

Electrophysiologic and Histopathological Evaluation the Fibrinolytic Effect of Streptokinase in Experimental Hematomyelia

Deneysel Hematomyelide Streptokinazın Fibrinolitik Etkisinin Elektrofizyolojik ve Histopatolojik Olarak Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to evaluate the local effects of streptokinase (SK) through histopathological analysis and electrophysiological assessment using somatosensory evoked pathway (SEP) measurements.

Material and Methods: A total of 54 male albino rabbits were used in this study. The rabbits were categorized into three groups: 6 for the standardization group; 24 for the experimental group, and 24 for the control group. Following the induction of experimental hematomyelia in both the control and experimental groups, SEP recordings were obtained on days 1, 3, 7, and 14. Frozen sections were also prepared for analysis.

Results: Findings indicated that recovery began on the third day in both the control and experimental groups, with SEP values being comparable. By the seventh day, improvement continued progressively in both groups, and SEP recordings remained similar. After 14 days, the greatest degree of recovery was observed in both groups, with SEP values approaching those of the standardization group.

Conclusion: This experimental study demonstrated that there was no therapeutic benefit when performing histopathologic evaluation and statistical analysis of electrophysiological amplitude and latency values. Therefore, local administration of SK was found to be ineffective in the treatment of hematomyelia.

Keywords: Streptokinase, hematomyelia, spinal local effects

ÖZ

Giriş: Bu çalışmanın amacı streptokinazın (SK) lokal etkilerini histopatolojik analiz ve somatosensoriyel uyartılmış yol (SEP) ölçümleri kullanılarak elektrofizyolojik değerlendirme yoluyla değerlendirmektir.

Gereç ve Yöntemler: Bu çalışmada toplam 54 erkek albino tavşan kullanıldı. Tavşanlar standardizasyon için 6, deney grubu için 24 ve kontrol grubu için 24 olmak üzere üç gruba ayrıldı. Hem kontrol hem de deney gruplarında deneysel hematomyeli indüksiyonunu takiben 1, 3, 7 ve 14. günlerde SEP kayıtları alındı. Analiz için don kesitleri de hazırlandı.

Bulgular: Bulgular hem kontrol hem de deney gruplarında iyileşmenin üçüncü günde başladığını ve SEP değerlerinin karşılaştırılabilir olduğunu gösterdi. Yedinci güne kadar, iyileşme her iki grupta da aşamalı olarak devam etti ve SEP kayıtları benzer kaldı. On dört gün sonra, her iki grupta da en yüksek derecede iyileşme gözlemlendi ve SEP değerleri standardizasyon grubununkilere yaklaştı.

Sonuç: Bu deneysel çalışma, histopatolojik değerlendirmenin ve elektrofizyolojik amplitüd ve latans değerlerinin istatistiksel analizinin terapötik bir fayda sağlamadığını göstermiştir. Bu nedenle, SK'nin lokal uygulamasının hematomyeli tedavisinde etkisiz olduğu bulunmuştur.

Anahtar Kelimeler: Streptokinaz, hematomyeli, spinal lokal etkiler

INTRODUCTION

Neurosurgeons frequently encounter traumatic or spontaneous hemorrhages of the central nervous system, particularly in treatment applications. While advancements

in diagnostic and imaging techniques have enabled rapid and precise identification of various neural pathologies, ongoing research aims to develop effective treatment protocols for conditions such as cerebral edema, spinal contusion, vasospasm, cerebral hemorrhages, hematomyelia.

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The primary mechanism in hematoma resolution is the activation of the fibrinolytic system. The compartments of the central nervous system, the brain enclosed by the cranium the spinal cord within the vertebral column, are anatomically similar due to their continuity and histologically identical neural elements. Studies on the fibrinolytic activity (FA) of brain tissue and its compartments have determined that, despite increased thrombolytic activation in brain tissue, FA is weak, while the meninges and choroid plexuses exhibit high activity. Studies on intracerebral hematomas have explored the use of streptokinase (SK), a fibrinolytic agent, demonstrating its efficacy by incorporating it into treatment protocols (1). However, no studies have evaluated the effects of fibrinolytic agents on hematomyelia. Hematomyelia can result in complete or partial lesions of the spinal cord, leading to motor and sensory deficits as well as autonomic dysfunctions such as sphincter impairment. It is recognized that comparing early electrophysiological recordings with clinical findings is valuable for evaluating the prognosis of neurological deficits following hematomyelia.

