한국임상수의학회지 15(2) : 378-385 (1998)
Korean J. Vet Clin Med. 15(2) : 378-385 (1998)

Comparison of Therapeutics on Chloramphenicol Injection-induced Sciatic Nerve Injury in Dogs

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개에서 Chloramphenicol주사에 의한 좌골신경손상시의 치료효과의 비교

이주명 · 연성찬 · 권오경 · 남치주
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요 약 : Chloramphenicol주사에 의한 좌골신경손상을 유발한 후 prednisolone을 이용한 약물처치군, 전침군 및 전침과 약물을 병용한 군에서 각각 회복속도를 비교하였다. 정상보행 횟수, pinching을 통한 감각신경의 통감반응, 그리고 병리조직소견 등을 조사한 결과를 요약하면 다음과 같다. Enrofloxacin, cefazolin, cephalexin, penicillin 등의 좌골신경주위 주사에서는 신경마비가 관찰되지 않았으나 chloramphenicol을 주사할 경우에는 좌골신경손상으로 인한 편측성 후지마비가 유발되어 knuckling 반응을 보였다. Chloramphenicol을 투여한후 좌골신경손상에 대한 각 처치에서 정상보행 횟수는 8~12주까지는 침술처치군이 약간 증가하였으나, 처리군간 유의성은 관찰되지 않았다. 실험기간동안 chloramphenicol 에 의한 신경손상에 대한 각 처치군별 병리조직 소견은 호전양상이 관찰되지 아니하였다.

Key words : Chloramphenicol, 좌골신경손상, 전침, 개

Introduction

Sciatic nerve paralysis occurs commonly after intramuscular (IM) antibiotics injection into the hindlimb in dogs.

Unilateral hindlimb paralysis was reported to be induced by intramuscular injection of various kind of antibiotics, such as, tetracycline[6,9], oxytetracycline[6,7], erythromycin[6,7,9], penicillin[7], chloramphenicol[9], sulfisoxazole[6] and streptomycin[7].

Intramuscular injection with vitamin K[9], ischial fracture[4], and sciatic nerve injury from artificial repairing of the femur fracture[8] were reported to induce sciatic nerve paralysis. Saline injection in sciatic nerve or needle insertion did not cause damage to sciatic nerve[6].

However, some degree of mechanical injury on nerve was reported to occur in relation to needle tip angle. The degree of peripheral nerve injury was more serious in 45° than in 14°[16].

Seddon *et al.* classified nerve injury into three groups (neuropraxia, axonotmesis, and neurotmesis) based on histopathology and electrical conductivity[15]. Neuropraxia is equivalent to the first-degree nerve injury. Anatomic continuity of the nerve is preserved, but there is selective demyelination of large nerve fibers that typically causes complete motor paralysis with very little muscle atrophy and considerable sparing of sensory and autonomic function. Electrical conductivity of the nerve distal to the lesion is preserved. Axonotmesis is equivalent to Sunderland's second-degree nerve injury. Anatomic continuity of the nerve and the Schwann sheaths is preserved, but the axons are interrupted. There is complete motor, sensory, and autonomic paralysis and progressive muscular atrophy. Surgery is not necessary for repair. Recovery

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occurs at the rate of about 1 mm a day. Neurotmesis is the most severe injury. There is significant disorganization within the nerve, or actual disruption of its continuity, which preclude recovery without surgical repair. In association with this, there is gradual loss of electrical conductivity in the distal portion of the nerve over a period of up to 3 days. Complete motor, sensory, and autonomic paralysis and progressive muscle atrophy started from the time of the injury.

According to the Sunderland's classification, there are five degrees of nerve injury on the basis of nerve anatomy[19]. And they are functional loss of axonal conduction, loss of axonal continuity without interruption of endoneurium, disruption of the endoneurium, disruption of fascicles and perineurium, disruption of the entire nerve continuity, including epineurium[21].

