FLUID THERAPY IN NEUROINTENSIVE CARE PATIENTS: ESICM CONSENSUS AND CLINICAL PRACTICE RECOMMENDATIONS

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ABSTRACT

Objective. To report the ESICM Consensus and clinical practice recommendations on fluid therapy in neurointensive care patients.

Design. A consensus committee including 22 international experts was conducted during ESICM LIVES2016 where a meeting was held for all participants in October 2016. Teleconferences and electronic-based discussions among the entire committee served as an integral part of the development of the consensus process.

Methods. Population, intervention, comparison, and outcomes (PICO) questions were reviewed and updated as needed, and evidence profiles were generated. The consensus focused on three main topics: (1) general fluid resuscitation and maintenance, 2) hyperosmolar fluids for ICP control, 3) fluids for the management of delayed cerebral ischemia). After literature search for best available evidence, the principles of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system were applied to assess the quality of evidence (from high to very low) and to formulate recommendations as strong or weak, or best practice statement when applicable. A modified Delphi process based on the integration of evidence provided by the literature and expert opinions – using a sequential approach for avoiding biases and misinterpretations – was used to generate final statements.

Results. The panel provided 28 statements, and a total of 11 strong recommendations and 15 weak recommendations. No recommendations were provided for 2 questions.

Keywords: Evidence-based medicine – Guidelines – Fluids – Traumatic brain injury – Subarachnoid hemorrhage – Intracerebral hemorrhage – Stroke – Mannitol – Hypertonic – Neurointensive care.

INTRODUCTION

Fluid therapy is a fundamental component of neurointensive care (NIC), with general indications (volume resuscitation and maintenance) and "neuro-specific" purposes (intracranial pressure [ICP] control, management of delayed cerebral ischemia [DCI]). Despite routine utilization, key questions – such as preferred composition, optimal volume, choice and dose of hyperosmolar fluids to control ICP – remain unanswered. There is no Level 1 evidence or specific recommendations to guide fluid therapy in NIC patients, and physiologic triggers and monitoring endpoints of fluid therapy are not precisely defined.

The recommendations herein are focused primarily on providing guidance to clinicians caring for NIC patients and are intended to be best clinical practice but not created to represent standard of care.

METHODOLOGY

Below is a summary of important methodological considerations for the development of these consensus guidelines.

Definitions

We defined NIC patients as adult critically ill patients with severe traumatic brain injury (TBI), high-grade aneurysmal subarachnoid hemorrhage (SAH), and severe stroke (ischemic [AIS] and hemorrhagic [ICH]).

Registration

The plan for this systematic review was registered on PROSPERO, International prospective register of systematic reviews, with the ID 42016052123 (http://www.crd.york.ac.uk/PROSPERO/) .

Sponsorship

No funding was provided.

Conflict-of-interest policy

No industry input into guidelines development occurred. No consensus member received honoraria and the process relied solely on personal disclosures.

Selection of committee members

Participants were members of the European Society of Intensive Care Medicine (ESICM), Neurocritical Care Society (NCS) and Latin America Brain Injury Consortium (LABIC). Chairs and co-chairs were appointed by the NIC section of ESICM, with an external member (DP) providing methodological expertise for the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.

Question development

Focus was on the management of NIC patients during the intensive care phase therefore we did not cover fluid management in the extra-hospital setting. The guideline panel was divided into three sections, according to the three main questions addressed:

1) General fluid management in ABI patients,
2) Hyperosmolar fluids for ICP control and
3) Fluid therapy for the management of DCI.

Topic selection was the responsibility of the group co-chairs (GM, NS, RH) and chairs (MO, GC), with input from the guideline panel in each group. All guideline questions were structured in the PICO format (population, intervention, control, and outcomes).

Search strategy, data analysis, and grading of evidence

In the ESM, all the details of the search strategy and grading of the evidence, including advanced statistical approach as in meta-analyses and meta-regression, are detailed.

Consensus methodology

We used a modified Delphi process based on the integration of evidence provided by the literature and expert opinions. All the results of the GRADING of the evidence were available to the panel through a web-based file. The chairs (MO, GC) integrated the initial questions with literature revision and grading, and formulated 4 mutually exclusive questions and 35 questions (clustered in five different sections) requiring a score ranging from 1 (strongly disagree) to 10 (strongly agree). These questions were submitted to the members of the panel through a web-based system. For each question or cluster of questions the experts could provide comments to integrate their answers. The answers were analysed by a non-voting member of the panel (DP). Answers providing scores were analysed as medians, 20^{th}, and 80^{th} percentiles. Further, scores were clustered into low (1-3), intermediate (4-7), and high (8-10), and analysed with correspondence analysis. Both approaches were used to spot answers that provided clear-cut positions among experts, particularly those polarized on agreement or disagreement. Correspondence analysis was used to assess if single members of the panel provided specific response patterns, especially when intermediate positions were taken. The results of the analyses were returned to the panel anonymously. The same list of question was then submitted to the panel in a second round.

On the basis of the analysis of the second round of questions, statements were formulated by the chairs (MO, GC) selecting questions with higher degrees of agreement, and then submitted to the panel. Answers were analysed with correspondence analysis to spot heterogeneity among the panel members. Single panel members, who presented heterogeneous answer patterns, were provided

feedbacks on their answers with request to confirm their vote, thereby allowing the detection of misinterpretations of some statements.

A final vote was required for confirmation, with >80% of voting members necessary for a *strong* recommendation (*for* or *against*). When votes *for* or *against* (a mix of *strong* and *weak* options) didn't reach the 80% threshold, then a *weak* recommendation was provided. In case of *minor concerns* panel members could declare *reservation*. In case of *major concerns* a stand aside position was adopted, no blocking option was permitted, and reasons for concerns were reported.

RESULTS

1. FLUIDS FOR THE GENERAL MANAGEMENT OF ABI PATIENTS

1.1. Analysis of available evidence

Question 1: *Is there evidence on efficacy and safety of albumin compared to crystalloids?*

One multicenter RCT in AIS patients found comparable 90-day outcome of 25% albumin (n=422) vs. normal saline (NS) (n=419), administered within 5 hours from ictus [19]. One single-center observational study (n=82) in AIS patients found that high-dose albumin was associated with better outcome (OR 1.81 [95% CI 1.11-2.94]) [21]. These two studies were considered sufficiently homogeneous to contribute to the same body of evidence. **GRADE: high quality evidence (against).**

The following studies, instead, were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the ESM), hence corresponds to the body of evidence grading.

A subgroup analysis performed on TBI patients from the multicenter SAFE trial found higher 2-year mortality (33.2 vs. 20.4%) of 4% albumin (n=214) vs. NS (n=206) [20]: excess mortality was strikingly higher in severe TBI (41.8 vs. 22.2%; RR 1.88 [95% CI 1.31-2.70]) vs. no significant difference in moderate TBI patients. **GRADE: low quality evidence (in favour).**

Two additional studies were analyzed. One multicenter propensity score adjusted study (n=5400) [22] and one retrospective single-center study (n=42) [23] in SAH patients found that albumin use was associated with better outcomes. **GRADE: very low quality evidence (in favour).**

Question 2: *Is there evidence on efficacy and safety of synthetic colloids compared to crystalloids?*

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading hence corresponds to the body of evidence grading.

One single-center propensity score matching study (n=123) in *SAH patients* found that colloids (plasma, dextran, starch and/or albumin amongst 41 patients) were associated with significantly worse NIHSS scale [24]. **GRADE: low quality evidence (against).**

Two additional studies were analyzed. One study, examining data from *SAH patients* recruited from two RCTs (n=160) found that the cumulative daily colloid dose (4% gelatin or 6% penta-starch) was associated with worse 6-month Glasgow Outcome Score (GOS: adjusted OR 2.53 [95% CI 1.13-5.68]), while crystalloids (L/day) promoted favorable recovery (adjusted OR 0.27 [95% CI 0.11-0.67]) [25] **GRADE: very low quality evidence (in favour)**.

In *severe TBI patients*, Cox proportional hazard modeling of single-center data (n=171) found no association between cumulative penta-starch dose and mortality [26]. **GRADE: very low quality evidence (against).**

Question 3: *Is there evidence on efficacy and safety of balanced crystalloid solutions compared to standard crystalloids?*

No studies considered robust outcomes as survival and good neurological recovery.

Two small single-center RCTs, one in *SAH patients* (n=36) [27] and another one in *TBI patients* (n=41) [28] found that, compared to NS, balanced solutions reduced the rate of hyperchloremia (a secondary outcome in our revision design). Despite the body of evidence was considered *low* (high degree of imprecision due to the small sample size and the risk of inflated effect [29]), a protective, although quantitatively small, effect of balanced solutions appears highly plausible. The studies had a sufficiently homogenous design to allow a meta-analysis (Figure in ESM). **GRADE: low quality evidence (in favour).**

In addition, one RCT in *TBI patients* (n=34, two centers) found that Ringer-lactate significantly reduced serum sodium and osmolarity compared to hypertonic saline, however average serum sodium and osmolarity (148 mEq/L and 320 mOsm/L, respectively) were never into the high range with the use of both fluids [30]. **GRADE: very low-quality evidence (in favour).**

Question 4: *Is there evidence on efficacy and safety of infusions of hypertonic fluids compared to isotonic fluids, given as resuscitation solutions?*

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading hence corresponds to the body of evidence grading. Importantly, all studies were performed in *TBI patients*.

One RCT comparing a bolus infusion (250 mL) of 7.5% HTS to RL (n=113 patients in each group) given in the pre-hospital setting reported no differences in 6-month mortality and GOS [31]. **GRADE: high quality evidence (against).**

Baker et al. in a RCT (n=64) compared 7.5% HTS/6% dextran solutions to NS (given as a single 250 mL resuscitation dose) and found no significant difference in 30-day mortality and GOS [32]. **GRADE: low quality evidence (against).**

Shackford et al. in a RCT (n=34, two centers) comparing 1.6% HTS to RL for resuscitation purposes reported no significant difference in GOS at hospital discharge [30]. **GRADE: very low quality evidence (against).**

1.2 FLUIDS FOR THE GENERAL MANAGEMENT OF ABI PATIENTS: RECOMMENDATIONS.

A total of 20 recommendations (8 strong and 12 weak recommendations) could be formulated. All are summarized in Table 1.

2. HYPEROSMOLAR FLUIDS FOR THE MANAGEMENT OF ELEVATED ICP

2.1. Analysis of the available evidence

Question 1*: Are available hyperosmolar fluids effective in reducing ICP?*

RCT's

We found one comparative RCT (60 patients, 2 centers) in severe TBI patients showing that hypertonic lactate, administered as a continuous prophylactic infusion over the first 48 hours from ICU admission, was more effective than NS in preventing episodes of elevated ICP (>20 mmHg) (% ICP reduction 30% [95% CI -50.4 to -4.8 %]; NNTB 3 [95% CI 2-21]) [33].

Observational studies

Despite limitations (limited sample size, no adjustments for confounders), a high number of before-after studies investigating the effectiveness of mannitol (MAN) and hypertonic saline (HTS) in reducing ICP across a spectrum of different acute brain conditions were available [34-60], allowing to perform specific meta-analysis to examine whether a common trend could be determined. The dedicated PubMed search code, the studies selection criteria, and the methodology used for meta-analysis and meta-regression are extensively reported in the ESM.

The flow chart of selection for inclusion of MAN and HTS studies in meta-analyses and meta-regressions is summarized in Figure in ESM.

Mannitol

Meta-analysis revealed that MAN resulted in an 11.4 mm Hg reduction in ICP (95%-CI 8.3-14.5 mm Hg, $p < 0.001$, Figure 1). Heterogeneity was statistically significant (I^2=69%; 95%-CI 38-88%, $p < 0.001$). The sensitivity analysis using high correlation between before and after measurements was consistent with these findings (ESM fig).

By meta-regression, for every 1 mm Hg increase in baseline ICP, MAN bolus yielded an extra 0.55 mm Hg ICP reduction ($p < 0.001$, Figure 2); the heterogeneity estimate dropped to 0% ($p = 0.573$). However, the degree of imprecision was high and this finding should be interpreted with prudence. The meta-regression assuming high correlation provided similar results, but heterogeneity was highly significant ($p < 0.001$), (fig ESM).

Using funnel plots, asymmetry was found to be statistically significant in the meta-analysis (p = 0.005, Figure in ESM) and improved strikingly with the meta-regression (p = 0.897, Figure in ESM), a result confirmed by the sensitivity analysis.

Mannitol dose

By meta-regression, the extent of ICP reduction did not correlate with MAN dose (0.2638 mm Hg per 100 mg, p = 0.711). However, by multivariable analysis after adjusting for initial ICP, the relationship of MAN dose with ICP was close to statistical significance in the main analysis (p = 0.065, **Table 1**) and was statistically significant in the less conservative sensitivity analysis (p = 0.0193, Table ESM). Obviously, heterogeneity p values had an opposite behaviour, with absence of statistical significance in the main analysis and highly significant heterogeneity in the sensitivity analysis. The results of this analysis should be treated with the greatest of caution because an insufficient number of studies were included in the model.

Hypertonic saline.

Hypertonic saline resulted in an average 8.8 mm Hg ICP reduction (95%-CI 6.5-11.1 mm Hg, $p < 0.001$, Figure 3). Heterogeneity was high (I^2=77%, 95%-CI 45-94, $p < 0.001$). The meta-regression using baseline ICP with post-HTS ICP reduction produced a statistically significant result (slope 0.343, p = 0.040), despite heterogeneity (CI 0-91%, Figure 4) and two studies with Cook distances of 3.4 and 1.8 that strongly influenced the slope.

In summary, there is enough evidence to conclude that MAN and HTS are both effective in reducing ICP. **GRADE: low quality evidence (in favour).**

Question 2: *Is there any evidence that hyperosmolar fluids have different efficacy (more or less effective) in reducing ICP?*

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading hence corresponds to the body of evidence grading. Heterogeneity in study design, mainly treatment protocols, did not allow us to perform a meta-analysis. Results were also heterogeneous and are reported in detail in the ESM.

Nine RCTs were found, comparing different hyperosmolar fluids administered as infusion boluses to treat elevated ICP: six studies were performed in *TBI patients* [35, 38, 61-64], two studies with an heterogeneous population of *TBI and SAH patients* [65, 66] and one study with *AIS patients* [57]. Eight studies compared MAN to HTS [35, 38, 57, 62], and one study compared MAN to HTL [61]. Evidence from all these RCTs (besides one [57]) was equally rated. **GRADE: low quality evidence (in favour or against according to specific study findings).**

One observational study comparing hypertonic drugs was found [67].

RCTs comparing hypertonic fluids given in equiosmolar doses (7 studies, N=186 patients)

One study (n=9 in a crossover design, single-centre) found that 7.5% HTS/6% dextran vs. 20% MAN yielded a greater ICP reduction at 60 min (-5 mmHg [95%-CI -10.8 to – 3], *p* 0.014) [65], while four other studies (n=20 [38], n=47 [35], n=38 [62], n=29 [63]) found that 7.5%, 3%, 15% HTS and 20% MAN were equally effective in reducing ICP. One study (n=9) investigating ICP reduction using 7.5% HTS/6% dextran and 20% MAN, did not compare the two groups with formal statistical tests and received a *very low* evidence grading [57].

Ichaï et al. (n=34, single-centre) found that half-molar hypertonic lactate was more effective than 20% MAN in reducing elevated ICP, however the difference in ICP decrease at 4 hours in favour of hypertonic lactate (2.7 mmHg), although statistically significant, was of limited clinical relevance [61].

RCTs comparing hypertonic fluids given in non equiosmolar doses (2 studies, n=52 patients)

In these studies, HTS osmotic charge was higher than that of MAN, therefore favouring HTS. Vialet et al. (n=20, single-centre) found that 7.5% HTS was more effective than half the osmotic dose of 20% MAN in reducing the daily number of episodes with elevated ICP <25 mmHg (6 vs. 13) [64]. A second study (n=32) found a statistically significant ICP percentage reduction with HTS/HES 200/0.5 compared to 15% MAN,[66].

Observational studies comparing hypertonic fluids

We found an additional multicentre observational study that reported superiority of 3% HTS over 20% MAN in reducing ICP. Evidence provided by this study was rated as **very low quality (in favour)** [67].

Question 3: *Is there evidence supporting the use of hyperosmolar fluids without ICP monitoring?*

One RCT performed on *ICH patients* (n=24) found that MAN and HTS had comparable effects on shift reduction as measured by MRI [68]. A second RCT in *severe AIS patients* (n=9) found that MAN and HTS had comparable effects on CBF increase measured by PET [69]. **GRADE: very low-quality evidence.**

Several observational studies investigated the effects of hyperosmolar fluids (MAN or HTS) in patients in whom monitoring consisted of trans-cranial Doppler [41, 59, 70], positron emission tomography [36, 55], Xenon-CT [59, 71, 72], CT scan (to measure brain volume and shift, water content) [44, 73-76] or EEG [77]. **GRADE: very low-quality evidence.**

Question 4: *Is there evidence that hyperosmolar fluids used improve outcome?*

Randomized controlled trials

The RCTs were heterogeneous and could not be combined in a meta-analysis. Their individual grading hence corresponds to the body of evidence grading.

One multicentre RCT performed in *TBI patients* (n=226) found that pre-hospital resuscitation with HTS vs. NS did not change 6-month GOS-E [31].**GRADE: high quality evidence**.

One RCT performed on *TBI patients* (n=60; two centers) and found that prophylactic half-molar hypertonic lactate although significantly reducing the number of episodes of ICPO increase over 20 mmHg it did not improve 6-month outcome compared to NS [33]. In a previous study in *TBI patients*, hypertonic lactate, given to treat elevated ICP, was associated with better 12-month outcome compared to MAN (69 vs. 35%), a barely non significant results (*p* 0.084) [61]

In another RCT in *TBI patients*, there was no mortality difference between 20% MAN and 7.5% HTS used to treat elevated ICP>15 mmHg [35].

The three RCTs were equally downgraded for methodological limitations. **GRADE: low quality evidence (in favour or against according to the study findings)**.

Observational studies

One study using a propensity-score matched design applied to data from *ICH patients* included in the INTERACT-2 trial found no significant outcome difference between MAN-treated (n=1533) and non-MAN treated (n=993) group [78]. **GRADE: low quality evidence**.

One study reported that MAN may negatively affect *AIS patients* outcomes [79], while in another study HTS/dextran improved survival of *TBI patients* with hypotension [80]. **GRADE: very low quality evidence**.

2.2 HYPEROSMOLAR FLUIDS FOR THE MANAGEMENT OF ELEVATED ICP: RECOMMENDATIONS.

A total of 9 recommendations (2 strong recommendations, 7 weak recommendations) could be formulated (see Table 1).

3. FLUIDS FOR THE MANAGEMENT OF CEREBRAL ISCHEMIA

3.1. Analysis of the available evidence

Question 1: Is there evidence to prefer specific fluids (crystalloids/colloids) in the prevention of DCI (CBF or clinical) in SAH patients?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading hence corresponds to the body of evidence grading. We considered studies focused on the prevention of new secondary cerebral ischemic events, i.e. vasospasm and DCI and its consequences, in SAH patients. We report separately RCTs and observational studies.

Randomized controlled trials.

Compared to normovolemia (2L/day crystalloids), triple H therapy (4 L/day hypervolemic hypertensive haemodilution fluid therapy, including colloids and crystalloids) did not change the proportion of patients with vasospasm signs on TCD, regional CBF, and 1-year GOS (n=32 patients, 2 centres) [81]. Lennihan et al. (n=82 patients, single-centre) similarly found no improvement of regional and global CBF, or differences in the rate of vasospasm and cerebral infarction between prophylactic hypervolemic therapy (including colloids and crystalloids) and normovolemic therapy [82]. **GRADE: very low-quality evidence (against).** A third RCT was not included in our analysis because it combined multiple interventions (including volume expansion) for the prevention of vasospasm, thus not providing reliable information of single elements of the therapeutic approach [83].

Observational studies.

We included 13 observational studies, all single-centre, including small sample sizes and having heterogeneous treatment protocols and outcomes. It was therefore not possible to combine them in a single body of evidence. We made a detailed reporting of our grading process only for six studies using statistical techniques to adjust for confounding factors: several studies found that higher fluid volumes and positive fluid balance were associated with worse morbidity and neurological outcomes [22, 84, 85] (see also chapter 1).

When examining studies specifically addressing the DCI phase, Ibrahim et al., using a propensity-score matched analysis on 123 patients found that the administration of colloids and a positive fluid balance were associated with significantly worse outcomes [24].

Another study (n=288 patients), also specifically addressing DCI and adjusting for confounders with propensity scores, found that positive fluid balance was associated with poor functional outcome [86]. Among studies not performing statistical adjustment for confounders, six examined the effect of fluid therapy on CBF and CBF surrogates. Hypervolemia (using colloids and crystalloids) modestly increased regional CBF but without improving $PbtO_2$ [87]. Volume expansion with HTS was associated with an improvement of $PbtO_2$ and CBF [71, 88, 89]. In contrast, volume expansion with albumin was associated with a CBF decrease [90], while NS had no effect on CBF [91].

All the studies were equally downgraded. **GRADE: very low quality evidence (in favour or against according to the study findings).**

Question 2: Does fluid therapy in the management of DCI influence outcome?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading hence corresponds to the body of evidence grading.

A multicenter RCT *AIS patients* (n=1267) found that haemodilution (by venisection followed by dextran replacement) vs. standard treatment did not change 6-month outcome [92]. **GRADE: moderate quality evidence (against)**.

In *AIS patients* (N=193) daily fluid intake > 1650 ml was associated with malignant brain oedema (OR 13.86 [95 % CI 5.11–37.60]) [93]. **GRADE: very low quality evidence (against).**

Additional observational studies (not performing any statistical adjustment for confounders, using small sample size and heterogeneous design to be assessed with a meta-analytical approach) are listed below for, at best, hypotheses-generating purposes:

- *CBF*: In patients with SAH and vasospasm, boluses of NS (n=6) [94] or HTS (n=35) [59] significantly improved CBF, whilst hypervolemia (albumin, dextran, and 10% glycerol) normalized CBF in the cerebral hemisphere where perfusion was reduced by vasospasm [95]. In contrast, volume expansion with colloids and albumin [96] and isovolemic hemodilution obtained by venisection and infusion of albumin and dextran [97] did not increase CBF.
- *Clinical endpoints*: Two studies found that hypervolemia (albumin, glycerol, dextran, or plasma) targeted to hemodynamic monitoring (Swan-Ganz catheter) [98, 99] led to neurologic improvement and absence of progression to infarction in most patients. Several limitations (small sample size, absence of an instrumental diagnosis of vasospasm, no specific definition of teatment, and lack of adjustment for confounding factors) preclude any definitive conclusion.

Question 3: Is there enough evidence to prefer specific fluids (crystalloids/colloids) in the management of cerebral ischemia for CBF augmentation/clinical outcome?

