Prostaglandin E1 Combined with Chitosan Conduit Improves Sciatic Nerve Regeneration in Rats

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Abstract

Objective- To study local effect of prostaglandin E1 on sciatic nerve regeneration
Design- Experimental study
Animals- Sixty male healthy white Wistar rats
Procedures- Sixty animals were divided into four experimental groups (n = 15), randomly; Transected (TC), Sham-operation (SHAM), control (CHIT) and prostaglandin E1 treated (CHIT/PGE) groups. In SHAM group after anesthesia left sciatic nerve was exposed through a gluteal muscle incision and after homeostasis muscle was sutured. In CHIT group the left sciatic nerve was exposed the same way and transected proximal to tibio-peroneal bifurcation leaving a 10-mm gap. Proximal and distal stumps were each inserted into a chitosan conduit and filled with 10 µL phosphate buffered solution. In CHIT/PGE group defect was bridged using a chitosan conduit filled with 10 µL PGE. Each group from four group was again subdivided into three subgroups of five animals each and were studied 4, 8, 12 weeks after surgery.

Results- In all subgroups behavioral testing and sciatic nerve functional study confirmed faster and better recovery of regenerated axons in CHIT/PGE than in CHIT group (P < 0.05). Gastrocnemius muscle mass in CHIT/PGE was significantly more than in CHIT group. Morphometric indices of regenerated fibers showed number and diameter of the myelinated fibers in CHIT/PGE were significantly higher than in control group. In immuohistochemistry, location of reactions to S-100 in CHIT/PGE was clearly more positive than in CHIT group.

Conclusions and Clinical Relevance- Response to local treatment of prostaglandin E1 demonstrates that it influences and improves functional recovery of peripheral nerve regeneration.

Keywords- Peripheral nerve repair, Prostaglandin E1, Chitosan conduit.

Introduction

Recent studies and clinical reports indicate that insertion of a conduit could be an interesting alternative to direct end-to-end suturing of nerve stumps or interposition of an autograft.1,2 Widely accepted method by most surgeons is bridging the defect with an autologous donor nerve. Different graft equivalents have also been applied to bridge the nerve stump and regulated through the interaction of a variety of protein and cell signals.3 Biodegradable nerve guides as a temporary scaffold are better than non-degradable biomaterials because the latter remain in situ as a foreign body and ultimately result in limiting recovery of nerve function.4 Nevertheless, the resistance to biodegradation can be a cause of chronic nerve compression in the long run and a second surgery may therefore be required for its removal. Beneficial effects of chitosan as a conduit in promoting nerve regeneration have already been documented and it seems chitosan as a natural polymer has excellent properties including biocompatibility, biodegradability, non-toxicity and adsorption properties, and might be a suitable functional material for peripheral nerve regeneration.5-7 Following nerve transection Wallerian degeneration occurs which is a sequential pattern of axonal degeneration, myelin degradation and supporting glial cell proliferation. During this process, various events take place, including blood-nerve barrier dysfunction, endoneural space reorganization, and most importantly the induction of an intense inflammatory response, constituted by inflammatory mediator release and production.8,9

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Axonal degeneration recruits this response activating Schwann cells and macrophages that proliferate and activate, clearing myelin debris and producing cytokines that perpetuate an inflammatory state. Axonal regeneration is then regulated by the interactions between all the involved cell types and by cytokines, chemokines, growth factors, and other inflammatory mediators. All these events culminate in the promotion of an environment suitable for subsequent regeneration, repair, and axon regrowth. Arachidonic acid and its metabolites are known to modulate neuronal function and survival. There is also evidence that arachidonic acid derivatives, such as prostaglandins, are centrally involved in Wallerian degeneration and in axonal regeneration.

Regarding the association that exists between arachidonic acid derivatives and nerve degeneration and regeneration, the therapeutic modulation of this pathway emerges as a novel strategy aimed at increased motor, sensory, and structural recovery after nerve injury.

Aimed to study local effects of prostaglandin E1 (PGE1) on peripheral nerve regeneration, the present study was designed to attempt to determine if local PGE1 does in fact reduce dysfunction after small gap nerve transection injury in the rat sciatic nerve transection model. Assessment of nerve regeneration was based on behavioral, functional (walking track analysis), histomorphometrical and immunohistochemical (Schwann cell detection by S100 expression) assessment at 4, 8, and 12 weeks after surgery.

