EFFICACY OF USING MELATONIN PER RECTUM FOR EXPERIMENTAL ACUTE CEREBRAL ISCHEMIA

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With limited efficacy and safety of the methods to treat ischemic stroke (IS), melatonin (MT) can be considered a promising neuroprotective agent having a pleiotropic mechanism of action. The study aimed to assess the effect of MT contained in original rectal suppositories on the neurological status and microcirculation in the injury focus in experimental acute cerebral ischemia (EACI) *in vivo*. A total of 30 sexually mature rats were divided into three groups, 10 animals per group: sham-operated (SO) animals; animals with EACI; animals with EACI receiving original rectal suppositories weighing 100 mg with 2.5 mg of melatonin (MT) throughout 7 days. On days 3 and 7, neurological status was assessed using the Garcia JH score, Placing test, Bederson test; microcirculation rate (MR) was assessed in the brain injury focus by laser flowmetry. A significant decrease in the Garcia JH scores by 58.3% ($p = 0.001$), Placing Test scores by 57.9% ($p = 0.002$), along with the significant increase in the Bederson Test scores in animals with EACI compared to SO animals was reported on day 3; the significant decrease in the Garcia JH scores by 75% ($p < 0.001$), Placing Test scores by 78.9% ($p < 0.001$) and the significant increase in the Bederson Test scores were reported on day 7. MR decreased by 30% on day 3 ($p = 0.02$), by 38% on day 7 ($p = 0.005$). The use of the MT-based rectal suppositories resulted in the neurological deficit restoration in the form of the significant increase in the Garcia JH scores by 53.3% ($p = 0.008$), Placing Test scores by 50% ($p = 0.016$) and the significant decrease in the Bederson Test scores by 50% ($p = 0.029$) on day 3; on day 7, the significant increase in the Garcia JH scores by 233% ($p < 0.0001$), Placing Test scores by 325% ($p < 0.0001$) and the significant decrease in the Bederson Test scores by 100% ($p < 0.0001$) were reported. MR increased by 12.5% on day 3 ($p = 0.016$), by 43.9% on day 7 ($p = 0.005$). The correlation analysis revealed the association between the neurological status and MR values: the neurological deficit improvement in animals with EACI in the context of receiving the MT-based rectal suppositories was associated with the MR increase in the ischemic focus in the brain. Thus, partial neurological status restoration in the context of using the MT-based rectal suppositories for EACI resulted from the MT vasoactive properties, which was reflected in the MR increase in the ischemic focus in the brain.

Keywords: melatonin, rectal suppositories, ischemic stroke

Author contribution: Osikov MV — study concept and design, manuscript editing and approval; Shelomentsev AV — data acquisition, literature review, analysis and interpretation of the results; Boyko MS — statistical analysis; Shishkova YuS, Fedosov AA — manuscript editing.

Compliance with ethical standards: the study was approved by the Ethics Committee of the South Ural State Medical University (protocol No. 5 dated 10 June 2024). Animals were kept and handled in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines and animal handling principles based on the provisions of the Declaration of Helsinki and the guidelines contained in the EU Council Directive 86/609/ECC and the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes.

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Received: 24.06.2025 **Accepted:** 21.07.2025 **Published online:** 26.07.2025

DOI: 10.24075/brsmu.2025.035

ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ МЕЛАТОНИНА PER RECTUM ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ ОСТРОЙ ИШЕМИИ ГОЛОВНОГО МОЗГА

