The Effect of Ulinastatin on Reduced Nerve Conduction Velocity and Blood Pressure

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Application of a pneumatic tourniquet in orthopedic surgery is sometimes followed by hypotension and paralysis. Seventy-five patients scheduled for knee joint surgery were examined to evaluate the effects of ulinastatin on changes in blood pressure, venous pH and motor nerve conduction by pneumatic tourniquet application above the knee joint. In fifty-five of the patients, the femoral vein of the operating side was cannulated with a catheter to obtain venous blood samples before and after tourniquet application. 300,000 Unit of ulinastatin (UST) was administered intravenously before inflation of the tourniquet in 10 patients. In the other sixteen patients, the motor nerve conduction velocity (MNCV) of the peroneal nerve was measured before inflation and after release of the tourniquet. In the UST-free group, the reduced blood pressure and pH persisted for more than 15 min, while in the UST-treated group, the reduced blood pressure returned to the normal leven in 15 min. In the control group, femoral venous Po_2 continued to increase after 10 min, but that in the UST-treated group returned to the normal range. Tourniquet application significantly reduced peroneal MNCV. Pre-and post-treatment with UST significantly lessened the reduction of MNCV induced by the tourniquet. It is concluded that UST may have protective and therapeutic effects on ischemic nerve injury, induced by the application of a turniquet. (Key words: pneumatic tourniquet, nerve conduction velocity, ulinastatin)

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The pneumatic tourniquet is widely used in current clinical orthopedic surgery in order to create a bloodless field. Its application to a limb is sometimes followed by severe hypotension and prolonged paralysis[1–3]. In the former complication certain metabolic factors may play a role as well as the decrease in peripheral vascular resistance. Nerve complication occurs usually at the tourniquet level by direct compression of a nerve, but ischemic nerve damage cannot be ruled out particularly in nerve conduction reduction at a point distal to the tourniquet because of hypoxia and ischemia induced by the tourniquet. It is well known that a compromised arterial blood supply induces anaerobic metabolism, requiring muscle cells to live on their own available energy supply. The complications induced by tourniquet application may be related to the energy metabolism in the ischemic regions. It is reported that ulinastatin (UST) (Mochida

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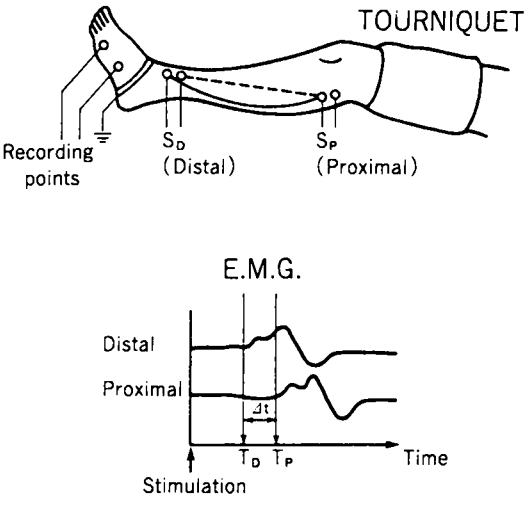
Pharmaceutical Co., Ltd., Tokyo), a human urinary trypsin inhibitor, has ameliorative effects on decreased blood pressure and cardiac index and on elevated betaglucuronidase following experimental shock in dogs[4]. Furthermore, Sato reported that ulinastatin improves the depressed energy metabolism in shock without affecting the normal energy metabolism. If ulinastatin improves energy metabolism in post-ischemic limbs, the complications following tourniquet application may decreased. This study shows the time sequence of the ameliorative effect of UST on the recovery of blood pressure and nerve conduction disorders following tourniquet application.

Method

Seventy-five consenting patients scheduled for surgery on the knee joint were examined. All were anesthetized by the lumbar epidural technique with 10 ml of 2% mepivacaine, using the L2–3 interspace. The tourniquet was applied above the knee joint, as far from operating site as possible. Arterial blood pressure was measured by the Rive Rocci method on the upper extremity at 5 min intervals. Meanwhile blood pressure was taken at thirty second intervals, ECG was monitored continuously. Lactated Ringer solution with 5% glucose was infused continuously at a rate of 5 ml/kg/hr during the procedure.

