Defence Science Journal, Vol 49, No 5, October 1999, pp. 371-380

Frostbite — Susceptibility, Prevention and Immediate Treatment

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ABSTRACT

Frostbite, the severest form of cold injury, is a major health hazard and a serious medical problem for the Armed Forces operating in snow-bound areas at high altitudes. Detailed experiments on susceptibility, prevention and treatment were conducted to find out suitable measures to prevent, treat and ameliorate cold injuries. Experiments conducted on monkeys have shown that animals with higher peripheral vascular response are better protected against cold injury. Measurements of cold-induced vasodilatation (CIVD), heat output and peripheral blood flow under local cold stress can be used to screen out highly prone individuals to frostbite. Cold acclimatisation was effective in raising the peripheral vascular response and thereby lessening the degree of injury. Frostbite having occurred, its treatment is not very satisfactory. This is primarily due to the time lag between occurrence of frostbite and initiation of therapy, which plays a vital role in its curative action. Keeping this in view, many experiments have been conducted on this treatment. Pilot studies were carried out using various drugs and vitamins, and also procedures like rapid rewarming in warm water, tea decoction, turnip (*shalgum*) decoction, etc., singly as well as in combination, for treatment. The most encouraging result was obtained by the procedure of rapid rewarming in tea decoction maintained at 37-39 °C immediately after cold exposure, followed by combined therapy of aspirin (5 mg/kg) and pentoxifylline (40 mg/kg) along with vitamin C (50 mg/kg) twice daily for 7 days.

1. INTRODUCTION

Frostbite is the severest form of cold injury responsible for the loss of extremities of our young jawans and officers posted in the vast Himalayan regions throughout the northern frontiers. It occurs on prolonged exposure to freezing temperature or even a brief exposure to very severe cold and windy environment. In civilian life, frostbite is not very common except for occasional cases seen among mountaineers. But it is a major health hazard and a serious medical problem for the Armed Forces, operating in snow-bound areas at high altitudes. During peace time, a few sporadic cases may occur, but under active operational conditions a large number of cases may seriously hamper the operational efficiency of the troops and present challenging administrative problems in their evacuation, treatment and rehabilitation.

As peripheral tissues cool faster than other parts of the body on exposure to cold, they are more liable to cold injuries[1]. The injury mostly occurs on the hands and feet. In the cold areas at high altitudes, the problem becomes more intense, since hypoxia is superimposed over cold stress, which results in marked reduction in extremity blood flow[2,3]. Severity of atmospheric cold, duration of exposure and high velocity wind are the main factors responsible for the occurrence of frostbite. Wetness (humidity) hastens tissue cooling. Besides these environmental factors, physical inactivity, inadequate nutrition, poor quality of protective clothing, lack of cold acclimatisation, physical

Revised 19 August 1999

exertion, fear and anxiety, local skin injury, consumption of alcohol, excessive smoking, touching of metal objects with bare hands, wet garments, and lack of personal hygiene are the other important factors responsible for the causation of cold injuries[4]. It is believed to occur partly due to direct freezing effect of cold and partly due to anoxia resulting from circulatory insufficiency. Insufficient circulation increases vascular permeability and leads to stasis in capillaries which blocks small blood vessels and results in thrombosis. Thrombosis aggravates anoxia, leading to necrosis or dying of the affected parts within 2-3 weeks[5-7]

2. HYPOTHESIS FOR MINIMISING TISSUE DAMAGE

If stagnation of circulation can be prevented and/or re-established at the earliest and the thrombus formation protected, the degree of cold-induced tissue damage can be minimised or curtailed to a great extent. Further, during rewarming of the frozen tissues, ischemia is relieved and reprerfusion takes place due to re-circulation in the affected organs, coupled with severe pain. Rewarming of frozen tissues is associated with generation of oxygen-derived free radicals which may lead to additional tissue injury[8]. At this stage, particularly during the rewarming phase, use of an analgesic, (which is also an inhibitor of thrombus formation and a haemorrheologic agent effective in increasing blood flow to the affected microcirculation and enhancing tissue oxygenation) along with the antioxidant (vitamin C), may provide adequate protection by scavenging singlet oxygen and free radicals[9,10] and help in preventing tissue damage to a great extent.

