Original research

CEREBROPROTECTIVE PROPERTIES OF ADEMOL IN TRAUMATIC BRAIN INJURY

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Key words: *traumatic brain injury, cerebroprotective effect, Ademol, magnesium sulfate, neurological deficit.*

Bukovinian Medical Herald. V.24, № 2 (94). P. 159-166.

DOI:
10.24061/2413-0737. XXIV.2.94.2020.58

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The goal of the work *– to compare the effect of adamantine 1-adamantylethyloxy-3-morpholino-2-propanol hydrochloride (Ademol) derivative and magnesium sulfate on mnestic function and neurological deficit in an experimental model of traumatic brain injury.*

Material and methods. *The therapeutic effect of Ademol on modulated traumatic brain injury was evaluated with the use of doses of 1, 2 and 4 mg / kg intravenously. Pseudoperated animals received 0.9% NaCl solution based on the volume of the most effective dose of Ademol. As a drug for the control group we used 0.9% NaCl solution at a dose of 2 ml / kg i/v and in the same mode. Neurological deficit in rats with traumatic brain injury was evaluated on the first day and at the end of the acute period (on the eighth day) on the stroke-index C.P. McGrow scale. The animals' ability to learn and remember the aversive stimulus was examined in conditional reaction of passive avoidance test. The technique is based on the innate instinct of rats to a limited darkened space. The conservation of the conditioned responce was checked in a day by the change of the latent time of rat entry to the dark compartment. We also noted the number of animals that tried to enter the dark compartment but did not complete the attempt.*

Results. *While analyzing the effect of course therapy with Ademol solution on the degree of de-escalation of neurological deficiency, it can be noted that by this property the investigated drug outweighed the magnesium sulfate solution on the first day of application by 24% and on the eighth day by 30% ($p<0.05$). Regarding the restoration of mnestic functions in traumatic brain injury, the eight-day treatment of rats with magnesium sulfate solution somewhat improved memory, but was inferior to the efficacy of Ademol, which approximated the results of the conditional reaction of passive avoidance test to the results of pseudoperated animals.*

Conclusions. *The results of the experimental study make it possible to confirm the lack of reliable effectiveness of using magnesium sulfate in the correction of neurological deficiency at traumatic brain injury in rats. Ademol, unlike the magnesium sulfate solution, contributed to the reduction of the severity of neurological disorders, which was accompanied by an improvement of mnestic functions in animals on the eighth day of traumatic brain injury.*

ЦЕРЕБРОПРОТЕКТОРНІ ВЛАСТИВОСТІ АДЕМОЛУ ПРИ ЧЕРЕПНО-МОЗКОВІЙ ТРАВМІ

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Ключові слова: *черепно-мозкова травма, церебропротекторний вплив, Адемол, магнію сульфат, неврологічний дефіцит.*

Буковинський медичний вісник. Т.24, № 2 (94). С. 159-166.

Мета роботи *– порівняти вплив похідної адамантану 1-адамантилетилокси-3-морфоліно-2-пропанолу гідрохлориду (Адемолу) та магнію сульфату на мнестичну функцію та неврологічний дефіцит на експериментальній моделі черепно-мозкової травми.*

Матеріал і методи. *Терапевтичну дію Адемолу на змодульованій черепно-мозковій травмі оцінювали при застосуванні доз 1, 2 та*

4 мг/кг внутрішньовенно. Псевдооперовані тварини отримували 0,9% розчин NaCl із розрахунку до об'єму найбільш ефективної дози Ademолу. Як лікарський засіб для контрольної групи застосовували 0,9% розчин NaCl у дозі 2 мл/кг в/в і у тому ж режимі. Неврологічний дефіцит у щурів із черепно-мозковою травмою оцінювали на першу добу та наприкінці гострого періоду (на восьму добу) за шкалою stroke-index C.P. McGrow. Здатність тварин до навчання та запам'ятовування аверсивного стимулу досліджували в тесті умовної реакції пасивного уникання. Методика заснована на природженому інстинкті щурів до обмеженого затемненого простору. Збереження умовної реакції перевіряли через добу за зміною латентного часу входу щура до темного відсіку. Також відзначали кількість тварин, які намагались увійти до темної камери, але не завершили спроби.

