THE CORRELATION BETWEEN CHANGING ESTROGEN AND PROGESTERONE LEVELS AND BLOOD GLUTAMATE LEVELS DURING NORMAL PREGNANCY

Honore N Shiyntum1, Michael Dubilet2, Olena Severynovska2, Matthew Boyko2, Ruslan Kuts1, Israel Melamed1, Dmitry Frank1, Dmitry Natanel1, Alexander Zlotnik1

1Department of Biophysics and Biochemistry, Oles' Honchar National University, Gagarin avenue 72, Dnipro 49010, Ukraine.
2Department of Anesthesiology and Critical Care, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel.

3Department of Physiology, Faculty of Biology, Ecology and Medicine, Oles' Honchar National University, Gagarin avenue 72, Dnipro 49010, Ukraine.

4Department of Neurosurgery, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel.

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1Department of Biophysics and Biochemistry, Oles' Honchar National University, Gagarin avenue 72, Dnipro 49010, Ukraine.
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3Department of Physiology, Faculty of Biology, Ecology and Medicine, Oles' Honchar National University, Gagarin avenue 72, Dnipro 49010, Ukraine.

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While strong correlations between blood and brain glutamate levels have been established by several investigators [7, 19], other researchers have been quick to point out that reduced blood glutamate levels provided neuroprotection [3, 18, 26-28]. We showed in our previous investigation that blood glutamate levels in male rats decreased when injected with E; we injected these rats with Premarin (a mixture of different estrogens), which resulted in a significant, long-term decrease in blood glutamate levels, correlating with a better neurological outcome [29]. There are suggestions that the glutamate-related mechanism serves as the route for the neuroprotective properties of E and P [2, 9]. E and P could reportedly also decrease the human blood glutamate levels, while there is evidence that levels of glutamate are significantly lower in healthy females of the human population [30]. Also, there is proof that blood glutamate levels correlate inversely with plasma E and P levels in ovulating women during menstruation [25].

Our investigation aimed to investigate the impact of changing E and P levels on blood glutamate levels during normal pregnancy. Fluctuating plasma E and P levels are predictable during normal pregnancy, with the overall levels of both hormones E and P highly elevated in pregnant women relative to their non-pregnant counterparts [21].

We expected that increasing blood glutamate concentrations would reach maximum levels during the first trimester of pregnancy, which coincided with minimal E and P plasma levels. We also anticipated that blood glutamate levels would slowly decrease with increasing plasma E and P levels. We deemed it essential to investigate the possibility of high levels of E and P typically seen during pregnancy impacting blood glutamate levels through a comparable mechanism to that engineering the fluctuation of glutamate during ovulation. Contrary to fluctuating E and P levels noted during the menstrual cycle, E and P levels are known to increase and are usually more pronounced during pregnancy. Our curiosity to this effect was to tell if higher E and P levels during pregnancy affect blood glutamate levels as is the case with lower E and P levels during ovulation. We measured levels of glutamate-pyruvate transaminase (GPT), glutamate-oxaloacetate transaminase (GOT), and glucose to determine their involvement in the possible glutamate-reducing abilities of E and P [24, 28].

Materials and Methods

Soroka University Medical Center, Beer Sheva, Israel was the site of our investigation, which was ratified by the Institutional Review Board. We received written and signed informed consent from each participant before the research, with 116 healthy pregnant women taking part in the study. The benchmark for exclusion included under 18 years candidates, known fetal anomalies, maternal co-morbidities, such as pregnancy-induced hypertension (or pre-eclampsia), renal or hepatic failure, chronic steroid treatment, estrogen or progesterone treatment, anemia (Hb < 12 g/dl), diabetes mellitus, or women with certain metabolic disorders.

Following their stages of gestation, we partitioned the women into 3 groups. First-trimester women (from 6 to 14 weeks) enrolled from candidates seeking elective termination of their pregnancies occupied group 1. Group 2 consisted of second-trimester women (14 + 1/7 weeks until 28 weeks) enrolled from candidates seeking elective clinical examinations, such as an ultrasound test. Group 3 was made up of third-trimester women (28 + 1/7 until 42 weeks) drafted from candidates who had pathological fetal presentations, macrosomia, or previous cesarean sections and were seeking elective clinical examinations or elective cesarean sections.

