Journal of Neurosurgery Imaging and Techniques
JNSIT, 1(2): 38-44
www.scitcentral.com
ISSN: 2473-1943
Original Research: Open Access

Progesterone Versus Placebo in Severe Traumatic Brain Injury: A Randomized Single Blinded Controlled Trial

Khaled Taher[1], Ahmed Hegazy[2*], Safinaz Hassan Osman[3], Ahmed Salah Kamel Abdelwahed[2], Mostafa Zein[2] and Algohary Mohammad Algohary[2]

[1]*Department of Neurosurgery, Al- Haram Hospital, Egypt*

[2]*Department of Neurosurgery, Cairo University, Cairo, Egypt*

[3]*Department of Anesthesia and Intensive Care Medicine, Cairo University, Egypt*

Received January 25, 2016; Accepted April 25, 2016; Published July 1, 2016

ABSTRACT

Traumatic brain injury (TBI) is the leading cause of morbidity and mortality in young adults [1], According to some estimates severe TBI will become the third most common cause of death and disability globally by the year 2020 [2]. In the past five years, many Neuroprotective agents were tested, both in the lab and in clinical settings, to determine which agent would show the best neurological outcome in TBI. In spite of very promising lab results, Progesterone particularly showed confusing clinical results, with some trials showing promising results and others showing disappointing results. The aim of our study is to perform a randomized, controlled, single blinded clinical trial to test the efficacy of progesterone versus placebo in severe TBI.

STUDY GOALS AND OBJECTIVES

The objective of the study is to compare early progesterone administration and placebo in patients with severe TBI with the following specific aims:

1. Compare the baseline GCS on admission and 15 days after initiation of treatment in both arms of the study.
2. Compare the TNF alpha levels at baseline and 15 days after initiation of treatment in both arms of the study.
3. Determine the GOS 15 after initiation of treatment in both arms of the study.

Determine whether there is a statistically significant difference between both study arms at the end of the study.

Study Design

The study is a multicenter, randomized, controlled, single blinded clinical trial.

METHODOLOGY

In the period between March and June 2015 30 patients with severe traumatic brain injury were enrolled in this randomized controlled single blinded multicenter study. The clinical, radiological as well as the laboratory assessments were performed on admission and 15 days after the commencement of treatment.

Subjects

Inclusion criteria

Eligible patients were adults who had severe TBI with a Glasgow coma Scale (GCS) score of 4 to 9. Patients were enrolled in the study, if the treatment could be initiated within 12 hours after injury.

Exclusion criteria

Patients who had sever anoxic brain damage or brain death;

Corresponding author: Ahmed Hegazy, MD, Department of Neurosurgery, Kasr Al-Ainy Medical College, Cairo University, Kasr Al-Ainy Road, 11559, Egypt, Tel: 02-2 233646394; Fax 02-23657104

Citation: Taher K, Hegazy A, Osman SH, Abdelwahed ASK, Zein M, et al. (2016) Progesterone Versus Placebob Severe Traumatic Brain Injury: A Randomized Single Blinded Controlled Trial. J Neurosurg Imaging Techniques, 1(2): 38-44.

history of hormonal therapy before injury; clinically unstable patients (PO2 < 60mmHg, or a systolic blood pressure <90mmHg, or if patients had cardio-pulmonary resuscitation); pregnant and lactating females; or had an associated spinal cord injury, were not included in the study.

Randomization strategy

Patients enrolled in the study were randomized to receive either progesterone or placebo. Randomization was done using a generation of random numbers protocol by the SPSS computer program version 20.0 with closed envelopes with disclosure of the treatment arm after confirming eligibility and exclusion criteria of the patient.

Informed Consent

Patients were enrolled in the study only after obtaining a written informed consent from legally authorized representatives of the patient, who were informed about inclusion in the study but blinded to the arm to which the patient would be allocated.

Study Interventions

Patients, who were assigned to the progesterone arm, were given hydroxyl-progesterone (Cidolut-Depot 250 mg/1ml) at a dose of (1 mg/kg twice daily by an intramuscular route for 5 consecutive days).

Outcome Measures AND Follow-UP

Primary Outcome Measures

The primary outcome measure is the GCS and TNF alpha on admission and 15 days after admission

Secondary Outcome Measures

The secondary outcome is the assessment of the GOS 15 days after admission and on discharge.

