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Research Article

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Mannitol versus Hypertonic Saline in Treatment of Cerebral Edema Post (MCA) Middle Cerebral Artery Infarction

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Abstract

Background: The incidence of hemispheric cerebral ischemia along middle cerebral artery is more than10 % of all ischemic strokes. Mortality rate is high post MCA infarction. This study was conducted to compare the effects of Hypertonic saline 3% and Mannitol 20% in treatment of cerebral edema post middle cerebral artery (MCA) infarction.
Methods: This prospective study was conducted on 50 adult patients suffered from brain edema as a result of ischemic infarction along middle cerebral artery terrority. Patients were divided into two groups; Group A: twenty five patients were treated with intravenous mannitol 20%, Group B: twenty five patients were treated with intravenous hypertonic saline 3% .Intracranial pressure was monitored non-invasively by : CT scan of brain at the start of hyperosmolar therapy and after 48 hours, Glasgow coma score [GCS] was assessed regularly every 6 hours for 48 hours and optic nerve sheath diameter assessment(ONSD) twice : firstly at time of brain edema diagnosis and 48 hours later after continuation of hyperosmolar therapy.
Results: GCS was higher in patients receiving hypertonic saline**,** ONSD was significantly lower in patients treated with hypertonic saline while there were no statistically significant difference in both groups as regard CT brain edema improvement.
Conclusion: Hypertonic saline can be used safely as alternative therapy to mannitol in management of brain edema post MCA.

Keywords: hypertonic saline HTS, mannitol, intracranial hypertension, ischaemic infarction.

Introduction

Raised intracranial pressure following cerebrovascular stroke is a serious complication because it leads to permanent tissue damage, cellular hypoxia and dysoxia due to the impairment of blood flow and tissue perfusion with the end result is brain herniation and brain death.

Medically this group of patients should be regularly monitored, well sedated, receiving analgesia and patient's head should be kept elevated 45^0 in a neutral position. Patient should be mechanically ventilated if indicated and any condition associated with intracranial hypertension as constipation, sneezing and coughing should be avoided. Moreover Optimization of cerebral perfusion pressure and reduction of intracranial pressure should always be managed simultaneously.

Multiple studies have concluded that surgical decompressive craniectomy can successfully improve the outcome in patients with malignant brain edema post hemispheric stroke. (1)

Therapeutic hypothermia could be used as an alternative line of management of malignant cerebral edema, but its neuroprotectiveis not approved in cerebrovascular infarctions. Barbiturate coma therapy may be given in order to decrease cerebral metabolic needs, but not commonly used due to its serious adverse effects. The standard treatment of intracranial hypertension is osmotherapy with mannitol, but hypertonic saline is also considered as an effective alternative.(1)

This study was conducted to compare the effects of Hypertonic saline 3% versus Mannitol 20% in the treatment of cerebral edema post MCA infarction.

Methods

A clinical prospective study was conducted in the Critical Care Medicine Department, Faculty of Medicine, Alexandria University. Due to the mental disability of the participants the informed consent for the enrollment in the study was obtained from patients' next of kin.

The study was conducted on adult patients [≥18 years old] suffering from brain edema as a result of ischemic infarction along middle cerebral artery terrority. Haemodynamic unstable patients, heart failure patients, renal impairment patients (creatinine clearance less than 30 ml/min), patients suffered from electrolytes and/or osmolarity abnormalities, pregnant females and post cardiac arrest patients were excluded. Fifty patients were enrolled for the study and randomly allocated into two groups. Group A included twenty five patients, participants in this group were treated with mannitol 20% intravenous through central venous catheter by loading dose 1gm/kg followed by 0.25gm/kg every 6 hours for 48 hours as maintenance dose.

Group B included twenty five patients who were treated with hypertonic saline 3% administered intravenously through central venous catheter by loading dose 5ml/kg followed by 2ml/kg every 6 hours for 48 hours as maintenance dose.

The following data were collected: Serum sodium (Na) and serum chloride (Cl) every 12 hours. Blood urea nitrogen (BUN), serum creatinine every 12 hours and creatinine clearance [ml/min] by Cockroft-Gault equation. Serum blood glucose level every 12 hours. Calculated serum osmolarity every 12 hours.

