Comparison of the effects of PRP and hyaluronic acid in promoting peripheral nerve regeneration
An experimental study with vascular conduit model in rats

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AIM: Peripheral nerve defects generally occur due to mechanical, chemical, thermal and pathologic causes and the reconstruction is still a challenging problem. In the present study, we aimed to compare the effects of platelet rich plasma (PRP) that has high levels of growth factors and hyaluronic acid (HA) that is known to have positive effects on nerve regeneration by decreasing scar formation in a rat model where they were injected through allogeneic aorta graft in peripheral nerve defects using histopathologic and functional methods.

MATERIAL AND METHODS: The study involved 20 Wistar Albino male rats that weighed 200 to 250 grams and aged about 1 year old. Of the rats, two were used as donor for PRP and aorta graft harvest. Three random groups of 6 rats were composed. In all of the groups, the left sciatic nerves were used and 1 cm of defects were created. The right sciatic nerves were used as control groups. Group 1 was the group repaired with autograft, Group 2 was the group repaired with HA injected through aorta graft and Group 3 was the group repaired with PRP injected through aorta graft. The findings were evaluated in terms of functional (electromyography and walk test analysis) and histopathologic parameters at 12 weeks.

RESULTS: In all of the groups varying degrees of axonal regeneration was observed. Group 1 was the closest group to the control group showing highest rate of nerve regeneration followed by Group 3 where PRP was injected through aorta graft and group 2 where ha was used respectively.

CONCLUSION: The study demonstrates that PRP enhances peripheral nerve regeneration more than HA when used in a vascular conduit model.

KEY WORDS: Hyaluronic acid, Peripheral nerve regeneration, PRP

Introduction

Peripheral nerve injury is a common casualty, considerably more common than spinal cord injury. Luckily, unlike injuries requiring reconstruction to the central
nervous system, delicate surgical treatments for peripheral nerve lesions do exist. Numerous experimental and clinical studies have been conducted in order to obtain better sensory and functional outcomes. The micro-instruments, conduit tubes, growth stimulators that increase nerve regeneration as well as advances in molecular biology enhanced success rates in peripheral nerve repair. Because complete nerve regeneration does not occur regardless of the cause of the injury, abnormal nerve regeneration usually results in functional loss and pain.

The basic principle for peripheral nerve repair is to excise the scar and fibrotic tissues of the proximal and distal edges of the nerve and a tension-free end-to-end approach preserving the neurotrophic factors within the repair site. In cases where primary repair is not possible, the gold standard is autograft, however some undesired results like scarring, neuroma and denervation of the donor site may be observed.

So far, several techniques and materials were tested as an alternative to autologous nerve grafts. One alternative is the use of allografts, which have shown promising results. Another option is the use of conduits. Autogenous conduits made of veins or arteries were evaluated, but they did not show any benefits and demonstrated the same donor area morbidity problems.

In order to increase the functional outcomes of the primary nerve repairs and autografts as well as to decrease the morbidity, many topical agents have been used on the anastomosis site including various neurotrophic factors like nerve growth factor (NGF), mitomycin C, aprotinin, thyroid hormone, human amniotic fluid, hyaluronic acid and platelet rich plasma (PRP). PRP is a biologic product that found clinical use especially in maxillofacial surgery offering positive impacts on bone healing in the recent years. The enhancing effect of PRP is based on the premise that the large number of platelets in PRP release significant quantities of growth factors that aid the healing process. Of the numerous growth factors contained, particularly PDGF, FGF, VEGF and IGF-I are well-known to have positive effects on nerve regeneration. Hyaluronic acid (HA) is another popular agent that is used both in experimental and clinical studies due to its effects on preventing scar formation. HA is a single-chain, unbranched glucose-amino-glycan polymer found mostly in the extracellular matrix of the soft connective tissue and synovial fluid of the humans. It is thought that topical application of HA may prevent from epineural and extraneural scar formation and facilitate nerve regeneration due to its effects on reducing the migration, proliferation and chemotaxis of lymphocytes as well as inhibiting effects on phagocytosis of granulocytes and macrophage motility.

