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European Journal of Cardio-thoracic Surgery 12 (1997) 648–653

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

Evaluation of pentoxifylline in experimental spinal cord ischemia[1]

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Received 18 November 1996; received in revised form 25 March 1997; accepted 25 March 1997

Abstract

Objective: Despite the advance of anesthesia and surgery, postoperative neurological dysfunction has remained a challenging problem after descending and thoracoabdominal aortic surgery. The pathophysiology of early and especially late paraplegia is not clearly understood. The effect of pentoxifylline (PTX), an agent known to inhibit invitro neutrophil activation and improve recovery after cerebral ischemia in animals, was investigated on spinal cord protection. **Methods:** Twenty four New Zealand white rabbits were used for spinal cord ischemia models. Infrarenal aortic occlusion devices were placed. After 48 h, the rabbits were randomly taken for study. The PTX groups ($n = 12$) was given PTX 40 mg/kg IV bolus followed by 0.2 mg/kg/min infusion. The control (CT) group ($n = 12$) received normal saline. Two groups underwent temporary (20–24 min) spinal cord ischemia in a conscious state. After the operation, the spinal cord function was assessed at 6, 12, 24, 48 and 72 h by the scale (score of 5 = normal hop, score of 0 = no movement). Histological analysis of the spinal cords was carried out immediately after acute paraplegia or within 24 h after development of delayed paraplegia. **Results:** During the aortic occlusion, the distal aortic pressures were the same in both groups (PTX group: 14.92 ± 3.78 mmHg; CT group: 17.42 ± 3.2 mmHg). At the 72nd h, the scores were not different in the PTX group (1.58 ± 2.11) and in the CT group (0.83 ± 1.95) ($P = 0.817$). Acute paraplegia developed in 3 rabbits (25%) of each group. Delayed paraplegia was observed in 6 rabbits (50%) in the PTX group and 7 rabbits (58%) in the CT group. On morphological examination on the spinal cords, ischemic changes were observed in both groups. Although neutrophil leukocytes were noted in the control group with acute paraplegia and macrophage infiltration was noted in the control group with delayed paraplegia, there was not any leukocyte or macrophage sequestration in the PTX group. **Conclusions:** Neurological deficits after spinal cord ischemic/reperfusion injury were not directly responsible for blood-originated phagocytic cells and the inhibition of this type of cell function did not change the outcome. © 1997 Elsevier Science B.V.

Keywords: Spinal cord injury; Spinal cord ischemia; Neutrophil; Leukocyte; Delayed paraplegia

1. Introduction

The prevalence of postoperative spinal cord injury after descending and thoracoabdominal aortic operation has not changed during the last decade, despite improvements in anaesthetic, surgical and perfusion techniques. The reported incidence of postoperative spinal cord injury after thoracoabdominal surgery is up to 31% [41].

Various techniques to prevent cord injury have been used both clinically and experimentally: shunting [24,27], partial bypass [3,25], drainage of cerebrospinal fluid [7,26], hypothermia [21], pharmacologic interventions such as steroids [12,22], barbiturates [31,34], superoxide dismutase [1,17], calcium channel blockers [14,36], prostaglandines [17], intrathecal papaverine [42]. However, their ability to prevent ischemic spinal cord damage remains controversial.

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[1] The work was performed at Dokuz Eylül University Animal Laboratory.

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PII S1010-7940(97)00115-2

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Recent studies have focused on monoclonal antibodies to the adhesion receptors of leukocytes which act by blocking leukocyte endothelial adhesion and subsequent migration [4]. Leukocytes potentiate neurologic injury by direct cytotoxic effect and by mechanical occlusion of the cord microcirculation [5]. Monoclonal antibodies to an intercellular adhesion molecule on the endothelium significantly reduced the neurologic injury in a reversible spinal cord ischemia model in rabbits [5].

Pentoxifylline (PTX), a methylxanthine derivative, inhibits in vitro neutrophil activation, including adhesion, chemotaxis, oxidant release and responses to inflammatory cytokine mediators [2,40]. In addition, PTX treatment improves recovery of cerebral electrical function after complete transient cerebral global ischemia in dogs [43]. In this study, the effect of PTX on spinal cord ischemia was studied on animals. We used a rabbit model for spinal cord ischemia because of the unique segmental arterial blood supply to the spinal cord from the infrarenal aorta in this animal.