One observational study (n=160 patients) found that colloid dose (L/day) was associated with unfavourable 6-month GOS (OR 2.53 [95% CI 1.13-5.68]), while at the contrary crystalloids were associated with a reduced likelihood of unfavourable outcome (OR 0.27 [95% CI 0.11-0.67]) [25]. **GRADE: very low quality evidence (against)**.

Question 4: Is brain monitoring useful as a trigger or endpoint to guide fluid therapy in the management of DCI?

One study on *SAH patients* (n=10) found that albumin (250 mL fluid bolus) increased cardiac index an improve $PbtO_2$ [100], however the limited sample size, despite using multivariable approach to account for multiple measurements, raises internal and external validity issues. **GRADE: very low quality evidence (in favour).**

Question 5: Should a change in neurological status trigger a modification in fluid management away from normovolemia in patients with cerebral ischemia?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading hence corresponds to the body of evidence grading.

Two studies treated new neurological symptoms in *SAH patients* with hypervolemia (albumin, glycerol, dextran, or plasma). A subset of patients were monitored with Swan-Ganz catheter: neurologic improvement and absence of progression to infarction in most cases led the authors to conclude that hypervolemic therapy was effective [98, 99]. The two studies, however, had very

serious limitations connected to the small sample size, to the absence of a instrumental diagnosis of vasospasm, no specific definition of teatment, and lack of adjustment for confounding factor. **GRADE for both studies: very low quality evidence (in favour).**

Question 6: Is there a place for early-goal directed fluid therapy in the management of DCI?

One RCT in *SAH patients* (n=160), comparing fluid management targeted to keep high global end-diastolic volume index (GEDI, measured by trans-pulmonary thermodilution) vs. standard management found no effect on DCI and 3 moths poor outcome frequency [101]. A predefined analysis on high-grade SAH patients that were stratified at randomization, showed a statistically significant reduction of both outcomes. However, according to our calculation that used the same statistical tests as the authors neither result was statistically significant (p=0.10 for DCI and p=0.07 for 3-month poor outcome). **GRADE: moderate quality evidence (against)**.

Three observational studies, using logistic regression models, found that trans-pulmonary thermodilution (with the use of Cardiac Function Index [102] and GEDI [103, 104]) was associated with better outcomes. **GRADE: very low quality evidence (in favour)**.

3.2 FLUIDS FOR THE MANAGEMENT OF CEREBRAL ISCHEMIA: RECOMMENDATIONS.

Two recommendations (1 strong recommendation, 1 weak recommendation) could be formulated (see Table 1).

A summary of all RCT's on fluid therapy in NIC patients is given in Table 2.

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Table 1: Summary of recommendations (see methods for details). Strong recommendation (for or against) >80% of voting members. When votes for or against (a mix of strong and weak options) didn't reach the 80% threshold, then a weak recommendation was provided. In case of minor concerns panel members could declare reservation. In case of major concerns a stand aside position was adopted.

	RECOMMENDATIONS
FLUIDS FOR THE GENERAL MANAGEMENT OF ABI PATIENTS	**1.** We recommend the use of crystalloids as preferred maintenance fluids in ABI patients (Strong recommendation). **2.** We do not recommend the use of colloids, hypotonic solutions, glucose-containing hypotonic solutions, or albumin as maintenance fluids in ABI patients (Strong recommendation). **3.** We do not recommend using high-dose albumin solutions in AIS patients (Strong recommendation). **4.** We suggest using crystalloids as first-line resuscitation fluids in ABI patients with low blood pressure (Weak recommendation). **5.** We suggest that synthetic colloids should not be used as resuscitation fluids in ABI patients with low blood pressure (Weak recommendation). **6.** We do not recommend using hypotonic solutions and glucose-containing hypotonic solutions as resuscitation fluids in ABI patients with low blood pressure (Strong recommendation). **7.** We suggest that 4% albumin solution should not be used as resuscitation fluid in ABI patients with low blood pressure (Weak recommendation). **8.** We suggest that 20% albumin should not be used as resuscitation fluid in ABI patients with low blood pressure (Weak recommendation). **9.** We suggest that hypertonic saline solutions should not be used as resuscitation fluids in ABI patients with low blood pressure (Weak recommendation). **10.** We suggest that clinicians consider targeting normovolemia during fluid replacement in ABI patients (Weak recommendation). **11.** We recommend that a multimodal approach, guided by the

	integration of more than a single hemodynamic variable, is used to optimize fluid therapy in ABI patients (Strong recommendation). **12.** We recommend that clinicians consider using arterial blood pressure and fluid balance as the main endpoints to optimize fluid therapy in ABI patients (Strong recommendation). **13.** We suggest that clinicians integrate other variables (such as cardiac output, SvO2, blood lactate, urinary output) to optimize fluid therapy in ABI patients (Weak recommendation). **14.** We do not recommend central venous pressure (CVP) alone as an endpoint for guiding fluid therapy in ABI patients (Strong recommendation). **15.** We do not recommend using restrictive fluid strategies (aiming for an overall negative fluid balance) in ABI patients (Weak Recommendation). **16.** We suggest using fluid balance as a safety endpoint for fluid therapy in ABI patients (Weak recommendation). **17.** We suggest monitoring electrolytes (Na+, Cl-) as a safety endpoint for fluid therapy in ABI patients (Weak recommendation). **18.** We suggest monitoring osmolarity as a safety endpoint for fluid therapy in ABI patients (Weak recommendation). **19.** We suggest that, when available, ICP should be used as a safety endpoint for fluid therapy in ABI patients (Weak recommendation). **20.** We do not recommend using CVP monitoring as safety endpoint for fluid therapy in ABI patients (Strong recommendation).
HYPEROSMOLAR FLUIDS FOR THE MANAGEMENT OF ELEVATED ICP	**1.** We suggest that either MAN or HTS solutions can be used for reducing increased ICP (Weak recommendation) **2.** We do not know whether hypertonic lactate solutions should be recommended as a first-line osmotic solutions for reducing increased ICP (No recommendation) **3.** We suggest that clinicians consider using a pre-defined trigger for starting osmotherapy to treat elevated ICP (Weak recommendation) **4.** We recommend that clinicians use a combination of clinical

	and neuromonitoring variables for starting osmotherapy to treat elevated ICP (Strong recommendation) **5.** We recommend a combination of neurological worsening (defined as a decrease of 2 points of the GCS motor score, or loss of pupillary reactivity or asymmetry, or deterioration of head CT findings) and ICP > 25 mmHg as a trigger for starting osmotherapy to treat elevated ICP (Strong recommendation). **6.** We suggest using an ICP threshold > 25 mmHg independent of other variables as a trigger for starting osmotherapy to reduce ICP (Weak recommendation). **7.** We are uncertain whether an ICP threshold 20-22 mmHg independent of other variables should be used as a trigger for starting osmotherapy to reduce ICP (No recommendation). **8.** We do not recommend using an ICP threshold of 15 mmHg independent of other variables as a trigger for starting osmotherapy to reduce ICP (Strong recommendation). **9.** We suggest monitoring serum osmolarity and electrolytes to limit the side effects of osmotherapy (Weak recommendation). **10.** We suggest monitoring ICP response to hyperosmolar fluids to limit the side effects of osmotherapy (Weak recommendation). **11.** We suggest monitoring the effects of hyperosmolar fluids on arterial blood pressure and fluid balance as secondary variables to limit the side effects of osmotherapy (Weak recommendation).
FLUIDS FOR THE MANAGEMENT OF CEREBRAL ISCHEMIA	**1.** We recommend assessing the efficacy of fluid infusion in SAH patients with DCI using a multimodal approach that includes arterial blood pressure and reversal of neurological deficit as the main endpoints (Strong recommendation). **2.** We suggest considering reduction of TCD flow velocities, improvements of cerebral perfusion and reduction of mean transit time on CT perfusion as secondary endpoints in assessing the efficacy of fluids for reversal of DCI in SAH patients (Weak recommendation).

Table 2. Summary of randomized controlled trials on fluid therapy in neurointensive care patients.

Reference	Population	Patient nr	Intervention	Control
Fluids for the general management (resuscitation and maintenance)				
Ginsberg, 2013	AIS	N=841	25% albumin	N-Saline
Myburgh, 2007	TBI	N=420	4% albumin	N-Saline
Lehmann, 2013	SAH	N=36	Balanced crystalloids/colloids	N-Saline/HES
Roquilly, 2013	TBI	N=41	Balanced crystalloids/HES	N-Saline/HES
Shackford, 1998	TBI	N=34	1.6% HTS	R-Lactate
Cooper, 2004	TBI	N=226	7.5% HTS	R-Lactate
Baker, 2009	TBI	N=64	7.5% HTS/6% dextran	N-Saline
Hyperosmolar fluids for the management of elevated ICP				
Ichaï, 2013	TBI	N=60	1/2-molar H-Lactate	N-Saline
Battison, 2005	TBI+SAH	N=18	7.5% HTS/6% dextran	20% MAN
Francony, 2008	TBI	N=20	7.5% HTS	20% MAN
Cottenceau, 2011	TBI	N=47	7.5% HTS	20% MAN
Ichaï, 2009	TBI	N=34	1/2-molar H-Lactate	20% MAN

Vialet, 2003	TBI	N=20	7.5% HTS	20% MAN
Harutjunyan, 2004	TBI+SAH	N=32	7.2% HTS/HES 200/0.5	15% MAN
Jagannatha, 2016	TBI	N=38	3% HTS	20% MAN
Sakellaridis, 2011	TBI	N=29	15% HTS	20% MAN
Schwarz, 1998	AIS	N=9	7.5% HTS/6% dextran	20% MAN
Misra, 2007	ICH	N=24	20% MAN	N-Saline
Diringer, 2011	AIS	N=9	23.4% HTS	20% MAN
Fluids for the management of cerebral ischemia				
Egge, 2001	SAH	N=32	Triple H therapy (4L crystalloids/colloids)	Normovolemia (2L crystalloids)
Lennihan, 2000	SAH	N=82	Triple H therapy (crystalloids/colloids)	Normovolemia (crystalloids/colloids)
Italian Acute Stroke Study Group, 1988	AIS	N=1267	Haemodilution (venisection/dextran replacement)	N-Saline
Mutoh, 2014	SAH	N=160	Fluid therapy targeted to transpulmonary thermodilution	Standard management

Abbreviations: AIS, acute ischemic stroke; CBF, cerebral blood flow; GOS, Glasgow Outcome Score; HES, hydroxyl-ethyl starch; H-lactate, hypertonic sodium lactate, HTS, hypertonic saline; ICH, intracerebral hemorrhage; ICP, intracranial pressure; MAN, mannitol; mRS, modified Rankin Scale; N-Saline, normal saline; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury

Figure 1. Meta-analysis examining the efficacy of mannitol in reducing ICP.

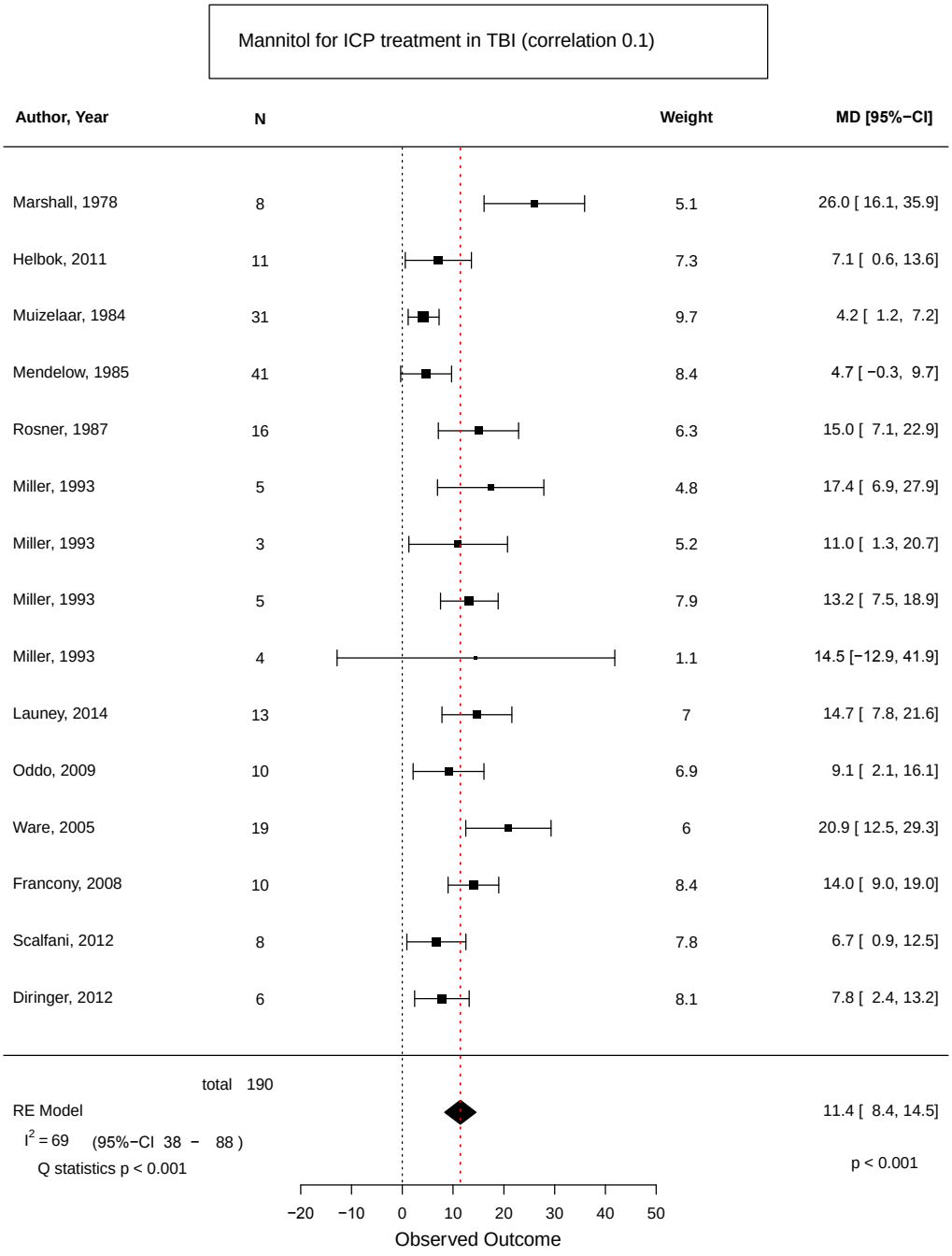


Figure 2. Meta-regression showing the magnitude of mannitol effect on ICP reduction, according to initial pre-treatment ICP.

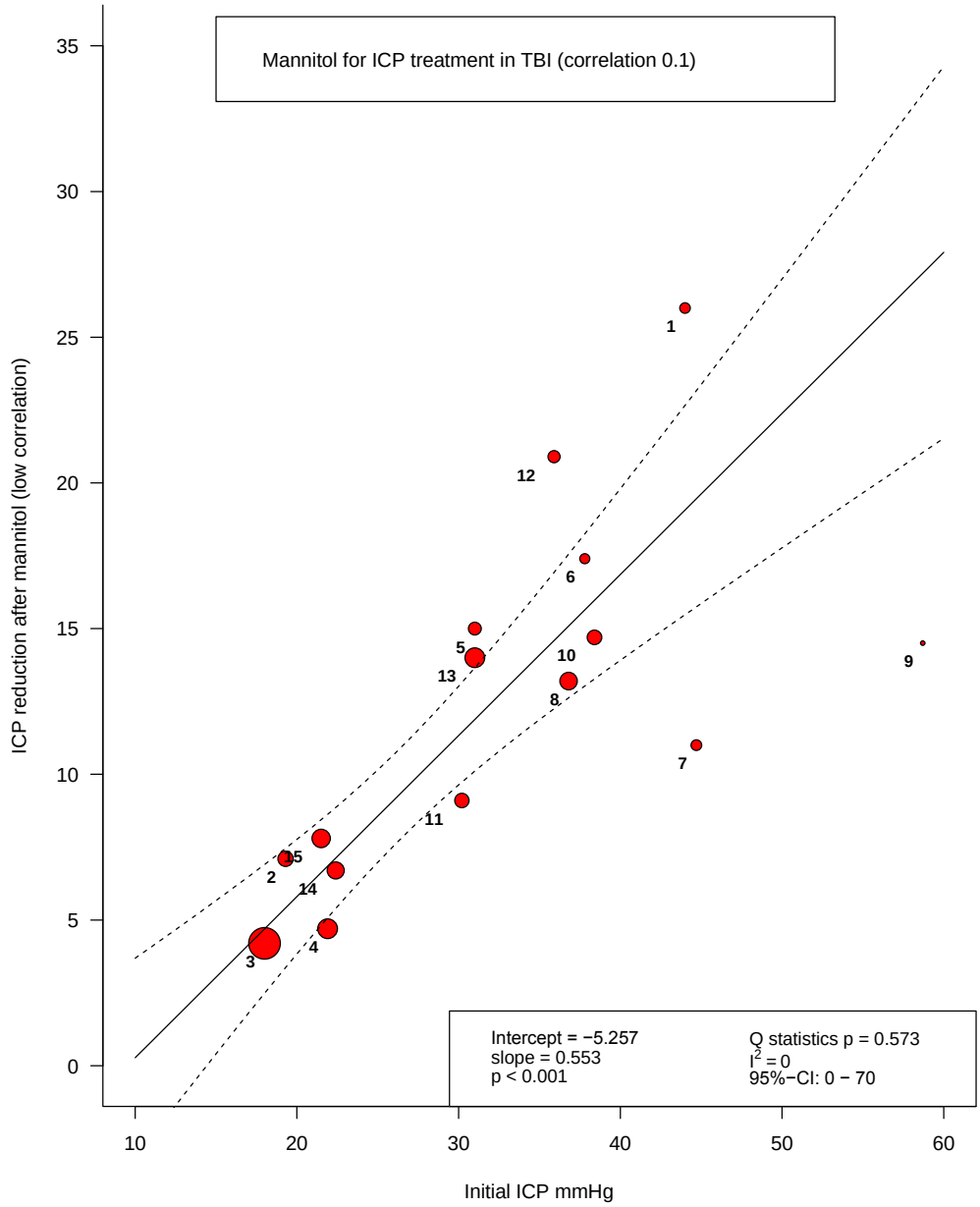


Figure 3. Meta-analysis examining the efficacy of hypertonic saline in reducing ICP.

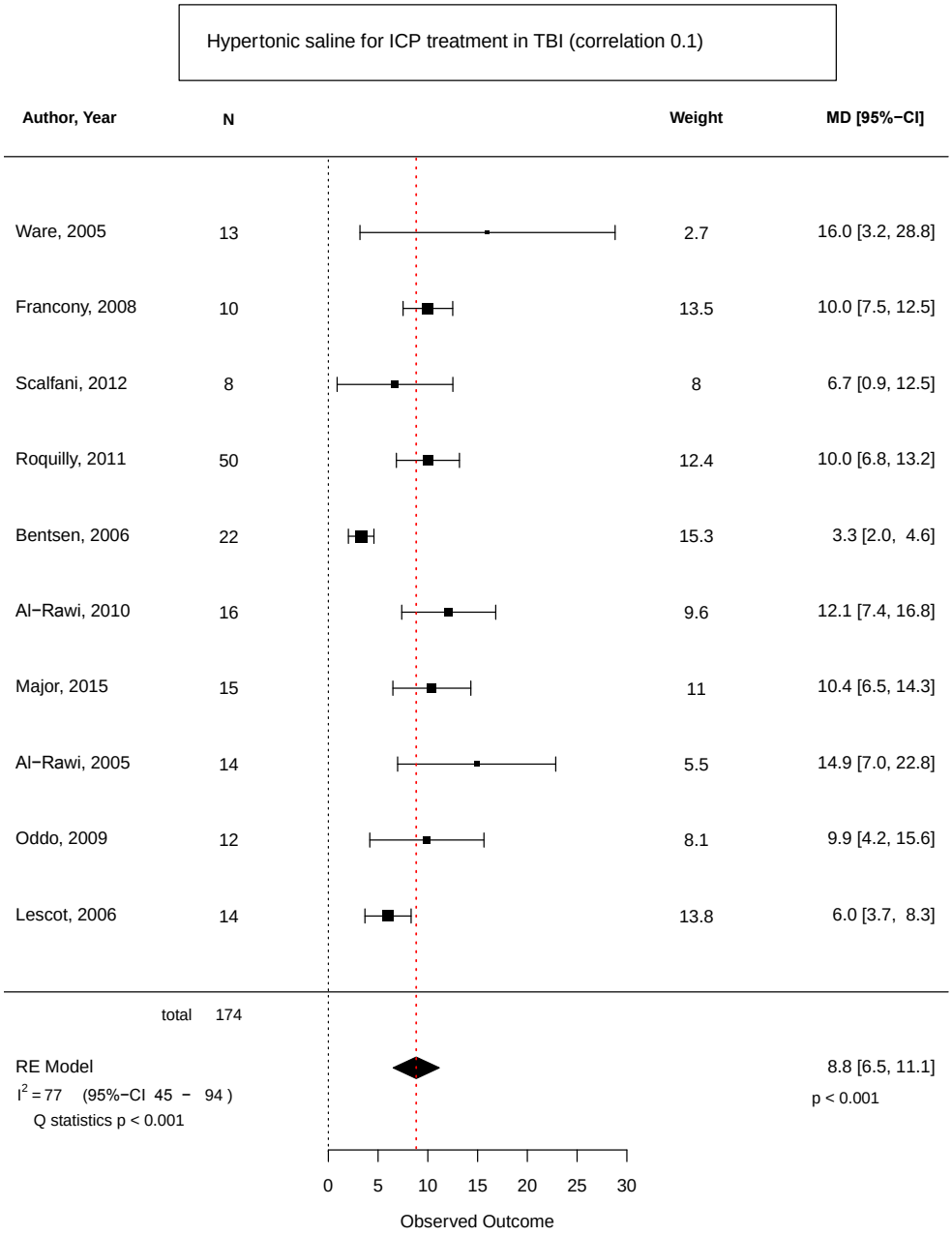
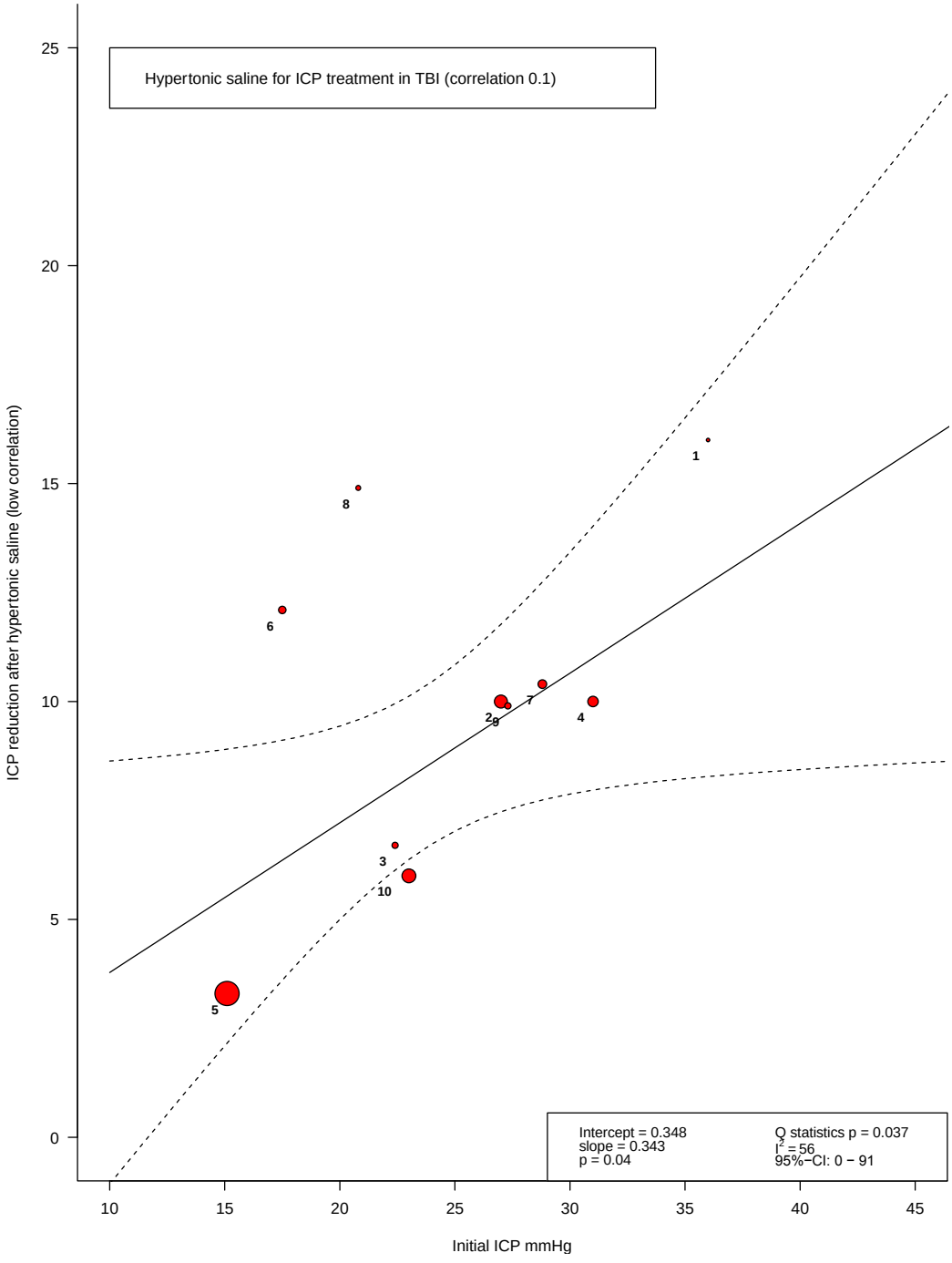


Figure 4. Meta-regression showing the magnitude of hypertonic saline effect on ICP reduction, according to initial pre-treatment ICP.



