EVALUATION OF ROLE OF MANNITOL IN THE ASSESSMENT OF CHANGE OF INTRACRANIAL HAEMATOMA VOLUME BY NEUROIMAGING CT IN ACUTE INTRACEREBRAL HAEMORRHAGE

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ABSTRACT

BACKGROUND
Mannitol has been used for several years to reduce cerebral oedema in acute ICH (intracerebral haemorrhage). Study on mannitol with its effect on haematoma volume and clinical outcome is limited.

The main aim of this study is to measure haematoma volume before and after mannitol therapy in acute spontaneous ICH.

MATERIALS AND METHODS
Total 60 patients were analysed after inclusion and exclusion criteria. On admission, non-contrast CT scan was done on day 1 and day 7. Infusion mannitol 20% of 100 mL every 6 hourly was infused. Clinical outcome was measured by National Institute of Health Stroke Scale (NIHSS). Haematoma volume was measured on day 1 and day 7 of hospital admission. Statistical analysis was done using SPSS software.
Settings and Design- A prospective observational study done in admitted patients presented in first day of onset of acute stroke.

RESULTS
The change of haematoma volume from day 1 value 21.7 cm^3 (±11.2) to day 7 value 15.4 cm^3 (±8.3) is significant (p value=0.008). Decreased NIHSS score from baseline value of 17.1 (±7.6) to 12.1 (±7.1) on day 7 is significant (p value=0.3). NIHSS score on day 7 was highly influenced by haematoma volume on day 1 (p value=0.001) and haematoma volume on day 7 (p value=0.01).

CONCLUSION
Mannitol therapy in first few days of hospital stay is effective in reducing haematoma volume and in improving clinical outcome.

KEYWORDS
Mannitol, Haematoma Volume, CT Scan, ICH.

BACKGROUND
For last few years, large number of researches has been done on drug therapy and treatment strategy in respect to management of acute stroke. For management of stroke patients with raised intracranial pressure, mannitol is being used as an osmotic agent.[1] Administration of mannitol, an osmotic diuretic has been reported to decrease cerebral oedema, neurological deficit in several cases of ischaemic stroke.[2] Mannitol has been used to treat human brain for more than 30 years. The action of mannitol is biphasic. An initial rapid fall in intracranial pressure is caused by plasma expansion and reducing blood viscosity. Cerebral blood flow increases and there is no compensatory vasoconstriction in normally perused areas, which reduces blood volume and intracranial pressure decreases.[3] Outcome after Intracerebral Haemorrhage (ICH) is closely tied to haemorrhage size. There are too many studies showing haematoma growth following intracerebral haemorrhage with poor GCS (Glasgow Coma Scale).[4] Haematoma growth is an independent determinant of both mortality and functional outcome after ICH.[5] So, there is a triad of mannitol therapy, haematoma volume and clinical outcome. Study on mannitol with its effect on haematoma volume and clinical outcome is limited. The main aim of this study is to measure haematoma volume before and after mannitol therapy in acute spontaneous ICH and its short-term in-hospital clinical outcome.

MATERIALS AND METHODS
This is a prospective observational study done in a rural based medical college and referral centre situated in the state of West Bengal, India. Study population was those who were admitted with acute non-traumatic spontaneous intracerebral haemorrhage in Medicine Ward. We have studied total 80 patients from the period of one year, January 2016 to December 2016. All patients were randomly selected irrespective of age, sex or other comorbidity.

Following were Inclusion Criteria-
1. Acute onset non-traumatic spontaneous intracerebral haemorrhage presented within 24 hours of stroke onset.
2. No history of any obvious head injury or prior established neurodeficit.
3. Non-contrast Computed Tomography (NCCT) showed supratentorial haemorrhage.

Following were Exclusion Criteria-
1. Patients presented more than 24 hours of stroke onset.
2. Prior established neurodeficit.
3. Non-willing to participate.
4. Those who died before completion of day 3.
5. Any rupture aneurysm, subarachnoid haemorrhage, traumatic ICH, cerebellar haemorrhage and brainstem haemorrhage.
6. Who needed urgent neurosurgical intervention.

