Name of Sponsor/Company : University Hospital of Bordeaux	Individual Study Table Referring to Part of the Dossier Volume : Page :	*(For National Authority Use only)*
Name of Finished Product : 1/ Hypertonic saline serum 2/ Mannitol maco-pharma 20% sol inj p perf IV		
Name of Active Ingredient : 1/ Sodium chloride 2/ Mannitol 20% 4ml/kg		

Title of Study :
Comparison of Effects of Equiosmolar Doses of Mannitol and Hypertonic Saline on Cerebral Blood Flow and Metabolism in Traumatic Brain Injury

Investigators :
Pr SZTARK - University Hospital of Bordeaux
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Study centre(s) :
- Surgical Intensive Care Unit – University Hospital of Bordeaux, France
- Department of Neurosurgery, Rambam Medical Center, Faculty of Medicine, Technion, Haifa, Israel

Publication (reference)
Comparaison of Effects of Equiosmolar Doses of Mannitol and Hypertonic Saline on Cerebral Blood Flow and Metabolism in Traumatic Brain Injury – Vincent COTTENCEAU, Françoise MASSON, Eugenia MAHAMID, Laurent PETIT, Venyamin SHIK
François SZTARK, 1 Menashe ZAAROOR, 2 and Jean François SOUSTIEL
JOURNAL OF NEUROTRAUMA : PMID: **21787184**
28:2003-2012 (October 2011)

Studied period (years) : - date of first enrolment : 18/05/2009 - date of last completed : 01/06/2010	Phase of development : IV

Objectives :
The main objective of this work is to compare the effect on DSC of administering equiosmolar doses of SSH and mannitol in severe traumatic brain injury.

Secondary objectives are to compare these two types of care on:
- cerebral metabolism;
- evolution of ICP / changes in intracranial pressure and cerebral perfusion pressure; ;
- mean arterial pressure stability;
- diuresis
- fluid intake required to maintain hydroelectrolytic balance;
- changes in natremia ;
- variation in chloraemia;
- patient outcome at 6 months.

Methodology :
Prospective single-blind clinical trial comparing two randomized treatment groups of equal size. Multicenter study, coordinated by an Israeli team

Number of patients (planned and analysed) :
- Number of patients planned : 40 (20 per center)
- Number of patients analysed : 5

Diagnosis and main criteria for inclusion : Severe head trauma with intracranial hypertension treated with hypertonic solutions without barbiturates

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Inclusion criteria

- Severe traumatic brain injury patients with intracranial hypertension.

Exclusion criteria

- Age < 16 years ;
- History of cerebrovascular disease;
- Bilateral non-reactive mydriasis on admission;
- Lesions requiring surgical decompressive craniectomy;
- Intracranial hypertension justifying barbiturate treatment;
- natraemia greater than 160 mmol/l and osmolality greater than 320 mOsm/l.
- Pregnant women

Test product, dose and mode of administration, batch number

- Mannitol 20% 4ml/kg
- Hypertonic saline serum : 7.5% 2ml/kg, (an iso-osmotic dose)

Duration of treatment :

30 minutes for the product, non-invasive cerebral blood flow test at 30 minutes and 120 minutes and follow-up at 6 months

Reference therapy, dose and mode of administration, batch number

1/ CHLORURE DE SODIUM AGUETTANT 10 %
2/ MANNITOL MACO-PHARMA 20 % sol inj p perf IV

Criteria for evaluation :

Efficacy :

The primary outcome is the change in cerebral blood flow in ml/100g/minute, measured by multiple-incidence Doppler between the value obtained 1 hour after injection and the baseline value before injection, relative to the initial cerebral blood flow value taken before injection of hyperosmolar product.

Secondary outcomes

- Number of attacks of HTIC greater than 20 mm Hg in the 6 hours following treatment
- Average hourly diuresis calculated over the 12 hours following injection

- Effect of each treatment on cerebral metabolism
  - cerebral oxygen consumption in ml/100g/min
  - Cerebral glucose consumption in mg/100g/min
  - Metabolic lactan production in mg/100g/min
- Effect of each treatment on intracranial pressure
  - Stabilization of ICP after injection judged by :
    * the number of accesses above 20 mmHg over the following 24 hours, calculated on the basis of ICP readings taken every 30 minutes;
    * the highest ICP in the 24 hours following injection;
    * the difference in ICP before and 2 hours after injection.
  - Relative increase in cerebral perfusion pressure from baseline to 2 hours post-injection.
  - The amount of noradrenaline required to maintain cerebral perfusion pressure between 60 and 70 mmHg in both groups.
  - Decreases in the pulsatility index calculated by transcranial Doppler at the carotid artery. This index, calculated from diastolic, systolic and mean flow velocities, increases with cerebral resistance.

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- Effects of each treatment on fluid and electrolyte balance
  - total diuresis in the 12 hours following injection;
  - fluid intake and output in the 12 hours following inclusion;
  - mean natraemia 2 hours after injection.
- Effects of each treatment on patient outcome
  - estimation of Glasgow Outcome Scale at 6 months.

Safety : Evaluation of natremia, blood urea

Statistical methods :

Quantitative values are analyzed by Student's t-test in the case of a normal distribution, or by Mann Whitney test if the distribution cannot be tested. Relationships between qualitative values will be studied using the Chi2 test or Fisher's exact test, depending on the theoretical numbers involved.

Summary – Conclusions

Efficacy Results : Mannitol and 7.5% hypertonic saline serum, used in equiosmolar doses, have a non-significantly different effect in reducing intracranial pressure. They produce a similar rise in cerebral perfusion pressure and cerebral blood flow, with a longer duration for hypertonic saline serum. Hypertonic saline serum has a more pronounced effect in diffuse lesions. Cerebral metabolism, as measured by cerebral oxygen and glucose consumption, was unaffected by either solution. Patient outcome did not differ between the two groups.

Safety Results : For some patients, infusion of hypertonic saline serum may result in prolonged elevations of natremia. This point should be taken into account when choosing a hypertonic saline solution.

Conclusion : The choice of treatment, the implementation of which depends on internationally-recognized best practice guidelines, can therefore be made on an individual basis for each patient, depending on his or her level of natremia and cerebral hemodynamics.

Date of report : 03/08/2012