HYPERTONIC SALINE VS. MANNITOL IN POST-TRAUMATIC INTRACRANIAL HYPERTENSION

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Abbreviations

BBB	Blood-Brain Barrier
CBF	Cerebral Blood Flow
CPP	Cerebral Perfusion Pressure
CT	Computerized Tomography
CVA	Cerebrovascular Accident
GCS	Glasgow Coma Score
GOS	Glasgow Outcome Scale
HES	Hydroxyethyl Starch
HSD	Hypertonic Saline/Dextran
HSL	Hypertonic Sodium Lactate
HTS	Hypertonic Saline
ICH	Intracranial Hypertension
ICP	Intracranial Pressure
MAP	Mean Arterial Pressure
MTL	Mannitol
OR	Odds Ratio
RCT	Randomized Controlled Trial
RR	Relative Risk
SAH	Subarachnoid Haemorrhage
TBI	Traumatic Brain Injury

Introduction

Traumatic brain injury (TBI) is a leading cause of mortality in all age groups[1], prolonged morbidity in young adults[2], and is the most common cause of early post-traumatic death, followed by haemorrhagic shock[3]. Emergency admissions for TBI to hospitals in England have been increasing year on year since 2002, and now stand in excess of 135,000 annually[4].

Severe TBI, defined as that with a Glasgow Coma Score (GCS) of 8 or less, occurs in as many as 11,000 patients annually[5]; fatal outcomes range from between 20-50%, and severe neurological disability can affect up to 50%[6] with obvious individual and wider socio-economic implications.

Hyperosmolar therapy has become an important tool in the management of intracranial hypertension (ICH) over the past three decades. Mannitol has been the osmotic agent of choice until now[7]; indeed surveys conducted in 2005 demonstrated that 83% and 100% of centers in the USA and UK respectively, used mannitol to control ICP[8]. Hypertonic saline (HTS) therapy following TBI was first described in 1919, but it is only over the past decade that research has emerged which has compared its efficacy with that of mannitol, and has subsequently advocated a change in practice[7,9].

An American study published in April 2011, detailing a survey of 295 neuro-intensive care clinicians, reported a distinct lack of consensus as to which particular agent is superior; 54.9% stated a preference for HTS, while the remaining 45.1% opted for mannitol. Dosing regimes were also noted to vary considerably[10].

It is this apparent lack of clarity and consensus upon the issue that first attracted me to the topic - I wondered how strong any evidence for the claim for HTS would prove to be - and whether or not I would be obliged to amend my own clinical practice in light of the findings. Any improvement in the management of post-traumatic ICH or subsequent mortality and neurological outcome would undoubtedly confer significant benefits not only to the individual, but to society at large.

Pathophysiology

The pathophysiology of ICH is complex, but can be broadly divided into two key components; that of an imbalance of Starling's forces, and that of the Monro-Kellie hypothesis[2,11].

- Starling's forces

These trans-capillary hydrostatic pressure gradients and counterbalancing osmotic pressure gradients regulate the magnitude of flow from cerebral capillaries into the brain parenchyma. This occurs across the blood-brain barrier (BBB) which is permeable to water but relatively impermeable to proteins and small solutes. Disruption of the BBB can occur in TBI, causing imbalance of these forces and subsequent leakage of proteins and electrolytes into the brain parenchyma. The osmotic pressure gradient is diminished, and the unregulated hydrostatic pressure gradient forces fluid from the intravascular compartment into brain tissue, leading to cerebral oedema and an elevation in ICP[2].

- Monro-Kellie hypothesis

This states that as the cranium is of fixed volume, the combined intracranial volumes of blood, brain tissue and cerebrospinal fluid must also remain constant at all times, creating a volume equilibrium. The presence of any resulting lesion, for example an extradural haematoma, causes an

increase in volume which then compresses and/or displaces the other constituents. These mechanisms allow for normal ICP to be maintained to a point, after which decompensation occurs and ICP rapidly increases[11].

- Hyperosmolar therapy in the prevention of secondary injury

Cerebral perfusion pressure (CPP) is calculated thus:

CPP = mean arterial pressure (MAP) - ICP

Hence any increase in ICP or any decrease in MAP resulting from systemic hypotension, causes a reflex decrease in CPP which results in hypoperfusion of the brain, subsequent cerebral ischaemia and when prolonged, infarction; this is referred to as secondary injury following TBI and is associated with significant neurological morbidity[3]. The aim of hyperosmolar therapy is to prevent such secondary injury. Given intravenously it exerts an osmotic gradient across the blood-brain barrier, which compels any fluid contributing toward cerebral oedema to be absorbed into the intravascular compartment, and subsequently diverted from the cranium[1]. This resulting decrease in intracranial volume counteracts the process of decompensation and lowers ICP, which in turn results in an increase in CPP and improved neurological outcome, assuming a constant MAP.

Clinical Dilemma

A 36 year-old cyclist is brought to the emergency department with TBI following a road traffic accident, sustaining significant bruising to the right side of his head. Subsequent CT scans reveal a right-sided extradural haematoma and transfer to a local neurosurgical center is arranged. Despite adequate initial management and resuscitation his condition continues to deteriorate. He has several episodes of vomiting, his GCS drops to 6/15 (E1 V2 M3) and his right pupil becomes dilated. Once intubated, ventilated and haemodynamically optimized, hyperosmolar therapy is suggested to

manage the ICH that is suspected to be resulting from his expanding intracranial haematoma. Local policy recommends mannitol as the first-line agent; the neurosurgical registrar however insists that hypertonic saline be given instead, citing anecdotal evidence of its superiority in managing ICH.

Clinical Question

In order to address the above clinical dilemma and provide structure for an effective literature search, the following 4-part question has been constructed based upon the PICO framework[12]:

- Population: In patients with intracranial hypertension (ICH) following traumatic brain injury (TBI),
- Intervention: is hypertonic saline (HTS)
- Comparison: more effective than mannitol (MTL) at
- Outcomes: controlling intracranial hypertension (ICH),
  reducing intracranial pressure (ICP),
  elevating cerebral perfusion pressure (CPP), and
  improving neurological outcome (GOS)?

