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Cytoprotective effect and clinical outcome of perioperative progesterone in brain tumors, a randomized microscopically evidence study

Omyma Shehata Mohamed[a], Mohab Mohamad Darwish[b], Marian fathy Gayyed[c], George abdelshaheed Hanna[a], Walid Zeidan Nanous[b] and Mina Maher Raouf[a]

[a]Anesthesia and Intensive Care Unit, Faculty of Medicine, Minia University Hospital, Minia University, Minia, Egypt; [b]Neurosurgery, Faculty of Medicine, Minia University Hospital, Minia University, Minia, Egypt; [c]Histopathology, Faculty of Medicine, Minia University, Minya, Egypt

ABSTRACT

Background and Aims: Although progesterone role on TBI patients and its antitumor activity have been proved, its perioperative use in surgical brain tumors remains unclear. Primary outcome is to investigate any neuroprotective effects of perioperative intramuscular progesterone on the brain's cellular inflammatory and neuro-excitotoxic response to tumor resection evidenced by neuronal cells immunohistochemistry and CT scanning. Secondary outcome is to explore the postoperative clinical course, any related complications, and post craniotomy short-term (3 months) outcome.

Methods: Two hundred fifty-two (252) adult patients, ASA class I-II undergoing elective craniotomy were randomly allocated into two groups: progesterone (PR) and control (C) groups to receive either 1.0 mg/kg progesterone (diluted to a total volume of 2 ml) or 2 ml of isotonic saline daily intramuscular for five days before and after craniotomy.

Results: Histopathological biopsies revealed significant increase the expression of active nuclear PR receptors on oligodendrocytes and astrocytes (P-value = 0.0001), cytoplasmic and nuclear neuro-quiescence endorsed by keeping blood vessel integrity and preventing neutrophilic infiltration and cytoplasmic oedema (P-value = 0.005) in PR group. Follow up CT2 (on the morning of surgery) and CT3 (on the 3rd postoperative day) recorded a significant reduction of brain oedema (P = 0.0001&0.001). Also, significant earlier weaning with shorter ICU stay (P = 0.0001) and better postoperative 3 months outcome (P = 0.001) were demonstrated in progesterone group without any detectable complications.

Conclusion: Perioperative progesterone offered anti-neuroinflammatory and neuroprotective effect and reduced cytoplasmic brain oedema evidenced by histopathological biopsies and CT scanning. Also, it improved postoperative course and 3 months neurological outcome in surgical brain tumors.

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Perioperative progesterone; brain tumors; immunohistochemistry; CT scanning

1. Introduction

Brain tumor can harm brain tissue by two mechanical forces: solid stress and tumor-associated edema [1]. Brain deformation resulted from tumor growth- is-called "mass effect" while the compressive forces exerted by cells and the matrix named solid stress [2]. Cytotoxic oedema around tumor can also add burden on healthy brain tissue around, through tumor secreted vasodilator materials as nitric oxide. No single drug endorsed to provide neuroprotection in such case [3]. Progesterone is considered a natural neurosteroid which can provide neuroprotective effects through pleiotropic pathways. Progesterone induces reduction of cerebral edema and inflammatory response, renovates the blood–brain barrier (BBB), and prevents the occurrence apoptosis and cellular necrosis [1]. Moreover, some studies demonstrated anticancer activity of progesterone, which is associated with its cytotoxic and chemosensitizing effect on different cancer cells [4]. It induced tumor cell death in a dose-dependent manner when was used repeatedly for 3 and 6 days in glioblastoma the most common and aggressive malignant brain tumor. Also, it potentiated the antitumor effect of temozolomide (TMZ) the standard chemotherapeutic agent for human glioblastoma and reduces its side effects [5].

Over the last 3 decades, the therapeutic role of progesterone in patients with TBI has been extensively researched but its potential role in surgical brain injuries (SBI) still not fully investigated although the pathological brain changes caused by surgical brain injury (SBI) are less heterogeneous, thus the response to progesterone may be more consistent [6]. Also, in neurosurgery, electrocautery is considered a standard technique for hemostasis by generating thermal energy, unfortunately, heat dissipation can cause additional brain injury. In experimental study, progesterone could significantly decrease macrophage infiltration and other inflammatory response to electrocautery [7].

CONTACT Omyma Shehata Mohamed Omaima.shehata@mu.edu.eg Anesthesia and Intensive Care Unit, Faculty of Medicine, Minia University Hospital, Minia University, Minia, Egypt

As relatively little researches are available that assess the neuroprotective properties of progesterone in the patients with surgical brain tumors despite of the potential advantages of progesterone described above, the current study aimed to exploit the hypothesis that can progesterone offer perioperative neuroprotection against surgical and tumor induced brain injury in elective craniotomies with the primary outcome is to investigate its effect on the brain's cellular inflammatory and neuro-excitotoxic response to tumor resection evidenced by neuronal cells immunohistochemistry and CT findings.

The secondary outcome was to explore its safety, the postoperative clinical course and short-term outcome 3 months after craniotomy as regards sensory, motor and autonomic functions.