Electronic Supplementary Material

FLUID THERAPY IN NEUROINTENSIVE CARE PATIENTS: ESICM CONSENSUS AND CLINICAL PRACTICE RECOMMENDATIONS

query and body of evidence grading

query and body of evidence grading

Search strategy

Consistently with the three research topics we searched the MEDLINE database for studies concerning NIC patients and fluid therapy. At least two members of each study group screened the titles, the abstracts, and retrieved the full-texts, and the methodologist (DP) selected the articles that met the inclusion criteria. Data extraction was performed according to a predefined plan, using dedicated electronic forms.

We presented categorical variables as event rates in treatment arms and controls, absolute risks, absolute risk reductions, and relative risks. We reported multivariate analysis results as adjusted odds (OR) or hazard ratios (HR). Numbers needed to treat (NNT) were calculated when appropriate. We calculated confidence intervals (CI) for all the above measures. CI for the NNT include the area of numbers to treat for benefit (NNTB) and the area of NNT to be harmed (NNTH), separated by an infinity value which corresponds to an absolute risk difference of zero. Continuous variables were reported as means or medians, standard deviation (SD) or interquartile ranges (IQR). We represented absolute and relative risks from randomized controlled trials (RCTs) in Forest plots.

When study design was sufficiently homogeneous, we combined studies in meta-analyses and meta-regressions. Heterogeneity was measured with I^2, the percentage of total variation attributable to true heterogeneity and not to chance [1, 2]. We used funnel plots to illustrate graphically presence of asymmetry and potential publication bias. We also used statistical tests to assess asymmetry formally [3], being cautious in their interpretation when significant degrees of heterogeneity (risk of false positive findings), limited number of available studies (lack of power of the test), and similar sample size of studies included in the meta-analysis (absence of meaningfulness of the test) were present [4].

query and body of evidence grading

Evidence grading

We ranked the evidence provided by RCTs and observational studies according to the GRADE criteria, rating evidence quality on a four-level scale ranging from "high" to "very low" [5] . RCTs provide default "high" quality that can be downgraded if bias or other limitations are present. Observational studies are initially rated as "low" quality but can be up- or down- graded depending on specific features. The GRADE system considers crucial adequate control for confounding which implies that when a model purpose is explanatory, at least most known prognostic factors should be measured and included in the model [6-8]. Although GRADE rating has been developed for bodies of evidence, we applied its evidence quality criteria first to single studies and proceeded with body evidence analysis only in a further step. According to GRADE rating, "very low" quality indicates that the degree of the estimate uncertainty of the documented effects is high and incompatible with substantially different true effects (including absence of any effect). We provided a further quality assessment based on statistics reporting ("partial" or "sufficient for quality assessment") and methodological/statistical quality ("low" or "high"). Finally, we verified the existence of external validity issues ("yes" or "no").

We rated evidence quality according to GRADE after verifying that the studies complied with three additional criteria: 1) high quality reporting (rated "partial" or "sufficient for quality assessment, as *per* Consolidated Standards of Reporting Trials [CONSORT] statement for RCTs [9]) and according to indications provided by literature for observational studies [10], 2) absence of methodological and statistical flaws (CONSORT recommendations) and 3) flaws that may affect observational studies, not detailed by the GRADE system such as risk of over-fitting when less than 10 outcomes per variable are available [11, 12], bivariate statistics tests used to screen variables for multivariable analysis [13], abuse of automatic variable selection procedures [14], not accounting for immortal-time bias when dealing with time-dependent treatments [15], not balancing the probability of receiving a specific treatment with propensity scores [16], absence of external validity issues, such as specificity of case-mix, of treatment protocols, of health-care settings [17].

If these criteria were not fulfilled we downgraded the GRADE rating.

The review was conducted complying with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations [18].

query and body of evidence grading

Consensus methodology

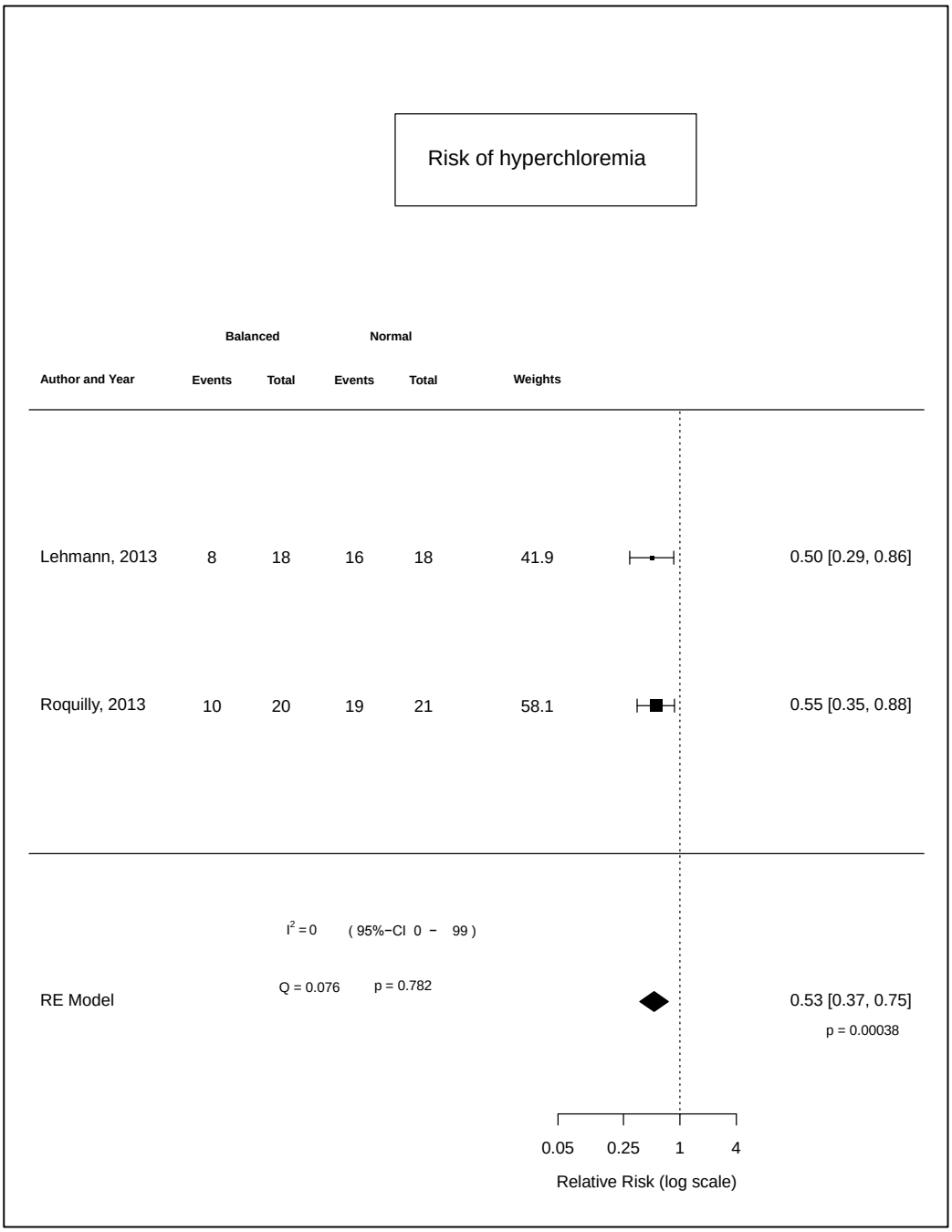
We used a modified Delphi process based on the integration of evidence provided by the literature and expert opinions. All the results of the GRADING of the evidence were available to the panel through a web-based file. The chairs (MO, GC) integrated the initial questions with literature revision and grading, and formulated 4 mutually exclusive questions and 35 questions (clustered in five different sections) requiring a score ranging from 1 (strongly disagree) to 10 (strongly agree). These questions were submitted to the members of the panel through a web-based system. For each question or cluster of questions the experts could provide comments to integrate their answers. The answers were analysed by a non-voting member of the panel (DP). Answers providing scores were analysed as medians, 20th, and 80th percentiles. Further, scores were clustered into low (1-3), intermediate (4-7), and high (8-10), and analysed with correspondence analysis. Both approaches were used to spot answers that provided clear-cut positions among experts, particularly those polarized on agreement or disagreement. Correspondence analysis was used to assess if single members of the panel provided specific response patterns, especially when intermediate positions were taken. The results of the analyses were returned to the panel anonymously. The same list of question was then submitted to the panel in a second round.

On the basis of the analysis of the second round of questions, statements were formulated by the chairs (MO, GC) selecting questions with higher degrees of agreement, and then submitted to the panel. Answers were analysed with correspondence analysis to spot heterogeneity among the panel members. Single panel members, who presented heterogeneous answer patterns, were provided feedbacks on their answers with request to confirm their vote, thereby allowing the detection of misinterpretations of some statements.

A final vote was required for confirmation, with >80% of voting members necessary for a *strong* recommendation (*for* or *against*). When votes *for* or *against* (a mix of *strong* and *weak* options) reached the 80% threshold, then a *weak* recommendation was provided. In case of *minor concerns* panel members could declare *reservation*. In case of *major concerns* a stand aside position was adopted, no blocking option was permitted, and reasons for concerns were reported.

query and body of evidence grading

Figure ESM1. Meta-analysis of studies investigating balanced crystalloids vs. normal saline in reducing the risk of hyperchloremia.



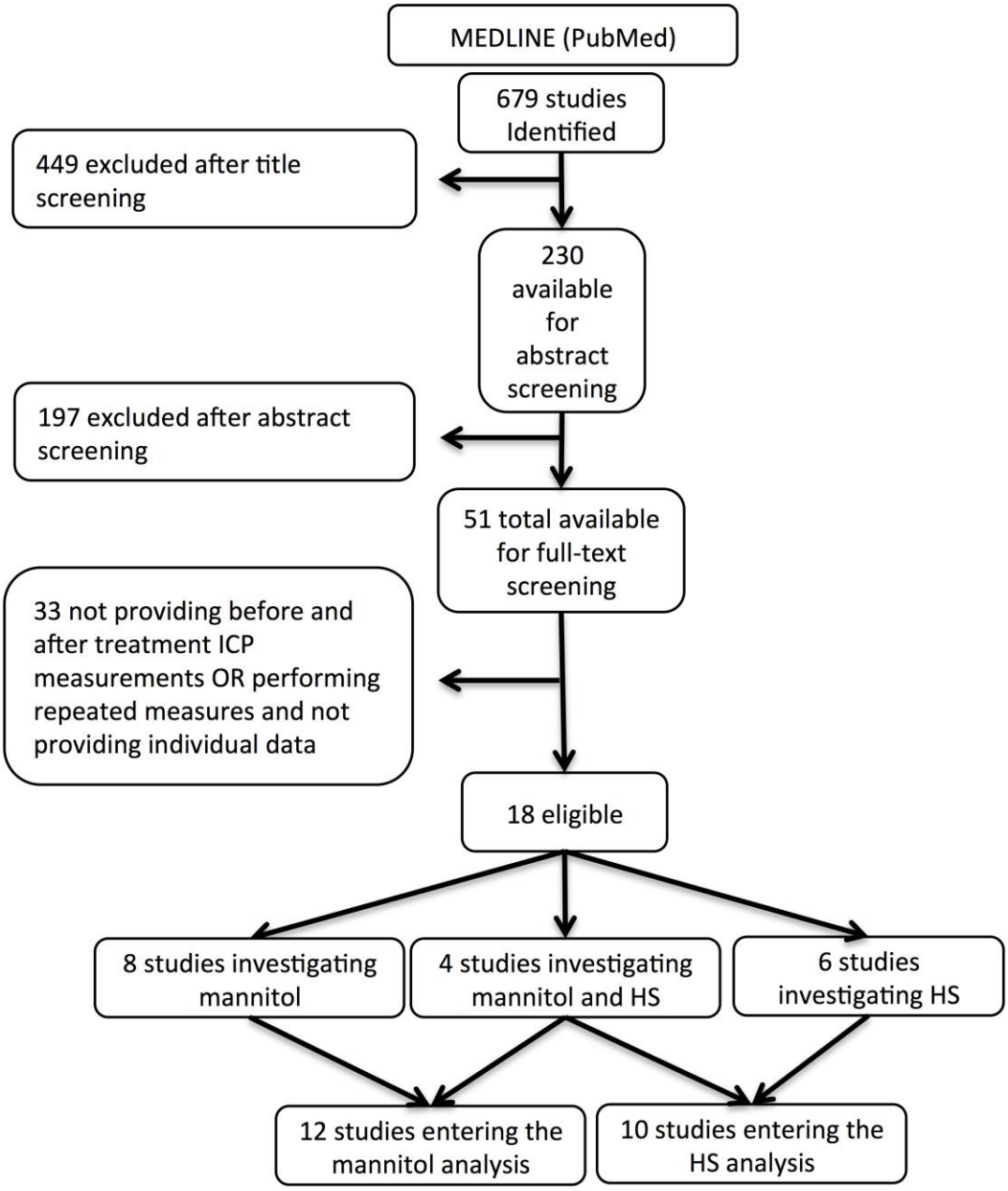
query and body of evidence grading

Figure ESM2. Flow-chart illustrating the process for study selection to be included in the meta-analysis and meta-regression, for examining the effectiveness of MAN and HTS in reducing ICP.

The PubMed search identified 679 titles. Only observational studies were found (Tables SM 2 and 3). A total of 12 studies (n=190 patients) were analysed for MAN (8 investigated MAN only [36, 40, 43, 46-49, 53], 4 MAN + HTS [38, 50, 55, 60]): for 1 study, in which three different doses were tested on the same patients at different times, the highest dose was chosen for inclusion in the analysis [46], and 1 study reported separate average measures for 4 subgroups of patients (therefore each subgroup was considered as an independent study) [48].

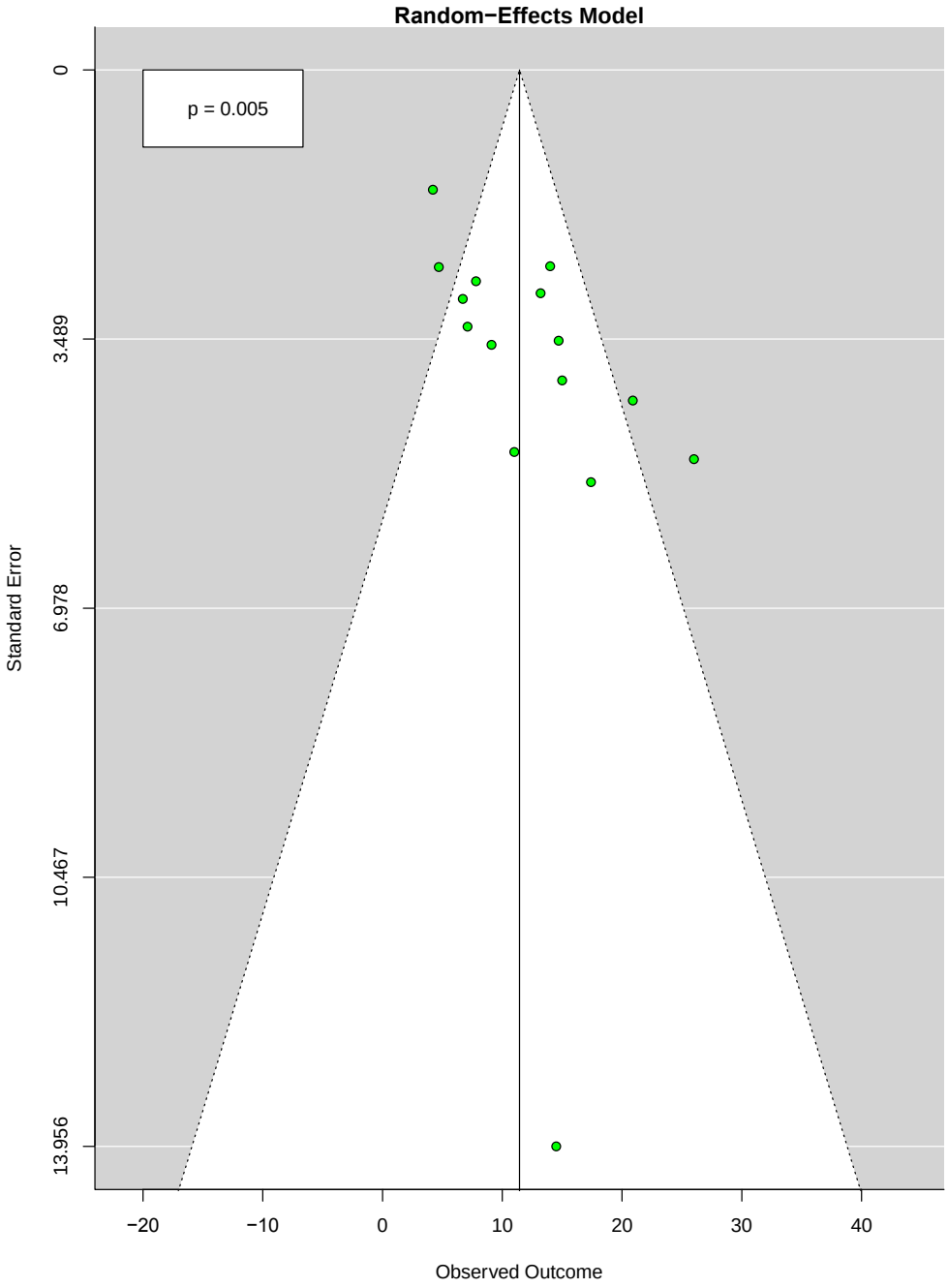
A total of 10 studies (N=174 patients) were analysed for HTS (6 investigated HTS only [34, 44, 45, 52, 71, 88], 4 HTS + MAN). The MAN studies investigated almost exclusively TBI patients (doses 0.25-1.0 mg/kg; ICP values were reported 10-60 minutes following bolus administration in 8 studies, whereas in 3 the lowest ICP value was recorded, and in 1 study the time of the ICP reading was not reported). The HTS investigated TBI in 6 studies and SAH in 2 studies (doses 100-1100 mOsmoL; in 6 studies ICP values were reported 60 minutes following bolus administration, in 1 study at 30 minutes, in 1 study at 5 minutes, while in 2 studies the lowest ICP values were reported).

query and body of evidence grading



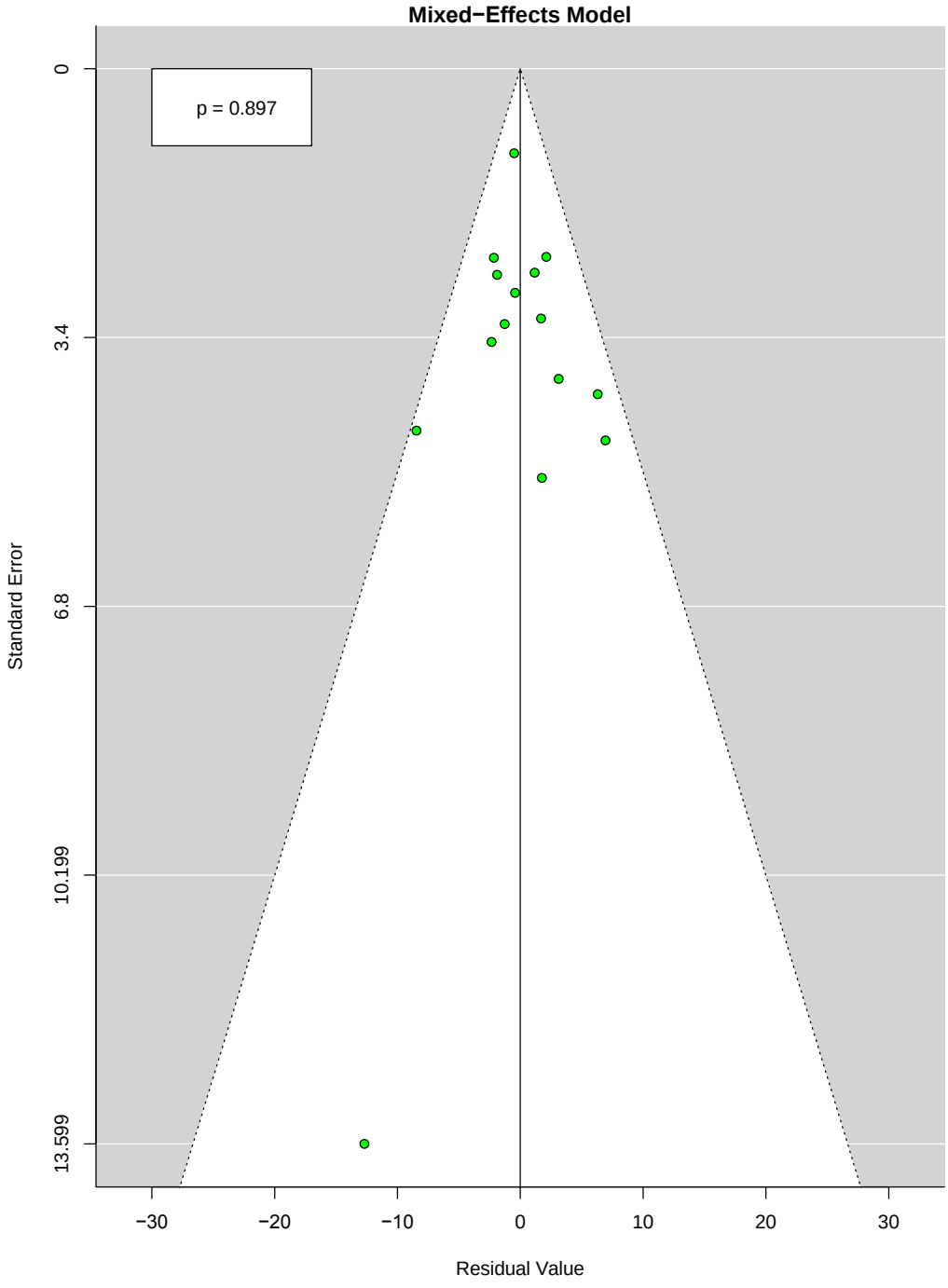
query and body of evidence grading

Figure ESM3. Funnel plot (to be specified)



query and body of evidence grading

Figure ESM4. Funnel plot (to be specified)



query and body of evidence grading

Table ESM 1. Efficacy of mannitol in reducing ICP, accounting for the initial ICP and the MAN dose.

