MICRONIZED PROGESTERONE AS A NEUROPROTECTOR IN PREGNANT WOMEN WITH POST-TRAUMA BRAIN SYNDROME

Irina Vasilivna Tsyganenko, Vasil Vasilyovich Simrok, Katerina Sergiivna Ruban

Lugansk State Medical University, Ukraine

ABSTRACT

The present article is concerned with the study of glial fibrillary acidic protein (GFAP) level in the blood serum of pregnant women with post–trauma brain injury syndrome (post-TBI syndrome) as the marker of hematoencephalic barrier status and predictor of obstetric and perinatal complications development.

UDC CODE & KEYWORDS

■ UDC: 617 ■ Pregnancy ■ Post–trauma brain syndrome ■ Hematoencephalic barrier ■ Glial fibrillar acidic protein

INTRODUCTION

It is known that central nervous system plays the most important role in maintenance and normal functioning of all systems and organs in human's organism, including pregnancy. Cipolla et al. (2011) writes diseases of central nervous system can be the reason of many maternal and fetal complications during pregnancy period.

Algattas et al. (2014) writes post–trauma brain injury syndrome (post-TBI syndrome) or post coma syndrome develops after brain trauma, which nowa-days takes 50% of all traumas. Statistically there is a progressive tendency as for brain traumas every year, what in most cases connected with car accidents (Daugaard et al., 2013). In last 10-15 years, according to dates of World Health Organization, there is brain traumas accidents growth up to 2% per year (Theadom et al., 2014). Simultaneously with the growth of brain traumas, connected with car accidents, there is a progressive growth of female drivers and as a result increased frequency of occurrence of post-TBI syndrome in women (Paul et al., 2013). During pregnancy there takes place progredience of post-TBI syndrome such as progression of neurologic symptoms, psychic and vascular dysfunction even after several years of stable compensation (Coelho, 2007). Such a progression is mostly connected with a dysfunction in permeability of hematoencephalic barrier and exhaustion of compensatory mechanisms, which maintain normal function of pregnant organism (Gao et al., 2011).

Liddelow (2011) writes hematoencephalic barrier includes endotheliocytes of brain vessels, astrocytes and pericytes (adventitial cells). Astrocytes and endotheliocytes are in close relationship one to each other – astrocytes produce substances, which influence on permeability of hematoencephalic barrier (Yang et al., 2013). The main function of astrocytes is to supply brain cells with cholesterol and maintenance of the necessary concentration of electrolytes. It is known that astrocytes are more sensitive to the influence of hypoxia. In stressful conditions they produce glial fibrillar acidic protein (GFAP), which can be an indicator of pathology in hematoencephalic system (Wang et al., 2008).

Modern scientific investigations pay a lot of attention to neuropeptides and their role in stabilization of hematoencephalic barrier and reparation processes in brain in the case of acute and chronic post-TBI syndrome (Gonzalez-Rey et al., 2010). It is proved that neropeptides positively influence on neuropsychic condition of pregnant woman which is based on their possibility to penetrate through hematoencephalic barrier and cause neuroprotective, anxyolitic, sedative, spasmolytic action, which are very necessary to pregnant woman's organism. If nervous system of pregnant woman is not in a physiologic inhibition condition it can't provide complete physiologic rest to a fetus, especially in case of brain trauma in a mother (Melcangi et al., 2011).

Among all neuropeptides the main attention is paid to the progesterone, as a major pregnant hormone. The presence of low molecule peptide in progesterone structure allows easy penetration through hematoencephalic barrier to reach directly nervous cells (Deutsch et al., 2013).

Progesterone is not only necessary to maintain normal pregnancy; it is also very important in development and protection of fetal brain especially in second and third trimester. Progesterone metabolizes into alopregnanolone, which increase resistance of fetal brain to the hypoxia, which develops in feto-placental insufficiency and preeclampsia (Giatti et al., 2012).

Analyses of the literature for the resent 5 years showed that there are no sufficient investigations concerning to pregnancy condition in women with Post-TBI syndrome: how can brain trauma influence on development of pregnancy and perinatal pathology, connected with abnormal function of hematoencephalic barrier (Kuvacheva et al., 2013). So, we decided to investigate the condition of hematoencephalic barrier in pregnant women with post-TBI syndrome in order to forecast and prevent obstetric and perinatal complications and to improve neuropsychic condition of pregnant women.

The aim of our work is to analyze the condition of hematoencephalic barrier in pregnant women with Post-TBI syndrome and check the effectiveness of usage of micronized progesterone as a neuroprotector for stabilization of hematoencephalic barrier and prophylaxes of fetal-placental insufficiency, preeclampsia and normalization of neuropsychic condition of pregnant women.