Blood sampling

To evaluate the effect of UST on blood pressure and metabolism, the femoral vein of the side due to receive surgery in fifty five of the patient was cannulated with a 21G teflon catheter to obtain venous blood, from the ischemic area for blood gas analysis and Na, K, Cl, and serum betaglucuronidase concentrations. These measurements were made 1 min before inflating and 1, 5, and 10 min following release of the tourniquet. Blood gas was measured with an ABL2 Blood Gas Analyzer (Acid-Base Laboratory, Radiometer, Denmark). UST (300,000 Units) was administration intravenously just before inflation of the tourniquet in 10 patients (UST pretreated patients). The other 45 patients were not given UST and served as the control group (UST-free patients).



$$MNCV = \frac{D\ (\text{distance} : S_D - S_P)}{\Delta t(\text{duration} : T_D - T_P)}$$

Fig. 1. The method of measuring the motor nerve conduction velocity of peroneal nerve.

The tourniquet placed above knee joint. The peroneal nerve was stimulated at the level of the fibular neck and at the level of the ankle joint by sets of proximal(Sp) and distal(Sd) stimulating percutaneous electrodes respectively. The recording electrode was placed over the extensor digitorum brevis muscle of the foot. (Upper part of the figure)

Middle figure shows the typical wave of action potentials of the extensor digitorum brevis muscle displayed on a electromyograph screen. The time between the stimulus and beginning of the action potential of the extensor digitorum brevis muscle was measured for the proximal and distal stimulation points. The difference between two latencies was result from the relationship between the MNCV and the distance of two electrodes. The maximum motor nerve conduction velocity was indicated by the equation (Lower equation).

Measurement of nerve conduction velocity

In 16 of the patients motor nerve conduction velocity (MNCV) was measured before inflation of the tourniquet, and at 30, 60 and 90 min after its release. The motor nerve conduction velocity (MNCV) was measured in a segment of the deep peroneal nerve (fig. 1). A set of proximal stimulating percutaneous electrodes was placed over the

Table 1. Age and tourniquet time distribution

Age	Total patients (n=75)	MNCV measuring patients (n=16)	
UST (+) (Before inflation)	49.58 + 13.9 (n=10)	Pre Post	44.6 + 13.4 (n=5) 49.2 + 14.0 (n=6)
UST (−)	54.2 + 11.9 (n=65)	60.4 + 14 (n=5)	

Duration of tourniquet inflation (min)

Age	Total patients	MNCV measuring patients	
UST (+) (Before inflation)	106.6 + 27.5 (n=10)	Pre Post	90.2 + 31.6 (n=5) 118.5 + 11.6 (n=6)
UST (−)	113.3 + 15.8 (n=65)	120.0 + 7.7 (n=5)	

There was no significant difference in the age and tourniquet inflation time. UST(+) means the patients who administered 300,000 unit of UST intravenously. In all UST(+) patients group were given just before inflation of tourniquet. [Pre] and [Post] mean the timing of administration of UST, pre-inflation of tourniquet and post deflaltion of tourniquet respectively.

common peroneal nerve at the level of the fibular neck, and a distal set over the deep peroneal nerve at the level of the ankle joint. The recording electrode was placed over the extensor digitorum brevis muscle of the foot. The nerve was stimulated by square wave pulses of one-tenth millisecond duration. The action potentials of the extensor digitorum brevis muscle were displayed on an electromyograph screen (MEB-3102, SEM-4201, Nihon Koden, Tokyo). The time between the stimulus and the beginning of the action potential or the maximum peak voltage of the response of the extensor digitorum brevis muscle was measured for each of the proximal and distal stimulation points. The distance between the stimulation points was divided by the difference between these two latencies to indicate the maximum motor nerve conduction velocity. The 16 patients were divided into 3 groups. Five were administered UST (300,000 Unit: i.v.) just before inflation (UST pre-treated group), and 6 were given it just after release of the tourniquet (UST post-treated group). The other 5 patients were given no UST and served as the control group.

Statistical analysis was performed using Student's t test, and differences were considered to be significant when $P<0.01$.

Results

There were no significant differrences in age, sex or body weight distributions among the UST-free group, and the UST pre-treated and post-treated groups (table 1). The pneumatic tourniquet was inflated to 350 mmHg. The average tourniquet inflation time (99 min) was essentially the same in all 3 groups. After release of the tourniquet pressure, no serious sequelae were found, but minor complications such as decreased systemic blood pressure and decreased MNCV of the deep peroneal nerve were seen.