In the present study, we aimed to evaluate and compare the effects of PRP that has high levels of growth factors and HA that is known to have promoting effects on nerve regeneration by decreasing scar formation in a 1 cm of rat sciatic nerve defect model using histopathologic and functional methods.

**Materials and Methods**

Twenty Wistar Albino male rats weighing from 200 to 250 g were involved in the study. Eighteen were divided into 3 groups with 6 rats randomly assigned to each. The remaining two rats were used as donor in order to harvest PRP and aorta graft. The left sciatic nerve was lesioned in all the groups and the right sciatic nerve remained intact and was used as the control. The rats were housed 3 or 4 to a cage under standard laboratory conditions and carefully observed during the preoperative and postoperative periods by expert veterinarians. The animals were fed regularly with food and water.

**SURGICAL TECHNIQUE**

The rats were anesthetized with the combination of 10 mg/kg Xylazine (Alfazine %2 20 mg/ml, Bayer) and 100 mg/kg ketamine (Ketalar 50 mg/ml, Pfizer) intraperitoneally. The required blood to prepare PRP was harvested from the donor rats taking the blood of the entire body through intracardiac way followed by harvesting aorta grafts. The left sides of the rats were shaved and cleaned with povidone-iodine followed by an oblique gluteal incision. The gluteal fascia and muscular structures were passed and the sciatic nerve was exposed. The defect was created by resecting a nerve segment 10 mm in length proximal to the bifurcation of peroneal and tibial branches. In Group 1, the excised nerve segment was back approached to the defect as an autograft using 10/0 nylon sutures in an epineural way. Both in Group 2 and Group 3, the defects were repaired using an allogeneic aorta conduit with 10/0 nylon sutures. In Group 2 0.3 ml of HA and in Group 3, 0.3 ml of PRP was injected through the aorta conduit (Figs. 1, 2).

**Fig. 1: HA injection into allogeneic aorta graft.**
EVALUATION

In all of the groups, a walk test analysis was applied 12 weeks after the left nerve surgery, followed by electromyographic (EMG) analysis. All the rats were sacrificed and samples from the proximal anastomosis, graft and 10 mm distally to the distal anastomosis of the left sciatic nerve were taken for histopathologic assessment.

WALK TEST ANALYSIS

Motor function was evaluated by analyzing free walking patterns. De Medinaceli was the first to describe this method.22,23 Walking test analyses were performed 12 weeks after the left nerve surgery. The following parameters were measured: print length (PL); the distance from the heel to the toe, toe spread (TS); the distance from the first to the fifth toes and intermediary toe spread (ITS); the distance from the second to the fourth toes. The sciatic functional index (SFI) was calculated for each animal using the formula proposed by Bain et al.24,25 The SFI is a measure of dysfunction and is expressed as a percentage. An SFI equal to -100% indicates that a complete sciatic nerve lesion is present, whereas SFI values from -10% to +10% reflect normal function.

\[
SFI : [-38.3 \times (EPL - NPL) / NPL] + [109.5 \times (ETS - NTS) / NTS] + [13.3 \times (EIT - NIT)/ NIT] - 8.8
\]

E = experimental, N = normal

ELECTROPHYSIOLOGICAL EVALUATION

In all of the groups, electrophysiological evaluation with close needle technique was applied following walk test analysis. Motor conduction from the sciatic nerve to the gastrocnemius muscle was measured in all animals. The latency and amplitude values of the compound maximal action potentials (CMAPs) of the gastrocnemius muscles both in the lesioned and non-lesioned legs were recorded followed by the calculation of lesioned/non-lesioned leg rates.

HISTOPATHOLOGIC EVALUATION

The tissue samples taken from the left sciatic nerves 12 weeks after the surgical process were fixed in 10% formalin for 24 hours for histopathological examination. After fixation and routine histologic tissue preparation procedures, the nerve tissue specimens were embedded in paraffin blocks. Sections of 4 μm thicknesses were prepared using a microtome and stained with phosphotungstic acid hematoxylin (PTAH), Giemsa, and Mason’s trichrome. Images were captured using a Leica DFC 280 light microscope and analyzed using the Leica QWin Image Analysis System (Leica Microsystems Imaging Solutions, Cambridge, UK). In the examination, myelination, edema, fibrosis and mast cell amounts were analyzed. The sections were scored in terms of myelination (no myelinated axons, 0; rare myelinated axons, 1; scattered, irregular, and thin myelinated axons, 2; dense, regular, and thick myelinated axons, 3), fibrosis (no fibrosis, 0; mild fibrosis, 1; moderate fibrosis, 2; severe fibrosis, 3), edema (no edema, 0; mild edema, 1; moderate edema, 2; and severe edema, 2), and mast cell density (no mast cells, 0; 1-2 mast cells, 1; 3-4 mast cells, 2; 5 or more mast cells, 3; observed at 12.6 magnification).

