The Effect of Tenoxicam on Histopathologic Healing of Penicillin G Induced Traumatic Sciatic Nerve Injury in Rats

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✔ The aim of this study was to evaluate the histopathologic healing of penicillin G induced traumatic sciatic nerve injury with tenoxicam. 22-gauge sharp edged needle was inserted into the sciatic nerve and 0.1 ml (25000 Ü) crystallized penicillin G was injected. Rats were randomly divided into four groups. 1 ml intraperitoneal 0.09% NaCl solution was administered daily for one week in group I and for three weeks in group III. Group II and IV received 10 mg kg-1 tenoxicam in 1 ml volume intraperitoneally daily, for one week in group II and for three weeks in group IV. At the end of the trial sciatic nerve was explored and evaluated histopathologically in all groups. Perineural or neural healing of groups treated with serum physiologic or tenoxicam in one or three weeks were not statistically different. There was not statistically significant difference between groups, when neural and perineural healing was evaluated together.

Anti-inflammatory drugs were not effective to obtain recovery after penicillin procaine induced injuries in the peripheral nerves, more research is needed for the effective management and treatment for sciatic nerve injury.

Key words: *Sciatic nerve, injury, tenoxicam*

✔ **Ratlarda Penisilin G İle Oluşturulan Travmatik Siyatik Sinir Hasarında Tenoksikamın Histopatolojik İyileşmeye Etkisi**

Bu çalışmanın amacı tenoksikamın penisilin G ile oluşturulan travmatik siyatik sinir hasarında histopatolojik iyileşme üzerine olan etkisini araştırmaktır. Siyatik sinire 22 gauge keskin uçlu iğne ile girilerek 0.1 ml (25000 Ü) kristalize penisilin G enjekte edildi. Ratlar cerrahi işlem sonrası rastgele 4 gruba ayrıldılar. Grup I ve III'e intraperitoneal %0.09 NaCl'den günde 1 ml bir kez uygulandı. Grup II ve IV'e 10 mg kg-1 tenoksikam 1 ml volüm içinde günde bir kez intraperitoneal uygulandı. Grup I ve II'de birinci haftanın sonunda, Grup III ve IV ise 3. hafta sonunda, uygun koşullarda siyatik sinir eksplorasyonu yapılarak histopatolojik değerlendirme yapıldı. Bir hafta ve 3 hafta serum fizyolojik veya tenoksikam tedavisi alan gruplar arasında perinöral veya nöral iyileşme bakımından farklılık yoktu (p>0.05). Perinöral ve nöral enflamasyon birlikte değerlendirildiğinde gruplar arasında istatistiksel farklılık yoktu (p>0.05).

Periferik sinirlerde, penisilin prokain enjeksiyonu sonucu ortaya çıkan sinir hasarında histopatolojik yönden iyileşme sağlanması için sadece antienflamatuar ilaç tedavisinin yeterli derecede etkin olmadığı ve daha etkin tedavi yöntemlerinin araştırılması gerektiği kanısına varıldı.

Anahtar kelimeler: *Siyatik sinir, hasar, tenoksikam*

INTRODUCTION

The accidental injection of various drugs into peripheral nerves has serious medical complications and medicolegal implications. Severe pain, loss of motor function, foot drop and loss of sensation on the innervated nerve region occurs following injection injury[(1)]. The degree of injury varies significantly, depending

upon the specific agent injected. The most neurotoxic substances or agents were penicillin G, diazepam, and chlorpromazine[2,3].

The site of injection was crucial for determination of degree of damage. Intrafascicular injection was invariably associated with severe nerve injury, but extrafascicular injection resulted in minimal damage[4].

Several treatment modalities are used for injection injury. The recommended treatment has ranged from a conservative approach to immediate operative exposure and irrigation, and has also included early neurolysis or delayed exploration with neurolysis or resection and anastomosis[5].

The aim of this study was to evaluate the histopathologic healing of penicillin G induced traumatic sciatic nerve injury with an anti-inflammatory agent, tenoxicam.

MATERIAL AND METHODS

Twenty-four Spraque-Dawley rats with weights ranging between 250-340 grams were used in this study. For the surgical procedure rats were anaesthetized by 12 mg 100 mg^{-1} body weight ketamine hydrochloride, local anesthetic agents were completely avoided throughout the study. Rats were positioned and under sterile conditions sciatic nerves were exposed by a vertical gluteal incision and blunt dissection. 22-gauge sharp edged needle was inserted into the nerve and 0.1 ml (25000 Ü) crystallized penicillin G (Penicillin-G®, Pfizer) was injected. In all rats, the same type of needle was used and only a single injection was made. The incision was then closed by 4/0 atraumatic silk sutures. Following the surgical procedure, rats were randomly divided into four groups and were kept under the same conditions. 1 ml intraperitoneal 0.09% NaCl solution was administered daily, for one week in group I and for three weeks in group III. Group II and IV received 10 mg kg^{-1} tenoxicam (Tilcotil®, Roche) in 1 ml volume intraperitoneally daily, for one week in group II and for three weeks in group IV. At the end of the experimental period in all groups sciatic nerve was explored and the site of injection including the distal and proximal section of the nerve was excised. Excised segments were fixed in 10% buffered neutral formaline and embedded in paraffin. 5 micron-thick sections were stained by hematoxilyn-eosin and were evaluated by a pathologist blind to the experimental groups. Histopathological evaluation was made according to the following criteria:

a) Perineural inflammation: Inflammatory reaction at the epineurium and the adjacent connective tissue was semi-quantitatively evaluated as none (0), mild (+) and marked (++).