Intracranial pressure was monitored non – invasively by 3 different methods;

1- Optic nerve sheath diameter (ONSD) assessment by applying ultrasound gel on the upper eyelid starting from the right side. A 7.5 MHz linear probe was placed gently over the lateral aspect of the closed eyelid. The probe was angled medially and anteriorly until the hypoechoic opticnerve could be clearly outlined behind the globe. The ONSD was measured 3mm behind the posterior scleral aspect of the globe at an angle perpendicular to the eye ball. An average of two measurements was recorded for each eye. (2)

2- CT scan of brain at the start of hyperosmolar therapy and after 48 hours. Brain CT scan showed brain edema with the following criteria; Effacement of the cerebral sulci, suprasellar and perimesencephalic cisterns. The ventricles appear small or compressed. Loss of the gray-white differentiation. The cerebellum may appear relatively hyper dense compared to the cerebral hemispheres.

3- Glasgow coma score (GCS) was assessed regularly every 6 hours for 48 hours.

Statistical analysis:

Data are presented as median with corresponding interquartile range (IQR) for continuous variables and as frequencies with corresponding percentages for categorical variables. Between groups comparison was done by Mann-Whitney U test for continuous variable and by χ^2 test for categorical variables. $P< 0.05$ was considered significant. Data were analyzed by IBM SPSS Statistics 21.

Results

As regard ONSD, at time of brain edema diagnosis, no significant difference was found between the two groups (p= 0.33), 48 hours after completion of osmolar therapy, ONSD was significantly lower in the group treated by hypertonic saline (p=0.01), table 1

Table 1: ONSD in both group of patients

	Group A (Mannitol)	Group B (Hypertonic Saline)	*P* ¶
ONSD 1 *(mm)*	6.1 (5.8 - 6.2)	5.9 (5.8 – 6.1)	0.333
ONSD 2 *(mm)*	4.8 (4.4 – 5.7)	4.4 (4.2 – 4.5)	0.019*
P §	<0.001*	<0.001*	

(*) *P*< 0.05 is significant
(¶) Mann-Whitney U Test
(§) Wilcoxon Signed Ranks Test

There were a significant difference be between the 2 groups as regard GCS. GCS was higher in patients receiving hypertonic saline (p < 0.005), table 2.

Table 2: effect of mannitol versus hypertonic saline on GCS over 48 hours.

	Group A (Mannitol)	Group B (Hypertonic Saline)	*P*
GCS 0	8 (7 - 8)	7 (6 – 8)	0.05
GCS 1	9.5 (7.8 – 10.3)	11 (9 – 12)	0.019*
GCS 2	10 (8.8 – 11)	12 (10.5 – 13.5)	0.027*

(*) *P*< 0.05 is significant

As regard brain edema showed in CT brain post osmolar therapy, there was no statistically significant difference in both groups (p = .06) as described in table 3.

Table 3: Brain edema criteria by brain CT scan after 48 hours.

CT Brain	Group A (Mannitol)	Group B (Hypertonic Saline)	*P*
Resolved Edema	17 (65.4%)	21 (84%)	0.06
No Change	6 (23.1%)	2 (8%)	
Rebound Edema	3 (11.5%)	0 (0%)	
Massive Edema	0 (0%)	2 (8%)	

While, there is a significant statistical difference in calculated osmolarity between the 2 groups over duration of therapy, as osmolarity was higher in patients receiving hypertonic saline (p < .005) as shown in table 4.

Table 4: Calculated serum osmolality after 48 hours.

	Group A (Mannitol)	Group B (Hypertonic Saline)	*P*
Osmolarity 0	287 (281 – 295)	290 (282 – 294)	0.559
Osmolarity 1	287 (285.5 – 300.3)	295 (288.5 – 302)	0.081
Osmolarity 2	293 (286.8 – 298.5)	298 (289.5 – 314)	0.041*
Osmolarity 3	298 (291.8 – 301)	309 (295.5 – 314)	0.005*
Osmolarity 4	299 (291 – 305)	308 (299.5 – 315)	0.001*

(*) $P < 0.05$ is significant

Discussion

Cerebrovascular stroke along the middle cerebral terrority accounts of 10% of patients with ischemic infarction. Patients suffering from ischemic infarctions especially sizable hemispheric infarctions are at a great risk of brain death due to malignant intracranial hypertension. Cerebral edemapost ischemic infarction begins within 1–3 days, and continues for 14 days. (1, 3) Mannitol is an osmotic diuretic sugar alcohol, its action starts15-20 minutes after intravenous administration and can last up to 6 hours depending into the etiology. (3)

Few studies evaluated the use of hyperosmolar therapy in treatment of post cerebral infarction patients with brain edema. As a result there is lack of information on the standard protocol to its use in the management of intracranial hypertension.