3. INDIVIDUAL SUSCEPTIBILITY, PREVENTION & TREATMENT

Individual susceptibility to the occurrence of cold injury is well known. It has been observed that when troops are exposed to identical severe cold conditions for a reasonable duration, only a few suffer from frostbite. Hence , detailed experiments on susceptibility, prevention and treatment have been carried out at DIPAS to find out suitable measures to prevent, treat and ameliorate cold injuries. These include: simple methods to screen out individuals who are more prone to this clinical condition[11] and to see the variations among the Indians in their susceptibility to cold injury[12]; to evaluate the effect of cold acclimatisation[13] and use of certain drugs and vitamins[14] along with simple treatment procedures suitable for field situations[15-17].

3.1 Screening Tests for Susceptibility

Experiments conducted on monkeys have shown that animals with higher peripheral vascular response under local cold stimulus are better protected against cold injury[11]. Monkeys with very good cold induced-vasodilatation (CIVD) response had the highest mean heat output values (index for peripheral vascular response), and had practically escaped from frostbite; whereas monkeys with poor CIVD response had the lowest values of heat output and suffered from severe to very severe type of injuries (Table 1). Another study on these lines showed that South Indians, who never face any cold climate throughout the year, are more susceptible to occurrence of cold injuries compared to North Indians and Gurkhas. The high altitude natives are most resistant to frostbite[12] under

Table 1. Relation of CIVD response with heat output and degree of cold injury in monkeys

Type of CIVD response	No. of animals	Mean heat output (cal/100ml/min)	Degree of injury
Very good CIVD response	6	139.5	NFB, PFB
Good CIVD response	8	122.6	NFB, PFB, MFB
Poor CIVD response	8	95.7	MFB, SFB, VSFB
No CIVD response	5	69.8	SFB, VSFB

NFB - No frostbite; PFB - primary frostbite; MFB - moderate frostbite; SFB - severe frostbite; VSFB - very severe frostbite.

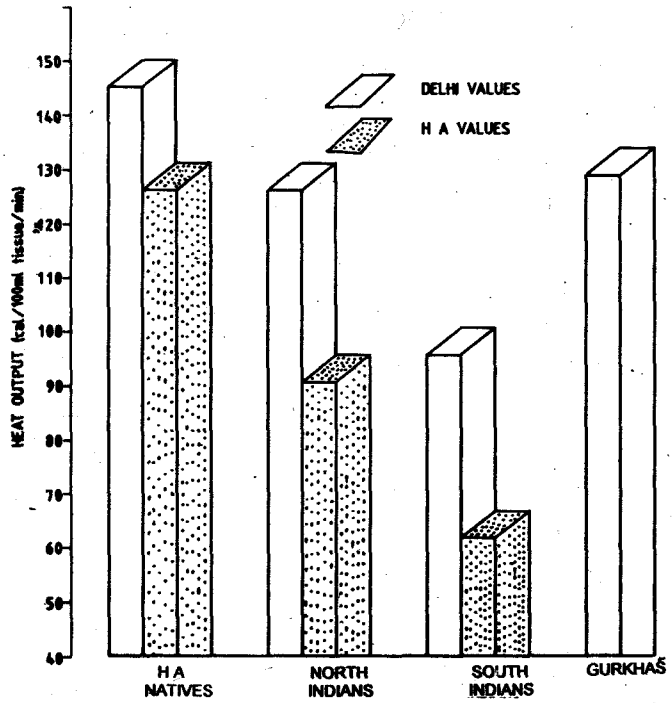

Figure 1. Values of heat output of different groups of subjects at Delhi and at high altitudes.

identical cold exposure. The data of heat output for various groups of subjects studied both at the sea level and at high altitudes are given in Fig. 1.