Materials and Methods

Animals and study design

Forty-five male white Wistar rats weighing approximately 290 g and 3 months age were divided into four experimental groups (n=15), randomly: Sham-operation (SHAM), control (CHIT) and prostaglandin treated (CHIT/PGE) group. Each group was further subdivided into three subgroups of five animals each. A random number generator was used to create a list of random numbers. Two weeks before and during the entire experiments, the animals were housed in individual plastic cages (50 x 40 x 20 cm) with an ambient temperature of 23 ± 3° C, stable air humidity, and a natural day/night cycle. The animals were handled on a regular daily basis for 2 weeks prior to the study in order to acclimatize them with testing area and experiments. This could minimize anxiety related testing inaccuracies. The rats had free access to standard rodent laboratory food and tap water.

Preparation of chitosan conduit

Chitosan solution was prepared by dissolving medium molecular weight, crab shell chitosan (~400kDa, 85% deacetylated) (Fluka, Sigma-Aldrich St. Louis, MO, USA) in an aqueous solution (1% v/v) of glacial acetic acid (Merck, Darmstadt, Germany) to a concentration of 2% (w/v) while stirring on a magnetic stirrer-hot plate. The solution was stirred with low heat (at 50° C) for 3 hours. The resultant chitosan solution was filtered through a Whatman No. 3 filter paper then vacuum filtration to remove any undissolved particles. To overcome the fragility of chitosan, glycerol (Sigma Chemical Co., St. Louis, MO, USA) was added as 30% (w/w) of the total solid weight in solution. Chitosan conduit was made according to the method described by others by gentle injection of the prepared solution into a home-made mold. The prepared conduit was 2 mm in external diameter, 1.8 mm in internal diameter and 10 mm in length. This internal diameter complies with optimal function in rat models.

Grafting procedure

Animals were anesthetized by intraperitoneal administration of ketamine 5%, 90mg/kg (Ketaset 5%; Alfasan, Woerden, The Netherlands) and xylazine hydrochloride 2%, 5mg/kg (Rompun 2%; Bayer, Leverkusen, Germany). The procedures were carried out based on the guidelines of the Ethics Committee of the International Association for the Study of pain. The University Research Council approved all experiments. Through a muscle splitting approach, the plane between gluteus maximus and biceps femoris was developed 13 and the right sciatic nerve was clearly visible on the underlying hamstrings muscles. Sutures were passed through the nerve epineurium (one on each side), 3 mm apart at a level of 1 cm above the trifurcation of the nerve. Sutures had the same circumferential orientation on the nerve to restore spatial longitudinal nerve continuity. Before transection, both needles were driven through chitosan conduit at each side 2 mm from the edge of the conduit. This facilitated proper and prompt insertion before endoneurial edema obscured the cut ends. Afterward, a complete transection between the sutures was undertaken and the cut ends of the nerve were driven carefully with the aid of the sutures inside the chitosan conduit and held in place. A second epineurial suture was placed, at each side and through the conduit. After placement, the chambers were filled with 10 μL PGE as CHIT/PGE group or with the same volume phosphate buffered solution as a control. In the sham-operation group (SHAM), the left sciatic nerve was exposed through a gluteal muscle incision and after careful homeostasis the muscle was sutured with Vicryl (Ethicon, Norderstedt) 4/0 sutures, and the skin with 3/0 nylon (Dafilon, B/Braun, Germany). The rats were observed on a heating pad during recovery. The animals of each group were anesthetized by intraperitoneal administration of ketamine-xylazine (see above) and were perfused via left cardiac ventricle with a fixative containing 2% paraformaldehyde and 1% formaldehyde. For histomorphometrical and immunohistochemical assessment at 4, 8, and 12 weeks after surgery.
glutaraldehyde buffer (pH 7.4) at 4, 8 and 12 weeks after surgery.

**Behavioral Testing**

Functional recovery of the nerve was assessed using the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale for rat hind limb motor function. The method has been described by others in a previous study. The method has been described by others in a previous study.