Patients, who were discharged from the hospital, were followed up on an outpatient basis. The post discharge follow-up was mainly clinical; however, no further radiological or laboratory investigations were performed unless an unexpected deterioration in the patient's clinical condition took place. Patients, who failed to attend follow up at the outpatient department, were contacted by phone to determine whether any deterioration or death took place. In this study the median follow-up period was 6.7 months.

Sample Size

Initially, 33patients were included in this study. However, the relatives of two patients refused to participate in the study, and one patient was transferred to another hospital.

ANALYSIS AND RESULTS

Sample homogeneity:
Demographic data (age and gender) were studied against both study groups (progesterone and placebo) P = 0.506 and 0.925 respectively (P>0.05). This was done using the (T-test for two independent groups and the Kolmogorov-Smirnov "K.S" test) respectively.

Table 1. Comparison between study and control groups for primary assessment of patients before medical treatment.

Index	Variables in study	Groups	Descriptive		Test statistics	P-value	Comment
			Mean	S.D			
1-	Mean Arterial Bl.p	Control(C)	89.97	17.09	0.803	0.429 (P>0.05)	S = C
		Study (S)	94.19	11.01			
2-	Temperature	Control(C)	37.11	0.50	0.845	0.405 (P>0.05)	S = C
		Study (S)	37.25	0.46			
3-	Pulse	Control(C)	92.60	16.22	0.233	0.817	S = C
		Study (S)	93.93	15.04		(P>0.05)	
4-	Respiratory Rate	Control(C)	24.87	3.42	0.235	0.816	S = C
		Study (S)	24.60	2.75		(P>0.05)	
5-	G.C.S	Control(C)	7.20	1.70	0.409	0.686	S = C
		Study (S)	6.93	1.87		(P>0.05)	
6-	S. TNF alpha	Control(C)	18.60	4.10	0.604	0.552	S = C
		Study (S)	19.80	6.52		(P>0.05)	

The table shows no significant differences between control and study groups, for all variables, before medical treatment, which reflects the homogeneity of the two samples.

Hypotheses

Hypothesis 1

Is to test whether there is a statistical significance between both arms of the study regarding:

a) Glasgow coma scale.

b) Glasgow outcome score.

c) Tumor necrosis factor alpha.

Before and after 15 days of starting progesterone treatment.

H_0:$\mu_0=\mu_1$where μ_0 represents GCS, GOS and TNF alpha before treatment, and $\mu_1$represents GCS, GOS and TNF alpha 15 days after treatment.

Hypothesis 2

Is to determine whether any of the variables in the study has a statistically significant effect on neurological outcome of patients included in the study.

H_0: Pi∉Gi for i=1,2 (1= favorable and 2= non-favorable outcomes). Where P=patients and G=groups.

Efficacy of progesterone group

Table 2. Comparing the results for the progesterone group before and after treatment.

Variables in study	Before (B)		After (A)		Test statistics	P-value	Comment
	Mean	S.D	Mean	S.D			
Mean arterial Bl.p	89.55	10.90	91.21	5.32	0.460	0.660 (P>0.05)	(B = A)
Temperature	37.19	0.36	37.66	0.56	2.596	0.036 (P<0.05)	(B < A)
Pulse	92.38	11.64	87.75	5.15	1.093	0.310 (P>0.05)	(B = A)
Respiratory rate	24.75	2.66	23.38	3.29	1.124	0.298 (P>0.05)	(B = A)
G.C.S	8.13	1.25	11.13	5.03	2.121	0.072 (P<0. 1)	(B < A)
S. TNF alpha	20.75	6.43	16.13	4.88	5.110	0.001 (P<0.01)	(B >A)

The following variables showed the following significant changes in the progesterone group:

1- Temperature: there is a mild increase in average temperature in patients after treatment compared to before treatment, but this remained within the average range.

2- G.C.S: There is a significant improvement in conscious level after treatment.

3- Serum TNF alpha: there is a significant decrease in serum TNF alpha level after treatment.

As regards the other variables, there is no significant difference, between values, before and after treatment.