It is well established that the onset of CIVD is quicker and better in those who are habituated to chronic cold exposure[18-20]. Based on these observations, studies were conducted on rats to see the effect of cold acclimatisation on the prevention of cold injuries. Heat output from the hind paws was determined using Bunsen's ice calorimeter in two groups (control and cold-acclimatised) of rats. Later, frostbite was produced in these animals by exposing them to –15 °C for 1 hr using harness technique[13]. Cold acclimatisation was found to be effective in raising the peripheral vascular response, and thereby lessening the degree of injury[13]. This is due to better cold tolerance and improved peripheral circulation. Data on heat output, changes in rectal temperature and the nature of injury in cold-acclimatised and control rats are presented in Table 2. These data suggest that methods that can increase peripheral circulation, can also be used in preventing this clinical syndrome. These experiments have shown that

Table 2. Heat output, changes in rectal temperature & nature of injury in cold-acclimatised and control rats

Parameters	Cold-acclimatised group (n = 15)	Control group (n = 15)
Heat output (cal/30 min)	168.60 + 37.87*	94.57+ 28.22
Fall in rectal temperature (°C)	17.50 + 1.30*	19.56 + 0.86
Nature of injury	No. of paws injured	
NFB - no frostbite	14	5
PFB - primary frostbite	8	4
MFB - moderate frostbite	2	6
SFB - severe frostbite	5	9
VSFB - very severe frostbite	1	6

* = P < 0.001 compared to control group

measurement of CIVD, heat output and peripheral blood flow under local cold stress can be used for screening those who are highly prone to frostbite[11-13].

3.2 Prevention of Cold Injuries

The most useful preventive measures are: to limit the period of outdoor cold exposure; to keep warm with proper insulating (multilayered) clothing and footwear; to maintain hydration and to keep the part dry and abrasion free. Two important basic factors involved in prevention of cold injury are : (i) heat production capacity of the body, and (ii) measures to conserve this heat[4]. Physical well-being, proper clothing, insulating footwear, nutritious diet, avoidance of wetting, good hygiene and intelligent field operations are probably important measures for its prevention. However, adoption of these measures is very difficult during military operations and accidental situations, such as sudden storm during a route march or trekking, road blockade in high mountain regions, etc. Under such circumstances, in addition to the above protective measures, the possibility of prevention through certain drugs and vitamins acquires importance. Our earlier studies suggested that methods which can improve peripheral vascular response and blood flow under local cold stimulus can be of use in preventing frostbite. Based on these

findings, the use of certain drugs and vitamins was tried experimentally in rats and monkeys. Even though pilot studies were carried out using a number of drugs, such as thyroxin, triiodothyronine, isoxsuprine hydrochloride, rovigon, xanthinol nicotinate and nicotonic acid, only tolazoline hydrochloride (Priscol) and vitamin C were tested at experimental level, as these had given encouraging results[14,15].

Administration of tolazoline hydrochloride 2 hr before cold exposure caused significant rise in the values of heat output and marked improvement in CIVD response (Fig. 2). This way, it was effective in reducing the severity of cold injury. But a marked fall in rectal temperature was also noticed in monkeys during severe cold exposure when tolazoline hydrochloride was given 2 hr before exposure[14]. Prolonged administration of a high dose of vitamin C (50 mg/kg bw) for 21 days prior to cold exposure caused significant improvement in extremity circulation and maintenance of higher rectal temperature during cold exposure and helped in reducing the incidence of frostbite in rats[15]. However, administration of vitamin C for 7 days prior to cold exposure gave no marked benefit. The patterns of fall in rectal temperature during cold exposure and percentage of distribution of degree of cold injury in control and vitamin C-treated groups are depicted in Figs 3 and 4, respectively. The beneficial effect of tolazoline hydrochloride