Результати. *Аналізуючи вплив курсової терапії розчином Ademолу на ступінь деескалації неврологічного дефіциту, можна зазначити, що за цією властивістю досліджуваний препарат переважав розчин магнію сульфату на першу добу застосування на 24% та на восьму добу - на 30% ($p<0,05$). Щодо відновлення мнестичних функцій при черепно-мозковій травмі, восьмиденна терапія щурів розчином магнію сульфату дещо покращувала пам'ять, але поступалась за ефективністю Ademолу, який наближав показники тесту умовної реакції пасивного уникання до результатів псевдооперованих тварин.*

Висновки. *Результати проведеного експериментального дослідження дають можливість стверджувати про відсутність достовірної ефективності застосування магнію сульфату щодо корекції неврологічного дефіциту при черепно-мозковій травмі у щурів. Ademол, на відміну від розчину магнію сульфату, сприяв зменшенню виразності неврологічних порушень, що супроводжувалося покращенням мнестичних функцій у тварин на восьму добу черепно-мозкової травми.*

Ключевые слова: *черепно-мозговая травма, церебропротекторное влияние, Ademол, магния сульфат, неврологический дефицит.*

Буковинский медицинский вестник. Т.24, № 2 (94). С.159-166.

ЦЕРЕБРОПРОТЕКТОРНЫЕ СВОЙСТВА АДЕМОЛА ПРИ ЧЕРЕПНО-МОЗГОВОЙ ТРАВМЕ

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Цель работы *– сравнить влияние производной адамантана 1-адамантилетилокси-3-морфолино-2-пропанола гидрохлорида (Адемола) и магния сульфата на мнестическую функцию и неврологический дефицит на экспериментальной модели черепно-мозговой травмы.*

Материал и методы. *Терапевтическое действие Адемола на смоделированной черепно-мозговой травме оценивали при применении доз 1, 2 и 4 мг / кг. Псевдооперированые животные получали 0,9% раствор NaCl из расчета к объему наиболее эффективной дозы Адемола. В качестве лекарственного средства для контрольной группы применяли 0,9% раствор NaCl в дозе 2 мл / кг в/в, в том же режиме. Неврологический дефицит у крыс с черепно-мозговой травмой оценивали в первые сутки и в конце острого периода (на восьмые сутки) по шкале stroke-index C.P. McGrow. Способность животных к обучению и запоминанию аверсивного стимула исследовали в тесте условной реакции пассивного избегания. Методика основана*

на врожденном инстинкте крыс к ограниченному затемненному пространству. Сохранение условной реакции проверяли через сутки по изменению латентного времени входа крысы до темного отсека. Также отмечали количество животных, которые пытались войти в темную камеру, но не завершили попытку.

Результаты. *Анализируя влияние курсовой терапии раствором Адемола на степень деэскалации неврологического дефицита, можно отметить, что за этим свойством исследуемый препарат преобладал раствор магния сульфата в первые сутки применения на 24% и на 30% на восьмые сутки (p <0,05). По восстановлению мнестических функций при черепно-мозговой травме, восьмидневная терапия крыс раствором магния сульфата несколько улучшала память, но уступала по эффективности Адемолу, который приближал показатели теста условной реакции пассивного избегания к результатам псевдооперированых животных.*

Выводы. *Результаты проведенного экспериментального исследования дают возможность утверждать об отсутствии достоверной эффективности применения магния сульфата относительно коррекции неврологического дефицита при черепно-мозговой травме у крыс. Адемол, в отличие от раствора магния сульфата, способствовал уменьшению выраженности неврологических нарушений, что сопровождалось улучшением мнестических функций у животных на восьмые сутки черепно-мозговой травмы.*

Introduction. According to the Consensus on studies of brain diseases in Europe, more than 700,000 Europeans suffer from traumatic brain injury (TBI) [1]. Annually, of the total number of people first recognized as disabled due to cerebral injuries, traumatic genesis of disability is reported in more than 35% [2]. Disability due to TBI is usually long-term, and in 30-35% of cases it is established indefinitely [3]. Development and implementation of emergency neurology and neurosurgical practice of new drugs capable of influencing the secondary damage of neurons in patients with TBI into doctors' practice has let significantly influence the recovery of such patients, reduce the length of stay in intensive care departments, reduce the mortality, improve the rehabilitation and the restoration of cognitive functions. The high expectations of modern medicine for neuroprotective therapy have stimulated scientists all over the world to actively seek new effective means of influencing the pathophysiological cascades of neuronal injury development [4, 5]. For today, the imbalance of neurotransmitters is the most promising target for pharmacological effects on secondary neuronal damage [6]. Studies have shown that at TBI there is an increased synthesis of neurotransmitters, which correlates with a deterioration in the prognosis of a patient with brain injury [7]. The greatest damaging effect is inherent in glutamate, which triggers the excitotoxicity cascade [8]. Hyperactivation of NMDA and AMPA receptors causes an excessive intake of calcium ions into the cell with the activation of phospholipases, endonuclease, caspase, etc.; which destroy cytosolic structures and lead to cell apoptosis [9]. Many studies have demonstrated the efficacy of glutamate NMDA receptor antagonists. Blockade of NMDA receptors is considered to be one of the main links of neuroprotection [10].