2. Material and methods

Based on the Declaration of Helsinki, this prospective randomized placebo-controlled, double blind single center study was conducted in compliance with the clinical protocol that approved by the local ethics committee of the Faculty of Medicine, Minia University with institutional review board number (623–4/2020) dated in April 2020 and registered on clinical trial (WWW.registry.nl. NCT04414020), detained on 30 of May 2020. The study followed the CONSORT Statement for Reporting Trials (Figure 1) and involved 252 adult (18–60y) male and female patients, ASA I–II, who were undergoing elective craniotomy. Exclusion criteria included patient refusal to participate, emergency craniotomy, those with risk of developing venous thrombo-embolism (previous deep venous thrombosis, systemic lupus or cerebrovascular stroke), morbid obesity, patients with stented coronary arteries, and those giving relevant history of endometrial or ovarian neoplasia. An informed written consent obtained from all participants who were randomly allocated into two equal groups through web-based randomizer (https://www.randomizer.org) using sequential numbered cards. A double-blind fashion disputed (the patients, the surgeon, treating physicians, nursing staff, and the histopathologist were

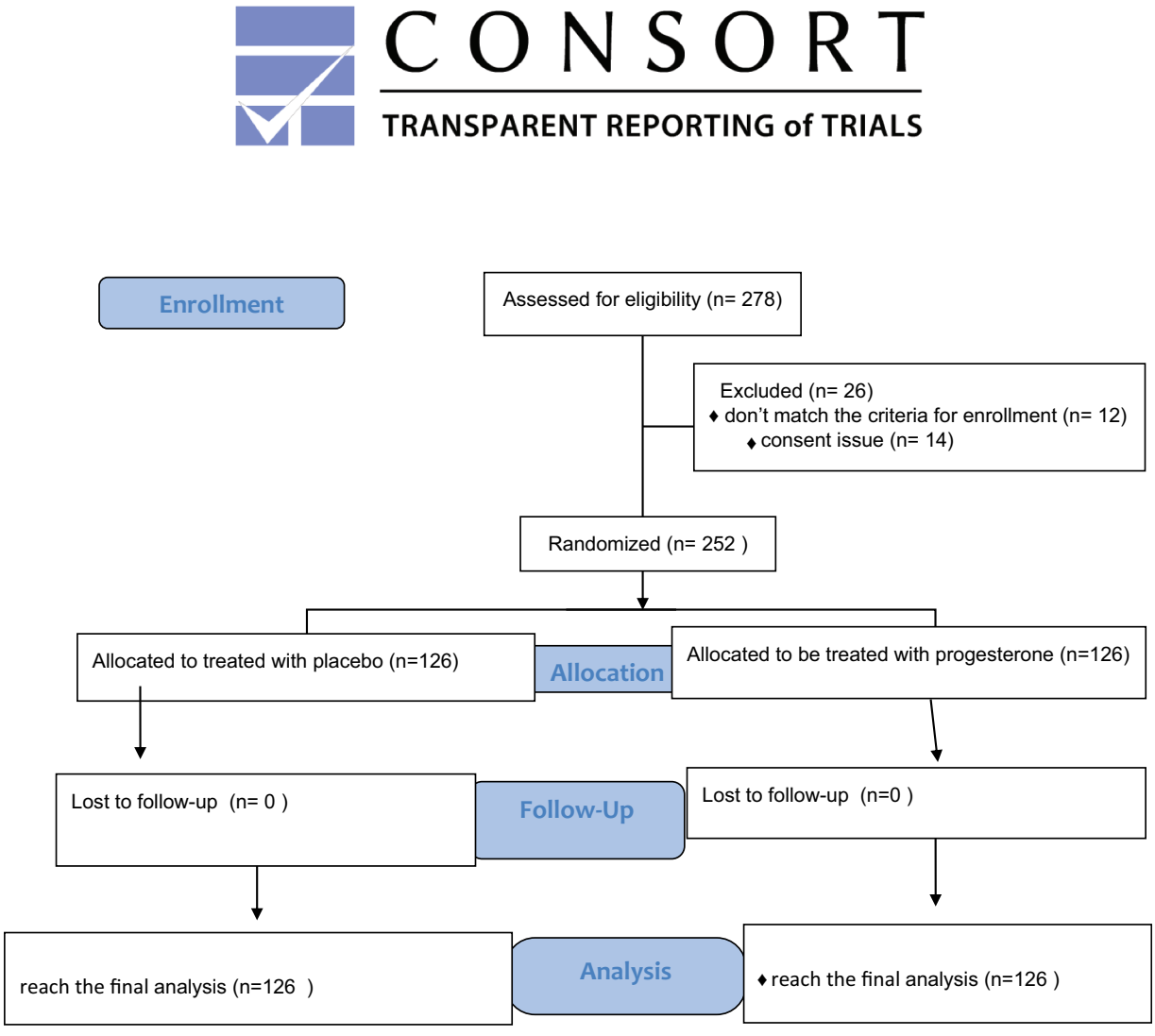


Figure 1. Consort flow chart.

blinded of patient allocation). Data acquisition was tasked by two anesthetic lecturers who were not aware about study design.

Patients in the treatment group received 1.0 mg/kg progesterone (prontogest 100 mg Marcyryl industries, Egypt) (PR group) [8] via intramuscular injection once per 24 hours for 5 consecutive days before and after surgery (total 10 days), while those in the control group (C group) received 2 ml of NaCL0.9% daily intramuscular as a placebo for the same period. Both injectate, progesterone and placebo were prepared and supplied via identical-looking solutions and volumes (by diluting progesterone with sterile water to a total volume of 2 ml) in identical coded syringes.

Participants were fully investigated on hospital admission and data of computerized tomography scan were obtained and considered as a basic (CT_1) for further follow up and comparison. A second brain CT (CT_2) scans were performed immediately preoperative on the morning of surgery and a third brain CT (CT3) scans on the third postoperative day (for early detection and management of any postoperative complications). Additional CT scans were requested according to on clinical condition but only CT1, 2 and 3 were analyzed. Also, we checked the serum progesterone twice, first immediately before initiating the first dose (base) and the second one was checked after therapy.

