Evidence for Mannitol as an Effective Agent Against Intracranial Hypertension: An Individual Patient Data Meta-analysis

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Abstract

Mannitol is currently used to reduce intracranial pressure (ICP), but the evidence supporting its usefulness has been questioned. We aim to meta-analyze the effectiveness of mannitol in reducing ICP in adult patients with cerebral injuries and its dependency on baseline ICP values, comparing findings from individual patient data (IPD) and aggregated data (AD) meta-analysis performed on the same studies. We searched the Medline database, with no time limitation, through March 1, 2019. We selected studies for which IPD were available, with a before-after design, concerning adult patients with traumatic cerebral hemorrhages, subarachnoid hemorrhages, or hemorrhagic and ischemic stroke, treated with mannitol for increased intracranial hypertension. We extracted ICP values at baseline and at different time-points, and mannitol doses. We used a multilevel approach to account for multiple measurements on the same patient and for center variability. The AD meta-analysis and meta-regression were conducted using random-effects models. Three studies published IPD, and four authors shared their datasets. Two authors did not own their datasets anymore. Eight authors were unreachable, while 14 did not answer to our request. Overall, 7 studies provided IPD for 98 patients. The linear mixed-effects model showed that ICP decreased significantly after mannitol administration from an average baseline value of 22.1 mmHg to 16.8, 12.8, and 9.7 mmHg at 60, 120, and 180 min after mannitol administration. ICP reduction was proportional to baseline values with a 0.64 mmHg decrease for each unitary increment of the initial ICP value. Dose did not influence ICP reduction. The AD meta-analysis, based on data collected between 30 and 60 min from mannitol administration not accounting for multiple time-point measurements, overestimated ICP reduction (10 mmHg), while meta-regression provided similar results (0.66 mmHg decrease for each unitary increase of initial ICP). Mannitol is effective in reducing pathological ICP, proportionally to the degree of intracranial hypertension. IPD meta-analysis provided a more precise quantification of ICP variation than the AD approach.

Introduction

Clinical practice guidelines propose evidence-based statements to assist healthcare providers, recipients, and other stakeholders to make informed decisions about appropriate treatment interventions. Rigorous review of the evidence must, therefore, be integrated with practical advice because clinicians rely on guidelines to guide treatment decisions in many areas of clinical practice [1]. Often, however, an apparently rigorous review of the literature and evidence-based recommendations fail to provide useful advice for clinicians.

In line with this, mannitol is commonly used for lowering increased intracranial pressure (ICP) after traumatic brain injury (TBI), and in other acute clinical conditions such as subarachnoid hemorrhage, intracerebral hemorrhage, and malignant stroke. ICP reduction after mannitol administration is a common and consistent observation; mannitol infusions may reverse life-threatening crises such as an impending brain stem herniation, within minutes. Despite such clinical experience, and established associations between intracranial hypertension and increased mortality, a clear link between ICP-lowering therapies and improved outcomes has not been confirmed, most likely because of the complexity of the underlying disease processes and interactions between multiple treatment interventions.

As a consequence, a rigorous review of the literature, particularly when focused on its failure to demonstrate improved outcomes, may lead to frustrating conclusions. For example, the latest iteration of the Brain Trauma Foundation guidelines (2016) states: "…there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe TBI" [2]. Consequently, the committee provided a recommendation "not supported by evidence meeting current standards," which, in the end, may discourage from the use of hyperosmolar agent to control ICP. Notwithstanding this, every clinician understands the importance of intracranial hypertension and the need for effective therapies to lower a pathologically increased ICP. The absence of clinical guidance in this regard is therefore unhelpful.

In a recent review, the authors performed a meta-analysis and meta-regression which suggested that mannitol effectively decreases ICP, and the reduction is proportional to the initial ICP value and to mannitol dose [3]. However, the limits of meta-analysis and meta-regression from aggregated data (AD) are well known, and meta-analyses from individual patient data (IPD) should be preferred whenever possible [4,5,6,7].

The aims of this study were twofold: to perform an IPD meta-analysis on the effects of mannitol on ICP and to compare this approach with the AD meta-analytical approach.

Methods

We searched the MEDLINE database running the following code, with no time limitations, on the March 1, 2019:

("mannitol"[MeSH Terms] OR "mannitol"[All Fields]) OR "hypertonic saline"[All Fields]) AND (ICP[All Fields] OR "intracranial hypertension"[All Fields] OR "intracranial pressure"[All Fields]) AND ("humans"[MeSH Terms] AND English[lang]).

