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pHPMA-hydrogel does not improve intensive autogenic recovery of motor function after lateral spinal cord fragment excision in adult rats

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Abstract: spinal cord injury (SCI) is a form of trauma with high prevalence, mortality, and disability. One approach in SCI rehabilitation is to create conditions for regenerative axon growth across the lesion site using tissue scaffolds. notably pHPMA-hydrogel (pHPMA – poly(N-[2-hydroxypropyl] methacrylamide)). Assessing the effectiveness of such approach can only be done in laceration models of SCI with reliable reproducibility. The aim of this work was to determine the effect of immediate implantation of pHPMA-hydrogel into the epicenter of a unilateral one-millimeter spinal cord defect in an adult rat on the paretic limb motor function in comparison with the effectiveness of the same intervention in young animals. The study was performed on white male outbred adult rats (3–4 months). For comparative analysis of the obtained data, the results of young animals from another institution, previously published in other works, were used. In both cases, a 1-mm excision of the spinal cord lateral half at the lower thoracic/upper lumbar level was maded, with immediate filling of the defect by a fragment of pHPMA-hydrogel. Over a period of 5 months after intervention, the motor function of the paretic limb in adult animals reached about one-third of normal levels, both with and without pHPMA-hydrogel implantation. Spasticity of the paretic limb was minimal in adult animals with or without hydrogel implantation. There is generally a negative correlation between motor function and spacticity. These data suggest that pHPMA-hydrogel implantation into a one-millimeter unilateral spinal cord defect, unlike in young animals, does not significantly affect recovery outcomes in adult animals. Based on a comparative analysis of the results of young and adult animals we hypothesize that the recovery of the paretic limb's motor function after unilateral SCI may be mediated with the participation of interneurons/propriospinal neurons in the contralateral part of the injured cord with a limited rostro-caudal axonal and dendritic extent.

Key words: Spinal Cord Injuries, Hindlimb, Paresis, Muscle Spasticity, Spinal Cord Regeneration, Hydrogels.

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Introduction

Spinal cord injury (SCI) is one of the most dramatic human pathologies, characterized by low annual incidence but relatively high prevalence [1], a significant proportion in combat trauma [2], high mortality [3], and, most importantly, a permanent disability and reduced life expectancy and quality due to various complications [4, 5]. A typical SCI is characterized by impairments of motor function, sensation, and autonomic innervation below the lesion level [6, 7], as well as numerous exhausting disorders, including lower urinary tract dysfunction [8], spasticity [9], and chronic pain [10]. When the lesion is located outside the motor innervation zones of the limbs, the primary goal of rehabilitation is to restore supraspinal innervation of motor neurons. A promising approach is bioengineered facilitation of axon regenerative growth through the lesion site by implanting artificial tissue scaffolds [11], for example, macroporous pHPMA-hydrogel (pHPMA – poly(N-[2-hydroxypropyl] methacrylamide)) [12-16]. The importance of this approach is underscored by the fact that mammals require preservation of even a small fraction of spinal cord white-matter fibers to maintain voluntary stepping [17, 18].

However, most SCIs are, from a pathomorphological point of view, belong to spinal cord contusion, compression, or crushing [6, 19]. In all this types of SCI at the trauma epicenter injured cord tissue remains, possibly containing surviving nerve fibers and serve as a matrix for regenerative growth of transected axons. It is possible to determining the results of such scenario and whether scar tissue can be replaced by an artificial scaffold in each individual case only retrospectively, after a long term observation, i.e., in a period that is unfavorable for regeneration. For this reason, early replacement of injured spinal cord tissue is feasible only if the implanted scaffold is guaranteed to provide better functional recovery than injured spinal cord tissue which are in a course of glio-fibrotic scar formation. At present, no artificial scaffolds demonstrate such guaranteed efficacy, even with added stem cells (see [11, 20]).

Most positive experimental results of SCI treatment in small mammals have not translated reliably to clinical confirmation [21]. Contributing factors include: (1) use of animals with standardized phenotypes under uniform care conditions – unlike real clinical situations; (2) large size differences between small mammals and humans [22]; (3) lack of an accurate model for common human SCI forms [19]; and (4) imperfect tools for assessing functional outcomes in experimental animals [23, 24].

Aim

The purpose of this work is to determine the effect of immediate pHPMA-hydrogel implantation into the unilateral one-millimeter spinal cord defect in an adult rat on the paretic limb motor function, based on the 5-month observation and in comparison with the effectiveness of the same intervention in young animals.

Materials and Methods

Research was conducted in accordance with bioethics and animal welfare rules.

White male outbred rats (250–300 g, 3–4 months old) from the vivarium of the State Institution "Romodanov Neurosurgery Institute National Academy of Medical Sciences of Ukraine", kept under natural light/dark cycles at room temperature and balanced feed and water ad libitum. Juvenile white male rats (~50 g, ~1 month old), wich results were included for comparative analysis, kept in the Bogomoletz Institute of Physiology vivarium (technical conditions described in [14, 23]) and underwent similar injury and treatment [14, 23, 25].