2. Materials and methods

Twenty eight adult New Zealand white rabbits, weighing 2–3 kg. (mean 2.8 kg), were used. All were anaesthesized by an initial intramuscular dose of ketamine (50 mg/kg) and xylazine (3 mg/kg) followed by ketamine (25 mg/kg/h) as required during the procedure. Intraoperative fractional doses of anaesthetics were used to maintain the appropriate levels of anaesthesia. The animals were allowed to breathe room air without mechanical ventilation. A thermostatically controlled heated operation table was used to prevent hypothermia. Four rabbits were eliminated from the study because of technical errors or deaths from the anaesthesia. An intravenous catheter (24 gauge) was placed in an ear vein, and preoperatively cefazolin 10 mg/kg was administered as a single dose. Maintenance fluid of 0.9% NaCl was infused at a rate of 25 ml/h through the intravenous catheter during the procedure.

The spinal cord ischemia model used in this study is the modified version of the technique previously reported by Naslund et al. [29]. The fur was clipped from the left flank and the skin was prepared with povidone iodine. Under aseptic conditions, the rabbit was placed in the supine position, with the pelvis rotated 45° to the right. After local skin infiltration with 0.5% Xylocain, the vertical incision was made from the left costal margin directed towards the pubis and the infrarenal aorta was exposed through a retroperitoneal approach. The monoflement suture (3/0 Prolene Ethicone Ltd UK) was passed around the aorta immediately inferior to the renal arteries. The snare (DLP, INC Grand Rapids, Michigan, USA) was cut to 2.5–3 cm. and a small Teflon button was sutured at the entrance hole of the snare at two points. The monoflement suture around the aorta was looped into the snare from the two sides of the button. The bottom side of the snare was placed near the aorta. The other side of the snare was left under the muscle. The layers of the muscle were closed except at the end of the snare and after the skin was closed. Postoperative analgesia was maintained with a subcutaneous single dose of buprenorphine (0.1 mg/kg). Both femoral pulses were checked. The rabbit was put in its cage.

Forty eight hours elapsed for recovery from the anaesthesia, and then the rabbit was taken for study. The selection for the control (CT) group and the PTX group was made randomly. An intravenous catheter was placed again in an ear vein and two arterial catheters were placed in an ear and a femoral artery. Blood pressure and heart rate were monitored. The CT group received normal saline. The PTX group was given PTX (40 mg/kg) intravenously as a slow bolus over a period of 5 min, followed by PTX (0.2 mg/kg/min) continuous infusion and normal saline until the end of the surgical procedure. After local skin infiltration with 0.5% Xylocain, the skin suture was removed and the snare was exposed. Heparine, 100 IU/kg was given intravenously 5 min. before aortic occlusion. Aortic occlusion was then achieved by tightening the snare with the rabbit in a conscious state. The distal aortic pressure decreased immediately and the rectal sphincter function was lost within 5–6 min. The occlusion times were varied from 20 to 24 min. All the rabbits became paraplegic during the aortic occlusion. At the end of a variable occlusion time, the snare was released and the proximal and the distal aortic pressures were equal. The heparine was not neutralised at the end of the procedure. The catheters were removed and the incisions closed. The neurological function was evaluated by an independent observer at periods of 6, 12, 24, 48 and 72 h after the operation. The neurological function of the hindlimbs was graded by the scale (0 = no movement, 1 = slight movement, 2 = sit with assistance, 3 = sit without assistance, 4 = weak hop, 5 = normal hop). The bowel and bladder sphincter function was checked. Credé's maneuver was used to empty the bladder.

The animals were sacrificed by intravenous injection of potassium chloride immediately after acute paraplegia or within 24 h after development of delayed paraplegia. A pathological evaluation was carried out in the spinal cords and abdominal aorta. The entire spinal column and abdominal aorta with lumbar arteries were removed and 10% formalin solution was used as a fixative for 24 h. The spinal cords were cut transversely and processed routinely. Five μm sections were cut from paraffin-embedded blocks and the sections were taken to poly-L-lysine coated slides. After deparaffinization and rehydration, the sections were stained with hematoxylin and eosin (H and E) and

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Table 1
The mean scores of the hindlimb neurologic function

