Research Article

Effect of Progesterone Therapy in Traumatic Subarachinoid Haemorrhage on Clinical Outcome, Resistive Vasculer Indices of Middle Cerebral Artery Transcranial Doppler and Thromboelastometry. A Promising Layout

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Abstract

Background: Primary outcome was to investigate progesterone actions on cerebral blood flow velocimetry using trans-cranial doppler and on visco-elastic properties of the coagulation and fibrinolytic system by rotational thrombo-elastometry (ROTEM) scanning. Secondary outcomes were tracking mortality rate and length of ICU stay.

Methods: Three hundred thirty two (332) adult patients of both sexes aged 20-65 years, recruited with solo tSAH (no other intra- axial lesions), neuro-critical care. Exclusion criteria included poly-trauma patients (accompanying bone fractures), pre-admission crystalloid infusion > 20 ml/kg, Glasgow coma scale less than 8, red blood cell transfusion during the first 6 hours after admission, history of deep venous thrombosis. Two groups were designed, Control group and Progesterone (PR) group. PR group received 100 mg (2ml) intramuscular seven days once daily from hospital admission, while Control group received intramuscular isotonic saline (2ml) daily for seven days as a placebo. Trans-cranial doppler was performed on admission, two days and seven days post-admission. ROTEM exploited on admission and seven days after admission.

Results: Progesterone ameliorated hyperfibrinolysis by ROTEM scanning without affecting other prameters. Progesterone statistically dampened resistive vascular indices namely pulsatility index (P value =0.001, 0.003) and resistive index (P value=0.001, 0.003) but no effect on mean flow velocity of bilateral middle cerebral artery scanning, Progesterone shortened ICU stay (P value=0.004).

Conclusions: Progesterone can offer neuronal protection in patients with tSAH by impeding over-fibrinolytic activation.

Keywords: Subarachnoid hemorrhage; Neuroprotection; Progesterone; Coagulopathy; Vasospasm; Doppler and neuroprotection

Introduction

Background

Secondary brain insult after tSAH as cerebral ischemia and coagulopathy are considered preventable causes of mortality and poor neurological outcome. Both lesions can leave survivors with permanent infirmity as motor deficits and cognitive dysfunction [1]. The risk of both is primarily related to the severity of the initial hemorrhage [2]. Many drugs used to offer pharmacological neuroprotection but yet no solid evidence to rely on. Examples include but not limited to, aspirin [3], magnesuim [4], erythropoietin [5] and progesterone

can offer neuro-protective effects via pleiotropic pathways. Progesterone decreases cerebral edema, restores blood-brain barrier integrity, reduces the inflammatory response and prevents cellular apoptosis. Trans-cranial Doppler ultrasonography is an operator dependant tool [6] and cannot be a sole tool for assessment of tSAH [7]. In fact, half of patients with progression of traumatic intracranial haemorrhage have been shown to exhibit normal routine coagulation tests. In contrast, ROTEM a point-of-care visco-elastic assay of whole blood, provides a dynamic scanning of coagulation and clot formation, reflecting the contribution of clotting factors, platelets, and red blood cells [8].

Material and methods

Ethical consideration

Based on declaration of Helsinki, This prospective randomized double-blinded single center study was approved by the local ethics committee of the faculty of medicine, institutional review board number was obtained before study ran-over on 21 of April 2020, and was registered on clinical trial (WWW.registry.nl, NCT04426487). Study started on 20 June 2020 till 30 of November 2020.

Setting

Minia university hospital. Trauma center. Neuro-trauma care unit. Floor one.

Design

Three hindered thirty two (332) adult patients of both sexes with solo traumatic tSAH. All candidates passed TRIAGE section before ICU admission, Abdominal ultrasound, Brain CT, Chest CT accomplished in all candidates. Traumatic subarachnoid hemorrhage was diagnosed after brain CT. Candidates with GCS from 9 to 12 were admitted to intermediate care unit with mechanical ventilation stand-by near every candidate, Patients with GCS from 12 to 15 were admitted to ward. Exclusion criteria included poly-trauma patients, GCS less than 8, massive tSAH (higher risk for disseminated coagulopathy), red blood cell transfusion during the first 6 hours after admission, recombinant factor VIIa administered during resuscitation, history of clopidogrel or warfarin use within 10 days of injur, pregnancy. Routine coagulation measures (prothrombin time, partial thromboplastin time) and arterial blood gas analysis were performed concurrently. Severe hypoperfusion was diagnosed by the presence of an arterial base deficit greater than 6mmol/L by arterial blood gas performed daily during study. In the current research, coagulopathy was diagnosed if 2 or more of the following were found (platelets number less than 100,000 per mm3, international normalized ratio >1.3, prolonged activated partial thromboplastin time >36 seconds).

