The effects of human umbilical cord blood transplantation in rats with experimentally induced spinal cord injury

Laboratory investigation

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Object. Even though there have been many efforts to recover neuronal dysfunction following spinal cord injuries, there are limitations to the treatment of these injuries. The purpose of this laboratory investigation was to determine the clinical and neurophysiological effects of human umbilical cord blood (HUCB) transplantation in a rat hemisection model of spinal cord injury.

Methods. In this study, experimental hemisection of the thoracic spinal cord was performed in rats. The rats were divided into 4 groups (6 rats in each group). One group of rats (Group 1) underwent thoracic laminectomy only. Rats in Group 2 underwent laminectomy and right hemisection of the thoracic spinal cord. Rats in Group 3 underwent right hemisection and implantation of freshly obtained HUCB on Day 0 postinjury. Rats in Group 4 underwent hemisection and implantation of freshly obtained HUCB on Day 4 postinjury. Clinical evaluations of rat motor function included the following: neurological examination, Rotarod performance, and inclined plane tests. Rats also underwent reflex evaluation.

Results. The neurological examinations revealed that the frequency of plegic rats was 70.8% at the beginning of the study across all 4 groups; this value decreased to 20.8% by the end of the study. The percentage of rats with a normal examination increased from 25% to 50%. The results of Rotarod performance and 8-week inclined plane performance tests showed statistical significance (p < 0.05) in an overall group comparison across all time points. At the end of the 8 weeks, a statistically significant difference was found in the inclined plane test results between rats in Groups 1 and 2. There were no statistically significant differences between Groups 1, 3, and 4 (p < 0.05). When the reflex responses of the hemisectioned sides were compared, statistically significant differences were detected between groups (p < 0.05). All groups were significantly different with regard to the right-side reflex response score (p < 0.05). Spinal cord preparations of rats in all groups were examined for histopathological changes.

Conclusions. Human umbilical cord blood is stem cell rich and easily available, and it carries less risk of inducing a graft-versus-host reaction in the recipient. Human umbilical cord blood serum is also noted to contain stem cell–promoting factors, which is why cell isolation was not used in this study. Freshly obtained cord blood was also used because storage of cord blood has been reported to have some negative effects on stem cells. Transplantation of freshly obtained HUCB into the hemisectioned spinal cord experimental model demonstrated clinical and neurophysiological improvement. (DOI: 10.3171/2010.4.SPINE09685)

Key Words • spinal cord • injury • human umbilical cord blood • stem cell • transplantation • regenerative therapy

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Cord injuries due to accidents are categorized as a tragic disease group not only because they result in high rates of morbidity and severe disability but also because they cause serious financial and emotional problems for the patients, relatives, the treating medical team, and society at large.23,24,53 Two-thirds of SCIs are the result of either traffic accidents or falling from heights, and more than half of the cases result in quadriplegia. Evaluation of neurological function during admission has revealed that the most frequently observed condition is incomplete quadriplegia, followed by complete paraplegia, complete quadriplegia, and incomplete paraplegia.61 The highest death rate is observed in the 1st year after trauma.9

Although a large amount of research has been and
continues to be done on the treatment of SCIs, we still do not have satisfactory treatment procedures. In this study, our goal was to determine the clinical and neurophysiological effects of HUCB transplantation on neuronal injury in rats with experimental SCIs.

**Methods**

The experimental portion of this study was done in the experimental research laboratory of Pamukkale University Medical School. The physiology laboratory for neurophysiological studies was also used. Animal protocols were approved by the Ethics Committee for Care and Use of Laboratory Animals of Pamukkale University. Animal care and experiments were in accordance with the Guide for the Care and Use of Laboratory Animals.