Blood pressure and heart rate

In the UST free group (n=60) and the UST post-treated group (n = 5), systolic and diastolic blood pressure decreased significantly and the heart rate increased at 5, 10 and 15 min after release of the tourniquet, while in the UST pre-treated group (n = 10) no significant changes in arterial blood pressure at 15 min were observed. Furthermore, no significant heart rate change occurred in

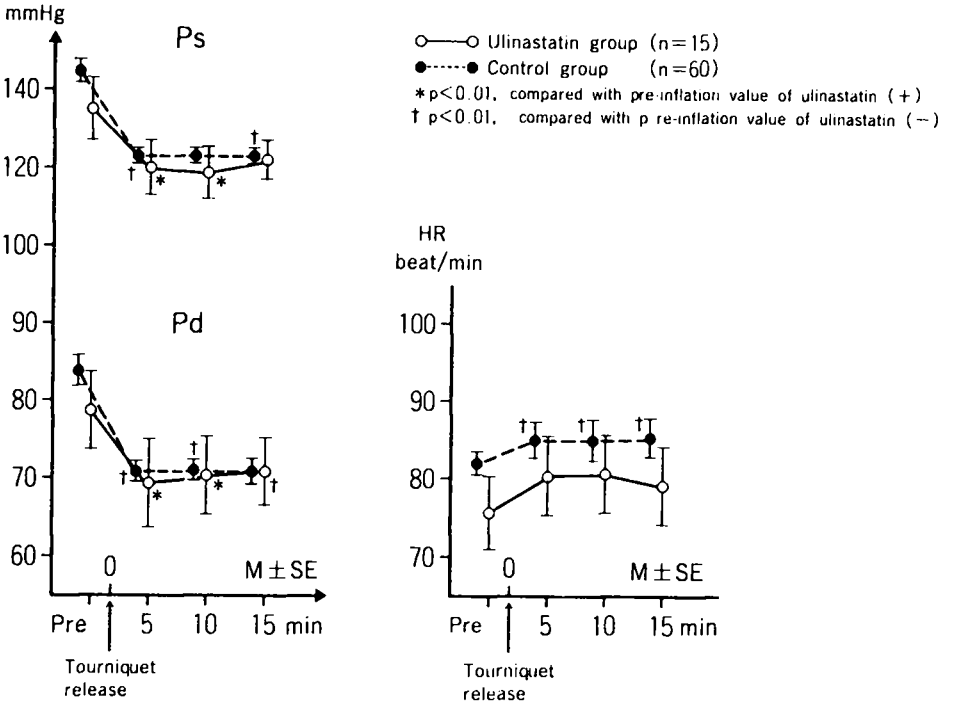


Fig. 2. Effects of UST on Blood pressure and heart rates.
In both UST treated (n = 10) and non-treated (n = 60) groups, blood pressure was reduced within 1 min following tourniquet release. In the UST free grouop (control), reduced blood pressure continued for more than 15 min, while in the UST pre-treated group at 15 min, the blood pressure resumed the normal value. The significant increase in heart rate was continued for more than 15 min in UST free group. In the UST treated group tended to increase the heart rate but not significantly.

the UST-treated group (fig. 2).

Blood gas analysis

Although venous blood pH and base excess decreased significantly at 1 and 5 min in the UST-free group, the UST pre-treated group showed no significant decrease in venous blood pH or base excess at 5 min. In all patients, a significant increase in Pv_{CO_2} (from 46.9 ± 6.7 to 67.0 ± 12.1; mean ± SD) was seen within 1 min after tourniquet release. Pv_{O_2} before tourniquet application was 78.6 mmHg and 68.7 mmHg in the UST free and UST pre-treated groups, respectively. The time course of Pv_{O_2} change in the UST free group showed decrease at 1 min and increase in Pv_{O_2} at 5 and 10 min. In UST pre-treated patients, Pv_{O_2} 5 min increased and at 10 min, returned to the normal range (fig.3).

Changes in electrolytes and betaglucuronidase

In the UST-free and UST pre-treated groups, potassium concentration increased by 27.95% and 24.45% of the pre-tourniquet value by 1 min after release. The control value was regained at 10 min in the UST-treated group. There were no significant changes in sodium or chloride concentration, or in any parameter studied between the pre-tourniquet period and 2 hours following re-perfusion in either group.