2.1. Anesthetic management

On arrival to the operating room, monitoring of the patients was accomplished with invasive blood pressure, pulse oximetry (SpO2), end-tidal carbon dioxide ($ETCO_2$), 5 lead electro-cardiogram, temperature probe, train of four and bispectral index (BIS). In both groups, general anesthesia and endotracheal intubation was performed with propofol (1–2 mg/kg) and fentanyl (2 mcg/kg) and neuromuscular blockade by cis-atracurium (0.2 mg/kg). Anesthesia was maintained with sevoflurane (2–4%) and boluses (0.03 mg/kg). of cis-atracurium. The amount of intraoperative blood lost and surgeon satisfaction about the surgical field bleeding, tissue edema and ease of dissection were determined. At completion of the procedure, the patients were transferred intubated, monitored, and ventilated to the postoperative ICU and extubation was permitted according to the patient clinical condition. The patients were followed for the time of extubation, the postoperative course, length of ICU stay, any adverse events, and neurologic evaluation (sensory, motor and autonomic functions) to be re-evaluated 3 months later for short term outcome.

2.2. Surgical biopsy

According to the standard surgical techniques as regard patient positioning, incision, craniotomy, opening of the dura, tumor dissection, hemostasis and closure, the tumors were dissected and excised. With aid of the surgical microscope, the biopsy was taken from several points at the edge of tumor-brain interface using cotton tipped swab and kept in sealed formalin container to be sent to pathologist.

2.3. Histopathology examination

2.3.1. Case selection and tissue sample preparation

Paraffin blocks of the patients' biopsies were collected. H&E slides were prepared to examine histopathological changes as cytoplasmic edema, congestion, necrosis and /or inflammation.

2.3.2. Immunohistochemistry

Serial sections were cut of 4 µm thick on positively charged slides. The slides were de-paraffinized with xylene, rehydrated through graded ethyl alcohol, immersed in 3% hydrogen peroxide for 30 min and rinsed in phosphate buffer solution (PBS). Citrate buffer (pH 6.0) was used for antigen retrieval by the microwave for 10 minutes and left to cool then washed in PBS. Afterwards, rabbit polyclonal anti-PR anti-body (ready to use, Abcam) was incubated overnight at 4°C in humidity chamber. After wash with PBS, streptavidin–biotin complex was added for 30 min. Brownish color developed by using diamino-benzoate (DAB), to be washed in distilled water. Lastly, the slides stained with hematoxylin, dehydrated, cleared by xylene and covered slipped.

2.3.3. Evaluation of immunostaining

Using Allred scoring system [9], we evaluated the intensity score (IS) of nuclear staining as follows: 0 = no positive cells, 1 = mild positivity, 2 = moderate positivity and 3 = strong positivity. The proportion of staining power calculated as the percentage of positive cells: 0 = negative, 1 = 1%, 2 = 2–35%, 3 = 36–65% and 4 = 66–100%. Progesterone immune-expression score was calculated as the algebraic summation of the intensity score of staining and the extent of staining power and finally classified into low (< 3) and high (≥ 3) [9].

3. Statistical analysis

3.1. Sample size calculation

The sample size was determined after a power calculation of data obtained by a pilot study performed on 10 patients, 5 in each group. The study revealed, 1 case with cytoplasmic oedema (20%) in progesterone group, and 4 cases have cytoplasmic degeneration in the control group (80%). By using G Power 3.19.2 software and with Fisher's exact test α of 0.05 significance, 126 patients in each group were required to provide 99% power.

3.2. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20 (Armonk, NY: IBM Corp) and reported as categorical variables using percentages, or continuous variables which compared with ANOVA test and expressed as mean ± SD or median and range. Chi-square and Fisher's exact tests were used to compare categorical variables. Results were considered statistically significant when P-value ≤ 0.05.

4. Results

The patients' demographics, the operative time, the intraoperative blood lose, the tumor type and site were comparable in the two groups (Table 1)

Table 2 shows the brain CT changes with significant difference in the incidence and severity of brain oedema -between the two groups was noticed in CT2, CT3. In PR group, CT2 showed 112 cases (88.8%) had free brain imaging while 14 case (11.2%) had mild peri-lesional brain oedema, in C group there were 94 cases (74.6%) with free brain scanning, 18 case (14.2%) with mild peri-lesional oedema, and 14 cases (11.2%) had moderate diffuse brain oedema, CT3 in PR group exploited an increase in the number of free brain CT to 117 cases (92.8%), only 3 cases (2.5%) have mild marginal oedema and 6 cases (5%) with moderate brain oedema. Control group CT3 brain imaging revealed 96 cases (76 .1%) with free brain imaging, 11 cases (8.7%) with mild peri-lesional brain oedema, and 19 cases (15.2%) declared moderate diffuse brain oedema. Comparing the degree of brain oedema in CT2 and CT3 in each group to the basal CT1, was statically significant in favor of PR group (0.003 vs 0.07) and (0.004 vs 0.08). Also, the incidence of postoperative complications (as hemorrhage, ischemia, or infarction) in CT_3 were significantly lower in PR group.

Table 1. Demographic and operative data.