STATISTICAL METHODS

All the data obtained after the functional and histomorphological evaluation of the groups were exported to SPSS for Windows v.10.0 (Statistical Package for the Social Sciences) for statistical analysis. A general comparison of the differences between groups was performed using the Kruskal-Wallis test, a nonparametric test, and the paired comparisons between groups were performed using the Mann Whitney U test. In the analyses, P<0.05 was accepted as statistically significant.

Results

WALK TEST ANALYSIS

In all of the groups, walk test analysis was applied 12 weeks after the surgical procedure. The sciatic function indexes (SFIs) were calculated following data records. The SFIs between the groups were analyzed with Kruskal-Wallis test, a nonparametric test, and the paired comparisons between groups were performed using the Mann Whitney U test. In the analyses, P<0.05 was accepted as statistically significant.
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ELECTROPHYSIOLOGICAL EVALUATION

The median latencies between the groups were analyzed with Kruskal-Wallis test and a statistically significant difference was detected (p<0.001). The other comparisons were made with Mann Whitney U test (P<0.05). Group 1 was the most similar to the control group and there was a statistically significant difference between all of the groups except Group 1-3.

However, a statistically significant difference in Kruskal-Wallis test was detected in the comparison of median amplitude values (p<0.001) and in Mann Whitney U test, a statistically significant difference between all of the groups was detected (p=0.004) (Fig. 4).

SUBJECTIVE HISTOLOGICAL FINDINGS OF PROXIMAL ANASTOMOSIS

Group 1: In the transverse sections stained with Giemsa and Mason, the connective tissue sheaths of the nerve were assessed in its normal structure. The vacuolizations between the axons were evaluated as minimal edema on the endonevrium layer. In the sections stained with phosphotungstic acid-hematoxylin (PTAH), irregularity and variations in the thicknesses of myelin sheaths were observed. Non-myelinated axons wrapped with Schwann cell sheaths existed among the myelinated axons. (Fig. 5).

Fig. 3: Comparison of the mean SFI values of the groups.

Fig. 4: Comparison of the mean latency and amplitude values between the groups.

Fig. 5: Histologic findings of proximal anastomosis in Group 1. Light microscopy images: A: PTAH x 12.6, B: Mason Trichrom x 25.2.
Group 2: In the sections stained with Giemsa and Mason, dense fibrosis and small axons around the peripheral site of the nerve were observed. However, on the central site of the nerve, medium sized axons were detected and no fibrosis was observed. In the sections stained with phosphotungstic acid-hematoxylin (PTAH), there was a majority of myelin sheaths with thin-medium thickness. In the myelin sheaths, occasional irregularities and undulation were observed. In the endonevrial tissue between the axons, a minimal level of fibrosis was detected. Non-myelinated axons were also observed (Fig. 6).

Group 3: In the sections stained with Giemsa and Mason, varying sizes of axon sections where minimal level of edema accompanied were detected. The sections stained with phosphotungstic acid-hematoxylin (PTAH) revealed mainly medium-sized myelinated axons wrapped with regular myelin sheaths. In some of the myelinated axons, vacuoles between axolemma and myelin sheaths were observed. Partially myelin-free axon sections also existed (Fig. 7).

Statistical Findings of Proximal Anastomosis

The median proximal myelination values between the groups were compared by the Kruskal-Wallis test and a statistically significant difference was detected (p=0.027). Mann Whitney U test showed statistically significant difference between Group 1 and Group 2 (p=0.007), Group 2 and Group 3 (p=0.018). However, there was no statistically significant difference between Group 1 and Group 3 (p=0.093).