Literature Search Strategy

Table 1: Search via Medline - 1950 to February 2012

No.	Search	Results
1	(TBI OR ((head OR brain) AND (traum$ OR injur$))).ti,ab	84,597
2	exp HEAD/ OR exp COMA, POST-HEAD INJURY/ OR exp HEAD INJURIES, CLOSED/ OR exp HEAD INJURIES, PENETRATING/	148,995
3	exp BRAIN/ OR exp BRAIN CONCUSSION/ OR exp BRAIN EDEMA/ OR exp BRAIN HEMORRHAGE, TRAUMATIC/ OR exp BRAIN INJURIES/ OR exp BRAIN ISCHEMIA/ OR exp HYPOXIA, BRAIN/ OR exp HYPOXIA-ISCHEMIA, BRAIN/	964,253
4	1 OR 2 OR 3	1,135,716
5	(HTS OR (hypertonic AND (saline OR sodium))).ti,ab	7,998
6	exp SALINE SOLUTION, HYPERTONIC/ OR exp SODIUM CHLORIDE/ OR exp HYPERTONIC SOLUTIONS/	57,877
7	5 OR 6	62,186
8	(MTL OR mannitol).ti,ab	14,266
9	exp MANNITOL/	10,546
10	8 OR 9	18,877
11	(ICP OR (intracranial AND (pressure OR hypertension))).ti,ab	26,231
12	exp INTRACRANIAL PRESSURE/ OR exp INTRACRANIAL HYPERTENSION/	32,812
13	(CPP OR CBF OR (cerebral AND (perfusion OR (blood AND flow)))).ti,ab	45,252

Table 1 (continued): Search via Medline - 1950 to February 2012

14	(neuro$ AND outcome).ti,ab	48,075
15	exp GLASGOW OUTCOME SCALE/ OR exp TREATMENT OUTCOME/ OR exp FATAL OUTCOME/	568,445
16	11 OR 12 OR 13 OR 14 OR 15	687,636
17	4 AND 7 AND 10 AND 16	158

Replacing any exploded thesaurus headings (prefix = exp) with searches via title & abstract revealed no additional articles. Eliminating the stages representing the treatment outcomes (11 to 16) also uncovered no additional articles of interest. The search was repeated using Embase (1974 onwards) and CINAHL (1982 onwards), again with no additional articles yielded.

Results of Literature Search

As detailed, the searches of Medline, Embase and CINAHL yielded 158 articles, of which only trials involving human beings were considered clinically applicable and hence included. On review of each of their titles and abstracts, fifteen articles were of direct relevance to the clinical question at hand including twelve clinical trials, a meta-analysis of RCTs[7], a bestBET[13] and a Cochrane review[14]. No restrictions on language were imposed; one article for inclusion was published in Russian. All but two articles were available online; one required ordering from the British Library[15], and the other was purchased directly from the publisher[16]. Further review and hand searches of these fifteen articles revealed no additional articles relevant for inclusion. Searches conducted on both Google Scholar and the GreyNet (Grey Literature Network Service) databases also revealed no additional articles relevant for inclusion.

Critical Appraisal of Literature

Each paper is appraised in chronological order, based on its date of publication. A table summarizing their relative strengths and weaknesses is presented thereafter for comparative purposes, and another summarizing the key elements and outcomes of each study is contained in Appendix I.

- **Schatzmann (1998, Germany) [17]**

This small prospective study recruited 6 subjects consecutively, leading to possible selection bias. HTS was only used as a second-line therapy; hence any direct comparison between agents was not possible, and any effects attributed to HTS may in actuality have been cumulative. With the exception of a percentage change in ICP from baseline following HTS administration, no further statistical analysis nor power calculation was attempted; indeed, any significance is not commented upon. Despite this, the study concludes that HTS administration is recommendable as part of a treatment protocol for ICP. Due to its size, multiple flaws and lack of statistically-supported conclusions, this study lacks both internal and external validity, and can be viewed as poor with regards to the level of evidence provided.

- **Vialet (2003, France) [18]**

This single blinded, prospective study randomly allocated 20 subjects to receive isovolumar but not equimolar infusions of either HTS or mannitol, resulting in some clinical heterogeneity. Although the groups were demographically well matched and allocation was concealed, neither the randomization nor blinding process were described, lending potential for selection bias. Data was collected electronically at 5min intervals; extreme interim physiological events may hence have

been missed. Despite no power calculation having been performed, the study concluded that HTS was the more effective agent.

- **Ware (2004, USA) [20]**

This retrospective cohort study reviewed the medical records of 13 subjects who received non-equimolar, non-isovolumar infusions of HTS or mannitol, with doses of the latter determined by the attending physician. A high proportion of patients (128/141) failed to meet the inclusion criteria and were excluded from the study, leading to possible exclusion bias. One important criterion was that cases of ICH must have already been refractory to an initial dose of mannitol. There is also potential for selection, observer and information bias from the retrospective study design, chart review methodology, absence of randomization and customized dosing strategy employed. Comprehensive data was provided regarding neurological outcomes, although 31% of subjects were lost to follow-up, suggesting some attrition bias. The study concluded that HTS was an effective alternative to mannitol.

- **Battison (2005, UK) [19]**

This small prospective crossover study detailed 9 subjects; 6 with TBI, 3 with atraumatic SAH. These were randomly allocated via card selection to receive equimolar infusions of either first 20% mannitol, and then HSD (7.5% NaCl/6% dextran) or vice versa so that each subject effectively became their own control, improving internal validity. An attempt was made to double-blind the study but this was abandoned due to the unequal infusion volumes. Data was collected electronically at 1min intervals and statistical techniques clearly stated. No demographic data on the subjects was provided and this combined with the small numbers in the study adversely affects its external validity. In addition, the HSD solutions were provided free-of-charge by its manufacturers, lending scope for possible partiality to HSD - which indeed was found to be the superior agent.