Variable	PR group (n = 126)	Cgroup (n = 126)	P value
Age (years)	50 ± 12 (38–62)	52 ± 9 (43–61)	0.517
Sex	M. 102 (80.9%). F. 24 (19.1%).	M.92 (73%). F.34 (37%)	0.312 0.261
Operative time (hours)	*3.5 ± 1*	*4 ± 1.5*	0.71
Intraoperative blood loss (ml).	600 ± 350	650. ± 200	0.072
Surgeon satisfaction (median +IQR)	9 8.5–9.5	7 6.5–7.5	0.001*
Tumor type			
1- Meningioma.	64 (50.7%)	59 (46.8%)	0.43
2- Astrocytoma.	27 (21.4%)	32(25.3%)	
3- Ependymoma	14 (11.11%)	19(15.07%)	
4- Schwanoma	15(11.9%)	11(8.7%)	
5-Others	6 (4.7%).	5(3.9%)	
Tumor site			
(1) Frontal lobe	*55 (43.6%)*	*46((36.5%)*	0.36
(2) Parieto-temporal	*24(19.04%)*	*19(15.07%)*	
(3) Post.fossa	*12(9.5%)*	*15(11.9%)*	
(4) Frontoparietal	*18(14.2%)*	*30(23.8%)*	
Occipito-temporal	*17(13.49%)*	*16(12%)*	

Data presented as mean ± standard deviation, numbers (proportion), or median± IQR

**Significance difference in between the two studied groups (p value ≤ 0.05)*

Table 2. Changes in brain computerized tomography.

Variable	PRgroup (126)	C group(126)	P values
CT1 (basal):			
Free (±minimal oedema)	97(71.5%)	90(71.4%)	
Mild oedema	20(15.8%)	19(15.2%)	
Moderate oedema	9(13.3%)	17(13.4%)	
CT2:			
Free(±minimal oedema)	112(88.8%)	94 (74.6%)	0.0001*
Mild oedema	14 (11.2%)	18(14.2%)	
Moderate oedema	0	14(11.2%)	
Pvalue**	0.003**	0.07	
CT3:			
Free(±minimal oedema)	117(92.8%)	96(76.1%)	0.001*
Mild oedema	3 (2.5%)	11(8.7%)	
Moderate oedema	6(4.7%)	19(15.2%)	
Pvalue**	0.004**	0.08	
Other complications:	4 (3.1%) (2 with hemorrhagic area -1 ischemia -1 with small infarction in Broca's area)	12(9.5%) (1with pnuemocephally, -8 with hemorrhage ± ischemia -3 with infarction	0.001*

Data presented as mean ± standard deviation or numbers (proportion), * *Significance difference between the two studied groups (p value ≤ 0.05)*

***Significance difference in incidence of brain oedema between each of CT2 and CT3 when compared to basal CT (CT1) (p value ≤ 0.05) CT1 = Brain CT accomplished before therapy initiation. CT2 = Brain CT accomplished on surgery morning, CT3 = Brain CT accomplished 3 days postoperative.*

4.1. The tissue biopsies & progesterone level

- Examination of the biopsies revealed a significance difference ($P = 0.005$) in favor of PR group (Table 3) as 116 cases (92.1%) were free of any signs of injury, and 10 cases (7.9%) only showed features of hydrophilic degeneration, while C group cytoplasmic injury was obvious as 15 cases (11.9%) had perivascular hemorrhage, 9 cases (7.1%) had severe cytoplasmic oedema, 5 cases (3.9%) had esinophilic infiltration, 12 cases (9.5%) had dense neutrophilic infiltration and 13 cases (10.3%) with hydrophilic degeneration. Figures 2, 3, 4 and 5 demonstrate examples of the examined biopsies in the studied groups (illustrative cases).
- Significant higher intensity score (score >3) and progesterone receptors proportion was recorded in PR group ($P = 0.0001$).
- Regarding the serum progesterone level before or after therapy, it was comparable between the two groups, however significantly higher after therapy level was detected within PR group when compared to the basal one.

Table 3. Changes in tissue biopsies, intensity score and proportion of progesterone receptors and serum progesterone level in both groups.

Variable	PR group (126)	C group (126)	P value
Biopsy:			
Free	116 (92.1%)	72 (57.1%)	0.005*
Perivascular hemorrhage & early necrosis	0	15 (11.9%)	
Severe cytoplasmic oedema	0	9 (7.1%)	
Eosinophilic infiltration	0	5(3.9%)	
Dense neutrophil infiltration	0	12(9.5%)	
Hydrophilic degeneration	10 (7.9%)	13 (10.3%)	
Intensity score and staining proportion	5 ± 1.4	2.5 ± 1.5	0.0001*
Serum progesterone (ng/L). (Before initiating therapy)	0.19 ± 0.1 (0.09–0.29)	0.177 ± 0.09 (0.08–0.26)	0.588
Serum progesterone (ng/L) (After therapy)	0.48 ± 0.15≠ (0.30–0.63)	0.52 ± 0.15 (0.37–0.67)	0.423

Data presented as mean ± standard deviation or numbers (proportion), – *No Significant difference P value ≥0.05*. **Significance difference in between the two studied groups (p value ≤ 0.05)*

≠ *Significance difference within the individual group (p value ≤ 0.05(=0.004)*

Table 4 demonstrates significant earlier extubation time in PR group with 119 case (92.3%) needed < 3 hours to wean from post-craniotomy mechanical ventilation and only seven cases needed more than 3 hours while it was 101 (80.1%) and 25 (19.9%) cases in C group respectively

Also, ICU stay was significantly shorter in PR group (28.6 ± 9.6 hours) in comparison to the control group (56.3 ± 16.5 hours) (P = 0.0001).

The postoperative 3 months outcome was significantly better in PR group (P value = 0.001) as 121 cases (96%) showed free neurological outcome, 5 candidates with either loss light reflex, agraphia, or fluent aphasia. In C group, 103 (81.7%) cases were free, 10 cases developed cerebellar ataxia, 5 cases with loss of light reflex, 6 cases with agraphia and 2 cases with fluent aphasia. No adverse events were detectable after progesterone administration up to 3 months in the trial.

