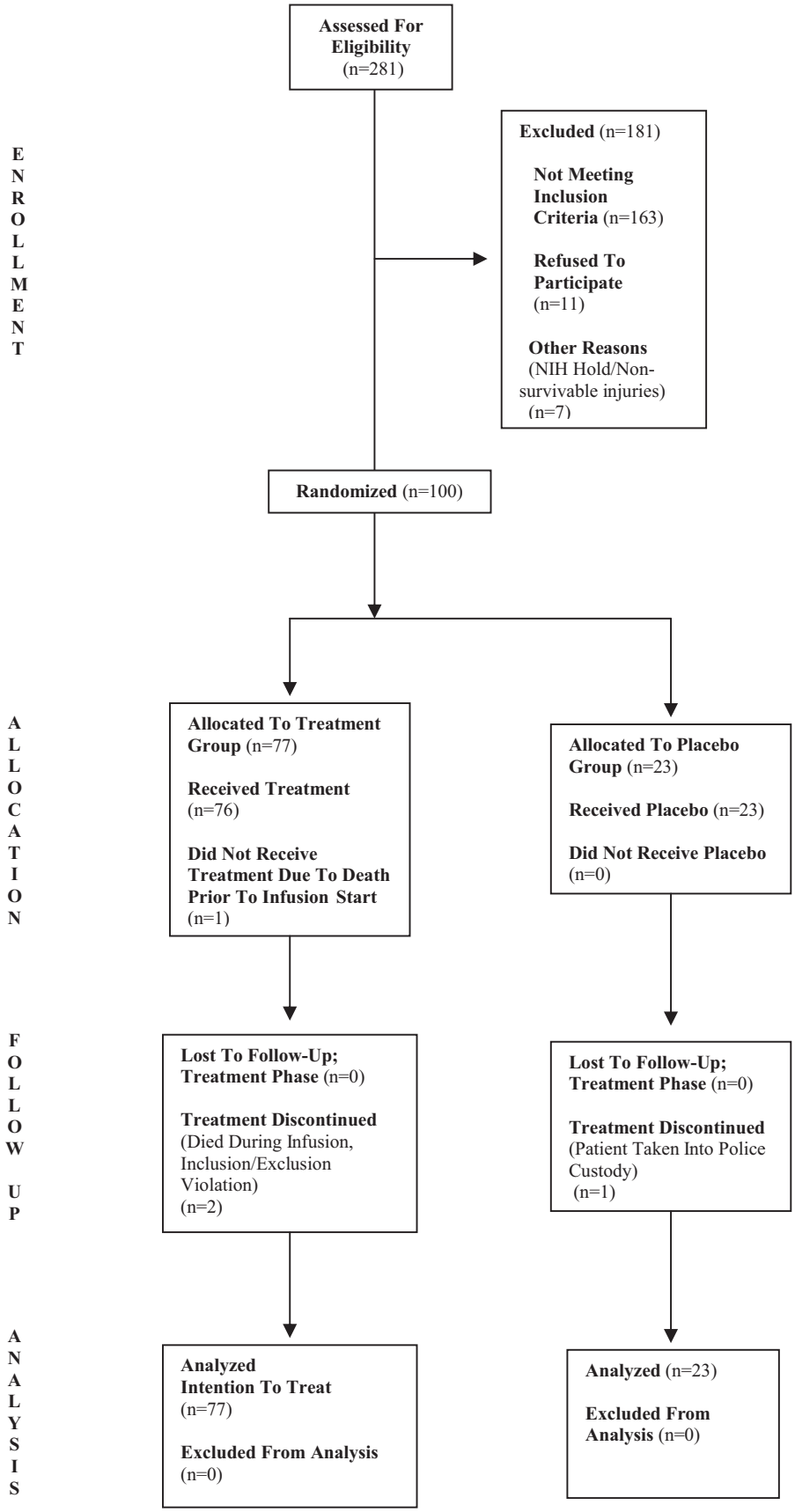

Figure. CONSORT diagram for the ProTECT™ I Clinical Trial.

lipid soluble, it rapidly crosses the blood-brain barrier and reaches equilibrium with the plasma within an hour of administration.[66] It has a long history of safe use in men and women.[47,67-70] The intravenous formulation we used can be easily administered by peripheral line.[49] Because the agent is widely available in generic forms, it is inexpensive.