Rate and success of nerve regeneration are influenced by several factors, such as age of patient, level of nerve injury and duration of denervation. Other factors, significant in the rate and success of nerve recovery, are the type of injury, length of the defect in the nerve, severity of association injury, and the nature and timing of surgical treatment[21].

In unilateral hindlimb paralysis, physical treatment, conservative treatment using corticosteroids, muscle relaxants, and splinting of the leg seldom re-established the functions of the damaged nerve[18,20].

Electro-stimulating method for treating the injured nerve was newly introduced[17]. In electrically treated larval lamprey (*Petromyzon marinus*), the axon regeneration across the lesion was improved at 44~63 days after transecting the spinal cord. Extracellular stimulation of spinal cord showed that action potentials were conducted in both directions across the lesion, but they were not conducted in either direction in most of the sham-treated controls[3].

Electro-stimulating treatment by the transcutaneous electroneural stimulator was good to cure the radial nerve paralysis[18].

The result of electroacupuncture treatment was better than that of non-treated control group in alcohol-induced sciatic nerve injury dogs[17]. However, so far, electroacupuncture of antibiotics-induced sciatic nerve injury has not been studied yet.

Thus, the purpose of this experiment is to investigate effects on intraneural antibiotics injection into the sciatic nerve and to examine the therapeutics after injecting the neurolytic antibiotics.

Materials and Methods

Exp. I: Effects on antibiotics injection into sciatic nerve

Experimental Animal: Fifteen dogs were used, and randomly assigned into 5 groups regardless of sex and age (Table 1).

One hindlimb was selected for antibiotics injection and the other hindlimb for control.

Anesthesia: Preanesthesia was performed by injecting 0.05 mg/kg of atropine sulfate (Atropine®, Jeil Pharm.) intramuscularly. Fifteen minutes after the first, 20 mg/kg of ketamine hydrochloride (Ketamine®, Yuhan Co.) and 0.05 ml/kg of propionyl promazine (Combelen®, Bayer Korea. Co.) were also injected together intramuscularly.

Approach to the sciatic nerve: After caudolateral dissection of the thigh, the space between the biceps femoris muscle and semimembranosus muscle was broadened to expose the sciatic nerve. Sciatic nerve is branched into 4 nerve. Antibiotics were injected into epineurium of sciatic nerve before the branching.

100,000 IU/kg of procaine penicillin G (Penicillin®, Green Cross Veterinary Pharm.) and 25 mg/kg of dihydrostreptomycin sulfate (Streptomycin®, Green Cross Veterinary Pharm.) were intramuscularly injected to protect infection.

Antibiotics: Enrofloxacin (Baytril®, Bayer Korea Co.), cefazolin natrium (Cefazolin®, Yuhan Co.), cephalexin (Colilex®, Virbac), procaine penicillin G (Penicillin®, Green Cross Veterinary Pharm.), and chloramphenicol (Leukomycin®, Bayer Korea Co.)

Table 1. Experimental design

Group	No. of dogs	Treatment	Dosage
I	2	enrofloxacin	2.5 mg/kg
II	2	cefazolin	20 mg/kg
III	2	cephalexin	20 mg/kg
IV	6	penicillin	100,000 IU/kg
V	3	chloramphenicol	40 mg/kg

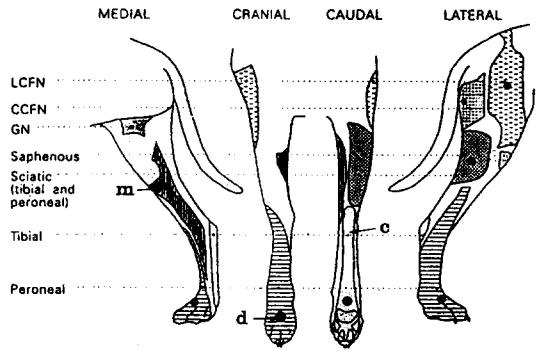

Fig 1. Distribution of sensory nerve in hindlimb of dog.
m: medial pinching region
d: dorsal pinching region
c: caudal pinching region
LCFN: Lateral Cutaneous Femoral Nerve
CCFN: Caudal Cutaneous Femoral Nerve
GN: Genitofemoral Nerve

were used as in Table 1.