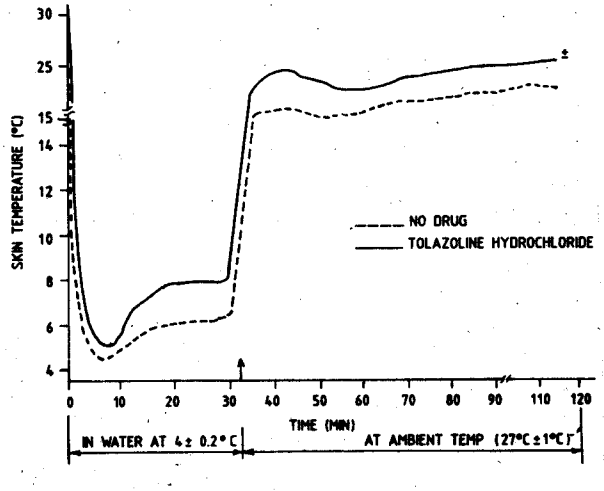

Figure 2. Effect of tolazoline hydrochloride in CIVD responses in man.

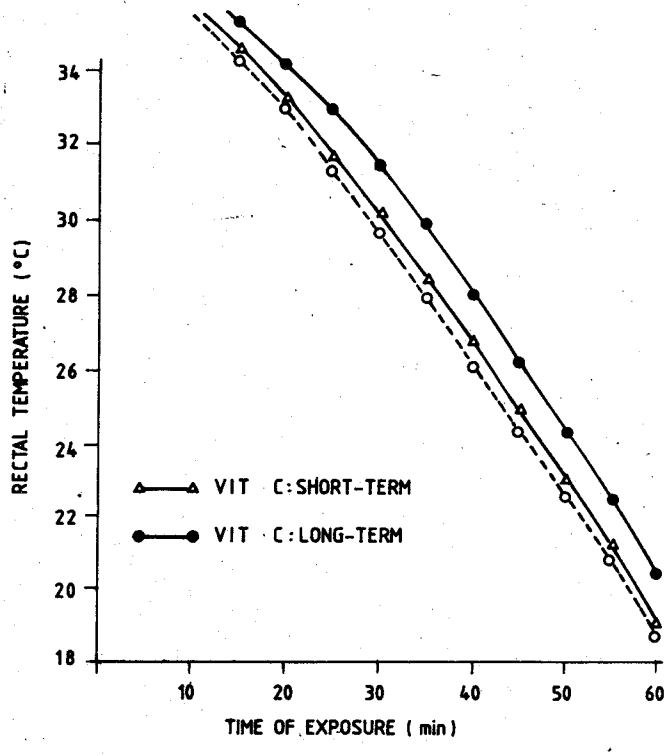

Figure 3. Pattern of fall in rectal temperature during cold exposure in control and groups treated with vitamin C.

might be due to increased blood supply and prevention of stasis in the capillaries at a critical stage of formation of thrombosis. Vitamin C might have improved the cold tolerance through its metabolic and thermogenic effects. Hence, in supplementation of the above-mentioned preventive measures, administration of a high dose of vitamin C prior to cold exposure may provide additional protection against cold injuries by way of increased cold tolerance.

3.3 Treatment of Cold Injuries

During war and accidental situations, due to unforeseen reasons, prolonged outdoor exposure to cold may sometimes become unavoidable and thus the possibility of getting cold injury cannot be avoided completely. Further, once frostbite has occurred, its treatment is not very satisfactory, particularly when there is delay in starting the therapy, and in extreme field situations there is always a delay in evacuating frostbite victims due to serious logistic problems. The time lag between the occurrence of frostbite and initiation of therapy