Two members of the study group (not among the authors) screened the titles and abstracts, including all studies investigating the use of mannitol for the treatment of intracranial hypertension in patients with cerebral injuries including traumatic cerebral hemorrhages, subarachnoid hemorrhages, or hemorrhagic and ischemic stroke. Studies testing mannitol continuous infusion, focused on children, case reports, letters to the editor, editorials, guidelines, surveys, and reviews were excluded.

If abstract evaluation did not provide sufficient information, full texts were retrieved and submitted to further selection that was performed by the methodologist (DP), who applied the same inclusion/exclusion criteria, including only studies with a before-after design.

Data extraction was performed according to a predefined plan, using dedicated electronic forms. We collected data on baseline ICP values and measurements after the administration of mannitol at different time-points, other osmotic treatment, any other intervention aimed at reducing ICP (such as sedative boluses, cerebral-spinal fluid drainage, fever control, interventions to modify arterial pressure), and the performance of decompressive craniotomy.

This search was part of a systematic review recently performed by the "ESICM Consensus on Fluids in Acute Brain Injury" [3]. This review was registered on PROSPERO with the ID 42016052123. One of the objectives of the review was to investigate the effectiveness of mannitol in reducing ICP and the dependency of this reduction on initial ICP values and mannitol doses, with AD meta-analysis and meta-regression. The analysis on IPD was part of the original plan but was not ultimately carried out because it was too extensive for the aims of the review. In the present review, we conclude the objectives of the original plan, with the analysis at patient level. We selected studies for which IPD were either published or provided by the authors that were contacted by email or through social networks for scientists between July and August 2019.

We complied with the PRISMA Statement for IPD reviews and meta-analyses [8]. The quality of evidence was assessed consistently with the GRADE criteria [9].

Statistical Analysis

The details are reported in Supplemental text 1. We performed our analyses at patient level with linear mixed effects (LME), using a one-step approach to account for clustering among patients in the same study. This statistical method is a multivariate approach that allows accounting for multiple measurements on single patients and for

heterogeneity between patients and groups of patients, providing more reliable regression parameters. The structure of the model was on three levels: mannitol boluses (each patient could receive more than one), nested in patients, nested in studies. This last level was considered to account for differences in case-mix and performance of the different centers.

To explore the effectiveness of mannitol, we developed the LME-time model, which investigated the variation of initial ICP (at time 0, just before mannitol administration) in relation to time. We could only use an exponential function to regulate this relation, implying that ICP tends to zero at infinite time, which may be questionable in theoretical terms, although in practice it should not substantially affect the shape of the regression line when monitoring the first few hours after mannitol administration. Nevertheless, we wanted to support the findings of this analysis using a mixed-effects nonlinear model (NLM-time), which allows assuming a more realistic regression line shape without, however, adjusting for confounders as the LME-time model did, for inherent limits of the statistical package.

Secondly, we tested the dependence of the largest ICP variation dependence on initial ICP values in the LME-ICP model.

Finally, we investigated the influence of dose, independently and associated with initial ICP with the LME-dose models.

To formally select the model that best fitted the data, we used the difference between the deviances the restricted maximum likelihood that is used to estimate parameters in LME models.

On the same dataset, we performed an AD meta-analysis and meta-regression, to assess the reliability of these two approaches compared to IPD meta-analysis. The meta-analysis was structured on a before-after design where ICP measurements were made at time zero and, in a timeframe, ranging between 30 and 60 min after mannitol bolus to include all the studies in the review (Supplemental text 1). We considered only the first bolus when multiple mannitol administrations were performed for studies for which IPD were available.

Meta-analysis was used as the comparator of the LME-time model. The meta-analysis measured the variation of ICP before and after mannitol administration in the considered timeframe. Its findings are thus only partially comparable with those of the LME-time model that investigate the same events in a larger timeframe. The correspondence between the two methods was more fairly assessed using the LME-time model structure (LME-time-60) limiting our analysis to observations within 60 min from mannitol administration, since the meta-analysis included only ICP measurements performed between 30 and 60 min. The meta-regression investigated the dependency of ICP variation after the mannitol bolus on initial ICP and dose.

We measured heterogeneity with I^2, the percentage of total variation attributable to true heterogeneity and not to chance [10, 11]. We calculated imprecision as the spread of heterogeneity 95% confidence interval (95% CI). The Cochran's *Q* test was used to assess statistical heterogeneity under the null hypothesis of homogeneity [12].