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Methods of investigation

We investigated 69 pregnant women who had in anamnesis Post-TBI syndrome. They were randomized into 2 groups: the main group (n = 36) and the group of compare (n = 33). Control group (n = 31) – healthy pregnant women. All women in both groups had normal level of progesterone in blood and moderate to high risk of development of fetal-placental insufficiency and preeclampsia. They received 75 mg of aspirin per day from 20 weeks up to labor for prophylaxes of preeclampsia (according to Ukrainian health organization protocol №417, proved on 15.07.2011). The main group additionally received micronized progesterone – Utrogestan 200 mg per day from 24 weeks up to labor as a neuroprotector.

The criteria of effectiveness were:

- The level of GFAP in plasma level of pregnant women as a marker of condition of hematoencephalic barrier before and after treatment.
- Nero-psychic testing with the help of Clinical Global Impression Scale (CGI) before and after treatment.
- Analyses of obstetric and perinatal complications in all groups after treatment.

Results and discussion

Concentration of GFAP in plasma level of pregnant women in different gestational age mustn't be higher then 4.0 ng/ml.

Table 1 : Concentration of GFAP in plasma level of pregnant women in different gestational age

Groups	Concentration of GFAP in plasma level of pregnant women, ng/ml					
	12 weeks	16 weeks	24 weeks	28 weeks	32 weeks	37 weeks
Main n=36	4.62±0.07	4.63±0.06	4.82±0.08#	4.81±0.06#	4.84±0.07#	4.85±0.06#
Compare n=33	4.59±0.09	4.62±0.06	4.84±0.07	4.97±0.08	5.07±0.08	5.03±0.07
Control n=31	3.29±0.08*	3.31±0.09*	3.32±0.09*	3.32±0.11*	3.29±0.09*	3.36±0.11*
Note: * - (P<0.05) between the main group, group of compare and control group; # – (P<0.05) between the main group and group of compare.						

Source: Authors

As you can see in a table 1, there is statistically reliable increase of concentration of GFAP in plasma level in women with Post –TBI syndrome correspondently to healthy pregnant women (P<0.05). It is also noticed that in the main group concentration of GFAP after 24 weeks of gestation was not enlarged in comparison to compare group, which can indicate positive influence of micronized progesterone on hematoencephalic barrier condition.

The general clinical condition of women included investigation of symptoms of such syndromes: insomniac, asthenic-vegetative, neuro-circulatory syndrome, migraine and psycho-emotional disturbance. The dynamics of improvement of clinical condition was tested with the help of Clinical Global Impression Scale.

Table 2 : Dynamics of general clinical condition of investigated women

Treatment result	The main group, n (%)	The group of compare, n (%)
Worsening	0 (0%)	4 (12.12%)
No dynamics	10 (27.78%)	19 (57.58%)
Moderate improvement	15 (41.67%)*	7 (21.21%)
Expressed improvement	11 (30.55%)*	3 (9.09%)
Complete regress of symptoms	0 (0%)	0 (%)

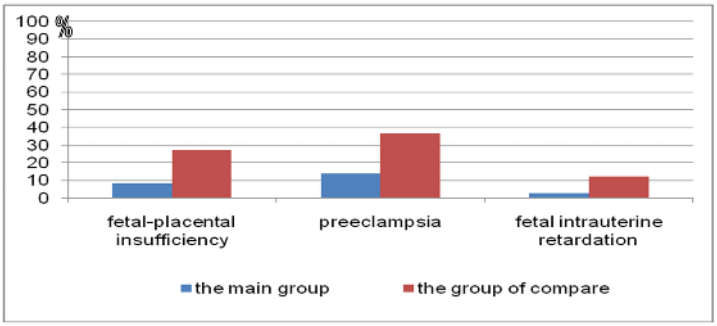
Source: Authors

As it is seen in the table 2, there is an improvement of general clinical condition in the main group in 72.22% of pregnant women, in the compare group improvement of general clinical condition appeared only in 30.03% of women.

Analyses of pregnancy showed that in compare group, where patients didn't get micronized progesterone, complications of pregnancy and labor developed more often. So, fetal-placental insufficiency in compare group developed in 3.54 times more often, preeclampsia – in 2.8 times and fetal intrauterine retardation development – in 3.21 times more often then in the main group. Cesarean section in 2.2 times higher, which was connected with progression of hypertension and worsening of neurologic status.

We also analyzed the condition of neonates and their possibility to adapt to extrauterine life. There are such signs of deadaptation: depression of tone and movement activity, tremor of extremities, regurgitation and local cyanosis of nasolabial triangular. These signs we met more rarely in the main group (8.3%) in comparison to the group of compare (24.2%). In the control group such deadaptation signs were registered in 3.2% cases. Moreover, signs of deadaptation in newborns from the main group disappeared on 5-6 day after labor and all the babies were discharged from labor house in satisfactory condition. In the compare group only 12.5 % were discharged from hospital on 5-6 day, 87.5% demanded additional correction of adaptative processes.