The Kruskal-Wallis test analysis revealed no statistically significant difference in the median values of proximal anastomosis fibrosis (P = 0.0758). The median values of fibrosis was as follows: Group 2 > Group 3 > Group 1. (Fig. 8)

Subjective Histological Findings of The Grafts

Group 1: In the sections stained with Giemsa and Mason, the connective tissue sheaths of the nerve were...
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observed to have normal structural formation. The enlargements between perineurium and endoneurium layers were assessed as minimal level of edema. The sections stained with Phosphotungstic acid-hematoxylin (PTAH) revealed irregularity, undulation, varying thicknesses of myelin sheaths as well as a majority of small sized axons wrapped with thin myelin sheaths. Periaxonal vacuolization existed in some of the myelinated axon sheaths. In the connective tissue between the axons, medium level of fibrosis and numerous non-myelinated axons were present (Fig. 9).

**Group 2:** In the sections stained with Giemsa and Mason, intraluminal connective tissue wrapped with vascular media layer was observed. In greater magnifications, it was noted that these connective tissues included varying sizes of axons. The sections stained with PTAH revealed clustered, thin myelin sheaths. Localized irregularities and periaxonal vacuolization on myelin sheaths were detected. Many Schwann cells were encountered in the examined sections. Fibrotic changes and edematous regions were noted in the endoneurium between axons. Non-myelinated axons were also observed (Fig. 10).

**Group 3:** In the sections stained with PTAH, Giemsa and Mason; some areas belonging to the vascular media layer on the peripheral site and partially; fibrotic connective tissue existence was noted. The transverse sections revealed clustered, small axon bundles in fibrous connective tissue. In the longitudinal sections, axons with myelin sheaths were also encountered. The increase in the amount of cells with big nuclei around connective tissue was assessed as Schwann cell hyperplasia. Mainly, small axons with thin-irregular myelin sheaths were detected. Edema was noted in all of the sections (Fig. 11).

**STATISTICAL FINDINGS OF THE GRAFTS**

The mean graft myelination rates between the groups were evaluated by the Kruskal-Wallis test, and a statistically significant difference was detected ($p=0.027$).

![Fig. 8: The mean myelination and fibrosis values of the proximal anastomoses.](image1)

![Fig. 9: Histologic findings of the graft in Group 1. Light microscopy images: A: PTAH x 12.6, B: Mason Trichrom x 25.2.](image2)
Mann Whitney U test revealed statistically significant difference between Group 1-2 (p=0.011), Group 2-3 (p=0.043), however there was not a difference between Group 1-3 (p=0.093)
The Kruskal-Wallis test was used for the statistical evaluation of the graft fibrosis averages, and a statistically significant difference was not detected (p=0.799). Group 2 and Group 3 had higher level of fibrosis. (Fig. 12)

**HISTOLOGIC FINDINGS OF DISTAL ANASTOMOSIS**

**Group 1:** In the sections stained with phosphotungstic acid-hematoxylin (PTAH), irregularity, undulation, and variations in the thicknesses of the myelin sheaths were noted, and mostly, small axons with thin myelin sheaths were observed. The sections stained with Giemsa and Mason revealed minimal fibrotic changes. Edema was present in the connective tissue between axons. In addition, many nonmyelinated axons of various sizes were observed (Fig. 13).

**Group 2:** The sections stained with phosphotungstic acid-hematoxylin (PTAH), Giemsa and Mason revealed highly irregular, deformed axons and severe edema as well as mast cells were detected between each other. The myelin sheaths around the axons were lost and transformed into neurokeratin network. Also, myelin-free axon sections wrapped with Schwann cell sheaths were encountered (Fig. 14).

**Group 3:** The sections stained with phosphotungstic acid-hematoxylin (PTAH) revealed small axons and edematous areas between each other. There was an increase in Schwann cells. In the sections stained with Giemsa and Mason, localized mast cells and small axons with thin-irregular myelin sheaths were detected. Minimal fibrotic changes in the connective tissue of endoneurium were observed (Fig. 15).
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**Statistical Findings of Distal Anastomosis**

The Kruskal-Wallis test revealed a statistically significant difference in mean distal anastomosis myelination rates between the groups (p=0.105). The order of the mean myelination rates was as follows: Group 1 > Group 3 > Group 2. Similarly, the mean distal anastomosis fibrosis rates were evaluated with the Kruskal-Wallis test and a statistically significant difference was detected (p=0.041). The order of the mean fibrosis rates was as follows: Group 2 > Group 3 > Group 1. However, Mann Whitney U test showed no statistically significant difference between the groups (Fig. 16).