The mechanisms behind progesterone's central nervous system effects are still being deciphered. Animal studies suggest that it modulates excitoxicity,[35,71-74] reconstitutes the blood-brain barrier,[14,27] reduces cerebral edema,[12,13,15] down-regulates the inflammatory cytokine cascade,[13,17,24,35,75-77] decreases apoptosis, and enhances recovery from cortical,[33] cerebral,[30,78] and spinal cord injury.[32]

Because progesterone has not been previously used to treat brain-injured humans, we conducted a pilot, phase II study. Ninety-nine percent of candidate patients were screened, and 90% of those who met study criteria were enrolled. Our treatment and control groups were well matched with regard to injury severity, time to treatment, and other predictors of outcome.

Proxy consent delayed initiation of treatment by several hours. One animal study has suggested that progesterone may produce salutatory effects as late as 24 hours postinjury. However, benefit was greatest if treatment was administered within 2 hours.[12] Early initiation of treatment, perhaps through exception to informed consent (federal regulation 21CFR50.24), would maximize the potential benefits of treatment and should be considered for future clinical trials of this agent.

Three patients randomized to progesterone developed deep venous thromboses 6 to 23 days after their infusion was completed. This incidence rate is well within historical boundaries for deep venous thrombosis among major trauma patients at Grady Memorial (unpublished data). With the exception of mortality, treatment and placebo groups experienced similar rates of adverse events and serious adverse events. They also had similar laboratory and physiologic values. This suggests, but does not prove, that administering progesterone to brain-injured patients is safe.

In animals, progesterone reduces development of cerebral edema if given within the first few hours of traumatic brain injury.[12,13,15] We observed no significant differences in mean intracranial pressure or intracranial pressure–therapeutic intensity levels between treatment and control patients, but our study lacked sufficient power to assess progesterone's effects on intracranial pressure.

Thirty-day mortality in the treatment group was less than half that of the control group. But because the number of subjects in our study is relatively small, the CI around this estimate approaches 1. Survival benefit was concentrated in patients with severe traumatic brain injury. If, as our findings suggest, a higher proportion of severely injured patients treated with progesterone survived, this might explain why members of this group had a longer mean duration of coma and a slightly lower percentage of subjects with moderate to good Glasgow Outcome Scale–Extended scores 30 days postinjury. One-year outcomes will be reported at a later date. Moderately injured patients who received progesterone achieved better Glasgow Outcome Scale–Extended and Disability Rating Scale scores than those who received placebo.

We previously reported that intravenous progesterone can be accurately administered to adult victims of acute traumatic brain injury.[49] This outcome analysis suggests, but does not prove, that progesterone causes no harms and may be a beneficial treatment for traumatic brain injury. A larger trial involving multiple clinical sites, 1:1 randomization, and rapid initiation of treatment is warranted.

This study is the product of a remarkable collaboration involving members of 7 departments in 3 professional schools. We are highly indebted to the staff of Grady Memorial Hospital, particularly members of Grady's inpatient pharmacy and the nursing staffs of the hospital's emergency care center, operating rooms, ICUs, and surgical floors. Numerous colleagues played instrumental roles in this effort, including Dan Barrow, MD; Gerry Brown, RPh; Scott Erwood, MD; Elizabeth Ferry, RN; Arlene Greenspan, DrPH, PT; Leon Haley, MD; Vernon Henderson, MD; Candace Howell, MS; Weimen (Bill) Lu, MS; Lisa Mack, MD; Megan B. Mitchell, BA; Tammie Quest, MD; Jonathan Ratcliff, MPH; Patty Springer, RN, MSN; Keith Stowell, MD; and Rick Woodcock, MD. We offer special thanks to Susan Rogers, RPh, and the Emory University Investigational Drug Service for drug compounding and skillful preparation of the drug kits. At several points in the study, we were capably advised by leading figures in the Atlanta community. We also benefited from the advice and suggestions of various members of our data safety monitoring board, including Daniel Hanley, MD, chair; Charles Contant, PhD; Sean Grady, MD; Ronald Hayes, PhD; Harvey Levin, PhD; Emmy Miller, PhD, RN; and our National Institutes of Health program officers, Mary Ellen Michel, PhD; and Scott Janis, PhD. Most of all, we are deeply indebted to the patients who participated in this study and the family members who entrusted us with their care.