**Functional assessment of reinnervation**

Sciatic functional index (SFI)

Walking track analysis was performed 4, 8 and 12 weeks after surgery based on the method described by others.

Static sciatic index (SSI)

The SSI is a time-saving and easy technique for accurate functional assessment of peripheral nerve regeneration in rats and is calculated using the static factors, not considering the print length factor (PL), that was described by the authors in previous studies. When no footprints were measurable, the index score of −100 was given.

**Muscle mass measurement**

Recovery assessment was also indexed using the weight ratio of the gastrocnemius muscles at 12 weeks after surgery based on a previous study. All measurements were made by two independent observers unaware of the analyzed group.

**Histological preparation and quantitative morphometric studies**

Midpoint of SHAM, CHIT and CHIT/PGE groups were harvested and fixed in 2.5 percent glutaraldehyde. The nerves were post fixed in OsO4 (2%, 2 h), dehydrated through an ethanol series and embedded in Epon. Semi thin transverse (5 µm) sections were next stained with toluidine blue and examined under light microscopy. Based on the previous studies an image analyzing software was used for histomorphometrical analysis.

**Immunohistochemical analysis**

For immunohistochemical studies, anti-S-100 (1:200, DAKO, USA) was used. Anti S-100 is a marker for myelin sheath. The procedures were based on a method described in a previous study.

**Statistical Analysis**

Experimental results were expressed as means ± SD. Statistical analyses were performed using PASW 18.0 (SPSS Inc., Chicago, IL, USA). Model assumptions were evaluated by examining the residual plot. Results were analyzed using a factorial ANOVA with two between-subjects factors. Dunnett’s test for pair-wise comparisons was used to examine the effect of time and treatments. The data were presented as mean ± SD and differences were considered significant when $P < 0.05$.

**Results**

**BBB recovery**

The recovery of hindlimb based on BBB scores are shown in Figure 1. The statistical findings showed that administration of PGE improved locomotion of injured limb compared to the control group ($P<0.05$).

**Recovery of sciatic nerve function and reinnervation**

SFI outcome

The findings of SFI assessments are shown in Figure 2. Transection of the nerved resulted in complete dysfunction immediately after operation. At the end of the study period, animals of PGE treated group achieved a mean value for SFI of $-19.8 ± -3.21$ whereas in control group a mean value of $-23 ± -3.6$ was found. The statistical analyses revealed that the recovery of nerve function was significantly ($P<0.05$) different between CHIT and CHIT/PGE groups and application of PGE in chitosan conduit significantly improved functional recovery in the course of time.

**Figure 1.** BBB score for all experimental groups. Local administration of PGE 1 with chitosan conduit entubulization gave better scores than in CHIT group. Standard error at each data point is shown with bars.
Figure 2. Box-and-whisker plots of sciatic nerve function index values in each experimental group during the study period. Local administration of PGE 1 with chitosan conduit entubulization gave better results in functional recovery of the sciatic nerve than in CHIT group.

Figure 3. Bar graph indicating static sciatic index (SSI) values in each experimental group during the study period. Local administration of PGE 1 with chitosan conduit entubulization gave better results in functional recovery of the sciatic nerve than in CHIT group. Data are presented as mean ± SD. * P<0.05 vs CHIT group.

Figure 4. Gastrocnemius muscle weight measurement. The gastrocnemius muscles of both sides (operated left and unoperated right) were excised and weighed in the experimental groups at 12 weeks after surgery. Data are presented as mean ±SD. * P<0.05 vs CHIT group.

**SSI outcome**

The findings of SSI assessments are depicted in Figure 3. Changes in SSI were significant at weeks 4, 8 and 12 weeks of recovery (P < 0.05). The contrasts indicated SSI values at week 12 to differ significantly from those obtained from control, a trend also noticed for SFI (P<0.05).

**Muscle mass measurement**

The findings of muscle mass assessments demonstrated that the weight of muscle in CHIT/PGE group was significantly higher than CHIT group (P<0.05).