On admission, first NCCT was done. On admission, they were put in standard treatment protocol as per textbook recommendation.[6] All physiological parameters like temperature and blood pressure were monitored and maintained thoroughly. All biochemical parameters like plasma glucose and serum electrolytes were corrected accordingly. This is done in view of that any change in clinical situation and haematoma volume will be nullified by other causes. Infusion mannitol 20% of 100 mL every 6 hourly was infused. All patients were reviewed by a single physician every 6 hourly. Clinical outcome was measured by National Institute of Health Stroke Scale (NIHSS).[7] This score is more useful predictor of mortality and morbidity and it provides reliable information on patients' short-term mortality risk. NCCT was done again on 7th day of hospital admission. Haematoma volume both on 1st and 7th day were measured by a single radiologist using specified software. This procedure involved to define a zone of interest of ICH at multiple CT section. Then, analyse software provided the area in square millimeter. Volume of ICH was calculated by multiplying the section thickness acquisition by the area. Primary endpoint was haematoma volume on day 7 and secondary endpoint was clinical outcome on day 7 of hospital admission.

Statistical Analysis- Data were analysed using SPSS software version 22. Chi-square test was applied for comparison of qualitative data. Paired t-test and unpaired t-test were applied for comparison of quantitative data in between two groups. Pearson correlation test was applied for identifying relation between haematoma volume and NIHSS score. Statistical significance was accepted as 'p' value <0.05 (two tailed). Quantitative data were expressed as mean ± SD and qualitative data as frequency (%).

RESULTS
After meeting inclusion and exclusion criteria, finally 60 patients were taken into consideration for statistical analysis. 13 patients (16.25%) died before day 7 and 6 patients (7.5%) needed neurosurgical intervention. So, 60 patients were analysed. Their demographic character is shown in Table 1. 42 patients (70%) were males and 18 patients (30%) were females. Mean age of presentation was 63.5 years (±8.6). Mean haematoma volume on day 1 was 21.7 cm^3 (±11.2) and mean NIHSS score on admission was 17.1 (±7.6). On day 7, mean haematoma volume was 15.4 cm^3 (±8.3). This change of haematoma volume from day 1 to day 7 is statistically significant (p value=0.008). Mean NIHSS score was decreased from baseline value to 12.1 (±7.1) on day 7. This change is also significant (p value=0.3). In correlation study, NIHSS score on day 7 was highly influenced by haematoma volume on day 1 of hospital admission (p value=0.001) and by haematoma volume on day 7 (p value=0.01). But, NIHSS score on admission was not influenced by haematoma volume on day 1.

Parameters	Value on Admission
Age (years)	63.5 (±8.6)
Sex (male)	42 (70%)
Sex (female)	18 (30%)
Haematoma volume (mL^3)	21.7 (±11.2)
NIHSS score	17.1 (±7.6)
Table 1. Demographic and Baseline Characteristic of Patients	

Data presented as numbers (%) or mean (±SD).

| Parameters	Day 1	Day 7	P Value	95% of CI for Mean Difference (Upper, Lower)
Haematoma Volume (mL^3)	21.1 (±11.2)	15.4 (±8.3)	**0.008**	-2.64, -0.40
NIHSS Score	17.1 (±7.6)	12.1 (±8.1)	**0.03**	0.25, 4.36
Table 2. Relationship of Haematoma Volume and NIHSS Score				

Significant 'p' value is shown in bold.

	NIHSS Score on Day 1		NIHSS Score on Day 7	
	Pearson's Correlation	**P value**	**Pearson's Correlation**	**P value**
Haematoma volume (mL^3) day 1	0.227	0.102	0.276	0.03
Haematoma volume (mL^3) day 7	-	-	0.351	0.01
Table 3. Correlation Study among Parameters on Day 1 and Day 7				