Adult animals were divided into two experimental groups: SCI – SCI modeling (n = 22, end-to-end observation – n = 19); HG (HG – hydrogel) – SCI modeling and immediate pHPMA-hydrogel implantation (n = 18, end-to-end observation – n = 15). Each group included animals from multiple litters from the same vivarium; animals from each individual litter were not specifically separated between the two groups. Reference groups of juvenile animals [14, 23, 25] included: SCIj (j – juvenile) – SCI modeling (n = 8); HGj – SCI modeling with immediate pHPMA-hydrogel implantation (n = 6).

The model used was a left-sided one-millimeter excision of the lateral half of the spinal cord at the lower thoracic-upper lumbar level, the technique of which is described in detail in previous works [14, 23]. Briefly, the interventions was performed under general anesthesia of the animal using intraperitoneal injection of xylazine (15 mg/kg) and ketamine (70 mg/kg). The zone of SCI modeling was selected by palpation of the caudal edge of the thoracic cage of a deeply anesthetized animal at the site of its fixation to the spine. Given the theoretically lower ossification in young individuals and the greater mobility of the anterior ends of the caudal pairs of ribs (costae fluctuantes), in the absence of surgical or radiographic visualization of the places of fixation of these ribs to the spine, the laminectomy site can be localized at the level of ~T_{11}–T_{12} vertebrae, which, taking into account skeletal data, corresponds to the spinal cord segments ~Th_{13}–L_1 (SCI and HG groups), and with

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correction for the young age of the animals, – to the segments ~T_{12}–T_{13} (SCIj and HGj groups) [14, 23]. A limited left-sided laminectomy was performed from a linear skin incision. Without separating the dura mater and spinal roots, along the left edge of the posterior median vessel at two points, at a distance of ~1 mm from each other the spinal cord was perforated in the ventral direction with insulin syringe needle. A longitudinal paramedian spinal cord incision was formed between the perforations with ophthalmic scissors, after which the tissue of the left half of the spinal cord was cut off at the rostral and caudal ends of the incision and removed from the wound with microtweezers with different geometries. The spinal cord defect formed in this way was left empty (SCI and SCIj groups) or filled with a fragment of pHPMA-hydrogel (HG and HGj groups). In all cases, the bone defect was covered with a fragment of subcutaneous fascia, the edges of the soft tissues and skin were connected in two rows of knotted sutures and, for prophylactic purposes, a solution of bicillin-5 (OJSC "Kyivmedpreparat"; 0.5 million U/kg) was injected subcutaneously into the posterior cervical region, and a solution of dexamethasone (KRKA, Slovenia; 5 mg/kg) was injected intraperitoneally. Until the complete restoration of motor activity, the animals were kept at elevated air temperature, and subsequently in standard vivarium conditions, 3–6 (SCI and HG groups) or 2–3 (HGj group) individuals in larger cages or in individual smaller cages (SCIj group) [14, 23].

The pHPMA-hydrogel was synthesized from N-(2-hydroxypropyl) methacrylamide by radical polymerization under heterogeneous phase-separation conditions in a porogenic medium [14-16]. After washing and high-temperature sterilization, macroporous hydrogel fragments were transported in distilled water in sealed containers [14-16].

A successfully modeled rat displayed a motor deficit of the hind limb on the SCI side as a spastic paresis. Motor activity (function index, FI) and spasticity (spasticity index, SI) of the paretic limb were evaluated using the Basso–Beattie–Bresnahan (BBB) scale and the Ashworth scale, respectively, in our technical modifications [23], without prior training. The BBB scale determines the degree of rat motor activity during free locomotion on an open plane in the following main intervals: 1) orchestration of movements in the three key joints of the hind limb (0–9 points), 2) maintenance of body weight by the hind limbs (9–11 points), 3) coordination of movements by different limbs (12–14 points), 4) fine mobility within the foot of the paretic hind limb (14–20 points), 5) keeping the tail above the plane of movement (19–20 points) and 5) translateral stability of the trunk (20–21 points) [23]. The Ashworth scale in rats allows for the assessment of spasticity mainly based on the mobility of the joints of the paretic limb during conditionally passive flexion-extension moovements, ranging from no resistance (0 points) to significant resistance in contracture and in some cases, ankylosis (4 points) [23].

The assessment of FI and SI was carried out by the same researcher, conditionally blinded both to the individual characteristics of all animals operated on by him and, usually, to the previous values of FI and SI in groups SCIj and HGj [14, 23], but not blinded to the previous values of FI and SI in groups SCI and HG. In case of doubt about the exact whole value of FI or SI, the half value was recorded.

FI and SI were recorded weekly at 1 and 2 weeks, then monthly up to 5 months for groups SCI and HG. A similar time scheme for displaying results was used for groups SCIj and HGj, however, actual testing intervals for this animals differed by ~29% at 1 week post-injury, and ≤7% thereafter [14, 23]. This nullifies the results of the comparative analysis involving the SCIj and HGj groups at the first two observation periods, however, due to the decrease in changes in FI and SI after the 2nd month of observation, these deviations are not of fundamental importance for assessing the significance of differences in FI and SI between the groups.

Animals with FI of the paretic limb >9 BBB points at first testing (SCIj – 1 animal, HGj – 2 animals) or persistent deficit of the contralateral hind limb (≤14 points; SCIj – 2 animals, HGj – 1 animal) were excluded [14, 23]. Throughout both experiments, no signs of self-injurious behavior, regional trophic and/or purulent-inflammatory processes that would require immediate euthanasia of the animal were detected. Animals with obvious signs of persistent peripheral paresis (L_3–L_6 motor neuron damage) were retained [23]. No cases of excessively rostral injury causing ipsilateral abdominal muscle paresis were noted. Cases of excessively rostral injury and obvious ipsilateral paresis of the abdominal wall muscles were not specifically recorded [23]; a frequent or characteristic manifestation of such a symptom for a particular group was not observed.