In 1998, Schwarz et al compared the effect of 100 ml, 75 ml of hypertonic saline, 60 g/l of hydroxyethyl starch HES and 200 ml of 20% mannitol in equiosmolar doses in 9 patients with 30 episodes of intracranial hypertension. Hyperosmolar agents was used in an alternating doses and intracranial hypertension was defined as an ICP >25mmHg or the presence of abnormal pupil. There outcome was a 10% decrease in ICP, and this occurred in 10 out of 14 patients received mannitol and in 16 patients given HS/HES. They conclude that single doses of 100 ml HS-HES or 40 g of mannitol are effective at reducing elevated ICP in patients with brain oedema and show no adverse effects on MAP or CPP, although Hypertonic saline appear to have more fast onset and more effective at lowering elevated ICP. This result was in agreement with ours as we found that HTS was more effective in improvement of GCS.(4)

They also recommended the use of hypertonic saline in case of failure to reduce the intracranial pressure by mannitol. Schwarz supported these recommendations in 2002 in a prospective study included 8 stroke patients and 22 episodes of raised intracranial pressure, which didn't resolve using 200 ml of 20% mannitol. Patients were treated using 75 ml of 10% hypertonic saline for 15 min. The research team reported an effective reduction of intracranial pressure in the 22 episodes, with increase of cerebral perfusion pressure which was still maintained up to 4h later (5).

In 2011, Diginger et al. (6) compared 20% mannitol versus 23.4% hypertonic saline in treating 9 patients diagnosed as brain oedem post cerebrovascular stroke with a midline shift >2mm. They measured cerebral blood flow, cerebral blood volume and CMRO2. They observe different degrees of improvement of CBF in the opposite hemisphere of patients with ischemic stroke after hyperosmolar therapy.

In our study, clinical outcome as GCS was better in patients receiving hypertonic saline HTS, this was in concordance with a retrospective cohort study conducted by Mangat et al, 2015, in patients suffered from severe traumatic brain injury. The study reported 35 patients only given hypertonic saline versus 477 patients received mannitol. The analysis was conducted by matching the patients between both groups. After the pairing, 25 patients were included in 20% mannitol group and similar number in hypertonic saline group (3% hypertonic Saline n = 24; 23.4% hypertonic Saline, n = 1) both study groups shared similar characteristics. The study conclusion was that hypertonic saline is superior to mannitol in reduction of intracranial pressure, also hospital stay in days was shorter in patients treated with hypertonic saline.

Their results were in concordance with our findings as regard clinical improvement inspite of the different type of patients in both studies. (7)

A 2016 systematic review conducted by Burgess et al, found that the outcome of patients with severe TBI treated with mannitol did not differ from those treated with hypertonic saline as regard mortality rate, intracranial pressure reduction and neurological improvement but the ICP-lowering therapy failure rate was still less in the hypertonic saline group and this result may favor the use of HTS as alternative to mannitol in treating brain edema.(8)

We found that 48 hours after completion of osmolar therapy, ONSD was significantly lower in the group treated by hypertonic saline, ONSD also favor the administration of hypertonic saline to treat brain edema. Also Soldatos et al.2008 concluded that an ONSD >5.7 mm can be used to determine non-invasively intracranial pressure with 74% sensitivity and 100% specificity when compared to results found via invasive intraparenchymal catheter (9) .

Major et al.2010 showed a significant positive correlation between brain CT scans and ONSD >5 mm with a high cerebral edema detection sensitivity and specificity (86% and 100%respectively)(10) Also Munawar et al 2019 found that ultrasound of the optic nerve is accurate in prediction of increased intracranial pressure when ONSD measured > 5.8 and this finding is in agreement with our results.(11)

Study Limitations:

Small sample size is the main limitation of the study followed by the inability to use intracranial pressure monitoring invasively for a more accurate results.

Conclusion

Hypertonic saline can be used safely as alternative therapy to mannitol in management of cerebral edema post MCA.

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