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Original Article

Intravenous Mannitol reduces intracompartmental pressure following tibia fractures: A randomized controlled trial

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ABSTRACT

Purpose: Impending compartment syndrome is a common event following closed tibia fractures, which can progress to sinister compartment syndrome. Fasciotomy is the only definitive treatment available, though it has its own drawbacks and complications. Medical management at present consists of limb elevation and adequate hydration. This study aims at determining whether intravenous administration of Mannitol reduced the intracompartmental pressure in patients with closed tibial fractures.

Methods: This is a double blinded, randomized control trial done in a single tertiary care center in India. Forty-five patients were recruited between February 2012 and October 2012. Forty patients who presented to the emergency department with isolated, closed, high velocity, and proximal 2/3 tibia fractures were included in this study. Patients with contraindication to Mannitol were excluded. They were allocated into 2 groups by the investigator using computer generated randomization. The pressure in the anterior compartment of the leg was measured with a handheld Stryker pressure monitor. Then either 20% Mannitol or 0.9% normal saline as given intravenously in a blinded manner, based on the randomization. The intracompartmental pressure was measured at 0, 1 and 3 h after the infusion. The participant, investigator and statistician were masked to the group assessment.

Results: There was no difference in intracompartmental pressures at 1 or 3 h, between the groups. However, in patients with the baseline of compartmental pressures $\geq$30 mmHg, Mannitol showed a marked reduction in pressure of 8.5 mmHg at 1 h compared to almost no change in pressure in the saline group. There were no adverse events with the use of Mannitol.

Conclusions: This preliminary study appears to show that Mannitol is useful in the management of the increased compartment pressure. The limitations of this study were that it only involved a small group of patients and the baseline pressures in both the groups were not comparable. More studies are required before the use of Mannitol as a standard of care in the management of compartment syndrome can be established.

Introduction

Compartment syndrome is a dreaded complication of fractures and soft tissue injuries.[1] Hence early recognition and management is imperative. Fasciotomy of the involved compartments to relieve tissue pressure is the only definitive treatment of compartment syndrome till date. However, fasciotomy is not without its own drawbacks.[2] When performed late, it can lead to sepsis and amputation.[3–5] The use of a non-invasive therapeutic agent would be most pertinent in the developing world, where most road traffic accidents occur and variable levels of care and delayed management are present.

Mannitol is an osmotic diuretic, which acts by extracting water from intracellular compartments and is used for patients with head injury to reduce cerebral edema.[6] In acute compartment syndrome, Mannitol is thought to act by reducing cellular edema through its hyperosmolar effect, and it is proposed that it reconstitutes normal cell energy production and reduces muscle cell necrosis through its free radical scavenging ability.[7] There are a few animal studies,

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which show the effect of Mannitol in reducing compartmental pressure.[8,9] The aim of this study was to assess the efficacy and safety of compartment pressure with the use of intravenous Mannitol.

Methods

This was a phase III, prospective, randomized control trial. This study was conducted at Christian Medical College hospital, a tertiary care teaching hospital in Vellore, India between February 2012 and October 2012. This study was started after getting the approval from the Institutional Review Board (IRB Min. No. 7611 dated 21.09.2011). The study was conducted on adult patients presenting with tibial fracture to the emergency department. The patients were recruited after obtaining written consent from them. Inclusion criteria: all adult (age >14 years) patients presenting to the emergency department with acute and closed tibia fractures (excluding AO type 4.4)[10] without any other fracture. Exclusion criteria: patients with contraindication to Mannitol including heart failure, pulmonary congestion, hypotension, anuria, liver failure, intracranial bleed, pregnant women and children ≤14 years.

Randomisation was done by computer generated randomisation permutation. Forty patients were divided into 2 groups: 20 received mannitol and 20 received saline after randomization. The randomization code was concealed in opaque envelope and given to the pharmacy department. In the pharmacy department, 40 bottles contained 100 ml of fluid were serially labelled from 1 to 40, twenty of which contained 20% Mannitol and another twenty contained 0.9% normal saline. The bottles appeared identical in both groups. The enrollment of the patient to the study groups was done by the investigator. The investigator and patients were masked in the treatment.