Results of the multivariable meta-regression analysis are shown using low and high correlation to calculate variance between before and after ICP measurements.

	Low correlation		High correlation	
	Estimate	**P value**	**Estimate**	**P value**
Intercept	-13.0148	<.0001	-8.9545	0.1304
Initial ICP	0.6958	<.0001	0.5866	<.0001
Dose	6.3386	0.0623	5.214	0.3145

Table ESM 2. Generalized estimated equations (GEE) model examining the effect of mannitol on ICP reduction variation across studies.

	Estimates	**wald**	***p***
Intercept	19.2	17.82	< 0.001
ICP variation	-9.9	-8.193	< 0.001
Launey [43]	16.7	8.963	< 0.001
Muizelaar [49]	1.2	0.9426	0.34
Oddo [50]	10.7	5.08	< 0.001
Ware [60]	12.6	3.462	< 0.001
The reference study is Helbok et al. **[40]**			

Table ESM 3. Generalized estimated equations (GEE) model examining the effect of mannitol on ICP reduction, according to baseline pre-treatment ICP.

	Estimates	**wald**	***p***
(Intercept)	-4.46	-1.637	0.10
ICP reduction	0.72	5.992	< 0.001
Launey [43]	-8.61	-2.568	0.001
Muizelaar [49]	-3.84	-1.983	0.005
Oddo [50]	-7.62	-3.017	< 0.001
Ware [60]	1.31	0.4505	0.65
The reference is the Helbok et al. study **[40]**.			

SG1 Q1 Is there evidence on efficacy and safety of crystalloid solutions compared to albumin, in the resuscitation of acute brain injury (TBI, SAH, ICH, severe MCA stroke)?

One trial compared the efficacy of high dose albumin vs. saline bolus administered in two hours within five hours from ischemic stroke [1]. The study was interrupted prematurely for futility. Evidence from this study was graded *high*. We considered this study among those focused on resuscitation and not maintenance fluid administration.

A previous observational study suggested that high dose albumin administered within 16 hours from ischemic stroke was strongly protective [2]. We graded this study as *very low* according to the GRADE and confirmed this grading in our final evaluation.

Only these two studies were considered sufficiently homogeneous to contribute to the same body of evidence that was graded (high against effectiveness of high dose albumin in stroke). The following studies, instead, were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

A subgroup analysis from the SAFE trial, reported a striking higher rate of deaths at 24 months in TBI patients treated with albumin compared to saline.[3] As the result of a subgroup analysis the study can only be used for hypothesis generation, and was grades as *low* (GRADE and methodologist final evaluation).

Finally, two observational studies investigating the use of albumin in SAH were downgraded to *very low* quality for several biases.[4, 5] Both studies dealt with fluid maintenance although the use of study fluids for resuscitation was not excluded.

albumin in ischemic stroke – RCT

RCT			
Year	2013	First Author	Ginsberg
Journal	Lancet Neurol		
Sample	Ischemic stroke		
Treatment	High dose albumin (2 gr/kg) within 5 hours from stroke		
Control	Saline		
Outcome	NIHSS and/or mRS 0-1 at 90 (±30) days		
		Outcome	
	n° pz	n	%
Treatment	422	186	44.1
Control	419	185	44.2
Total	841	371	44.1
Centres	5 Centres	delta 0.1 (95%-CI -6.8 to 6.6)	
Power	0.026	NNTB 1300 (95%-CI NNTB 15 to ∞ to NNTH 15)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	Yes
		Bias	No
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		Indirectness	No
		Publication bias	No
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Early stopping: For futility after scheduled interim analysis; Methodological and statistical quality: To have a 0.84 power to detect a 10% reduction of the primary outcome a sample of 980 patients was required. Although the required sample size was not reached, it is unlikely that a clinically significant of the outcome;	
Up-grading			

	GRADE rating	High evidence
	Statistical reporting	Sufficient for quality assessment
	Methodological and statistical quality	High
	External validity issues	No
	Final grading	No grading modification
	Final level of evidence	High evidence

albumin in ischemic stroke – OBS

Observational	3	Very low evidence → No grading modification
Year	2006	
Journal	Stroke	
First Author	Palesch	
Statistical method	Logistic regression	
Inclusion criteria	Ischemic stroke	
Treatment	High dose albumin	
		Outcome
		Good outcome (Rankin scale 3-6 at 90 days): 40 (48.8%)
Centres	2	**Variable: OR 95% CI**
N° patients/centre/year	NA	Albumin HD/LD: 1.81 (1.11-2.94)
Study duration (days)	NA	
Total (included in the model)	82	
	GRADE CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	No
	GRADE overall	
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Adequate control for confounding: The model adjusted only for IPA. Statistical quality: Clearly underfitted model not accounting for important predictors of good outcome.	
Up-grading		
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	No grading modification
	GRADE rating	Very low evidence
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

albumin in TBI – subgroup analysis of RCT

RCT			
Year	2007	First Author	Myburgh
Journal	JAMA		
Sample	TBI patients from the SAFE trial		
Treatment	4% albumin		
Control	0.9% saline		
Outcome	Good outcome (GOS) 24 months after randomization		
		Outcome	
	n° pz	n	%
Treatment	214	71	33.2
Control	206	42	20.4
Total	420	113	26.9
Centres	16 Centres	delta 12.8 (95%-CI 4.3 to 21)	
Power	0.850	NNTH 8 (95%-CI NNTH 23 to NNTH 5)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Sufficient for quality assessment
		Indirectness	No
		Imprecision	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Bias: The study is a subgroup analysis of the SAFE trial. In subgroup analysis the benefits of randomization cannot be extended to subgroups and the study can only be useful for hypothesis generation;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		External validity issues	No
		Final grading	Downgrading
		Final level of evidence	Low evidence

albumin in SAH – OBS

Observational study	1	Very low evidence – Downgraded study
Year	2013	
Journal	JN	
First Author	Kuwabara	
Statistical method	Logistic regression with propensity score adjustment	
Inclusion criteria	SAH undergoing surgical/interventional procedures	
Treatment	Albumin (from procedure to the 4th day)	
		Outcome
		Hospital mortality: 33 (0.6%)
Centres	550	**Variable: OR 95% CI**
N° patients/centre/year	NA	Albumin g/kg/day (continuous) Pre-DCI: 4.39 (0.9-21.37)
Study duration (days)	364	Albumin g/kg/day (continuous) DCI: 2.55 (0.29-22.65)
Total (included in the model)	5400	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	Yes
	Bias	very serious
	GRADE Overall	
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Bias: Data from an administrative database with doubts on the quality of clinical data and missing information. Statistical quality: The 4th day was arbitrarily considered the cut-off for delayed cerebral ischemia, without any direct diagnosis. This assumption substantially biased the study. The reporting is confusing. In the same model we absolute doses and doses adjusted for weight are included. The reported ORs are not consistent.	
Up-grading	Size of effect: High imprecision, result statistically not significant.	
External validity	No external validity issues	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	No
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

albumin in SAH – OBS

Observational study	2	Very low evidence – Downgraded study
Year	2004	
Journal	JN	
First Author	Suarez	
Statistical method	Logistic regression	
Inclusion criteria	SAH, clipped ruptured aneurysm	
Treatment	Albumin	
		Outcome
		GOS 1-4: 43 (51.2%)
Centres	1	**Variable: OR (95%-CI)**
N° patients/centre/year	42	Albumin: 3.2 (1.1-11.0)
Study duration (days)	731	
Total (included in the model)	84	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
	GRADE overall	
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Adequate control for confounding: Important predictors were not included in logistic regression (only age, sex, race, GCS 3-9, and treatment entered the model).. Statistical reporting: Insufficient information on how the model was developed (e.g. variable selection, management of continuous variables) were provided. No information on the fit of the model was available.. Statistical quality: The small sample size hampered the development of a multivariable approach with explanatory purposes. The model was underfitted but it could not include more variables because of the risk of overfitting (there were already only 8 outcomes per variable). No propensity score was developed.	
Up-grading	Size of effect: Large protective effect generated, however, by a potentially biased model. No upgrading indicated.	
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

albumin in SAH – OBS

References

1. Ginsberg MD, Palesch YY, Hill MD, Martin RH, Moy CS, Barsan WG, Waldman BD, Tamariz D, Ryckborst KJ, Alias, Neurological Emergencies Treatment Trials I, (2013) High-dose albumin treatment for acute ischaemic stroke (ALIAS) Part 2: a randomised, double-blind, phase 3, placebo-controlled trial. The Lancet Neurology 12: 1049-1058
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SG1 Q2 Is there evidence on efficacy and safety of crystalloid solutions compared to synthetic colloids (starches, gelofusin), in the resuscitation of acute brain injury (TBI, SAH, ICH, severe MCA stroke)?

Q6 Are there any studies that have compared 2 or more amounts of maintenance fluids, in acute brain injury (TBI, SAH, ICH, severe MCA stroke), a more restrictive versus a more liberal strategy?

Q7 Is there any evidence to support that aiming for a negative fluid balance is superior or inferior to aiming for a positive fluid balance, in acute brain injury (TBI, SAH, ICH, severe MCA stroke)?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

One observational study concerning patients with subarachnoid hemorrhage investigated the effect of colloid administration (plasma, dextran, starch, and/or albumin) and positive fluid balance during the delayed ischemic neurologic deficit (DIND) risk period (3-14 days) [1]. This study answered to

albumin in SAH – OBS

the maintenance Q6 and Q7 queries. The study adjusted for confounders using propensity score matching, *low* quality of evidence for observational studies was thus confirmed.

A second observational study also targeted on subarachnoid hemorrhage, investigated the effect on outcome of colloids and crystalloids used as maintenance fluids reporting a significant increase of 6-month poor outcome with colloids and a protective effect of crystalloids [2]. The study, however, was downgraded to *very low* evidence because of relevant methodological biases. The study answered to the Q6 query.

Two studies investigated fluid balance influence on outcome in SAH patients [3, 4]. The studies were heterogeneous in terms of design but especially in terms of outcomes (a combined outcome of new stroke and hospital mortality in one case, 6-month GOS in the other). The second study, which did not appear to be substantially biases although it had some generalizability issues, indicated a significant influence of positive balance on long-term outcome. The study was graded *low*. The other study was downgraded to *very low*. Both studies provided evidence for Q6 and Q7.

Only one observational study dealt with fluid balance in TBI providing evidence for Q6 and Q7 [5]. The study had several shortcomings and insufficient reporting and was downgraded to *very low*.

Finally, one observational study dealing with traumatic brain injury (TBI) patients investigated the effect of cumulative pentastarch doses [6]. This study answered query Q6 and was also downgraded to *very low*. No studies dealing specifically with resuscitation (query Q2) were found, although those dealing with maintenance were probably using the same fluid administration approach when resuscitation was required.

albumin in SAH – OBS

Observational study	1	
Year	2013	
Journal	NC	
First Author	Ibrahim	
Statistical method	Propensity score matching	
Inclusion criteria	SAH	
Treatment	Colloids (plasma, dextran, starch, and/or albumin)	
		Outcome
		Delayed cerebral infarcts: 60 (48.8%)
Centres	1	Delta 8.7 (95%-CI 14.5 to 21.6)
N° patients/centre/year	NA	NNTH 27 (95%-CI NNTB 7 to ∞ to NNTH 5)
Study duration (days)	365	p = 0.71
Total (included in the model)	123	power 0.057
	GRADING CRITERIA	
	Statistical reporting	Partial
	Methodological and statistical	High
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	Yes
	Bias	No
Up-grading	Size of effect	
	Residual confounding	Does not indicate upgrading
	Dose/response	No
	DETAILS	
Downgrading	Statistical reporting: It is not clear which formal criteria were adopted to establish the adequacy of matching. Methodological and statistical quality: Underreporting of the statistical approach that, however, appears substantially correct. Imprecision: Statistically non significant result. Wide range of the confidence interval.	
Up-grading		
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Low evidence
	Statistical reporting	Partial
	Methodological and statistical	High
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Low evidence

albumin in SAH – OBS

Observational study	2	
Year	2008	
Journal	BJN	
First Author	Tseng	
Statistical method	Logistic regression	
Inclusion criteria	SAH from aneurysmal rupture	
Treatment	Daily colloid (4% succinylated gelatine or 6% pentastarch) dose (L/day)	
		Outcome
		Unfavourable GOS at 6 months: 52 (32.5%)
Centres	NA	**Variable: OR 95%-CI**
N° patients/centre/year	NA	Daily colloid (4% succinylated gelatine or 6% pentastarch) dose (L/day): 2.53 (1.13-5.68)
Study duration (days)	820	
Total (included in the model)	160	Variable: OR2 (95%-CI)
Unfavourable GOS at 6 months	52 (32.5%)	Cristalloids daily dose (L/day): 0.27 (0.11-0.67)
	GRADING CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	Not reported
	Bias	serious
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Statistical reporting: The variables included in the model were not reported and insufficient accounting for confounders could not be ruled out. No information on the fit of the model was available. Methodological and statistical quality: Undereporting.	
Up-grading	Size of effect: No upgrading because the result of a potentially biased model.	
External validity	NA	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Methodological and statistical qu	Low
	External validity issues	No
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

albumin in SAH – OBS

Observational study	4	
Year	2002	
Journal	CCM	
First Author	Clifton	
Statistical method	Logistic regression	
Inclusion criteria	TBI GCS 3-8	
Treatment	96-hour fluid balance: minus 594 ml after enrollment in the trial	
		Outcome
		6-month GOS 3-5: 211 (57.3%)
Centres	11	**Variable: OR p value**
N° patients/centre/year	9	96-hour fluid balance: minus 594: NA 0.0048
Study duration (days)	1338	
Total (included in the model)	368	
	GRADING CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	serious
Up-grading	Size of effect	NA
	Residual confounding	Does not indicate upgrading
	Dose/response	No
	DETAILS	
Downgrading	Adequate control for confounding: Insufficient number of variables for an explanatory model: although some important variables were inlcuded other variables concerning overall severity were omitted. Statistical reporting: No ORs were reported but only p values. Methodological and statistical quality: The model was underfitted..	
Up-grading		
External validity		
Conclusive evaluation	GRADE rating up/down	No grading modification
	GRADE rating	Low evidence
	Statistical reporting	Partial
	Methodological and statistical quali	Low
	External validity issues	No
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

albumin in SAH – OBS

Observational study	5	
Year	2012	
Journal	NC	
First Author	Martini	
Statistical method	Logistic regression	
Inclusion criteria	SAH patients	
Treatment	3-day positive fluid balance	
		Outcome
		Hospital mortality and new stroke: 117 (32.9%)
Centres	1	**Variable: OR (95%-CI)**
N° patients/centre/year	63	3-day positive fluid balance: 1.47 (0.85-2.54)
Study duration (days)	2071	
Total (included in the model)	356	
	GRADING CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	serious
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	No
	DETAILS	
Downgrading	Adequate control for confounding: Variables were selected according to an a priori design. Important predictors however were not included in the model. The inclusion of troponin in the model was not explained. GCS was not included in the model preferring the more subjective Hunt-Hess and Fisher scores. Methodological and statistical quality: The model was underfitted.	
Up-grading		
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Sufficient for quality assessment
	Methodological and statistical	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

albumin in SAH – OBS

Observational	6	
Year	2015	
Journal	JSCD	
First Author	Kissoon	
Statistical method	Logistic regression with propensity score adjustment	
Inclusion criteria	SAH	
Treatment	Net fluid balance	
		Outcome
		mRS score 3-6: 101 (40%)
Centres	1	**Variable: OR (95%-CI)**
N° patients/centre/year	30	Liter increase fluid balance: 1.18 (1.08-1.29)
Study duration (days)	3559	
Total (included in the model)	288	
	GRADING CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	High
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	serious
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not Indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading		
Up-grading		
External validity	Single center study carried out on a wide time span	
Conclusive evaluation	GRADE rating up/down	No grading modification
	GRADE rating	Low evidence
	Statistical reporting	Sufficient for quality assessment
	Methodological and Statistical	High
	External validity issues	Yes
	Final grading	No grading modification
	Final level of evidence	Low evidence

albumin in SAH – OBS

Observational	3	
Year	2011	
Journal	JCC	
First Author	Sekhon	
Statistical method	Cox proportional hazards	
Inclusion criteria	TBI GCS ≤ 8	
Treatment	Cumulative pentstarch volume	
Control	No pentstarch	**Outcome**
		Hospital mortality: 37 (21.6%)
Centres	1	**Quintiles pentastarch (ref 1): OR (95%-CI)**
N° patients/centre/year	29	2: 1.4 (0.43-4.5)
Study duration (days)	2160	3: 1.1 (0.32-2.8)
Total (included in the model)	171	4: 1.2 (0.34-4.1)
	GRADING CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	No
	DETAILS	
Downgrading	Adequate control for confounding: Overfitted model. Methodological and statistical quality: Hospital mortality is not a good outcome when dealing with TBI. The model was clearly overfitted since 115 variables were included when only 37 events (hospital deaths) occured. No propensity score was developed.	
Up-grading		
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Sufficient for quality assessment
	Methodological and statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

query and body of evidence grading

References

1. Ibrahim GM, Macdonald RL, (2013) The effects of fluid balance and colloid administration on outcomes in patients with aneurysmal subarachnoid hemorrhage: a propensity score-matched analysis. Neurocritical care 19: 140-149
2. Tseng MY, Hutchinson PJ, Kirkpatrick PJ, (2008) Effects of fluid therapy following aneurysmal subarachnoid haemorrhage: a prospective clinical study. British journal of neurosurgery 22: 257-268
3. Kissoon NR, Mandrekar JN, Fugate JE, Lanzino G, Wijdicks EF, Rabinstein AA, (2015) Positive Fluid Balance Is Associated With Poor Outcomes in Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis 24: 2245-2251
4. Martini RP, Deem S, Brown M, Souter MJ, Yanez ND, Daniel S, Treggiari MM, (2012) The association between fluid balance and outcomes after subarachnoid hemorrhage. Neurocritical care 17: 191-198
5. Clifton GL, Miller ER, Choi SC, Levin HS, (2002) Fluid thresholds and outcome from severe brain injury. Crit Care Med 30: 739-745
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SG1 ***Q3 Is there evidence on efficacy and safety of balanced crystalloid solutions compared to sodium chloride, in the resuscitation of acute brain injury (TBI, SAH, ICH, severe MCA stroke)?***

Q8 Is there evidence on efficacy and safety of balanced crystalloid solutions compared to sodium chloride, as maintenance fluids in acute brain injury (TBI, SAH, ICH, severe MCA stroke)?

No studies considered robust outcomes as survival and good neurological recovery.

One RCT comparing hypertonic saline and ringer lactate solutions for resuscitation in TBI patients, reported significant higher serum sodium and osmolarity, but the average values were not reported and only illustrated in a graph. Eyeballing the plot it seems that average natremia and osmolarity were never higher than 148 meq/L and 303 mOsm/L, respectively [1]. Evidence was downgraded because of methodological

query and body of evidence grading

drawbacks to *low* according to the GRADE classification. The final grading was however *very low* considering additional parameters as the insufficient reporting and risk overestimation related to the small sample size. The grading report form for this study is available in the SG1 Q4 file.

We also retrieved two small RCTs investigating the effect on chloremia (a secondary outcome in our revision design) of balanced solutions vs. saline administered as continuous infusion to patients with SAH or TBI in the first 48 hours from admission [2, 3]. These studies are thus focused on early fluid administration for maintenance, but their use for resuscitation was not explicitly excluded. We thus considered them for both queries Q3 and Q8. Both studies showed a striking protective effect against hyperchloremia of balanced solutions.