Significant 'p' value is shown in bold.
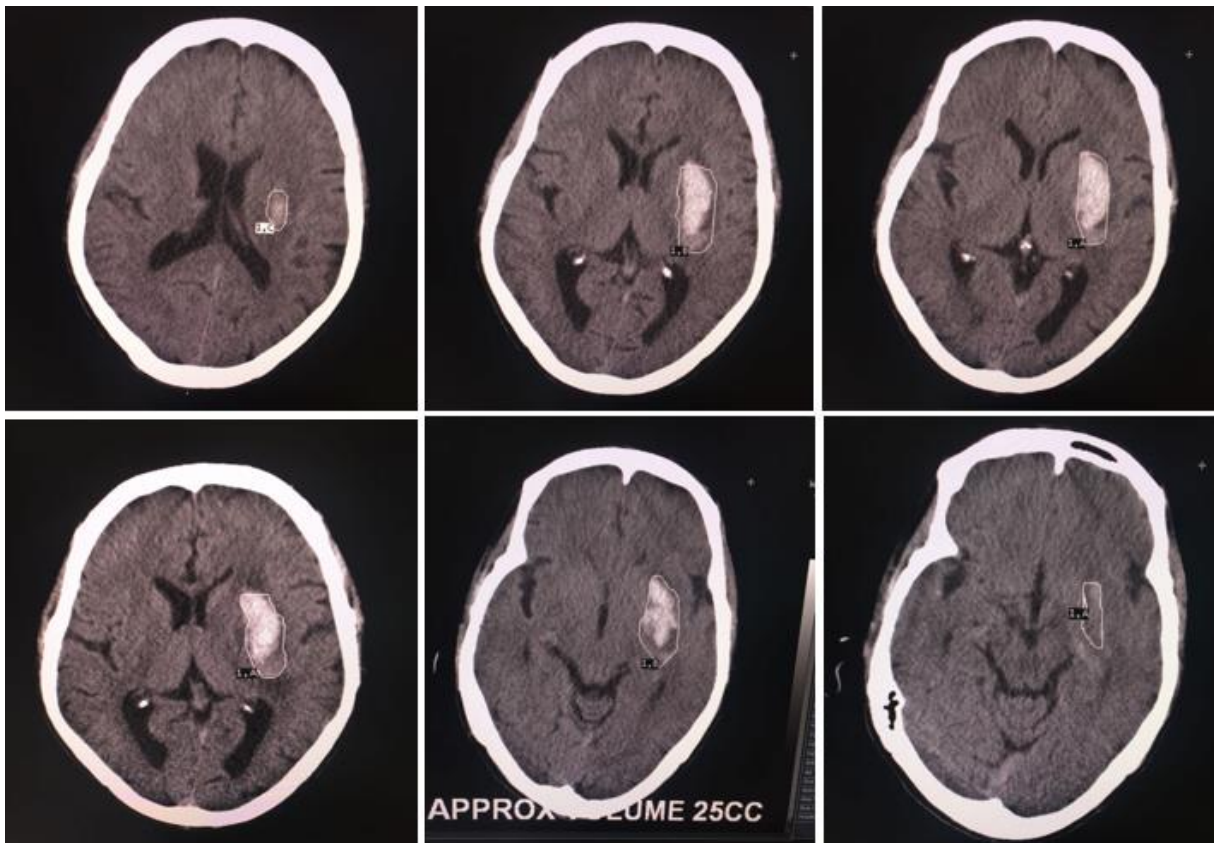
Figure 1. Non-Contrast CT Scan of Brain of a Patient showing Haemorrhage at Different Level at the Time of Admission on Day 1. Above Pictorial Presentation shows Different Sectional Level of Brain of a Same Patient. Haematoma Volume Measured by Software was 25 cc Approximately.
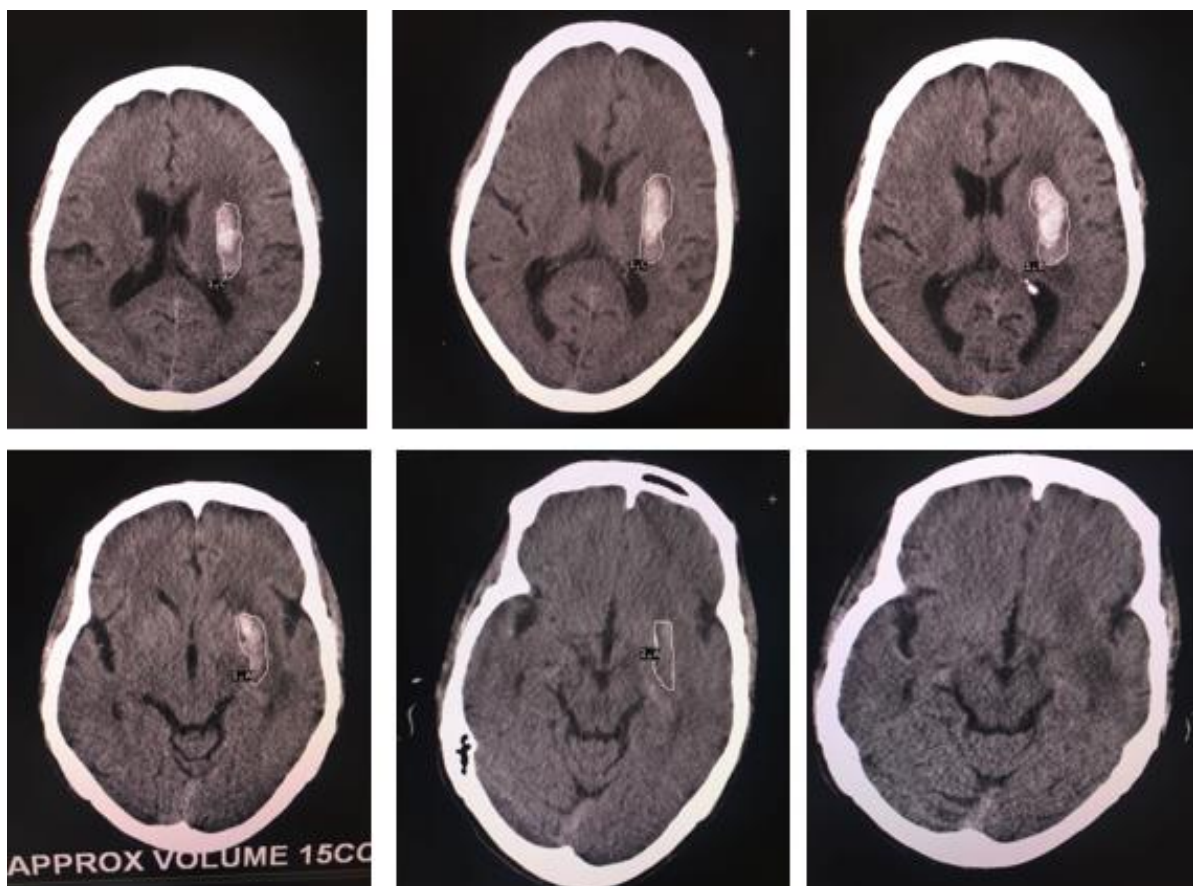
Figure 2. Non-Contrast CT Scan of the Same Patient on Day 7 After Mannitol Therapy. Above Pictorial Presentation shows Haemorrhage at Different Level of Brain. Haematoma Volume Measured by Software was 15 cc Approximately.