During the experiment, animal deaths were recorded, the causes of which were not specifically investigated: in the SCI group – 3 animals (at the 2nd and 3rd months; 13 %), in the HG group – 3 animals (at the 4th month; 17%). The FI and SI of these animals was taken into account for intergroup comparisons at the observation periods, when they were part of the experimental groups.

Statistical processing of numerical data was performed using the EZR software package (R Statistics), which is freely available (https://www.softpedia.com/get/Science-CAD/EZR.shtml), on a personal computer. The distribution pattern was assessed using the Shapiro-Wilk test. Mean values of FI and SI in the compared samples were presented as Median (Q I; Q III), when parameters distribution in the samples differed from normal, or as M ± SD (M – mean, SD – standard deviation) for normally distributed data.

To identify differences in individual values of FI and SI (performed only for animals that were observed throughout the experiment; SCI – n = 19, HG – n = 15; SCIj and HGj – in full) at different observation time points within each group, repeated-measures ANOVA (rANOVA) or the Friedman test was used; in both cases, the Bonferroni correction was applied for multiple comparisons. Pairwise comparisons of related samples were performed using the Wilcoxon signed-rank test (T-test).

The significance of differences in FI and SI between different experimental groups at each observation time point, under normally distributed data, was determined using ANOVA after assessing the homogeneity of variances with Bartlett's test, followed by Tukey's post hoc test for pairwise comparisons. In cases where the distribution of FI or SI values differed from normal or when variances were non-homogeneous, the significance of differences was assessed using the Kruskal–Wallis test, followed by the Steel-Dwass test for post hoc comparisons. The results of the described analysis were further supplemented by pairwise comparisons of FI or SI values between experimental groups using the Wilcoxon-Mann-Whitney test.

Statistical correlation between FI and SI values was assessed for data of animals, which are observed throughout the experiment (see above), using Pearson's correlation coefficient (r_s; when at least one variable was normally distributed) and Spearman's rank correlation test (r_p; when the distributions of both variables were non-normal).

In all cases, the results were considered statistically significant when the probability of the opposite assumption was less than 0.05 ($p < 0.05$).

Results

Dynamics of the paretic limb motor function.

At 1 week after injury, the median of FI values in the SCI group were 1 (1; 1) BBB score, in the HG group – 3 (1; 6), in the SCIj group – 0.5 (0; 1), in the HGj group – 3.5 (1.5; 5.5) BBB score (Fig. 1 A). FI values at this time point were significantly different for the comparison pairs SCI and HG group, as well as SCI and SCIj group ($p<0.05$; Wilcoxon-Mann-Whitney test) (Fig. 1 A). Subsequently, a significant increase in FI in the SCI group (n = 19) occurred within 2 months after injury, and in the HG group (n = 15) – within one month ($p<0.05$; Friedman criterion with Bonferroni correction; Wilcoxon T-test). At 5 months after injury, the median of FI values in the SCI group were 7 (6; 8.5) BBB points, in the HG group – 8 (4; 11) BBB points (Fig. 1 B).

Changes in FI values in the groups of young animals during the experiment were mostly statistically insignificant. However, during the 4th-5th month of observation, a decrease in FI level to 0.5 (0; 1.3) BBB points was recorded for the SCIj group ($p<0.05$ when compared with the value at the 2nd observation period; Wilcoxon T-test and Friedman test with Bonferroni correction) and decrease in FI level to the 4.6±4.3 BBB points was detected for the HGj group (Fig. 1 B).

During the experiment, significant differences in FI values for the SCI and HG groups were detected only after 1 week ($p<0.01$, Wilcoxon-Mann-Whitney test), and for the SCIj and HGj groups – after 5 months after injury ($p<0.05$; Wilcoxon-Mann-Whitney test) [14], however, in the current statistical analysis – significant differences were not detected ($p>0.05$; Wilcoxon-Mann-Whitney test). The FI values of the SCI and SCIj groups were significantly different at all observation times ($p<0.05$, Wilcoxon-Mann-Whitney test). No significant differences in the FI values of the HG and HGj groups were found at any of the observation times ($p>0.05$, Wilcoxon-Mann-Whitney test). As a result, the highest FI values according to the results of both experiments were observed in the HG group, the lowest in the SCIj group.

Dynamics of the paretic limb spasticity.

The distribution of SI values in all experimental groups 1 week after injury differed from normal ($p<0.01$; Shapiro-Wilk test). At this observation point, the median of SI values in the SCI group were 1 (1; 1) Ashworth score, in the HG group – 1 (0; 1), in the SCIj group – 0.5 (0.5; 0.8) and in the HGj group – 0.5 (0.5; 0.7) Ashworth score (Fig. 1 C). The SI values of the experimental groups at this time point did not differ from each other ($p>0.05$; Wilcoxon-Mann-Whitney test).