Random-effects models were used for the meta-analysis and mixed-effects models for the meta-regression. We used funnel plots to graphically illustrate presence of asymmetry and potential publication bias, and statistical tests to assess asymmetry formally [13], 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 [14].

Predefined sensitivity analyses were performed using those studies not included in the main analysis, investigating the effect of mannitol and of initial ICP on ICP reduction. Results were considered significant at $p < 0.05$. All calculations were performed with the *metaphor, nlme*, and the *saemix* packages for R (version 3.4.3 for Mac) [15,16,17,18].

Results

The study selection process is reported in the PRISMA-IPD flowchart (Supplemental Fig. 1). The compliance to the PRISMA-IPD Statement recommendations is summarized in the PRISMA checklist (Supplemental text 2). Thirty-one studies including 766 patients were selected. IPD was published in three studies [19,20,21], while four authors of the remaining studies provided IPD [22,23,24,25], that was thus available for 7 single center studies accounting for 98 patients (Table 1). The reporting of variable that could affect ICP variations was overall scanty and did not allow adequate adjustment for confounders. However, since the before-after design of the study has intrinsic strengths (i.e., testing the effects of therapy on the same patient over a narrow time frame accounts for many patient-related variables), the overall quality of these studies was not downgraded and considered *low* according to the GRADE parameters.

LME-time models versus meta-analysis

The best LME-time model (Fig. 1; Table 2, Supplemental Table 1) that showed a statistically significant exponential relation between ICP and time after mannitol bolus (the latter being the only fixed effect according to the statistical design), included as random variables *study* and *patient* (both intercept and slope), and *bolus* (only intercept). Overall there were 523 observations nested in 143 boluses, for 98 patients, divided in 7 studies. At time zero (before mannitol was administered), the ICP value according to the regression function was 22.1 mmHg. τ was the time at which ICP decreased to 36.8% of its initial value (i.e. about 8 mmHg) and was equal to 220 min. Other ICP values derived with the regression parameters were 16.8, 12.8, and 9.7 mmHg measured at 60, 120, and 180 min from mannitol administration. The

correspondent ICP values calculate using the NLM-time models were 24.0 mmHg (at time zero), 20.1, 17.2, and 15.2 at the three time-points (Fig. 2).

The meta-analysis on AD included 91 of 98 patients, because seven did not have any ICP measurement in the study timeframe (30 and 60 min from mannitol bolus). ICP reduction was 10.0 mmHg (95% confidence interval 6.7–13.3, $p < 0.001$) with the weighted initial average ICP equal to 26.4 mmHg and a weighted mean time for ICP measurements of 46 min after mannitol bolus. Heterogeneity was high and statistically significant (I^2 69%, $p < 0.001$, Supplemental Fig. 2).

According to our LME-time model instead, at 46 min, ICP decrease was 4.1 mmHg from an initial value of 22.1 mmHg. The LME-time-60 model, instead, indicated a 10.6 mmHg reduction from the initial value of 25.9 mmHg (Table 2).

LME-ICP and LME-Dose Models Versus Meta-Regression

The best LME-ICP model according to the deviance difference statistical test, included as random variables *bolus* (only intercept), *patient* (intercept and slope), and *study* (only slope) (Supplemental Table 2). It showed a statistically significant linear relation between initial ICP and delta ICP with a 0.64 mmHg increase for each unitary increase in initial ICP ($p < 0.001$, Table 2, Fig. 3). Overall, we had 143 observations (one for each mannitol bolus), in 98 patients from 7 studies.

According to the meta-regression, based on the same set of studies as the meta-analysis, ICP reduction increased linearly by 0.66 mmHg for each unitary increase of initial ICP ($p < 0.001$, Supplemental Fig. 3). This relation was visually confirmed on the analysis on the single studies (Supplemental Fig. 4). Heterogeneity was no longer statistically significant compared to the meta-analysis (I^2 28%, $p < 0.105$), although the high level of imprecision (95% CI 0–89) did not allow ruling out high degrees of heterogeneity between studies. Symmetry improved after accounting for initial ICP (Supplemental Fig. 5).