Nerve conduction velocity

The average MNCV in the pre-tourniquet period (control) was 43.3 ± 3.3 m/sec (mean ± SE). The post tourniquet MNCV was determined as soon as possible after surgery and removal of the operation dressing. In all patients, especially UST-free patients, the MNCV was reduced significantly. In the UST free group, the MNCV at 30,

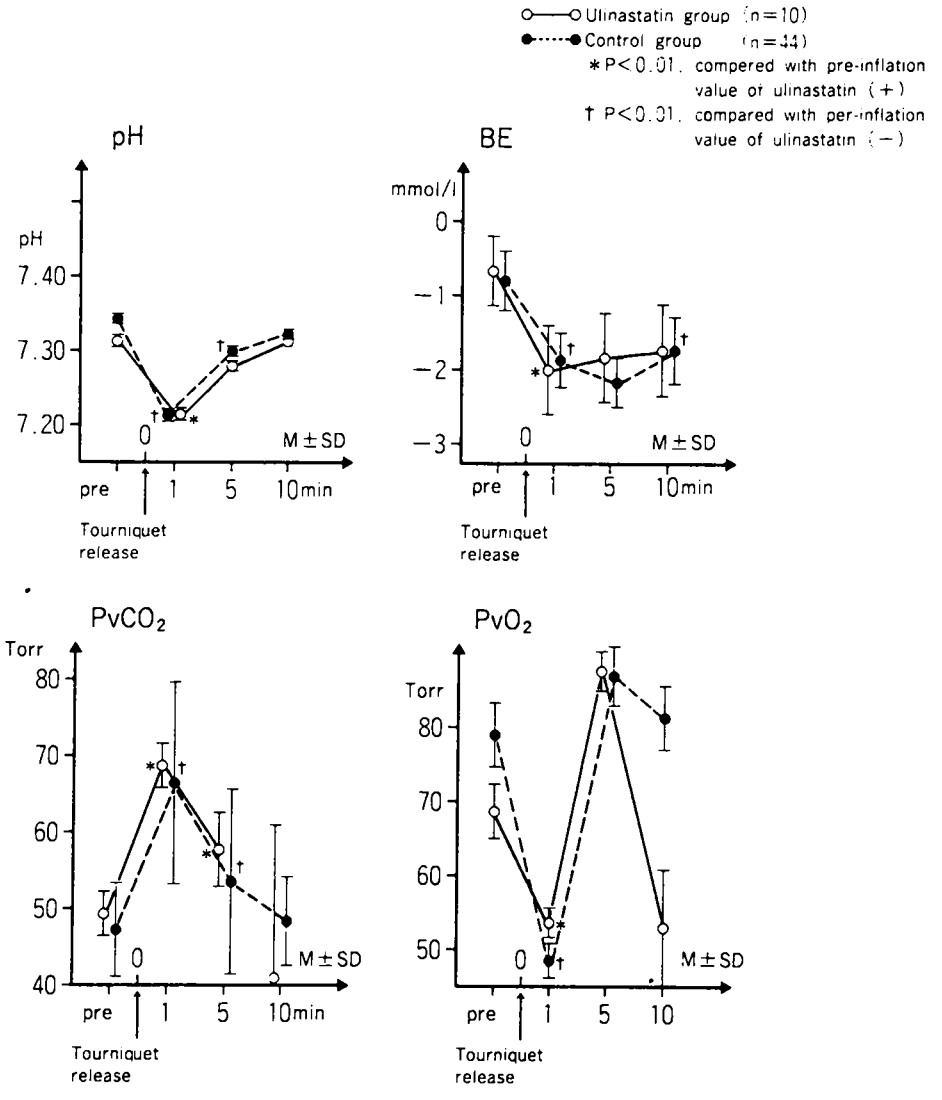


Fig. 3. Effects of UST on blood gas analysis in venous blood.

Although pH decreased significantly at 1 and 5 min in the control grooup, the UST treated group showed no significant decrease in pH at 5 min after release of the tourniquet. In all patients, a significant increase in Pv_{CO_2} was seen within 1 min after the release. The time course of Pv_{O_2} change in the UST free group showed decrease at 1 min and increase in Pv_{O_2} at 5 and 10 min. In UST treated patients, Pv_{O_2} at 5 min increased and at 10 min, resumed the normal value.