The SI level in the experimental groups increased during the total observation period in an unequal and uneven manner. Thus, 1 month after the injury, the distribution of SI values in all experimental groups differed from normal ($p<0.05$; Shapiro-Wilk test) and the median of SI values in the SCI group were 1 (1; 1) Ashworth score, in the HG group – 0.8 (0; 1) points, in the SCIj group – 3.5 (1.8; 4) points, and in the HGj group – 0.8 (0.5; 1.8) points. The values of SI

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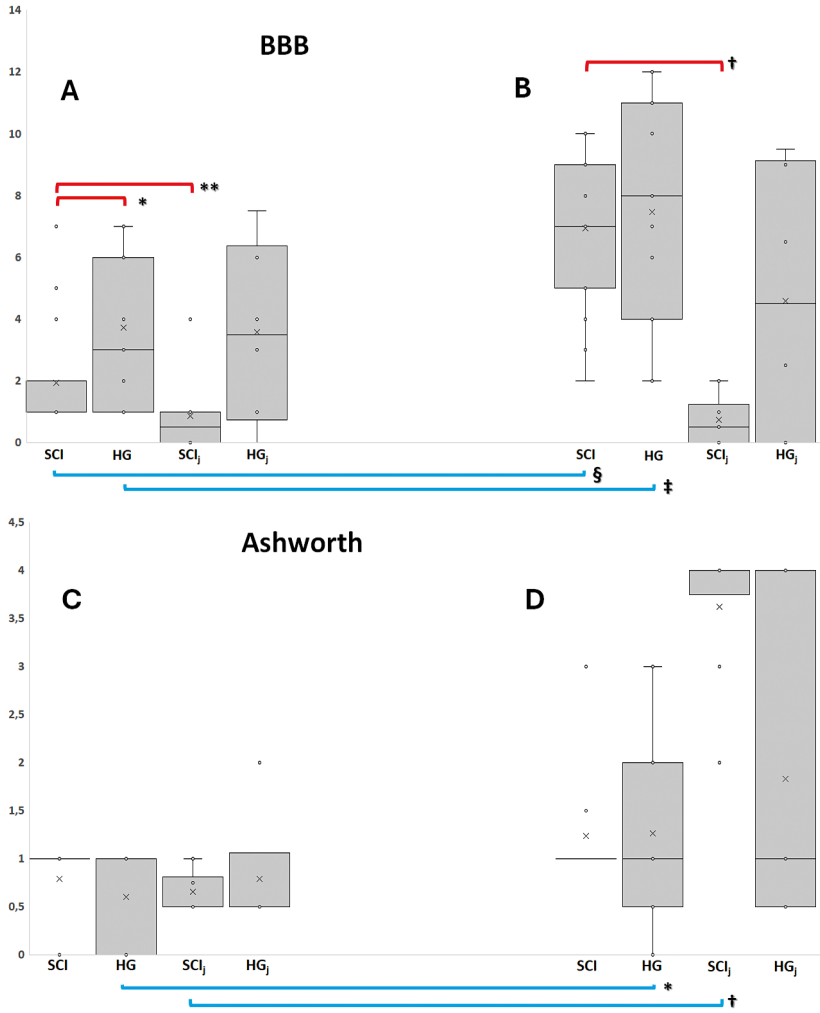

Notes for statistical significance of differences.

BBB-part (A, B):
* – group SCI vs group HG, at 1 week time point, Wilcoxon–Mann–Whitney test, p<0.01;

** – group SCI vs group SCIj, at 1 week time point, Wilcoxon–Mann–Whitney test, p<0.05;

† – group SCI vs group SCIj, at 5-month time point, Wilcoxon–Mann–Whitney test, p<0.001;

§ – within the SCI group, between the 1 week and 5-month time point, Wilcoxon signed-rank test, p < 0.001 (performed for animals that were observed throughout the experiment, n = 19);

‡ – within the HG group, between the 1 week and 5-month time point, Wilcoxon signed-rank test, p < 0.01 (performed for animals that were observed throughout the experiment, n = 15).

Ashworth-part (C, D):
** – within the HG group, between the 1 week and 5-month time point, Wilcoxon signed-rank test, p<0.01 (performed for animals that were observed throughout the experiment, n = 15);

† – within the SCIj group, between the 1 week and 5-month time point, Wilcoxon signed-rank test, p<0.05.

Figure 1. Median values of FI (A, B) and SI (C, D) (horizontal lines inside the boxes), the limits of the first and third quartiles (the shaded portions of the box located below and above the median line at each time point, respectively), mean values (×), standard deviations (the average distance between the lower or upper edge of each box), and the range of data dispersion (outliers) beyond the upper and lower quartiles (horizontal caps of the whiskers at each observation time point) in four experimental groups (SCI, HG, SCIj, and HGj) at 1 week (A, C) and 5 months (B, D) after injury modeling.

in the HG and SCI groups (p<0.01, Steele-Dwass test for posterior comparisons; p<0.01, Wilcoxon-Mann-Whitney test – in the case of pairwise comparisons) and in the SCI and SCIj groups (p<0.01, Wilcoxon-Mann-Whitney test) significantly differed at this observation point.

Two months after the injury, the distribution of SI values in all experimental groups differed from normal (p<0.01; Shapiro-Wilk test) and the median of SI values in the SCI group were 1 (1; 1) Ashworth points, in the HG group – 1 (0.6; 1) points, in the SCIj group – 4 (2.8; 4) points, and in the HGj group – 0.8 (0.5; 2.5) points. SI values in the SCI and HG groups, as well as SCI and SCIj groups, differed at this observation point in a pairwise comparison (p<0.05; Wilcoxon-Mann-Whitney test).