b) Neural inflammation: Tissue within the epineurial membrane was evaluated for inflammation and regenerative activity as reflected by Schwann cell proliferation. The results were expressed as none (0), minimal (+/-), mild (+) or marked (++). Criteria for minimal changes included edema and the presence of single perivascular inflammatory cells. Mild (+) and marked (++) criteria required more inflammatory cells and Schwann cell proliferation and were assigned according to the severity of these findings. The latter two categories were also labelled focal if a single fascicle was involved or widespread if more than one fascicle or more than 50% of the nerve section's area was involved. Each separate category obtained was assigned a numerical score and perineural and neural scores as well as the total score for each specimen was calculated (Table I).

Statistical analysis: Results were evaluated using the individual scores for per neural and neural score and the total scores. Scores from all four groups were statistically evaluated using Wilcoxon Rank Sum test. $p<0.05$ were accepted significant.

RESULTS

Perineural tissue and nerve findings were scored and total scores of every nerve were obtained. The sum of perineural inflammation and neural inflammation scores equaled total score (Table II).

Tablo I. Numerical scoring system for perineural and neural inflammation.

Perineural inflammation		Neural inflammation	
None	0	None	0
Mild (+)	1	Minimal (+/-)	1
Marked (++)	2	Mild	
		Focal (+)	2
		Widespread (++)	3
		Marked	
		Focal (+)	3
		Widespread (++)	4

Tablo II. Perineural and Neural Inflammation Scores of Groups.

	Perineural inflammation score	Neural inflammation score	Total score
Group I	1.17±0.98	1.67±0.82	2.83±1.60
Group II	0.17±0.41	0.50±1.22	0.67±1.63
Group III	0.67±0.82	1.00±1.1	1.67±1.75
Group IV	0.17±0.41	1.17±0.75	1.33±1.03

Perineural or neural healing of groups treated with serum physiologic or tenoxicam in one or three weeks were not statistically different ($p>0.05$). There was not statistically difference between neither groups, when neural and perineural healing was evaluated together ($p>0.05$).

DISCUSSION

Muscular paralysis may occur because of sciatic nerve injury related with intramuscular gluteal injection to wrong localization. The suggested treatment models after traumatic injection to sciatic nerve are dilution of the agent with saline, neurolysis at early stages, conservative approaches, physiotherapy, using anti-inflammatory drugs and vitamins[5]. In our study, we have investigated histopathologic effects of anti-inflammatory treatment after injection injury (mechanical + chemical) of the sciatic nerve in rats.

Perineural administration of the local anaesthetics showed to cause an endoneural edema and than to neurotoxic injury by spoiled permeability[6]. To impede effect of histopathologic changes on our study which may occur because of toxic effects of local anaesthetics we didn't apply local anaesthetic infiltration to gluteal area in any case.

Nerve injury after incorrect injection is an important clinical problem. A trauma related directly with needle, neural compression secondary to scar tissue formation and neural fiber injury caused directly by neurotoxic chemicals within the injected agent are accounting for the injection injury occurred in peripheral nerves[5]. Pathologic changes begin 30 minutes after the injection to nerve[1]. Neurotoxic effects of injected medication influences the axons and Schwann cells within the nerve cluster, so the blood nerve barrier spoils and serial immunochemical mechanisms (such as mast cell degranulation, vasoactive amines, plasma kinins, compleman and prostaglandins) are activated. An edema raised in the nerve fascicule through these two mechanisms increases the endoneural pressure 4-5 fold and it spoils both blood flow and conduction of nerve fascicule. Endoneural pressure returns to normal level after 3 weeks[6]. A protein rich edema through increased collagen production causes acceleration of fibrosis and to irreversible nerve injury by compressing the nerve. In other content, while protein rich edema has a "tissue culture" feature, this may provide an appropriate proliferation environment for fibroblasts, mast cells and Schwann cells[7]. Therefore, counteraction of fibrosis through decreasing the edema formation by using anti-inflammatory drugs is desirable.

Penicillin injury in nerves is more related with chemical effects of the drug than mechanical injury[5]. In a partial injection injury, a recovery may occur spontaneously to some degree. However, prognosis is not good if injury is huge. Although, in our study, in a control group on perineural and neural compartments of the formed nerve injuries a spontaneous recovery was observed between the first and

third weeks, this was not statistically significant.

We didn't find any study evaluating the response of the histopathologic changes related with experimental chemical injury formed by penicillin injection or the other agents. In our study, we didn't find a significant difference in the histopathologic recovery rate between groups following administration of anti-inflammatory medication (Tenoxicam) for 1 and 3 weeks to treat penicillin induced sciatic nerve injury. There was also no statistically significant difference between treatment and control groups.

In conclusion; anti-inflammatory drugs were not effective to obtain recovery after penicillin procaine induced injuries in the peripheral nerves, more research is needed for the effective management and treatment for sciatic nerve injury.

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