Evaluation of normal walking: Degree of sciatic nerve injury was evaluated by average number of normal walking out of 10 walkings up to 12th week after the surgery. If the dog shows knuckling, it was regarded as positive.

Evaluation of sensory nerve injury: Degree of sensory nerve injury was evaluated by pain response of damaged limb through pinching to medial area of stifle joint (medial surface), dorsal area of the 3rd phalange (dorsal surface) and caudal area of hock joint (caudal surface) (Fig 1).

Hooked forceps was used in pinching. It was recorded as positive when the dog showed pedal reflex.

To know the effects of each antibiotics injected into sciatic nerve, normal walking and pain response were examined on the 3rd day after antibiotics injection.

Exp II: Comparison of therapeutics on chloramphenicol injection-induced sciatic nerve injury

Experimental Animal: Twenty six healthy dogs were used, and divided into 5 groups at random regardless of sex and age (Table 2).

One hindlimb was selected for antibiotics injection and opposite limb was treated as control.

Anesthesia: Anesthesia was the same as in Exp I.

Table 2. Experimental design

Group	No. of dogs	Treatment
I	6	control
II	5	medication
III	5	electroacupuncture
IV	5	medication+electroacupuncture
V	5	Sham-treated control

Approach to the sciatic nerve: Approaching method was the same as in Exp I, but the injected antibiotic was only 40 mg/kg of chloramphenicol (Leukomycin®, Bayer Korea Co.).

Medication and electroacupuncture: In groups II and IV, 1 mg/kg of prednisolone (Solon-M®, Daesung Co.) was injected bid, IM for the first 5 days, 1 mg/kg/day for 5 days followed, then 0.5 mg/kg/day for the third 5 days, and then 0.25 mg/kg/day for the last 5 days[14].

In groups III and IV, Tian ping(+)~Hou san li(-), or Huan do(+)~Hou san li(-) acupoints (Fig 2, 3) were electrostimulated together. Round straight needle and electrostimulator (TEC AM-3000®, Tokyo Electric

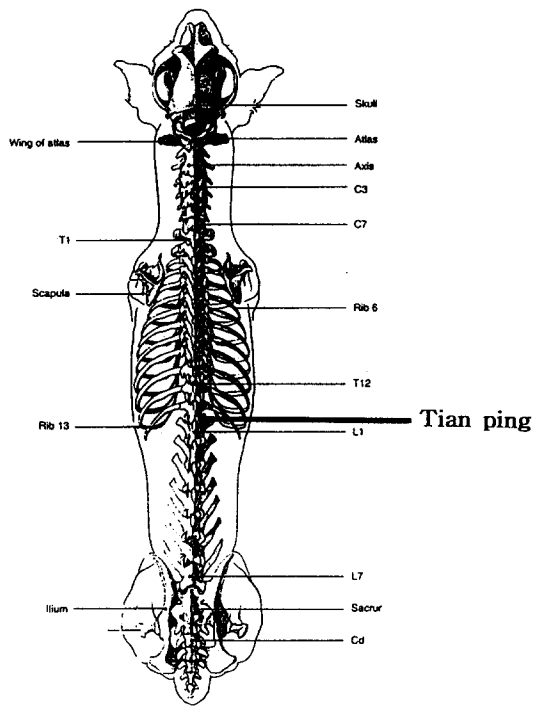

Fig 2. Tian ping acupoint in a dog.