Five months after injury, the distribution of SI values was normal only in the HG group (p>0.05; Shapiro-Wilk test), and the median of SI values in the SCI group were 1 (1; 1) Ashworth score, in the HG group – 1 (0.8; 1.5) score, in the SCIj group – 4 (3.8; 4) points, and in the HGj group – 1 (0.6; 3.3) point (Fig. 1 D). At this observation point, SI values were significantly different only for the SCI and SCIj groups (p<0.001, Wilcoxon-Mann-Whitney test) (Fig. 1 D).

Overall, an increase in SI was observed in the SCI group during the first month, in the HG group – during the 2nd and 3rd months, in the SCIj group – during the first 2 months, and in the HGj group – during the 1st and 3rd months after the injury. Statistical analysis, performed for animals that were observed throughout the experiment, generally confirmed these observations. Thus, in the SCI group sample (n = 19), a significant change in SI values was detected only during the second week of the

experiment ($p<0.001$; Friedman test with Bonferroni correction) or was not detected at all ($p>0.05$; Wilcoxon T-test for all pairs of comparisons). In the HG group sample (n = 15), a significant increase in SI relative to values at 1 week after injury was detected during the period from the 3rd to the 5th month after the injury ($p<0.05$, Wilcoxon t-test, Friedman test with Bonferroni correction). In the SCIj group, a significant increase in SI was observed during the first two months ($p<0.03$, Wilcoxon T-test; $p<0.05$, Friedman test with Bonferroni correction), while in the HGj group, SI values did not change significantly throughout the experiment ($p>0.05$, Wilcoxon T-test; $p<0.01$, Friedman test with Bonferroni correction).

Correlation of motor function and spasticity values.

As already noted, in general, after 5 months from the experiment beginning, the highest FI values were observed in the HG group, the lowest – in the SCIj group, and intermediate values were observed in the remaining two groups. On the contrary, highest SI values were observed in the SCIj group, and lower values were observed in the remaining three groups. Such an inverse relationship between FI and SI probably has a pathophysiological basis: it is well known that the limitation of voluntary muscle control after SCI due to the damage of supraspinal innervation of the corresponding motor neurons (state of central paresis, decrease in FI) is accompanied by an increase in the involuntary activity of denervated motor neurons, i.e., the formation of spasticity (increase in SI). Correlation analysis of the data, obtained from animals, which are observed throughout the experiment (SCI group – n = 19, HG group – n = 15; groups SCIj and HGj – in full), generally confirmed this opinion (Fig. 2).