- **Harutjunyan (2005, Germany)** [8]

This prospective RCT randomized 32 subjects into either a 15% mannitol or HyperHES (7.2% NaCl + hydroxyethyl starch 200/0.5) treatment arm. Osmolar doses or infusion volumes were not stated, damaging internal validity. Although the randomization process was not described, the groups appeared demographically well matched. Statistical techniques and significance levels were stated, but no power calculation was attempted. Data collection was continuous. HyperHES produced significantly more marked effects than mannitol on both ICP ($p<0.01$) and CPP ($p<0.05$), faster achievement of ICP control ($p<0.0002$), and was hence declared the more effective agent. There was considerable heterogeneity of cases, only 31% of which had TBI; the remainder included 28% with atraumatic SAH and 23% with CVA. This adversely affects the external validity of the study and the degree to which its conclusions can be extrapolated to patients with TBI only.

- **Francony (2008, France)** [21]

This parallel RCT detailed 20 subjects who were randomly allocated via sealed envelopes to either 20% mannitol or HTS (7.45% NaCl) treatment arms, which were demographically well matched. Doses were equimolar which improved internal validity, but blinding was not considered feasible due to the unequal infusion volumes. Multiple exclusion criteria were applied, including haemodynamically unstable patients or those with impaired pressure autoregulation, resulting in scope for exclusion bias. Statistical techniques were stated, power calculations were attempted, and results analyzed on an intention-to-treat basis. It was concluded that consideration of haemodynamic and biochemical factors in a given target patient would be key to determining which agent was most suitable.

- **Wakai (2008, Canada)** [14]

This Cochrane review comprised of 4 RCTs which compared mannitol with either a placebo (0.9% NaCl), phenobarbital, HTS (7.5% NaCl) or with an alternative regimen of mannitol, highlighting clinical heterogeneity between trials. Only the study involving HTS was of direct relevance (Vialet[18]), and has already been appraised in this CTR. For mannitol vs. HTS, the relative risk (RR) of death was 1.25 (0.47-3.33). This was not significant; nor was death stated as an outcome under investigation in Vialet[18], bringing the validity of any subsequent conclusions based upon the data into question. The review concluded that there was insufficient reliable evidence to make recommendations on the use of mannitol.

- **Ichai (2009, France)** [6]

This prospective open randomized study included only 34 subjects from 132 patients assessed for eligibility due to stringent inclusion criteria; those over the age of 65, those with polytrauma, and those requiring neurosurgical intervention were excluded amongst others, resulting in possible exclusion bias and adversely affecting external validity. However, a power calculation was performed and found this to be the only adequately powered study; both intention-to-treat and actual-treatment-received analyses were also provided. Random allocation took place via sealed envelopes, minimizing selection bias, to either 20% mannitol or an equimolar, isovolumar half-molar sodium lactate (HSL) infusion, which in turn minimizes clinical heterogeneity and improves internal validity. The study concluded that HSL was the more effective agent and resulted in better long-term neurological outcomes, although data is not presented for the latter conclusion.

- **Kerwin (2009, USA)** [22]

This retrospective study reviewed the records of 22 subjects with TBI. No randomization nor blinding took place; allocation to either treatment arm was at the discretion of the attending

surgeons and doses were neither equimolar nor isovolumar, leading to clinical heterogeneity. The study concludes that HTS is the more effective agent, but is beset by multiple flaws. Its retrospective design of a manual review of patient records, lack of randomization and treatment standardization, and surgeon-led allocation process introduce huge potential for selection, observer and information bias, and greatly damage both its internal and external validity.

- **Oddo (2009, USA)** [23]

This retrospective study consecutively recruited 12 adult subjects, all of whom had TBI. No randomization took place and allocation to the HTS treatment arm was employed only at the surgeon's discretion as a rescue therapy following failure of the mannitol infusion; there is hence considerable potential for both selection bias and information bias, due to the cumulative effect of HTS augmenting that of the mannitol already given. In addition, infusions were neither equimolar nor isovolumar, resulting in clinical heterogeneity. Nevertheless, despite the absence of a power calculation and the difficulties surrounding any direct comparison between the two agents, this flawed study goes on to report that HTS is the more effective agent.

- **Polushin (2009, Russia)** [16]

This multicenter RCT of 25 subjects conducted across 3 institutions was published in Russian. Extensive exclusion criteria were applied, and only 15 subjects included had TBI, lending scope for exclusion bias and adversely affecting external validity. Subjects were randomly allocated to receive either 15% mannitol, HTS (10% NaCl) or HyperHES (7.2% NaCl + hydroxyethyl starch 200/0.5). However, neither the randomization, allocation, nor blinding processes are described. Infusions were neither equimolar nor isovolumar, resulting in clinical heterogeneity. ICP and haemodynamic monitoring was invasive and continuous. Statistical techniques and significance

levels were clearly stated, and data clearly presented. It was concluded that HyperHES was significantly more effective than either HTS or mannitol at reducing ICP and elevating CPP.

- **Rickard (2011, UK)** [13]

This bestBET reviewed 5 papers already appraised in this CTR[6,8,19,20,23] and concludes that HTS is more effective than mannitol, although no overall statistical analysis was attempted. Its search strategy is flawed, and fails to identify 5 papers that the search employed in this CTR has yielded. In addition, only English language papers are included, resulting in a foreign language bias and overlooking Polushin[16], one of the higher-quality RCTs.

- **Sakellaridis (2011, Greece)** [24]

This prospective RCT detailed 29 subjects, allocated via an alternating protocol following an unspecified randomization performed by the author for the first case of ICH in each subject, introducing potential for selection bias. Subjects were given either an infusion of 20% mannitol or a bolus of HTS (15% NaCl); doses were equimolar but not isovolumar, and the difference in administration adds to clinical heterogeneity and adversely affects internal validity. Data collection was continuous and invasive, and a power calculation was attempted which showed the study to be underpowered. Indeed, no significant differences were found between the agents which may implicate the study as being at risk of a type 2 error.