The goal of the work. To compare the effectiveness of using adamantane 1-adamantylethyloxy-3-morpholino-2-propanol hydrochloride (Ademol) and magnesium sulfate derivatives for correction of mnestic function and neurological deficit in a model of traumatic brain injury in rats.

Material and methods. The experiments were conducted on white male rats weighing 160-190 g, which were under standard vivarium conditions, in accordance with the ethical standards of conducting experimental studies. The TBI experimental model was caused by the action of a carbon dioxide stream under pressure created using a gas balloon pneumatic gun. Rats under conditions of propofol anesthesia (60 mg / kg), after catheterization of the femoral vein and adjusting the possibility of making infusion through the infusomat, were performed right-sided bone-plastic trepanation of the skull of the projection of the middle cerebral artery, with a hole diameter of 5 mm2. After fixation of the rat in a position on the abdomen upside down, a shot was taken from a fixed distance (close-up shot), the bone fragment on the periosteum together with aponeurosis, was returned to the site and the wound was sutured in layers. Thus, severe TBI was modeled.

The therapeutic effect of Ademol on model TBI was evaluated at applying doses of 1, 2, and 4 mg / kg intravenously. Pseudoperated animals received 0.9% NaCl solution from calculation to the most effective in volume dose of Ademol. As a drug for the control group we used 0.9% NaCl solution at a dose of 2 ml / kg i/v in the same mode.

Neurological deficit in rats with severe TBI (as well as other functional and laboratory parameters) was evaluated on the scale of stroke-indexC.P. McGrow on the first day and at the end of the acute period 12 h after the last injection of drugs (on the 8th day) [10]. The severity of the condition was defined by the sum of the corresponding points: up to 3 points - a mild degree, from 3 to 7 points - an average degree, above 7 points - a severe degree. There were tremors, paresis, limb paralysis, ptosis, arena movements, lateral position, the ability of rats to hold on rods with a diameter of 15 cm, rotating at a speed of 3 rpm. We tested animals on the 8th day, determined the amount of points (unilateral half-ptosis - 0.5 points; unilateral ptosis - 1 point; tremor - 0.5 points; arena movements - 0.5 points; paresis of limbs (for each limb) - 1 point; limb paralysis (for each limb) - 2 points; lateral position - 3 points; inability to stay on the rotating rod for 4 minutes - 3 points). The ability of animals to learn and memorize aversive stimulus was investigated in a same period (8th day) of TBI in a conditional reaction of passive avoidance test (CRPA) [11]. The technique is based on the inborn instinct of rats to a limited darkened space. Rats were trained in a two-chamber facility consisting of two compartments, light and dark. The animal was placed in the light compartment, latent time of entry into the dark compartment was recorded, where the rat received electrical irritation and ran out into the light compartment. CRPA conservation was checked in 24 hours by the change of the latent time of rat entry to the dark compartment. We also noted the number of animals that tried to enter the dark compartment but did not complete the attempt.

Quantitative data were processed using the statistical processing program StatPlus 2009. We used parametric criterion t Student in cases of normal distribution of the variation series, nonparametric criterion W White - in cases of its absence, paired criterion Ť Wilcoxon - to determine changes in dynamics within the group, angular transformation Fisher - when accounting for the results in an alternative form (presence or absence of a certain sign) [12]. The differences were considered statistically significant at $p<0.05$.