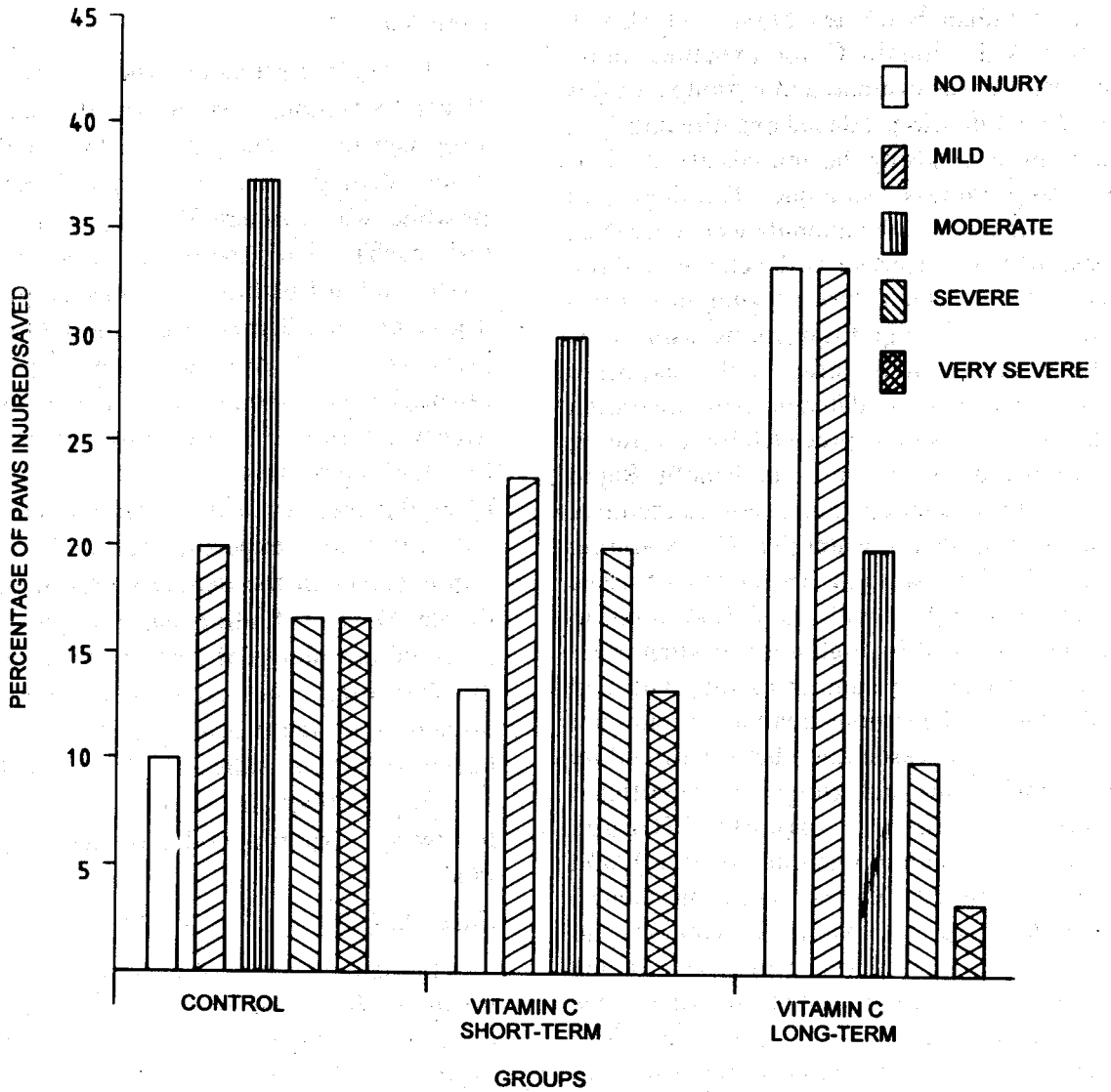

Figure 4. Percentage distribution of degree of cold injury in control and vitamin C-treated groups

plays a vital role in the curative process. The purpose of treatment is to prevent secondary effect, to re-establish stagnant circulation as quickly as possible to prevent stasis in the capillaries at a critical stage of formation of thrombosis, and to provide antioxidant defence so as to avoid the need for amputation. The treatment must, therefore, be immediate, intense and as conservative as possible. Hence, some simple procedures for treatment of frostbite, applicable in the field situation itself, were tried at DIPAS. The first step in this respect was to stop exposure to cold and apply rewarming. (But the exposed parts should never be rewarmed in direct fire heat. This is dangerous).