	1 h	6 h	12 h	24 h	48 h	72 h
PTX Group	3.16 ± 1.58	3.25 ± 1.86	2.16 ± 1.99	1.75 ± 2	1.58 ± 2.1	1.58 ± 2.1
CT Group	3.16 ± 1.26	3.25 ± 1.71	1.91 ± 1.72	1.25 ± 1.86	1 ± 1.9	0.83 ± 1.94

immunostaining was performed. Streptavidin-biotin complex immunoperoxidase method was used. CD 15 (Immunon) and CD 68 (Immunon) monoclonal antibodies were used for the primary antibodies to demonstrate neutrophil leukocytes and macrophages, respectively. Nonspecific binding of the antibody was blocked with normal serum, then the sections were incubated with the primary antibody for 30 min. The binding primary antibody was visualised by means of the LSAB immunostaining kit for mouse antibody (Novostain Super ABC kit). Sections were then incubated in 0.02% 3.3′-diaminobenzidine with 0.05% H_2O_2 in 0.05 mol/L phosphate buffer solution (pH 7) for 5 min and counterstained with Mayer's hematoxylin. All the immunostaining steps were completed at 37°C in a humidity chamber. Abdominal aorta and lumbar arteries were processed in the same manner and the H and E stained sections were interpreted by light microscopy for thrombosis or emboli.

The results are presented as mean ± standard deviation. The Mann-Whitney U test was used to evaluate the differences. The Fisher exact probability test was used in the analysis of the bowel and bladder sphincter function between the two groups. Statistical significance was accepted at a P value of less than 0.05.

All the animals received humane care in compliance with the 'Principles of Laboratory Animal Care' formulated by the National Society for Medical Research and the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Institutes of Health (NIH Publication No. 86 – 23 revised in 1985). The experimental protocol was reviewed and approved by Dokuz Eylül University Ethical Committee on the care and use of laboratory animals.

3. Results

The mean aortic occlusion times were not different between the two groups (PTX group: 22.58 ± 1; CT group: 21.75 ± 1.06). During the occlusion, there was no difference in the distal aortic pressures between the two groups (PTX group: 14.92 ± 3.78 mmHg; CT group: 17.42 ± 3.2 mmHg) The scores during the observation period are shown in Table 1. At the 72nd h, the scores were not different in the PTX group (1.58 ± 2.11) and in the CT group (0.83 ± 1.95) ($P = 0.817$). Acute paraplegia developed in 3 rabbits (25%) of each group. Delayed paraplegia was observed in 6 rabbits (50%) in the PTX group and 7 rabbits (58%) in the CT group. Also, there was no difference in the loss of bowel and bladder sphincter control between the two groups.

On microscopic examination of the medulla spinalis', ischemic necrosis was observed with preferential involvement of the spinal gray matter and relative sparing of the white matter, although in some sections almost the entire cross-sectional extent of the spinal cord was affected. The ischemic changes were observed in the sections of lumbar and sacral regions in both groups but not cervical region section (Fig. 1). There was no leukocyte sequestration in the PTX group (Fig. 2) but neutrophil leukocyte or macrophage infiltration were noted in the control group. Infiltration of the neutrophils in acute paraplegia (Fig. 3) and macrophages in delayed paraplegia (Fig. 4) of the control group were observed.

Interpretation of the aorta and lumber arteries sections did not reveal any evidence of thrombosis or emboli.

4. Discussion

Two main mechanisms can cause spinal cord injury during descending and thoracoabdominal aortic operations: distal aortic hypoperfusion with temporary anterior spinal cord ischemia and permanent exclusion of

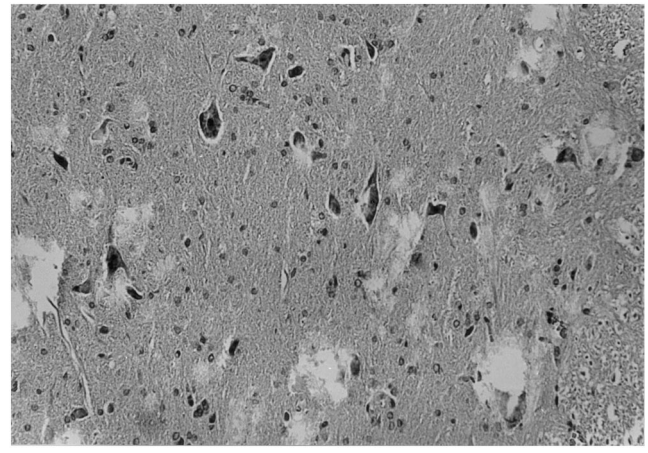


Fig. 1. Gray matter within normal morphological limits (Cervical region of the spinal cord, × 100, Hematoxylin and Eosin).