These two studies were downgraded to *moderate* because of their small sample size and imprecision according to the GRADE, and further downgraded to *low* applying criteria not specifically considered by the GRADE classification, in relation to the risk of having an inflated estimate of the true effect due to the limited sample size [4]. We considered the different kind of brain injuries objective of the studies were uninfluential on the degree of chloremia. Other important features were instead sufficiently consistent and homogenous to allow a meta-analytical approach. The overall body of evidence was considered *moderate* notwithstanding the high degree of imprecision due to the small sample size and the risk of inflated effect, because the results were strongly plausible and consistent between studies. Thus the protective effect of balanced solutions was judged highly probable although the quantitative assessment may have been overestimated.

balanced solutions vs. saline in SAH – RCT

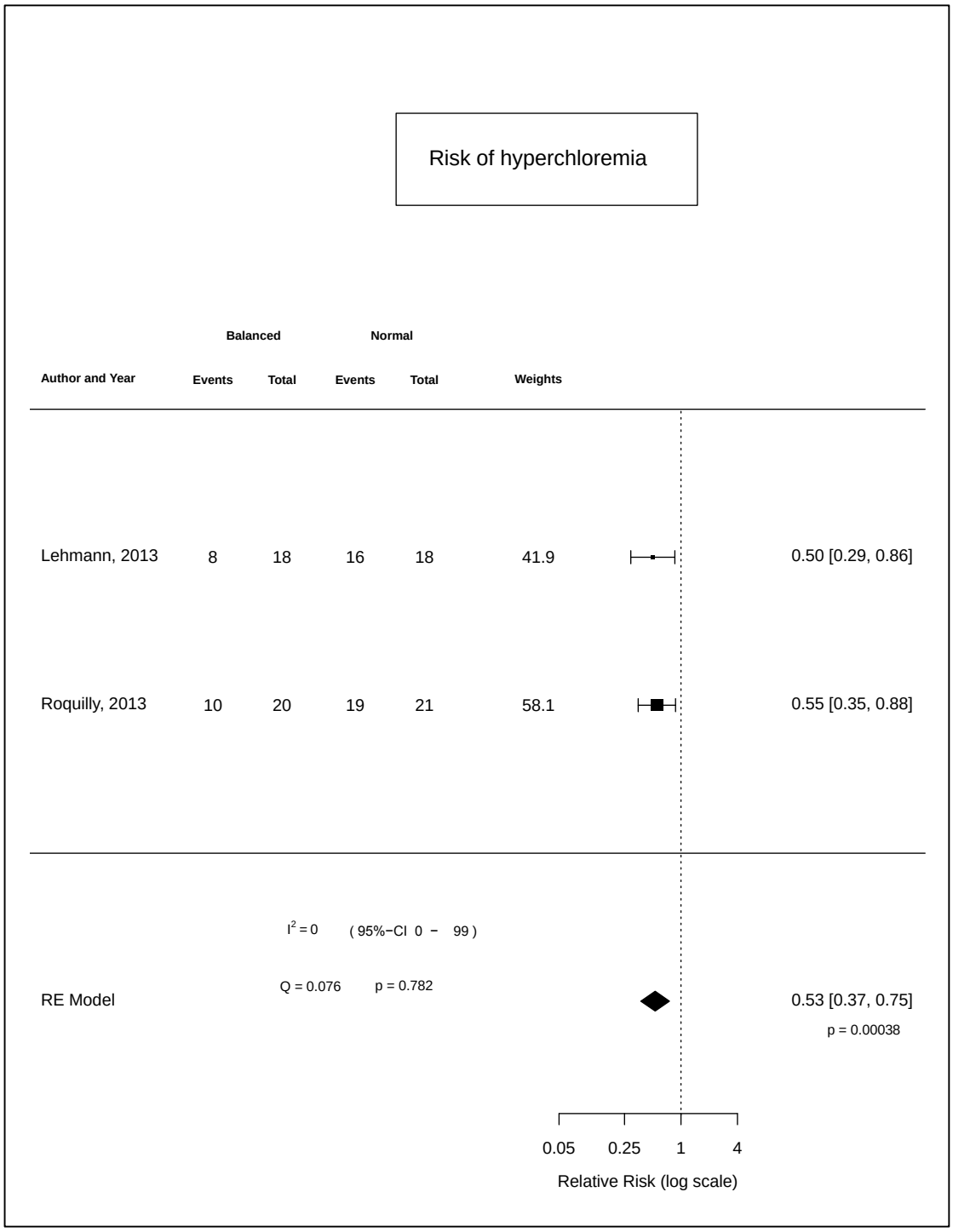
RCT			
Year	2013	First Author	Lehmann
Journal	Neurosurgery		
Sample	SAH		
Treatment	balanced crystalloid and colloid solutions for 48 h		
Control	normal saline and hydroxyethyl starch for 48 h		
Outcome	Chloraemia > 108 meq/L		
		Outcome	
	n° pz	n	%
Treatment	18	8	44.4
Control	18	16	88.9
Total	36	24	66.7
Centres	Single Center	delta 44.4 [95%-CI 65.9 to 13.7)	
Power	0.894	NNTB 2 [95%-CI NNTB 2 to NNTB 7)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Not reported
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Bias	No
		Statistical reporting	Sufficient for quality assessment
		Indirectness	No
		Imprecision	very serious
		Publication bias	Not assessable
		Inconsistency with other trials	No
Up-grading		Size of effect	Large
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Methodological and statistical quality: Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No power calculation was performed. The very low sample size can determin an exagerated statistically signficant effect; Imprecision: The very small sample size determined a large confidence interval;	
Up-grading		Size of effect Large: Not reliable because of imprecision.	
		GRADE rating	Moderate evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

balanced solutions vs. saline in TBI – RCT

RCT			
Year	2013	First Author	Roquilly
Journal	CC		
Sample	TBI (GCS ≤ 8) or SAH		
Treatment	balanced saline and hydroxyethyl starch for 48 h		
Control	normal saline and hydroxyethyl starch for 48 h		
Outcome	Hyperchloraemic acidosis		
		Outcome	
	n° pz	n	%
Treatment	20	10	50.0
Control	21	19	90.5
Total	41	29	70.7
Centres	Single Center	delta -40.5 (95%-CI -61.7 to -12.6)	
Power	0.881	NNTB -2 (95%-CI NNTB -2 to NNTB 8)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	No
		Inconsistency with other trials	No
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Methodological and statistical quality: Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No power calculation was performed. The very low sample size can determin an exagerated statistically signficant effect; Imprecision: The very small sample size determined a large confidence interval;	
Up-grading			
		GRADE rating	Moderate evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

balanced solutions vs. saline in TBI – RCT

balanced solutions vs. saline in TBI and SAH – metanalysis



query and body of evidence grading

References

1. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE, (1998) Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. The Journal of trauma 44: 50-58
2. Lehmann L, Bendel S, Uehlinger DE, Takala J, Schafer M, Reinert M, Jakob SM, (2013) Randomized, double-blind trial of the effect of fluid composition on electrolyte, acid-base, and fluid homeostasis in patients early after subarachnoid hemorrhage. Neurocritical care 18: 5-12
3. Roquilly A, Loutrel O, Cinotti R, Rosenczweig E, Flet L, Mahe PJ, Dumont R, Marie Chupin A, Peneau C, Lejus C, Blanloeil Y, Volteau C, Asehnoune K, (2013) Balanced versus chloride-rich solutions for fluid resuscitation in brain-injured patients: a randomised double-blind pilot study. Critical care 17: R77
4. Ioannidis JP, (2008) Why most discovered true associations are inflated. Epidemiology 19: 640-648

SG1 ***Q4 Is there evidence on efficacy and safety of hypertonic solutions compared to isotonic solutions, in the resuscitation of acute brain injury (TBI, SAH, ICH, severe MCA stroke)?***

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

Two RCTs using different hypertonic solutions in severe TBI, but focused on the same outcome (early GOS) were found.[1, 2] One study comparing 1.6% hypertonic saline to ringer lactate for resuscitation purposes did not report blinding was seriously biased (downgrading to *low* quality according to the GRADE classification).[2] We further downgraded the study to *very low* because of statistical underreporting, absence of power calculation, and high risk of unbalances in important prognostic factors between the study arms because of the small sample size. The second study investigated 7.5%/6% dextrane solutions compared to normal saline.[1] According to the GRADE the study was graded as *moderate*, but downgraded to *low* in our final evaluation, for the same reasons that led to downgrade the previous study.

query and body of evidence grading

Finally, we found RCT comparing 7.5% hypertonic saline and ringer lactate bolus in the prehospital setting in severe head trauma.[3] The trial was of *high* quality according to the GRADE and to our final evaluation.

hypertonic saline vs. ringer lactate in TBI – RCT

hypertonic saline vs. ringer lactate in TBI – RCT

RCT			
Year	1998	First Author	Shackford
Journal	JT		
Sample	TBI any GCS		
Treatment	1.6% hypertonic saline for resuscitation		
Control	Ringer lactate for resuscitation		
Outcome	GOS at hospital discharge		
		Outcome	
	n° pz	GOS at hospital discharge	
		mean	SD
Treatment	18	2.7	0.9
Control	16	2.5	0.8
Total	34	0.2	0.0
Centres	2 Centres		
Power	0.096	p value ns	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Not reported
		Blinding	Not reported
		Completement of follow-up	Yes
		Early stopping	Not reported
		Bias	very serious
		Statistical reporting	Partial
		Indirectness	No
		Imprecision	Not assessable
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No reporting of allocation concealment or blinding although technically possible; Methodological and statistical quality: No reporting on how randomization was performed. Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms, as demonstrated by the evidence lower mean GCS in the study group (p=0.057). No sample size calculation based on power and effect size was performed. In neurointensive studies longterm (i.e. 6 or 12 months) GOS should be the outcome of choice;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Very low evidence

hypertonic saline vs. normal saline in TBI – RCT

RCT			
Year	2009	First Author	Baker
Journal	JNT		
Sample	TBI GCS ≤ 8		
Treatment	7.5% saline/6% dextran 250 ml (single resuscitation dose)		
Control	0.9% saline 250 ml (single resuscitation dose)		
Outcome	GOS at hospital discharge or at 30 days		
		Outcome	
	n° pz	GOS	
		mean	SD
Treatment	31	3.3	1.4
Control	33	3.3	1.4
Total	64	0	0.0
Centres	Single Center		
Power	NA	p value ns	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Not reported
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	Yes
		Bias	serious
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: Allocation concealment was not reported; Methodological and statistical quality: Sample size calculations were not performed. Very small samle with high risk of unbalances between study and control group. The attempt to adjust for confounders with a multivariable analysis was limited by the small sample size (risk of overfitting) and only age, initial GCS and three biomarkers were included. The statistical reporting concerning this analysis was too scanty. In neurointensive studies longterm (i.e. 6 or 12 months) GOS should be the outcome of choice;		
Up-grading			
		GRADE rating	Moderate evidence
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline vs. ringer lactate– RCT

RCT			
Year	2004	First Author	Cooper
Journal	JAMA		
Sample	TBI GCS ≤ 8 and SAP < 100 mmHg		
Treatment	Prehospital 250 ml hypertonic saline 7.5%		
Control	Prehospital 250 ml ringer lactate		
Outcome	6-months GOSE		
		Outcome	
	n° pz	% ICP reduction at 60 min	
		median	IQR
Treatment	113	5	(3-6)
Control	113	5	(5-6)
Total	226	0	0
Centres	12		
Power	not available	p value ns	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Bias	No
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading			
Up-grading			
		GRADE rating	High evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		External validity issues	No
		Final grading	No grading modification
		Final level of evidence	High evidence

query and body of evidence grading

References

1. Baker AJ, Rhind SG, Morrison LJ, Black S, Crnko NT, Shek PN, Rizoli SB, (2009) Resuscitation with hypertonic saline-dextran reduces serum biomarker levels and correlates with outcome in severe traumatic brain injury patients. Journal of neurotrauma 26: 1227-1240
2. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE, (1998) Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. The Journal of trauma 44: 50-58
3. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J, Investigators HTSS, (2004) Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. Jama 291: 1350-1357

SG2 Q1 Efficacy: do we have osmotic drugs capable of reducing ICP?

Body of evidence evaluation according to the GRADE classification: *low*.
Final evaluation of body of evidence according to integrative parameters: *low*.

Only one trial tested sodium lactate against placebo in TBI comatose patients. Evidence was downgraded to *moderate* according to the GRADE criteria but was further downgraded to *low* when considering other parameters the GRADE does not account for.

Numerous observational studies dealing with mannitol or hypertonic saline for intracranial hypertension treatment in cerebral injuries were found, none of which had sufficient quality and enrolled a sufficient number of patients. We only included studies in which either mannitol or hypertonic saline was administered to adult patients (i.e. those older than 17 years of age) with ICP monitoring before and after osmotic agent administration. No study made adjustments for confounders.

We thus selected those studies with a before-after design reporting ICP values as means and standard deviations, to perform our analysis [1-27]. We further selected

query and body of evidence grading

those studies that did not perform repeated administration of mannitol or hypertonic saline, because we could not account for repeated measures (tables 1 and 2).

After the selection process was concluded, eight studies were available for analysis in the mannitol group [3-7, 9, 14, 19] plus four that investigated both mannitol and hypertonic saline [2, 8, 12, 13]. One study reported separate average measures for four subgroups of patients, so we considered each subgroup as an independent study [19].

Overall, fifteen different studies/patient-clusters and 190 patients were included in the meta-analysis and meta-regression (SM fig. 1). In one study, in which three different doses were tested on the same patients at different times, we arbitrarily chose the highest dose for inclusion in this analysis [5].

Six studies investigating only hypertonic saline remained after the inclusion criteria were applied [20-22, 25, 28, 29]. The meta-analysis and meta-regression was performed on a total of ten studies after adding the four that investigated both osmotic agents, resulting in 174 patients being included in the hypertonic saline analysis (SM fig. 1).

Most studies investigated the effectiveness of both osmotic drugs in patients with TBI.

The overall effectiveness of the two osmotic agents in reducing ICP was assessed using a meta-analytical approach. The meta-analysis required knowledge of the average difference in ICP measured before and after osmotic drugs administration and its sampling variance, but this information was not available for most studies. Sampling variance can be calculated with the following equation:

$$vi = \frac{sdi^2}{ni},$$

where $sdi = \sqrt{sd1i^2 + sd2i^2 - 2 \times ri \times sd1i \times sd2i}$,

$sd1i$ and $sd2i$ are the standard deviation of the outcomes at time 1 and 2 (i.e. before and after osmotic agent administration), ri is the correlation between the outcomes at the two-time points, and ni is the number of treated patients [30]. As ri was not available for most studies, we tested two extremes correlation values, 0.1 and

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0.9, focusing on the results of the first and using the second, less conservative in terms of variance calculation, as a sensitivity analysis.

We performed two analyses on each group of studies, using low (0.1) or high (0.9) correlations between before and after measurements to compute the sampling variance, since we did not have single studies individual measurements to calculate the exact correlation.

Our results are presented in terms of meta-analysis that has several limits, especially heterogeneity of the studies, the paucity of the information available, aside from the intrinsic limits of the meta-analytical approach.

In our analysis mannitol and hypertonic saline turned out to be effective in reducing ICP (figures 1 to 4). Heterogeneity was high and statistically significant.

Although we are dealing with observational studies there are several strengths of our approach parameters First, there is strong plausibility that osmotic drugs are effective in treating intracranial hypertension because of their pharmacokinetics and pharmacodynamics properties [31]. Second, the effects of osmotherapy in clinical practice are evident and reproducible, and this is probably the reason why clinicians continue to use mannitol despite strong warnings against its use in the literature. Third, there is very high consistency among studies that report the ICP-reducing effects of osmotic agents and, fourth, although observational, these studies adopted a before-after design that has several strengths in their relevance to clinical practice. In general, they have the advantage of testing the effects of therapy in the same patient, thus accounting for many patient-related variables. Moreover, in the specific case of intracranial hypertension, they are carried out over a short time frame when other conditions that could influence ICP have a high probability of remaining constant.

In this context, the role of our analysis is to highlight the consistency of results across different studies, as confirmed by the multivariable approach carried out at an individual patient level (although controlling only roughly for centre case-mix and performance).

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A limitation of our analysis is that we could not account for other interventions that might have been performed simultaneously with osmotic drugs administration in situations when ICP had increased to dangerously high levels, such as deepening sedation, draining cerebral-spinal fluid, moderate hyperventilation the patient, or optimizing systemic arterial pressure. Notwithstanding this limitation we argue that the evidence provided by our study, although low according to the GRADE scale, is sufficient to recommend the use of mannitol for the treatment intracranial hypertension and that its use could also reasonably be extended to other clinical conditions besides TBI such as subarachnoid haemorrhage or stroke. It goes without saying that the potential adverse effects of mannitol, such as hypovolemia and osmolarity derangements, must be prevented or treated in all cases.

Mannitol studies

First author, Year	patients	N	dose (g/Kg)	ICP measurement time after bolus (min)	initial ICP (mmHg)	ICP Reduction (mmHg)
Marshall, 1978 [5]	TBI	8	1	lowest	44	26
Helbok, 2011 [3]	SIH	11	1	60	19.3	7.1
Muizelaar 1984 [7]	TBI	31	0.66	25	18	4.2
Mendelow1985 [6]	TBI	41	0.25-0.5	10-20	21.9	4.7
Rosner 1987 [9]	TBI, ICH (3 Pts), neoplasia (1 Pt)	16	1	Lowest	31	15
Miller 1993 [19]	TBI	5	0.5	NA	37.8	17.4
Miller 1993 [19]	TBI	3	0.5	Na	44.7	11
Miller 1993 [19]	TBI	5	0.5	Na	36.8	13.2
Miller 1993 [19]	TBI	4	0.5	Na	58.7	14.5
Launey 2014 [4]	TBI , SAH (3 Pts)	13	0.5	20	38.4	14.7
Oddo 2009 [8]	TBI	10	0.75	30	30.2	9.1
Ware 2005 [12]	TBI	19	0.86 (mean)	Lowest	35.9	20.9
Francony 2008 [2]	TBI, SIH, ISC*	10	0.6	60	31	14
Scalfani 2012 [13]	TBI	8	1	60	22.4	6.7
Diringer 2012 [14]	TBI	6	1	60	21.5	7.8

Table 1: observational studies with a before-after design investigating the efficacy of mannitol in patients with cerebral injuries and increased intracranial pressure.

Hypertonic saline studies

First author, Year	patients	N	%	HS (ml)	mOsmol dose	ICP measurement time after bolus (min)	initial ICP (mmHg)	ICP Reduction (mmHg)
Ware, 2005 [12]	TBI	13	23.4	30	240	Lowest	36	16
Francony, 2008 [2]	TBI	10	7.45	100	254	60	27	10
Scalfani, 2012 [13]	TBI	8	23.4	48 *	384	60	22.4	6.7
Roquilly, 2011 [21]	TBI	50	20	NA	Na	60	31	10
Bentsen, 2006 [22]	TBI	22	7.2	140 §	344	Lowest	15.1	3.3
Al-Rawi, 2010 [28]	SAH	16	23.5	140 §	1125	60	17.5	12.1
Major, 2015 [20]	TBI	15	30	10	102	60	28.8	10.4
Al-Rawi, 2005 [29]	SAH	14	23.5	140 §	1125	60	20.8	14.9
Oddo, 2009 [8]	TBI	12	7.5	250	641	30	27.3	9.9
Lescot, 2006 [25]	TBI	14	20	40	273	5	23	6

Table 2: observational studies with a before-after design investigating the efficacy of hypertonic saline in patients with cerebral injuries and increased intracranial pressure.

mannitol meta-analysis

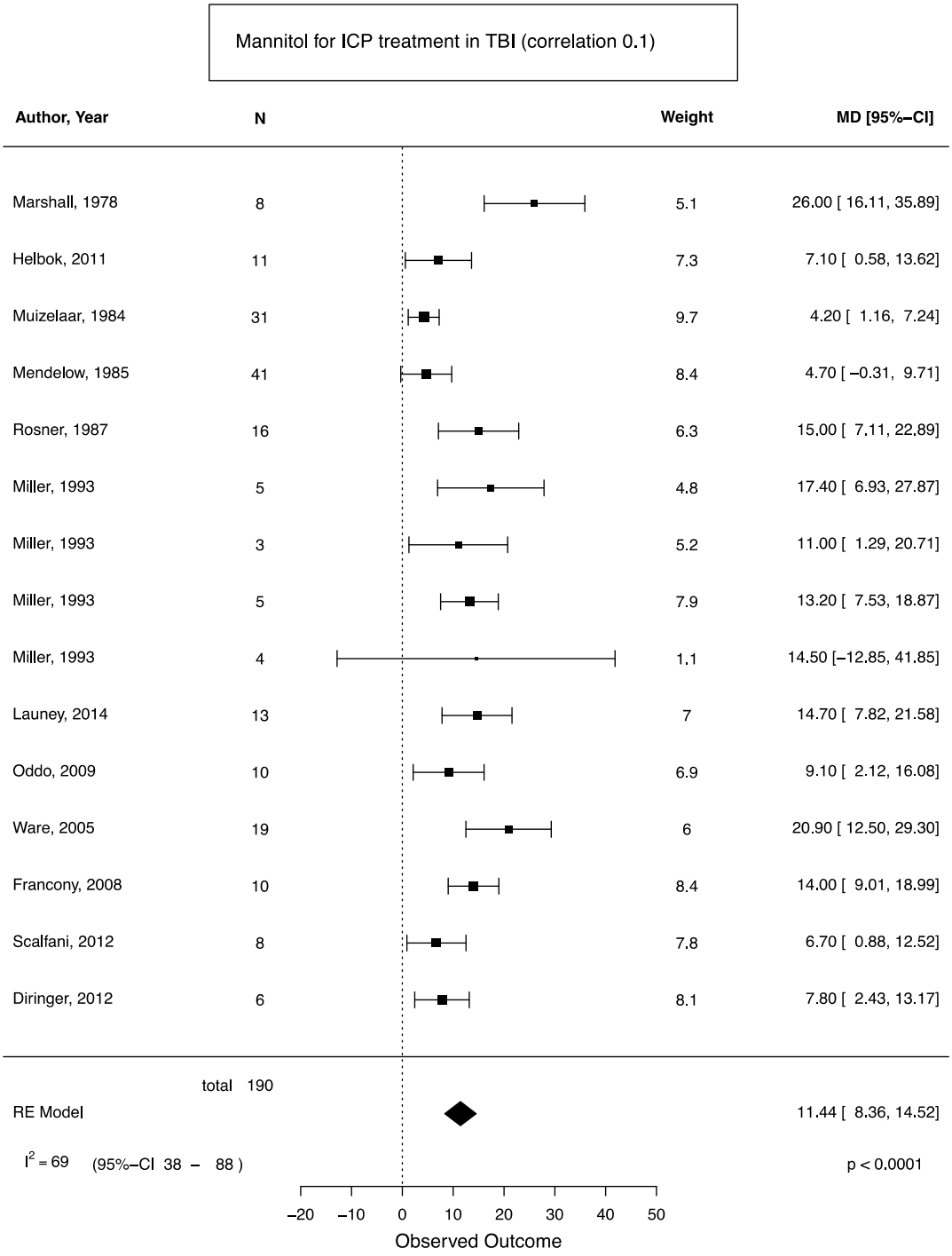

Figure 1: meta-analysis of studies investigating mannitol efficacy in reducing ICP, low correlation between before-after measures was used for variance calculation.