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При лечении ишемического инсульта (ИИ) мелатонин (МТ) может быть перспективным нейропротектором с плейотропным механизмом действия. Цель исследования — *in vivo* изучить влияние МТ в составе оригинальных ректальных суппозиториев (РС) на неврологический статус (НС) и микроциркуляцию в очаге повреждения при экспериментальной острой ишемии головного мозга (ЭОИГМ). 30 крыс разделили на три группы по 10 особей: 1) ложнооперированные (ЛО); 2) особи с ЭОИГМ; 3) особи с ЭОИГМ, получающие оригинальные РС с МТ на протяжении 7 суток. Животным групп 2 и 3 моделировали ЭОИГМ по модифицированной методике Chen S. T., et al. На 3 и 7 сутки оценивали НС по шкалам Garcia J. H., Placing test, Bederson test и показатель микроциркуляции (ПМ) в очаге повреждения головного мозга методом лазерной флуометрии. У животных с ЭОИГМ по сравнению с ЛО на 3 сутки зафиксировано значимое снижение баллов по шкале Garcia на 58,3% ($p = 0,001$), по Placing test — на 57,9% ($p = 0,002$), увеличение баллов по Bederson test; на 7 сутки зафиксировано значимое снижение баллов по шкале Garcia J. H. на 75% ($p < 0,001$), по Placing test — на 78,9% ($p < 0,001$), увеличение баллов по Bederson test. ПМ на 3 сутки снизился на 30% ($p = 0,02$), на 7 сутки — на 38% ($p = 0,005$). Применение РС с МТ приводило к восстановлению неврологического дефицита в виде значимого увеличения баллов на 3 сутки по шкале Garcia на 53,3% ($p = 0,008$), по Placing test — на 50% ($p = 0,016$) и снижения баллов по Bederson test на 50% ($p = 0,029$); на 7 сутки фиксировали значимое увеличение баллов по шкале Garcia J. H. на 233% ($p < 0,0001$), по Placing test — на 325% ($p < 0,0001$) и снижение баллов по Bederson test на 100% ($p < 0,0001$). ПМ на 3 сутки повысился на 12,5% ($p = 0,016$), на 7 сутки на 43,9% ($p = 0,005$). Установлено, что уменьшение неврологического дефицита у животных с ЭОИГМ в условиях применения РС с МТ ассоциировано с повышением ПМ в очаге ишемического повреждения головного мозга. Таким образом, частичное восстановление НС в условиях применения РС с МТ при ЭОИГМ обусловлено его вазоактивными свойствами.

Ключевые слова: мелатонин, ректальные суппозитории, ишемический инсульт

Вклад авторов: М. В. Осиков — концепция и дизайн исследования, редактирование и утверждение рукописи; А. В. Шеломенцев — сбор данных, обзор литературы, анализ и интерпретация результатов; М. С. Бойко — статистический анализ; Ю. С. Шишкова, А. А. Федосов — редактирование рукописи.

Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГБОУ ВО ЮУГМУ Минздрава России (протокол № 5 от 10 июня 2024 г.). Условия содержания животных и работы с ними соответствовали руководству ARRIVE (Animal Research: Reporting of In Vivo Experiments) и правилам работы с животными на основе положений Хельсинкской декларации и рекомендаций, содержащихся в Директиве ЕС 86/609/ЕСС и Конвенции Совета Европы по защите позвоночных животных, используемых для экспериментальных и других научных целей.

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Статья получена: 24.06.2025 **Статья принята к печати:** 21.07.2025 **Опубликована онлайн:** 26.07.2025

DOI: 10.24075/vrgmu.2025.035

Today, ischemic stroke (IS) ranks second among the causes of death and third among the causes of disability all over the world [1]. More than 450,000 cases of stroke are reported annually in the RF, and case fatality rate varies between 17.6 and 20.7% [2]. The IS pathogenesis is multifaceted; it involves such mechanisms, as neuroinflammation, glutamate-induced excitotoxicity, and oxidative stress resulting in the death of neurons in the ischemic focus [3]. The existing pathogenetic approaches to treatment of IS show limited efficacy and safety due to narrow therapeutic window, high risk of hemorrhagic transformation, low permeability of the blood-brain barrier (BBB) for neuroprotective agents, as well as poor knowledge about their pharmacokinetics and rather frequent adverse effects, which emphasizes the need to develop new therapeutic strategies aimed at neuroprotection [4]. In this regard, melatonin (MT) possessing pleiotropic effects, including antioxidant, anti-inflammatory, vasoactive, anti-apoptotic ones, is of interest [5–7]. A number of papers demonstrate the MT neuroprotective effect in IS realized through its direct binding to free radicals, increase in activity of key antioxidant enzymes (glutathione peroxidase, catalase), inhibition of caspase-3 and NF-κB pathway, as well as the decrease in expression of AQP4 and enhanced SIRT-1 synthesis in the ischemic brain lesion and, therefore, cerebral infarction volume decrease with subsequent neurological deficit improvement [8–10]. However, the use of MT as a potential neuroprotective agent in oral dosage forms can be considerably limited by post-stroke dysphagia reported in 81% of cases in patients post IS [11]. The use of injectable dosage forms as an alternative allows one to work around the issue of post-stroke dysphagia, but it is associated with constant re-traumatization of the patient when performing injections, high risk of microbial contamination, etc. [12]. The MT-based rectal suppositories represent a promising dosage form ensuring the atraumatic administration and low risk of microbial contamination. In the RF, there are no approved MT-based rectal dosage forms for neuroprotective therapy of IS that could effectively deliver the drug and have a systemic effect on the ischemic injury focus in the brain, thereby minimizing the risk of injury and infectious complications. The development and assessment of the use of MT-based rectal suppositories in IS are relevant due to potential benefits of atraumatic administration routes. The study aimed to perform *in vivo* experimental assessment of the effect of melatonin contained in original rectal suppositories on the neurological status and microcirculation in the ischemic brain injury focus in experimental acute cerebral ischemia.