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Author contributions: DWW, ALK, VSH, FCG, DWL, DDD, MMW, SWH, MF, and DGS conceived the study and designed the trial. DWW, ALK, VSH, PLC, MF, FCG, JPS, LLD, OAH, DSA, DWL, MMP, DDD, ABG, and SG participated in the clinical trial and obtained research funding. ALK, DWW, and PLC, supervised the conduct of the trial and data collection. DWW, ALK, DWL, DSA, PLC, and MMP undertook recruitment of patients and managed the data, including quality control. DDD provided the pharmacokinetic support for the study, including design and analyses. VSH and ABG provided statistical advice on study design and analyzed the data. DWW and ALK drafted the manuscript, and all authors contributed substantially to its revision. DWW takes responsibility for the paper as a whole.

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Table E1.

Inclusion Criteria	Measure	Rationale
Age ≥ 18	Years of age /Tanner Stage	Administration of sex steroids to children during growth is untested.
Blunt Mechanism only	History of blunt trauma	Anatomical and physiologic differences with penetrating trauma
Moderate to Severe Brain Injury (*i*GCS 4-12)	*Index* Glasgow Coma Score	Group most likely to benefit from treatment
Arrival < 11 hours after Injury	Time from accident	Early administration provides maximum potential benefit

Exclusion Criteria	Measure	Rationale
Non- English speaking	Family History	Current outcomes testing measures are only validated in the English
Penetrating brain injury	Penetrating Trauma	Anatomical and physiologic differences
Non-Survivable Injury	Neurosurgical Assessment	Patients not going to be aggressively managed by the treating team
No neurological activity	*i*Glasgow Coma Score = 3	Death highly likely; treatment benefit doubtful.
Mild TBI	*i*GCS 13-15	Recovery likely without treatment
Unknown time of injury	Injury un-witnessed	Cannot establish time from injury to drug administration
Severe Intoxication (ETOH ≥250 mg%)	Stat ETOH measurement	Significant ETOH intoxication can alter GCS calculations
Spinal Cord Injury with Neuro Deficits	Neurological exam	Spinal cord injury alters rehabilitation potential
Cardiopulmonary Arrest	Clinical exam/CPR	Death highly likely
Status Epilepticus on arrival	Clinical exam	Inability to obtain *index* Glasgow Coma Score
Blood Pressure < 90 systolic – on arrival or for at least 5 minutes prior to enrollment	Clinical exam	Independent confounder of brain injury
Hypoxia on arrival pO2 < 60 – on arrival or for at least 5 minutes prior to enrollment	Clinical exam	Independent confounder of brain injury
Prisoner or Ward of the State	History/Deputy present	Informed consent issues
Pregnant	Stat positive pregnancy test	Drug may be contraindicated in pregnancy
Active breast or reproductive organ cancers**	History, when available	Drug may be contraindicated in active breast cancer and other hormone-sensitive cancers
Known allergy to progesterone, or Intralipid components (egg yolk or peanut oil)****	History, when available	Allergic reactions could complicate treatment

*If age is not available within 90 minutes of injury, enrollment will commence on patients who are determined to be Tanner Stage 5, which corresponds to post-puberty development. If the subject is subsequently found to be less than 18, drug infusion will cease.
**If patients are enrolled that are subsequently found to have, by history or medical record, active breast or reproductive organ cancer, drug infusion will cease. These patients will be followed closely for cancer related complications.
***If a patient is presumptively enrolled and later determined by history to be allergic to progesterone or any of the Intralipid components (egg yolk and peanut oil), the infusion will be stopped and the patient will be closely followed for allergic complications.

Table E2.

Subject Initials: _____ _____ _____ Subject Number: _____ _____ _____ Reviewer Initials:_____ _____ _____ Date: _____/_____/_____