In this study, experimental hematomyelia was induced to examine the local effects of SK through histopathological analysis and electrophysiological assessment using somatosensory evoked potential measurements. Changes were evaluated over specific time intervals.

MATERIALS and METHODS

A total of 54 male albino rabbits, each weighing between 2500 and 3000 g, were used in the study. Electrophysiological assessments were conducted using a Medelec-Teca Premiere Plus EMG device. Anesthesia was induced with ketamine hydrochloride, a dissociative anesthetic.

SK was administered as a thrombolytic agent in the experimental groups. All rabbits were fasted 6 h prior to the procedure. For prophylactic purposes, ceftriaxone was administered intramuscularly at a dose of 50 mg/kg. Just before the experiment, anesthesia was induced with an intramuscular injection of 60 mg/kg ketamine hydrochloride. The rabbits were positioned prone on the operating table with their extremities and tails secured. The thoracic region and the upper lateral aspects of the right knee were shaved and disinfected with 10% povidone-iodine. A midline vertical incision, approximately 6-7 cm in length, was made in the upper thoracic region. The skin, subcutaneous fascia, and muscle layers were separated using blunt dissection. Laminectomy was performed at the T1-T4 levels to expose the spinal cord.

In the standardization group, somatosensory evoked pathway (SEP) recordings were obtained from six rabbits using a REM Medelec-Teca Premiere Plus EMG device. The recording parameters included a low filter of 20 Hz, a high filter of 10 kHz, a scan time of 10 msec, a sensitivity of 10 microvolts, a stimulation intensity of 12 milliamps, and a repetition rate of

2 pps. One electrode was placed subdurally at the T2 spinal segment, while the reference electrode was positioned on the adjacent muscle tissue. Dorsal column spinal cord potentials, consisting of a positive wave measuring 7.9 ± 1.15 microvolts followed by 4 or 5 negative waves, were recorded 5.5 ± 0.5 msec after stimulation.

The remaining 48 rabbits were assigned to control and experimental groups. Hematomyelia was induced in these rabbits by collecting 0.1 mL of autologous blood from the femoral artery using an insulin syringe, and injecting it intraspinally at a depth of 2 mm from the dura at the T4 segment with the aid of a guiding frame.

Among the rabbits with hematomyelia, the experimental group received 10,000 U/0.1 mL of SK, while the control group was administered 0.1 mL of saline. Both groups were further divided into four subgroups, each consisting of six rabbits. SEP recordings were performed on days 1, 3, 7, and 14. At the end of the follow-up period, the rabbits were euthanized using a high dose of the same anesthetic. The affected spinal cord segment was promptly extracted and fixed in 10% formalin. The tissue samples were then dehydrated in graded alcohol concentrations, cleared in xylene, embedded in paraffin, and sectioned into blocks. For light microscopic examination, 3–5 micron-thick sections were prepared using a microtome, stained with hematoxylin and eosin, and analyzed under an Olympus BX-50 1 light microscope in the Department of Pathology.

Magnetic resonance imaging (MRI) is specific and sensitive in the radiological diagnosis of hematomyelia. A Siemens Healthineers Magnetom Sola 1.5T was used as an MRI device. In the subject who underwent hematomyelia, the lesion appears hyperintense in the sagittal and axial planes at the T4 level on the T1 sequence MRI.

Histopathological grading was determined as grade 0 for a bleeding area of less than 5% at 40x magnification, grade 1 for 5-25%, grade 2 for 25-50%, and grade 3 for 50% or more.

Statistical Analysis

The electrophysiological results were statistically analyzed using the Student's t-test. Data obtained at the end of the study were evaluated according to this method. A p value of >0.05 was considered not statistically significant, while a p value of <0.05 was considered significant.

RESULTS

There were 6 rabbits in the standardization group. SEP recordings were performed at T2. Table 1 presents information on amplitude and latency values.

SEP measurements performed at the T2 spinal segment level in the dorsal cord 1 day after hematomyelia + saline fluid did not yield measurable amplitude or latency values for tractus functions.

There were 24 rabbits in the control group. SEP recordings were taken on the 3rd, 7th, and 14th day after hematomyelia.

Table 2 presents information on amplitude and latency values. Similarly, SEP measurements at the T2 spinal segment level 1 day after hematomyelia + SK did not show any measurable tract function values. The observed SEP potential damage was identical in both the control and experimental groups after 1 day.

There were 24 rabbits in the experimental group. SEP recordings were taken on the 3rd, 7th, and 14th day after hematomyelia. Table 3 presents information on amplitude and latency values.