**Experimental Model**

In this study, 24 female adult Wistar albino strain rats (age range 6–7 years old, average weight 200 g) were used as test animals. The study was conducted at room temperature (average 22°C) in 50% humidity with a 12-hour light, 12-hour dark cycle. Test animals were divided into 4 groups of 6 rats each (Table 1). One group of rats (Group 1) underwent thoracic laminectomy only. Rats in Group 2 underwent laminectomy and right hemisection of the thoracic spinal cord. Rats in Group 3 underwent hemisection and implantation of freshly obtained HUCB on Day 0 postinjury. Rats in Group 4 underwent hemisection and implantation of freshly obtained HUCB on Day 4 postinjury. To achieve prophylaxis, all of the rats included in the study were given a single dose of 50 mg/kg ceftriaxone (Rocephin, Roche) intraperitoneally 30 min before the operation. For anesthesia in all rats, an intramuscular injection of 5 mg/kg xylazine hydrochloride (2% injectable Rompun, Bayer Türk Kimya Sanayi Ltd.) and 100 mg/kg ketamine hydrochloride (Ketalar zefarz, 50 mg/ml, Eczacıbası Pharmaceuticals and Trading A.S.) was used. Drugs were administered intramuscularly with a single injector to the right quadriceps femoris muscle. The rats were then placed prone on an operating table. The lower thoracic and upper lumbar regions of the animals were shaved. The shaved area was cleaned with pyrolidone polyvinyl iodine complex (10% Betadine, Adeka Pharmaceutical and Chemical Products San. and Tic. A. S.).

**Surgical Procedure**

In the subthoracic interscapular area, a subcutaneous skin incision was made from the middle of the spinous processes between T-8 and T-12. The incision was extended to the thoracolumbar fascia from the spinous process edges, and the bilateral paravertebral muscles were peeled off in a subperiosteal fashion from the spinous processes and above the lamina. Then, using an operating microscope (107 series, Seiler Precision Microscopes), a 2-level total laminectomy was performed between T-10 and T-12 for all 24 rats.

While only a 2-level total laminectomy was performed with the aid of an operating microscope in the rats in Group 1, the 6 rats in Group 2 were also subjected to postlaminectomy spinal cord hemisection. After centering the posterior spinal artery, a spinal half incision was made in the right posterior half of the spinal cord using a No. 11 lancet under the operating microscope.

Two-level total laminectomy and spinal cord right hemisections were performed on rats in Group 4 under a microscope on the same day as Groups 1 and 2. The previous operating field was reached by opening the incision sutures on the Day 4 in Group 4 rats, and 0.5 ml of heparinized HUCB was injected into the damaged region. The skin was sutured primarily.

On the same day, 6 rats in Group 3 also received spinal cord right hemisections under a microscope after laminectomy, as in Group 4, and 0.5 ml of heparinized HUCB was injected into the damaged region. The skin was sutured primarily.

The study and follow-up duration for rats was 8 weeks. During this period, normal nutrition and care of the rats were continued.

**Human Umbilical Cord Blood Derivation**

A total of 15 ml of blood was taken from the umbilical cord of 2 women who had just given birth. Informed consent was obtained from the pregnant mothers. Those women from whom umbilical cord blood was obtained had normal, uncomplicated pregnancies. Blood was derived from the placenta through the umbilical cord vein using a heparinized injector just after the cord was separated from the baby. Then, 0.5 ml whole HUCB was administered to all rats in Groups 3 and 4 by injection into the spinal cord hemisectioned field. The HUCB was injected into the sectioned ends of the spinal cord and also filled the gap formed by the hemisection. The total volume of injected HUCB was 0.5 ml. We did not use any immunosuppression or corticosteroids as adjuvant therapy.

**The Rotorod Performance Test**

The position of the lower extremities in rats during walking was evaluated as a neurological examination once a week for the entire 8-week period of the study. Performance during the neurological examination was rated using 3 categories: plegic, paretic, or normal, according to the state of joint movements and forces during walking in the lower extremities (Table 2). During these testing sessions, the strength in the lower extremities was measured by the Rotorod performance test in all rats. In this test,
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the longest time that a rat could stay on the Rotarod system was recorded as a performance score. Weekly measurements of all animals were taken during the 8-week study. The speed of the rotating rod was 10 rpm, and the longest riding time (in seconds) for 3 consecutive tries on the same day was recorded as the Rotarod performance value. Performance was evaluated as complete when a rat remained on the Rotarod system for 180 seconds. The strength of the rats was alternatively measured by the inclined plane method of Rivlin and Tator.48 In this test, the highest angle at which the rat could stay for 5 seconds on an elevated tray was recorded as the angle score.