The LME-dose models including both dose and initial ICP or only dose as fixed effects did not show any statistically significant effect of dose on ICP variation (Table 2). The model was not significantly different from the LME-ICP model, with the same structure but without dose as fixed effect ($p = 0.523$). Mannitol doses within the 10th and the 90th percentile (80% of all doses) ranged from 0.54 to 1.01 g/kg. The meta-regression analysis, using dose as the only moderator, provided similar findings with no statistically significant effect on ICP (Table 2). We could not develop a multivariate model including both dose and initial ICP because of the limited number of studies available.

Sensitivity Analysis on Studies Not Providing IPD

Of the 24 studies for which IPD were not available, 10 did not provide means and standard errors needed to perform meta-analytical computations, while in 8 there were

multiple comparison issues, for which we reported only crude estimates with confidence intervals. Thus, only 6 (including 96 patients) were available for a sensitivity analysis using a meta-analytical and meta-regression approach (Supplemental text 3 and Supplemental Figs. 6, 7, 8). The meta-analysis showed similar ICP reductions compared to the main AD meta-analysis (12.5 vs. 10 mmHg) and the dependency of ICP reduction on initial ICP values at meta-regression.

In the 8 studies not suitable for meta-analysis, we reported ICP reductions that were consistent across studies and comparable with findings from the sensitivity AD meta-analysis and the main analysis (Supplemental Fig. 9).

Discussion

Main Findings

The first objective of our analysis was to verify the capability of mannitol administration to reduce ICP by examining seven studies at the patient level. According to our LME-time model, mannitol reduced an elevated ICP. This positive effect was rapid, with a clear ICP reduction during the first hour after injection from 22.1 mmHg to 16.8, down to 12.8 at the end of the second hour, and still detectable at 3–4 h after infusion. The confirmatory analysis applying the NLM-time model showed similar variations between time-points, but set at higher values, consistently with the fact that ICP was tied to a plateau by the model, while it tended to zero in the LME-time model. This model, however, did not adjust for confounders as the main analysis did. Indeed the LME-time model included, for example, *study* as a random variable, thus controlling for case-mix and study designs differences.

Both models, however, showed that mannitol administration reduces ICP pathological values to normality.

This ICP-reducing effect of mannitol was more pronounced at higher ICP values, so a quantifiable relationship between the baseline ICP value and the extent of pressure reduction was identifiable. A plausible interpretation of this finding refers to the exponential shape of the pressure/volume curve of the intracranial content [19, 26].

Our sensitivity analysis conducted on the studies not providing IPD confirmed the findings of the main analysis meta-analysis and meta-regression.

The second objective of our study was to compare IPD with AD meta-analysis. The meta-analytical approach at study level has several serious limitations that are overcome by the use of IPD meta-analysis, such as the possibility to account for multiple measurements on same patients performed at different time-points [4]. Thus, not surprisingly, our LME-time model indicated a less sharp ICP reduction, compared to the meta-analysis, since it accounted and modeled measurements performed in a wider timeframe, providing a more reliable picture, overall providing more reliable predictions.

Although meta-regression may be a useful tool to assess the influence of moderators on the outcome reducing heterogeneity, it may provide misleading results depending on the use of average patient features measured at study level as covariates [5]. In our case, we detected a dependency of ICP decrease on initial ICP values between studies, but, theoretically, we did not know whether within each study this dependency was present or not. However, our LME-ICP model that measured the same outcome (i.e., the lower ICP value after mannitol administration) but accounted for multiple measurements on same patients and on study, provided strikingly similar results. This means that meta-regression was a reliable approach in our case.

Our results are less informative as far as the mannitol dose is concerned. The LME models, adjusting for dose alone and combined with initial ICP, found no statistically significant effect (Table 2), which corresponded to the meta-regression findings. However, the studies report extremely variable doses (from 0.54 to 1.5 g/kg) but with a narrow spread (80% of doses were within 0.5 and 1 g/kg) in a relatively limited sample, so that any meaningful interpretation could not be supported.

How Our Data Compare with the Previous Literature and Guidelines

Our analysis at patient level confirms a recent meta-regression and meta-analysis elaborated by the European Society of Intensive Care Medicine [3]. Those analyses have documented an ICP reduction by mannitol, more striking when the baseline ICP value was elevated. Our findings, however, seem to conflict with other available evidence.

A systematic literature review published in 1998 [27] selected only one single trial on mannitol, including 41 patients, and concluded that its effectiveness in clinical management was questionable. When mannitol was evaluated together with other common interventions, as barbiturates or hyperventilation, the conclusions were that, based on rigorous evidence, current therapies (including mannitol) could be associated either with a limited benefit or with a moderate increase of unfavorable outcome.