Results and Their Discussion. Most researchers view magnesium as an ion with neuro-sedative properties due to its ability to block the nerve impulse [13]. In clinical practice, magnesium sulfate has been long used as an antihypertensive agent and a means of reducing intracranial pressure [14]. It has been established that Mg2 + ions block NMDA-associated channels in a potential-dependent way and, by engaging with glutamate in non-competitive antagonism, inhibit its release, inhibiting excitotoxicity [15]. Despite the fact that magnesium sulfate is a long-known medicinal product and, according to many neurologists, "obsolete approach", the study of its pathophysiological effects continues today, opening new horizons for using in clinical practice. In 2018, while studying on rats, K.S. Vujoviis, S. Vuskoviis, Durovic A., et al. found that inhibition of neuronal NO synthase is one of the pathophysiological mechanisms of the development of hypothermia with the infusion of a combination of ketamine and magnesium sulfate [16]. In preclinical studies, a significant decrease in ischemia zone was observed when using magnesium sulfate; in patients with ischemic stroke, the use of this agent in the first hours of the disease improved the end result, and at the TBI simulation significantly reduced the level of glutamate and apoptosis of neurons [17]. However, the results of the multicenter MASH-II study that studied the effect of magnesium sulfate on the delay of cerebral ischemia due to subarachnoid hemorrhage of aneurysmal origin cannot fail to attract the attention of the scientific community [18]. The injection of magnesium sulfate did not show a significant difference in the effect on the zone of ischemia and ischemic injury and this fact gave an impetus to scientific disputes about the prospects of further use of the drug in neurological and neurosurgical practice [19]. Our interest was aroused by a thorough, literary review of all the successful and failed studies of using magnesium sulfate in neuro-practice published by I. Lingam, N.J.Robertson in 2018 [19]. Scientists have come to the conclusion that further studies of this drug are needed, studies that would reveal to science the additional possibilities of its prescription, and the prescription of magnesium sulfate at TBI is still a subject of scientific debate today [19].

The efforts of modern neuropharmacology are aimed at finding effective molecules that can prevent secondary neuronal damage, which is the most promising target of the effect of pharmaceuticals at acute brain injury by far. Primary neuroprotection is aimed at inhibiting rapid reactions of the glutamate calcium cascade. The greatest hopes in this direction are laid on NMDA receptor blockers. Promising for further study is a compound that has neuroprotective properties, synthesized under the guidance of academician M.O. Lozynskyi in the Institute of Organic Chemistry NAS of Ukraine, derivative of adamantane 1-adamantylethyloxy-3-morpholino-2-propanol hydrochloride (laboratory code is YUK-1, conditional name is Ademol) [20, 21, 22]. The impetus for in-depth study of the cerebroprotective effect of Ademol was the fact that it is a low-affinity non-competitive blocker of the polyamine site of the NMDA receptors of the ionophore complex of pyramidal neurons of the hippocampus with very fast kinetics of NMDA receptors release [23].

The neuroprotective effects of Ademol are, to some extent, related to the presence of a stimulating effect on cerebral blood supply. Studies have shown the presence in Ademol of a stimulating effect on cerebral blood flow in the basin of the internal carotid artery at acute cerebral blood circulation disorder by ischemic type [24], similar positive effect on cerebral hemodynamics was also obtained on models of hemorrhagic stroke [25]. It should be noted that integrative indicators of the effect of the neuroprotector on the ischemic brain are, along with

the decrease in mortality, the rapid elimination of neurological deficit and the restoration of cognitive-mnestic functions, which was the case in studies of Ademol [26].

That is why it was advisable to evaluate the cerebroprotective properties of intensive care of TBI by Ademol of a certain conditionally effective dose of 2 mg / kg i/v on the dynamics of the neurological status of rats in comparison with the magnesium sulfate solution, which showed a positive effect on the course of brain injury, however, according to the result of the meta-analysis, it requires further study (table 1).

The study showed that both at the end of the first day of TBI and after 8 days after pathology modeling, rats had severe neurological changes: convulsions, paralysis, paresis and ptosis, which did not disappear completely in the control pathology group. However, on points on a scale of S.R. McGrow, neurological deficiency in rats with severe TBI, which received only 0.9% NaCl solution at 24 h after injury, was comparable to the one, occurring at day 8, but was not significantly different. Thus,for animals that received only 0.9% NaCl solution (control pathology) as TBI therapy, the average score on the scale of S.R. McGrow at day 1 and day 8 of the study was: 16.25 ± 0.25 and 15.80 ± 0.62 respectively, which corresponds to a severe degree of neurological symptoms and correlates with a high mortality rate (90%). It should be noted that the use of 0.9% NaCl solution for 8 days did not cause the decrease in mortality and neurological deficits, respectively.