Sciatic Nerve Reflex Study of the Front Root

At the end of the study, the areas of the operation were opened in all rats, and bilateral roots were exposed by a 3-level total laminectomy at L-3, L-4, and L-5, which is a lower level than the previous laminectomy. The dura was extended laterally to full length, and the front roots were dissected from behind the roots. To record the reflex response, the front roots were cut from the distal direction. Sciatic nerves were revealed by obtuse dissection after skin incision in the rear thigh in both subextremities. Silver/silver chloride was placed on a wire electrode. After placing electrodes on the same sides of the front roots and sciatic nerves of the rats, a 10-V impulse with a 2-msec delay time and a 0.2-msec warning period was given to both sciatic nerves via polygraph 30 times. Reflex potentials were recorded using the silver/silver chloride wire electrode that was located on the same side of the front root (stimulus: single pulse, 10 V, 0.20-msec duration; Dual BIO Amp/Stimulator, PowerLab/8SP, AD Instruments). All animals were exsanguinated at the end of the experiment by decapitating under anesthesia.

Statistical Analysis

For rats with experimental SCIs, data from the Rotarod system and the inclined plane tests, which were used as performance tests, as well as reflex study data were analyzed by Kruskal-Wallis analysis of variance and the Mann-Whitney U-test with post hoc Bonferroni analysis. Neurological examination findings were analyzed using the chi-square test.

Results

During the 8-week study, neurological examinations, Rotarod system performance scores, and Rivlin and Tator’s48 inclined plane test performance scores were recorded weekly for all rats. In the 8th week, after recording the animals’ follow-up scores, spinal front root reflexes of the sciatic nerve were recorded on the same day. At the end of the study, when the incision area was opened, granulation tissue and fibrotic tissues at the site of the laminectomy seemed to be white, soft, and low in density in rats in Groups 1 and 2. However, in rats in Groups 3 and 4, the tissue that covered the laminectomy defect was brown and denser due to the presence of fibrotic tissue.

Results of Neurological Examination

For the neurological examination, the lower-extremity view during walking was evaluated as plegic, paretic, or normal in strength and scored. The distribution of the neurological examinations by group in the 1st week and at the end of the 8th week is presented in Table 3 and Figs. 1–4.

Results of Rotarod Performance

During the 8-week study period, the Rotarod system was used as another method to assess strength. At 8 weeks, the inclined plane performance scores showed statistically significant differences (p < 0.05) in overall group comparisons across all weeks. Week 0 inclined-plane test performances were compared among the 4 groups. When comparing the Week 0 incline plane test performances among the groups, there were statistically significant differences (p < 0.05) between Group 1 and Groups 2, 3, and 4. At the end of the 8 weeks, a statistically significant difference was found in the incline plane test results between Groups 1 and 2. There were no statistically significant differences between Group 1 and Group 3 or 4 (p < 0.05).

Results of the Neurophysiological Reflex Study

After administering 30 impulses to the sciatic nerve in the sciatic nerve–anterior root reflex procedure, the amplitudes of the reflexes from both sides of the anterior root were recorded in millivolts for each rat during the last week of the study. The average score of the reflex amplitudes was calculated for each group. These values were converted to the percentage of amplitude because basal individual and group distribution differences could affect the standard deviation. Initially, right and left reflex potentials were recorded within each group. Then, the amplitudes of the healthy left side were set to 100%, and the percentages of amplitudes on the right side were compared to identify statistically significant differences between groups (Fig. 5).18

When comparing the sciatic nerve–anterior root reflex study data recorded from the left and right sides, there were no statistically significant differences between rats in Group 1 (p > 0.05). However, when comparing the same data within Groups 2, 3, and 4, there were statistically significant differences between the amplitudes recorded for the left and right sides (p < 0.05). Reflex responses, which were obtained from the lower-right extremities in