Single samples of venous blood (10 ml, via the antecubital vein) were drawn from the women and subjected to analyses for estrogen, progesterone, glutamate, GPT, and GOT levels. A blood glucose monitoring device, “glucocheck sensor” (Roche, Germany) helped evaluate blood glucose levels immediately after drawing blood from patients. Portions of the collected blood were centrifuged, and the serum analyzed to assess plasma GOT and GPT levels using the fluorescent method and Olympus AU 2700 Assay (Minnesota, USA).

To determine plasma E and P levels, blood samples were again subjected to centrifugation, with the resulting serum analyzed immediately or stored in a freezer at -80°C till it was evaluated with an ADVIA Centaur Estradiol/Progesterone Assay (Bayer, NY, USA), whose principle is based on competitive immunoassay; this allows measurement, by a direct chemiluminescent technology, of the highly specific antibodies produced. For the evaluation of blood glutamate levels, we added an identical volume of ice-cold 1M perchloric acid (PCA) to whole blood (200 µl aliquot) and then centrifuged at 10000 x g for 10 min at 4°C, deproteinizing it. The resulting pellet was then washed away, leaving the supernatant, whose pH was subsequently adjusted to 7.2 with the use of 2M KCO₃; some amounts of the supernatant was stored at -80°C in case later analyses were required. We then applied Graham and Aprison’s fluorometric method [8] to quantify the levels of glutamate as follows: we added a PCA supernatant aliquot (20 µl) to a mix of 0.3 M glycine, 0.25 M hydrazine hydrate buffer (480 µl) and 1N H SO₄ and 15 U of glutamate dehydrogenase in 0.2 mM NAD that adjusted the pH to 8.6. The mixture was then incubated, and after a 30-45 min incubation at room temperature, we measured the fluorescence at 460 nm, with 350 nm the excitation mark. The concentrations of glutamate used for the glutamate standard curve were between 0 and 6 µM. Every measure carried out was duplicated.

For statistical analysis, we used the SPSS 17 package (SPSS Inc., Chicago, USA). We used the two-tailed t-test for equality of means and Levene’s Test for Equality of Variances to compare glutamate, glucose, GOT, and GPT levels between various groups. p<0.05 was considered significant and p<0.001 highly substantial. The presentation of data is means ± SEM.

Results

Our research included 116 pregnant women in all: 43 of the pregnancies were first-trimester, 43 were third-trimester, and only 30 were second-trimester because we found it hard enrolling healthy pregnant women during this trimester. Figure 1 contains changes in the level of blood glutamate during all three trimesters of pregnancy. Blood glutamate levels in second-trimester pregnancies decreased significantly (98.3 ± 6 µM/L) in comparison to those in first-trimester pregnancies (167 ± 13 µM/L) (P<0.0001). Blood glutamate levels in third-trimester pregnancies were at comparable levels to those in second-trimester pregnancies (88.9 ± 8 µM/L) but were substantially lower than those in first-trimester pregnancies (P<0.0001).

Figure 2 is a representation of Blood E and P levels. Plasma E levels increased significantly in second-trimester pregnant women (8158 ± 1030 pg/mL) in comparison to the levels in first-trimester pregnant women (1780 ± 190 pg/mL) (P<0.0001). Plasma E levels rose further in third-trimester pregnant women, reaching 20735 ± 1620 pg/mL (P<0.0001). Similar changing patterns were observed with regards to P levels, with significant increases noted in second-trimester pregnant women (65 ± 5 ng/mL) when compared to levels in first-trimester pregnant women (23 ± 2 ng/mL) (P<0.0001). As
with plasma E levels, quantities of Plasma P increased further in third-trimester pregnant women, reaching 200 ± 14 ng/mL (P<0.0001).

Table 1 displays values for blood glucose, plasma GOT, and plasma GPT during all three trimesters of pregnancy. The levels of blood glucose or GOT stayed constant for the entirety of pregnancies and were comparative among all groups. GPT levels did stay constant during trimesters one and two but diminished significantly by the third pregnancy trimester in comparison to first-trimester levels (P=0.01).