The intervention used was 20% Mannitol and given over a period of 10 minutes and the comparator used was 0.9% normal saline, given over the same period. After the patients in the emergency room were stabilized, the limb was immobilized by a splint above the knee and elevated with one standard size pillow. The site of compartment pressure measurement was marked with a marker approximately 4 cm from the fracture site. Under aseptic precautions, 2 ml of 2% Xylocaine was instilled subcutaneously and the pressure was measured with a hand held pressure monitor system from Stryker (Stryker ® Surgical, Kalamazoo, Michigan, USA) using the side ported, non-coring needle (SPM). The angle of insertion was 45° to the limb. Pressures in the injured leg were measured with SPM at 1 and 3 h after the start of the infusion. All patients were serially monitored for the development of compartment syndrome and adverse effects of the drug.

The primary outcome was intracompartmental pressures at 1 and 3 h after administration of 20% Mannitol and saline intravenously. The secondary outcome was the development of compartment syndrome.[11] The clinical criteria to diagnose compartment syndrome were increase in swelling, ischemic pain at rest, pain at passive stretch, decreased range of motion, sensory and motor dysfunction. The sample size for the study was calculated after a pilot study on 6 patients who had isolated, closed tibial shaft fractures without any contraindications to Mannitol (Table 1). In this pilot study, 3 patients received mannitol, and 3 received saline. Pressures were measured in the limbs prior to the administration, 1 and 3 h later. Using this data, the sample size was calculated to be 20 per arm, with a power of 90% and alpha error of 10%.

The statistician who performed the final data analysis was blinded to the groups. Data analysis was done using STATA software version 12.0 (Statacorp LP, TX) and SPSS 17.0 (SPSS Inc. Chicago). All continuous variables were assessed using independent *t*-test and all categorical variables were assessed using the Chi square test. As there was a difference in the baseline pressure between the Mannitol and the saline groups, regression analysis was performed to eliminate the difference of pressure between the Mannitol and the saline groups, in which p values <0.05 was considered significant.

Table 1
Pilot study data on intracompartmental pressures (mmHg) for patients with tibial fractures given Mannitol or saline.

Intervention	Time point		
	Before administration	1 h	3 h
20% Mannitol			
Patient 1	28	25	20
Patient 2	65	52	44
Patient 3	63	40	43
0.9% normal saline			
Patient 1	38	40	28
Patient 2	31	38	55
Patient 3	40	55	46

Results

Forty-five patients were eligible to be included during the time period from February 2012 to October 2012. Two patients refused to participate, 1 had contraindication to Mannitol and 2 were already given one dose of Mannitol. The remaining 40 patients were included in this study (Fig. 1).

Age group of the patients ranged from 18 to 70 years with a mean age of 44.3 years. Thirty were male and 10 were female patients. Co-morbidities like diabetes mellitus, hypertension and epilepsy were equally distributed in both groups (Table 2). There was an overall predominance of Grade II fractures (Tscherne classification).[12] The baseline compartment pressure was different in the 2 groups. Though there was a difference in the pressure at 1 and 3 h, it was not statistically significant (Table 3). As there was this difference, for analysis, patients were divided into 2 groups, based on the baseline intracompartmental pressures as ≤29 mmHg and ≥30mmHg (Table 4). We found that among patients with pressures ≥30 mmHg, there was a reduction of 8.5 mmHg (18%) in the Mannitol group at 1 h and no change in pressure in the saline group. However, as this was a post hoc analysis, the groups (≤29 mmHg and ≥30 mmHg) were not comparable. To eliminate the difference of the baseline pressures, logistic regression and analysis of covariance was done with change in pressure as the dependent variable. This analysis showed that the difference in the pressures between the 2 groups at 1 and 3 h was significant (Table 5). Linear regression to predict intracompartment pressure at 3 h with variables of age, gender, presence of diabetes, drugs administrated and the Tscherne classification suggested the female had lower pressures while a Tscherne Grade II also predicted higher pressures. Mannitol showed a swift response in patients with raised intracompartmental pressure, which was evident at 1 h and maintained at 3 h. No patient developed compartment syndrome or had any adverse events in either groups.

Discussion

Mannitol plays a role in reducing high compartment pressures though it was not statistically significant in this study. This was because of the disparity in baseline pressures. The post hoc analysis showed a marked reduction of pressure 1 h after the administration of Mannitol.