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<p>| Table 2: Grading of the Rotarod performance during the neurological examination |
|-----------------|-----------------|-----------------|</p>
<table>
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<th>Score</th>
<th>Motor Examination</th>
<th>Definition</th>
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<tr>
<td>1</td>
<td>plegic</td>
<td>no tonus observed in lower extremities during walking or very little tonus observed on proximal evaluation</td>
</tr>
<tr>
<td>2</td>
<td>paretic</td>
<td>leg participated in movement during walking, but direction of walking changed as a result</td>
</tr>
<tr>
<td>3</td>
<td>normal</td>
<td>spontaneous leg movement was observed during walking with no disintegration in the shape or direction of the walk</td>
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all rats, were compared as percent amplitudes using the Kruskal-Wallis analysis of variance method for the statistically significant differences between groups. When the reflex responses from the right side were compared, statistically significant differences were detected between groups (p < 0.05). To analyze the differences between the groups with regard to the right-side reflex responses, a Mann-Whitney U-test with post hoc Bonferroni adjustment was used. Statistically significant differences were found among all groups with regard to the right-side reflex response score (p < 0.05).

**Discussion**

Despite all of the research, a treatment method to completely prevent or cure the damage caused by SCI is still not available. Prevention of further neural damage and regeneration of wounded spinal cords has not been achieved yet for SCI in humans.2,26,55

Embryonic brain and spinal cord tissue transplantations are widely used strategies in spinal cord regeneration studies for spinal cord lesions. Iwashita et al.23 grafted an embryonic rat donor spinal cord into a neonatal rat host spinal cord and observed major regeneration and functional improvements in corticospinal axons along the graft. In another study by Nakamura et al.,40 SCIs were experimentally provoked in newborn rats, and rat embryo spinal cord tissues were transplanted to the site of injury. The authors showed that cell migration and differentiation mostly to oligodendrocytes and neuronal cells; a few differentiated into astrocytes.

In 1988, the first cord blood transplant was performed in a patient with Fanconi anemia in France.13 In 1990, a cord blood transplant was performed in patients with leukemia in Minnesota for the first time.12,13 After collecting umbilical cord blood with sufficient hematopoietic stem cells, the human leukocyte antigen–compatible umbilical cord blood was transplanted to the patient, and a cure was achieved. After this success, umbilical cord blood collection, cord blood banking, and the number of transplantations increased rapidly.12,13,25

Currently, researchers are conducting studies on stem cell treatments that could replace organ transplantation and offer alternatives for patients who lack the opportunity for organ transplantation. However, stem cell therapy is still theoretical in the context of SCI cases, and research continues. Among research studies investigating the use of stem cells, recently developed stem cell cultures and their potential role in the treatment of CNS diseases are very popular topics.17,45,54

Neural stem cells have been used in experimental studies on neurodegenerative disease and neurotrauma, such as Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, ischemic brain damage, and multiple sclerosis. Neural stem cells for traumatic brain injury have been studied in rats with experimental cerebral infarcts by transplanting vascular endothelial growth factor–secreting neural stem cells after experimental cerebral ischemia. Differentiation in neural cells and decreased neurological deficiency were observed 12 weeks after the transplantation.1–5,7,8,22,28,29,32,35,36,44,46,47,50,57,59 The application of stem cells for the treatment of experimental SCI is performed in 3 ways: via lumbar puncture with intrathecal injection,30 intravenously,6 and via an intraspinal approach, where the cells are implanted directly in the area of the lesion.58

Because of recent progress in stem cell biology, research studies on the use of stem cells in experimental SCIs have led to insights into new therapeutic approaches targeting the regeneration of the damaged CNS.6,10,16 The principles of therapy are divided into the following 2 subgroups: the activation of endogenous neural stem cells and cell transplantation approaches. For both approaches, it is very important to understand the protection, activation, and differentiation mechanisms of neural stem cells as well as the later stages, including migration, survival, and functional maturation of the differentiated cells.48