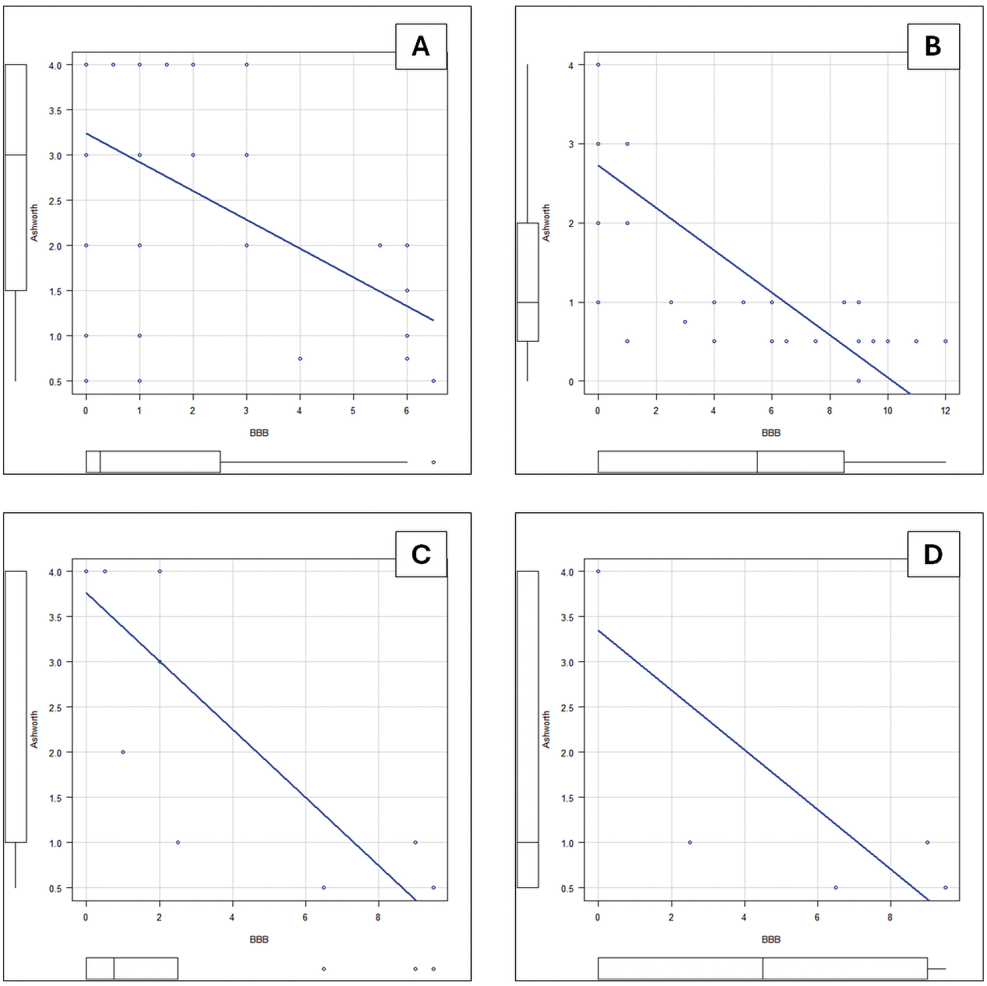

Figure 2. Examples of correlations between individual FI and SI values: A – a moderate negative correlation between FI and SI values in the SCIj group recorded throughout the entire experiment ($r_s = -0.47$, $p<0.001$); B – a strong negative correlation between FI and SI values in the HGj group recorded throughout the entire experiment ($r_s = -0.77$, $p<0.001$); C – a strong negative correlation between FI and SI values in both the SCIj and HGj groups at 5 months after injury modeling ($r_s = -0.87$, $p < 0.001$); D – a strong negative correlation between FI and SI values in the HGj group at 5 months after injury ($r = -0.84$, 95% CI −0.98 … −0.102, $p<0.05$). The ordinate axis represents SI values, and the abscissa axis represents FI values.

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For example, 1 week after injury in the SCI group sample, a moderate negative correlation was found for FI and SI values (r_s = -0.53, p<0.05), and 1 month after injury a strong negative correlation was found in the HGj group (r_p = -0.86, 95% CI -0.98 ... -0.14, p<0.03). At 2 months after injury in the SCI group sample, a moderate negative correlation was found (r_s = -0.68, p<0.01), and a strong negative correlation was found in the SCIj and HGj groups (r_s = -0.71, p<0.05, and r_p = -0.96, 95% CI -1.00 ... -0.70, p<0.002, respectively). Similarly, 3 months after injury, in the SCI group sample, a moderate negative correlation was found (r_s = -0.63, p<0.01), and a strong negative correlation was found in the SCIj and HGj groups (respectively, r_s = -0.83, p<0.01, and r_p = -0.98, 95% CI -1.00 ... -0.80, p<0.001). At 4 months after injury, a strong negative correlation was found in the SCI group sample (r_p = -0.73, 95% CI -0.89 … -0.41, p<0.001), and moderate negative correlation was found in the HG group sample (r_p = -0.57, 95% CI -0.84 … -0.08, p<0.05). At the same observation point a strong negative correlation in the SCIj and HGj groups was found (respectively, r_s = -0.88, p<0.01, and r_p = -0.88, 95% CI -0.99 … -0.23, p<0.05). At 5 months after injury, a moderate negative correlation was found in the SCI group sample (r_p = -0.7, 95% CI -0.87 … -0.35, p<0.001), and a strong negative correlation was found in the HGj group (r_p = -0.84, 95% CI -0.98 … -0.10, p<0.05).

Discussion

SCI is a severe pathology wich lead, among other things, to the loss of supraspinal innervation of motor neurons due to axonal tracts disruption. Therefore, the main goal of SCI treatment is restoration of this innervation, for example, by creating an artificial environment for axon growth through the lesion site using tissue scaffolds [11], notably pHPMA-hydrogel [12-16]. In this context, here we obtained two main results: 1) the same volume of SCI in adult animals, compared to young animals, leads to a smaller neurological deficit; 2) against the background of significant autogenic recovery of the motor function, the effect of pHPMA-hydrogel on the outcome of the regeneration process is not significant. Both results were unexpected, based on the available literature data, and require discussion.

Regarding the first result, it is well known that mechanisms of autogenic regeneration after SCI include rewiring motor system networks at supraspinal [21, 22, 26, 27] and spinal [21, 22, 26-28] levels and involve propriospinal neurons [26, 28-30], and injured long projection axons [22]. For example, it was found that damaged spinal cord axons can sprout over short distances, branch, and form new synapses [21], and this process, at least in rats, begins within the first 6 hours after SCI [31]. Apparently, thanks to such mechanisms, a significant proportion of SCI patients exhibit spontaneous recovery of neurological functions [32-34].

Literature data indicate significant autogenic restoration of motor activity of the paretic limb after lateral hemisection of the rat spinal cord. Mills et al. (2001) [35] report that after lateral hemisection at the lower thoracic level in male rats (100-125 g), the function of the paretic limb is restored on the 35th day, depending on the breed of animals, to the level of ~15-17 BBB points. At the same time, the authors consider the motor function of the posterior contralateral limb to the site of injury to be intact in this observation. These results are consistent with the data of a number of other works [36-39]. However, Arvanian et al. (2009) [37], and later Li et al. (2017) [39], report a deficit in motor function of the contralateral hind limb one month after lateral hemisection of the thoracic spinal cord at the level of ~15 BBB points, only a few points less than the deficit in the paretic limb. Apparently, similar results of autogenic restoration of motor function of paretic limbs are inherent in the crossing of the dorsal half of the spinal cord or the corticospinal, rubrospinal or other descending supraspinal pathways in the rat, with the exception of the reticulospinal pathway, which in animals of this species plays a leading role in ensuring walking locomotion [40].