Legality

An informed written consent was obtained from all participant next of kinn.

Randomozation, concealment and material

Computerized randomization using variable block sizes. Opaque sealed envelopes were used for allocation concealment. After a written informed consent, patients were randomized to receive either progesterone (100mg, intramuscular) or sterile saline for one week after admission. Boxes with patient numbers containing unlabeled coded vials were provided for all patients. Saline prepared for injection was in equi-volume with progesterone. Both injectate, progesterone and placebo were similar regarding color, duration of therapy and route of injection. Serum progesterone was checked twice, first immediately before initiating first dose and the second one was taken at one week after therapy. Double blind fashion disputed (neither the radiologist performed scanning nor patient next to kin was aware of patient allocation). Neither of them was aware who was taking progesterone nor who was taking placebo. Participants enrollment and their assignment to intervention tasked by two anesthetics physicians. The statistics physician was responsible for generating the random allocation sequence and assigned participants to interventions. Candidates were assigned in two equal groups, Control group received intramuscular saline (2ml- NaCL0.9%) as a placebo for seven days daily ,while progesterone group (PR group) received intramuscular progesterone (100mg/ 2ml) for seven days daily from admission. Using methodology published in the manufacturer's insert for (ROTEM) 2008 machine, a citrated kaolin-activated device (ROTEM Delta, Instrumental laboratory, Bedford, MA, USA) was performed using 1 ml of whole blood. Sample was automated pipetting. This was performed two hours from admission and one week after admission due to high cost of scanning. A trans-cranial doppler (Sonosite, energy, USA) probe (2 Mega-hert) used to insonate the M1 (first 4 cm of the middle cerebral artery) portion of the middle cerebral artery by means of the trans-temporal approach then pulstality index, resistive index and mean flow velocity values were recorded. Reading taken 2 hours after admission (basal), two days and one week serially. All candidates underwent CT angiography assessment on day of admission and one week later.

Study endpoint

Primary endpoint was observing the effect of intramuscular progesterone on cerebral resistive indices of middle cerebral artery (pulsatality index, resistive index and mean flow velocity) and blood visco-elastic dynamics by rotational thromboelastometry. Secondary endpoint was impact on mortality rate and length of ICU stay.

Statistical analysis

Sample size calculation: Before the study runover, the number of patients required in each group was determined according to data obtained by a Pilot study performed on twenty candidates consented by their next to kin, ten in each

group. In that study, Pilot study reported the mean one week post-traumatic PI level is 1.49 in control group, 0.99 in PR group (SD within each group was 0.1). A sample size of 166 patients in each group was determined to provide 99% power at the level of 5% significance using G Power 3.1 9.2 software.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20.

- Descriptive statistics were done for Parametric quantitative data by mean, standard deviation , while they were done for categorical data by number and percentage.

- Analyses were done for parametric quantitative data between two groups using independent t test between each two groups. Analyses within each group were done for parametric quantitative data using paired sample t test.

- The level of significance was taken at (P value < 0.05).

Results

1-Transcranial Doppler indices:

Pulsitaility index (PI):

There was a statistical significant difference between studied groups at two days and seven days post- admission with (p value =0.001 in both readings) for the Rt side and (0.003 and, 0.004) for the Lt side. There was also a significant difference between the PI values inside (PR) group at two days and seven days compared with basal value on both sides.

There was a significant statistical difference between studied groups at two days and seven days post- admission with (p value <0.001) for the Rt and left sides. There was also a significant difference between the RI values within (PR) group at two days and seven days compared with basal value on both sides.

ICU data

Table 4 showing sequele post-admission regarding improvement of GCS, development of cerebro-vasculer stroke and development of coagulopathy. 144 candidates in PR group exhibit improvement in GCS opposite to 104 population in Control group with significant statistical difference (P value= 0.0001). New cerebro-vascular insufficiency is diagnosed by cerebral angiography in nine cases in PR group and thirty six cases in control group. Hyper-fibrinolysis was diagnosed in 22 populations in PR group and in 62 in control group.

No statistical significant difference between ROTEM readings at admission and one week after.