Recent guidelines also did not recommend the use of mannitol, because of insufficient evidence about effects on outcome. Notably, the previous guidelines edition identified the effectiveness of mannitol to control a raised ICP. The newest edition, on the contrary, states that current standards for evidence no longer support that statement [2].

As a result, a purer quest for evidence concludes that the use of mannitol is not supported by adequate demonstration.

Medicine Based on Published Evidence, Facts, and Clinical Reasoning

Hyperosmolar agents are still part of the therapeutic arsenal to treat intracranial hypertension in many centers, even when their use is not supported by international guidelines and while strong criticisms have been raised in the literature. These criticisms are mainly based on the lack of studies that could demonstrate a beneficial outcome. However, clinicians still use mannitol for several reasons. First, there is strong plausibility that osmotic drugs are effective in intracranial hypertension, in relation to their pharmacokinetics and pharmacodynamics proprieties

[28,29,30,31,32]. Second, the effects of therapy in clinical practice are clear and reproducible at the bedside. Third, there is very high consistency among studies that report the effect of mannitol in lowering ICP.

This reproducible effect and high consistency have been confirmed by our review. Although the included studies are observational, they adopted a before-after design that has several strengths. In general, they have the advantage of testing the effects of therapy on the same patient, thus accounting for many patient-related variables. Moreover, in the specific case of intracranial hypertension treatment, they are carried out in a narrow time frame, when other conditions that could influence the response have an acceptable probability of being constant.

Our study provides evidence in support of the effect of mannitol to reduce ICP, but at the same time, we acknowledge that the effect on long-term outcomes remains unproven. Setting up large RCTs to demonstrate such benefit is a challenge. The heterogeneity of TBI and the complexity of the overall intensive care management would make the isolation of the net effect of a single intervention, such as mannitol, on outcome extremely cumbersome, or impossible. Perhaps large multicenter observational studies would shed light on middle and long-term efficacy. Comparative effectiveness research as currently explored in ongoing data collections worldwide (https://www.center-tbi.eu/, http://creactive.marionegri.it/, https://tracktbi.ucsf.edu/) seems a possible answer [33].

However, imperfect evidence and a lack of large randomized controlled trials (RCTs) should not lead to therapeutic skepticism. Clinical reasoning, based on the demonstrated dangerousness of raised ICP, an event that may directly damage the brain and kill the subject if untreated, mandates the use of therapies for lowering ICP, with or without RCTs.

Conclusions

Our review confirms the consistent and clear effect of osmotic therapy on acutely life-threatening intracranial hypertension. This is the best possible evidence currently available, and should support clinical practice development and updates.

Electronic supplementary material

The online version of this article (https ://doi.org/10.1007/s1202 8-019-00771 -y) contains supplementary material, which is available to authorized users.

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Author's Contributions

DP, NS, and GC provided substantial contributions to the conception and design of the work. All authors contributed to the interpretation of the findings, drafted the work, and revised it critically for important intellectual content. DP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors approved the final version to be published.

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Conflict of interest

No potential conflicts of interest are declared.

Ethical Approval/Informed Consent

No ethical approval is required for this type of study.

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Table 1 Main features of the studies included in our review

From: Evidence for Mannitol as an Effective Agent Against Intracranial Hypertension: An Individual Patient Data Meta-analysis