- **Kamel (2011, USA)** [7]

This meta-analysis included only RCTs which compared equimolar doses of HTS to mannitol for the treatment of elevated ICP in human subjects. Five trials met these criteria, including three already appraised in this CTR[6,19,21]. The remaining two trials comprised almost exclusively of subjects with either brain tumour or CVA respectively, and hence were not as clinically relevant to

our clinical question. Meta-analysis was performed via random-effects models, allowing for mild heterogeneity between the trials. The pooled RR of ICP control was significant at 1.16 (1.00-1.33, p=0.046) in favour of HTS, but no significant difference was found in ICP reduction. The 112 subjects included left this meta-analysis inadequately powered and hence at risk of a type 2 error; despite this and the methodological differences between the included studies, they do however conclude that HTS is the superior agent.

- **Cottenceau (2011, France & Israel)** [15]

This international, bi-center RCT prospectively recruited 47 subjects with severe TBI, who were then randomized via a computerized system to receive equimolar infusions of either HTS or mannitol. Allocation was concealed, via sealed envelopes. The groups were demographically well matched, statistical techniques fully explained, and methodology well-defined and consistent between centers. With the exception of the fact that the infusions were not isovolumar and CBF values were calculated via indirect means, the study design minimizes bias and consequently improves both its internal and external validity. The study concludes that it could not support any definite advantage of HTS over mannitol, but admits to having been underpowered and would hence be at risk of a type 2 error.

Overview of Appraisal

A table summarizing each studies' relative strengths and weaknesses is presented overleaf for comparative purposes, and another summarizing their key elements and outcomes is contained in Appendix I.

Table 2: Summary of studies' relative strengths and weaknesses

	Strengths	**Weaknesses**
Schatzmann [17] 1998 Germany	Prospective design. 83% of subjects had TBI.	Least subjects of any trial (6). Consecutive recruitment. HTS only as rescue therapy; hence no direct comparison possible. Cumulative effects not considered. Minimal statistical analysis. No power calculation.
Vialet [18] 2003 France	Prospective design. 100% of subjects had TBI. Randomized allocation. Demographically similar groups. Single blinded. Isovolumar infusions. Followed up at 90 days.	Consecutive recruitment. Randomization process not described. Non-equimolar doses. Data collected only every 5min. No power calculation.
Ware [20] 2004 USA	100% of subjects had TBI. Followed up at 6 months.	Retrospective design. Chart review methodology; recall bias. Extensive exclusion criteria. Few subjects (13). No randomization. Doses decided by physician. Non-equimolar doses. Non-isovolumar infusions. 31% lost to follow-up; attrition bias.
Battison [19] 2005 UK	Prospective design. Randomized allocation. Single blinded. Equimolar doses. Each subject acts as own control. Good internal validity.	Few subjects (9). Only 66% of subjects had TBI. No demographic data. HTS/Dextran combination used. Non-isovolumar infusions. Possible conflicting interests. Poor external validity.

Table 2 (continued): Summary of studies' relative strengths and weaknesses

	Strengths	**Weaknesses**
Harutjunyan [8] 2005 Germany	Prospective design. Demographically similar groups. Continuous data collection. Highly significant findings.	Considerable case heterogeneity. Only 31% of subjects had TBI. Randomization not described. HyperHES used instead of HTS. Osmolar doses not stated. Infusion volumes not stated. No power calculation. Poor external validity.
Francony [21] 2008 France	Prospective design. 85% of subjects had TBI. Randomized, concealed allocation. Demographically similar groups. Equimolar doses. Intention-to-treat analysis given. Good internal validity.	Extensive exclusion criteria. Non-isovolumar infusions. Statistically underpowered.
Wakai [14] 2008 (Cochrane)	Cochrane-endorsed review.	Only 1 of 4 included trials relevant to clinical question. Outcome analyzed was not under specific investigation in original article.
Ichai [6] 2009 France	Prospective design. 100% of subjects had TBI. Randomized allocation. Equimolar doses. Isovolumar infusions. Study adequately powered. Intention-to-treat analysis given. Good internal validity. Followed up at 1 year.	Extensive exclusion criteria. HSL used instead of HTS. Both HSL and mannitol employed as rescue therapy on occasion. No long-term neurological data given.

Table 2 (continued): Summary of studies' relative strengths and weaknesses

	Strengths	**Weaknesses**
Kerwin [22] 2009 USA	100% of subjects had TBI. Highly significant findings.	Retrospective design. Chart review methodology; recall bias. No randomization. Allocation at surgeons' discretion. Doses at surgeons' discretion. Non-equimolar doses. Non-isovolumar infusions. Huge potential for bias. Poor internal and external validity.
Oddo [23] 2009 USA	100% of subjects had TBI.	Retrospective design. Consecutive recruitment. No randomization. HTS only as rescue therapy; hence no direct comparison possible. Allocation at surgeons' discretion. Non-equimolar doses. Non-isovolumar infusions. No power calculation.
Polushin [16] 2009 Russia	Multicenter study. Prospective design. Randomized allocation. Unspecified blinding. Continuous data collection. Statistical techniques well described. Direct comparisons between HTS, mannitol and HyperHES.	Required translation from Russian. Only 60% of subjects had TBI. Extensive exclusion criteria. Non-equimolar doses. Non-isovolumar infusions. Statistically underpowered.
Rickard [13] 2011 (BestBET)	Directly addresses clinical question.	Flawed search strategy; fails to identify 5 relevant articles. Foreign language bias. No overall statistical analysis.