Figure 1: Characteristic of the main complications of pregnancy and labor in the main group and group of compare



Source: Authors

Conclusion

The results of our investigation are proving the effectiveness of usage of mi-cronized progesterone for prophylaxes and correction of obstetric and perinatal complications in patients with Post TBI syndrome. This effect is based on neuroprotective influence on mother's and fetus's nervous system – stabilization of hematoencephalic barrier and improvement of neuro-psychic condition, what prevents progression of Post-TBI syndrome during pregnancy and development of obstetric and perinatal complications.

REFERENCES

1. Algattas, H., Huang, J. (2014, January).Traumatic Brain Injury Pathophysi-ology and Treatments: Early, Intermediate, and Late Phases Post-Injury [Article]. Int J Mol Sci. doi: 10.3390/ijms15010309. http://www.mdpi.com/1422-0067/15/1/309

2. Cipolla, M., Sweet, J., Chan, S. (2011, February). Cerebral vascular adaptation to pregnancy and its role in the neurological complications of eclampsia [Article]. J Appl Physiol (1985); 110(2): 329–339. doi: 10.1152/japplphysiol.01159.2010 http://jap.physiology.org/content/110/2/329

3. Coelho, C. (2007, May). Management of discourse deficits following traumatic brain injury: progress, caveats, and needs [Article]. Semin Speech Lang.;28(2):122-35.

4. Daugaard, M., Nielsen, L. (2013, December). Specialised early rehabilitation of brain injury performed in an intensive care setting [Article]. Ugeskr Laeger. 9;175(50):3101-3104.

5. Deutsch, E., Espinoza, T., Atif , F., Woodall, E., Kaylor, J., Wright, D. (2013, September). Progesterone's role in neuroprotection, a review of the evidence. J Mol Endocrinol. 10;49(3):R125-34. Gao, X., Chen, J. (2011, March). Mild Traumatic Brain Injury Results in Extensive Neuronal Degeneration in the Cerebral Cortex [Article] . J. Neuropathol. Exp. Neurol.; 70(3): 183–191.

6. Giatti, S., Boraso, M., Melcangi, R., Viviani, B. (2012, October). Neuroactive steroids, their metabolites, and neuroinflammation [Article]. J Mol Endocrinol. 10;49(3):R125-34. doi: 10.1530/JME-12-0127. http://jme.endocrinology-journals.org/content/49/3/R125

7. Gonzalez-Rey, E., Ganea, D., Delgado, M. (2010, August). Neuropeptides: Keeping The Balance Between Pathogen Immunity and Immune Tolerance. Curr Opin Pharmacol [Article]. Curr Opin Pharmacol.; 10(4): 473–481. doi: 10.1016/j.coph.2010.03.003 http://www.sciencedirect.com/science/article/pii/S1471489210000342

8. Kuvacheva, N., Salmina, A., Komleva, Y., Malinovskaya, N., Morgun, A., Pozhilenkova, E., Zamai, G., Yauzina, N., Petrova, M. (2013). Permeability of the hematoencephalic barrier in normalcy, brain development pathology and neurodegeneration [Article]. Zh. Nevrol. Psikhiatr. Im S. S. Korsakova.;113(4):80-5.

9. Liddelow, S. (2011). Fluids and barriers of the CNS: a historical viewpoint [Article].2011;8:2.doi:10.1186/2045-8118-8-2 http://www.fluidsbarrierscns.com/content/8/1/2

10. Melcangi, R., Panzica, G., Garcia-Segura, L. (2011, September). Neuroactive steroids: focus on human brain [Article]. Neuroscience. 15;191:1-5. Paul, E., Rosenberg, M., Keyser, D. et al. (2013). Patient Characterization Protocols for Psychophysiological Studies of Traumatic Brain Injury and Post-TBI Psychiatric Disorders [Article]. Front Neurol. 2013; 4: 91. doi: 10.3389/fneur.2013.00091 http://journal.frontiersin.org/Journal/10.3389/fneur.2013.00091/full

11. Theadom, A., Starkey, N., Dowell, T., Hume, P., Kahan, M., McPherson, K., Feigin, V., BIONIC Research Group (2014, February). Sports-related brain injury in the general population: An epidemiological study [Article]. J Sci Med Sport. 9. pii: S1440-2440(14)00029-2. doi: 10.1016/j.jsams.2014.02.001.

12. Wang, D., Bordey, A. (2008, December).The Astrocyte Odyssey. Prog Neurobiol; 86(4):342–367.doi:10.1016/j.pneurobio.2008.09.015 http://www.sciencedirect.com/science/article/pii/S030100820800110X

13. Yang, Y., Higashimori, H., Morel, L. (2013, August). Developmental maturation of astrocytes and pathogenesis of neurodevelopmental disorders (Review). Journal of Neurodevelopmental Disorders. doi:10.1186/1866-1955-5-22 http://www.jneurodevdisorders.com/content/5/1/22