Comparison between Progesterone and Placebo Groups after Medical Treatment

Table 3a. Comparison between study and control groups for secondary assessment of patients, 14 days after medical treatment

Index	Variables in study	Groups	Descriptive		Test statistics	P-value	Comment
			Mean	S.D			
1-	Mean Arterial Bl.p	Control(C)	89.96	10.24	0.317	0.755	S = C
		Study (S)	91.21	5.32		(P>0.05)	
2-	Temperature	Control(C)	37.68	0.70	0.042	0.967	S = C
		Study (S)	37.66	0.56		(P>0.05)	
3-	Pulse	Control(C)	90.00	7.78	0.717	0.483	S = C
		Study (S)	87.75	5.15		(P>0.05)	
4-	Respiratory rate	Control(C)	24.42	1.93	0.896	0.382	S = C
		Study (S)	23.38	3.29		(P>0.05)	
5-	G.C.S	Control(C)	10.50	4.96	0.275	0.787	S = C
		Study (S)	11.13	5.03		(P>0.05)	
6-	S. TNF alpha	Control(C)	15.50	3.09	0.352	0.729	S = C
		Study (S)	16.13	4.88		(P>0.05)	

The results of the table above show no significant difference between control and study groups, for all variables under assessment, 14 days after treatment.

Table 3b. Regarding ventilation (dummy variable), the following table shows a comparison between study and control groups, which was done 14 days after treatment.

Control (n_0 = 12)		**Study (n_1 = 8)**	
No.	%	No.	%
2	16.7	3	37.5
Test statistics (K.S) = 0.456, Sig = 0.984 (P>0.05)			

The results show no significant difference between both groups, regarding ventilation. Sig = 0.984 (P>0.05)

Tables (3a and 3b) show that, for all variables, there is no statistically significant difference between both groups. Accordingly, progesterone failed to produce a statistically significant improvement in outcome for patients included in this study group.

The Effect of Different Variables on Patient Outcome

The following table shows the most important variables, which have been found to influence the neurological outcome (favorable, and unfavorable), for all patients included in the study. This was done using a stepwise linear binary discriminate function.

Table 4. The result of the binary discriminate function, for the most assessed variables, which have been found to discriminate the patients into one of two groups (favorable and unfavorable).

Z = -4.571 + 0.425 G.C.S (with cut off point = -0.363)
Where if the predicted value is less than (-0.363) then this case belongs to the unfavorable outcome group and vice versa.
Chi-square = 26.392, df = 1, sig. = 0.000 (P<0.01)
Canonical correlation = 0.882, Wilks' Lambda = 0.221

The equation shows that the GCS is the single most important variable resulting in a highly significant discriminate function, where the Chi-square test (P-value <0.01), also with an increased value of Canonical correlation and decreased Wilks' Lambda coefficient.

Table 5. The degree of the prediction for the discriminate function

Predicted values **Actual values**	**Unfavorable**	**Favorable**
Unfavorable	7	1
%	87.5	12.5
Favorable	0	12
%	0	100
Total correctly classified (%)	95.0	

From the above table, it can be found that the ability of the model to predict is excellent, where it succeeded in discriminating 95% of the total observation.

DISCUSSION

Our results indicate no statistically significant difference in GOS or TNF alpha levels (P>0.05) between both groups included in the study.

This shows that, when compared to placebo, progesterone failed to produce a statistically significant improvement in patient outcomes as measured by GOS 14 days after initiation of treatment. This did not change over a median follow up of 6.7 months.

Our results contradict early (published) results [1, 3-5]. In the meantime, they coincide with the results of [6-11].

This discrepancy is created by the fact that the results of early single center studies indicated, that the administration of progesterone in TBI patients was both effective and well tolerated. However, the two most recent, large, phase-III, multicenter, controlled, double-blinded, randomized clinical trials namely, the PROTECT III study and the SYNAPSE study, which enrolled more than 2000 patients, came out with disappointing results, and revealed failure of progesterone to achieve any improvement in the neurological outcome of patients with severe TBI.

The recent poor results of the PROTECT and SYNAPSE trials, for progesterone in TBI, have induced researchers to seek possible causes for the negative outcome, which these two studies have reported. Possible explanatory factors, which have been indicated by researchers include; 1) the patho-physiological complexity of TBI; 2) issues with the quality and clinical relevance of the preclinical animal models; 3) insufficiently sensitive clinical endpoints; and 4) inappropriate clinical trial designs and strategies. Additionally, other factors, which may have contributed to the negative results include: 1) suboptimal doses and treatment durations in the Phase 2 studies; 2) lack of Phase 2B studies to optimize these variables before initiating Phase 3; and 3) the lack of incorporation of the preclinical and Chinese Phase 2 results, into the Phase 3 designs. Given these circumstances and the exceptional potential of progesterone as a TBI therapeutic, recent studies recommend a return to phase 2B trials [12].

