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Research Protocol

Paediatrics Section

Comparison of 3% Hypertonic Saline and Mannitol in the Management of Children with Raised Intracranial Tension: A Research Protocol

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ABSTRACT

Introduction: Raised Intracranial Tension (ICT) is a common medical emergency with varied aetiology. Immediate medical or surgical intervention is mandated in most cases. Conservatively, osmotherapy with 3% Hypertonic Saline (HTS) or mannitol is the mainstay to reduce raised ICT. Additionally, the patient may also need surgical intervention along with osmotherapy.

Need of the study: Cerebral oedema and raised ICT in children and its treatment protocol are under-estimated and need further research and study in terms of identification of the condition and the choice of osmotherapy, which is the cornerstone in treating raised ICT among others.

Aim: To analyse the role of 3% HTS and mannitol and their individual efficacy in reducing intracranial pressure in children.

Materials and Methods: This open-labelled protocol for prospective study will be conducted in the Department of Paediatric Intensive Care Unit (PICU) of Acharya Vinoba Bhave Rural Hospital associated with Jawaharlal Nehru Medical College, a tertiary care center situated in the state of Maharashtra, in India, from November 2020 to October 2022. Patients between the age group of one month to 16 years will be taken alternatively and admitted to the Paediatric Intensive Care Unit (PICU) of a designated tertiary care hospital situated in the state of Maharashtra, in India diagnosed to have or showing signs and symptoms of raised ICT. They will be given 3% HTS or mannitol after considering the exclusion criteria for each if any will be conducted. The patient will be treated with a fixed dose of either drug as pre-decided by the principal investigator and the secondary investigator and the patient will be monitored within the next hour for immediate effects and improvement in the clinical state of the patient as well as the immediate general outcome in terms of vitals and sensorium and final outcome in terms of discharge rate with neuromorbidity, if any, or resulting death in patients treated with either drug will be noted. The Chi-square test, Fischer's-exact test for categorical data, and independent t-test for continuous data with normal distribution will be used to assess the relationship between various demographic, clinical, and aetiological characteristics and outcomes. The parameters that will be compared are sensorium, heart rate, respiratory rate and pattern, and Blood Pressure (BP) at admission. The above parameters will be monitored immediately after infusion of osmotherapy and the final outcome, as mentioned above, of patients on either of the drugs will be noted. The p-value <0.05 will be considered significant.

Keywords: Cerebral oedema, Intracranial pressure, Osmotherapy, Sodium chloride

INTRODUCTION

A Glasgow Coma Scale (GCS) of less than or equal to eight is defined as severe brain injury [1]. This can be caused not only by traumatic brain injury but also by other processes like intracranial haemorrhage, malignancy, meningoencephalitis, and even severe metabolic derangements that can lead to an elevation in ICT. Both medical and surgical CNS causes, when severe, lead to cerebral oedema and in turn raised ICT. Diagnosis and prompt treatment of raised ICT is crucial as it may be life threatening due to impending herniation of brain matter. Diagnosis of raised ICT can be made through clinical examination, by fundus examination and by invasive techniques in a well-equipped PICU setup [2]. The second important parameter that comes into consideration is the Cerebral Perfusion Pressure (CPP). CPP is the net pressure difference or gradient that drives oxygen delivery to cerebral tissue. In such case scenarios, it becomes important to maintain the CPP which is primarily hampered which could otherwise lead to cerebral ischaemia. CPP is a measure of Mean Arterial Pressure-Intracarnial Tension (MAP-ICT). It is important to maintain the CPP of more than or equal to 60 mmHg to avoid cerebral ischaemia [3]. Treatment is mainly aimed at reducing the raised ICT. Various methods are employed for lowering ICT of which most importantly is by osmotherapy wherein 3% HTS or mannitol are the most commonly used agents [4]. ICT has been shown to be a better predictor of neurological impairment than CPP in individuals with brain injury.