METHODS

The experiment involved 30 sexually mature male Wistar rats weighting 220–240 g obtained from the experimental biology clinic of the South Ural State Medical University of the Ministry of Health of the Russian Federation in spring and summer. The animals were kept with natural light, at a temperature of 20–22 °C and relative humidity of 60–70%. Simple randomization was used to divide the rats into three groups, 10 animals per group: group 1 — sham-operated (SO) animals, group 2 — animals with experimental acute cerebral ischemia (EACI), group 3 — animals with EACI receiving original rectal suppositories weighing 100 mg with 2.5 mg of MT every 24 h throughout 7 days [13].

EACI was simulated using the modified method by Chen ST under the combination zoletil-xylazine anesthesia [14, 15]. In animals of groups 2 and 3, skin incision with the length of up to 2 cm was performed between the left auricle and left eye. In the incision site, soft tissues were dissected up to the skull bones, and a burr hole 5 mm in diameter was created using a high-speed bur (20,000 rpm) with constant irrigation-induced cooling. Selective diathermocoagulation of the cerebral pial vessels (15 V, 3 s) in the cortical zone of the middle cerebral artery was performed using the operating microscope with the 10× magnification. All methodological aspects of the study were compliant with modern standards of experimental cerebral ischemia modeling [16, 17]. Animals of group 1 underwent all consecutive surgical interventions, including selective diathermocoagulation of the cerebral pial vessels.

Three animals were excluded from further assessment (two in group 2 and one in group 3), since these died within 6 h after surgery. Thus, three groups of animals were created: group 1 (n = 10), group 2 (n = 8), group 3 (n = 9).

On days 3 and 7, neurological status was assessed in all groups using the Garcia JH score, Placing test, Bederson test [18–20]. The results of each particular test were expressed in points.

Microcirculation rate (MR) was assessed in ischemic brain injury focus by laser Doppler flowmetry for 5 min using the LAAK-01 system (Lazma, Russia). The values were processed using the software package by Lazma (Russia), and MR was calculated using the following formula: MR = Ne + Vav, where Ne was the concentration of erythrocytes in the probed tissue volume, Vav was the average erythrocyte sedimentation rate. MR was expressed in perfusion units (PU).

Statistical data processing was performed using the IBM SPSS Statistics 19 software package. The quantitative data distribution was tested for normality using the Shapiro–Wilk test. Since the distribution of most studied parameters was non-normal, nonparametric methods were used for analysis. Intergroup comparison was performed using the Kruskal–Wallis test (when comparing three or more groups), Mann–Whitney U-test (when performing pairwise comparison of groups). The paired Wilcoxon signed-rank test for related samples was used to estimate the intragroup dynamics (to compare the values on days 3 and 7); Spearman's rank correlation coefficient (r) was used for correlation analysis. The data were presented as the median (Me), lower and upper quartiles (Q_1; Q_3). The differences were considered significant at $p < 0.05$.

RESULTS

Animals with EACI showed focal neurological deficit in the form of right hemiparesis, stato-locomotor disorder on days 3 and 7. Animals with EACI demonstrated a significant decrease in Garcia JH scores by 58.3% (p = 0.001), Placing test scores by 57.9% (p = 0.002), along with the significant increase in Bederson test scores compared to SO animals; on day 7, the significant decrease in Garcia JH scores by 75% ($p < 0.001$), Placing test scores by 78.9% ($p < 0.001$), along with the increase in Bederson test scores were reported. Animals with EACI showed the significant decrease in Garcia JH scores by 40% (p = 0.008), Placing test scores by 50.0% (p = 0.003), along with the increase in Bederson test scores by 100% (p = 0.001) on day 7 compared to day 3 (Table 1).

Microcirculation assessment showed the decrease in MR on day 3 by 30% (p = 0.02), by 38% on day 7 (p = 0.005) in animals with EACI compared to SO ones. Animals with EACI showed the significant MR decrease by 11% (p = 0.03) on day 7 compared to day 3 (Table 2).