Because progesterone has been proven to be safe and well tolerated in all patients with severe TBI, no adverse effects of progesterone administration have appeared in our study. In this study, the I.M route has been used, to avoid an increased risk of phlebitis or thrombo-phlebitis of I.V use, and fortunately no females, where menstrual disturbances may take place, have been included in the study group.

A small number of patients and lack of long term follow limit our study up. Adherence to the strict inclusion criteria and accurate data collection and analysis have resulted in a small number of patients being enrolled. However, the results, presented in the study, coincide with the most recent published series reported in the literature [6, 8, 10].

Although the remarkable potential neuro-protective effects of progesterone, in TBI, stroke, intracranial hemorrhage, epilepsy and other neurological diseases in all age groups, have been proven more than once in preclinical studies [13-30] clinical trials have failed to reproduce the results obtained in the laboratory setting. The causes behind this discrepancy warrant further investigation [9,12]. Also, as multiple pathways are involved in the secondary cascade of TBI, combination of pharmacological therapies targeting various mechanisms may work better than mono-therapy with progesterone alone. As proven in other studies, progesterone was reported to be more effective in treatment of TBI, when administrated with Vitamin D than progesterone given individually [31, 32].

Progesterone with other chemicals such as nicotinamide, magnesium sulphate, and thyrotropin releasing hormone (TRH) was also investigated on animal models of TBI, and better outcome was observed [33, 34].

CONCLUSION

This study failed to show an improvement in neurological outcome for patients with severe TBI, who received progesterone compared to placebo with a median follow up of 6.7 months. However, the small number of patients, the short period of follow- up and the potential remarkable Neuro-protective benefits of progesterone, which have been proven in a laboratory setting, warrant further studies to find out the reason behind this discrepancy.

REFERENCES

1. Wei J, Xiao GM (2013) The neuroprotective effects of progesterone on traumatic brain injury: current status and future prospects. Acta pharmacologica Sinica 34: 1485-1490.

2. Tolias CM, Bullock MR (2004) Critical appraisal of neuroprotection trials in head injury: what have we learned? NeuroRx 1: 71-79.

3. Stein DG (2008) Progesterone exerts neuroprotective effects after brain injury. Brain Res Rev 57: 386-397.

4. Stein DG, Wright DW (2010) Progesterone in the clinical treatment of acute traumatic brain injury. Expert Opin investig Drugs 19: 847-857.

5. Xiao GM, Wei J, Wu ZH, Wang WM, Jiang QZ, et al. (2007) Clinical study on the therapeutic effects and mechanism of progesterone in the treatment for acute severe head injury. Chin J Surg 45: 106-108.

6. Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, et al. (2014) Very early administration of progesterone for acute traumatic brain injury. N Engl J Med 371: 2457-2466.

7. Zeng Y, Zhang Y, Ma J, Xu J (2015) Progesterone for Acute Traumatic Brain Injury: A Systematic Review of Randomized Controlled Trials. PloS one 10: e0140624.

8. Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, et al. (2014) A clinical trial of progesterone for severe traumatic brain injury. N Engl J Med 371: 2467-2476.

9. Schumacher M, Denier C, Oudinet JP, Adams D, Guennoun R (2015) Progesterone neuroprotection: The background of clinical trial failure. J Steroid Biochem Mol Biol.

10. Meyfroidt G, Taccone FS (2015) Another failed attempt of neuroprotection: Progesterone for moderate and severe traumatic brain injury. Minerva anestesiologica.

11. Lin C, He H, Li Z, Liu Y, Chao H, Ji J, et al. (2015) Efficacy of progesterone for moderate to severe traumatic brain injury: a meta-analysis of randomized clinical trials. Sci Rep 5:13442.

12. Howard RB, Sayeed I, Stein D (2015) Suboptimal dosing parameters as possible factors in the negative Phase III clinical trials of progesterone in TBI. J Neurotrauma.

13. Pettus EH, Wright DW, Stein DG, Hoffman SW (2005) Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury. Brain Res 1049: 112-119.

14. De Nicola AF, Gonzalez SL, Labombarda F, Gonzalez Deniselle MC, Garay L, et al. (2006) Progesterone treatment of spinal cord injury: Effects on receptors, neurotrophins, and myelination. J Mol Neurosci 28: 3-15.