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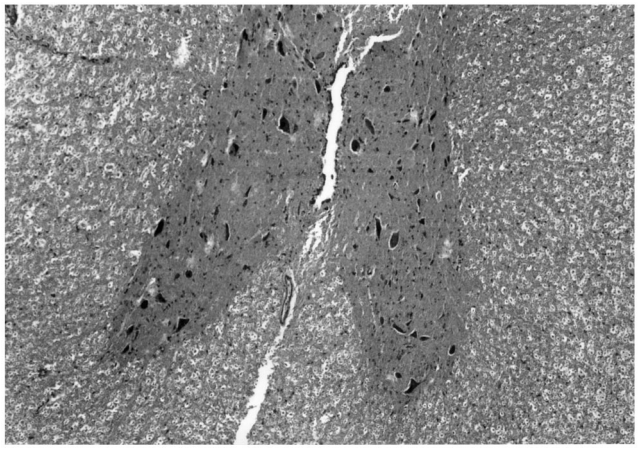


Fig. 2. Photomicrograph of spinal cord showing ischemic damage limited mainly to spinal gray matter (Sacral region, PTX group, × 40, Hematoxylin and Eosin).

intercostal arteries with cord infarction. In addation to various surgical techiniques such as mechanical shunts, hypothermia, reimplantation of critical intercostal or lumber arteries, a number of pharmacological agents have been used both experimentally and clinically in an attempt to reduce the severity of spinal cord ischemic injury.

The purpose of this study was to assess the effect of PTX on spinal cord protection. PTX has been shown to decrease blood viscosity by increasing erythrocyte deformability [8], reducing platelet aggregation [9], and promoting thrombolysis [13]. It also causes vasodilation [18]. The drug is widely used in patients with peripheral vascular disease to increase blood perfusion and improve oxygen delivery [33]. PTX also inhibits the function of polymorphonuclear neutrophils and monocytes and decreases production of superoxide anion by these cells [2]. Recent studies have shown the possible relation between leukocytes and pathogenesis and extension of ischemic injury [10,35]. Inflammatory cells, including mononuclear phagocytes are responsible for ischemic neuronal injury because these cells are found in the motor dysfunction area and direct phagocyte effect or the secretion of toxins from these cells have cytotoxic effects [16,30]. Inhibitions of these inflammatory cells have been shown to improve neurological function [16]. In addition, leukocytes potentiate ischemic injury by microvascular occlusion from direct mechanical obstruction [37]. The leukocyte-mediated tissue damage may be irreversible even if the blood flow is restored [19]. Monoclonal antibodies to adhesion receptors on the surface of leukocytes (CD18) and intercelluler adhesion molecules (ICAM) on the endothelium have been shown to attenuate leukocyte endothelial adhesion in vitro [38,39,44]. These types of antibodies significantly reduce the neurological deficits in reversible spinal cord ischemia models [4,5]. However, in another study, treatment with a specific monoclonal antibody that binds to the CD11/CD18 surface glycoprotein complex of the neutrophil leukocyte membrane which prevents neutrophil aggregation and adherence to the vascular endothelium, did not attenuate reversible spinal cord ischemia in rabbits [11]. Although PTX has been shown to ameliorate the inflammatory effect of neutrophils [2], haemorrheological properties [9], vasodilatory effects [18], and to improve the recovery of cerebral electrical function after complete transient cerebral ischemia [43]. The dose of PTX (40 mg/kg bolus followed by infusion at 0.2 mg/kg/min) was used as a same dose of the transient cerebral ischemia study [43]. However, we did not find any difference between the PTX group and the CT group regarding the clinical neurological assessment.

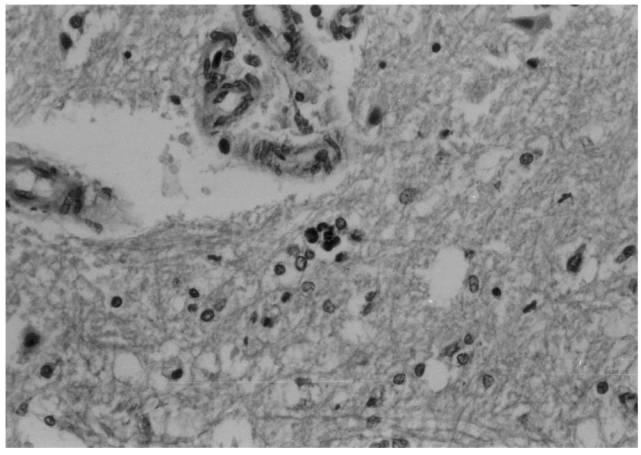


Fig. 3. Central coagulative necrosis, capillary proliferation and neutrophil leukocytes (Sacral region, CT group, acute ischemia, × 200, Hematoxylin and Eosin).