mannitol meta-analysis

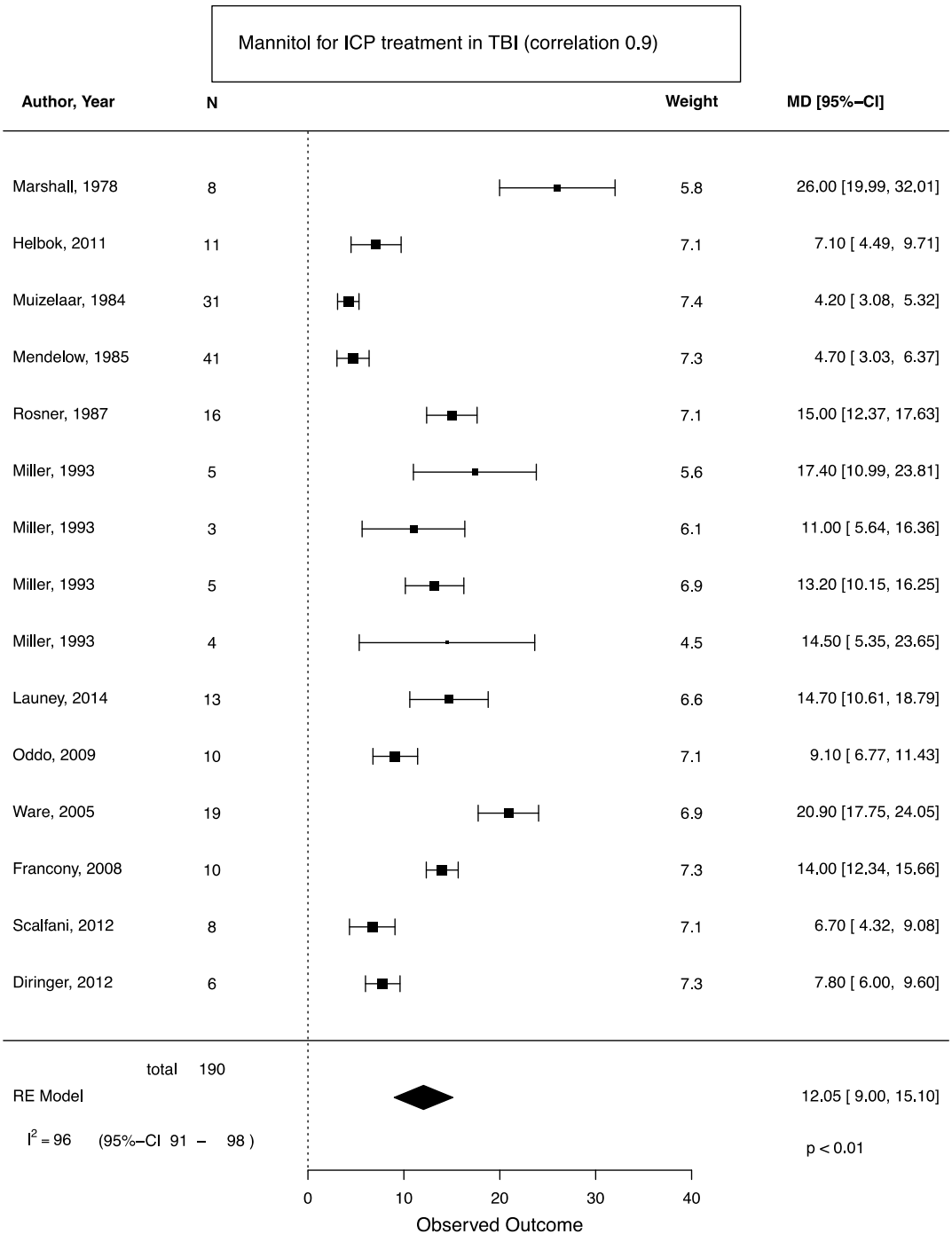

Figure 2: meta-analysis of studies investigating mannitol efficacy in reducing ICP, high correlation between before-after measures was used for variance calculation.

hypertonic saline meta-analysis

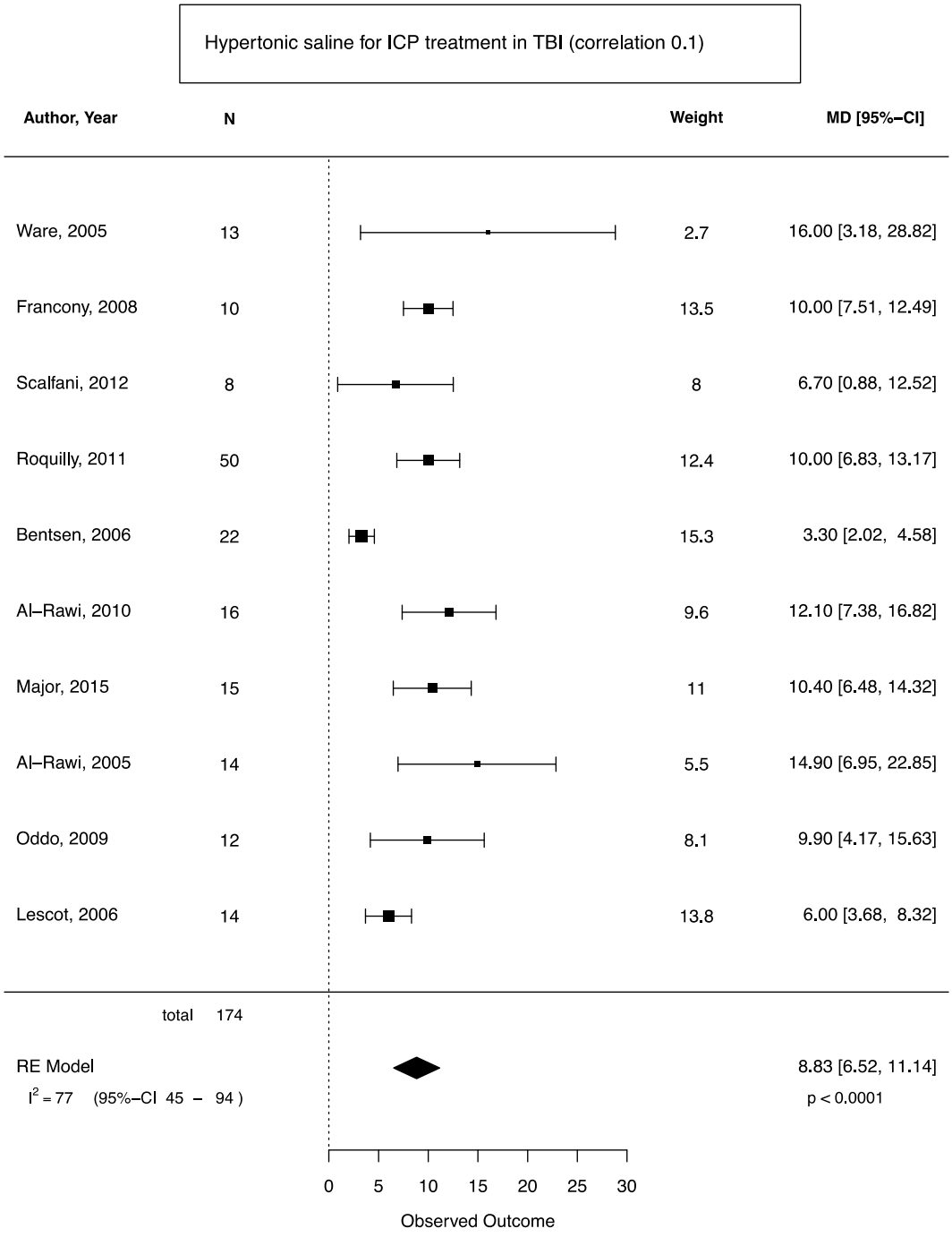

Figure 3: meta-analysis of studies investigating hypertonic saline efficacy in reducing ICP, low correlation between before-after measures was used for variance calculation.

hypertonic saline meta-analysis

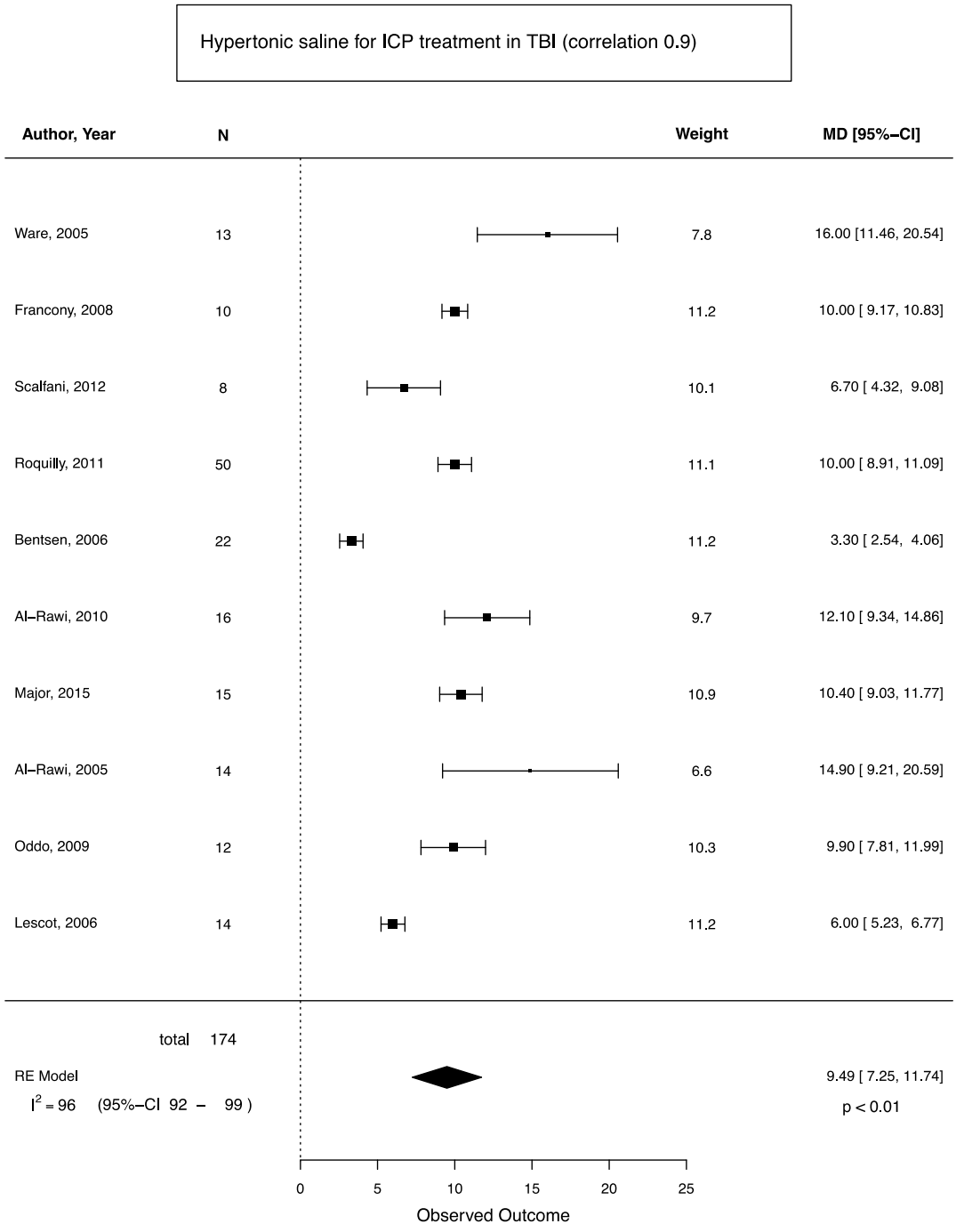

Figure 4: meta-analysis of studies investigating hypertonic saline efficacy in reducing ICP, high correlation between before-after measures was used for variance calculation.

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sodium lactate vs. 0.9% saline - RCT

RCT 1			
Year	2013	First Author	Ichai
Journal	ICM		
Sample	TBI GCS 3-8		
Treatment	Sodium lactate 1100 mosm/kg 0.5 ml/Kg/h		
Control	0.9% saline 286 mosm/kg 0.5 ml/Kg/h		
Outcome	ICP episodes > 20 mmHg and > 10 min during the 48-hour infusion		
		Outcome	
	n° pz	n	%
Treatment	30	11	36.7
Control	30	20	66.7
Total	60	31	51.7
Centres	2 Centres	delta 30 (95%-CI 50.4 to 4.8)	
Power	0.683	NNTB 3 (95%-CI NNTB 2 to NNTB 21)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Bias	No
		Indirectness	No
		Imprecision	serious
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Methodological and statistical quality: Small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms and a high risk of overoptimistic estimates; Imprecision: There is a 45% relative risk reduction, with wide confidence intervals, and a sample size below the GRADE optimal information size threshold;	
Up-grading			
		GRADE rating	Moderate evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

7.2% saline in 200/0.5 HSS vs. 0.9% saline - RCT

RCT	1		
Year	2006	First Author	Bentsen
Journal	CCM		
Sample	SAH with normal ICP		
Treatment	7.2% saline in 200/0.5 HSS 2 ml/kg		
Control	0.9% saline 2 ml/kg		
Outcome	ICP reduction difference		
		Outcome	
	n° pz	ICP reduction	
		mean	SD
Treatment	11	3.3	2.6
Control	11	0.3	1.3
Total	22	3	0.0
Centres	Single Center		
Power	0.902	p value 0.004	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Sufficient for quality assessment
		Indirectness	No
		Imprecision	Not assessable
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No reporting of allocation concealment, no blinding was performed although technically possible; Methodological and statistical quality: Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No sample size calculation based on power and effect size was performed. Limited clinical relevance because ICP was low in the patients and the ICP reduction consequently low;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Very low evidence

query and body of evidence grading

Observational study	1	Very low evidence ⇒ Downgraded study
Year	2013	
Journal	JT	
First Author	Cooper	
Statistical method	linear mixed model with random intercept	
Inclusion criteria	TBI patients from the SAFE trial	
Treatment	4% albumin	
Control	0.9% saline	**Outcome**
		ICP increase: 33 (19.9%)
Centres	16	**Variable: Slope (mmHg/day) SD**
N° patients/centre/year	NA	4% albumin: 1.31 0.33
Study duration (days)	606	0.9% saline: 0.37 0.36
Total (included in the model)	166	
	GRADE CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
	GRADE overall	
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Statistical quality: The study is a subgroup analysis of the SAFE trial, as such the benefits of randomization applied to the entire study sample cannot be extended to the TBI subgroup. Linear regressions has explanatory purposes but it include only age, GCS, arterial pressure, and CT evidence of subarachnoid hemorrhage for mortality prediction (probable underfitting). Finally, although investigating a treatment a propensity score is not applied to account for selection bias.	
Up-grading		
External validity	No external validity issues	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	Low
	External validity issues	No
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

query and body of evidence grading

SG2 Q2: Efficacy: in TBI, is there evidence that osmotic drugs have different efficacy (more effective or less effective in reducing ICP)

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

We found nine RCTs comparing different osmotic fluids in different clinical conditions.

Six studies dealt exclusively with TBI,[1-6] two with TBI or non-traumatic haemorrhage,[7, 8] and one with ischemic stroke.[9]

All studies compared hypertonic saline with mannitol,[1, 2, 4-9] besides one that compared sodium lactate and mannitol.[3]

All the studies enrolled very few patients generating a bias due to the small sample sizes (i.e. low power to detect clinically relevant differences, the “winner curse” risk, the high probability of unbalances of important prognostic factors between study arms). Other important biases were also detected. Their heterogeneity in terms of design, especially treatment protocols, advised against the meta-analytical combination.

Only one trial investigated sodium lactate vs. mannitol in severe TBI patients.

All studies evidence was downgraded to *low*, according to the GRADE and our supplemental criteria.

hypertonic saline vs. mannitol – RCT

RCT			
Year	2003	First Author	Vialet
Journal	CCM		
Sample	TBI with persistent coma and ICP > 25 mmHg		
Treatment	7.5% hypertonic saline 2400 mosm/kg 2 ml/Kg		
Control	20% mannitol 1160 mosm/kg 2 ml/Kg		
Outcome	number of ICP > 25 mmHg episodes		
		Outcome	
	n° pz	N episodes/day	
		mean	SD
Treatment	10	13.3	14.2
Control	10	6.8	5.5
Total	20	6.5	0.0
Centres	Single Center		
Power	NA	p = 0.02	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Not reported
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Partial
		Indirectness	No
		Imprecision	Not assessable
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No reporting of allocation concealment, no blinding was performed although technically possible; Methodological and statistical quality: The study compares non equimolar doses, favouring hypertonic saline. Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No sample size calculation based on power and effect size was performed;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline vs. mannitol – RCT

RCT			
Year	2005	First Author	Battison
Journal	CCM		
Sample	TBI or SAH with ICP > 20 mmHg		
Treatment	7.5% saline/6% dextran 2498 mosm/kg 100 ml		
Control	20% mannitol 1245 mosm/kg 200 ml		
Outcome	ICP reduction		
		Outcome	
	n° pz	ICP reduction at 60 min	
		median	95%-CI
Treatment	9	7.5	NA
Control	9	13	NA
Total	9 (crossover)	-5	(-10.8; 3)
Centres	Single Center		
Power	NA	p 0.014	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	Yes
		Bias	very serious
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No blinding was performed although technically possible; Methodological and statistical quality: Crossover trial: potentially treatment was provided in different moments of cerebral injuries evolution. Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No sample size calculation based on power and effect size was performed;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline vs. mannitol – RCT

RCT			
Year	2008	First Author	Francony
Journal	CCM		
Sample	TBI with sustained ICP > 20 mmHg		
Treatment	7.45% hypertonic saline 2548 mosm/kg 100 ml		
Control	20% mannitol 1100 mosm/kg 231 ml		
Outcome	Percentage ICP reduction		
		Outcome	
	n° pz	% ICP reduction at 60 min	
		mean	SD
Treatment	10	31	6.0
Control	10	27	3.0
Total	20	4	0
Centres	2		
Power	0.416	p 0.06	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No blinding was performed although technically possible; Methodological and statistical quality: Very small sample with high chance of unbalanced important prognostic factors (measured and unmeasured) between the two study arms, no reporting of blinding. The effect size used for sample size calculation was very large (40% reduction in favour of hypertonic saline), with a high risk of overestimation.;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline vs. mannitol – RCT

RCT			
Year	2005	First Author	Harutjunyan
Journal	CC		
Sample	Neurosurgical patients with TBI, SAH, or IPH and ICP > 20 mmHg		
Treatment	7.2% NaCl/HES 200/0.5 (2440 mOsm/Kg) 1.4 ml/Kg		
Control	15% mannitol (1870 mOsm/Kg) 1.8 ml/Kg		
Outcome	% ICP reduction		
		Outcome	
	n° pz	% ICP reduction	
		%	SD
Treatment	17	57	NA
Control	15	48	NA
Total	32	9	
Centres	1		
Power	not available	p < 0.01	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No blinding was performed although technically possible; Methodological and statistical quality: Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No sample size calculation based on power and effect size was performed. Repeated measurements on single patients were performed but it is unclear if the statistical test accounted for repeated measures;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline vs. mannitol – RCT

RCT			
Year	2016	First Author	Jagannatha
Journal	JCN		
Sample	TBI patients with ICP > 20 mmHg		
Treatment	3% hypertonic saline (1027 mOsm/Kg) 2.5 ml/Kg		
Control	20% mannitol (1160 mOsm/Kg) 2.5 ml/Kg		
Outcome	% time ICP < 20 mmHg		
		Outcome	
	n° pz	% time ICP < 20 mmHg	SD
Treatment	18	63	NA
Control	20	49	NA
Total	38	14	0
Centres	1		
Power	not available	p 0.3	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose / response	Not investigated
		DETAILS	
Downgrading		Bias: No blinding was performed although technically possible; Methodological and statistical quality: No sample size calculation based on power and effect size was performed. Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. Repeated measurements on single patients were performed but it is unclear if the statistical test accounted for repeated measures;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline vs. mannitol – RCT

RCT			
Year	2011	First Author	Sakellaridis
Journal	JN		
Sample	TBI GCS ≤ 8 and ICP > 20 mmHg		
Treatment	Hypertonic saline 15% (5135 mOsm/Kg) 0.42 ml/Kg		
Control	20% mannitol (1160 mOsm/Kg) 2 ml/Kg		
Outcome	Maximum ICP reduction		
		Outcome	
	n° pz	mean	SD
Treatment	29	7.96	5.8
Control	29	8.43	6.7
Total	29 (crossover)	-0.47	0
Centres	1		
Power	0.046	p 0.586	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Partial
		Methodological and statistical quality	High
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: The design seems to resemble a cross-over trial. No blinding was performed although technically possible; Methodological and statistical quality: It is unclear how authors dealt with multiple measurements on the same patient using a paired t test (29 patients alternatively receiving mannitol or HS, with 199 measures performed). Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No sample size calculation based on power and effect size was performed;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Partial
		Methodological and statistical quality	High
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline vs. mannitol – RCT

RCT			
Year	2011	First Author	Cottenceau
Journal	JNT		
Sample	TBI GCS ≤ 8 and ICP > 15 mmHg		
Treatment	Hypertonic saline 7.5%		
Control	20% mannitol		
Outcome	Hospital mortality		
		Outcome	
	n° pz	mean	SD
Treatment	22	5.7	8.2
Control	25	5.8	8.1
Total	47	-0.10	
Centres	2		
Power	0.027	p ns	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	Yes
		Bias	very serious
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No blinding was performed although technically possible; Methodological and statistical quality: Repeated measurements on single patients were performed that the authors seem to have accounted for. No sample size calculation based on power and effect size was performed. Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

sodium lactate vs. mannitol - RCT

RCT			
Year	2009	First Author	Ichai
Journal	ICM		
Sample	TBI GCS ≤ 8 and ICP > 25 mmHg for > 5 min		
Treatment	Sodium lactate 1100 mosm/kg 1.5 ml/Kg		
Control	20% Mannitol 1160 mosm/kg 1.5 ml/Kg		
Outcome	ICP decrease at the fourth hour		
		Outcome	
	n° pz	ICP decrease at the fourth hour	
		mean	SD
Treatment	17	5.9	4.1
Control	17	3.2	3.7
Total	34	2.7	
Centres	Single Center		
Power	0.492	p value 0.009	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting not for quality assessment	
		Indirectness	No
		Imprecision	Not assessable
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No blinding was performed although technically possible. It is unclear how treatment assignment was concealed after envelopes with the 5:5 block randomization were opened; Methodological and statistical quality: Small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. A 2.7 mmHg ICP reduction although statistically significant was not clinically meaningful;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline in HES vs. mannitol - RCT

RCT	1		
Year	1998	First Author	Schwarz
Journal	Stroke		
Sample	Stroke (mainly ischemic)		
Treatment	hypertonic saline hydroxyethyl starch (osmolarity 2570 mosm/L) 100 ml		
Control	20% mannitol (1100 mosm/L) 200 ml		
Outcome	ICP reduction		
		Outcome	
	n° pz	ICP reduction	
		mean	SD
Treatment	9	11	na
Control	9	6.4	na
Total	9 (crossover)	4.6	0.0
Centres	Single Center		
Power	na	p value ha	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Not reported
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Partial
		Indirectness	No
		Imprecision	Not assessable
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No reporting of allocation concealment, no blinding was performed although technically possible; Methodological and statistical quality: Repeated measures and crossover between study groups were performed, but there was neither a clear crossover design nor a statistical approach that could account for repeated measures. Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No sample size calculation based on power and effect size was performed;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Very low evidence

hypertonic saline vs. mannitol - observational

Observational study	1	Very low evidence ?? Downgraded study
Year	2015	
Journal	JN	
First Author	Mangat	
Statistical method	Optimal matching	
Inclusion criteria	TBI	
Treatment	Hypertonic saline 3%	
Control	Mannitol 20%	
		Outcome
		NA
Centres	22	**ICP reduction: ??**
N° patients/centre/year	na	mean (SD)
Study duration (days)	na	Treatment: 15.2 (19.9)
Total (included in the model)	50	Control: 36.5 (30.9)
		Difference: 21.3: p= 0.003
	GRADE CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Methodological and statistical	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
	GRADE overall	
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	No
	DETAILS	
Downgrading	Adequate control for confounding: Few important clinical variables selected for matching (initial GCS, hypotension, pupil reactivity, surgical lesion). Methodological and statistical quality: The study does not account sufficiently for confounding.	
Up-grading		
External validity	Sufficient number of centers but on average only about 2 patients for centers were enrolled in the study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Sufficient for quality assessment
	Methodological and statistical	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

query and body of evidence grading

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query and body of evidence grading

SG2 Q3: Efficacy: is there evidence supporting osmotic drugs use in patients with intracranial pathologies but without ICP monitoring?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

We retrieved only two small RCTs bearing serious methodological limitations. One RCT randomized to 20% mannitol or 23.4% HS 9 patients, measuring one hour after administration cerebral blood flow (CBF), blood volume (CBV), oxygen extraction fraction (OEF), and oxygen metabolism (CMRO2) [1]. No significant differences were found. The second RCT compared 20% mannitol and the same volume of normal saline, in patients with supratentorial intracerebral hemorrhage and midline shift of at least 3 mm. No differences in shift reduction were found [2]. In both studies no preliminary sample size calculation was performed, and the study were clearly underpowered and unable to show and clinically meaningful difference. Evidence provided by both studies was downgraded to *very low*.