Table 1

Effect of course infusion of Ademol and magnesium sulfate on neurological deficiency in rats with traumatic brain injury on the 8th day of the experiment (M±m, n=10)

Group of animals	Neurological deficit on a scale of S.R. McGrow	
	1 day	8 day
Pseudoperated animals + 0.9% NaCl solution	0.3±0.25	0.00±0.00
TBI + 0.9% NaCl solution (control pathology)	16.25±0.25	15.80±0.62
TBI + Ademol, 2 mg / kg i/v	12.3±0.23 º*●	9.40±0.29 º*●
TBI + magnesium sulfate, 250 mg / kg i/v	15.33±0.30 º*	12.30±0.31 º*

Notes:
1. TBI - traumatic brain injury;
2. º – p<0.05 relative to pseudoperated animals;
3. * - p<0.05 relative to the control pathology group;
4. ● - p<0.05 relative to the magnesium sulfate group (250 mg/kg i/v).

Analyzing the effect of course therapy with Ademol solution on the degree of reduction of neurological deficiency, it can be noted that, by this property, the study drug outweighed the magnesium sulfate solution on the first day of application by 24% (p<0.05). Analyzing the effectiveness of the therapy of TBI on the eighth day of observation, the study drug reliably outweighed the magnesium sulfate solution by 30% - when the average score on a scale of S.R. McGrow was 9.40 ± 0.29 (Ademol) versus 12.30 ± 0.31 (magnesium sulfate) in the study groups.

Table 2

Influence of course infusion of Ademol and magnesium sulfate on training and memory of rats with traumatic brain injury by conditioned response of passive avoidance test (the end of 8th day) (M+m, n=10)

Group of animals	The latent period of entering the dark chamber, sec	
	before studying	24 hours after studying
Pseudoperated animals + 0.9% NaCl solution	5.30±0.42	223.80±1.66
TBI + 0.9% NaCl solution (control pathology)	19.70±0.47 º (+271.7%)	48.90±0.96 º (-78.2%)
TBI + Ademol, 2 mg / kg i/v	11.00±0.28 º*● (+107.5%) [-44.7%]	98.80±2.50 º*● (-55.7%) [+102.0%]
TBI + magnesium sulfate, 250 mg / kg i/v	15.30±0.28 º* (+188.7%) [-22.4%]	65.0±1.04 º* (-70.9%) [+32.9%]

Notes:
1. TBI - traumatic brain injury;
2. º – p<0.05 relative to pseudoperated animals;
3. * - p<0.05 relative to the control pathology group;
4. ● - p<0.05 relative to the magnesium sulfate group (250 mg / kg i/v);
5. In round brackets - changes (%) relative to the indicator of pseudoperated rats, in square brackets - relative to the indicator of animals with TBI, which were injected 0.9% NaCl solution (control group).

Regarding the restoration of mnestic functions at TBI, eight-day treatment of rats with magnesium sulfate solution was inferior to the efficacy of Ademol with a 2 mg / kg i/v conditionally effective dose, which approximated the results of the conditional reaction of passive avoidance (CRPA) to the results of pseudoperated animals better (table 2).

The latent period of CRPA in rats, treated with Ademol and magnesium sulfate, improved significantly, probably improved relatively: 11.00 and 15.3 compared with control group 19.7 (p<0.05) (table 2).

Studies have shown that the neuroprotective effect of Ademol is associated with a modulating effect on the activity of NMDA receptors, it was also found that the drug has a complex effect, showing the properties of both primary and secondary cerebroprotectors, with significant advantages compared to others, presented in modern pharmaceutical market, neuroprotectors [27]. Acute excitotoxic neurodegeneration, caused by excessive activation of NMDA receptors and pathological reactions of glutamate-calcium damage, develops not only at brain strokes. By far, its determining role in the initiation of secondary damage at traumatic brain injuries has been proved [27]. The results obtained in our study are pathogenetically reasoned and substantially open up the prospects for further research.

Conclusions

1. Rats with severe TBI experienced severe neurological deficits, impaired learning and memory in the recovery period.

2. The obtained results regarding the correction of neurological deficiency in rats with severe TBI by comparator drugs showed the lack of reliable efficacy of magnesium sulfate at experimental TBI in rats.

3. Ademol had a significantly better effect on the reduction of neurological disorders compared with the magnesium sulfate solution, which was accompanied by an improvement in mnestic functions in animals with TBI.

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Надійшла до редакції 02.04.2020

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