**Histological and morphometric findings**

Table 1 shows quantitative morphometric analyses of regenerated nerves for each of the experimental groups. Statistical analysis by means of a one-way ANOVA test showed that 4 weeks after surgery, CHIT/PGE group presented significantly greater nerve fiber, axon diameter and myelin sheath thickness compared to CHIT animals (P<0.05). Using Factorial ANOVA analysis with two between-subjects factors (Group × time); in CHIT/PGE group axon diameters did not show significant difference between 8 and 12 weeks (P>0.05). Increase in mean thickness of myelin sheath did not show statistical difference between 8 and 12 weeks inside CHIT/PGE and CHIT groups (Fig 5-7) (P> 0.05).

**Immunohistochemistry**

The finding of immunohistochemical assessments showed more positive reaction of myelin sheath in CHIT/PGE group compared to CHIT group. Figure 8 shows immunohistochemical analysis of the regenerated nerves in experimental group.
The graph shows the quantitative results of fiber counting. The mean number of nerve fibers in SHAM group was nearly 8276±189 (mean±SD). Both groups of CHIT and CHIT/PGE showed the lower number of fibers than the sham-operated group even at the end of the study period. Data are presented as mean ± SD. * P<0.05 vs CHIT group.

The graph shows the quantitative results of mean diameter of nerves fibers. The mean diameter of nerve fibers in SHAM group was nearly 12.5 ± 0.19 (mean ± SD). Both groups of CHIT and CHIT/PGE showed the lower mean diameter of nerve fibers than the sham-operated group even at the end of the study. Data are presented as mean±SD. * P<0.05 vs CHIT group.

The graph shows the quantitative results of mean thickness of myelin sheath. The mean thickness of myelin sheath in SHAM group was nearly 2.3 ± 0.06 (mean ± SD). Both groups of CHIT and CHIT/PGE showed the lower mean diameter of axons than the sham operated group even at the end of the study period.

Immunohistochemical analysis of the regenerated nerves. Representative cross section taken from midpoint of SHAM group(A), TC (B), CHIT (C) and CHIT/PGE (D)12 weeks after surgery. There is clearly more positive staining of the myelin sheath-associated protein S-100 (arrows) within the periphery of nerve, indicating well organized structural nerve reconstruction in PGE 1 treated nerve compared to that of the CHIT during the study period. Scale bar:10μm

| Table 1. Morphometrical analyses of regenerative nerves for each of the experimental groups: values are given as mean ± SD |
|-----------------|---|---|---|---|---|---|---|---|---|
|                 | SHAM | CHIT | CHIT/PGE |
| Weeks           | 4    | 8    | 12   | 4    | 8    | 12   | 4    | 8    | 12   |
| N               | 8156 ± 395 | 8321 ± 387 | 8111 ± 389 | 1378 ± 176 | 2661 ± 236 | 3101 ± 201 | 3289 ± 236† | 3875 ± 237† | 4621 ± 277† |
| D               | 12.03 ± 0.04 | 11.93 ± 0.17 | 12.04 ± 0.21 | 2.83 ± 0.18 | 4.51 ± 0.24 | 4.85 ± 0.19 | 8.43 ± 0.59† | 10.05 ± 0.18† | 10.32 ± 0.33† |
| d               | 7.03 ± 0.02 | 6.93 ± 0.39 | 7.05 ± 0.46 | 2.12 ± 0.22 | 3.74 ± 0.26 | 3.77 ± 0.23 | 4.65 ± 0.27† | 5.71 ± 0.79† | 5.95 ± 0.60† |
| T               | 2.58 ± 0.02 | 2.44 ± 0.03 | 2.53 ± 0.01 | 0.41 ± 0.02 | 0.43 ± 0.03 | 0.63 ± 0.02 | 2.24 ± 0.19† | 2.37 ± 0.33† | 2.41 ± 0.26† |
| G-ratio         | 0.58 | 0.58 | 0.58 | 0.74 | 0.82 | 0.77 | 0.55 | 0.56 | 0.57 |

N: Number of fibers D: Diameter of fibers (μm) d: Diameter of axon (μm) T: Thickness of myelin sheath (μm)
†Results were significantly different from those of chitosan entubulated animals (P< 0.05)
Discussion

In the present study we used chitosan as a scaffold for keeping the delivered drug in situ. Selection of an appropriate method to evaluate functional recovery of nerve regeneration is extremely influential. Castaneda et al.,\(^2\) suggested that arrival of sprouts from the proximal nerve regeneration is extremely influential. Information taken from BBB scale may be invaluable in evaluation of peripheral nerve process. Results of the present study showed that PGE treated animals had been improved in locomotion of the operated limb compared to the control group during the study period. Walking track analysis and static sciatic index has frequently been used to reliably determine functional recovery following nerve repair in rat models.\(^3\) The present study again showed similar results taken from both SFI and SSI assessments.