Thus, focal neurological deficit and the decrease in cerebral blood flow in the ischemic brain lesion were reported in animals with EACI on days 3 and 7, which was confirmed by the significant decrease in Garcia JH, Placing test scores, as well as by the increase in Bederson test scores and MR decrease.

Table 1. Effect of MT on neurological status in EACI (Me [Q_1; Q_3])

Indicator	Group 1		Group 2		Group 3	
	Day 3 (n = 10)	Day 7 (n = 10)	Day 3 (n = 8)	Day 7 (n = 8)	Day 3 (n = 9)	Day 7 (n = 9)
Garcia JH score	18.00 [18.00; 18.00]	18.00 [18.00; 18.00]	7.50 [7.00; 8.00]*	4.50 [3.00; 6.00] *&	11.50 [10.00; 13.00] *#	15.00 [14.00; 16.00] *#&
Placing test score	9.50 [9.00; 10.00]	9.50 [9.00; 10.00]	2.00 [2.00; 3.00]*	4.00 [4.00; 4.00] *&	1.00 [1.00; 2.00] *#	0.00 [0.00; 1.00] *#&
Bederson test score	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	4.00 [3.00; 4.00]*	2.00 [1.00; 2.00] *&	6.00 [6.00; 7.00] *#	8.50 [8.00; 9.00] *#&

Note: significant differences based on the Mann–Whitney *U*-test are designated as follows: * — compared to group 1 ($p < 0.05$); # — compared to group 2 ($p < 0.05$); & — significant differences based on the Wilcoxon test between days 3 and 7 within the same group ($p < 0.05$).

The use of MT-based rectal suppositories on days 3 and 7 led to the right hemiparesis and stato-locomotor disorder severity decrease. The animals receiving MT showed the significant increase in the Garcia JH scores by 53.3% ($p = 0.008$), Placing test scores by 50% ($p = 0.016$), along with the significant decrease in Bederson test scores by 50% ($p = 0.029$) compared to animals with EACI on day 3; on day 7, the significant increase in Garcia JH scores by 233% ($p < 0.0001$), Placing test scores by 325% ($p < 0.0001$) and the significant decrease in Bederson test scores by 100% ($p < 0.0001$) were reported. The significant increase in Garcia JH scores by 30.4% ($p = 0.004$), Placing test scores by 41.7% ($p = 0.002$) and the significant decrease in Bederson test scores by 100% ($p = 0.003$) upon MT administration on day 7 compared to day 3 were reported (Table 1).

Microcirculation assessment showed the increase in MR by 12.5% on day 3 ($p = 0.016$), by 43.9% on day 7 ($p = 0.005$) in the animals receiving MT compared to the ones with EACI. The animals showed the significant MR increase by 13.8% ($p = 0.028$) upon MT administration on day 7 compared to day 3 (Table 2).

The animals receiving MT showed the significant decrease in Garcia JH scores by 36.1% ($p < 0.001$), Placing test scores by 36.8% ($p < 0.001$) and the significant increase in Bederson test scores by 100% ($p = 0.002$) compared to SO animals on day 3; on day 7, these demonstrated the decrease in Garcia JH scores by 16.7% ($p < 0.008$), Placing test scores by 10.5% ($p < 0.038$) and the significant increase in Bederson test scores by 0% ($p = 0.157$) (Table 1).

The correlation analysis of Garcia JH scores, Placing test scores, and MR values on days 3 and 7 revealed a positive correlation, along with the negative correlation between Bederson test scores and MR: the neurological deficit improvement in animals with EACI in the context of using MT-based rectal suppositories was associated with the MR increase in the ischemic brain lesion (Table 3).