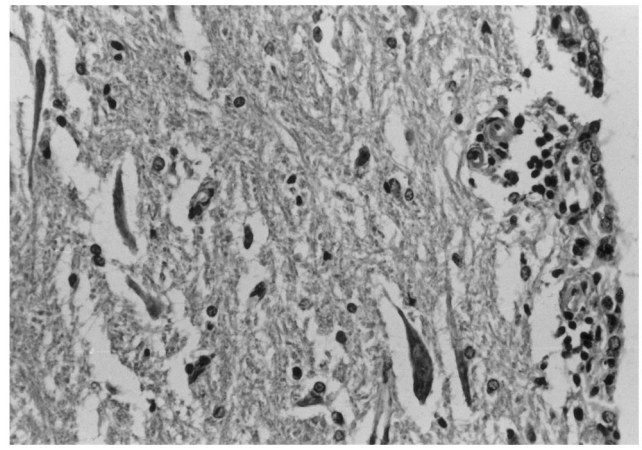


Fig. 4. Coagulative necrosis with macrophage infiltration and dissolution of Nissl substance and capillary proliferation (Sacral region, CT group, delayed ischemia, × 200, Hematoxylin and Eosin).

After aortic surgery, immediate or delayed neurological complications may develop. Delayed neurological

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deficits have been reported to occur from between 1 to 21 days postoperatively [6]. The mechanism of the delayed paraplegia has not yet been correctly understood. Postoperative hypotension, thrombosis or embolization of the spinal arteries may be responsible for the occurrence of delayed paraplegia [7,23,29]. Recently, it has been postulated that delayed paraplegia might develop as a result of cord edema in a confined space, cytotoxic action from leukocytes or microglia, and free-radical injury because of metabolic by-products of ischemia [4,20,28]. In addition, delayed paraplegia might be a result of 'borderline' ischemia which is subclinical initially, but subsequently, deleterious metabolic cascade advance in neuronal tissue and paraplegia occur [28,29]. Moore and Hollier found that 71% of rabbits returned to normal neurological function after 20–21 min spinal cord ischemia but developed delayed paraplegia 14 to 48 h later [28]. In our study, delayed paraplegia was observed in 54% of animals after 20–24 min spinal cord ischemia. Maximum central nervous system leukocyte infiltration does not occur until 24–48 h after ischemia and delayed leukocyte tissue infiltration and direct neuronal injury is believed to be involved in the delayed deterioration following delayed paraplegia [20]. Conversely, on a histopathological examination of our rabbits' spinal cords, neutrophils or monocytes were not found in those which received PTX but were present in the CT group. Within the central nervous system, two classes of mononuclear phagocytes appear after ischemic injury: microglia and blood-borne macrophages [15,32]. Both classes of mononuclear phagocytes in the central nervous system display cytotoxic activities that are capable of inducing neuronal cell death and neurological dysfunction [15,32].

The prevention of spinal cord injury by the agents such as steroids [12,22], superoxide dismutase [1,17], and prostaglandines [17], which are known to be antioxidants against the oxygen free radicals that are the products of neutrophil leukocytes and macrophages, support the hypothesis that the neutrophil leukocytes and macrophages are responsible for this injury. Our results with PTX also supports the inhibitory effect of PTX on neutrophil activation. Despite this effect of PTX, ischemia observed in both PTX and CT groups suggest that microglia or other mechanisms with or without blood-originated phagocytic cells may be responsible for the ischemic injury of the neuronal tissue as neurological deficits developed both in the CT and PTX groups without any leukocyte sequestration. Glutamate appears to be a remarkably potent and rapidly active neurotoxin.

In conclusion, neurological deficits after spinal cord ischemic/reperfusion injury were not directly related to blood-originated phagocytic cells and the inhibition of these cells did not change the outcome.

Acknowledgements

The authors wish to thank Prof. Dr. Ataman Güneri for their untiring support in this project.

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