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ORIGINAL ARTICLE

Effect of mannitol on cerebrovascular pressure reactivity in patients with intracranial hypertension

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Background/Purpose: Mannitol is commonly used in patients with increased intracranial pressure (ICP), but its effect on cerebrovascular pressure reactivity (CVPR) is uncertain. We analyzed the changes of pressure reactivity index (PRx) during the course of mannitol treatment.
Methods: Twenty-one patients who received mannitol treatment for increased ICP were recruited prospectively. Continuous waveforms of arterial blood pressure (ABP) and ICP were collected simultaneously for 60 minutes (10 minutes at baseline and 50 minutes since mannitol administration) during 37 events of mannitol treatment. The correlation coefficients between the mean ABP and ICP were averaged every 10 minutes and labeled as the PRx. The linear correlation of six time points of PRx in each event was calculated to represent the trend of CVPR changes. The negative slope of correlation was defined as improvement in CVPR under mannitol treatment and vice versa.
Results: At baseline, the average of ICP was 26.0 ± 9.1 mmHg and the values of PRx were significantly correlated with ICP ($p = 0.0044$, $r = 0.46$). After mannitol administration, the average of ICP decreased significantly to 21.2 ± 11.1 mmHg ($p = 0.036$), and CVPR improved in 59.4 % of all events. Further analysis showed that low baseline cerebral perfusion pressure was the only

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hemodynamic parameter significant association with the improvement of CVPR after mannitol treatment ($p = 0.039$).
Conclusion: Despite lowering ICP, mannitol may have diverse effects on CVPR in patients with intracranial hypertension. Our study suggests that mannitol infusion may have a beneficial effect on CVPR, particularly in those with a low cerebral perfusion pressure at baseline.

Introduction

Elevated intracranial pressure (ICP) has long been recognized as a serious complication in neurocritical diseases, including traumatic brain injury (TBI), acute stroke, central nervous system infections, and intracranial neoplasms.[1–5] Among the many strategies for lowering ICP, intravenous mannitol is the most widely used solute for the treatment of brain edema due to increased ICP.[6] Its effect in lowering ICP usually starts in few minutes after initiation of mannitol administration with a peak effect at 20–60 minutes.[6] Previous studies have demonstrated the effect of mannitol in lowering ICP,[7–9] but the underlying mechanisms remain a matter of debate. Possible theories include decreasing cerebral volume due to extracting water from the brain tissue, a fall in cerebral blood flow due to cerebral vasoconstriction from increasing blood pressure, and a decrease of serum viscosity.[6,10–13] Recently, one study used an intraparenchyma microdialysis method and demonstrated a significant decrease of lactate–pyruvate ratio, which indicated an improvement of intracranial metabolism following mannitol treatment in patients with severe hemorrhagic stroke.[14] However, lowering ICP via the use of mannitol in patients with increased ICP did not refer to an overall beneficial effect on functional outcome in various neurological diseases.[6,15,16]

Cerebrovascular pressure reactivity (CVPR) is the ability of cerebral vessels to respond to changes in transmural pressure, which indicates that cerebral arterioles would constrict in response to an increase in cerebral perfusion, and vice versa.[17] CVPR represents a key element of cerebral autoregulation (CA) and the status of CVPR has been shown to be critical in maintaining proper cerebral blood flow and global oxygenation.[17,18] The pressure reactivity index (PRx), which is determined as the moving correlation coefficient between ICP and arterial blood pressure (ABP), can quantify the status of CVPR.[19–24] In patients with TBI or severe stroke, several studies have shown that the values of PRx were correlated with the levels of ICP, and were also found to be an independent predictor of outcome.[19–23] However, whether lowering ICP via mannitol administration confers some improvement on CVPR is uncertain. The aim of our study was to investigate the effect of mannitol on CVPR by analyzing the sequential change in PRx through a 1-hour course of mannitol treatment.

Methods

Study participants

Twenty-one patients (mean age: 47.7 ± 21.2 years; male: 57.1 %) receiving ICP monitoring and intravenous bolus of mannitol treatment due to increased ICP (≥15 mmHg) in the stroke and neurosurgical intensive care units of National Taiwan University were prospectively recruited. The etiologies of the study participants included TBI ($n = 8$), acute stroke ($n = 10$), and brain tumor ($n = 3$).

Patients were excluded if they were younger than 18 years, pregnant, or had concomitant use of other osmotic agent such as glycerol or hypertonic saline. All patients were artificially ventilated to prevent hypoxia and hypercapnia. This study involved observational data collection and did not interfere with the management and clinical decision-making of the intensivists. This study was approved by the Research Ethics Committee, National Taiwan University Hospital and was conducted in accordance with human ethics regulations.

Management of increased ICP

A standard treatment approach was used for the management of increased ICP.[17] The therapeutic targets were adjusted to maintain ICP ≤ 15 mmHg or cerebral perfusion pressure (CPP) ≥ 60 mmHg. The standard protocol included elevating the head of the bed by 15–30°, administering sedation (lorazepam) or analgesia (fentanyl) if patients were agitated, and intermittent drainage of cerebrospinal fluid if an external ventricular drain was in place.[1,14,15] ABP was continuously measured using a radial artery fluid-coupled system. ICP was monitored using flexible intraparenchymal probes (Codman Microsensors ICP Transducer; Codman and Shurtleff, Raynham, MA, USA; and Licox CCI.SB; Integra NeuroSciences, Plainsboro, NJ, USA, respectively) inserted via a double-lumen skull bolt kit (Licox IM2; Integra Neuro-Sciences). For patients with ICP ≥ 15 mmHg for > 5 minutes, intermittent intravenous bolus of 20% mannitol 150 mL (approximately 0.5 g/kg) was infused over 20 minutes every 6–8 hours.

Data collection and analysis

Continuous waveforms of ABP and ICP were collected simultaneously for a mean duration of 60 minutes (60.3 ± 5.4 minutes), starting from 10 minutes prior to mannitol administration. Data was not collected if the patients were undergoing routine nursing or rehabilitation activities during the 1-hour course of mannitol treatment. These two waveforms (ABP and ICP) were captured digitally, with a sampling rate of 100 Hz, using a data acquisition card (National Instruments, Austin, TX, USA) on a bedside laptop computer. Artifacts were identified and excluded from analysis after data collection was completed. The software for this data collection was