

CLINICAL APPLICATIONS OF MANNITOL IN COMPLEX REGIONAL PAIN SYNDROME (CRPS)

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The Mechanism of Action of Mannitol

Mannitol has been used as an effective intracellular type of diuretic for more than four decades.

There are mainly two different types of diuretics: The first type exerts its effect in the plasma and acts as an extracellular diuretic by excreting the extra water in the extracellular space through the kidney.

The best example of such a diuretic is Lasix. Also, Hydrochlorothiazide (HCTZ) has been used for quite a few decades on the same diuretic basis. Such diuretics only passively and secondarily influence any intracellular water retention.

The intracellular water retention is quite important, especially in the following conditions:

In any condition that causes traumatic or toxic metabolic water retention in the nerve cells, especially the brain, as well as in the peripheral nervous system.

The best example of such as condition is water retention secondary to disturbance of pituitary and adrenal hormones. This is seen in conditions such as Diabetes Insipidus, hyper corticosteroid dysfunction such as Cushing's Disease, hypothyroidism, and a condition Pseudotumor cerebri. In such diseases, the water concentration in the nerve cells is selectively increased. This causes water toxicity, increased intra-cranial pressure, and even death.

Another example of intercellular edema is glaucoma involving the eyes.

The third type of intercellular water retention is the typical inflammatory changes seen in neuropathic pain, such as diabetic neuropathy or complex regional pain syndrome (CRPS). The inflammation in neuropathic pain causes the disturbance of permeability of the cell membrane allowing the water, along with electrolytes such as sodium and calcium, to enter the nerve cells. This cell membrane disturbance causes the death of nerve cells, especially in the grey matter of the spinal cord, in the dorsal root ganglia (DRG), and in the peripheral nerves.

The inflammation becomes manifested in the form of edema of the extremities, severe vascular headaches, spontaneous cell membrane permeability of the arterioles and venules resulting in cutaneous bleeding and skin rash in absence of any kind of trauma.

Such water retention and disturbance of cell membrane function causes edema of the brachial plexus, edema at the ankle or wrist, and these conditions become mistaken for thoracic outlet syndrome, carpal tunnel syndrome, tarsal tunnel syndrome, etc.

Traditionally, such compression neuropathies (entrapment neuropathies) are treated surgically. Unfortunately, the trauma of the surgery adds to the trauma of the neuropathic pain and neuropathic vascular dysfunction. As a result, the inflammation undergoes a vicious circle of more neurovascular damage, more inflammation, trauma of surgery, and secondary more inflammation.

One phenomenon noted after surgery for entrapment neuropathies was the spread of CRPS to the opposite extremity. This was mistaken for the development of carpal tunnel syndrome in the opposite extremity. This was in spite of the fact that the nerve conduction times did not show any definite entrapment neuropathy, but a mild reduction of the amplitude of nerve response.

Such erroneous interpretation of the spread of the CRPS post-operatively leads to further unnecessary surgery, with dire consequences.

In 1969 and 1972 the research by my colleagues and me showed the efficacy of Mannitol in counteracting such intracellular edema [1-3].

Mannitol is very well tolerated. The only contraindications are in patients who have practically total renal failure and in patients who already have a dead space of intra-cerebral hemorrhage or necrotic brain tumor, which can cause entrapment of the Mannitol in the dead space.

Mannitol Treatment vs. Surgery

In the past decade we have applied the treatment with Mannitol to patients with compression neuropathies, as mentioned above (conditions mimicking carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome and rotator cuff tear), as well as the patients who, due to CRPS, suffer from severe edema, neurodermatitis, and trophic ulcers. There were surgical candidates with the compression neuropathies who were divided into two groups. Both groups were given the option of surgery or treatment with IV Mannitol. The entire subject was discussed in detail with the patient and with their referring physician. One group underwent surgery, and the other underwent Mannitol treatment. After comparing 32 patients in each group, it became obvious that Mannitol treatment was quite successful and would eliminate the necessity for surgery.

The surgical group had a more rapid deterioration of their CRPS post-operatively. The CRPS changed from stage II to stage III in 2/3 of such patients, and the edema continued to show a tendency for further recurrence.