A 3% of HTS has been compared to the age-old choice of osmotherapy for raised ICT, mannitol, which is considered as the gold standard. HTS is preferred more in cases of trauma, IC bleeding, burns, and patients suffering from a stroke [5]. It has also been found useful in cases where mannitol has failed and also has a potentially longer duration of ICT-lowering effect [6]. Serum sodium levels need to be monitored at least every 6th hour and a serum sodium value of 155 mEq/L is usually considered as an upper limit for discontinuation of HTS and other forms of ICT lowering methods should be then considered [6]. Mannitol, on the other hand, is a sugar alcohol that occurs naturally. It is primarily used for its osmotic diuretic properties. Mannitol has been the most widely used agent as osmotherapy for the reduction of raised ICT. Mannitol lowers ICT through two mechanisms: an instantaneous effect due to volume expansion of plasma and a somewhat delayed effect due to its osmotic properties [7]. Mannitol, when given intravenously, constitutes a new solute in the plasma, which raises the tonicity of the plasma. As mannitol cannot cross the intact Blood Brain Barrier (BBB), the increased tonicity from the mannitol drives water out of the brain parenchyma and into the intravascular space. This water then travels with the mannitol to the kidneys, where it gets excreted

in the urine [8]. There are no big-scale, comparisons between the above two drugs, or long-term functional outcome studies, proving the superiority of one over the other.

Brain oedema is a life-threatening complication. The cornerstones of osmotherapy in treating raised ICT have been mannitol and HTS. Although osmotherapy helps reduce brain water and is used to treat brain oedema, its efficacy is yet to be proven. As the molecular pathophysiology becomes more evident, novel treatment protocols that help curb various stages of this cascade will be available to be clinically tested.

Thus, the use of osmotherapy in lowering ICT has been known for about a century, yet, there is a paucity of evidence and application of the known knowledge, particularly in the paediatric population. Both mannitol and HTS are known to have favorable, well-defined osmotic, as well as, rheological properties. The paediatric population presenting with raised ICT is a good mixture of both medical and traumatic causes. Acute and effective management of raised ICT can be challenging and, as well as, sensitive as mostly it has an acute presentation. The choice of osmotherapy to be made in treating a particular case and further evaluation of its efficacy on the child is challenging. A study focusing on the paediatric population presenting signs and symptoms of raised ICT and the study of the action of osmotherapy, causing immediate and long term effects, thus warrants a step towards understanding this whole mechanism better in this particularly vulnerable population. Thus, the aim of the present study is to compare and evaluate the efficacy of 3% HTS and 20% mannitol in the treatment of patients with elevated ICT, in a PICU setting.

The primary objective of the study was to study the immediate effects of the above-mentioned drugs on heart rate, BP, the respiratory pattern when administered in an acute setting. The secondary objective is to assess the final outcome of children in terms of discharge with neuromorbidity or death with raised ICT treated with either of the above two drugs. The null hypothesis is that, 3% HTS is not better than 20% mannitol in the treatment of raised ICT in children in an acute setting. The alternate hypothesis is that, 3% HTS is better than 20% mannitol in the treatment of raised ICT in children in an acute setting.

REVIEW OF LITERATURE

The research question of the present study is mainly to determine whether any of the two agents mainly used as osmotherapy i.e., 3% HTS or mannitol, is superior to the other in any way. In medical emergencies, dealing with a confirmed case of raised ICT/cerebral oedema, is of pivotal importance to determine which drug to be used in the given setting that will provide more desired results, immediately as well as in the general outcome. Upadhyay P et al., in their study concluded that in the treatment of cerebral oedema in children of infectious, anoxic, haemorrhagic, and traumatic origin, administration of HTS is probably more effective and safer than mannitol [9]. Another systematic review by Gwer S et al., also concluded that HTS appears to achieve a greater reduction in ICT than other osmotic agents [10]. Historically, mannitol was the osmotic agent of choice and mannitol has been the most commonly used hyperosmolar agent for the treatment of intracranial hypertension [11]. The benefits of conducting the present study will be to help conclude a better drug for osmotherapy, if so. A 3% of HTS and mannitol are the two most commonly used drugs for osmotherapy, the reason why this study is based on comparing the above mentioned two drugs.

