



# Efficacy of Hyaluronidase in the Mannitol Extravasation Induced Compartment Syndrome-A Case Report and Review of Literature

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**Cite this article as:** Kaur M, Balakrishnan N, Gosal JS, Bhatia P, Bhaskar S, Jha DK. Efficacy of Hyaluronidase in the Mannitol Extravasation Induced Compartment Syndrome—A Case Report and Review of Literature. *Turk J Anaesthesiol Reanim.* 2021; 49(4):329-333.

## Abstract

Mannitol is one of the indispensable drugs in neurosurgery to manage the raised intracranial pressure. Though considered safe, extravasation of mannitol into the tissues can cause considerable morbidity with the consequent development of compartment syndrome. We report a case of a 50-year-old female who developed forearm compartment syndrome due to mannitol extravasation after undergoing surgery for frontal glioma under general anaesthesia. The severe forearm compartment syndrome could be successfully managed without fasciotomy using hyaluronidase. We describe the pathophysiology, prevention and treatment strategies emphasising the use of hyaluronidase in the management of mannitol extravasation induced compartment syndrome.

**Keywords:** Mannitol extravasation, compartment syndrome, hyaluronidase, neuroanaesthesia, glioma

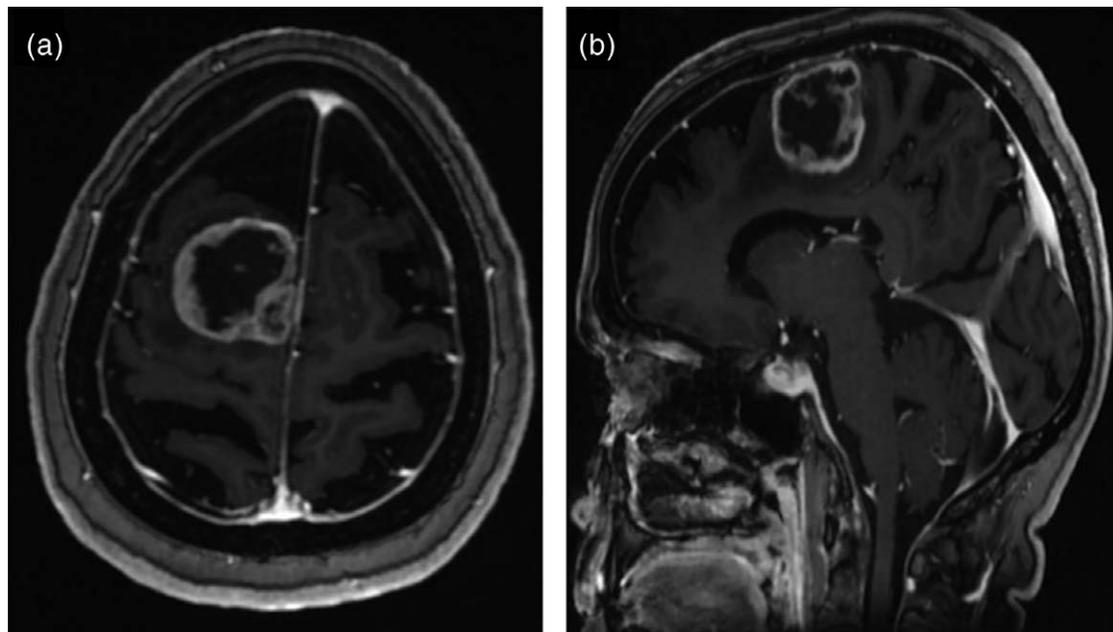
## Introduction

Mannitol extravasation causing compartment syndrome is a rare complication.<sup>1-5</sup> Mannitol is commonly used in neuro anaesthesia to decrease brain swelling intraoperatively. However, mannitol is a highly osmolar fluid, and its extravasation into soft tissues around the venous access can rapidly raise the tissue oncotic pressure leading to the formation of compartment syndrome. If diagnosis and the treatment are delayed, this can even eventually lead to emergent fasciotomy, wound debridement, or even limb amputation.<sup>6-8</sup> There have been only five reported cases of mannitol extravasation induced compartment syndrome to date.<sup>1-5</sup> We report the first minimally invasive and successful management of a case of mannitol extravasation induced compartment syndrome using hyaluronidase who underwent surgery under general anaesthesia for a frontal glioma, thus avoiding the morbidity of fasciotomy.