R time (reflecting clotting factor activity and initial fibrin formation), K (reflecting the interaction of clotting factors,

fibrin, and platelets), α-angle (reflecting the rate of fibrin cross-linking and fibrinogen function), maximum amplitude (the widest amplitude of the TEG tracing, reflecting overall clot strength and platelet function), and LY30 (the percent of clot lysis at 30 min after start of the assay, reflecting fibrinolysis). CI= confidence interval.

R time (reflecting clotting factor activity and initial fibrin formation), K (reflecting the interaction of clotting factors, fibrin, and platelets), α-angle (reflecting the rate of fibrin cross-linking and fibrinogen function), maximum amplitude (the widest amplitude of the TEG tracing, reflecting overall clot strength and platelet function), and LY30 (the percent of clot lysis at 30 min after start of the assay, reflecting fibrinolysis). Statistical significant difference between fibrinogen lysis after 30 minutes (LYS30) after progesterone treatment and with basal value. No statistical significant difference between the rest of ROTEM readings at admission and one week after.

Table 1: PI among studied groups (data expressed as mean±SD)

		progesterone group N=166	Control group N=166	P-value
		Mean ±SD	Mean ±SD	
	Basal	1.17±0.56	1.36±0.64	0.121
RT	Two days	0.77±0.46#	1.41±0.67	<0.001*
	seven days	0.72±0.49#	1.39±0.67	<0.001*
	Basal	1.18±0.6	1.23±0.67	0.147
LT	Two days	0.83±0.56#	1.23±0.74	0.003*
	seven days	0.79±0.47#	1.12±0.63	0.004*

Analysis of quantitative data by independent sample t-test
*: significant difference between two studied groups at <0.05
Analysis of dependent quantitative data by paired sample t-test
#: significant difference from basal value at level of <0.01.

Table 2: Mean flow velocity (MFV) among studied among studied groups (data expressed as mean±SD). There was no significant statistical difference in between or within studied groups by comparing the MFV.

		progesterone group (N=166)	Control group (N=166)	P-value
		Mean ±SD	Mean ±SD	
	Basal	65.5±17.8	61.9±25.3	0.411
RT	Two days	64.7±20.8	61.6±23.5	0.476
	Seven days	65.8±18.7	62.7±20.1	0.43
	Basal	61.8±19.9	65.7±20.2	0.326
LT	Two days	66.3±21.4	62.8±19.5	0.395
	Seven days	64.4±22.2	61.4±20.5	0.482

Analysis of quantitative data by independent sample t-test
*: significant difference between two studied groups at <0.05
Analysis of dependent quantitative data by paired sample t-test
#: significant difference from basal value at level of <0.01.

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Statistical Significant difference was obtained in comparison between two groups regarding length of ICU stay and mortality rate. Population treated with progesterone consumed much less time in ICU (12 ±1.8 days) in comparison with those in control group (18± 2.1 days) with (p value=0.004). Mortality rate is clearly noticeable in control group (22 candidates) rather than progesterone group (6 candidates). No significant difference among two groups regarding age groups and sex.

Table 3: Resistive index among studied groups (data expressed as mean±SD)

		progesterone group (N=166)	Control group (N=166)	P-value
		Mean ±SD	Mean ±SD	
RT	Basal	0.69±0.30	0.79±0.34	0.127
	Two days	0.56±0.26#	0.81±0.33	<0.001*
	Seven days	0.51±0.19#	0.74±0.30	<0.001*
LT	Basal	0.76±0.23	0.67±0.23	0.057
	Two days	0.50±0.21#	0.69±0.27	<0.001*
	Seven days	0.49±0.24#	0.68±0.35	0.003*

Analysis of quantitative data by independent sample t-test
*: significant difference between two studied groups at <0.05
Analysis of dependent quantitative data by paired sample t-test
#: significant difference from basal value at level of <0.01.

Table 4: Showing sequele post-admission regarding improvement of GCS, new insult on brain imaging, development of vasospasm development of coagulopathy.

Significance (P value)	"Control" group	"PR" group	Variable
0.001*	104 (62.6%)	144 (86.7%)	Improvement in GCS
0.25	36 (21.8%)	29 (17.4%)	Cerebral infarction
0.001*	62 (37.4%)	22 (17.4%)	Coagulopathic cases

P value calculated by Chi-square test (<0.05 is considered significant).
*: Significant difference at P value < 0.05 between the two groups.

Table 5: Showing the new intra-axial injury by ROTEM (Control group).