Table 1

| Trimester | 1      | 2      | 3      |
|-----------|--------|--------|--------|
| Glucose (mg/dL) | 86 ± 2 | 89 ± 4 | 80 ± 2 |
| GOT (IU/L)     | 21 ± 1 | 20 ± 1 | 20 ± 1 |
| GPT (IU/L)     | 19 ± 2 | 14 ± 1 | 12 ± 1* |

Discussion

Our main finding showed that an inverse correlation exists between increasing E and P levels during advanced stage pregnancies and the blood glutamate levels of the pregnant women. Increasing E and P levels in second-trimester pregnancies were involved with significant decreasing blood glutamate levels, even though the continuing rise in E and P levels in third-trimester pregnant women did not trigger further substantial reductions in blood glutamate levels.

Another primary outcome of our research was the fact that reduced blood glutamate levels were not a sign of rising blood GOT or GPT levels. This finding suggests that if increasing E and P levels can lower blood glutamate amounts, the phenomenon does not include oxaloacetate- and pyruvate-driven GOT and GPT, respectively, converting glutamate to 2-ketoglutarate (inactive form).

E and P reportedly act as great neuroprotectors in several neurodegenerative disorders [14]. An E treatment [9] and pre-treatment [1, 9] of a middle cerebral artery occlusion (MCAO)-induced neurological damage has been shown to lessen the injury. Furthermore, the occurrence of Alzheimer’s disease in postmenopausal women reportedly is diminished by E-replacement therapy [11]. According to one finding, E can also delay the onset of clonic seizures caused by kainic acid and cut deaths related to seizures in rats [22]. Still, another finding reports P as neuroprotective during an ischemic stroke [1] and TBI in rats [23].

Despite the continuous assertion that E and P can and serve as neuroprotectors, no elucidation of the exact mechanism of how this assertion works had been forthcoming. Well demonstrated, though, is the fact that glutamate is involved in synthesizing and producing hormones like gonadotropin-releasing hormone (GnRH) [15] and E through hypothalamic neuron-bound precursors of cholesterol [2] upon exposure of in-vitro hypothalamus to glutamate. Increased levels of E subsequently triggers a feedback-engineered down-regulation of concomitant raised plasma glutamate levels in the brain. E and P may, therefore, have an essential role in auto-regulating glutamate levels in the brain and blood.

Very little is known to date with regards to the effects of sex differences on the levels of glutamate. Reports have it that levels of blood glutamate are in women lower than those in men among healthy individuals [30], supported by Stover and Kemp斯基’s investigation, which showed that male patients had higher glutamate levels than their female counterparts, while also establishing baseline glutamate levels in female patients after they were all given isoflurane during neurosurgical procedure [17]. Despite not performing this procedure in the present study, our finding is consistent with claims that decreasing levels of blood glutamate are capable of stimulating neuroprotection in women. We also demonstrated recently that naïve and TBI male rats that received E via performing this procedure in the present study, our finding is consistent with claims that decreasing levels of blood glutamate are capable of stimulating neuroprotection in women. We also demonstrated recently that naïve and TBI male rats that received E via...
on the levels of glutamate in the blood. Increased P levels have, in the past, been shown to cause a decrease in the levels of glutamate in the blood in a dose-response mode likened to a bell-shape, with this impact also noted to die down at both higher and lower concentrations [16]. This explanation could be given to account for why glutamate reduction in the blood during third-trimester pregnancies was not as significant as it was during the second trimester. Hence, it would be of some assistance taking into consideration our finding when deciding on the suitable theoretical E and P doses for treatment as discoveries of new therapeutic modalities are put forward for the improvement of neurological outcomes in the event of an acute neurological attack.

The maintenance of GOT and GPT at constant levels for the entire pregnancy period suggested the existence of a different E and P-mediated blood glutamate reducing mechanism from the one that ensures that glutamate is converted to its inactive form. This result affirms interpretations made by previous investigators that women have lower blood glutamate, GOT, and GPT levels than men [30], and the levels of GOT and GPT stay unchanged for the entirety of the menstrual cycle [25] and at different pregnancy stages [20].