The other equally comparable group of 32 patients, who underwent Mannitol therapy, did not require surgery, and their condition improved. The pain rating post-operatively dropped from an average of 6-9 prior to treatment with Mannitol, to an average of 2-5 after treatment with Mannitol.

Medical Necessity for I.V. Mannitol Treatment

Many CRPS patients suffer from attacks of inflammation in the form of edema in the extremities and bouts of reddish discoloration of the skin over the extremities.

The sympathetic system has three main functions:

1. Control of the vital signs (BP, pulse and respiration)
2. Control of the temperature
3. Regulation of the immune system

The sympathetic dysfunction results in disturbance of the immune system. It manifested by attacks of fever, swelling, skin rash and spontaneous bruises.

These symptoms cause clinical pictures identical to Carpal Tunnel Syndrome, Tarsal Tunnel Syndrome or Thoracic Outlet Syndrome. Instead of surgery, the patient should be treated with medications such as Mexitil 150 mg bid, ACTH, Epsom Salt, as well as Mannitol. Surgery causes disastrous deterioration of CRPS.

The patient needs to be treated with a specific type of medication that counteracts inflammation without any side effects.

Mannitol, an inert sugar, is a selective, strong diuretic which exclusively reduces the intracellular water retention. As such, it does not cause electrolyte imbalance, weakness or fatigue.

The Mannitol is helpful in counteracting the neuroinflammation in postoperative stage, and specifically in patients who cannot tolerate the inflammatory response against hardware inserted surgically.

Necessity for Removal of Hardware

Because the patient has sympathetic dysfunction (CRPS), the foreign body of devices such as screws, spinal cord stimulators, etc, is considered by the immune system as an extraneous agent. The immune system is stimulated (by sympathetic system) to mobilize WBC's and macrophages to attack the foreign body. This in turn leads to edema and osteopenia. Removal of the foreign body and treatment with I.V. Mannitol thru central line, as well as staying active are effective treatments for this condition.

When CRPS patients are treated with this medication, the swelling of the extremities is reduced and symptoms suggestive of Carpal Tunnel or Thoracic Outlet Syndrome disappear. The treatment is done as an outpatient. The dosage is 100 grams Mannitol in 500 cc D5W over 45-60 minutes. Usually 1 to 3 treatments are all the patient needs for inflammation of RSD.

Conclusion

In the past decade, we have noted the beneficial effect of I.V. Mannitol in neuroinflammation. This is especially true in patients suffering from post herpetic neuralgia, CRPS, and other forms of neuropathic pain. The common denominator in the various neuropathic pains is involvement of thermoreceptor sensory nerves and the sympathetic system at some stage of the disease. As you are well aware, the sympathetic system has three main functions. 1. Thermal regulation; 2. Control of vital signs; 3. Regulation and modulation of the immune system function. In the neuropathic pain patients, it is not unusual for the dysfunctional immune system to cause neuroinflammation accompanied by intercellular and axonal edema. If such patients are treated with plasma diuretics such as Hydrochlorothiazide or Lasix, these diuretics reduce the plasma volume which can have the potential of causing edema ex-vacuole and aggravate the neuroinflammatory edema.

On the other hand, intracellular dehydrants such as Mannitol and Diamox selectively counteract neuroinflammation and reduce the intracellular edema. On this basis, we in our clinic and as well as Doctor Veldman's group in Holland have applied IV Mannitol to counteract neurogenic edema [4, 5]. Such neurogenic edema is especially more prominent in patients who have undergone surgery for sympathectomy, infusion pump treatment, and spinal stimulators. At times the neuroinflammation is severe enough to cause a skin rash and neurodermatitis as well.

As long as the patient has normal renal clearance (no protein in the urine), the IV Mannitol treatment is quite safe. As the Mannitol has a tendency to crystallize, the IV should be applied in 1-1 ½ hours. If the IV drip is prolonged up to 4-6 hours, there is the risk of crystallization of the Mannitol. Certainly, a filter should help prevent any such risk as well. The usual dose is 100gm Mannitol in 500cc D5W.

References

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