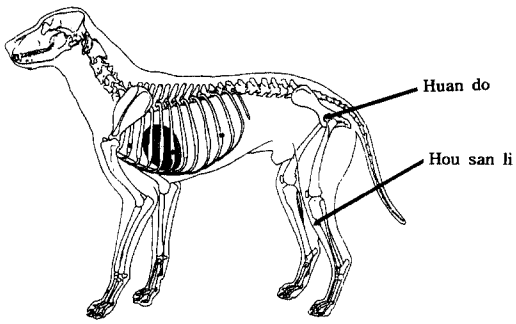

Fig 3. Huan do and Hou san li acupoint in a dog.

Co.) were used. And stimulating condition was 20 Hz, 2 volt, and 20 min, once a day.

Evaluation of motor and sensory nerve injury: Evaluation of nerve injury was the same as in Exp I.

Histopathology of sciatic nerve: One dog was selected randomly from each group at the 3rd day, 4th, 8th, and 12th week after chloramphenicol injection. Two centimeter segment of sciatic nerve including injection site was resected and fixed in 10% phosphate buffered formalin for 24 hours. Hematoxylin and Eosin (H&E) staining was performed.

Effect of therapeutics after sciatic nerve injury by chloramphenicol injection was evaluated by normal walking, pain response and histopathological findings.

Results

Exp I: Effects on antibiotics injection into sciatic nerve

In enrofloxacin, cefazolin, cephalexin, and penicillin injected groups, all dogs responded with normal walking and normal pain reaction by pinching (Table 3). But the dogs of chloramphenicol injected group showed knuckling and no pain response after injection of the antibiotic.

Exp II: Comparison of therapeutics on chloramphenicol injection-induced sciatic nerve injury

In all groups except group V, the number of normal walking showed mild increasing tendency up to the 12 weeks, however no difference was found among those groups.

Table 3. Clinical effects of antibiotics injection into sciatic nerve

Antibiotics	Knuckling*	Pedal reflex by pinching**	
		dorsal	caudal
Enrofloxacin	-	+	+
Cefazolin	-	+	+
Cephalexin	-	+	+
Penicillin	-	+	+
Chloramphenicol	+	-	-

*Knuckling: + abnormal gait, - normal gait
**Pedal reflex: + positive, - negative

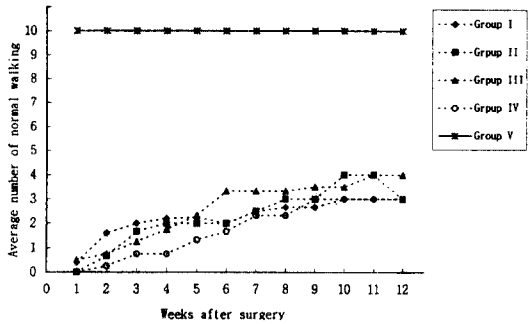

Fig 4. Average number of normal walking out of 10 walkings.

Average numbers of normal walking out of 10 walkings in group I~V were 0.4, 0.0, 0.5, 0.0, 10.0 on the 3rd day, 2.2, 2.0, 1.8, 0.8, 10.0 on the 4th week, 2.7, 3.0, 3.3, 2.3, 10.0 on the 8th week, and 3.0, 3.0, 4.0, 3.0, 10.0 on the 12th week, respectively (Fig 4).

As shown in Table 4, pain response from medial surface in all the tested groups were positive throughout the experiment.

In sham-treated control group (V), the response of dorsal and caudal surface pinching test showed positive response in all individuals.

In control group(I), acupuncture group(III), and acupuncture plus medication group(IV), the results of dorsal and caudal pinching test were all negative.

In medication group(II), both in dorsal and caudal pinching resulted in negative, which one individual responded positively to caudal pinching.