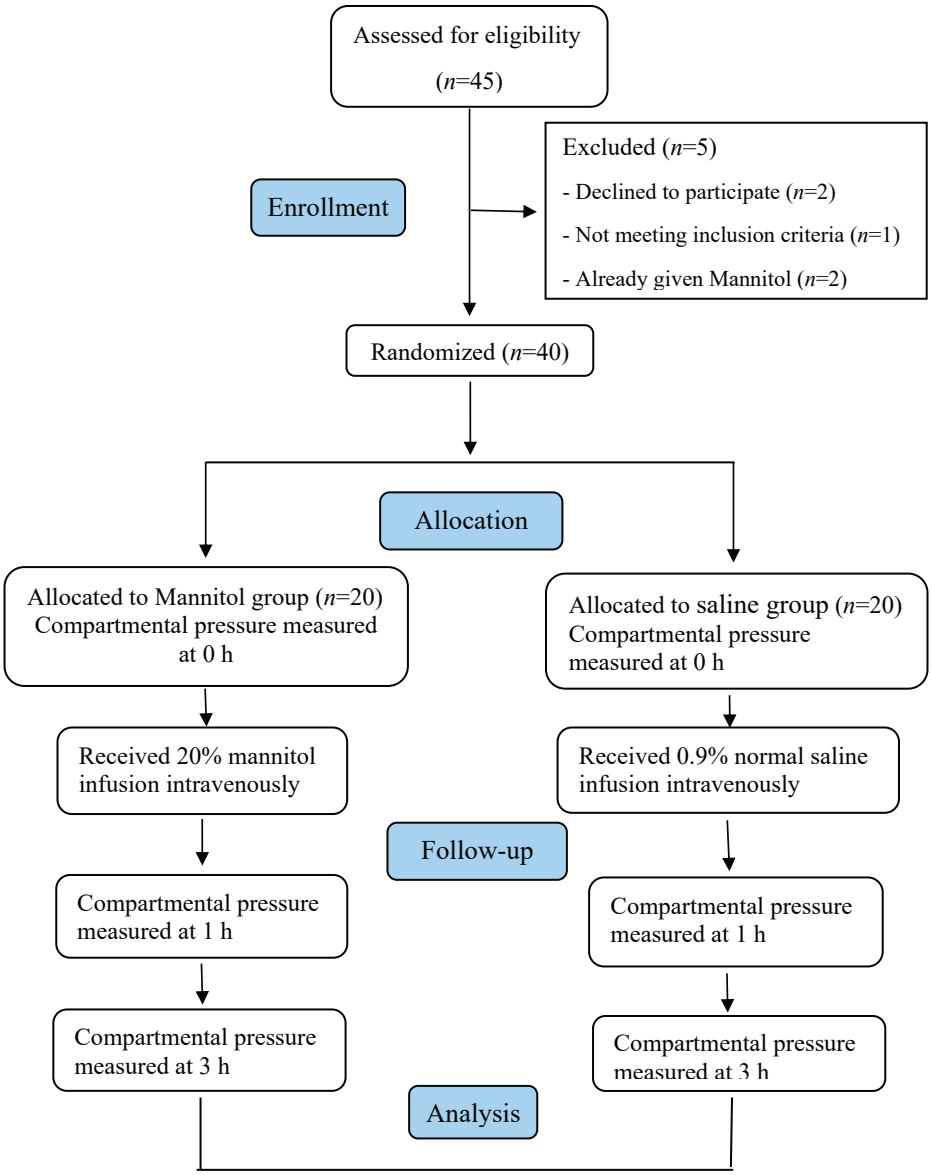

Fig. 1. Consort figure for the Mannitol versus the saline study for raised compartment pressures following tibial fractures.

Impending compartment syndrome is a common event following closed tibia fractures, which can progress to a much severe compartment syndrome. Fasciotomy is the only definitive treatment available, though it has its own problems and complications. In the developing world, because of a delay in transportation and inadequate primary management, the duration of raised compartment pressure is often difficult to ascertain, and thus the time of injury is usually taken as the time of onset of compartment syndrome. This may not be a true duration of the injury, and a further problem arises if the patient is intoxicated or unconscious. Adding to this conundrum, the fact is that fasciotomy, the only curative option, is time-dependent and should be ideally done within 12 h.[13] Fasciotomy done late can be disastrous and result even in amputation of the limbs, as it has been well established that skeletal muscle can tolerate ischemia for only 4 h.[2] Moreover, increased compartment pressures have been recorded in several studies as the initiating factor at the early stages of acute compartment syndrome, which affects the local circulation and oxygen delivery.[14] This in turn produces further physiological changes that propagate to a full-blown compartment syndrome, through a vicious cycle. If the administration of Mannitol can interrupt this chain, it could avoid an uneccesary fasciotomy.