**Discussion**

The treatment of the peripheral nerve injuries has still been a challenging problem and there is not a certain compromise for the treatment protocol and outcomes.

The gold standard for treating large peripheral nerve defects is reconstruction with autologous nerve grafts. However, the extent of the injury may be a limiting factor for autografts. During repair, altered fascicular architecture in the graft may hinder nerve regeneration due to the scattering of axons. Graft donor-site morbidity is another limitation, since serious problems may occur such as loss of sensation and donor-site nerve function, as well as painful neuroma. Therefore, in consideration of these disadvantages, many studies have been conducted in search of alternatives against autologous nerve grafts that offer easier methods with better functional outcomes and less morbidity in peripheral nerve defect repairs.

Vein tracts are frequently used as conduits for peripheral nerve defect repair, offering less donor site morbidity and harvesting without the need of a secondary incision. However, limitation of nerve regeneration due to the collapse of the vein grafts is still a problem that could not be overcome. In order to prevent vein graft collapse,
metal spiral supports and nerve grafts placed into the vein grafts were studied. Therefore, we used aorta allograft to obtain least collapse by intraluminal injection of HA and PRP in our study. PRP is a fraction of autologous plasma that contains higher rates of platelet than in the normal blood. As a concentrated source of autologous platelets, PRP contains all of the coagulation factors and many growth factors as well as other cytokines that stimulate wound healing. Of the main growth factors it primarily includes PDGF, TGF-beta, VEGF, EGF and IGF. The effect of the PRP occurs due to the synergistic impact of these growth factors. PRP preserves its bioactive property duration for a long time due to fibrin clotting by the activation of platelets through thrombin on the applied region. Aspenberg et al. reported that PRP continued to effect on the Achilles tendon of the rats for 4 weeks following a single dose application. The studies revealed that the scarring around the nerve just affected, the early term of the healing and the actual part of the regeneration realized before the developed scar tissue. In the studies where the effects of PRP on wound healing were investigated, it was prompted that PRP caused extracellular matrix collection and increased connective tissue proliferation particularly due to TGF-beta and PDGF. In contrast, Anitua et al. observed that PRP applied on the titanium implants decreased inflammation. Hyaluronic acid (HA) is another popular agent that is used both in experimental and clinical studies due to its effects on preventing scar formation. HA is a single-chain, unbranched glucose-amino-glycan polymer found mostly in the extracellular matrix of the soft connective tissue and synovial fluid of the humans. HA exists almost in all of the extracellular spaces and holds important roles in the maintenance of hydrodynamic property of the extracellular matrix. It has various structural functions in nerve cell as well as many cellular interactions such as migration, adhesion, neu-

Fig. 14: Histologic findings of the distal anastomosis in Group 2. Light microscopy images: A: PTAH x 12.6, B: Mason Trichrom x 25.2.

Fig. 15: Histologic findings of the distal anastomosis in Group 3. Light microscopy images: A: PTAH x 12.6, B: Mason Trichrom x 25.2.
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...ronal scattering. The most important difference of the adult tissue from the fetal tissue is the HA content, and in studies where the fetal wound healing is imitated, HA is used in order to provide scarless wound healing. Büngner bundles that occur during Wallerian degeneration are formed by extracellular matrix elements like HA primarily and it was shown that blockade of HA receptors inhibit cellular migration. In the studies done for this purpose, HA was administered to the nerve repair site with a pump, however this application is not a practical method. Composition of HA with carboxymethyl cellulose (CMC) as a film sheet partially facilitated the application. It was reported that the film sheet composed of HA and CMC maintained its effect till 4 weeks while CMC was inert and underwent degradation in the body. Mohammad et al. observed increased axonal regeneration in an animal model where they injected HA through a biodegradable nerve guide harvested from human amniotic membrane. Similarly, Seckel et al. and Wang et al. applied HA injection on the nerve repair site stated that the peripheral nerve regeneration process enhanced.