1 Variable (ROTEM on admission)	OR (CI 95%)	P Value
R	1.05 (0.79-1.49)	0.123
K	1.20 (0.52-1.95)	0.245
Alpha angle	0.94 (0.9-1.1)	0.18
Maximum amplitude	0.91 (0.88-0.95)	0.18
LY30	0.82(0.77-1.4)	0.09
2 change in ROTEM (1 week)		
R	1.21 (1.03-1.33)	0.73
K	1.71 (1.42-1.91)	0.632
Alpha angle	0.91 (0.82-1.2)	0.22
Maximun amplitude	0.93 (0.81-1.50)	0.41
LY 30	0.89 (0.79-1.52)	0.312

Analysis of quantitative data by independent sample t-test.
*: significant difference between two studied groups at <0.05

Table 6: Odds for new intra-axial injury in progesterone group.

Variable	OR (CI 95%)	P Value
1-ROTEM on admission.		
R	1.01 (0.73-1.44)	0.12
K	1.28 (0.56-1.90)	0.32
Alpha angle	0.98 (0.92-1.31)	0.32
Maximum amplitude	0.91 (0.84-1.25)	0.51
LY30	0.89 (0.79-0.94)	0.09
2- change in ROTEM (1 week)		
R	1.21(1.18-1.34)	0.22
K	1.71(1.56-1.91)	0.19
Alpha angle	0.98 (0.90-1.44)	0.12
Maximun amplitude	0.99 (0.89-1.5)	0.133
LY 30	1.21 (0.81-1.42)	0.002*

Analysis of quantitative data by independent sample t-test
*: significant difference between two studied groups at <0.05
(inter-group Analysis of dependent quantitative data by paired sample t-test

Table 7: Representing demographic data, duration of ICU stay and mortality rate among studied groups (mean± SD).

Variable	PR group (166)	Control group(166)	P value
ICU stay (days)	12± 1.8	18 ± 2.1	0.004*
Mortality	6(3.6%)	22(12.2%)	0.002*
Age(ys)	41(38-57)	44(39-59)	0.2
sex	M (102-61.4%) - F (64-38.6%)	M (96-57.8%) - F (70-42.2%)	0.39

Analysis of quantitative data by independent sample t-test
*: significant difference between two studied groups at <0.05 (inter-group Analysis of dependent quantitative data by paired sample t-test.
M=male. F=Female.

Declaration of interest

None.

Discussion

Decision to choose tSAH in particular rather than other TBIs presentations was that tSAH occupies 30-40% of all TBI patients presented to our neuro-trauma center besides avoiding risk of inclusion bias of other neuronal injuries with different patho-physiological mechanisms. We preferred to exclude poly-trauma population and massive tSAH as risk of disseminated co-agulopathy is high beside need for frequent blood transfusion and use of anti-fibrinolytic drugs that can falter readings of ROTEM. Large pool population recruited in the current study provided versatility to assess both vascular and hemostatic derangement post-tSAH owing to presence of 3 neuro-ctitical care units in our center with total capacity of 34 beds fully monitored. Vascular impedence and coagulopathy are the points of concern being attributed to new brain insult. Hemostasis includes both normal serum

level and functional inter-balance between co-agulation and fibrinolytic system. Coagulopathy after TBI has been shown to include abnormalities of both coagulation and fibrinolysis. Coagulopathic derangement after tSAH is linked to consumption, dilution of coagulation factors, thromb-athenia and increase in fibrinolysis. The fibrinolytic product D-dimer and fibrinogen degradation products are first detected within minutes of injury [9]. This rapid response raises the concern about the mechanism that brain injury can trigger early hyperfibrinolytic state. Under non traumatic state, Tissue plasminogen activator (tPA) proteolytically activates plasminogen to plasmin, which cleaves and dissolves fibrin polymers. This fibrinolytic process is dynamically slow and local during normal hemostasis because tPA has limited access to fibrin polymers trapped in a platelet clot, yet it is much rapid and systemic in TIBs [10]. Nested randomized studies pointed to the use of antifibrinolytic treatment in significant traumatic intracranial hemorrhage with improved outcomes, if administered soon after injury. Another route for coagulopathy derangement is deliberate hypothermia which is in use to decrease cerebral metabolism- can aggrevate coagulopathy. Thromboplastin that enters the circulation released from astrocytes is incriminated in activation of extrinsic coagulation pathway to produce a fibrin clot, leading to disseminated intravascular coagulopathy and hyperfibrinolysis [11]. Dose choice was based upon a previous randomized controlled trial that used progesterone in traumatic brain injury in a dose 100mg intramuscular for 5 days (Hassan et al., 2017) [12]. In the current research, coagulopathy was diagnosed if 2 or more of the following were found (platelets number less than 100,000 per mm^3, international normalized ratio >1.3, prolonged activated partial thromboplastin time >36 seconds). Hypoperfusion was defined as arterial base deficit >6 mmol/L [13]. All candidates in the current study who experienced coagulopathy showed criteria for hypoperfusion. Our results ran hand by hand with Thomas et al. 2010 [13] who conducted a retrospective analysis of a prospectively collected cohort study recruited 132 patients from June 2005 to December 2007 about the incidence of tissue hypoperfusion in victims of severe traumatic brain injury and to determine the associations and links between hypoperfusion and TBI coagulopathy. They used the same diagnostic protocol in confirming post-TBIs coagulopathy and hypoperfusion as we did. They concluded that hypoperfusion is an independent risk factor for the development of early coagulopathy in patients with isolated TBI. Zhao etal 2019 [14], in a wide spectrum meta-analysis consisting of eight randomized clinical trials hosting 2251 patients searching for both safety and efficacy of injected progesterone on TBIs population. The regimen included 1 mg/kg intramuscular progesterone every 12 hours for five days. Their results are compliant with us regarding candidates with progesterone group had less ICU time, better neurologic outcomes (RR =1.51; P=0.007)