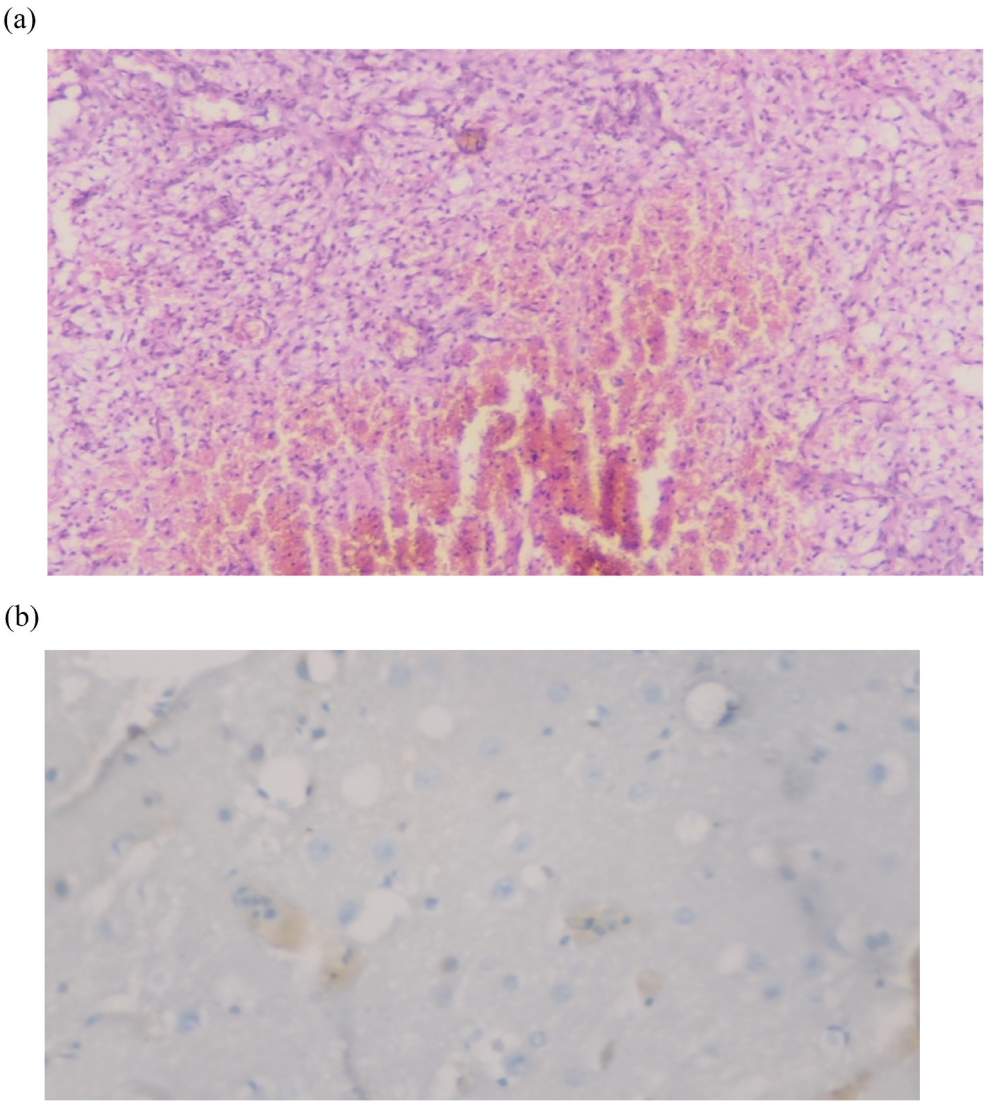
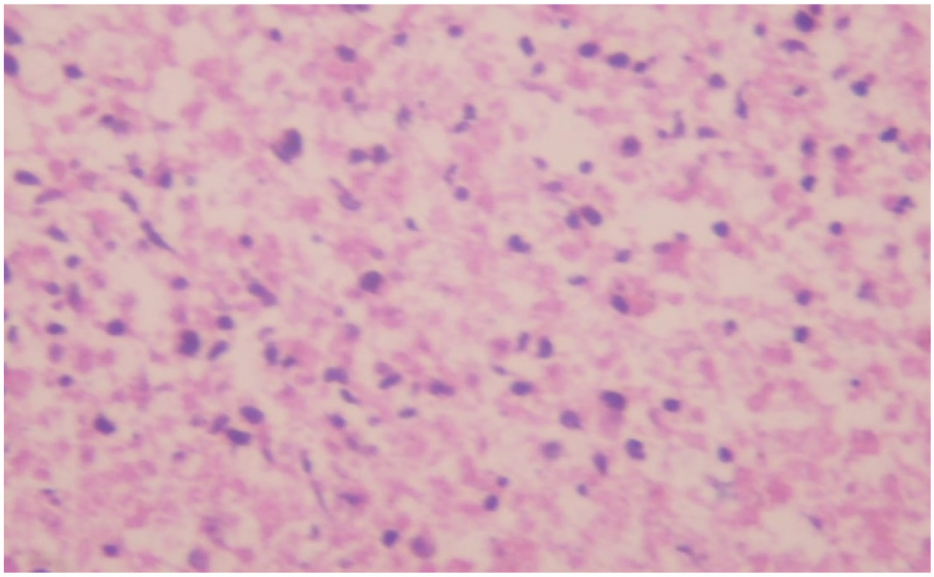


Figure 2. (A): H&E stain biopsy of 44 years male candidate had temporal glioma with cytoplasmic hydrophilic degeneration and cytoplasmic hemorrhage. Follow up brain imaging 72 hours post-operative showed moderate brain oedema. (B): same patient biopsy examined by immunohistochemistry revealing complete absence of PR receptors.