Given that GOT and GPT are scavengers of blood glutamate, it would be anticipated that elevated levels in women are required to ensure lower blood glutamate levels. The thought of women having both diminished blood glutamate levels and reduced GOT and GPT levels would, thus, sound contradictory. Our observation may, hence, only be attributed to E or P impacting female glutamate levels via an independent GOT/GPT-scavenging mechanism. In this scenario, a lesser amount of GOT or GPT would be sufficient to trigger the conversion of the diminished glutamate levels to inactive forms. Another justification for our observation may also lie in the fact that E and P are capable of playing roles in the rise of plasma oxaloacetate and pyruvate levels that operate as GOT and GPT co-enzymes, respectively. If so, then the equation for the Michaelis-Menten enzyme rate would predict lower GOT and GPT levels necessary for the conversion of equal amounts of glutamate to 2-ketoglutarate, which would ensure sustainability of lower blood glutamate levels [26, 28].

The one major drawback of our research would be our measuring of glutamate levels only in the blood and not in the brain, which would have been a benediction of our previous investigation in rats, where we revealed that there is a strong correlation between low levels of glutamate in the blood and low levels of glutamate in the ECF of the brain [7, 19]. However, there is also a correlation between levels of low blood glutamate and an improved neurological outcome post-TBI as reported in the past [26-28]. In this regard, we elected to go for a less invasive approach to measure glutamate levels, which is in the blood, instead of the overly intrusive brain ECF-related evaluation. Our theory, therefore, based on our findings, stipulates that the blood glutamate-reducing hormones, E and P, could also cause brain glutamate reductions. Nevertheless, additional studies are required to back this concept.

The second drawback to our research would be the need for establishing a direct association between E, P, and glutamate levels and its impact on neurological outcomes post-acute brain attacks. To that effect, more in-depth studies are needed. Furthermore, we are still to decipher the precise mechanisms for the mediation of blood glutamate reduction by E and P. Nuances notwithstanding, we were able to provide useful insights into the impactful role E and P occupy during blood glutamate reduction, which is a significant step to understanding the blood glutamate-regulating physiological mechanisms and could aid in the establishment of new therapeutic modalities that seek to better neurological outcomes post-acute neurological attacks.