4. TREATMENT OF EXPERIMENTAL FROSTBITE

Case Study 1

The studies illustrated the synergistic effect of vitamin C in amelioration of cold injury, if it was coupled with rapid rewarming at 37 °C in decoction of tea leaves. Rewarming in decoction of Indian tea maintained around normal body temperature (37-39 °C) followed by a high dose of vitamin C (50 mg/kg bw) for 15 days is very effective immediate treatment for frostbite in rats[16]. In this series , the effect of treatment with a high dose of vitamin C , rapid rewarming with 37 °C water alone and with vitamin C; rapid rewarming with 37 °C

decoction of Indian black tea alone and also in combination with vitamin C for experimentally-induced frostbite was evaluated in 6 groups of rats (25 each). Frostbite was produced experimentally in the hind limbs by exposing the animals at -15 ±1 °C for 1 hr using harness technique. The degree of injury was assessed and the animals were classified on the basis of tissue necrosis at the end of 15 days. Administration of a high dose of vitamin C for a prolonged period and rapid rewarming with 37 °C water bath immediately after cold exposure apparently reduced tissue damage. Administration of a high dose of vitamin C preceded by rewarming in plain warm water gave additional benefit. Rapid rewarming in tea decoction alone showed identical beneficial effect as that of water (37 °C) rewarming plus vitamin C administration. The degree of tissue preservation was highest with rapid rewarming in tea decoction followed by high dose of vitamin C. The results showing the number of rats with and without frostbite in the various treatment groups are given in Table 3. The association between frostbite status (present/absent) and group was significant compared to control animals. Groups (iv) (rewarmed in water + vitamin C-treated), and (v) (rewarming in 37 °C tea decoction alone), showed significant ($p < 0.05$) improvement in tissue preservation, while group (vi) (rewarmed in tea decoction followed by high dose of vitamin C) was highly significant ($p < 0.01$) (Table 3). The percentage of animals that remained free from any type of injury was also highest[15] in group (vi).

Case Study 2

In another series of experiments, the efficacy of pentoxifylline, a haemorrheologic agent, along with aspirin, an analgesic in the amelioration of tissue damage due to experimentally-induced frostbite was evaluated in 5 groups of rats[17] (20 each). The methods employed for the production of frostbite as well as assessment of the degree of tissue damage were similar to those in the previous series. Administration of pentoxifylline (40 mg/kg bw) 30 min before and 30 min after cold exposure followed by two doses of the same daily for the next five days along with aspirin (5 mg/kg bw) twice daily for the same duration, only after cold exposure, resulted in significant improvement in the degree of tissue preservation (Table 4). This finding has brought to light the potential usefulness of these drugs in the treatment of frostbite. The combined pharmacological properties of these drugs might have altered the haemorrheologic status of blood and produced beneficial effect in improving tissue survival following experimentally-induced frostbite in rats[17].

Case Study 3

In the next series of experiments, the effect of treatment by rapid rewarming in tea decoction maintained at 37-39°C, immediately after experimentally-induced frostbite followed by combined aspirin-pentoxifylline-vitamin C therapy

Table 3. Frostbite status (absence / presence) with different degrees of injury in various groups

Groups (n = 25 each)		Frostbite		Frostbite present (different degrees)			
		Absent number (%)	Present number (%)	PFB number (%)	MFB number (%)	SFB number (%)	VSFB number (%)
Group - 1	Control	3(12)	22(88)	6(24)	8(32)	4(16)	4(16)
Group - II	Vitamin C	5(20)	20(80)	7(28)	6(24)	4(16)	3(12)
Group - III	Water	8(32)	17(68)	6(24)	4(16)	4(16)	3(12)
Group - IV	Water + Vitamin C	11(44)*	14(56)	6(24)	3(12)	3(12)	2(8)
Group - V	Tea decoction	10(40)*	15(60)	7(28)	4(16)	2 (8)	2(8)
Group - VI	Tea decoction + Vitamin C	13(52)**#	12(48)	6(24)	3(12)	1 (4)	2(8)

The values are shown as number and percentage.

* = $P < 0.05$; ** = P, 0.01 compared with control group I and

= $P < 0.05$ compared with vitamin C-treated group II, using Chi-Square test.