(a)



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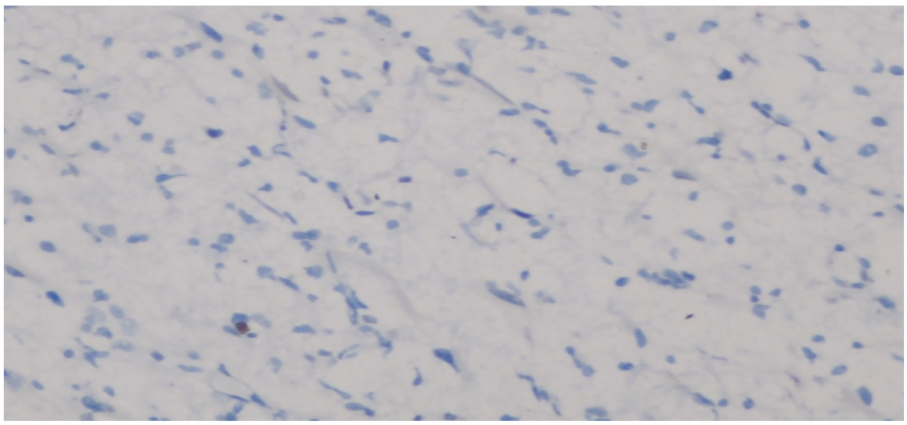

Figure 3. (A): – H&E stain biopsy of 41 years old lady with suprasellar meningioma, showing dense neutrophilic infiltration, shredded cytoplasmic vacuoles. Three months follow up was free. (B): by immuno-histo-chemistry revealing no PR receptors.

5. Discussion

Progesterone is a very versatile pleiotropic agent that is synthesized in the central nervous system (CNS) where it plays many important biological functions [10] thus, besides it is commonly known as a gonadal hormone, it is now also recognized as an important neuroprotective neurosteroid that opens a window to get a potentially safe anti-neuro inflammatory drug that can slow down injury induced inflammation [8]. Many studies have proven the efficacy and the safety of progesterone administration in acute severe TBI patients but relatively low studies that investigated it in case of surgical brain tumors despite the huge number of the daily elective neurosurgical operations worldwide, also theoretically the sequalae of these injuries can be preventable and amendable to pre-emptive treatment.

In the present research, progesterone efficacy and safety were confirmed in patients with surgical brain tumors as our results showed that its administration remarkably decreased perioperative neuronal cell oedema and injury and cytotoxic inflammatory response evidenced by neuronal cells immunohisto-chemistry and CT findings, also it enhanced the post-operative functional recovery presented by earlier weaning of mechanical ventilation and short post-operative ICU stay in addition to improved outcome with no adverse events related to progesterone administration or further late toxicity up to 3 months postoperatively.

Neuronal injury in surgical brain tumors is due to craniotomy and the direct pressure by the tumor itself that hampering the blood supply to the adjoining healthy tissue [11]. Other forms of surgical brain injury (SBI) as lobectomy or evacuation of intracerebral hemorrhage all are considered as a type of brain trauma. Post-operative brain edema that occurs after SBI usually peaks on days 3 to 7 which if severe may cause increase in the intracranial pressure (ICP), impaired cerebral blood flow, neuronal loss or even death. Also, SBI may cause disruption of the barrier (BBB) and release of the inflammatory mediators in