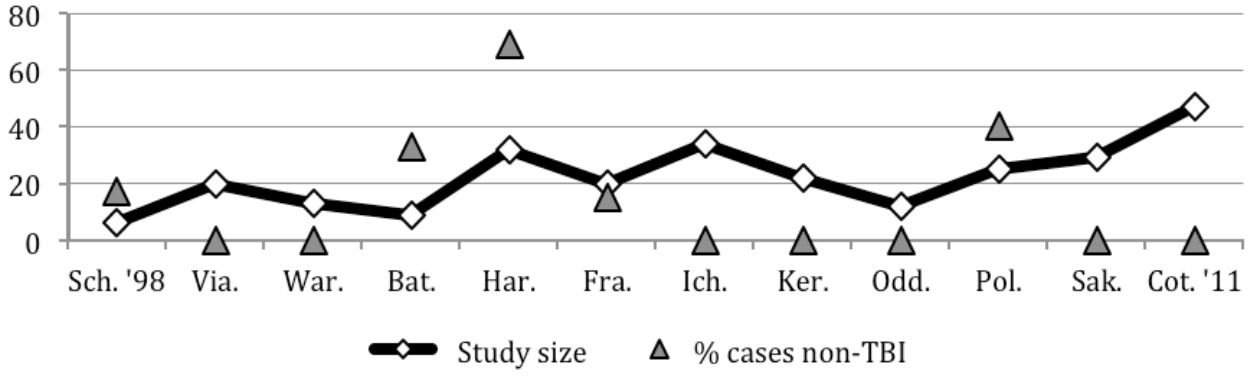
Table 2 (continued): Summary of studies' relative strengths and weaknesses

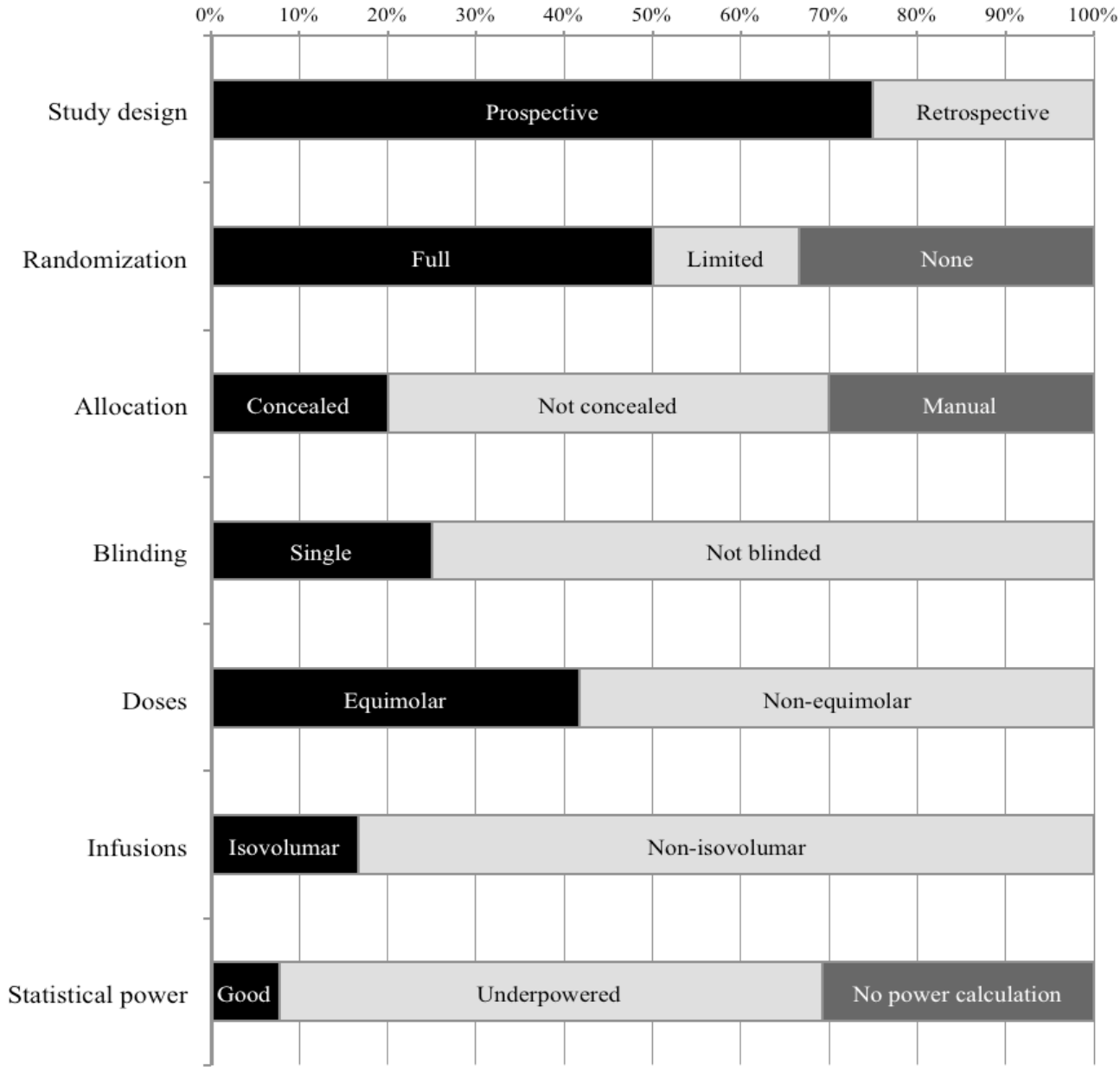
	Strengths	**Weaknesses**
Sakellaridis [24] 2011 Greece	Prospective design. 100% of subjects had TBI. Limited randomization. Equimolar doses. Continuous data collection.	Alternating protocol. Non-isovolumar infusions. Difference in administration. Statistically underpowered. No significant findings; possible type 2 error.
Kamel [7] 2011 USA	Meta-analysis. Random-effects model appropriate. Directly addresses clinical question.	Only 3 out of 5 trials relevant to TBI. Limited outcomes addressed. Statistically underpowered; risk of a type 2 error.
Cottenceau [15] 2011 France & Israel	International, two-center study. Prospective design. Most subjects of any trial (47). 100% of subjects had TBI. Randomized, concealed allocation. Equimolar doses. Followed up at 6 months. Good internal & external validity.	Non-isovolumar infusions. Indirect calculation of CBF. Statistically underpowered.