In both the control and experimental groups, improvement was observed starting on the third day, with recorded SEP values being similar between the groups. By the seventh day, the improvement continued progressively, and SEP values remained comparable. After 14 days, the highest level of recovery was recorded in both groups, with SEP values approaching those of the standardization group

In both the control and experimental groups, erythrocyte density, edema, inflammatory cell infiltration, and astrogliotic cell proliferation were assessed using a four-grade scale:

Grade 0: None

Grade 1: Mild

Grade 2: Moderate

Grade 3: Intense

Histopathologic results of the control group were obtained on the 1st, 3rd, 7th, and 14th days. Results over 4 grades are shown in table 4

Histopathologic results of the experimental group were obtained on the the 1st, 3rd, 7th, and 14th days. Results over 4 grades are shown in table 5.

DISCUSSION

Spinal cord injury results in the loss of supraspinal control of sensory, autonomic, and motor functions below the lesion level (2). This functional loss occurs suddenly and is irreversible following traumatic spinal cord injury, with secondary lesions developing due to a reactionary cascade. To facilitate the assessment of recovery of spinal cord injury in our model, we determined through histopathological examination that 1 µL of blood was sufficient to induce a neurological deficit in rats weighing approximately 250 g.

MRI has significantly improved the evaluation of various spinal pathologies and remains the primary radiologic diagnostic method for evaluating hematomyelia (2,3). In our study, we experimentally induced hematomyelia and confirmed hematoma formation using MRI. A total of 0.1 cc of autologous blood, collected from the femoral artery, was injected at a depth of 2 mm from the dura mater into the

Table 1. Amplitude and latency values of the first positive wave in the standardization group (n=6)

Subject	1	2	3	4	5	6	X ± SD (n=6)
Amplitude (µV)	8.7	7.5	6.3	8.7	7.5	8.7	7.9±1.15
Latency (ms)	5.7	5.7	5.1	6.0	5.1	5.4	5.5±0.5

µV: Microvolt, ms: Milliseconds, SD: Standard deviation

Table 2. Amplitude and latency values of the first positive wave in the control group at 3, 7, and 14 days after hematomyelia

	Subject	1	2	3	4	5	6	X ± SD (n=6)
Day 3	Amplitude (µV)	2.5	2.5	3.7	2.5	2.5	2.5	2.37±0.327
	Latency (ms)	6.2	6.1	6.3	5.7	6.0	5.7	6.37±0.225
Day 7	Amplitude (µV)	2.5	2.5	3.7	2.5	2.5	2.5	2.7±0.490
	Latency (ms)	6.2	6.1	6.3	5.7	6.0	5.7	6.0±0.234
Day 14	Amplitude (µV)	9.0	6.2	6.9	6.9	7.5	6.2	7.2±1.886
	Latency (ms)	5.6	5.5	5.7	5.9	5.1	5.8	5.6±0.297

µV: Microvolt, ms: Milliseconds, SD: Standard deviation

Table 3. Amplitude and latency values of the first positive wave in the experimental group at 3, 7, and 14 days after hematomyelia + SK

	Subject	1	2	3	4	5	6	X ± SD (n=6)
Day 3	Amplitude (µV)	2.6	2.5	2.6	2.5	2.5	2.8	2.68±0.445
	Latency (ms)	6.3	6.1	6.2	6.5	6.6	6.3	6.24±0.234
Day 7	Amplitude (µV)	2.5	2.5	3.2	2.6	2.5	3.6	3.0±0.441
	Latency (ms)	6.1	6.2	5.8	5.7	6.0	5.9	5.87±0.187
Day 14	Amplitude (µV)	8.9	11.3	6.2	7.5	6.9	6.9	8.7±1.876
	Latency (ms)	5.5	5.4	5.7	5.9	5.2	5.8	5.52±0.264

µV: Microvolt, ms: Milliseconds, SD: Standard deviation, SK: Streptokinase

dorsal funiculus at the T4 spinal segment, using a guiding frame. Histopathological analysis revealed that this amount of blood was sufficient to induce a neurological deficit.

Previous studies have examined hematomyelia induction using different volumes. Fehlings al. (4) reported that 1 µL of hemorrhage in the human brain was equivalent to 0.75 mL in rats weighing approximately 250 g. Similarly, Milhorat et al. (2) used 2 µL of donor blood to experimentally induce hematomyelia in the dorsal funiculus of the spinal cord in rats. Given the morphological differences in spinal cord structure, weight, and volume between rats and rabbits, we aimed to create hematomyelia using 10 µL of autologous blood in our model.