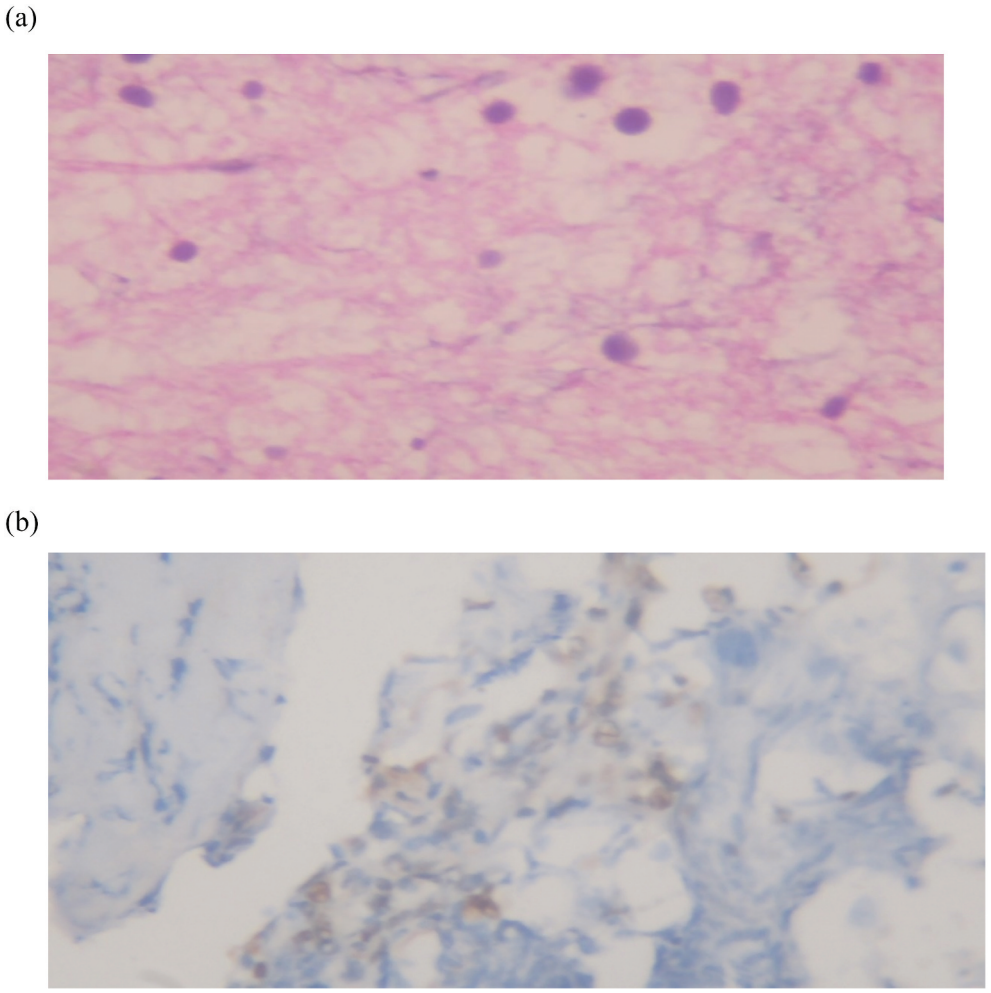

Figure 4. (A) H&E stain biopsy of a male patient in the control (C) group with occipital hemangio-pericytoma shows massive interstial oedema displacing cells from each other. (B) of the same patient by immunohistochemistry shows weak positive PR receptors.

addition to the delayed sensory-motor and cognitive dysfunctions [12]. This may justify why we performed the postoperative follow up on the 3rd postoperative day not on the 5th day with the completion of progesterone therapy for early detection and management of any postoperative complications mostly brain oedema and its sequalae, hemorrhage, ischemia, or infarction without any delay, taking into consideration the patient safety has the priority. As mentioned before other CT scans were performed according to the individual clinical condition but for the purpose of statistical comparison and to avoid repeated radiology exposure or wasting of resources the above-mentioned times of CT were essential for all. The main mechanism in ameliorating surgery induced cerebral injury is maintaining selective controlled BB permeability and the extent of brain edema because of its serious consequences [13,14].

Selection of the route of delivery, the dose and duration of administration of the therapeutic drug is very important that influence the clinical efficacy. In this double-blind trial, 1 mg/kg progesterone diluted with saline to 2 ml, or an equal volume of placebo was administered intramuscular daily for 5 days before and 5 days after surgery for patients with operable brain tumors and safe neuroprotective properties of progesterone in those patients were confirmed. In a wide spectrum meta-analysis, the beneficial neuroprotective effect was recorded in those treated with intramuscular progesterone with lower mortality than the intravenous route and authors could not explain this discrepancy in the efficacies between the two routes [12]. Regarding the dosage, Howard et al., found that doses below 8 mg/kg/day were more effective in humans than the higher one [15]. In addition, postinjury administration of progesterone for 5 days was found to result in a reduction of the behavioral and neuropathological abnormalities in experimental TBI. Also, when administered repeatedly for 3 and 6 days on human glioblastoma cells either alone or in combination with temozolomide, progesterone individually suppressed cell proliferation and reduced its migration and did so more effectively in synergistic manner with temozolomide beside reducing the side effects of the later [5]. In consistent with our research, Xiao et al., used 1.0 mg/kg progesterone initially as a single I.