DISCUSSION

It can be assumed that neurological deficit we have detected results from local critical decrease in cerebral blood flow in the brain matter and activation of the cascade of pathochemical reactions, including mitochondrial dysfunction with subsequent neuronal energy deficiency, oxidative stress activation, glutamate-induced excitotoxicity, neuroinflammation resulting in neuronal damage in the ischemic injury focus [21]. The use of MT-based rectal suppositories resulted in partial restoration of neurological status and cerebral blood flow in the ischemic injury focus, which could be due to the MT pharmacological features and pleiotropic effects, including neuroprotective and vasoactive effects. The MT relatively low molecular weight (232 g/mol), moderate lipid solubility (Log $p = 3$), and moderate bioavailability when administered rectally (54–72%) can ensure penetration of the blood-brain barrier and have a systemic effect on the ischemic injury focus and potential penetration [22, 23]. We believe that MT contained in the rectal suppositories entered the systemic blood flow and reached the ischemic lesion in the brain, showing the neuroprotective effect. The MT pleiotropic effects determining its possible neuroprotective effect can be associated with the activity mediated by specific membrane and nuclear receptors (MT1, MT2, ROR), as well as with the direct effect [24]. The MT binding to the MT receptors of microglial cells through the STAT3 pathway inhibition contributed to the reduced synthesis of pro-inflammatory cytokines in the ischemic injury focus and reduced neuroinflammation [25]. Furthermore, MT could cause inhibition of NADPH reductase activity and enhanced synthesis of glutathione peroxidase, thereby decreasing the activity of oxidative stress processes in the ischemic brain injury focus [26]. MT enhanced the 90RSK activity resulting in the Bad pro-apoptotic protein inactivation through ERK1 phosphorylation, thereby contributing to the increased survival of neurons in the ischemic injury zone [27]. The MR increase in the ischemic brain injury focus can be associated with the vasoactive effect of MT, which enhanced NO synthesis in endothelial cells and increased cerebral blood flow through the increased activity of endothelial NO synthase [28]. The findings clearly demonstrate clinical prospects for the use of MT-based rectal suppositories as adjunctive therapy for IS, especially in the elderly and seriously ill patients, in whom standard treatment methods show limited efficacy. The data obtained provide a strong basis for further research aimed at in-depth study of the mechanisms underlying the MT neuroprotective effect via monitoring of the dynamic changes in the levels of biochemical markers (MDA, S100β) and their correlation with clinical outcomes. The promising areas for scientific research can be

Table 2. Effect of MT on microcirculation values in EACI (Me [Q_1; Q_3])

Indicator	Group 1 (n = 10)		Group 2		Group 3	
	Day 3 (n = 10)	Day 7 (n = 10)	Day 3 (n = 10)	Day 7 (n = 10)	Day 3 (n = 10)	Day 7 (n = 10)
Microcirculation value, PU	22.11 [20.65; 22.69]	22.11 [20.65; 22.69]	15.51 [15.48; 15.88]*	13.79 [13.49; 14.09]*&	17.45 [17.33; 18.83]*#	19.85 [19.44; 19.90]*#&

Note: significant differences based on the Mann–Whitney U-test are designated as follows: * — compared to group 1 ($p < 0.05$); # — compared to group 2 ($p < 0.05$); & — significant differences based on the Wilcoxon test between days 3 and 7 within the same group ($p < 0.05$).

Table 3. Correlation between neurological status indicators and MR in EACI in the context of using MT-based rectal suppositories

Indicators	Microcirculation rate, PU	
	Day 3	Day 7
Garcia JH score	$r = 0.63$	$r = 0.67$
Placing Test score	$r = 0.77$	$r = 0.64$
Bederson Test score	$r = -0.61$	$r = -0.60$

Note: r — Spearman's rank correlation coefficient ($r < 0.05$).

as follows: development of differentiated MT dosing algorithms considering the patients' individual characteristics; assessment of delayed therapy effects between 6 and 12 months of follow-up; study of the possibilities of using combination therapy with other neuroprotective agents. Successful introduction of this method into wide clinical practice requires large-scale multicenter randomized trials involving the use of standardized assessment protocols. The development of personalized approaches to therapy considering the age-related specifics, comorbidities, and individual characteristics of the patients' cerebral hemodynamics is of special importance.

CONCLUSIONS

Selective diathermocoagulation of the cerebral pial vessels performed on days 3 and 7 resulted in the critical cerebral blood flow decrease with subsequent development of neurological deficit in the form of right hemiparesis and stato-locomotor disorder manifested by the progressive decrease in Garcia JH, Placing test scores and increase in Bederson test scores, as well as in the reduced MR in the ischemic brain injury focus. The use of original rectal suppositories with the weight of 100 mg containing 2.5 mg of MT every 24 h throughout 7 days resulted in partial neurological deficit restoration manifested by the increase in Garcia JH, Placing test scores, decrease in Bederson test scores and increased MR not reaching the values of the SO animals in the ischemic brain injury focus. The correlation analysis revealed the association between the neurological status indicators and MR: the neurological deficit improvement in animals with EACI in the context of using MT-based rectal suppositories was associated with the MR increase in the ischemic brain injury focus.

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