In our experimental study, we found that SK increases FA, although it is possible to delay the improvement due to its toxic effect on the tissue. We determined that six subjects died when we administered the SK dose as intramedullary from "15000/kg." We thought that high mortality may be caused by the administration of the SK dose in the hospital, and we adjusted the dose. We determined that there was no mortality at a dose of SK given at 10,000 U/kg.

Hematomyelia triggers two distinct local responses. In the acute phase, a localized cellular response occurs, characterized by microglial cell proliferation. In the subacute phase, astrocyte proliferation results from hypertrophy and

hyperplasia (2). Additionally, the second specific response involves the drainage of varying amounts of blood and blood products into the central canal of the spinal cord.

In our experimental study, histopathological examination on the first day revealed a high density of erythrocytes in the dorsal column, the presence of erythrocytes in the central canal, and tissue edema in both the control and experimental groups. By the 3rd day, erythrocyte levels began to decline, while polymorphonuclear leukocytes increased, and mononuclear leukocytes were observed, and edema became more pronounced. On the 7th day, there was a gradual reduction in erythrocyte density and edema, along with an expansion of the central canal, which contained blood and blood products proximal to the lesion site. By the 14th day, erythrocyte numbers continued to decrease, edema had resolved, and the central canal exhibited further widening at and proximal to the lesion site. Additionally, necrotic cells, blood products, and astroglial cell proliferation were detected within the central canal.

Our study also found enlargement of the central canal proximal to the lesion site. This enlargement can be attributed to several factors. In deep intramedullary hemorrhages during the acute phase, blood components drain into the central canal at varying levels within 2-6 hours after hemorrhage. In cases of superficial hemorrhage, secondary blood products

Table 4. Histopathological findings of the control group, classified into four grades based on follow-up periods of 1, 3, 7, and 14 days

Days	Erythrocyte count						Edema						Inflammatory cell count PNL (P) MN (m)						Astrogliotic cell count					
1	3	3	3	3	3	3	2	2	2	2	2	2	1 p	1 p	1 p	1 p	1 p	1 p	0	0	0	0	0	0
3	2	2	2	2	2	2	3	3	3	3	3	3	3 p	2 p	3 p	3 p	2 p	3 p	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	2 m	2 m	2 m	2 m	2 m	2 m	2	2	2	2	2	2
14	1	0	0	1	0	0	0	0	0	0	0	0	1 m	1 m	1 m	1 m	1 m	1 m	2	2	2	2	2	2

PNL: Polymorphonuclear leukocytes, MN: Monocyte

Table 5. Histopathological findings of the experimental group, categorized into four grades according to follow-up periods of 1, 3, 7, and 14 days

Days	Erythrocyte count						Edema						Inflammatory cell count PNL (P) MN (m)						Astrogliotic cell count					
1	3	3	2	3	3	3	2	1	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0
3	2	2	2	2	2	2	3	3	3	3	3	3	1 p	1 p	1 p	1 p	1 p	1 p	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1	1 m	1 m	1 m	1 m	1 m	1 m	1	1	1	1	1	1
14	1	1	0	0	1	1	1	1	1	1	1	1	1 m	1 m	1 m	1 m	1 m	1 m	1	1	1	1	1	1

PNL: Polymorphonuclear leukocytes, MN: Monocyte

such as fibrin and necrotic cells may be observed in the central canal within 24 hours post-hemorrhage.

The volume of the central canal increases due to the mass effect exerted by blood and secondary blood products. Additionally, the ciliary movement of ependymal cells occurs in a proximal direction, causing the central canal to remain open in the upper part of the spinal cord near the fourth ventricle, while it is closed in the lower region (5). Due to the toxic effects of secondary blood products, necrosis and structural degradation of ependymal cells occur, leading to disruption of the central canal. As a result, syrinx formation may develop rostral to the lesion site due to the accumulation of necrotic tissue, blood, or blood product drainage (2).

Following hemorrhage, coagulation and tissue organization take place. Within a few days, the coagulum undergoes fibrinolysis and liquefies. Masuda et al. (6) demonstrated that FA is absent during the initial days of intracerebral hematoma formation but begins to increase from day 3, reaching its peak around day 10.