Other selected studies were observational, investigating very small samples, without any adjustment for confounders and are briefly described below. No detailed grading form was filled for these studies. Differently from Q1, where numerous studies were sufficiently homogenous in terms of treatment and outcome, the high heterogeneity hampers the finding of a common pathophysiological base and advises against combination of results. Evidence provided by these studies was graded as *very low.*

Available studies investigated mostly alternative monitoring strategies to assess mannitol effect. No evidence was found concerning mannitol administration in the presence of clinical changes without ICP monitoring.
Only one study investigating EEG modifications after mannitol administration in stroke patients performed a multivariable analysis on 37 hemorrhagic stroke.[3] The

query and body of evidence grading

reporting of statistics was partial and confused, and results were not clearly illustrated. Aside from these shortcomings, the model was clearly overfitted, with 7 variables tested in the model.

Most studies focused the effects of mannitol or hypertonic saline on cerebral hemodynamics in patients with spontaneous intracerebral hemorrhage or TBI, measured with transcranial doppler,[4-6] positron emission tomography,[7, 8] Xenon-133 inhalation method.[9, 10] Other studies considered brain volume and shift, or its water content.[11-15]

Another interesting study reported the differential effect of hypertonic saline bolus on the volume of contused (increased) and non-contused cerebral (decreased) areas by CT scan measurements.[13] Unfortunately the study was carried out on 14 patients only and cold not provide robust evidence, although generating an important hypothesis.

Several other studies evaluated cerebral blood flow changes after osmotic therapy was administered.

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mannitol vs. normal saline (outcome shift reduction at MRI)

RCT	1		
Year	2007	First Author	Misra
Journal	EJN		
Sample	Intracerebral hemorrhage with shift > 3 mm		
Treatment	20% mannitol 1.5 gr/Kg 2 ml/Kg		
Control	0.9% saline 2 ml/Kg		
Outcome	Shift reduction at MRI		
		Outcome	
	n° pz	N episodes/day	
		mean	SD
Treatment	12	6.8	2.2
Control	12	6.6	2.2
Total	24	0.2	0.0
Centres	Single Center		
Power	0.039	p value hs	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Not reported
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	very serious
		Statistical reporting	Partial
		Indirectness	No
		Imprecision	Not assessable
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading		Bias: No reporting of allocation concealment, no blinding was performed although technically possible; Methodological and statistical quality: Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No sample size calculation based on power and effect size was performed. The study was underpowered to detect any realistic effect; Imprecision: Although not measurable;	
Up-grading			
		GRADE rating	Very low evidence
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Very low evidence

query and body of evidence grading

RCT 2			
Year	2011	First Author	Diringer
Journal	NCC		
Sample	Acute hemispheric acute stroke		
Treatment	23.4% hypertonic saline 0.686 ml/Kg		
Control	20% mannitol 1 gr/Kg		
Outcome	CBF increase (measured with PET)		
		Outcome	
	n° pz	CBF increase	
		mean	SD
Treatment	4	1.4	10.5
Control	5	1.3	4.6
Total	9	0.1	0.0
Centres	Single Center		
Power	p value ns	p value ns	
		GRADE CRITERIA	
Downgrading		Allocation concealment	No
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	Yes
		Bias	very serious
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose /response	Not investigated
		DETAILS	
Downgrading		Bias: No blinding was performed although technically possible; Methodological and statistical quality: Very small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. No sample size calculation based on power and effect size was performed. The study was underpowered to detect any realistic effect;	
Up-grading			
		GRADE rating	Very low evidence
		Statistical reporting	Partial
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Very low evidence

query and body of evidence grading

SG2 Q4: Efficacy: is there evidence that osmotic therapies used in TBI (or other intracranial pathologies) improve outcome?

Three trials and three observational studies were graded.

The trials were heterogeneous in terms of design and could not be combined in a meta-analysis [1-3]. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading. The first RCT compared sodium lactate vs. normal saline infusion for the prevention of ICP increases over 20 mmHg in TBI in the first 48 hours from admission. The study showed a statistically significant reduction of the number of such episodes but no improvement in the 6-months neurologic outcome (two form are reported below, one for the surrogate and one for the robust outcome). The second RCT could not demonstrate the superiority of sodium lactate on mannitol in TBI patients in terms of long-term neurologic outcome. The third RCT did not show any beneficial effect of HS on ringer lactate.

The three observational studies dealt with TBI, SAH, and intracerebral hemorrhage. The first two were downgraded for methodological biases [4, 5]. The third was of high quality according to the GRADE classification and to our final evaluation [6].

Sodium lactate vs. saline – RCT

RCT			
Year	2013	First Author	Ichai
Journal	ICM		
Sample	TBI GCS ≤ 8		
Treatment	Sodium lactate infusion		
Control	0.9% saline infusion		
Outcome	n of ICP > 20 mmHg episodes		
		Outcome	
	n° pz	n	%
Treatment	30	11	36.7
Control	30	20	66.7
Total	60	31	51.66666667
Centres	2	delta 30 (95%-CI -50.4 to 4.8)	
Power	0.683	NNTB 3 (95%-CI NNTB 2 to NNTB 21)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	No
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Methodological and statistical quality: Small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms and a high risk of overoptimistic estimates; Imprecision: Confidence interval includes a wide range of possibilities from strongly protective to strongly detrimental effects. Power was very low in relation to the measured effect;	
Up-grading			
		GRADE rating	Moderate evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

Sodium lactate vs. saline – RCT

RCT			
Year	2013	First Author	Ichai
Journal	ICM		
Sample	TBI GCS ≤ 8		
Treatment	Sodium lactate infusion		
Control	0.9% saline infusion		
Outcome	6-months GOS (poor outcome)		
		Outcome	
	n° pz	n	%
Treatment	30	12	40.0
Control	30	15	50.0
Total	60	27	45.0
Centres	2 Centres	delta -10 (95%-CI -32.8 to 14.4)	
Power	0.119	NNTB -10 (95%-CI NNTB -3 to ∞ to NNTH 7)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Bias	No
		Statistical reporting	Sufficient for quality assessment
		Indirectness	No
		Imprecision	very serious
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Methodological and statistical quality: Small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms and a high risk of overoptimistic estimates; Imprecision: Confidence interval includes a wide range of possibilities from strongly protective to strongly detrimental effects. Power was very low in relation to the measured effect;	
Up-grading			
		GRADE rating	Moderate evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

Sodium lactate vs. mannitol – RCT

RCT			
Year	2009	First Author	Ichai
Journal	ICM		
Sample	TBI GCS ≤ 8 and ICP > 25 mmHg for > 5 min		
Treatment	Sodium lactate		
Control	20% Mannitol		
Outcome	12-months GOS (poor outcome)		
		Outcome	
	n° pz	n	%
Treatment	17	6	35.3
Control	16	11	68.8
Total	33	17	51.5
Centres	Single Center	delta -33.5 (95%-CI -58.3 to -0.3)	
Power	0.532	NNTB 3 (95%-CI NNTB 2 to ∞ to NNTH 316)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	No
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	serious
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	No
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose / response	Not relevant
		DETAILS	
Downgrading		Bias: No blinding was performed although technically possible. It is unclear how treatment assignment was concealed after envelopes with the 5:5 block randomization were opened; Methodological and statistical quality: Small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms. The effect size was very large with a high risk of overestimation, particularly relevant when combined with a high degree of imprecision; Imprecision: Wide confidence interval with a high degree of uncertainty;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Low evidence

hypertonic saline vs. ringer lactate - RCT

RCT			
Year	2004	First Author	Cooper
Journal	JAMA		
Sample	TBI GCS ≤ 8 and SAP ≥ 100 mmHg		
Treatment	Prehospital 250 ml hypertonic saline 7.5%		
Control	Prehospital 250 ml ringer lactate		
Outcome	6-month GOSE		
		Outcome	
	n° pz	6-month GOSE score	
		median	IQR
Treatment	113	5	(3-6)
Control	113	5	(5-6)
Total	226	0	0.0
Centres	12 Centres		
Power	not available	p value 0.45	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Bias	No
		Statistical reporting	Sufficient for quality assessment
		Indirectness	No
		Imprecision	No
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not assessable
		Residual confounding	Not assessable
		Dose/response	Not investigated
		DETAILS	
Downgrading			
Up-grading			
		GRADE rating	High evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		External validity issues	No
		Final grading	No grading modification
		Final level of evidence	High evidence

hypertonic saline - OBS

Observational study	1	Very low evidence ?? Downgraded study
Year	1997	
Journal	JT	
First Author	Wade	
Statistical method	Logistic regression	
Inclusion criteria	AIS for head region >2	
Treatment	Prehospital hypertonic saline 7.5%/dextran-70 250 ml	
		Outcome
		Hospital mortality: 33 (19.9%)
Centres	NA	**Variable: OR (95%-CI)**
N° patients/centre/year	NA	Hypertonic saline yes/no: 2.12 (1.01-4.49)
Study duration (days)	NA	
Total (included in the model)	166	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
	GRADE overall	
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Statistical reporting: The reporting of multivariable results is insufficient to understand how the model was developed in detail. Statistical quality: The logistic regression model has explanatory pruposes but it includes few variables for mortality prediction (probable underfitting). On the other hand the study runs a high risk of bening overfitted since 55 variables entered the model with only 33 events available (ratio events/variables 10/1). Finally, although investigating a treatment a propensity score is not applied to account for selection bias.	
Up-grading	Size of effect: The result of a biased analysis. To not indicate upgrading.	
External validity	No external validity issues	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	No
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

mannitol - OBS

Observational study	2	Very low evidence - Downgraded study
Year	2003	
Journal	Stroke	
First Author	Bereczki	
Statistical method	Logistic regression	
Inclusion criteria	SAH patients	
Treatment	Mannitol (dose and timing not specified)	
		Outcome
		1-year mortality: 35 (6.5%)
Centres	3	**Variable: OR (95%-CI)**
N° patients/centre/year	180	Mannitol yes/no: 0.53 (0.36-0.79)
Study duration (days)	365	
Total (included in the model)	540	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	serious
	GRADE overall	
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Measurement of outcome: A combined outcome including severe disability besides mortality is to be preferred to mortality alone when dealing with long-term neurologic outcome. Statistical quality: Although dealing with a treatment no propensity score was developed to account for selection bias. Heterogeneous findings concerning mannitol effectiveness were provided by different models, which appeared to be underfitted to explain mortality.	
Up-grading		
External validity	No external validity issues	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

mannitol - OBS

Observational	3	Low evidence No grading modification
Year	2015	
Journal	Stroke	
First Author	Wang	
Statistical method	Logistic regression with propensity score adjustment	
Inclusion criteria	Acute cerebral hemorrhage	
Treatment	mannitol within 7 days from admission, dose not defined	
		Outcome
		Rankin scale 3-6 at 90 days: 1341 (53.1%)
Centres	NA	**Variable: OR (95%-CI)**
N° patients/centre/year	NA	Mannitol yes/no: 1.02 (0.81-1.30)
Study duration (days)	NA	
Total (included in the model)	2526	
	GRADE CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	High
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	Yes
	Bias	No
	GRADE overall	
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading		
Up-grading		
External validity	No external validity issues	
Conclusive evaluation	GRADE rating up/down	No grading modification
	GRADE rating	Low evidence
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	High
	External validity issues	No
	Final grading	No grading modification
	Final level of evidence	Low evidence

query and body of evidence grading (SAH)

1. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J, Investigators HTSS, (2004) Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. Jama 291: 1350-1357
2. Ichai C, Armando G, Orban JC, Berthier F, Rami L, Samat-Long C, Grimaud D, Leverve X, (2009) Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive care medicine 35: 471-479
3. Ichai C, Payen JF, Orban JC, Quintard H, Roth H, Legrand R, Francony G, Leverve XM, (2013) Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. Intensive care medicine 39: 1413-1422
4. Bereczki D, Mihalka L, Szatmari S, Fekete K, Di Cesar D, Fulesdi B, Csiba L, Fekete I, (2003) Mannitol use in acute stroke: case fatality at 30 days and 1 year. Stroke 34: 1730-1735
5. Wade CE, Grady JJ, Kramer GC, Younes RN, Gehlsen K, Holcroft JW, (1997) Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. The Journal of trauma 42: S61-65
6. Wang X, Arima H, Yang J, Zhang S, Wu G, Woodward M, Munoz-Venturelli P, Lavados PM, Stapf C, Robinson T, Heeley E, Delcourt C, Lindley RI, Parsons M, Chalmers J, Anderson CS, Investigators I, (2015) Mannitol and Outcome in Intracerebral Hemorrhage: Propensity Score and Multivariable Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 Results. Stroke 46: 2762-2767

SG3 Q1 Is there enough evidence to prefer specific fluids (crystalloids/colloids) in the prevention of cerebral ischemia (CBF or clinical) in patients with stroke (subarachnoid hemorrhage)?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

query and body of evidence grading (SAH)

We considered studies focused on the prevention of new ischemic events, i.e. vasospasm and its consequences, in subarachnoid haemorrhage (SAH).

We found two small randomized controlled clinical trials (RCTs), one adopting a triple H protocol for the treatment arm, and for this reason a confounding effect of hypertensive therapy could not be ruled out [1]. The study could not demonstrate any differences in terms of occurrence of vasospasm, of regional cerebral blood flow (CBF), and of one-year GOS. The other study compared hypervolemic and normovolemic approaches based on hemodynamic parameters [2]. The study did not show either any improvement of regional and global CBF, or differences in the frequency of vasospasm and cerebral infarction. The two RCTs were small and consequently prone to several biases.

A third RCT was not included in our analysis because it combined multiple interventions (including volume expansion) for the prevention of vasospasm, thus not providing reliable information of single elements of the therapeutic approach [3].

We also found several observational studies that were so heterogeneous in terms of treatment protocols and outcomes that it was not possible to combine in a single body of evidence. We made a detailed reporting of our grading process only for studies using statistical techniques to adjust for confounding, while graded the others as *very low quality*.

Among studies not performing statistical adjustment for confounders we report six with a before-after design that appeared more interesting than others in terms of hypothesis generation. However, results appeared to be conflicting although differences in treatment and study design could explain inconsistencies. The studies we carried out in few patients and in single centres that raises external validity issues.

One study investigated an hypervolemic approach reporting an increase in regional CBF dissociated from any significant variation of cerebral oxygenation (PbtO2) [4]. In a second study, hypertonic saline infusion in fourteen patients was associated with PbO2 increase [5]. Volume expansion with albumin and hypertonic saline was associated with CBF reduction and increase, respectively [6-8], while it remained unchanged when normal saline was used [9].

query and body of evidence grading (SAH)

Among studies carrying out statistical adjustment for confounders we excluded one that used a combined outcome including delayed cerebral ischemia (DCI), hydrocephalus, and rebleeding, because it did not provide specific information on the outcome of interest [10]. Among the other six observational studies retrieved that used a multivariable approach, only two investigated DCI specifically [11, 12]. The other studies investigated mortality or long-term neurologic outcome [13-16], and are thus of interest also for SG1.

Hypervolemia vs. Normovolemia - RCT

RCT			
Year	2001	First Author	Egge
Journal	Neurosurgery		
Sample	aSAH patients		
Treatment	Triple-H treatment 2L Saline - 2L 5%-500-1000 ml colloids (albumin or rheomacrodex) dextrose/day		
Control	No triple-H treatment 1L Saline - 1L 5% dextrose/day		
Outcome	vasospasm (TDS + Lindegaard index)		
		Outcome	
	n° pz	n	%
Treatment	16	4	25.0
Control	16	5	31.3
Total	32	9	28.1
Centres	2 Centres	delta 6.3 (95%-CI 34.8 to 23.6)	
Power	0.059	NNTB 16 (95%-CI NNTB 3 to ∞ to NNTH 4)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Not reported
		Intention to treat principle observed	Not reported
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	No
		Statistical reporting	Sufficient for quality assessment
		Indirectness	No
		Imprecision	very serious
		Publication bias	Not assessable
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Methodological and statistical quality: Small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms and a high risk of overoptimistic estimates;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Very low evidence

Hypervolemia vs. Normovolemia - RCT

RCT			
Year	2000	First Author	Lennihan
Journal	Stroke		
Sample	SAH patients with clipped aneurysm		
Treatment	PADP 14 or CVP 8 mmHg		
Control	PADP 7 or CVP 5 mmHg		
Outcome	symptomatic vasospasm		
		Outcome	
	n° pz	n	%
Treatment	41	8	19.5
Control	41	8	19.5
Total	82	16	19.5
Centres	Single Center	delta 0 (95%-CI 17.2 to 17.2)	
Power	0.025	NNTB/NNTH ~ (95%-CI NNTB 6 to ~ to NNTH 6)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	No
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early Stopping	No
		Bias	very serious
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		Indirectness	No
		Publication bias	No
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Bias: No blinding or allocation concelament were performed although technically possible.; Methodological and statistical quality: Small sample with high chance of unbalances in important prognostic factors (measured and unmeasured) between the two study arms; Imprecision: Wide confidence interval with a high degree of uncertainty;	
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	Low
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Very low evidence

Hypervolemia vs. Normovolemia - RCT

RCT			
Year	2000	First Author	Lennihan
Journal	Stroke		
Sample	SAH patients with clipped aneurysm		
Treatment	PADP 14 or CVP 8 mmHg		
Control	PADP 7 or CVP 5 mmHg		
Outcome	Cerebral infarction		
		Outcome	
	n° pz	n	%
Treatment	41	7	17.1
Control	41	4	9.8
Total	82	11	13.4
Centres	1	delta 7.3 (95%-CI 8.1 to 22.7)	
Power	0.163	NNTH 14 (95%-CI NNTB 12 to ∞ to NNTH 4)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	No
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	No
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		Indirectness	No
		Publication bias	No
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading			
Up-grading			
		GRADE rating	Low evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Very low evidence

Different fluid administration approaches – OBS

Observational study	1	
Year	2013	
Journal	JN	
First Author	Kuwabara	
Statistical method	Logistic regression with propensity score adjustment	
Inclusion criteria	SAH	
treatment	Albumin	
control	no albumin	**Outcome**
		Hospital mortality
Centres	NA	**Variable: OR (95%-CI)**
N° patients/centre/year	NA	Albumin g/kg/day (continuous) Pre-DCI: 4.39 (0.9-21.37)
Study duration (days)	NA	Albumin g/kg/day (continuous) DCI: 2.55 (0.29-22.65)
Total (included in the model)	5400	
	GRADING CRITERIA	
	Statistical reporting	Partial
	Methodological and statistical	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose/response	No
	DETAILS	
Downgrading	Adequate control for confounding: Data from administrative database. Few important clinical variables included in the model. Statistical reporting: The reporting of multivariable results is insufficient to understand how the model was developed in detail. There is insufficient information on the variable selection procedure. Methodological and statistical quality: It seems that DCI diagnosis was attributed on the basis of the number of days from admission, individuating a pre-DCI and a DCI period, and not on the basis of a clinical/instrumental diagnosis. The definition of these periods was crucial in the development of the model that was prone to misleading interpretations.	
Up-grading	Size of effect: Large non statistically significant effects with high level of imprecision.	
External validity	0	
Conclusive evaluation	GRADE rating up/down	Downgrading
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Methodological and statistical	Low
	External validity issues	No
	Final grading	Downgrading
	Final level of evidence	Very low evidence

Different fluid administration approaches – OBS

Observational study	2	
Year	2004	
Journal	JN	
First Author	Suarez	
Statistical method	Logistic regression	
Inclusion criteria	SAH	
treatment	Albumin	
control	no albumin	**Outcome**
		GOS 2-4: 43 (51.2%)
Centres	1	**Variable: OR (95%-CI)**
N° patients/centre/year	42	Albumin: 3.2 (1.1-11.0)
Study duration (days)	731	
Total (included in the model)	84	
GOS 2-4	43 (51.2%)	
	GRADING CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Adequate control for confounding: Important predictors were not included in logistic regression (only age, sex, race, and treatment entered the model).. Statistical reporting: Insufficient information on how the model was developed (e.g. variable selection, management of continuous variables) were provided. No information on the fit of the model was available.. Methodological and statistical quality: The small sample size hampered the development of a multivariable approach with explanatory purposes. The model was underfitted but it could not include more variables because of the risk of overfitting. No propensity score was developed..	
Up-grading	Size of effect: Large protective effect generated, however, by a potentially biased model. No upgrading indicated.	
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgrading
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Methodological and statistical qu	Low
	External validity issues	Yes
	Final grading	Downgrading
	Final level of evidence	Very low evidence

Different fluid administration approaches – OBS

Observational	3	
Year	2015	
Journal	JSCD	
First Author	Kissoon	
Statistical method	Logistic regression with propensity score adjustment	
Inclusion criteria	SAH	
treatment	Positive fluid balance	
control	Even fluid balance	**Outcome**
		DCI: 190 (66%)
Centres	1	**Variable: HR (95%-CI)**
N° patients/centre/year	28	Positive fluid balance: 1.18 (1.08-1.29)
Study duration (days)	3803	
Total (included in the model)	288	
	GRADING CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Only 5 variables selected in the model, an insufficient number for explanatory purposes. Statistical reporting: Insufficient information on how the model was developed (e.g. variable selection, management of continuous variables) were provided. No information on the fit of the model was available.. Methodological and statistical quality: The model was underfitted given its explanatory purposes.	
Up-grading	Dose/response: The model was too weak to take in account the positive dose/response relation.	
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgrading
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Methodological and statistical quality	Low
	External validity issues	Yes
	Final grading	Downgrading
	Final level of evidence	Very low evidence