All other comparisons were statistically not significant.

was evaluated in two (control and experimental) groups of rats (25 each). Frostbite was induced in all the animals by exposing one of the hind limbs in a freezing machine by maintaining the temperature at -12 ±1 °C with wind flow of 25-30 l/min for 30 min. While standardising the method, it was observed that with this degree and duration of exposure, about 50 per cent of the animals suffered from severe and 30-40 per cent from moderate degree of frostbite. The remaining 10-20 per cent animals suffered from very severe type of injury. In the present series also, 14 out of 25 control animals (56 per cent), who remained untreated after exposure, suffered from severe degree of frostbite (SFB) and 3 animals (12 per cent) from very severe degree of frostbite (VSFB). The remaining 8 animals (32 per cent) suffered from moderate degree of frostbite (MFB). The exposed limbs of the experimental group (n = 25) of rats, immediately after exposure, were rewarmed in tea decoction maintained at 37°-39°C for 30-35 min with simultaneous oral ingestion of about 5 ml warm tea decoction. Then they were orally administered aspirin (5 mg/kg bw), pentoxifylline (40 mg/kg bw) and vitamin C (50 mg/kg bw) twice daily for the next 7 days. Rewarming in tea decoction was done on for two successive days, once daily for 30-35 min. From day 2 onwards, silver sulphadiazine, an antiseptic cream, was also applied externally on the skin to prevent secondary infection. Out of 25 animals in the experimental group, 13 (52 per cent) showed no tissue loss, while the remaining 12 animals suffered, respectively from primary frostbite (PFB) or very mild (n = 8, 32 per cent) and MFB (n = 4, 16 per cent). No animals in this group

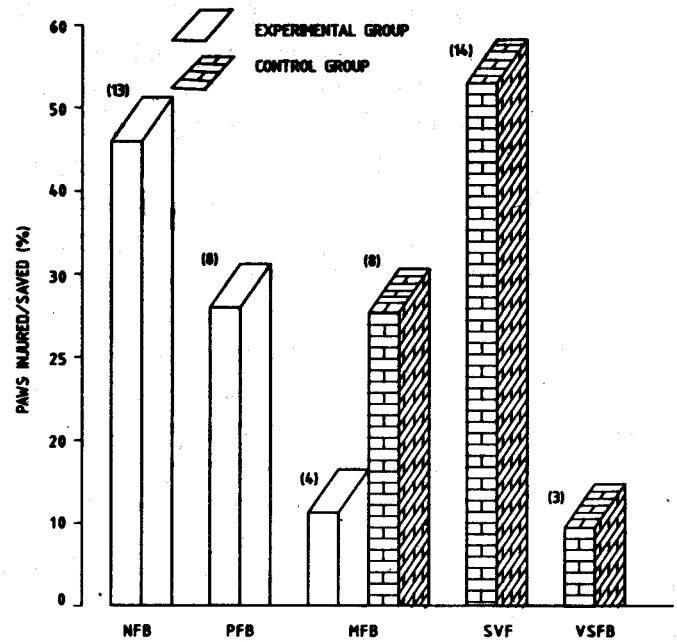

Figure 5. Percentage distribution of the degree of cold injury in control and experimental groups (number of animals given in paranthesis). NFB (no frostbite), PFB (primary frostbite), MFB (moderate frostbite), SFB (sévere frostbite), and VSFB (very severe frostbite).

suffered either from SFB or VSFB (Fig. 5). This clearly indicates the highly beneficial effect of this combined therapy as an immediate treatment for frostbite in rats.

5. DISCUSSION

These findings suggest that rapid rewarming of the exposed area soon after cold exposure possibly acts by restoring blood flow rapidly so that there is inadequate time for plasma to be lost and the red

Table 4. Frostbite status (absence / presence) with different degrees of injury in various groups

Groups (n = 20 each)		Frostbite		Frostbite present (different degrees)			
		Absent number (%)	Present number (%)	PFB number (%)	MFB number (%)	SFB number (%)	VSFB number (%)
Group - 1	Control	2(10)	18(90)	4(20)	6(30)	4(20)	4(20)
Group - II	Vitamin C	2(10)	18(90)	6(30)	6(30)	3(15)	3(15)
Group - III	Water	2(10)	18(90)	5(25)	6(30)	4(20)	3(15)
Group - IV	Water + Vitamin C	4(20)	16(80)	7(35)	6(30)	2(10)	1(5)
Group - V	Tea decoction	9*(45)	11*(55)	6(30)	3(15)	2 (10)	0(0)

The values are shown as number and percentage.