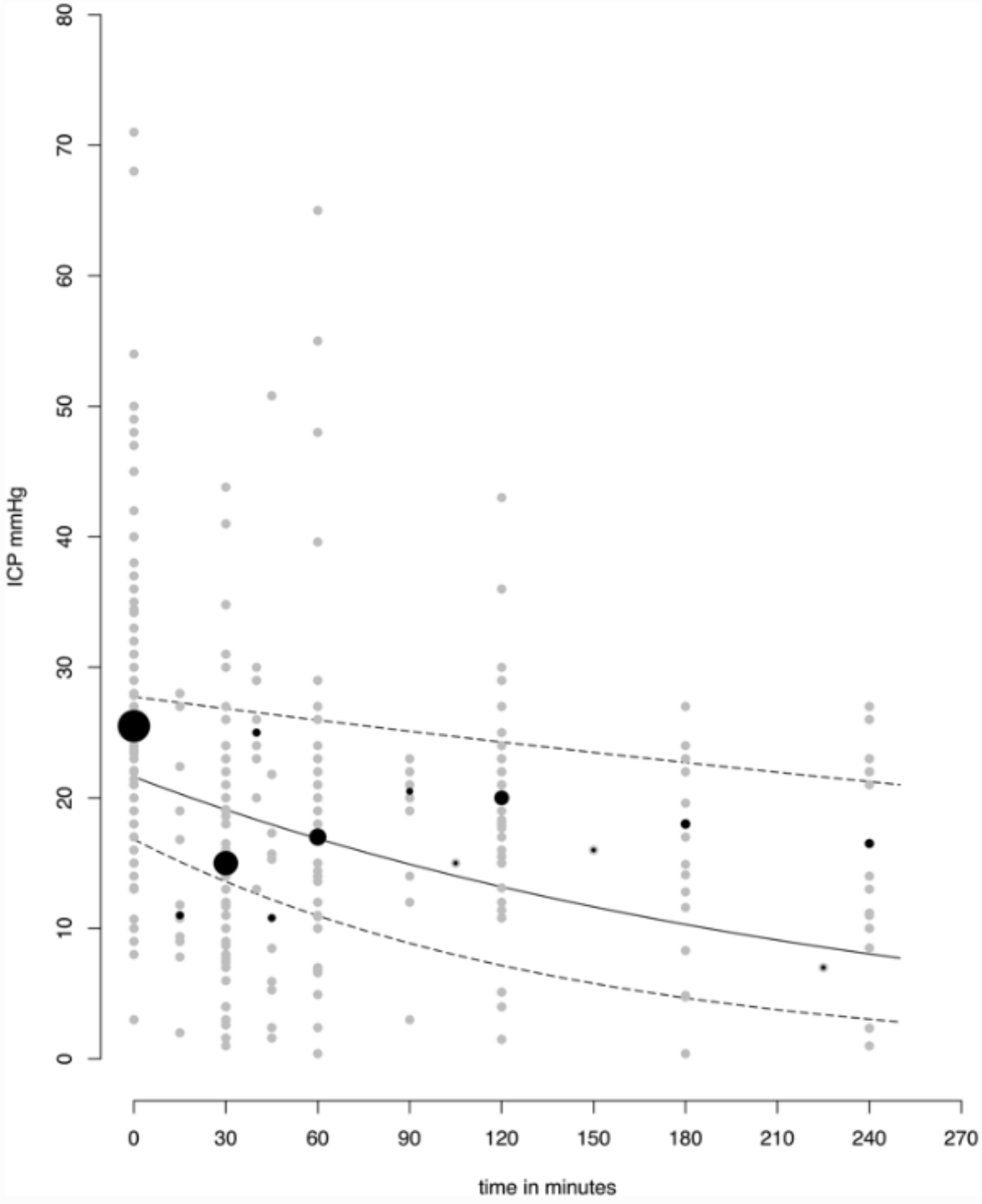
Author, year	Cerebral injury	Patients *n*	ICP measurement time (min)	Mannitol dose g/kg
Francony [22]	TBI	9	0, 30, 60, 90, 120	0.60
Helbok et al. [23]	SAH, ICH	11	0, 15, 30, 45, 60, 120, 180, 240	1.00
Ichai et al. [24]	TBI	9	0, 30, 60, 120, 180, 240	1.50
Launey et al. [19]	TBI, SAH	13	0, 40	0.54 §
Muizelaar et al. [20]	TBI	32	0, 30	0.66 §
Oddo et al. [25]	TBI	11	0, 30, 60, 120	0.75
Ware et al. [21]	TBI	13	0–225*	1.01

Doses were the same for all patients in the studies besides § which provided average values

ICH intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *TBI* traumatic brain injury

*In this study, measurements were performed at non-fixed time-points; thus, the range is provided

Fig. 1



LME-time model according to an exponential relation between time and ICP variation. Medians for single time-points are reported as black circles with a diameter proportional to the number of observations

Table 2 Comparison between LME models and meta-analytical approaches investigating the effects of time, initial ICP, and dose on ICP variation after mannitol bolus

From: Evidence for Mannitol as an Effective Agent Against Intracranial Hypertension: An Individual Patient Data Meta-analysis