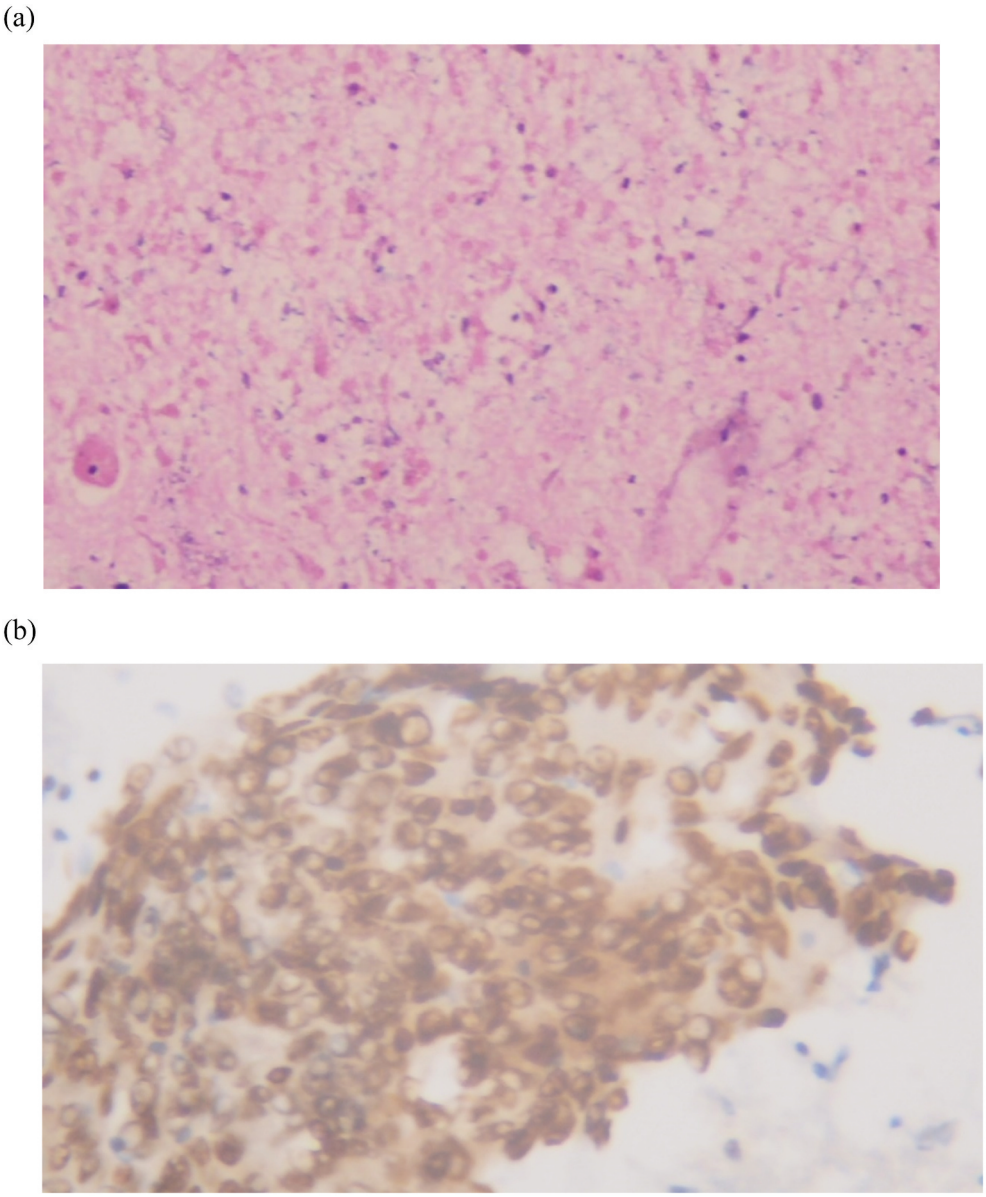

Figure 5. **(A)** H&E stain biopsy of a female patient had astrocytoma with completely normal cytoplasmic architecture and astrocytes arranged adjacent to each other. **(B)**: of the same patient with immuno-histo-chemistry. PR receptors are up regulated and deeply stained.

M. injection and then every 12 hours for 5 successive days. Their results showed that this dose was protective and did not cause any serious side effects [8].

The main aspect highlighted in our study is that progesterone administration for 5 days preoperatively was beneficial not only postoperative but also intraoperative proved by significant higher surgeon satisfaction score (9 vs 7) as it offered better surgical field and brain relaxation (which is the state of the size and firmness of brain tissue) by reducing tumor-induced edema, and lower blood loss even it was not statistically significant. Most important of all the brain CT2 that were performed immediately preoperative and were demonstrative of significant decrease in perilesional oedema in therapeutic (PR) group when compared to their basal CT1 and to the control group with further ongoing significant decrease detected in brain CT3 performed 3 days postoperatively (*p- 0.0001)*.

Also, the biopsies that were obtained from the tumor-brain interface confirmed the above-mentioned beneficial effects of progesterone by showing significant reduction of interstitial oedema, cytoplasmic hydration, congestion and neutrophilic infiltration in PR group compared to C group *(P-0.005)*. This action can be explained by the suppressing effect of progesterone on inflammatory vasodilators and enhancement of the endothelial progenitor cells [16] also its active metabolite has GABA mimetic effect which counteracts excitatory action of glutamate on neuronal injury [17].

When compared with dexamethasone, the advantageous effects of progesterone on the inflammatory responses and brain edema were

Table 4. Extubation time, ICU stay and 3 months neuronal follow up.

Variable	PR group (126)	C group (126)	p- value
Extubation:			
No. of patients extubated within 3 hours	119 (92.3%)	101 (80.1%)	0.0001*
No. of patients extubated within More than 3 hours	7 (7.7%)	25 (19.9%)	
ICU stay (hours)	28.6 ± 9.6 (19–38.2)	56.3 ± 16.5 (39.8–72.8)	0.0001*
Postoperative 3 months examination:			
Free	121 (96.0%)	103 (81.7%)	0.001*
Lacunar infarction	0	0	
Cerebellar ataxia	0	10 (7.9%)	
Others (loss of light reflex, agraphia & fluent aphasia)	5 (4%)	13 (10.4%)	

Data presented as mean ± standard deviation or numbers (proportion), –No Significant difference *P* value ≥0.05. * *Significance difference in between the two studied groups (p value ≤ 0.05)*

significantly higher as demonstrated in an experimental trial performed by Xu et al., 2014 following a partial frontal lobectomy that mimics brain tumor excision [18].

The current study recognized upregulation of nuclear receptors for progesterone with enhanced intensity and proportion of staining uptake in participants treated by progesterone (PR group) presented by high significant difference in the score (*p*-0.0001) and better postoperative course (earlier weaning and shorter ICU stay). Progesterone has multiple widely distributed receptors in the brain and through activation of tow common pathways (genomic and non-genomic) may exert its neuroprotective actions [19]. In the genomic pathway, progesterone binds to its intracellular receptor (PR) and activate a transcription factor which in turn regulate the gene expression. Meanwhile, through the non-genomic route progesterone exerts an activating effect on G protein (mPRs) [20]. **T**he antitumor effect of progesterone has been proven to be produced **by** restoring the proliferative balance, the ability for apoptosis, and increasing the drugs chemosensitivity [4].

In conclusion, the current study detected the effective role of progesterone usage as a perioperative neuroprotective therapy in neurosurgical brain tumors without any serious side effects or any obvious manifestations of hormone reaction. Accordingly, progesterone can be anticipated to have a great therapeutic potential as a protective agent in surgical brain tumors as it is available, inexpensive, and safe within the range of 3 months postoperative follow up, however, this must be noted as a study limitation and long track record of its safety needs be researched.

Another limitation is that our research is a single center study which if performed on multicenter scale can provide further valuable data.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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