Discussion

Sciatic nerve is a mixed nerve that arises from

Table 4. Pain response to pinching test in hindlimb

Group	Examined Area	Weeks after chloramphenicol injection			
		3rd day	4th	8th	12th
I	medial	6/6*	5/5	4/4	3/3
	dorsal	0/6	0/5	0/4	0/3
	caudal	0/6	0/5	0/4	0/3
II	medial	5/5	4/4	3/3	2/2
	dorsal	0/5	0/4	0/3	0/2
	caudal**	1/5	1/4	1/3	1/2
III	medial	5/5	4/4	3/3	2/2
	dorsal	0/5	0/4	0/3	0/2
	caudal	0/5	0/4	0/3	0/2
IV	medial	5/5	4/4	3/3	2/2
	dorsal	0/5	0/4	0/3	0/2
	caudal	0/5	0/4	0/3	0/2
V	medial	5/5	4/4	3/3	2/2
	dorsal	5/5	4/4	3/3	2/2
	caudal	5/5	4/4	3/3	2/2

*: individuals responded positively/total individuals examined

**: one case of this group did not represent obviously on the 3rd day, and positive on the 4, 8, 12th week

spinal cord segments L6~2. Because the spinal cord ends at the middle of the 6th lumbar vertebra in the dog, the sciatic nerve fibers travel caudally within the vertebral canal before exiting from the canal.

The course of these sciatic nerve fibers makes them particularly subject to injury from lumbosacral fractures and subluxation, lumbosacral stenosis and pelvic fracture. Damage to the fibers within the vertebral canal usually results in bilateral injury, producing pelvic limb paresis[3].

After giving off branches within the pelvis, the major portion of the sciatic nerve exits at the greater ischiatic foramen and courses caudal to the coxofemoral joint, between and deep to the tuber ischii and the greater trochanter of the femur.

It continues to course distally between the semimembranosus and biceps femoris muscles. Branches of the sciatic nerve supply muscles that help extend the hip and flex the stifle. Between the hip and the stifle, the sciatic nerve branches into the peroneal and tibial nerves. These latter nerves supply all muscles below the stifle and provide sensation to all areas of the foot except the medial digit, which is innervated by the saphenous branch of the femoral nerve[13].

Injuries below the distal third of the femur produce loss of function in the peroneal and tibial nerves. Damage to the proximal sciatic nerve results in severe monoparesis, because the extensor muscles of the stifle are the only group that remains functional.

Although the animal may bear weight, the stifle does not flex. Hock and the digits will not flex or extend because of tibial and peroneal nerve involvement. So, the animal stands "knuckled over" and the hock usually is dropped[13]. In this experiment, all dogs showed knuckling after chloramphenicol injection.

There is gradual loss of electrical conductivity in the distal portion of the nerve up to 3 days after the nerve injury. At 10 to 20 days, fibrillations in the denervated muscles may be detected firstly by electromyography[21].

If the distal portion of the sciatic nerve is injured, sensation below the stifle is severely compromised. But normal sensation is perceived from the medial surface of the limb or the medial digit[13]. In this experiment, the dosage of chloramphenicol was based on the weight of animal, so the degree of nerve injury was not exactly equal in all the groups. That might be the biggest reason why all dogs in a groups did not represent all the same clinical signs and recovery time.

The dorsal surface of the foot is frequently ulcerated from the animal's dragging or walking on the knuckled-over foot[13]. In this experiment, all dogs showed variable range of ulceration on the dorsal surface in affected limb.

Self-mutilation can be caused by a neurologic abnormality of the peripheral sensory nerve, sensory spinal cord, and brain stem pathways, thalamus, or somatosensory cortex of the cerebrum[5]. In this experiment, self-mutilation on affected limb was observed in one case of group II at the 28th day. But, histopathological findings in that individual were same as the others'. So, it was regarded that self mutilation in this experiment could have resulted from the interception of peripheral sensory nerve pathway and individual variation.

Self mutilation occurred in 15% of the animal that had fracture or fracture-dislocation of the pelvis in dog and cat[11].

The best way to measure the severity of injured nerve is using the needle EMG5. In this experiment, this method was not used, and normal walking, pain response and histopathological findings were examined from the 3rd day to the 12th week after chloramphenicol injection into sciatic nerve.