15. Djebaili M, Hoffman SW, Stein DG (2004) Allopregnanolone and progesterone decrease cell death and cognitive deficits after a contusion of the rat pre-frontal cortex. Neurosci 123: 349-359.

16. Gonzalez SL, Labombarda F, Gonzalez Deniselle MC, Guennoun R, Schumacher M, et al. (2004) Progesterone up-regulates neuronal brain-derived neurotrophic factor expression in the injured spinal cord. Neurosci 125: 605-614.

17. Guo Q, Sayeed I, Baronne LM, Hoffman SW, Guennoun R, et al. (2006) Progesterone administration modulates AQP4 expression and edema after traumatic brain injury in male rats. Exp Neurol 198: 469-478.

18. He J, Evans CO, Hoffman SW, Oyesiku NM, Stein DG (2004) Progesterone and allopregnanolone reduce inflammatory cytokines after traumatic brain injury. Exp Neurol 189: 404-412.

19. Limmroth V, Lee WS, Moskowitz MA (1996) GABAA-receptor-mediated effects of progesterone, its ring-A-reduced metabolites and synthetic neuroactive steroids on neurogenic oedema in the rat meninges. Br J Pharmacol 117: 99-104.

20. Loane DJ, Faden AI (2010) Neuroprotection for traumatic brain injury: translational challenges and emerging therapeutic strategies. Trends Pharmacol Sci 31: 596-604.

21. Luoma JI, Kelley BG, Mermelstein PG (2011) Progesterone inhibition of voltage-gated calcium channels is a potential neuroprotective mechanism against excitotoxicity. Steroids 76: 845-855.

22. Moorthy K, Sharma D, Basir SF, Baquer NZ (2005) Administration of estradiol and progesterone modulate the activities of antioxidant enzyme and aminotransferases in naturally menopausal rats. Exp Gerontol 40: 295-302.

23. Roof RL, Hall ED (2000) Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. J Neurotrauma 17: 367-388.

24. Roof RL, Hoffman SW, Stein DG (1997) Progesterone protects against lipid peroxidation following traumatic brain injury in rats. Mol Chem Neuropathol 31: 1-11.

25. Schumacher M, Guennoun R, Robert F, Carelli C, Gago N, et al. (2004) Local synthesis and dual actions of progesterone in the nervous system: neuroprotection and myelination. Growth Horm IGF Res 14: S18-S33.

26. Schumacher M, Guennoun R, Stein DG, De Nicola AF (2007) Progesterone: therapeutic opportunities for neuroprotection and myelin repair. Pharmacol Ther 116: 77-106.

27. Schumacher M, Robel P, Baulieu EE (1996) Development and regeneration of the nervous system: a role for neurosteroids. Dev Neurosci 18: 6-21.

28. Smith SS (1991) Progesterone administration attenuates excitatory amino acid responses of cerebellar Purkinje cells. Neurosci 42: 309-320.

29. VanLandingham JW, Cutler SM, Virmani S, Hoffman SW, Covey DF, et al. (2006) The enantiomer of progesterone acts as a molecular neuroprotectant after traumatic brain injury. Neuropharmacol 51: 1078-1085.

30. Wright DW, Bauer ME, Hoffman SW, Stein DG (2001) Serum progesterone levels correlate with decreased cerebral edema after traumatic brain injury in male rats. J Neurotrauma 18: 901-909.

31. Cekic M, Cutler SM, VanLandingham JW, Stein DG (2011) Vitamin D deficiency reduces the benefits of progesterone treatment after brain injury in aged rats. Neurobiol Aging 32: 864-874.

32. Aminmansour B, Nikbakht H, Ghorbani A, Rezvani M, Rahmani P, et al. (2012) Comparison of the administration of progesterone versus progesterone and vitamin D in improvement of outcomes in patients with traumatic brain injury: A randomized clinical trial with placebo group. Adv Biomed Res 1: 58.

33. Peterson TC, Hoane MR, McConomy KS, Farin FM, Bammler TK, et al. (2015) A Combination Therapy of Nicotinamide and Progesterone Improves Functional Recovery following Traumatic Brain Injury. J Neurotrauma 32: 765-779.

34. Uysal N, Baykara B, Kiray M, Cetin F, Aksu I, Dayi A, et al. (2013) Combined treatment with progesterone and magnesium sulfate positively affects traumatic brain injury in immature rats. Tur Neurosurg 23: 129-1237.