ЛІТЕРАТУРА
1. Neuroprotective effects of female gonadotropin steroids in reproductively senescent female rats. / N.J. Alkayed [et al.] // Stroke. – 2000. – Vol. 31(1). – P. 161-168.
2. Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. / D.W. Brann [et al.] // Steroids. – 2007. – Vol. 72(S). – P. 381-405.
3. Blood levels of glutamate oxaloacetate transaminase are more strongly associated with good outcome in acute ischemic stroke than glutamate pyruvate transaminase levels. / F. Campos [et al.] // Clin Sci (Lond). – 2011. – Vol. 121(1). – P. 11-17.
4. Neuroprotective action of amino acids and their relation to infarct size and neurological deficit in ischemic stroke. / I. Castillo [et al.] // Stroke. – 1996. – Vol. 27(6). – P. 1060-1065.
5. Increased glutamate in CSF and plasma of patients with HIV dementia. / C. Ferrarese [et al.] // Neurology. – 2001. – Vol. 57(4). – P. 671-675.
6. Differential regulation of NMDAR1 mRNA and protein by estradiol in the rat hippocampus. / A.H. Gazziar [et al.] // J Neurosci. – 1996. – Vol. 16(21). – P. 6830-6838.
7. Blood-mediated scavenging of cerebrospinal fluid glutamate. / M. Gottlieb [et al.] // J Neurochem. – 2003. – Vol. 87(1). – P. 119-126.
8. Fluorometric determination of aspartate, glutamate, and gamma-aminobutyrate in nerve tissue using enzymic methods. / L.T. Graham [et al.] // Anal Biochem. – 1966. – Vol. 15(3). – P. 487-497.
9. Neuroprotective effects of estrogen: potential mechanisms of action. / P.S. Green [et al.] // Lnt J Dev Neurosci. – 2000. – Vol. 18(4-5). – P. 347-358.
10. Effects of estrogen on glutamate uptake in cultured human astrocytes derived from cortex of Alzheimer’s disease patients. / Z. Liang [et al.] // J Neurochem. – 2002. – Vol. 80(5). – P. 807-814.
11. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. / W.A. Rocca [et al.] // Neurology. – 2007. – Vol. 69(1). – P. 1074-1083.
12. Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. / R.L. Roof [et al.] // J Neurotrauma. – 2000. – Vol. 17(5). – P. 367-388.
13. CSF and plasma amino acid levels in motor neuron disease: elevation of CSF glutamate in a subset of patients. / P.L. Shaw [et al.] // Neurodegeneration. – 1995. – Vol. 4(2). – P. 209-216.
14. Estrogen use and early onset Alzheimer’s disease: a population-based study. / A.I. Slooter [et al.] // J Neurol Neurosurg Psychiatry. – 1999. – Vol. 67(6). – P. 779-781.
15. Different responses of gonadotropin-releasing hormone (GnRH) release to glutamate receptor agonists during aging. / M.A. Sortino [et al.] // Brain Res Bull. – 1996. – Vol. 41(6). – P. 359-362.
16. Progesterone exerts neuroprotective effects after brain injury. / D.G. Stein // Brain Res Rev. – 2008. – Vol. 57(2). – P. 386-397.
17. Anesthesia increases circulating glutamate in neurosurgical patients. / J.F. Stover, O.S. Kempski // Acta Neurochir (Wien). – 2005. – Vol. 147(8). – P. 847-853.
18. From the liver to the brain across the blood-brain barrier. / V.I. Teichberg // Proc Natl Acad Sci U S A. – 2007. – Vol. 104(18). – P. 7315-7316.
19. Homeostasis of glutamate in brain fluids: an accelerated brain-to-blood efflux of excess glutamate is produced by blood glutamate scavenging and offers protection from neuroapthologies. / V.I. Teichberg [et al.] // Neuroscience. – 2009. – Vol. 158(1). – P. 301-308.
20. Accuracy of liver function tests for predicting adverse maternal and fetal outcomes in women with preeclampsia: a systematic review. / S. Thangaratinam [et al.] // Acta Obset Gynecol Scand. – 2011. – Vol. 90(6). – P. 574-585.
21. Plasma human chorionic gonadotropin, estrone, estradiol, estriol, progesterone, and 17 alpha-hydroxyprogesterone in human pregnancy. 3. Early normal pregnancy. / D.Tulchinsky, C.J. Hobel // Am J Obset Gynecol. – 1973. – Vol. 117(7). – P. 894-893.
22. Neuroprotective effects of estrogens on hippocampal cells in adult female rats after status epilepticus. / V. Veliskova [et al.] // Epilepsia. – 2000. – Vol. 41, Suppl 6. – P. 30-33.
23. Serum progesterone levels correlate with decreased cerebral edema after traumatic brain injury in male rats. / D.W. Wright [et al.] // J Neurotrauma. – 2001. – Vol. 18(9). – P. 901-909.
24. The Effects of Insulin, Glucagon, Glutamate, and Glucose Infusion on Blood Glutamate and Plasma Glucose Levels in Naive Rats. / A. Zlotnik [et al.] // J Neurosurg Anesthesiol. – 2011.
25. The Effects of Estrogen and Progesterone on Blood Glutamate Levels: Evidence from Changes of Blood Glutamate Levels During the Menstrual Cycle in Women. / A. Zlotnik [et al.] // Biol Reprod. – 2010. – P. 2010.
26. The neuroprotective effects of oxaloacetate in closed head injury in rats is mediated by its blood glutamate scavenging activity. / V. Veliskova [et al.] // J Neurosurg Anesthesiol. – 2007. – Vol. 20(3). – P. 235-241.
27. The contribution of the blood glutamate scavenging activity of pyruvate to its neuroprotective properties in a rat model of closed head injury. / A. Zlotnik [et al.] // Neurochem Res. – 2007. – Vol. 18(9). – P. 901-909.
28. Brain neuroprotection by scavenging blood glutamate. / A. Zlotnik [et al.] // Exp Neurol. – 2007. – Vol. 203(1). – P. 213-220.
29. Effect of estrogens on blood glutamate levels in relation to neurological outcome after TBI in male rats. / A. Zlotnik [et al.] // Intensive Care Medicine. In press.
30. Determination of factors affecting glutamate concentrations in the whole blood of healthy human volunteers. / A. Zlotnik [et al.] // J Neurosurg Anesthesiol. – 2011. – Vol. 23(1). – P. 45-49.