60 and 90 min after release of the tourniquet and re-perfusion was reduced at 70, 75 and 85% of the control values, respectively. Pre- and post-tourniquet inflation treatment with UST significantly lessened the reduction of MNCV induced by tourniquet application. The UST pre- and post-treated groups showed recovery of 90% and 95% of the pre-tourniquet level of MNCV, respectively.

Discussion

Tourniquet application designed to provide a bloodless field in operations on the extremities is sometimes accompanied by severe hypotension, called tourniquet shock, and prolonged tourniquet nerve paralysis[1–3].

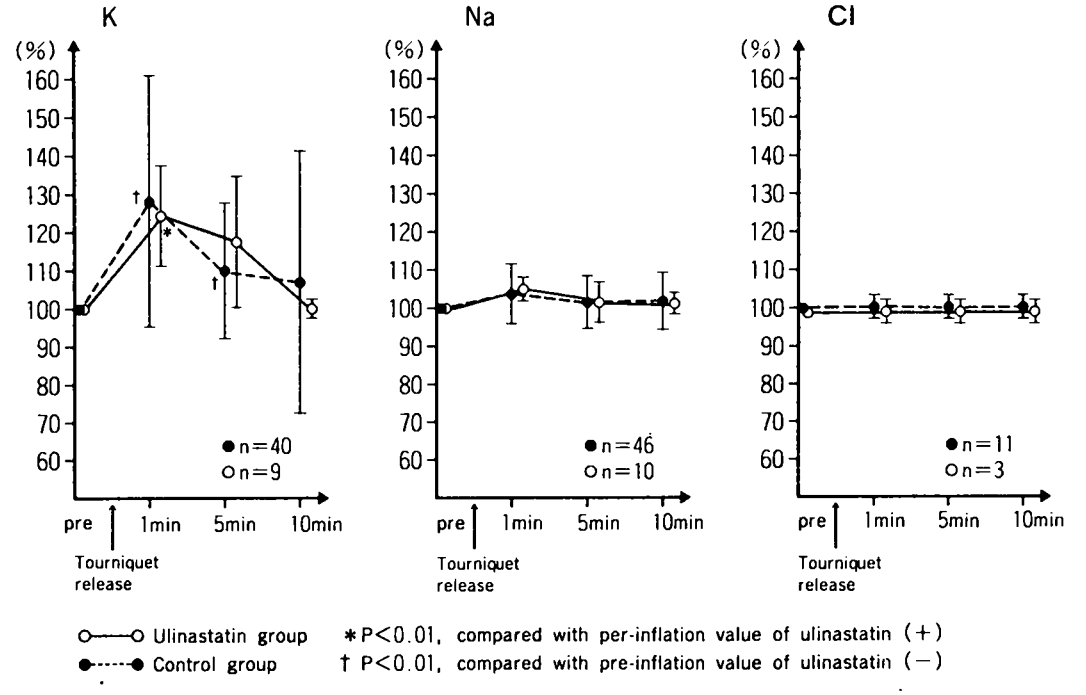


Fig. 4. Changes in serum electrolytes.

The percent changes from pre tourniquet inflation level in serum potassium, sodium and chloride are shown. In both groups, potassium concentration increased 1 min after the tourniquet release. The control value was resumed at 10 min in the UST treated group. There were no significant changes in sodium or chloride concentrations.

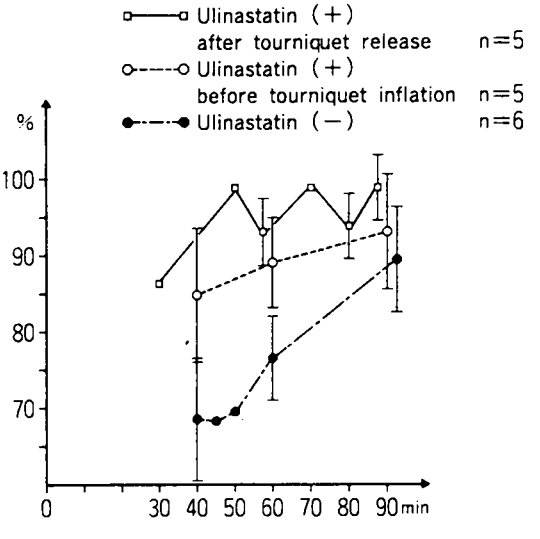


Fig. 5. Recovery effect of UST on reduced peroneal nerve conduction velocity.