DISCUSSION

Study on mannitol on effect of haematoma volume is limited. This is one of the very few studies, which measured haematoma volume and clinical outcome with mannitol therapy. Where most of the studies used GCS as clinical outcome parameter, we have used NIHSS score for accessing functional status and outcome of stroke patients.[7] This study measured haematoma volume as change of parameter with mannitol therapy. Exact relationship in between these two is yet to be established. Our study found significant improvement of clinical outcome with mannitol therapy on first few days of their hospital admission. Haematoma volume and clinical outcome also depend on several other physiological (like blood pressure, temperature, etc.) and biochemical parameters (serum sodium, potassium, glucose level, etc.). We have tried to nullify effect of these parameters with careful monitoring of all patients and corrected accordingly. So, any neurological improvement or deterioration, if any was due to haematoma volume or mass effect.

This study found significant clinical improvement with regression of haematoma volume. This is contrary to the view of Arima et al. They found that degree of perihaematomal oedema strongly related to the size of the underlying haematoma of acute ICH. They said this is not a major determinant of clinical outcome of acute stroke.[8] Again, haematoma volume in our study was regressed with mannitol therapy in first few days of hospital. This observation is supported by Ye H. Su Y. They found mannitol infusion in patients can improve cerebral blood flow in bilateral hemispheres and decrease intracranial pressure.[9] But, this is against the observation by Mishra et al where they said low-dose mannitol does not seem to be beneficial to patients with acute ICH.[10] Though, we have not used SPECT to measure cerebral blood flow, our observation again does not support the view of Kalita et al where they said that mannitol does not seem to change the regional cerebral blood flow in ICH by SPECT study.[11] Venkatasubramanian C had observed that timing and magnitude of PHE volume are associated with haematologic factors.[12] Our study thought that haematoma volume is influenced by mannitol therapy, which may affect haematologic factors. Again, we have found that there is significant decrease in haematoma volume in first 7 days of hospital stay. This is not in line with the observation to StyStaykov D. et al. They said that perihaematomal oedema developed early after ICH and double after 7 to 11 days.[13]

CONCLUSION

Mannitol therapy in first few days of hospital stay is effective in reducing haematoma volume and in improving clinical outcome. Haematoma volume is highly influenced by mannitol therapy. Not only that, patients with acute spontaneous intracerebral haemorrhage gain significant clinical improvement if all other parameters are controlled carefully. Major limitation of the study is that there is no control group for comparison of mannitol effect. This is short-term in-hospital outcome study. So, large number of patients with long-term follow up is necessary for measurement of mannitol effect on haematoma volume.

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