In our study, a practical method was applied by intraluminal administration of HA in Group 2 and PRP in Group 3 through an aorta allograft offering a longer duration of effect and prevention of vessel collapse. In the evaluation of the functional results, walk test analyses were used in the end of 12th week and calculated SFI's were statistically compared. Group 1 in which the autografts were used was the closest one to the control group in terms of the mean latency values and had shorter duration of latency than the other groups. Group 3 in which PRP was used had shorter duration of latency than Group 2 and a statistically significant difference was detected (p=0.004). In the comparison of amplitude rates, Group 1 was the closest to the control group with a significantly higher rate than the others. A statistically significant difference was detected between Group 1-2, Group 1-3, Group 1- control group, Group 2-3, Group 2-control group and Group 3- control group (p=0.004).

Of the parameters that we used in our study, histomorphologic evaluation was performed at 12th week following walk test and electrophysiological analyses. Samples from different sites of the left sciatic nerve (proximal anastomosis, graft, distally to the distal anastomosis) were taken and in these samples a scale was created assessing myelination and fibrosis under light microscope. This was thought to be a better way to evaluate axonal regeneration. Myelination as a marker for axonal regeneration decreased distally in all of the groups while edema, fibrosis and mast cell density increased.

In the proximal anastomoses, a statistically significant difference in terms of myelination was not detected between Group 1 and the control group, or Group 3 where PPR was used. The myelination rates in descending order was: Group 1> Group 3> Group 2. Group 2 had the highest fibrosis rate but there was no statistically significant difference between the groups (Fig. 8).

In the sections taken from the graft the mean myelination rate was highest in Group 1, followed by Group 3 and Group 2. A statistically significant difference was found between all of the groups. Group 3 was close to Group 1 and Group 2 had a scattered and irregular myelination. Group 1 fibrosis rate was lower than Group 2 and Group 3. But there was no statistically significant difference between the groups (Fig. 12).

Of the sections taken from the distal of the distal anastomoses, Group 1 had the highest myelination rate and then Group 3 and Group 2 in descending order (Figs. 16 A). The fibrosis rate was highest in Group 2 followed by Group 3 and 1 (Figs. 16B).

The use of the agents investigated for the effects on regeneration in primary nerve repair or nerve defect models may result in different data. Welch et al. reported that combination of PDGF and IGF-I showed positive effects on peripheral nerve defect models, but the same

Fig. 16: The mean myelination and fibrosis values of the distal anastomoses.
agents did not show the similar effects on primary nerve repair model\(^1\). The same authors concluded that in case the nerve edges came end-to-end tightly without gap formation, mechanical factors would act and this effect would be more dominant than the trophic effect that would develop due to the tested factors. Although Welch et al. declared that primary nerve repair model was not a proper model in search for the effects of trophic factors on regeneration, in numerous studies where this model was used it could be possibly seen that trophic factors had positive effects \(^{12, 14, 45, 46}\).

In the previous studies, it was strongly recommended that a six-week period for epineural scarring formation was sufficient while a twelve-week healing period was required for the evaluation of functional recovery \(^{47}\). Therefore, end of the 12nd week when the functional recovery is complete was waited for evaluation. In the current literature allogeneic vessel grafts, muscle, cartilage, polyglycolic acid (PGA) and silicone tubes were used successfully as alternative to the gold standard treatment of autograft use \(^{12}\).

The rate of myelination in the PRP group gave better results than the HA group in all sections. Although there was not statistically significant difference in terms of fibrosis rates between the groups, the rate of fibrosis in the PRP group was lower compared to the HA group. In our this study we compared the effects of PRP and HA on nerve regeneration, by intraluminal injection through aorta conduit in terms of functional and histomorphologic parameters. In the study revealed varying degrees of nerve regeneration in all of the groups, however PRP showed higher rate of axonal regeneration than HA. In conclusion, this study demonstrates that PRP enhances peripheral nerve regeneration more than HA when used in a vascular conduit model. We believe that these findings will enlighten further studies on the alternative treatment of nerve injuries.

**References**

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