## Case Report

A 50-year (60 kg) female, ASA II, presented with complaints of headache, focal seizures left upper and lower limbs, and progressively increasing weakness in the left upper limb for 1 month. MR brain was done, suggestive of a right frontal high-grade glioma (Figure 1). We scheduled her for right frontal craniotomy and tumour excision. The patient had a history of hypothyroidism for 6 years and was on tablet thyroxine 75 µg once daily. Her recent thyroid profile and all other investigations were within normal limits. Written and informed consent was obtained.

In the operating room, the patient was placed supine, and monitors were attached. An 18G intravenous (IV) catheter was placed, secured in the antecubital vein over her right forearm, and the arm was tucked to the side of the patient. Premedication was done with injection midazolam 1 mg IV and injection fentanyl 120 mcg IV. She was induced with injection propofol 120 mg, and muscle relaxation was obtained by injection rocuronium 50 mg. The



**Figure 1. a,b. Preoperative MR contrast-enhanced axial (a) and sagittal (b) images showing a well-defined intra-axial right posterior frontal mass lesion with heterogeneous contrast enhancement with perilesional oedema suggestive of high-grade glioma.**

extension line (100 cm) was attached over this cannula. We did the oro-tracheal intubation, adequate padding of the eyes and pressure points. The patient was draped from head to toe, and surgery was started. Approximately 45 minutes after the beginning of the surgery, injection mannitol 20% 100 mL was given IV slowly over 30 minutes through the same extension line. The surgery lasted 3 hours. After the completion of the surgery, the patient was extubated uneventfully.

However, after undraping, the right forearm was seen to be oedematous and swollen. The swelling increased rapidly to such an extent that the whole limb below the elbow became tense and swollen. Multiple large vesicles were formed around the IV catheter (Figure 2a, b). These blisters sloughed off to denude the dermis below. The right radial

pulse also became feeble. The pulse oximeter on the right index finger showed a damped waveform. However, the patient was able to move the fingers of her hand without any difficulty. We made the diagnosis of compartment syndrome caused by mannitol extravasation. The IV catheter was taken out, the limb was elevated, and injection hyaluronidase (150 units in 10 mL normal saline) given through multiple subcutaneous injections of 1 mL each over the affected limb around the location of the catheter with a 25G needle.

Meanwhile, an emergent plastic surgery consult was taken. After the injection of hyaluronidase, the swelling did not increase further. We observed the limb every 15 minutes. Gradually the forearm became less tense, and swelling began to decrease. Radial pulse volume and waveform started improving. There was a significant reduction in swelling at 6 hours. By the next day, blisters started healing and got healed entirely at 2 weeks follow-up (Figure 2c).

### Main Points

- Mannitol extravasation induced compartment syndrome is a rare but avoidable complication causing significant morbidity.
- Various preventive measures and *early* diagnosis are the key to manage mannitol induced compartment syndrome successfully.
- *Early* diagnosis by a vigilant anaesthetist provides the “window period” during which hyaluronidase can be given.
- Hyaluronidase helps in mannitol induced compartment syndrome by avoiding the morbidity of invasive procedures like fasciotomy.