In SCIs, undifferentiated cells derived from cells near the central channel around the lesion area and that are positive for the intermediate filament nestin reproduce, migrate to the region of the lesion, and then differentiate into astroglia. Although there are endogenous neural stem cells in the spinal cord that replicate after an SCI, most of them differentiate into astroglia rather than neurons or oligodendroglia. Furthermore, since astroglia form glial scars around cysts over time after the injury, thereby damaging axon regeneration, the extension of axons through the injury zone and remyelination of demyelinated neural axons seems to be impossible. However, it has been shown that neural stem/progenitor cells derived from adult mammalian spinal cord give rise to neurogenesis when they are transplanted to the hippocampus.52
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McDonald et al.37 showed that the transplantation of neural-differentiated rat embryonic stem cells to the rat spine 9 days after traumatic injury resulted in survival of the transplant source cells and differentiation to astrocytes, oligodendrocytes, and neurons. These cells demonstrated an 8-mm migration from the lesion edge. Furthermore, walking analyses of the rats revealed that rats that underwent transplantation could carry their weight with their back legs, but control rats could not.39

The increased reactivity of astroglia in damaged spinal cords inhibits axonal regeneration due to their expression of chondroitin sulfate proteoglycans, which are inhibitors of axonal development.38,39 In the acute phase of the injury, levels of neurotoxic or proinflammatory cytokines that affect astrocyte induction rise and then fall sharply within 24 hours.38 Therefore, the microenvironment of the acute phase is unsuitable for the survival of transplanted cells and/or neuronal differentiation.42,43 However, over time, the microenvironment changes so that it is favorable for survival and neuronal differentiation. In fact, in vitro–produced neural stem/precursor cell transplantation results in mitogenic neurogenesis when performed 9 days after the injury, but not when performed within a few days.41 The chronic phase of SCI is unsuitable for therapeutic transplantation due to the lack of facilitating factors for neurogenesis and the development of large cysts and glial scars that can inhibit axonal regeneration.42,43

Human umbilical cord blood has a heterogeneous cell population rich in hematopoietic CD34-positive stem cells.11,34 However, a small CD34-negative mononuclear HUCB cell population, with features of pluripotent stem cells, has also been described.14,20,60 One interesting feature of HUCB cells is their ability to target and migrate to damaged areas after intravenous infusion.15,33 These cells are an important cell source for transplantation as they are readily available, expandable, and can target damaged nerve tissue by entering the venous circulation.51 While direct implantation of HUCB cells produces highly dense therapeutic cells at the boundary, these cells do not migrate to areas distant from the transplant region. Not all HUCB cells that settle in the spinal cord differentiate into an astrocytic or neuronal type. Additionally, the existence of fewer than 1000 HUCB cells in the area of the damaged spinal cord is sufficient to restore motor functions. The release of trophic factors by HUCB cells may be

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**Fig. 1.** Bar graph showing neurological evaluation of the rats at the beginning (Week 0) and at the end of the study (Week 8).

**Fig. 2.** Bar graph showing neurological evaluation of the rats in Group 2 at Weeks 0 and 8.
sufficient to support damaged tissue. Human umbilical cord blood cells are pluripotent and can differentiate into various types of cells. They are more pluripotent and genetically flexible than bone marrow neural stem cells and are easily obtainable. It has been reported that neural stem cells can differentiate into oligodendrocytes and astrocytes and achieve remyelination of damaged axons via axon regeneration when transplanted into damaged areas. Furthermore, HUCB cells can differentiate into muscle, myocardium, skeletal cells, hepatocytes, oligodendrocytes, and neurons. Neural stem cells can both repair damaged neural tissue and secrete nerve growth factors, such as nerve growth factor, BDNF, glial cell-source growth factor, and fibroblast growth factor. These 3 neurological factors (BDNF, fibroblast growth factor, and nerve growth factor) facilitate regeneration in damaged axons and the recovery of neurological function.

In a study by Saporta et al., an experimental SCI was induced by the aneurysm clip method in rats. They divided rats into the following 5 groups: laminectomy only, laminectomy plus prelabeled human cord blood infusion (intravenous injection), SCI plus cord blood infused 1 day postinjury, SCI plus cord blood infused 5 days postinjury, and SCI only. The neurological status of the rats was evaluated using the BBB scale. Over a 3-week period, they observed improvement, even in the rats that underwent infusion 5 days after injury. Human cord blood–derived cells were observed in injured areas but not in noninjured areas of the rat spinal cords.