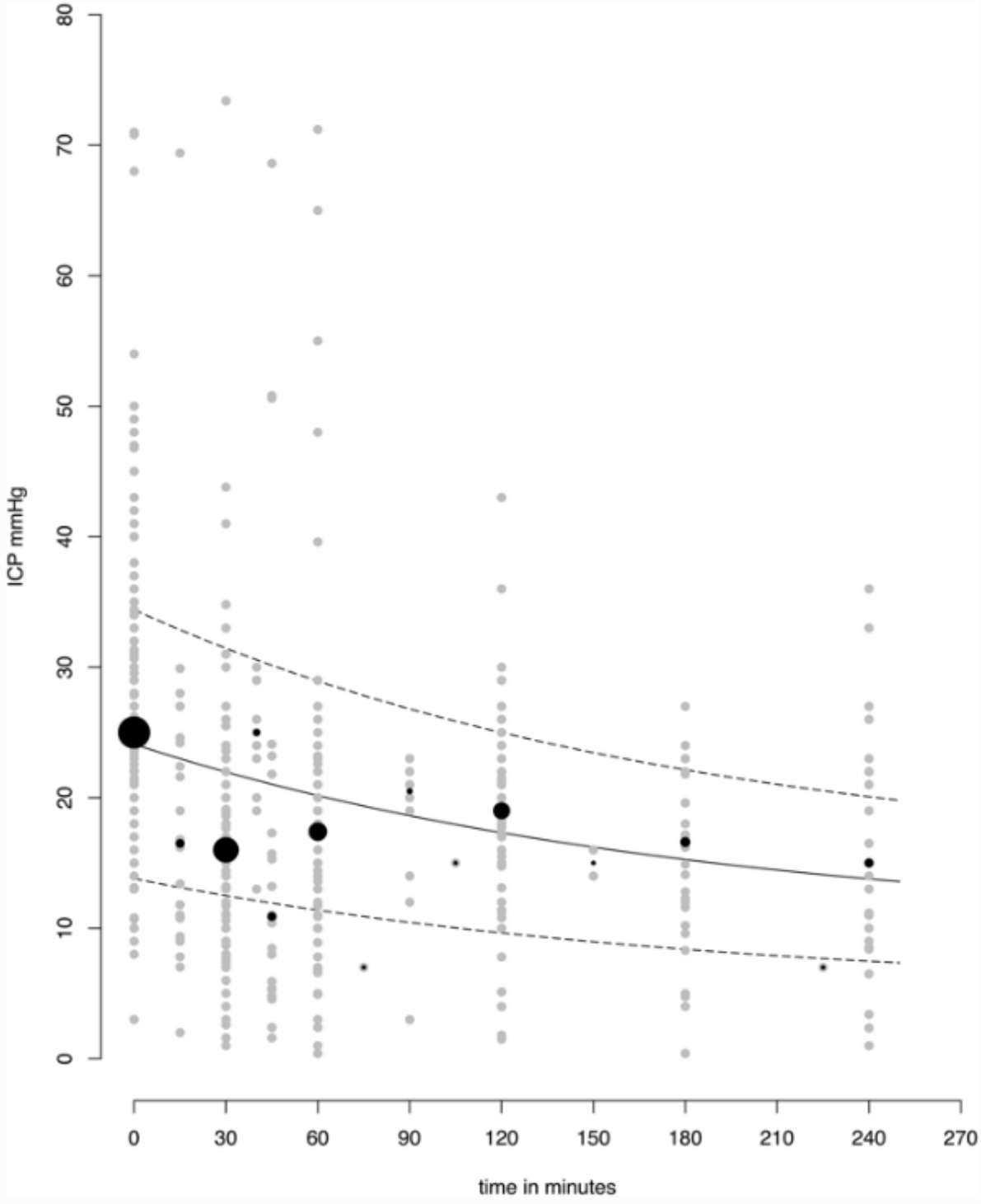
Effect on ICP variation	Model	Initial ICP (mm Hg)	ICP decrease at 46 min (mm Hg)	*p* value
Effect of time	LME-time	22.1	4.1	<0.001
	LME-time-60	25.9	10.6	<0.001
	Meta-analysis	26.4	10.0	<0.001

ICP intracranial pressure, *LME* linear mixed effects

	Model	ICP decrease for unitary Initial ICP increase (mm Hg)	*p* value
Effect of initial ICP	LME-ICP	0.64	<0.001
	Meta-regression-ICP	0.66	<0.001
Effect of dose	LME-dose-ICP	− 0.37	0.305
	LME-dose	0.34	0.329
	Meta-regression-dose	0.16	0.852