### Discussion

Mannitol is the standard of care for managing the raised intracranial pressure (ICP) in neurosurgical patients.<sup>9</sup> It is an osmotic diuretic (1098 mOsm L<sup>-1</sup>) that has a multitude of other actions by which it decreases ICP. Apart from rheological properties (reducing the blood viscosity, thus improving flow and oxygenation in cerebral microvasculature) and the free radical scavenging effect, mannitol elevates blood



**Figure 2. a-c. (a and b) Right upper limb of the patient showing tense swelling, blister formation and sloughing of the epidermis of the skin due to mannitol extravasation. (c) Lesions healed at 2 weeks follow-up.**

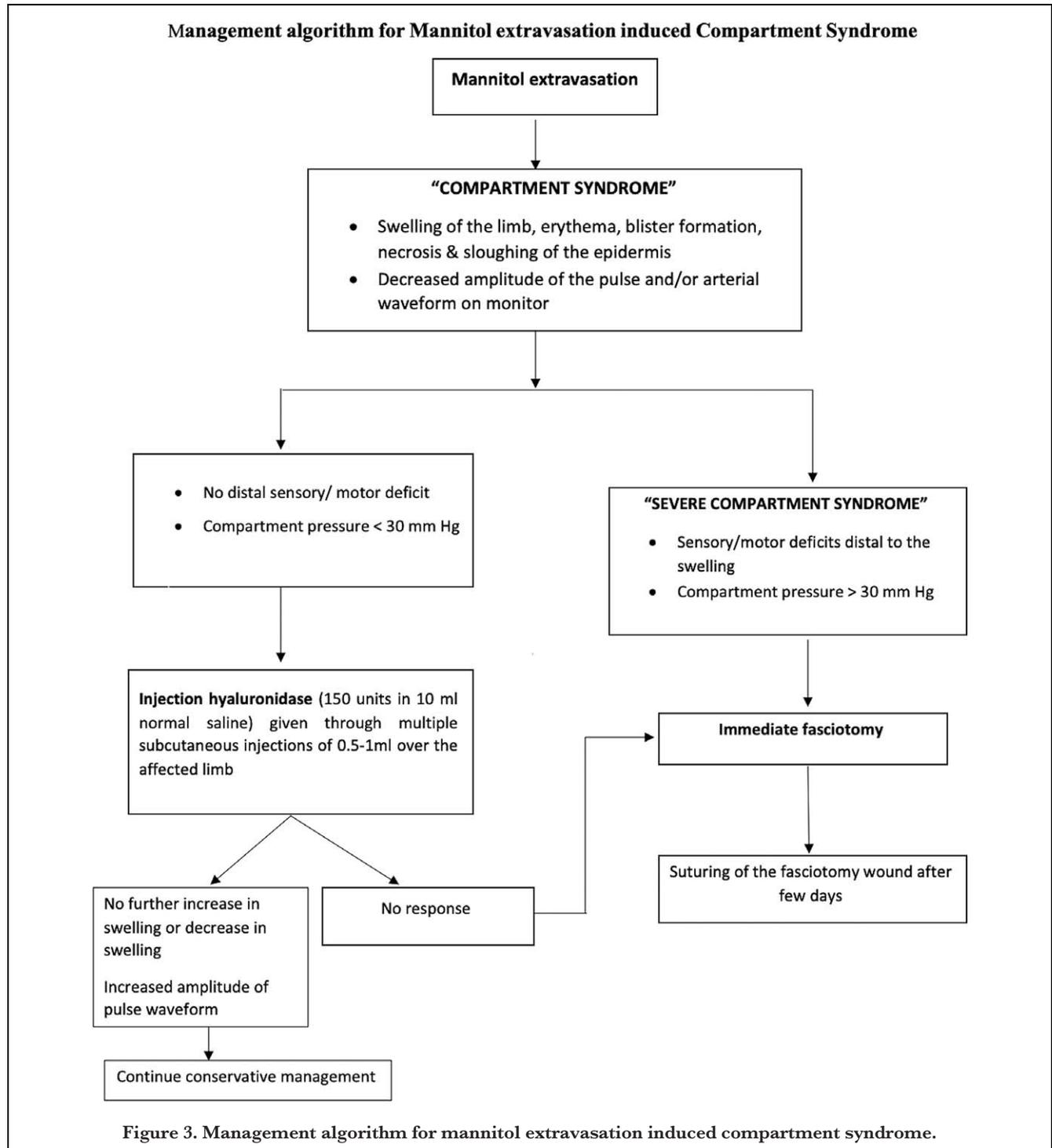
plasma osmolality. This allows large volumes of extracellular fluid in cerebral parenchyma to go across the intact blood–brain barrier into the cerebral vasculature, thus reducing the cerebral oedema and the raised ICP.<sup>9</sup> Inadvertent leakage of such a high osmolar fluid in soft tissue compartment around the venous access can, therefore, cause sudden oedema and swelling by drawing fluid from the vasculature into the tissues.<sup>5</sup> When the tissue pressure rises above the capillary filling pressure, compartment syndrome ensues, which leads to continued reduction in blood flow, thus causing cell death, tissue necrosis and nerve damage.<sup>10</sup>