Kuh et al. induced acute SCIs at the subthoracic vertebral level in rats using the weight-drop method. Seven days after injury, the authors injected HUCB in one group and HUCB with BDNF in another group. Neurological evaluation of rats was performed using BBB rating scores over the course of 8 weeks. The BBB scores of the group that received HUCB with BDNF transplantation improved more than those of the HUCB-only group. At the end of the study, the differentiation of cord blood cells to neural cells was shown. This study showed that additional neurotrophic factors could contribute to axonal regeneration and cell differentiation in stem cell therapy.

Li et al. performed intraspinal transplantation of CD34-positive cells that were marked with BrdU plus HUCB cells to the damaged area after inducing experimental half-incision in one group of rats; the control group received laminectomy after SCI and phosphate-buffered saline. During the 4-week follow-up period, they used the Tarlov score to evaluate neurological function and ob-
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served statistically significant recovery in the group that received the CD34-positive cord blood cells in comparison with the control group. At the end of the study, they observed GFAP staining in 7% of the CD34-positive cells that were immunohistochemically marked with BrdU and neural nuclear-specific proteins in 2% of the cells in the damaged area and its microenvironment.

In a similar study, Zhao et al.58 implanted CD34-positive cells marked with BrdU plus HUCB cells after inducing spinal half-incision in the spinal cords of one group of rats. A second group of rats received bone marrow stromal cells, and a third group of rats received phosphate-buffered saline. The duration of the study was 4 weeks. The authors reported statistically significant neurological recovery (based on Tarlov scores) in the groups that received cord blood and stromal cells. The improvement in functional score in the group that received umbilical cord blood in the first 2 weeks after the transplantation was significantly higher than in the group that received bone marrow stromal cells. Histological evaluations revealed that CD34-positive HUCB cells and bone marrow stromal cells migrated to the lesion areas. The migrating cells expressed the neural nuclear antigen and GFAP.

In this study, we performed a spinal cord hemisection in the subthoracic region in rats and directly implanted HUCB in the lesion area. Groups that were given HUCB cells and a group that was not given HUCB cells were compared using the data obtained during the study, including reflex scores that were recorded before the rats were killed. During the 8-week study, neurological examination scores, scores from Rotarod and inclined plane tests, and the results of a sciatic nerve–front root reflex study were found to be significantly different between groups that were given HUCB cells and the control group. Transplantation of the HUCB into the hemisectioned spinal cord caused clinical and neurophysiological recovery compared with the control group.

Conclusions

Although there are numerous claims about spinal cord regeneration in the clinical and experimental literature today, none of the studies has yet attained major functional regeneration of mammalian spinal axons. Recently, it has been suggested that stem cells that can replicate and migrate to the adult spinal cord, in combination with processes that facilitate axonal regeneration, such as stem cell transplantation and the application of exogenous growth factors, could provide significant and meaningful neurological recovery in SCIs. The results of ongoing studies make the availability of effective regenerative treatments for human SCIs a realistic aim and not just speculation. In this study, we used a spinal cord hemisection model, and transplantation of HUCB was performed. During an 8-week follow-up period, the experimental groups that received transplanted HUCB demonstrated significant recovery both clinically and neurophysiologically.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Cirak. Acquisition of data: Kaner, Erken, Kiroglu, Colakoglu. Analysis and interpretation of data: Kaner, Erken, Kiroglu. Drafting the article: Cirak, Kaner. Critically revising the article: Cirak, Akkaya. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Karadag. Administrative/technical/material support: Karabulut, Akkaya, Acar, Coskun. Study supervision: Cirak, Acar, Genc. Other: Karadag (performed the experimental study), Erken (performed electrophysiological evaluation and experimental study), Karabulut (obtained human umbilical cord blood), Colakoglu (laboratory study).

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Fig. 5. Bar graph showing the anterior rootlets reflex measurement of the right and left sciatic nerve (amplitude).


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