In contrast, after excision of a lateral half fragment of the rat spinal cord substance at the mid- or lower thoracic level, autogenic restoration of motor function is generally less effective. For example, Jian et al. (2015) [41] after a three-millimeter excision in adult female rats (Sprague-Dawley) obtained a FI value of the paretic limb at the level of ~6 BBB points after 8 weeks. Zhang et al. (2016) [42] after a two-millimeter excision in adult male rats (Sprague-Dawley) as of the 70th day describe a FI of the paretic limb at ~4.8 BBB points, demonstrating data (fig. 4 A–D) on the deficit of motor function of the hind contralateral limb as of the 30th day. Pertici et al. (2013) [13] in adult male rats (Sprague-Dawley) 14 weeks after a one-millimeter excision found a FI of the paretic limb at 8-9 BBB points. In contrast, Hsieh et al. (2010) [43] 55 days after a one-two-millimeter excision in adult male Wistar rats recorded a FI of the paretic limb at the level of ~11 BBB points, and of the hind contralateral limb at the level of ~15 BBB points, and the next day after the intervention, the function of the hind contralateral limb was described at the level of ~3 BBB points. Ke et al. (2022) [44] 4 weeks after an approximately two-millimeter excision in

six-week-old male Sprague-Dawley rats detected a FI of the hind limbs at the level of ~15 BBB points.

According to our early observations [45], lateral spinal cord hemisection in male rats with the procedure for verifying its completeness is accompanied by a profound persistent deficit in motor function of the paretic limb – in young animals at the level of ~5 BBB points, in adults – ~3 BBB points. In these observations, signs of damage to the contralateral part of the spinal cord were recorded in almost every third case, and signs of peripheral paresis, i.e. caudalized spinal cord injury or more caudal spread of secondary alteration, were recorded in almost every fifth case [23], which indicates significant injury to the areas of the spinal cord adjacent to the hemisection zone. By the way, Zhang et al. (2019) [46] 4 weeks after modeling a lateral half-section of the spinal cord in adult male rats (Sprague-Dawley line) with similar intraoperative pathomorphological consequences (Fig. 1 c), describe a FI of the paretic limb of ~8 BBB points, without revealing the condition of the contralateral hind limb. More careful lateral hemisection in young animals, without significant trauma to the butt ends of the transected half of the spinal cord, according to our data, is accompanied by spontaneous restoration of motor function of the paretic limb up to ~10 BBB points [14, 23], one-millimeter excision of the lateral half of the spinal cord in young animals (**SCIj** group) leads to a deficit of motor function of the paretic limb at the level of ~1 BBB point, and in adult animals (**SCI** group) – to a deficit at the level of ~7 BBB points, without signs of impaired motor function of the contralateral limb.

In our opinion, the differences between the data of several of our experimental series [14, 23, 45], as well as between the experimental data of other authors, can, among other factors, be associated with the hemisection technique, in particular, with injury to adjacent areas of the spinal cord and the rostrocaudal and translateral spread of post-traumatic inflammation, which makes it difficult to involve contralateral and bilaterally distributed interneurons of the spinal cord in the formation of supraspinal reinnervation pathways of the paretic limb motoneurons "bypassing" the epicenter of the injury. This interpretation is consistent with another observation–a significant difference in the results of the autogenous repair process after a careful one-millimeter excision of the lateral half of the spinal cord in young (**SCIj** group) and adult (**SCI** group) animals. A possible explanation for this difference may be the small (less than 1 mm) rostrocaudal distribution of the axonal and dendritic apparatus of most of those interneurons of the contralateral part of the spinal cord of the young rat, through which the alternative supraspinal innervation pathway is established. Under these conditions, implantation of pHPMA-hydrogel (apparently, precisely as a matrix for axon growth) has a significant positive effect on the restoration of motor function (HGj group [14]). Since significant postnatal neurogenesis in the mammalian spinal cord is most likely absent, the increase in the size of this part of the nervous system during the animal's maturation is accompanied by an increase in the length of the processes of neurons – participants in the supraspinal innervation pathways of motor neurons. Under such conditions, the zone of a one-millimeter defect of the lateral half of the spinal cord in adult animals, unlike young ones, can be covered by the rostrocaudal spread of the processes of many interneurons of the contralateral part, with the participation of which an alternative path of supraspinal innervation of caudal motor neurons will be established. Within this hypothesis, if the primary or secondary damage at the level of spinal cord unilateral injury spreads contralaterally, the effectiveness of such a mechanism will be significantly reduced due to the damage to the corresponding interneurons of the contralateral part.

Also, from the point of view of the same hypothesis, in the case of spinal cord lateral hemisection in young animals (see [14]), or one-millimeter spinal cord lateral hemi-excision in adult animals (**SCI** group), the role of the pHPMA-hydrogel in restoration of motor function is insignificant (see [14, 23], as well as the **HG** group in this work), since the establishment of an alternative pathway with the participation of contralateral interneurons is likely faster and more extensive than the growth of injured fibers through the pHPMA-hydrogel. However, in the case of a rough spinal cord lateral hemisection in adult animals (see [45; 47, p. 136-138]), the pHPMA-hydrogel implanted immediately after the injury may limit secondary damage to the spinal cord substance, increase survival of the opposite part interneurons population and therefore increases motor function restoration [47, p. 136-138].