than those who received placebo. Progesterone offered neuroprotection till 3 months after impact [14]. Another conflicting large pool two clinical trials phase-III prospective, multi-center, controlled, double-blind study (the PROTECT III study; the SYNAPSE study) evaluated the effectiveness of an early administration of progesterone in patients with moderate to severe traumatic brain injury (TBI). In the PROTECT III Trial, patients were included if the admission Glasgow Coma Scale (GCS) was within 4-12, whereas the SYNAPSE Trial only included patients with GCS 4-8. In the PROTECT Trial, primary outcome was 6-month favourable neurological outcome (defined using the Glasgow Outcome Scale), while in the SYNAPSE Trial it was the 6-month Glasgow Outcome Scale (GOS). Secondary outcomes, in both studies, included 6-month mortality. The PROTECT trial recruited 882 patients randomized out of the 1140 initially planned; the SYNAPSE trial included 1195 patients. In PROTECT, the proportion of patients with favourable outcome was similar between groups (51% for progesterone vs. 56% for placebo; RR 3.03 [95% CI 1.96-4.66]); in SYNAPSE, no difference in GOS between the progesterone and placebo group was found (OR 0.96 [95% CI 0.77-1.18]). There was no difference in 6-month mortality or any of the other secondary outcomes between groups in the two trials. These results are totally against us which can be defended by inclusion bias (enrolling all patients with head trauma even with extra-neuronal brain injury) can disrupt integrity of these papers in comparison with us handling only traumatic subarachinoid haemorrhage [15]. Another experimental study conducted by Jacob et al. 2008 [16] focused on effect of progesterone on blood coagulability declared that progesterone prevented TBI induced fibrinolysis and hypocagulability. Adult male Sprague - Dawley rats were given bilateral contusions of the medial frontal cortex followed by treatments with PROG (16mg/kg), or vehicle (22.5% hydroxypropyl-β-cyclodextrin). Progesterone generally maintained procoagulant (thrombin, fibrinogen, and coagulation factor XIII). In addition, PROG significantly increased the ratio of tPA bound to neuroserpin, a serine protease inhibitor that can reduce the activity of tPA. Cerebral vasospasm - is a quite common complication that occurs in up to two thirds of patients. Cerebral vasospasm can occur as early as first 24 hours of TBI event but more frequently begins 48 hours after trauma, reaching a peak after 7 days. New brain insult was defined as persistent newly presented motor or sensory deficit or acute decrease of GCS of 2 points or new CT angiography finding. Vascular derangement after TBI - explained by - but not niched to - oxy- hemoglobin and the potent vasoconstrictor- endothelin- in particular, are incriminated to play a key role. The prominent action is attributed to nitric oxide scavenging, direct vasoconstriction, and induction of cytotoxic free oxygen radicals. Activation of protein kinase C, another proposed item, interacts with myosin light chain kinase, nitric oxide, intracellular Ca^{2+},