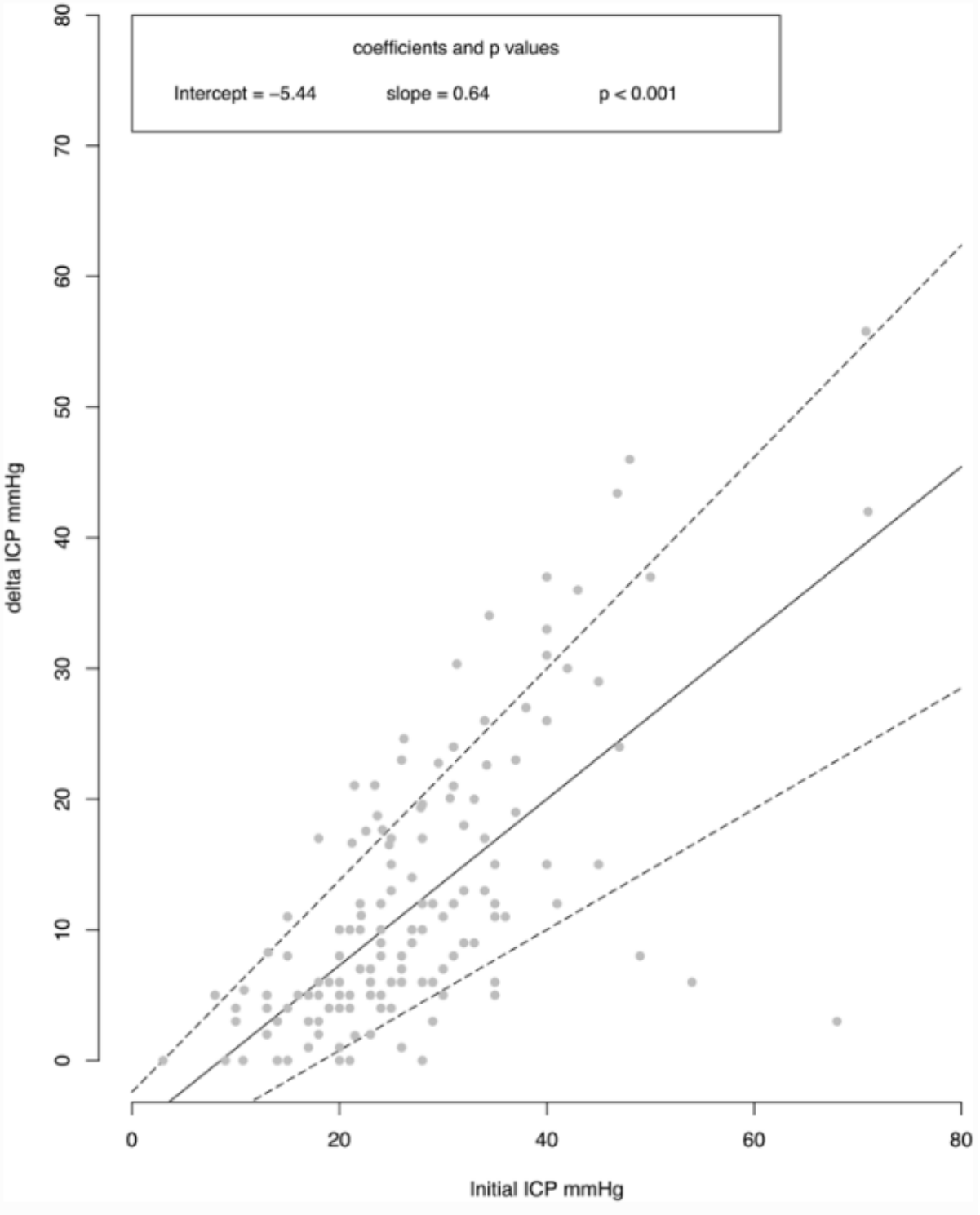
ICP intracranial pressure, *LME* linear mixed effects

Fig. 2



NLM-time model including in the function a plateau value, resembling a pharmacokinetic mono-compartmental model. Medians for single time-points are reported as black circles with a diameter proportional to the number of observations

Fig. 3


coefficients and p values
Intercept = −5.44
slope = 0.64
p < 0.001
delta ICP mmHg
Initial ICP mmHg
0
10
20
30
40
50
60
70
80
0
20
40
60
80