* = $P < 0.05$ as compared to group I, using Chi square test.

No significant difference was seen between other groups in absent/present of frostbite.

cells to sludge during passage of blood through the tissues[15]. The exact mechanism behind the beneficial effect of rewarming in tea decoction is not very clear. It may be attributed to the possible role of the constituents of tea leaves, which include volatile oils, tannic and gallic acids, quercentin, theine (identical with caffeine), xanthine, theophylline and theobromine. Quercentin is known to reduce abnormal capillary fragility, thereby maintaining its integrity. Theine relaxes smooth muscles and is a powerful nerve stimulant[21,22]. The role of aminophylline/ theophylline (constituents of tea leaves) in improving thermogenesis, cold tolerance and prevention of hypothermia has also been reported[23-25]. All these might have helped in reducing tissue damage when rapid rewarming was done in tea decoction.

Hastening recovery through administration of vitamin C is possibly due to its antioxidant effect[10] as well as increased metabolism and thermogenic properties which might have helped in restoring the general body warmth by increasing extremity blood flow. Due to its labile nature, Vitamin C rapidly enters from plasma into leukocytes and potentates cellular immunity, thus providing protection against subsequent infection, which is a major contributory factor in determining the severity of the injury. Vitamin C also helps in collagen synthesis and is known for its use in accelerating wound healing process[16,26]. The protective effect of vitamin C against cold and frostbite has also been demonstrated[15,16,26].

Among the haemorrheologic agents, pentoxifylline a dimethylxanthine derivative, has been shown to be effective in increasing blood flow to the affected microcirculation by decreasing blood viscosity and enhancing tissue oxygenation[27]. Pentoxifylline improves red blood carpuscles flexibility, reduces platelet aggregation and increases fibronolytic activity[28]. Aspirin is an analgesic, anti-inflammatory, antipyretic and an inhibitor of prostaglandin. It acts at the cyclo-oxygenase level, preventing the conversion of arachidonic acid to prostaglandin, thus inhibiting thrombus formation. Aspirin also acts as an effective pain reliever during postexposure rewarming phase[29]. Application of pentoxifylline with aspirin might have brought about maximum improvement in extremity blood flow and thus tissue oxygenation, thereby preventing complete thrombosis, anoxia and necrosis of the tissues. It appears that both anti-platelet activity and analgesic action of aspirin[29] potentate the effect of pentoxifylline. The combined pharmacological effects of these drugs might have altered the haemorrheologic status of blood and played a protective beneficial role in treating experimentally-induced frostbite in rats.

6. CONCLUSION

Among the various anti-frostbite drugs, the combined therapy of pentoxifylline and aspirin along with a high dose of vitamin C, preceded by rapid rewarming in decoction of tea leaves maintained at 37-39 °C seems to be very promising as an immediate treatment for frostbite. These findings call for clinical studies so as to confirm the beneficial effects of the above combination therapy in man. Positive findings in human subjects, if established, will help to formulate a simple treatment procedure, self-applicable in the field situation, by the victim himself, immediately on recognition of the cold injury and will be a real boon to the humanity, particularly to the Armed Forces personnel operating in the snow-bound areas at high altitudes.

ACKNOWLEDGEMENTS

Authors thankfully acknowledge the technical assistance provided by Sarvashri P.C. Chhabra and S.K.S Chauhan.

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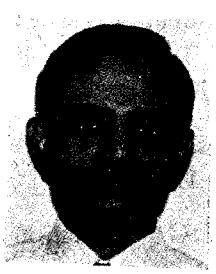

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