There are several ways to treat the nerve injury. Since medication or conservative therapy have been known to be not so effective, new therapeutic strategy using electroacupuncture have been tried. Electroacupuncture in group III and group IV was performed once a day for 4 weeks. The treatment condition of electrostimulation was 20 Hz, 2 volt and 20 minute. But frequency, voltage and duration of electrostimulation was not guided yet. Therefore, it is thought to be necessary to confirm about the exact condition of stimulation.

The sciatic nerve is the major nerve evaluated by the pelvic limb flexor reflex. In proximal sciatic nerve injuries, the digits, the hock, and the stifle does not flex when the toes are stimulated. Stimulation of the medial digit or the medial distal leg elicits pain response and flexion of the hip, but the remainder of the joints of the affected limb is not flexed. In this experiment, there was no pain reaction in dorsal and caudal surface by pinching in chloramphenicol-injected groups. However, they showed pain reaction in medial surface.

Atrophy of the caudal thigh muscles and the muscles below the stifle after sciatic nerve injury may be severe[13]. In this experiment, there was significant muscle atrophy in chloramphenicol-injected groups, so it was regarded that its primary cause was sciatic nerve injury.

Proximal portion of the sciatic nerve is most frequently damaged by fractures of the shaft of the ilium, acetabular fractures, fractures of the proximal femur, following retrograde placement of intramedullary pins in the femur, and during calving injuries in cattle. Less common causes include severe hip dysplasia and surgical procedures involving the coxofemoral joint. The prognosis is poor if these injuries are severe. Partial deficits may be temporary. Surgical relief of compression injuries may be rewarding.

Damage to the sciatic nerve, or to the peroneal or tibial nerves, may occur in association with injection injuries or femoral fracture. Injections intended for the biceps femoris or semimembranosus muscles may go into the fascial plane between these muscles. Injury may be from direct laceration of the nerve by the needle, from the agent being injected directly into the nerve, or from secondary scarring around the nerve. Injection injuries may be prevented by selecting suitable site for intramuscular injections, such as the quadriceps or lumbar muscles.

The diagnosis of nerve injury is based on the history. The prognosis and management plan depend on the severity of the injury. Careful assessment of the motor and sensory function can determine whether peroneal and tibial components are affected or not.

Tibial paralysis is more easily accommodated than peroneal paralysis. If the peroneal and tibial components are affected, it is important for the sensory nerve evaluation to determine whether the lesion is severe. If there is some remaining function, especially in the peroneal distribution, conservative treatment is recommended and prognosis is fairy good. Many of these injuries are apraxia, and function of nerve will be recovered[13].

If the lesion is severe, more aggressive treatment is indicated. Conservative treatment includes protecting the foot from injury with a boot or splint, and physical therapy to maintain muscle mass and range of motion. Boots for dogs are available[18]. If the injury is severe, the resection and anastomosis of the damaged area are required. In this experiment, sciatic nerve with chloramphenicol injection showed a little increase in average number of normal walking, and no improvement in pain response and histopathological findings.

Sciatic nerve exploration in dogs, a month after injections of antibiotics, usually revealed gross neuropathological changes[6]. In this experiment, histopathological findings represented axonal degeneration regardless of duration. Pain response on dorsal and caudal surface showed no improvement, and histopathological findings showed no difference among the chloramphenicol-injected groups up to 12th week. However, average number of normal walking represented slowly increasing tendency in chloramphenicol-