In general, the participation of propriospinal interneurons in establishing connections with motor neurons of the paretic limb after lateral hemisection of the spinal cord is quite well known [28-30], however, the nature, diversity and functions of this neuronal population, despite long-term study [49] remain fragmentary [49, 50], not enough to confirm or refute our interpretation of the results proposed above. However, the literature also describes cases

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of significant recovery of the ipsilateral paretic limb motor function after adult rat lateral spinal cord hemisection in the lower thoracic region with morphological signs of paramedian contrlateral damage [36], or with signs of significant motor deficit of the contralateral hind limb [37, 39].

Study limitations

The methodology of this study has a number of limitations. First of all, the differences found between the results of the recovery process in young and adult animals may be associated with genetic characteristics and differences in the maintenance and nutrition of both groups of animals in two different institutions [23]. For example, differences of ~2 points on the BBB scale have been described between the results of one month regeneration in adult rats of different stocks after unilateral spinal cord injury [35]. Second, the data obtained using the BBB scale after unilateral spinal cord injury should be evaluated with caution in the range of motor function values above 8 points [23]. Also, the lack of consensus among numerous experimental data on the results of the recovery process after unilateral spinal cord injury in rats [13, 14, 23, 35-46], in our opinion, indicates the significant importance of certain, currently unexplained surgical features of modeling this type of injury, which could also be reflected in the differences in the results of the two experimental series discussed in this article. At the same time, the lack of classical blinding and randomization in this work, in our opinion, did not have a significant impact on the reliability of the data obtained, since the result of the experiment turned out to be opposite to our research hypothesis. Finally, our assumption regarding the role of propriospinal neurons of the contralateral spinal cord part, although contextual to the classical ideas about the mechanisms of supraspinal reinnervation of paretic limbs motor neurons after SCI [26, 28-30], requires complex verification involving modern neurophysiological studies on living spinal cord preparations, viral tracing of neuronal pathways, and optogenetic confirmation of their participation in the motor function. Therefore, our data, obtained in this study, require further careful verification.

Conclusions

1. Despite the fact that in young rats, a one-millimeter defect in the lateral half of the spinal cord is accompanied by a profound permanent deficit in the motor function of the paretic limb, in adult animals, after such an injury, the motor function of the paretic limb recovers quite quickly to ~30% of its normal level.

2. In contrast to the significant positive effect of pHPMA-hydrogel implantation on the motor function restoration after a one-millimeter excision of the spinal cord lateral half in young rats, the role of pHPMA-hydrogel in adult animals under similar conditions is not significant.

3. Spasticity of the paretic limb is minimal in adult animals with or without pHPMA-hydrogel implantation, and also minimal in young animals with pHPMA-hydrogel implantation; only young animals without pHPMA-hydrogel implantation exhibit maximal spasticity.

4. There is generally a negative correlation between motor function and spacticity after 1-mm excision of the spinal cord lateral half.

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pHPMA-гідрогель не покращує інтенсивне автогенне відновлення рухової функції після висічення бічного фрагменту спинного мозку у дорослого щура

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Анотація: травма спинного мозку (ТСМ) є видом ушкодження з високою поширеністю, смертністю та рівнем інвалідизації. Одним із підходів у реабілітації при ТСМ є створення умов для регенеративного росту аксонів через зону ушкодження за допомогою тканинних каркасів, зокрема pHPMA-гідрогелю (pHPMA – полі(N-[2-гідроксипропіл] метакриламід)). Оцінка ефективності такого підходу можлива лише в моделях перерізу спинного мозку з високою відтворюваністю. Метою цієї роботи було визначити вплив негайної імплантації pHPMA-гідрогелю в епіцентр однобічного дефекту спинного мозку довжиною 1 мм у дорослого щура на рухову функцію паретичної кінцівки у порівнянні з ефективністю аналогічного втручання у молодих тварин. Дослідження проведено на білих безпородних дорослих самцях щурів (3–4 місяці). Для порівняльного аналізу використано результати, отримані на молодих тваринах в іншій установі та раніше опубліковані в інших роботах. В обох випадках виконували висічення латеральної половини спинного мозку на рівні нижнього грудного/верхнього поперекового відділу довжиною 1 мм з негайним заповненням дефекту фрагментом pHPMA-гідрогелю. Протягом 5 місяців після втручання рухова функція паретичної кінцівки у дорослих тварин досягала приблизно третини від норми як при імплантації pHPMA-гідрогелю, так і без неї. Спастичність паретичної кінцівки у дорослих тварин була мінімальною незалежно від імплантації гідрогелю. Загалом спостерігалася негативна кореляція між рівнем рухової функції та спастичністю. Отримані дані свідчать, що імплантація pHPMA-гідрогелю в однобічний дефект спинного мозку довжиною 1 мм, на відміну від молодих тварин, не має суттєвого впливу на відновлення у дорослих тварин. На основі порівняльного аналізу результатів у молодих і дорослих тварин висунуто гіпотезу, що відновлення рухової функції паретичної кінцівки після однобічної ТСМ може відбуватися за участю інтернейронів/пропріоспінальних нейронів контралатеральної частини ушкодженого спинного мозку з обмеженою ростроаудальною протяжністю аксонів і дендритів.

Ключові слова: травма спинного мозку, задня кінцівка, парез, м'язова спастичність, регенерація спинного мозку, гідрогелі.