REFERENCES
1. Alkayed NJ, Murphy SJ, Traystman RJ, Hurn PD, Miller VM. Neuroprotective effects of female gonadal steroids in reproductively senescent female rats. Stroke. 2000 Jan;31(1):161-8.
2. Brann DW, Dhanapani K, Wakade C, Mahesh VB, Khan MM. Neurotrophic and neuroprotective actions of estrogens: basic mechanisms and clinical implications. Steroids. 2007 May;72(5):481-405.
3. Campos F, Rodriguez-Vazquez M, Castellanos M, Arias S, Perez-Mato M, Sobrino T, et al. Blood levels of glutamate oxaloacetate transaminase are more strongly associated with good outcome in acute ischaemic stroke than glutamate pyruvate transaminase levels. Clin Sci (Lond). 2011 Jul;121(1):11-7.
4. Castillo J, Davalos A, Naveiro J, Noya M. Neuroexcitatory amino acids and their relation to infarct size and neurological deficit in ischemic stroke. Stroke. 1996 Jun;27(6):1060-5.
5. Ferranese C, Aliprandi A, Tremolizzo L, Stanzani L, De Micheli A, Dolara A, et al. Increased glutamate in CSF and plasma of patients with HIV dementia. Neurology. 2001 Aug;57(4):671-5.
6. Gazzaley AH, Weiland NG, McEwen BS, Morrison JH. Differential regulation of NMDAR1 mRNA and protein by estradiol in the rat hippocampus. J Neurosci. 1996 Nov 1;16(21):6830-8.
7. Gottlieb M, Wang Y, Teichberg VI. Blood-mediated scavenging of cerebrospinal fluid glutamate. J Neurochem. 2003 Oct;87(1):119-26.
8. Graham LT, Jr, Aprison MH. Fluorometric determination of aspartate, glutamate, and gamma-amino butyrate in nerve tissue using enzymic methods. Anal Biochem. 1966 Jun;15(3):487-97.
9. Green PS, Simpkins JW. Neuroprotective effects of estrogens: potential mechanisms of action. Int J Dev Neurosci. 2000 Jul-Aug;18(4-5):347-58.
10. Liang Z, Valla J, Sefidvash-Hockley S, Rogers J, Li R. Effects of estrogen treatment on glutamate uptake in cultured human astrocytes derived from cortex of Alzheimer’s disease patients. J Neurochem. 2002 Mar;80(5):807-14.
11. Rocca WA, Bower H, Marangarone DM, Alhskgov E, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 2007 Sep;11;69(11):1074-83.
12. Roof RL, Hall ED. Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. J Neurotrauma. 2000 May;17(5):367-88.
13. Shaw PJ, Forrest V, Ince PG, Richardson JF, Wastell HJ. CSF and plasma amino acid levels in motor neuron disease: elevation of CSF glutamate in a subset of patients. Neurodegeneration. 1995 Jun;4(2):19-26.
14. Slooter AJ, Bronzova J, Witteman JC, Van Broekhoven C, Hofman A, van Duijn CM. Estrogen use and early onset Alzheimer’s disease: a population-based study. J Neurol Neurosurg Psychiatry. 1999 Dec;67(6):779-81.
15. Sortino MA, Alleppo G, Scapagnini U, Canpoli PL. Different responses of gonadotropin-releasing hormone (GnRH) release to glutamate receptor agonists during aging. Brain Res Bull. 1996;41(6):359-62.
16. Stein DG. Progesterone exerts neuroprotective effects after brain injury. Brain Res Rev. 2008 Mar;57(2):386-97.
17. Stover JF, Kempski OS. Anesthesia increases circulating glutamate in neurosurgical patients. Acta Neurochir. 2005 Aug;147(8):847-53.
18. Teichberg VI. From the liver to the brain across the blood-brain barrier. Prog Natl Acad Sci U S A. 2007 May 1;104(18):7315-6.
19. Teichberg VI, Cohen-Kashi-Malina K, Cooper I, Zlotnik A. Homeostasis of glutamate in brain fluids: an accelerated brain-to-blood efflux of excess glutamate is produced by blood glutamate scavenging and offers protection from neuropsychopathologies. Neuroscience. 2009 Jan 12;158(1):301-8.
20. Thangaratinam S, Koopmans CM, Iengar S, Zamora J, Ismail KM, Mol BW, et al. Accuracy of liver function tests for predicting adverse maternal and fetal outcomes in women with preeclampsia: a systematic review. Acta Obset Gynecol Scand. 2011 Jun;90(6):574-85.
21. Tulchinsky D, Hobel CJ. Plasma human chorionic gonadotropin, estrone, estradiol, estriol, progesterone, and 17 alpha-hydroxyprogesterone in human pregnancy. 3. Early normal pregnancy. Am J Obset Gynecol. 1973 Dec 1;117(7):894-93.
22. Veliskova J, Velisek L, Galanopoulou AS, Sperber EF. Neuroprotective effects of estrogens on hippocampal cells in adult female rats after status epilepticus. Epilepsia. 2000;41 Suppl 6:630-5.
23. Wright DW, Bauer ME, Hoffman SW, Stein DG. Serum progesterone levels correlate with decreased cerebral edema after traumatic brain injury in male rats. J Neurotrauma. 2001 Sep;18(9):901-9.
24. Zlotnik A, Gruenbaum BF, Klin Y, Gruenbaum SE, Ohayon S, Sheiner E, et al. The Effects of Insulin, Glucagon, Glutamate, and Glucose Infusion on Blood Glutamate and Plasma Glucose Levels in Naive Rats. J Neurosurg Anesthesiol. 2011 Aug 10.
25. Zlotnik A, Gruenbaum BF, Mohar B, Kuts R, Gruenbaum SE, Ohayon S, et al. The Effects of Estrogen and Progesterone on Blood Glutamate Levels: Evidence from Changes of Blood Glutamate Levels During the Menstrual Cycle in Women. Biol Reprod. 2010 Oct 27;2010.
PREVENTION OF SYSTEMIC INFLAMMATORY RESPONSE DURING LONG-STANDING CARDIOPULMONARY BYPASS IN PATIENTS WITH COMORBIDITIES