protein tyrosine kinase, mediating cerebral vasoconstrictions. Since vasospasm is an angiographic phenomena, all population were prone to CT angiography provided that serum creatinine is less than 1mg/dl. In the current study, Progesterone dampened but did not prevent cerebral vasospasm. This may be explained by that prominent interaction of ptn C and myosin light chain interaction that lead to increased cerebrovascular resistant. Our results are compatible with Hassan et al. 2017 regarding progesterone induced shortened neuro-critical ICU stay. They conducted prospective, randomized trial hosting 100 patients with severe TBI. The selected patients were categorized at random into two equal groups - the control group and the progesterone group. In the control group, patients were given conventional therapy. The progesterone group was given 1 mg/kg progesterone by intramuscular injection within 8h of admission and then every 12 hours for 5 consecutive days in addition to the conventional therapy. The neurological outcome after 30 days was evaluated using the Glasgow Outcome Scale score as well as duration of ICU stay. Length of ICU stay had a mean value of 10.88±7.98 days in the progesterone group versus 19.96±10.36 days in the control group (P<0.001). Another supporting material supplied by Nagy et al. 2015 [17] about the use of progesterone alone or in combination with omega3, glutamine and vitamin D3 in moderate to severe traumatic brain injury. Sixty adult patients of both sexes were recruited with moderate or severe TBI [Glasgow coma score (GCS) 4-12)] within 8 hours of impact, were equally randomly assigned to three groups: the control (C) group, which received the standard care and medications according to the guidelines of head trauma protocol; the progesterone (P) group, which received progesterone; and the combination therapy (T) group, which received a half dose of progesterone combined with vitamin D3, ω3 fatty acids, and glutamine. The GCS, ICU and hospital stay, computed tomography findings, mortality rate, and the Glasgow outcome scale (GOS) at 3 months after trauma were recorded and analyzed. They concluded that both progesterone and the combination therapy improved outcome in acute TBI, although progesterone dose was halved in the latter. On the other hand, our results are in contrary with sumit et al. 2017 [18] who conducted a randomized placebo controlled trial, the primary objective of this study was to evaluate the efficacy of progesterone with or without prophylactic hypothermia in acute TBIs patients. It was a prospective, statistician blinded, randomized, and placebo-controlled phase II trial of progesterone with or without hypothermia (factorial design). All adult patients (18-65 years) with acute TBIs (Glasgow coma score of 4-8) and presenting to trauma center within 8 h after injury were included in the trial. The enrollment duration was from January 2012 to October 2014. The primary endpoint was dichotomized Glasgow outcome score (GOS) [poor recovery = GOS 1-3; good recovery = GOS 4-5] and mortality rate at 6 and 12 months follow-up after recruitment.

A total of 107 patients were randomized into four groups (placebo [n = 27], progesterone [n = 26], hypothermia alone [n = 27], and progesterone + hypothermia [n = 27]).The mortality rates were similar in all the groups at 6 and 12 months (P = 0.78 and 0.52 respectively). This discrepancy can be explained by disparity in patient categorization and bias in dose design. Despite the multifactorial benefits of progesterone obtained in the experimental models of TBI and the promising results of two Phase II clinical trials [19,20], two Phase III clinical trials failed to show benefits of progesterone [21,22]. Among the concerns that have been raised and cited: diversity of the enrolled patients concerning sex, age, and severity of TBI; the multiple doses of progesterone used; the lack of stratification of patients; the subjective outcome measures. Limitations addressed in the current paper included variable time for patient arrival from impact site as our hospital is a tertiary center. Strict exclusion criteria forced us to exclude many patients. ROTEM use was costy that limit multi-readings from it.

Conclusion

Progesterone can resist hyper-fibrinolysis after tSAH and impede development on coagulopathy. Mortality and length of ICU stay was also significantly decreased.

Declarations

Ethics approval and consent to participate. Institutional review approval waived on number (625-4-2020).

Availability of data and materials

ALL data supporting results in the current research sent with submission for clarity.

Competing interests

No competing interest

Funding

Authors' information

All authors whose names appear on the submission

1) Made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) Drafted the work or revised it critically for important intellectual content;

3) Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Abbreviations

Blood brain barrier	BBB
Computerized tomography	CT
Interntional normalized ratio	INR
Mean flow velocity	MFV
Pulsatality index	PI
Resisitve index	RI
Subarachinoid haemorrhage	SAH
Intensive care unit	ICU
Institutional review board	IRB
Gamma amino butyric acid	GABA
Glascow coma scale	GCS
Thromboelastogeam	TEG
Traumatic brain injury	TBI
Traumatic intracranial haemorrhage	TICH

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