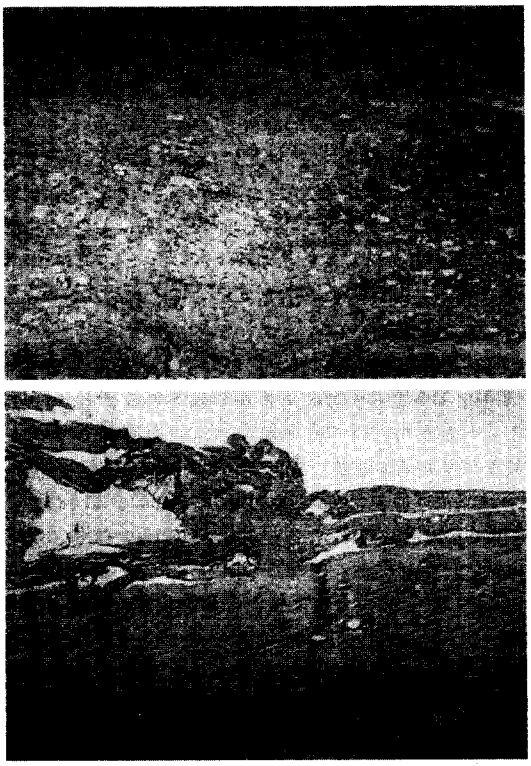

Fig 5. Sciatic nerve on the 3rd day after chloramphenicol injection (a. ⇨: axonal degeneration, ➡: hemorrhage b. ➡: fibrin).

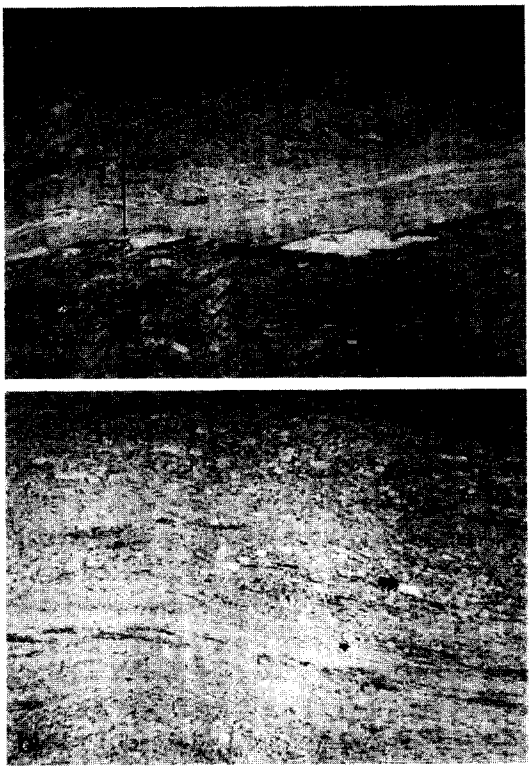

Fig 6. Sciatic nerve on the 4th week after chloramphenicol injection (×100) (a. ↕: thickened epineurium, ➡: axonal degeneration).

injected groups but there was no difference among the groups.

In saline-injected group, they showed normal walking through all experiment.

As experiment above, there was no significant improvement after chloramphenicol injection into sciatic nerve in treatment groups (medication, electroacupuncture, and medication plus electroacupuncture).

Therefore, chloramphenicol injection-induced sciatic nerve injury is not thought to be cured by prednisolone-using medication, electroacupuncture, and medication plus electroacupuncture methods up to 12th week.

Histologically, sciatic nerve taken on the 3rd day after chloramphenicol injection showed axonal degeneration and perineural hemorrhage with infiltration of neutrophils and fibrin (Fig 5-a, b).

There were thickened epineurium and axonal degeneration on the 4th week (Fig 6-a, b). And the histological findings on the 8th and 12th week did not show the difference with those of the 3rd day and 4th week. No difference in histological findings was observed among the groups from the 3rd day up to 12th week.

Conclusion

Sciatic nerve paralysis was not induced by injection with enrofloxacin, cefazolin, cephalexin and penicillin injection into the nerve, but chloramphenicol injection induced nerve paralysis.

Control, medication, electroacupuncture, medication plus electroacupuncture groups did not return to normal walking up to 12th week in chloramphenicol-induced sciatic nerve injury. And no difference was found among those groups during the observation period.

On the histopathological examination, chloramph-

enicol induced sciatic nerve injury was not improved through all experiment.

As mentioned above, since no special therapeutics was found to cure sciatic nerve injury due to chloramphenicol injection, it could be recommended that intramuscular injection with chloramphenicol around the sciatic nerve should be avoided in dogs.

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