Vladimir Chagirev, Mikhail Rubtsov, Giorgiy Edzhibiya, Valeriya Komkova, Georgiy Plotnikov, Dmitriy Shukevich

A.V.Vishnevsky National medical research center of surgery, Moscow, Russia. Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russia.

Meta. To evaluate the effectiveness of preventive strategies to prevent systemic inflammatory response in the period of long-term use of extracorporeal circulation (ECC) in patients with comorbidities.

Materials and methods. Prospective randomized clinical study, which included 60 male patients with expected duration of ECC > 120 min due to comorbidities. Inclusion criteria: patients with ischemic heart disease and/or valve disease with atrial fibrillation and comorbidities (chronic pyelonephritis, chronic obstructive lung disease, diabetes), which require ASHK and/or valve surgery, and procedures “Maze”. Patients who underwent urgent surgery were excluded from the study.

A standard anesthetic protocol was used. Cardioplegia was achieved using Custodiol solution. The study included 3 groups: 1st group (control, n = 20), included patients with standard duration of ECC, 2nd group (n = 20), that underwent perfusion with high volume hemofiltration and polyanionic buffer solution throughout the duration of ECC, 3rd group (n = 20) – ASHK with PMMA-gemodialfiltration and polimethylmetakrilat (PMMA). Envelope randomization was used. Required parameters were measured 1 hour and 1 day after the procedure (leukocytes, Hb, platelets, IL-6, IL-10, lactate, procalcitonin, CRP). Clinical data, such as respiratory and renal complications, blood loss through drains, bleeding, hemostasis, and intensive care and hospital treatments were also evaluated.

Results. Filtration and sorbent components reduce the level of proinflammatory cytokines, as well as triglyceride components and markers of systemic inflammatory response. Over 1 hour, the IL-6 level was significantly lower than in the control group. There was also a tendency to decrease the IL-6 level over 1 day after the procedure. The level of anti-inflammatory IL-10 was significantly higher in comparison to patients who underwent PMMA-sorption, which facilitates the clinical course.