Adverse Event (Possibly due to Progesterone)	Occurrence	Adverse Event#	Serious Adverse Event*
Death	Yes ☐ No ☐	->	**H&P or EEG findings consistent with death**
Brain death	Yes ☐ No ☐	->	**EEG findings consistent with brain death**
Thromboembolic disease (DVT, PE, MI, CVA)	Yes ☐ No ☐	Presence of a DVT**	**Pulmonary Embolism, CVA, MI**
Pulmonary Embolism	Yes ☐ No ☐	->	**High Probability on V/Q or Chest CT**
Increase liver enzyme (hepatitis)	Yes ☐ No ☐	AST 500-999 U/L ALT 500-999 U/L	**AST ≥1000 U/L** **ALT ≥ 1000 U/L**
Cholestatic Jaundice	Yes ☐ No ☐	Total Bilirubin >2.0-4.9 mg/dl	**Total Bilirubin ≥5.0 mg/dl**
Rash or hives	Yes ☐ No ☐	Maculopapular rash	**Anaphylaxis**
Fever	Yes ☐ No ☐	Temperature >38.0° C Recorded 2 hours apart	Oral body temperature >41.0° C Recorded 2 hours apart
Phlebitis at Injection site	Yes ☐ No ☐	Localized erythematous reaction	NA
Hyperglycemia - non DM	Yes ☐ No ☐	Glucose > 200	Glucose > 500 x 2 readings
Intercurrent complications			
Sepsis	Yes ☐ No ☐	Symptoms without positive cultures (tachycardia, hypotension, fever)	Finding on H&P consistent with sepsis (tachycardia, hypotension, fever) and positive blood cultures ½ - ¼.
Pneumonia	Yes ☐ No ☐	Fever > 100.4 + Hypoxemia (pulse ox <92) and Chest X-ray findings– resolves or no prolonged stay	Fever > 100.4 + Hypoxemia (pulse ox <92) and Chest X-ray findings and prolonged ICU or Hospital stay
CNS infection	Yes ☐ No ☐	->	Positive cultures and symptoms of infection
ARDS	Yes ☐ No ☐	Consistent AE‡ consensus criteria of ARDS – resolves or no prolonged stay	Consistent AE‡ consensus criteria of ARDS and prolonged ICU or Hospital stay due to ARDS
Hypoxemia	Yes ☐ No ☐	Oximetry < 90 for 3 min – 1 hr; pO2 < 60	Oximetry < 90 for > 3 min; pO2 < 60 for > 1hr
Hypotension	Yes ☐ No ☐	Systolic Blood Pressure <70-90; > 5min	Systolic Blood Pressure <70; > 5min
Shock	Yes ☐ No ☐	->	Occurrence
Hypertension	Yes ☐ No ☐	Systolic and Diastolic Blood pressure >140/90-200/120 or MAP > 107-150	Systolic and Diastolic Blood pressure >200/120 or MAP > 150
Bradycardia	Yes ☐ No ☐	Heart Rate 40-30 BPM responsive to fluids or atropine	Heart Rate < 30 BPM not responsive to therapy
Tachycardia	Yes ☐ No ☐	Heart Rate >140 BPM without hypotension	Heart Rate >140 BPM with hypotension, not related to sepsis or hypovolemia
Cardiac Arrhythmia	Yes ☐ No ☐	Afib, Aflutter	V-tach, V-fib, Asystole
GI Bleed	Yes ☐ No ☐	Positive evidence for GI bleed with minimal drop in hematocit or BP	Positive evidence for GI bleed with drop in hematocrit > 4 points and/or BP < 70
SIADH	Yes ☐ No ☐	Diagnosis of SIADH & hyponatremia and electrolyte imbalance serum Na > 115	SIADH and severe electrolyte imbalances and osmolar shifts Na < 115 and/or related seizures
Hypothermia	Yes ☐ No ☐	Temperature <96.0-94.0 F Recorded 2 hours apart	Oral body temperature <94.0 F Recorded 2 hours apart
Seizures	Yes ☐ No ☐	New seizure activity	Status Epilepticus

Individual: Stopping Infusion

The criteria for interrupting the study infusion after enrollment in the ProTECT clinical trial are listed below.

- **Evidence of an acute pulmonary embolism, new DVT, myocardial infarction, acute CVA, or other serious thromboembolic event**
  Evidence of an acute anaphylactic reaction
- **Marked increase in liver enzymes (ALT or AST > 1000, Bili > 10) not explained by direct mechanical insult such as the original trauma or surgical intervention.**

Daily Exams (new or unexplained)

Vital Signs: RR >24, O2 Sat <90, Sys BP < 90 or >140, HR >140, Temp >38° C

Physical: lower extremity asymmetry > 1cm; yellow skin (jaundice) or sclera, new rash or hives, phlebitis at the injection site.