Walking is a coordinated activity involving sensory input, motor response and cortical integration.\(^4\) Therefore, walking track analysis, sciatic function index, is a comprehensive test. The results of the present study showed that PGE 1 when loaded in a chitosan conduit ended up a faster functional recovery of the sciatic nerve.

As the posterior tibial branch of the sciatic nerve regenerates into the gastrocnemius muscle, it will regain its mass proportional to the amount of axonal reinnervation.\(^5\) In the present study 12 weeks after surgery the muscle mass was found in both experimental groups. However, CHIT/PGE group showed significantly greater ratios of the mean gastrocnemius muscle weight than CHIT group indicating indirect evidence of successful end organ reinnervation.

Although both morphological and functional data have been used to assess neural regeneration after induced crush injuries, the correlation between these two types of assessment is usually poor.\(^6\) Classical and newly developed methods of assessing nerve recovery, including histomorphometry, retrograde transport of horseradish peroxidase and retrograde fluorescent labeling\(^7\) do not necessarily predict the reestablishment of motor and sensory functions.\(^8\) Although such techniques are useful in studying the nerve regeneration process, they generally fail in assessing functional recovery.\(^9\) Therefore, research on peripheral nerve injury needs to combine both functional and morphological assessment.

In the histological studies, quantitative morphometrical indices of regenerated nerve fibers showed significant difference between CHIT/PGE and CHIT groups indicating beneficial effect of local PGE 1 on the nerve regeneration. However, there was no significant difference in functional and morphometric indices in animals of CHIT/PGE group within study period. Regarding better functional and morphometric indices in group CHIT/PGE versus group CHIT at the end of the study period, it could be stated that local administration of prostaglandin E1 both accelerated and improved the process of nerve regeneration.

In immunohistochemistry the expression of axon and myelin sheath special proteins was evident in both groups which indicated the normal histological structure. The location of reactions to S-100 in CHIT/PGE group was clearly more positive than CHIT group further implying that both regenerated axon and Schwann cell-like cells existed and were accompanied by the process of myelination and the structural recovery of regenerated nerve fibers.

After nerve injury, increased cyclooxygenase expression induces the production of PG in nerve terminals and nonneural cells in the surrounding areas. This process is known to initiate hyperalgesia and neuropathic pain.\(^10\) Prostaglandins are produced in important quantities, and for prolonged time periods, both directly by injured nerves and macrophages in response to soluble factors produced by injured nerves.\(^11\) It has been shown that prostanoid receptors, effectors of biological actions of prostaglandins, are expressed in Schwann cells and could modulate Schwann cell function in vivo.\(^12\) Moreover, it has been shown that prostaglandin E2 could modulate microglial migration and function.\(^13\)

Prostaglandins have also been shown that interact with nerve growth factor in the regulation of inflammatory responses and degeneration following injury.\(^14\) After nerve injury prostaglandins play a crucial role in nerve degeneration and regeneration. These are vasoactive molecules and their action in blood-flow homeostasis and inflammation during nerve injury could be important. Prostaglandin E1 diminishes peripheral nerve ischemia-reperfusion injury, probably through such a mechanism.\(^15\) Following nerve crush injury, PG E1 treatment has resulted in reduced injury, increased repair rates and the upregulation of vascular endothelial growth factor.\(^16\) Schratzberger et al.,\(^17\) showed that vascular endothelial growth factor gene transfer significantly increased nerve blood flow as well as the amount of vasculature in nerves, suggesting that the induction of local angiogenesis ameliorates experimental neuropathy. One mechanism that PGE1 can promote the repair of peripheral nerve with crushing lesion, could be via increasing the expression of vascular endothelial growth factor.\(^18\) It has been reported by clinical and experimental studies that vasoactive treatment can alleviate the effects of lesions in peripheral nerves.\(^19\)