The Abscissa indicates the time after release of tourniquet cuff. The Ordinate shows the recovery rate of MNCV. Pre tourniquet application MNCV in defined as 100% recovery. MNCV in UST free group is significantly depressed even at 90 min after release of tourniquet. ($P<0.01$) In UST treated groups MNCV were tended to depressed but not significantly.

The mechanisms of these complications remain to be clarified.

Effects of ulinastatin on blood pressure and metabolic changes

Some systemic effects on the cardiovascular system following tourniquet release are due to the return of extremity blood into the systemic circulation. In both UST free and -treated groups, the blood pressure and pH of the venous blood were reduced within 1 min following tourniquet release. The pH in the UST pre-treated group returned to the control value within 5 min after release of the tourniquet. In the UST free group, reduced blood pressure persisted for more than 15 min, while in the UST pre-treated group at 15 min the blood pressure had resumed a normal value. Changes in blood pressure were preceded by the pH changes in venous blood. These results suggested that not only an increase in the volume of the vascular bed but also metabolic factors may possibly be involved in the reduction of blood pressure following tourniquet release. Our results for blood pressure and heart rate change following UST administration are essentially in agreement with those of other reports indicating that UST significantly regains cardiac work and mean arterial blood pressure, without changing heart rate in dog hemorrhagic shock[4,5]. After being cut off from the circulation, the ischemic limb switches to anaerobic glycolysis after tissue oxygen has been consumed. During a 2 hour tourniquet application, a consequent drop in pH has been reported[6]. The significant increase in Pv_{CO_2} under the above conditions seems to reflect metabolic change in the ischemic limb. Hassan[7] has described a decrease in Pa_{CO_2} in spontaneous breathing patients, and Deen et al.[8] reported increase in Pa_{CO_2} in controlled ventilated patients. Following deflation of the tourniquet cuff, acidotic products are released into the systemic circulation through the femoral vein. In the present study venous blood was measured to allow detection of direct changes in the ischemic extremity, to rule out the possibility of the effect of breathing, and to bring about an increase in Pv_{CO_2}, and decrease in pH and in base excess after tourniquet release. The results were indicative of acidotic metabolic changes in the ischemic limb. Following deflation of the tourniquet cuff, a low Pv_{O_2} was found, which may have be due to admixture with stagnant hypoxic blood in the lower limb by tourniquet. A few minute after tourniquet deflation, Pv_{O_2} increased transitorily, as was also noted in the experiments of Rorabeck in dogs[9]. Since in our study patients breathed spontaneously, the increase value of Pv_{O_2} may have indicated the depression of oxygen consumption and metabolism or arterio- venous shunting in the reperfused area. A second reduction in Pv_{O_2} at 10 min, which was noted following deflation in the UST-treated groups, may have indicated an increase of oxygen consumption in the reperfused area. It is widely accepted that ischemia caused by circulatory deficiency is a major factor in the pathogenesis of cell injury involving the disruption of lysosomes, and that the formation of toxic substances by various proteases results in further tissue injury in shock. In this regard, it appears reasonable to consider that an enzyme inhibitor may lessen the degree of shock by inhibition of a lysosomal enzyme. Proteases may function as toxins in shock, giving rise to a vicious cycle. The ameliorating effect of UST on beta-glucuronidase release from lysosomes in a shock state has also been reported[4,10]. We investigated changes in serum beta-glucuronidase, but no increase was noted, even in the UST-free group. Thus, the 2 hours ischemia may not be sufficient to bring about either the release of beta-glucuronidase from the lysosomes of muscular cells or lysosomes destruction in the cells. Furthermore, the hypotensive reaction following tourniquet deflation is less likely to contribute to serum beta-glucuronidase release. UST had ameliorative effects on the decreased blood pressure and the altered acid-base balance induced by ischemia resulting from tourniquet application, and so UST may possibly lower the level of the anaerobic metabolites which depress the cardiovascular system.

The only electrolyte changes found was

an increase in potassium. Two other electrolytes, sodium and chloride, did not change significantly. This potassium increase may result from a decrease in the pH of the venous blood.