Preliminary Analysis

As already discussed in some depth, the included trials vary widely in their overall quality, bias and validity. This is demonstrated in the graph below, and provides further insight into the analyses, conclusions and meta-analyses detailed subsequently.

Figure 1: Summary of key quality indicators of included trials





Seven papers including the meta-analysis[7] and bestBET[13] concluded that HTS solutions, ranging from 7.45 to 23.4% NaCl and extrapolated to include HSD and HSL, were more effective than mannitol[6,7,13,18,19,22,23]. Six papers found that although both agents were effective, HTS did not provide any definitive benefit over mannitol[15,16,17,20,21,24]. The remaining two papers concluded that HyperHES had been more effective than either HTS or mannitol[16], or mannitol alone[8]. Mannitol was not found to be a superior agent in any of the papers included in this CTR.

- Effective control of ICH

Three papers found in favour of HTS solutions[6,18,22], none in favour of mannitol, and four found no significant difference[8,15,16,21]. The six remaining studies yielded no conclusions[13,17,19,20,23,24].

- Reduction of ICP

Four papers found in favour of HTS solutions[6,19,22,23], none in favour of mannitol, and five found no significant difference[15,16,20,21,24]. The four remaining studies yielded no conclusions[15,16,20,21].

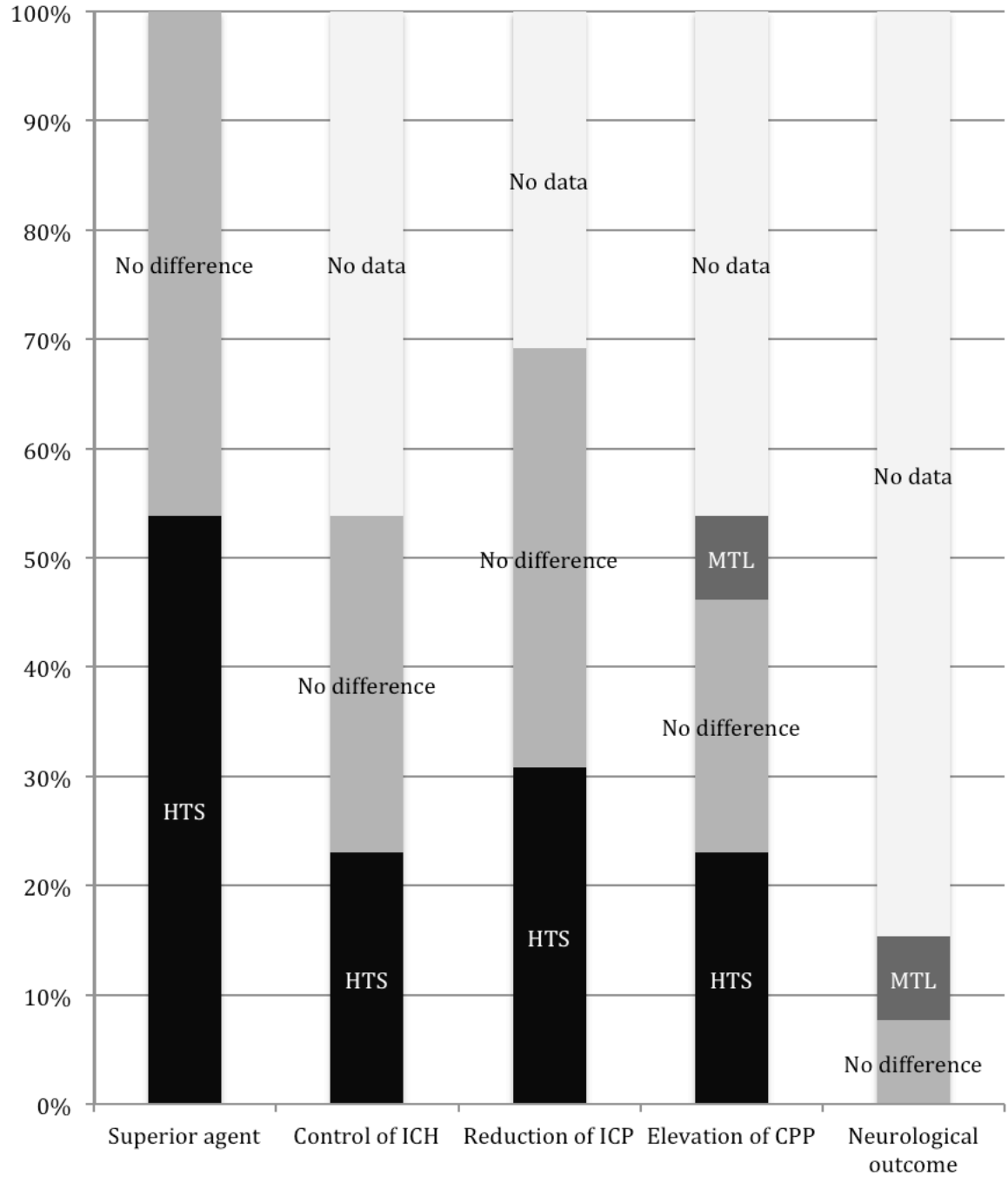
- Elevation of CPP

Three papers found in favour of HTS solutions[6,19,23], one in favour of mannitol[21], and three found no significant difference[15,16,18]. The two papers which included HyperHES found it had been more effective than either HTS or mannitol[16], or mannitol alone[8]. The six remaining papers yielded no conclusions[13,14,17,20,22,24].

- Improvement in neurological outcome / GOS score

One paper found in favour of mannitol[21], and another found no significant difference[20]. The eleven remaining papers yielded no conclusions[6,7,13,15,16,17,18,19,22,23,24].