Different fluid administration approaches – OBS

Observational study	4	
Year	2012	
Journal	NC	
First Author	Martini	
Statistical method	Cox proportional hazards	
Inclusion criteria	SAH patients	
treatment	Positive fluid balance after the first 3 days	
control	Negative fluid balance after the first	**Outcome**
		Hospital mortality or new stroke: 117 (32.9%)
Centres	1	**Variable: HR (95%-CI)**
N° patients/centre/year	63	3-day positive fluid balance: 1.47 (0.85-2.54)
Study duration (days)	2071	
Total (included in the model)	356	
	GRADING CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Insufficient number of variables for an explanatory model. Statistical reporting: Insufficient information on how the model was developed (e.g. variable selection, management of continuous variables) were provided. Methodological and statistical quality: The model was underfitted. No propensity score was developed.	
Up-grading		
External validity	Single center study.	
Conclusive evaluation	GRADE rating up/down	No grading modification
	GRADE rating	Low evidence
	Statistical reporting	Partial
	Methodological and statistical quali	Low
	External validity issues	Yes
	Final grading	Downgrading
	Final level of evidence	Very low evidence

Different fluid administration approaches – OBS

Observational study	5	
Year	2013	
Journal	NC	
First Author	Ibrahim	
Statistical method	Case-control with matcting	
Inclusion criteria	SAH	
treatment	Colloids administration	
control	No colloids	**Outcome**
		DCI: delta 3.7 (95%-CI 14.5 to 21.6)
Centres	1	DCI: NNTH 27 (95%-CI NNTB 7 to ∞ to NNTH 5)
N° patients/centre/year	106	p = 0.71
Study duration (days)	424	
Total (included in the model)	123	
	GRADING CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	High
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	
	Residual confounding	Does not indicate upgrading
	Dose/response	No
	DETAILS	
Downgrading	Adequate control for confounding: Important predictors were not included in the propensity score.	
Up-grading		
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgrading
	GRADE rating	Very low evidence
	Statistical reporting	Sufficient for quality assessment
	Methodological and statistical	High
	External validity issues	Yes
	Final grading	Downgrading
	Final level of evidence	Very low evidence

Different fluid administration approaches – OBS

Observational	6	
Year	2014	
Journal	NC	
First Author	Tagami	
Statistical method	Cox proportional hazards	
Inclusion criteria	SAH	
treatment	Triple H	
control	No triple H	**Outcome**
		Hospital mortality: 35 (19.7%)
Centres	9	**Variable: HR (95%-CI)**
N° patients/centre/year	6	Triple H: 1.27 (0.62-2.62)
Study duration (days)	1247	
Total (included in the model)	178	
	GRADING CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Adequate control for confounding: Only five variables remained in the final model, insufficient number for explanatory purposes. No propensity score included in the model. Statistical reporting: No mention of the variable selection method. No detailed statistical reporting. Methodological and Statistical quality: Hazard proportional assumption not checked. Few variables entered the prediction model.	
Up-grading		
External validity	Multicenter study, with an acceptable number of patients treated per center.	
Conclusive evaluation	GRADE rating up/down	Downgrading
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Methodological and Statistical	Low
	External validity issues	No
	Final grading	Downgrading
	Final level of evidence	Very low evidence

query and body of evidence grading (SAH)

1. Egge A, Waterloo K, Sjoholm H, Solberg T, Ingebrigtsen T, Romner B, (2001) Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. Neurosurgery 49: 593-605; discussion 605-596
2. Lennihan L, Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, Wu YC, Klebanoff LM, Raps EC, Solomon RA, (2000) Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage : a randomized controlled trial. Stroke 31: 383-391
3. Rosenwasser RH, Delgado TE, Buchheit WA, Freed MH, (1983) Control of hypertension and prophylaxis against vasospasm in cases of subarachnoid hemorrhage: a preliminary report. Neurosurgery 12: 658-661
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5. Al-Rawi PG, Zygun D, Tseng MY, Hutchinson PJ, Matta BF, Kirkpatrick PJ, (2005) Cerebral blood flow augmentation in patients with severe subarachnoid haemorrhage. Acta neurochirurgica Supplement 95: 123-127
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SG3 Q2 Does fluid therapy in the management of cerebral ischemia influence outcome (CBF or clinical)?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

We only retrieved observational studies, which did not perform any statistical adjustment for confounders. Studies were small and those with a before-after design that may provide some interesting information were too heterogeneous in terms of design to be combined with a meta-analytical approach. Moreover, studies did not always provide consistent findings. We briefly summarise some of these studies that, at the best, may only provide hypotheses.

Normal saline bolus in six patients with vasospasm determined a significant CBF increase in areas with low perfusion [1]. In 35 patients with vasospasm receiving hypertonic saline boluses also experienced an increase of CBF [2]. Finally,

query and body of evidence grading (SAH)

hypervolemia obtained with albumin, low-molecular-weight dextran, and 10% glicerol was associated with normalization of CBF in the cerebral emisphere where it was reduced by vasospasm [3].

In two studies volemia expansion with hetastarch and albumin, or isovolemic hemodilution obtained by venisection and infusion of albumin and dextran 70, respectively, did not increase CBF [4, 5].

Two studies treated new neurological symptoms in SAH with hypervolemia using albumin, glicerol, dextran, or plasma, monitoring part of these patients with a Swan-Ganz catheter. Neurologic improvement and absence of progression to infarction in most cases led the authors to conclude that hypervolemic therapy was effective [6, 7]. The two studies, however, had very serious limitations connected to the small sample size, to the absence of a instrumental diagnosis of vasospasm, no specific definition of teatment, and lack of adjustment for confounding factor.

query and body of evidence grading (SAH)

1. Jost SC, Diringer MN, Zazulia AR, Videen TO, Aiyagari V, Grubb RL, Powers WJ, (2005) Effect of normal saline bolus on cerebral blood flow in regions with low baseline flow in patients with vasospasm following subarachnoid hemorrhage. J Neurosurg 103: 25-30
2. Tseng MY, Al-Rawi PG, Czosnyka M, Hutchinson PJ, Richards H, Pickard JD, Kirkpatrick PJ, (2007) Enhancement of cerebral blood flow using systemic hypertonic saline therapy improves outcome in patients with poor-grade spontaneous subarachnoid hemorrhage. J Neurosurg 107: 274-282
3. Mori K, Arai H, Nakajima K, Tajima A, Maeda M, (1995) Hemorheological and hemodynamic analysis of hypervolemic hemodilution therapy for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 26: 1620-1626
4. Kim CY, Paek SH, Seo BG, Kim JH, Han DH, (2003) Changes in vascular responses of the basilar artery to acetylcholine and endothelin-1 in an experimental rabbit vasospasm model. Acta Neurochir (Wien) 145: 571-577
5. Ekelund A, Reinstrup P, Ryding E, Andersson AM, Molund T, Kristiansson KA, Romner B, Brandt L, Saveland H, (2002) Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien) 144: 703-712; discussion 712-703
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7. Shimoda M, Oda S, Tsugane R, Sato O, (1993) Intracranial complications of hypervolemic therapy in patients with a delayed ischemic deficit attributed to vasospasm. J Neurosurg 78: 423-429

SG3 Q3 Is there enough evidence to prefer specific fluids (cristalloids/colloids) in the management of cerebral ischemia for CBF augmentation/clinical outcome?

We retrieved only one observational study that considered long-term outcome that was not the kind of objective subgroup 3 was specifically dealing with (probably it overlaps with SG1 objectives) [1]. We however performed the grading, that was *very low*.

References

1. Tseng MY, Hutchinson PJ, Kirkpatrick PJ, (2008) Effects of fluid therapy following aneurysmal subarachnoid haemorrhage: a prospective clinical study. Br J Neurosurg 22: 257-268

query and body of evidence grading (SAH)

Observational study	1	Very low evidence Downgraded study
Year	2008	
Journal	BJN	
First Author	Tseng	
Statistical method	Logistic regression	
Inclusion criteria	SAH	
Treatment	Synthetic colloids	
		Outcome
		unfavourable 6-month GOS (1-3): 52 (32.5%)
Centres	1	**Variable: OR (95%-CI)**
N° patients/centre/year	NA	Colloids 1/day: 2.53 (1.13-5.68)
Study duration (days)	820	Crystalloids 1/day: 0.27 (0.11-0.67)
Total (included in the model)	160	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
	GRADE overall	
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Statistical reporting: The reporting of multivariable results is insufficient to understand how the model was developed in detail. Statistical quality: Variables were selected with an automatic procedure which does not grant the development of a reasonable model especially when the sample size is small. No propensity score was developed although the research was dealing with a treatment. The number of variables were probably too few to predict a complex outcome.	
Up-grading	Size of effect: We did not upgrade for the large effect because it was the result of a biased model.	
External validity		
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

query and body of evidence grading (SAH)

SG3 Q4 Can brain multimodal neuromonitoring parameters (CBF, PbtO2, TCD) be used as trigger or endpoint to guide fluid therapy in the management of cerebral ischemia?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

Two studies investigated fluid administration effect on brain tissue oxygen partial pressure. When a fluid bolus with 250 ml of albumin determined an increase of the cardiac index an improvement in tissue oxygenation was measured [1]. Although the study used a multivariable approach that accounted for multiple measurements, it was carried out on ten patients only raising both internal and external validity issues. The study evidence was, hence, rated *very low*. The second study was carried out on patients with vasospasm following subarachnoid haemorrhage. It concluded that hypervolemia combined with hypertension determined tissue oxygenation improvement but frequent adverse effects. We could not evaluate clearly the effect of hypervolemia alone because of the study design. Evidence was considered *very low*, in this case also.

Several studies used micro-dialysis to measure extracellular glucose, lactate, lactate/pyruvate ratio, glutamate, and glycerol in patients with subarachnoid hemorrhage to detect ischemia [2-7]. These studies, however, did not test the effectiveness of fluid therapy in reversing ischemia. Thus, for the purpose of our review they do not provide useful evidence.

Another study with the same limitations was focused on the comparison of transcranial Doppler and cerebral arterial-venous oxygen differences [8].

query and body of evidence grading (SAH)

1. Kurtz P, Helbok R, Ko SB, Claassen J, Schmidt JM, Fernandez L, Stuart RM, Connolly ES, Badjatia N, Mayer SA, Lee K, (2014) Fluid responsiveness and brain tissue oxygen augmentation after subarachnoid hemorrhage. Neurocrit Care 20: 247-254
2. Sarrafzadeh A, Haux D, Sakowitz O, Benndorf G, Herzog H, Kuechler I, Unterberg A, (2003) Acute focal neurological deficits in aneurysmal subarachnoid hemorrhage: relation of clinical course, CT findings, and metabolite abnormalities monitored with bedside microdialysis. Stroke 34: 1382-1388
3. Unterberg AW, Sakowitz OW, Sarrafzadeh AS, Benndorf G, Lanksch WR, (2001) Role of bedside microdialysis in the diagnosis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 94: 740-749
4. Sarrafzadeh AS, Haux D, Ludemann L, Amthauer H, Plotkin M, Kuchler I, Unterberg AW, (2004) Cerebral ischemia in aneurysmal subarachnoid hemorrhage: a correlative microdialysis-PET study. Stroke 35: 638-643
5. Sarrafzadeh A, Haux D, Plotkin M, Ludemann L, Amthauer H, Unterberg A, (2005) Bedside microdialysis reflects dysfunction of cerebral energy metabolism in patients with aneurysmal subarachnoid hemorrhage as confirmed by 15 O-H2 O-PET and 18 F-FDG-PET. J Neuroradiol 32: 348-351
6. Skjoth-Rasmussen J, Schulz M, Kristensen SR, Bjerre P, (2004) Delayed neurological deficits detected by an ischemic pattern in the extracellular cerebral metabolites in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 100: 8-15
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8. Oertel MF, Scharbrodt W, Wachter D, Stein M, Schmidinger A, Boker DK, (2008) Arteriovenous differences of oxygen and transcranial Doppler sonography in the management of aneurysmatic subarachnoid hemorrhage. J Clin Neurosci 15: 630-636

SG3 Q5 Should a change in neurological status trigger a change in fluid management away from euvolemia in stroke patients with cerebral ischemia?

Studies were too heterogeneous to be combined in an overall body of evidence. Their individual grading (reported in the quality assessment forms at the end of this document) hence corresponds to the body of evidence grading.

query and body of evidence grading (SAH)

Two studies treated new neurological symptoms in SAH with hypervolemia using albumin, glicerol, dextran, or plasma, monitoring part of these patients with a Swan-Ganz catheter. Neurologic improvement and absence of progression to infarction in most cases led the authors to conclude that hypervolemic therapy was effective [1, 2]. The two studies, however, had very serious limitations connected to the small sample size, to the absence of a instrumental diagnosis of vasospasm, no specific definition of teatment, and lack of adjustment for confounding factor.

Both GRADE and our final evaluations rated evidence provided by both studies as *very low*.

1. Tanabe T, Saitoh T, Tachibana S, Takagi H, Yada K, (1982) Effect of hyperdynamic therapy on cerebral ischaemia caused by vasospasm associated with subarachnoid haemorrhage. Acta Neurochir (Wien) 63: 291-296
2. Shimoda M, Oda S, Tsugane R, Sato O, (1993) Intracranial complications of hypervolemic therapy in patients with a delayed ischemic deficit attributed to vasospasm. J Neurosurg 78: 423-429

SG3 Q6 Should early goal directed fluid therapy (GEDI) have a place in the management of DCI?

SG1 Q5 Is there evidence to support the use of hemodynamic monitoring or echocardiography to guide the fluid management in the resuscitation of acute brain injury (TBI, SAH, ICH, severe MCA stroke)?

The answer to Q6 also provided the answer to SG1 Q5.

Only one RCT and three observational studies received a detailed reporting of grading. The RCT was focused on the maintenance of a high global end-diastolic volume index (GEDI) measured using invasive cardiac monitoring compared to standard treatment [1]. The trial was negative in terms of DCI and 3 moths poor outcome frequency. A predefined analysis on patients with poor grade subarachnoid hemorrhage that were stratified at randomization, showed a statistically significant reduction of both outcomes. However, according to our calculation neither results was statistically significant (p = 0.10 for DCI and p = 0.07 for 3-month poor outcome) using the same statistical tests as the authors. Either way, the latter was a subgroup analysis and thus could only generate hypothesis and not provide definitive conclusions. We graded evidence provided by the study as *moderate* but raising doubts on the reliability of the statistical significance of the study.

The observational studies were methodologically biased and provided *very low* quality evidence [2-4].

We only mention, without reporting in detail our grading process, other observational studies heterogeneous in design and methodologically poor providing evidence [5-9].

Reference

1. Mutoh T, Kazumata K, Terasaka S, Taki Y, Suzuki A, Ishikawa T, (2014) Early intensive versus minimally invasive approach to postoperative hemodynamic management after subarachnoid hemorrhage. Stroke 45: 1280-1284
2. Mutoh T, Kazumata K, Terasaka S, Taki Y, Suzuki A, Ishikawa T, (2014) Impact of transpulmonary thermodilution-based cardiac contractility and extravascular lung water measurements on clinical outcome of patients with Takotsubo cardiomyopathy after subarachnoid hemorrhage: a retrospective observational study. Crit Care 18: 482
3. Tagami T, Kuwamoto K, Watanabe A, Unemoto K, Yokobori S, Matsumoto G, Yokota H, Group SAHPS, (2014) Optimal range of global end-diastolic volume for fluid management after aneurysmal subarachnoid hemorrhage: a multicenter prospective cohort study. Crit Care Med 42: 1348-1356
4. Yoneda H, Nakamura T, Shirao S, Tanaka N, Ishihara H, Suehiro E, Koizumi H, Isotani E, Suzuki M, Group SAHPS, (2013) Multicenter prospective cohort study on volume management after subarachnoid hemorrhage: hemodynamic changes according to severity of subarachnoid hemorrhage and cerebral vasospasm. Stroke 44: 2155-2161
5. Kim CY, Paek SH, Seo BG, Kim JH, Han DH, (2003) Changes in vascular responses of the basilar artery to acetylcholine and endothelin-1 in an experimental rabbit vasospasm model. Acta Neurochir (Wien) 145: 571-577
6. Mori K, Arai H, Nakajima K, Tajima A, Maeda M, (1995) Hemorheological and hemodynamic analysis of hypervolemic hemodilution therapy for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 26: 1620-1626
7. Tanabe T, Saitoh T, Tachibana S, Takagi H, Yada K, (1982) Effect of hyperdynamic therapy on cerebral ischaemia caused by vasospasm associated with subarachnoid haemorrhage. Acta Neurochir (Wien) 63: 291-296
8. Shimoda M, Oda S, Tsugane R, Sato O, (1993) Intracranial complications of hypervolemic therapy in patients with a delayed ischemic deficit attributed to vasospasm. J Neurosurg 78: 423-429
9. Kurtz P, Helbok R, Ko SB, Claassen J, Schmidt JM, Fernandez L, Stuart RM, Connolly ES, Badjatia N, Mayer SA, Lee K, (2014) Fluid responsiveness and brain tissue oxygen augmentation after subarachnoid hemorrhage. Neurocrit Care 20: 247-254

GEDI - RCT

RCT 1			
Year	2014	First Author	Mutoh
Journal	Stroke		
Sample	Poor grade SAH (subgroup analysis)		
Treatment	GEDI ≥ 680 ml/m2		
Control	Standard treatment		
Outcome	DCI		
		Outcome	
	n° pz	n	%
Treatment	80	4	5.0
Control	80	11	13.8
Total	160	15	9.4
Centres	Single Center	delta 8.8 (95%-CI 18.5 to 0.5)	
Power	0.484	NNTB 11 (95%-CI NNTB 5 to ∞ to NNTH 190)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	No
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	No
		Statistical reporting	Sufficient for quality assessment
		Indirectness	No
		Imprecision	serious
		Publication bias	Not assessable
		Inconsistency with other trials	No
Up-grading		Size of effect	Large
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Methodological and statistical quality: A stratified randomization was wisely performed on the basis of WFNS I-III and IV-V. Outcome assessment was performed by a blinded investigator. The sample size was based on a very large reduction of DCI incidence (25%) assuming a very high incidence in the control group (40%), that were not supported by literature data;	
Up-grading		Size of effect Large: The large relative risk reduction (64%) was barely not statistically significant, but confidence intervals were large and methodology was not sufficiently robust. There was no indication for upgrading.	
		GRADE rating	Moderate evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Moderate evidence

GEDI - RCT

RCT			
Year	2014	First Author	Mutoh
Journal	Stroke		
Sample	Poor grade SAH (subgroup analysis)		
Treatment	GEDI 680 ml/m2		
Control	Standard treatment		
Outcome	3-months mRS 4-6		
		Outcome	
	n° pz	n	%
Treatment	80	53	66.3
Control	80	64	80.0
Total	160	117	73.1
Centres	Single Center	delta 13.8 (95%-CI 26.9 to 0)	
Power	0.510	NNTB 7 (95%-CI NNTB 4 to ∞ to NNTH 8762)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	No
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	No
		Bias	serious
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		Indirectness	No
		Publication bias	No
		Inconsistency with other trials	No
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose/response	Not relevant
		DETAILS	
Downgrading		Bias: A stratified randomization was wisely performed on the basis of WFNS I-III and IV-V. Outcome assessment was performed by a blinded investigator. The sample size was based on a very large reduction of DCI incidence (25%) assuming a very high incidence in the control group (40%), that were not supported by literature data; Publication bias: The large relative risk reduction (64%) was barely not statistically significant, but confidence intervals were large and methodology was not sufficiently robust. There was no indication for upgrading;	
Up-grading			
		GRADE rating	Moderate evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		External validity issues	Yes
		Final grading	Downgrading
		Final level of evidence	Moderate evidence

OBSERVATIONAL

Observational study	1	Very low evidence - Downgraded study
Year	2014	
Journal	CC	
First Author	Mutoh	
Statistical method	Logistic regression	
Inclusion criteria	SAH in Takotsubo cardiomyopathy	
Risk factor	Cardiac Function Index (CFI) > 4.2/min	
		Outcome
		#VALUE!
Centres	1	**Variable: OR (95%-CI)**
N° patients/centre/year	NA	CFI > 4.2 duration (days): 2.14 (1.33-2.84)
Study duration (days)	2921	
Total (included in the model)	46	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
	GRADE overall	
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose / response	Not applicable
	DETAILS	
Downgrading	Statistical reporting: The reporting of multivariable results is insufficient to understand how the model was developed in detail. Statistical quality: Bivariate analysis was used for variables selection using 0.05 cut-off for p-value, which generates a high risk of excluding important predictors. It was followed by an automatic procedure which does not grant the development of a reasonable model. Finally, logistic regression is not the best statistical tool for managing time-dependent variables. With only 46 patients included in the model (the number of outcomes were not specified) and three variables included the model was surely overfitted. On the other hand the only three variables generate an underfitted model for its explanatory purposes.	
Up-grading	Size of effect: We did not upgrade for the large effect because it was the result of a biased model.	
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

OBSERVATIONAL

Observational study	2	Very low evidence ? Downgraded study
Year	2014	
Journal	CCM	
First Author	Tagami	
Statistical method	Cox proportional hazards	
Inclusion criteria	SAH	
Risk factor	Mean GEDI (ml/m2)	
		Outcome
		1-year mortality: 35 (19.4%)
Centres	9	**Variable: OR (95%-CI)**
N° patients/centre/year	6	Mean GEDI (100 units variation): 0.72 (0.58-0.91)
Study duration (days)	1277	
Total (included in the model)	180	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	serious
	GRADE overall	
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose / response	Not applicable
	DETAILS	
Downgrading	Measurement of outcome: A combined outcome including severe disability besides mortality is to be preferred to mortality alone when dealing with long-term neurologic outcome. Statistical quality: With only 35 patients developing DCI and at least eight variables included the model was surely overfitted. On the other hand only 3-4 variables that could have been included in the model to avoid overfitting would have generated an underfitted model for its explanatory purposes.	
Up-grading		
External validity	No external validity issues	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	No
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

OBSERVATIONAL

Observational	3	Very low evidence - No grading modification
Year	2013	
Journal	Stroke	
First Author	Yoneda	
Statistical method	Logistic regression with propensity score adjustment	
Inclusion criteria	SAH patients	
Risk factor	Mean GEDI (ml/m2)	
		Outcome
		DCI: 52 (25.5%)
Centres	9	**Variable: DCI (95%-CI)**
N° patients/centre/year	6	Mean GEDI (per unit variation): 0.997 (0.995-1.0)
Study duration (days)	1278	
Total (included in the model)	204	
	GRADE CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	No
	GRADE overall	
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose/response	Not applicable
	DETAILS	
Downgrading	Statistical quality: Insufficient information on how the model was developed (e.g. variable selection, management of continuous variables) and on the results of the modewere provided. We suppose that the risk of underfitting on one hand and and overfitting on the other, have limited the reliability of the analyses.	
Up-grading		
External validity	No external validity issues	
Conclusive evaluation	GRADE rating up/down	No grading modification
	GRADE rating	Very low evidence
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	Low
	External validity issues	No
	Final grading	No grading modification
	Final level of evidence	Very low evidence