Compartment syndrome is a clinical diagnosis. Its signs/symptoms are usually remembered as “six P’s”—pain with passive stretch, pressure, paraesthesia, paresis and pink colour.<sup>4</sup> However, the problem ensues when the patient is under general anaesthesia, thus underscoring the importance of continuous, direct visual inspection of the venous catheter site. Diminished pulse is a late sign. Severe compartment syndrome is defined as the development of neurological signs, viz. any weakness in the limb or the compartment pressure more than 30–45 mmHg.<sup>2</sup> Once severe compartment syndrome develops, then it is a surgical emergency, and fasciotomy is required urgently to save the limb. That is why *early* diagnosis is essential since it gives us the window to use other less invasive therapies like hyaluronidase.<sup>11</sup>

When injected into tissues, hyaluronidase (a parenteral protein enzyme) breaks down the glycosaminoglycans and hyal-

uronic acid (HA). As both these are an essential component of connective tissues, hyaluronidase renders tissues more permeable to injected fluids. Hyaluronidase, thus, reduces the viscosity of HA, improving tissue diffusion and the resorption rate of excess fluids.<sup>12,13</sup> This action of hyaluronidase has been exploited successfully in the extravasations of chemotherapeutic drugs.<sup>14</sup> Unfortunately, however, it has not been used to that extent by anaesthetists in the management of mannitol induced compartment syndrome. There has only been a single report of its successful use in mannitol extravasation.<sup>3</sup> Obviously, due to ethical reasons and rarity of the condition, there are no controlled studies on the role of hyaluronidase in mannitol induced compartment syndrome. The recommended dose of hyaluronidase in this setting is 150–900 units.<sup>3,12</sup> The successful management (avoiding the fasciotomy) of our case adds on to evidence that hyaluronidase helps in the mannitol induced compartment syndrome.

Prevention is the key to avoid this complication. Regular visual monitoring of the catheter through which such a drug is given, avoiding tucking the limb on to the side of the patient, using saturation probe in the same limb to monitor for pulse waveform and using central venous access where possible, are some of the preventive measures to avoid this unfortunate complication and for practicing safe anaesthesia. Early diagnosis cannot be overemphasised as hyaluronidase can be used effectively before the development of severe compartment syndrome to avoid fasciotomy (Figure 3).



### Conclusion

Prevention and early diagnosis is the key to avoiding the debilitating complications of mannitol induced compartment syndrome. Hyaluronidase should be used to avoid further morbid procedures like fasciotomy and limb amputation.

**Informed Consent:** Written informed consent was obtained from the participant who participated in this study and her relatives.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Conception - M.K.; Design - M.K.; Materials - N.B.; Data Collection and/or Processing - J.S.G.; Analysis and/or

Interpretation - S.B.; Literature Review - S.B., J.S.G.; Writing - M.K., J.S.G.; Critical Reviews - P.K.B., D.K.J.

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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