Figure 2: Most effective hyperosmolar agent by outcome



Conclusions

All available literature has now been critically appraised, compared and synthesized into a preliminary analysis. Relevant data has also been extracted to perform three meta-analyses, documented fully in Appendix II. Their findings are summarized below:

Table 3: Summary of meta-analyses' overall findings

Meta-analysis	OR	95% C.I.	P-value	Direction
1. Effective control of ICH	3.625	1.437 to 9.146	0.006	In favour of HTS
2. Reduction of ICP	1.719	1.106 to 2.673	0.016	In favour of HTS
3. Elevation of CPP	1.618	0.957 to 2.736	0.073	In favour of HTS

Thus, the following conclusions may be drawn in relation to the clinical question:

- HTS-based formulations are more effective at controlling episodes of ICH than mannitol.
- HTS-based formulations result in a greater reduction in ICP than mannitol.
- There is no significant difference between the efficacy of HTS-based formulations and mannitol in elevating CPP.
- There is insufficient evidence to form any conclusions regarding which agent has a more positive effect on neurological outcome.

A major limitation to these conclusions stem from clinical heterogeneity among the studies; the variety of hyperosmolar agents employed make direct comparison difficult[6,8,19]. Other limitations arise from poor study design, widespread recall and exclusion bias, questionable external validity, and the fact that all but one study were inadequately powered[6].

Despite these, the conclusions retain the potential to argue for a change in current clinical practice, and may support a shift toward the use of HTS-based formulations as the hyperosmolar agent of choice in post-traumatic ICH. However, the haemodynamic qualities and biochemical profiles of each agent ought to be taken into consideration, and usage tailored to each individual patient in order to gain optimal benefit[21]. The limited data suggesting the superiority of HyperHES (7.2% NaCl + hydroxyethyl starch 200/0.5) over both HTS and mannitol[8,16] certainly warrants further research by way of an adequately powered, blinded RCT comparing equimolar, isovolumar infusions of HyperHES against HTS (7.5-23.4% NaCl) and mannitol (15- 25%) in order to provide accurate and conclusive data as to which is the superior agent.

Based upon the findings and conclusions of this CTR, an algorithm for the appropriate usage of hyperosmolar therapy in patients with post-traumatic ICH is suggested in Appendix III.

Appendix II - Meta-Analyses:

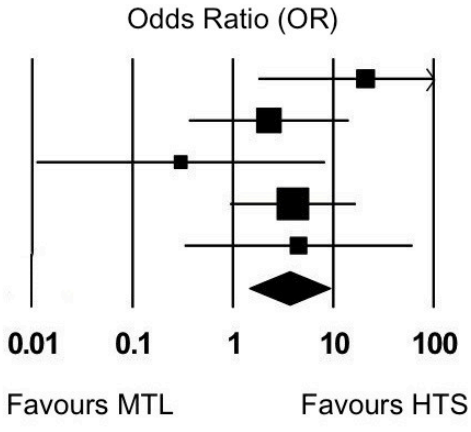
In order to further analyze the available data with respect to the outcomes declared in our 4-part question, the following meta-analyses have been conducted using the Comprehensive Meta-Analysis V2 software package, from Biostat (USA):

1. Effective control of ICH
2. Reduction of ICP
3. Elevation of CPP

Insufficient data was available to address the fourth outcome, that of any improvement in neurological outcome. All meta-analyses were conducted using fixed-effects models. Forest plots together with explanations are presented for each of the above; studies are listed in chronological order.

Meta-analysis 1: Effective control of ICH

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Vialet	21.000	1.777	248.103	2.417	0.016
Battison	2.285	0.362	14.440	0.879	0.380
Francony	0.302	0.011	8.332	-0.708	0.479
Ichai	3.959	0.926	16.926	1.856	0.063
Kerwin	4.512	0.327	62.266	1.125	0.261
	3.625	1.437	9.146	2.728	0.006

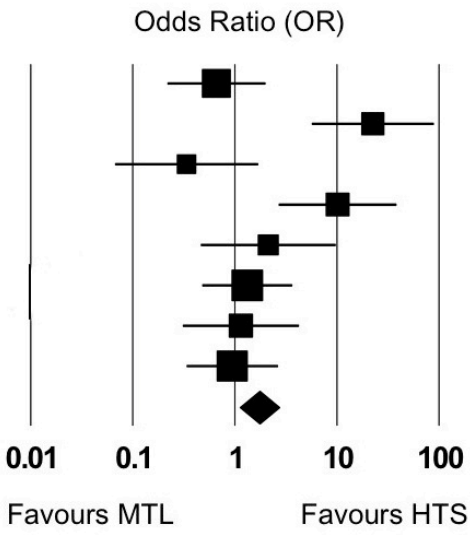


This first meta-analysis includes the five studies[6,18,19,21,22] that provide both a definition of effective control of ICH and a detailed breakdown by agent. Three of these (60%) involved equimolar doses[6,19,21]; only one (20%) involved isovolumar infusions[6]. It can be deduced that HTS-based

formulations are more than three times as likely as mannitol to effectively control episodes of ICH (OR 3.625, 95% C.I. 1.437-9.146, p=0.006). Although the 95% confidence intervals given are wide, that of the overall measure (diamond) does not cross the line of no effect (OR of 1) and has a very low p-value, from both of which statistical significance can be inferred.

Meta-analysis 2: Reduction of ICP

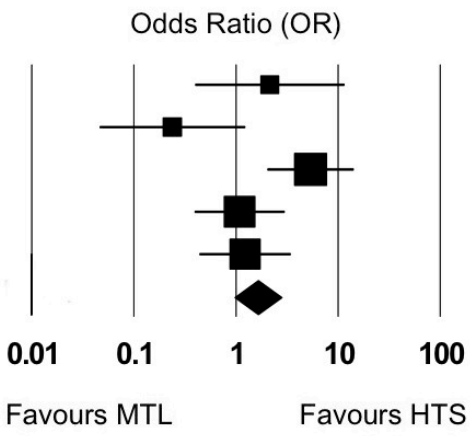
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ware	0.660	0.216	2.016	-0.730	0.466
Battison	22.487	5.623	89.929	4.402	0.000
Francony	0.337	0.066	1.712	-1.312	0.190
Ichai	10.154	2.664	38.701	3.395	0.001
Kerwin	2.124	0.459	9.831	0.964	0.335
Polushin	1.322	0.474	3.692	0.533	0.594
Sakellaridis	1.147	0.306	4.295	0.203	0.839
Cottenceau	0.944	0.334	2.670	0.108	0.914
	1.719	1.106	2.673	2.406	0.016