MATERIALS AND METHODS

This open-labelled, prospective observational study will be held in the PICU of Acharya Vinoba Bhave Rural Hospital associated with Jawaharlal Nehru Medical College, a tertiary care centre situated in the state of Maharashtra, in India, between the time frame of November 2020 to October 2022. The study will be conducted after taking consent from parents of the paediatric population admitted to PICU with a diagnosis or suspicion of raised ICT. The Institutional Ethical Clearance (IEC) has been obtained prior to the study-DMIMS(DU)/IEC/2020-21/9281.

Inclusion criteria: All children in the age group of one month to 16 years admitted to the PICU were diagnosed with raised ICT. Raised ICT is defined as an appropriate clinical pathology of the central nervous system presented with altered sensorium, altered respiratory pattern, relative bradycardia/tachycardia, hypertension, or raised MAP will be included in the study [12].

Exclusion criteria: Children with serum sodium value of more than 150 mEq/L will be excluded from the study.

Sample size calculation: The estimated sample size for a two-sample comparison of means

Test Ho: m1=m2, where m1 is the mean of the parent study taken as reference in population 1 and m2 is the mean in population 2.

Assumptions:

Alpha=0.0500 (two-sided)

Power=0.9000

m1=7

m2=8.2

sd1=1.88

sd2=1.74 [10]

n2/n1=1.00

Estimated required sample sizes:

n1=48

n2=48

Final sample size: 96

• Primary outcome

The immediate outcome will be assessed using the following parameters:

1. Change in heart rate from baseline.
2. Change in respiratory rate and pattern of respiration from baseline.
3. Blood Pressure (BP).
4. Mean Arterial Pressure (MAP).
5. GCS scoring.
6. Pupillary reflex.
7. Deep tendon reflexes.
8. Plantar reflex.

• Secondary/general outcomes will be measured on the basis of:

1. Morbidity and mortality rate.
2. Any neurological focal deficit.
3. Development of seizures in an initially seizure-free case.
4. Patients requiring mechanical ventilation.
5. Patients requiring ICU stay (>/=7 days).

Study Procedure

The patient's age, sex, presenting complaints, history of presenting illness, and associated illness will be noted. The patient's heart rate, respiratory rate, level of consciousness, and neck stiffness will be examined for clinical diagnosis of raised ICT. Tachycardia/bradycardia, altered respiratory pattern, altered level of consciousness, and presence of neck stiffness are some of the signs of raised ICT. Patients presenting with acute onset of a

seizure, altered consciousness, and vomiting associated with other neurological symptoms will be taken into consideration as signs of raised ICT. ICT will be tentatively calculated using the formula ICT=MAP-CPP; where MAP is Mean Arterial Pressure and CPP is Cerebral Perfusion Pressure. The value of CPP remains constant in health and disease.

Patients will be divided into either an M group (receiving 5 mL/kg of 20% mannitol) or HTS group (receiving 5 mL/kg of 3% HTS), according to the hyperosmolar solution used depending on the clinical scenario. The data will be collected after the first loading dose received by the patient. Immediate changes in vitals like heart rate, BP, MAP, and the respiratory pattern will be studied and recorded in case record form. The sensorium will be assessed and evaluated on the basis of GCS scoring immediately after the administration of osmotherapy and as a long-term effect.

Final outcome in terms of discharge rate with neuromorbidity, if any, or resulting death in patients treated with either of the drugs will also be studied and recorded in case record form.

STATISTICAL ANALYSIS

Data will be entered into Microsoft Excel sheet and statistical analysis will be done in Statistics and Data (STATA) 10 software. The Chi-square test, Fischer's-exact test for categorical data, and independent t-test for continuous data with normal distribution will be used to assess the relationship between various demographic, clinical, and aetiological characteristics and outcomes. The parameters that will be compared are sensorium, heart rate, respiratory rate and pattern, BP at admission. The above parameters will be monitored immediately after infusion of osmotherapy and the final outcome of patients on either of the drugs will be noted. A p-value <0.05 will be considered significant.

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