The induction of neuronal apoptosis is a recognized phenomenon after nerve injury that contributes to the physiopathology of nerve degeneration. The administration of PGE1 inhibits neuronal apoptosis in the spinal cord after sciatic nerve constriction injury, independently of changes in local blood flow.\(^20\) This suggests that neuroprotective mechanism of PG E1 is not solely dependent on its vasoactive properties. Apart
from hyperalgesia and blood-flow regulation, prostaglandins also reported to contribute to the molecular and cellular process of nerve degeneration and regeneration. Further studies on sciatic nerve crush injury also showed that PGE1 both reduced apoptosis and improved neuronal regeneration. Prostaglandins are known to modulate the upregulation of heat-shock protein-70 expression, a protein response known to participate in the maintenance of neuron survival after nerve injury. After nerve injury, macrophages migrate into the area and initiate degenerative and regenerative processes. Even though our study shows the neuroprotective action of local PGE in peripheral nerve injuries, data regarding the molecular mechanisms leading to the neuroprotective action remain to be investigated in depth. We have not given the histological and molecular evidence for neuroprotective action of PGE. This may be considered as a limitation to our study. Therefore, the authors stress that the aim of the current investigation was to evaluate a single local dose and clinical treatment potential of prostaglandin E1 on nerve regeneration. The results of the present study indicated that a single local administration of PGE at the site of transected nerve could be of benefit after chitosan graft tubulization.

Conclusions

In conclusion, in the present study prostaglandin E1 applied locally at the time of sciatic nerve repair using chitosan conduit neurorrhaphy demonstrated promising results in nerve regeneration. Thus, dose-response studies should be conducted prostaglandin E1 to determine the combination of graft and the compound that achieve maximal efficacy in nerve transection models.

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چکیده

پروستاگلاندین E1 همراه با کاندولیت کیتوزاتی سبب بهبود ترمیم عصب سیاتیک رت می‌گردد

علاوه‌اً نجف بور

گروه علوم دماگاهی، دانشکده دامپزشکی، واحد ارومیه دانشگاه آزاد اسلامی، ارومیه، ایران

هدف - مطالعه تاثیر پروستاگلاندین E1 همراه با کاندولیت کیتوزاتی بر روی ترمیم عصب سیاتیک رت
طرح مطالعه - مطالعه تجربی در شرایط زندگی حیوانات - چهلم و پنجم رت ویستار سفید نر سالم
روش کار - رهایی بطور تصادفی به چهار گروه 15 تابی تقسیم شدند. در گروه کنترل منفی نقش ۱۰ میلی‌متری در عصب سیاتیک سمت چپ ایجاد گردید. در گروه گردید. در گروه کنترل کیتوزاتی پس از ایجاد نقش ۱۰ میلی‌متری، انتهای قطع شده پروکارمیال و دستمال عصب با استفاده از کاندولیت کیتوزاتی به هم مرتبط شدند. در گروه درمان کاندولیت کیتوزاتی با ۱۰ میکرولیتر پروستاگلاندین بر شد و گروه متعاقبا به سه زیر گروه ۱ تابی تقسیم گردیده و در مقاطع زمانی ۴، ۸ و ۱۲ هفته بعد از جراحی مورد مطالعه قرار گرفتند.

نتایج - تست فاکتوریال نشان داد که عملکرد عصب سیاتیک در رهایی دریافت کننده پروستاگلاندین بهبودی قابل ملاحظه‌ای بی‌پدیدا کرده بود (P<0.05). شاخص‌های مورفومتریک و ارزیابی‌های ایمنی‌های ایمنوهیستوپتیپی‌ها و نتایج ترمیم قابل ملاحظه‌ای در گروه درمان در مقایسه با گروه شاهد نبود (P>0.05).

نتیجه‌گیری و گزارش نهایی - از نظر بالینی تجویز موضعی پروستاگلاندین سبب بهبود عملکرد عصب سیاتیک می‌گردد.