Effects of UST on nerve conduction

Although 2 hours has been described as a safe period from the view point of avoidance of nerve injury[11] for keeping a pneumatic tourniquet application, no standard period has been definitely established. It is said that the incidence of limb paralysis following tourniquet application in human subjects is low[12]. Middleton and Varian, in their survey of orthopedic surgery, cited the incidence of tourniquet associated upper limb paralysis at 1:5000[13]. However, Wingarden et al. report prolonged postoperative EMG abnormalities in 72 percent of patients following meniscectomy even at 10 to 35 days postoperatively[14]. Makitie reported indications of microscopical nerve degeneration appearing after 2 hours of ischemia due to the use of tourniquet in rats[15].

The question as to whether nerve injury subsequent to tourniquet application is consequential to ischemia per se or to mechanical crushing remains to be resolve. The mechanical "cuff effect" of the tourniquet on nerve injury is supported by Ochoa et al. They reported displacement of the nodes of Ranvier away from the cuff edges and nodal invagination into adjacent myelin segments[16]. Ochoa concludes that conduction block and morphologic changes are due to direct mechanical compression[16]. Other experimental investigations have demonstrated impairment of sciatic nerve conduction velocity as a results of tourniquet application at 250 mmHg. In this study, complete blocking of conduction across the cuff occurred after 50 min of application at 250 mmHg, while in a segment distal to the tourniquet, the conduction was not blocked completely. On increasing the tourniquet pressure to 500 mmHg for 2 hours, even distal to the tourniquet, sciatic nerve conduction was completely blocked[17]. The etiology of impairment of nerve conduction distal to the tourniquet is obscure. Direct pressure by a tourniquet causing distal nerve ischemia is obviously not the reason. Ischemia, local tissue anoxia, and metabolic acidosis may play very important roles in nerve conduction impairment in this portion.

The data in this report were obtained from clinical experiments, so that the tourniquet inflation time and pressure cannot be varied freely and nerve conduction velocity could not be measured continuously during inflation and the early period of the deflation of tourniquet cuff under the conditions of a surgical operation. Hurst has shown completely blocked nerve conduction within 60 min of inflation[18]. In our experiments, the average time of tourniquet inflation was 100 min and therefore peroneal nerve conduction may have been blocked completely. The reduced MNCV after deflation of the tourniquet seen in the present study suggests that pneumatic tourniquet application cause electrical abnormalities indicative of nerve injury. Hurst et al. found that, following release at 60 min, conduction velocity recovered the pre-tourniquet functional level in less than 80 min[18]. The recovery time from ischemic nerve injury does not always depend on blood flow. Rorabeck and Clarke noted that the longer the period of ischemia, the longer was the period of recovery from reduced conduction velocity, and that, regardless of the time of reperfusion, the blood flow to the ischemic lesion became normal within 2 hours[19]. The recovery time from reduced nerve conduction in the UST-treated groups was much faster than that in the UST-free group.

The question whether morphological change in a short period can be lessened through administration of a drug is of interest. In our study, the reason for reduced nerve conduction, particularly distal to the tourniquet, was probably ischemia rather than any mechanical factor. We found that both pre- and post-tourniquet administration of UST shifted the recovery time course curve toward to the left, meaning readier return of nerve conduction velocity. Thus, UST may have protective and therapeutic effects on ischemic nerve injury. Alghough

the reason for its ameliorative effects on reduced nerve conduction is still obscure, they could be related to the oxygen and energy utilization in the reperfused lesion. Sato et al. reported that UST improves the depression of energy metabolism in shock without affecting normal energy metabolism, possibly by preventing a decrease in the adenine nucleotide pool[20]. The mechanism for the restorative effect of UST on reduced nerve conduction may be related to promotion of oxygen re-uptake and to energy metabolism in the ischemic lesion. The most interesting and significant effect of UST is that it ameliorates ischemic nerve depletion even on administration in the post-ischemic period. This effect suggests the possibility of facilitation of recovering in the CNS following ischemic brain damage.

Conclusions: We concluded that UST facilitates normalization of reduced blood pressure and improves ischemic nerve conduction disturbance due to pneumatic tourniquet application. The present data indicate that protease and oxygen may be involved in cardiovascular depression and nerve conduction depletion due to tourniquet application.

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