At present, there is no alternative to fasciotomy and medical management at best consists of elevation and adequate hydration. In this scenario, a therapeutic agent would be ideal. The animal studies involving Mannitol are few.[8,9] Though clinical studies using Mannitol may be few, we suspect that Mannitol is being used empirically, but without an analysis.[15,16]

This preliminary study appears to show that Mannitol has a useful role in the management of increased compartment pressure, especially when the pressures are above 30 mmHg. The limitations of this study were that there is only a small group of patients and the baseline pressure in Mannitol group were not comparable. However, stratification could not be done as the investigator was blinded to the therapeutic agent used and it was noted only at the end of analysis. The strength of this study was that it is a double blinded randomized control trial. The investigator, patient and the

Table 2
Baseline characteristics of study patients (n=20 for each group).

Variables	Mannitol group	Saline group
Age (year), range (mean)	29–70 (44.2)	23-65 (41.3)
Sex, *n* (%)		
Male	14 (70)	16 (80)
Female	6 (30)	4 (20)
Diabetes, *n* (%)	5 (25)	5 (25)
Hypertension, *n* (%)	3 (15)	2 (10)
Tscherne classification, *n* (%)		
Grade 0	0	0
Grade 1	9 (45)	13 (65)
Grade 2	11 (55)	7 (35)
Grade 3	0	0
Location of fracture, *n* (%)		
Proximal 1/3	7 (35)	10 (50)
Middle 1/3	8 (40)	4 (20)
Distal 1/3	5 (25)	6 (30)
Fracture pattern, *n* (%)		
Simple	6 (30)	4 (20)
Comminuted	13 (65)	16 (80)
Mode of injury, *n* (%)		
Two wheeler	9 (45)	11 (55)
Four wheeler	4 (20)	2 (10)
Pedestrian	4 (20)	3 (15)
Fall from height	3 (15)	4 (20)
Baseline intracompartmental pressure (mmHg) (mean ± SD)	34.2 ± 16.7	24 ± 12.2

Table 3
intracompartmental pressures (mmHg) between the Mannitol and saline group in the tibial fracture study (n=20 for each group) (mean ± SD).

Time point	Mannitol group	Saline group	Mean difference with *CI*	*p* value
Before administration	34.2 ± 16.7	24.0 ± 12.2	10.2 (0.83–19.57)	0.035
1 h	27.7 ± 15.3	20.6 ± 14.4	7.1 (−2.48–16.58)	0.140
3 h	25.10 ± 17.04	19.4 ± 12.5	5.7 (−3.9–15.3)	0.240

Table 4
Intracompartment pressure reduction in patients stratified based on baseline intracompartmental pressures, ≤ 29 mmHg or ≥30 mmHg, (n=20 for each group).

Variables	Mannitol group	Saline group	Mean difference with 95% *CI*	*p* value
Baseline pressure ≤29 mmHg (n = 23)				
Before administration	16.6 ± 6.0	18.2 ± 6.6	−1.6 (−7.5–4.2)	0.56
1 h	13.1 ± 7.5	13.8 ± 8.2	−0.68 (−7.9–6.6)	0.88
3 h	11.8 ± 7.9	13.9 ± 8.8	−2.2 (−9.9–5.6)	0.57
Baseline pressure ≥30 mmHg (n = 17)				
Before administration	45.92 ± 9.2	41.2 ± 8.2	4.7 (−5.4–14.8)	0.34
1 h	37.4 ± 10.6	41.2 ± 7.2	−3.8 (−14.9–7.4)	0.48
3 h	34.0 ± 15.7	35.8 ± 4.9	−1.8 (−17.3–13.68)	0.81

statistician who analyzed were all blinded till the analysis was completed.

Ideally, a larger randomized controlled trial with stratification into high and low-pressure groups, so that the baseline pressures are comparable would be more conclusive. Further studies are also required to study the frequency of administration of Mannitol. These studies using Mannitol could radically alter the management of compartment syndrome in the world.

Table 5
Analysis of covariance in pressure between Mannitol and saline groups.

Parameters	β coefficient	Mean difference with 95% *CI*	*p* value
Baseline to 1 h			
Mannitol group	1.72	(1.06–2.37)	<0.001
Mannitol group	1.00		
Before administration	0.14	(0.16–161.04)	<0.001
Baseline to 3 h			
Mannitol group	2.04	(1.38–2.70)	<0.001
Saline group	1.00		
Before administration	0.24	(0.22–0.26)	<0.001

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Ethical statement

This study was approved by the Institutional Review Board (IRB Min. No. 7611 dated 21.09.2011).

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Declaration of competing interest

There are no competing interests.

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