They highlighted the significance of FA elevation in the early stages of hematoma formation, particularly in promoting hematoma lysis (7). Based on these findings, some researchers have conducted studies aimed at enhancing hematoma lysis. Matsumoto and Hondo (8) utilized computed tomography-guided stereotactic injections into hematomas and reported successful outcomes following hematoma aspiration with urokinase administration.

Based on this approach, we experimentally induced hematomyelia in the dorsal column of the spinal cord using 0.1 cc of autologous blood obtained from the femoral artery, and applied SK, a first-generation fibrinolytic agent. Our study found no significant difference between the results of the control and experimental groups.

Concerns regarding the adequacy of the SK dose in pharmacotherapy include the lack of prior studies examining its effects on hematoma resorption, and axonal regeneration following FA in hematomyelia. Additionally, its short-term and single-use administration did not show sufficient impact on the recovery of sensory, autonomic, and motor functions after spinal cord injury (9). Consequently, the search for more effective pharmacological agents continues.

In our experimental study, we used a "frame" to position the injection site close to the clot and administered SK into the dorsal funiculus at the T4 spinal segment.

We did not perform surgical evacuation of the lysed hematoma; instead, we allowed for spontaneous absorption. The rate of FA may depend on the hematoma size. The hematoma's mass effect is significant, leading to ischemia and increasing secondary damage. Additionally, impaired circulation delays absorption and prevents inflammatory cells responsible for FA from reaching the injury site.

SEP has become a valuable tool for assessing spinal cord injury severity (10,11). Acute SEP measurements are effective

for predicting recovery (12,13), while chronic SEP recovery has not been shown to correlate with functional improvement (12). In our study, SEP was used as a diagnostic tool to evaluate functional recovery following hematomyelia. However, we found no significant differences in the amplitude and latency values recorded electrophysiologically. There are certain electrophysiological limitations affecting SEPs' efficacy in pharmacotherapy. The disappearance of SEPs does not necessarily indicate the loss of axons, as conduction deficits can arise from multiple factors, including demyelination, changes in excitability at proximal and distal sites, and extracellular ion imbalances.

SEP is most effectively used during spinal surgery or experimental spinal cord injury studies (11), as it monitors acute axonal stress during these procedures. A decline in SEP potentials serves as a key criterion for alerting the surgeon to modify the procedure, helping to prevent postoperative neurological deficits. However, it is important to note that SEPs only assess dorsal spinal cord function. To achieve a more comprehensive evaluation of spinal cord integrity, improvements in motor evoked potential (MEP) monitoring are needed.

MEP amplitudes are highly variable, making their interpretation less reliable, as they tend to be significantly suppressed (14). In our experimental hematomyelia study, MEPs were not utilized due to their sensitivity to segmental excitability changes, and their incompatibility with anesthesia. Additionally, intraoperative SEPs do not always accurately reflect motor function (15,16).

Between 1980 and 1987, Blight and Young (17) conducted SEP studies on 500 patients with acute and chronic spinal cord injuries, aiming to establish correlations between SEP findings and neurological scores. In a spinal cord injury model, evaluating SEP changes over time may provide more valuable insights (17,18). Based on this, our study examined hematomyelia over specific time points—1, 3, 7, and 14 days—to assess the observed changes.

The presence of low-amplitude dorsal column potentials with delayed latencies in both the saline and SK-treated hematomyelia groups, without significant statistical differences from normal values, indicates a higher degree of axonal degeneration in this region.

Action potentials, which began appearing at low amplitudes by day 3, correlated with histopathological signs of tissue healing. However, dorsal column potential amplitudes in both the SK-treated and saline-treated groups were not significantly different on days 3, 7, and 14, suggesting that SK did not enhance axonal regeneration.

Study Limitation

The advantage of this study is that it was performed with experimentally homogeneous groups. The limitation could have been the addition of other markers in the activity in hematomyelia.

CONCLUSION

In our experimental study, the histopathological examination of the control and experimental groups, along with the statistical analysis of the electrophysiologically recorded amplitude and latency values, indicated that there was no observed benefit in terms of treatment outcomes. It was concluded that local SK treatment was not effective in hematomyelia.

Ethics

Ethics Committee Approval: Approval was obtained from the Surgical Medical Sciences Committee of Atatürk University Faculty of Medicine (decision no: 9, date: 04.05.1999).

Informed Consent: Experimental animal model study on the electrophysiological and histopathological effects of streptokinase in hematomyelia; therefore, informed consent could not be obtained.

Footnotes

Authorship Contributions

Conflict of Interest: No conflict of interest was declared by the authors.

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