This second meta-analysis includes the eight studies[6,15,16,18,19,20,22,24] that provide data regarding the change in ICP pre- and post-infusion of each agent. One study was excluded[8] as it only compared HyperHES with mannitol. Five of those included (62.5%) involved equimolar doses[6,15,19,21,24], while only one (12.5%) involved isovolumar infusions[6]. It can be deduced that HTS-based formulations are almost twice as likely as mannitol to cause a greater reduction in ICP than vice versa (OR 1.719, 95% C.I. 1.106-2.673, p=0.016). The 95% confidence interval of the overall measure (diamond) approaches, but does not cross, the line of no effect and has a low p-value, again suggesting statistical significance.

Meta-analysis 3: Elevation of CPP

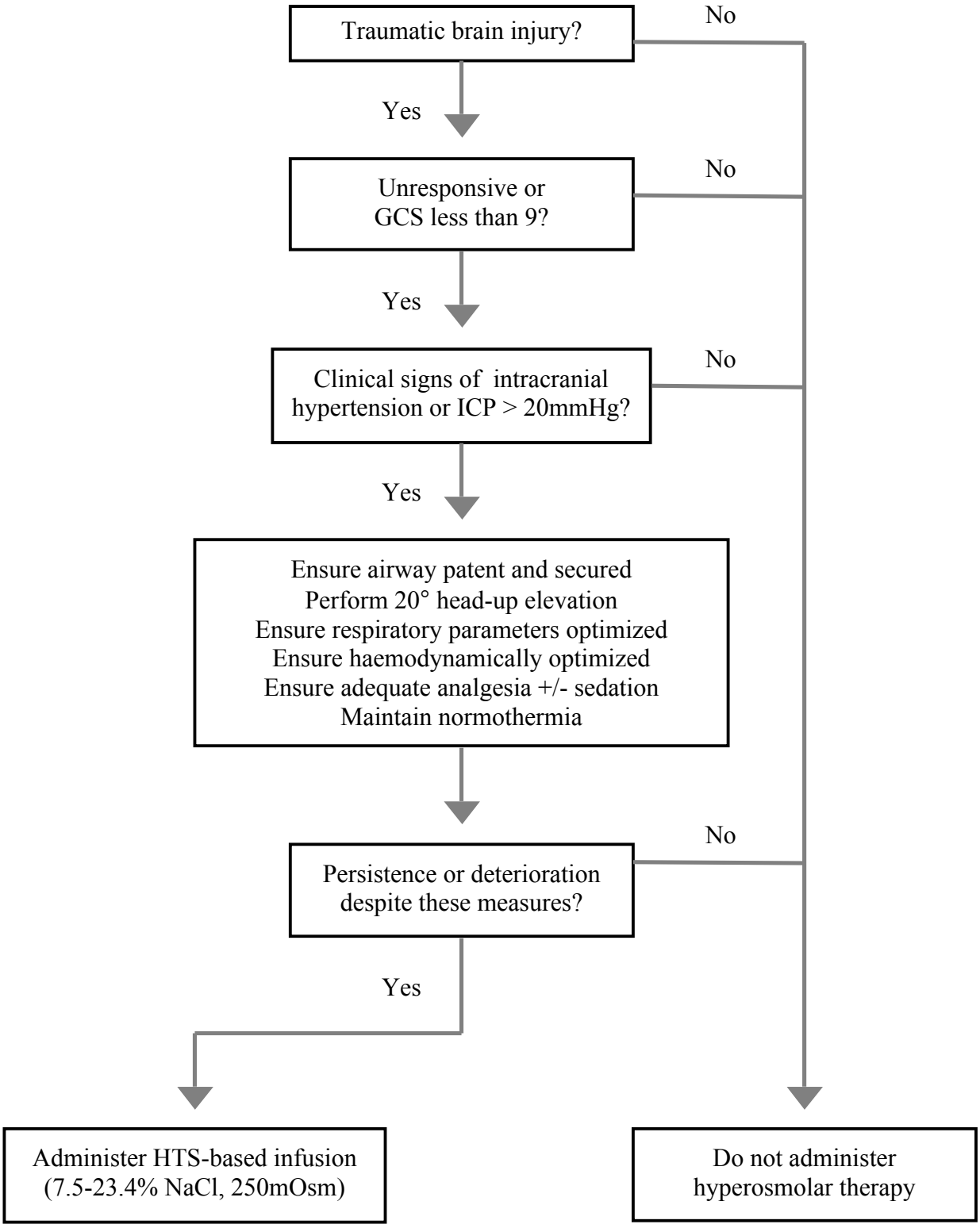
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Battison	2.142	0.394	11.656	0.881	0.378
Francony	0.238	0.046	1.242	-1.702	0.089
Ichai	5.370	2.006	14.372	3.346	0.001
Polushin	1.086	0.390	3.030	0.158	0.874
Cottenceau	1.229	0.434	3.476	0.388	0.698
	1.618	0.957	2.736	1.794	0.073



This third meta-analysis includes the five studies that provide data regarding the change in CPP pre- and post-infusion of each agent. Four of these (80%) involved equimolar doses[6,15,19,21]; only one (20%) involved isovolumar infusions[6]. While it appears, with the notable exception of the study by Francony[21], that HTS-based formulations are more likely to result in a greater elevation of CPP (OR 1.618, 95% C.I. 0.957-2.736, p=0.073), the 95% confidence interval of the overall measure (diamond) just crosses the line of no effect at is lower limit. This infers that no significant conclusion can be drawn from these particular results; the high overall p-value serves to compound this.

Appendix III - Algorithm:

Hyperosmolar therapy in post-traumatic ICH:



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