Mannitol and Outcome in Intracerebral Hemorrhage

Propensity Score and Multivariable Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 Results

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Background and Purpose—Mannitol is often used to reduce cerebral edema in acute intracerebral hemorrhage but without strong supporting evidence of benefit. We aimed to determine the impact of mannitol on outcome among participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2).

Methods—INTERACT2 was an international, open, blinded end point, randomized controlled trial of 2839 patients with spontaneous intracerebral hemorrhage (<6 hours) and elevated systolic blood pressure allocated to intensive (target systolic blood pressure, <140 mm Hg within 1 hour) or guideline-recommended (target systolic blood pressure, <180 mm Hg) blood pressure–lowering treatment. Propensity score and multivariable analyses were performed to investigate the relationship between mannitol treatment (within 7 days) and poor outcome, defined by death or major disability on the modified Rankin Scale score (3–6) at 90 days.

Results—There was no significant difference in poor outcome between mannitol (n=1533) and nonmannitol (n=993) groups: propensity score–matched odds ratio of 0.90 (95% confidence interval, 0.75–1.09; *P*=0.30) and multivariable odds ratio of 0.87 (95% confidence interval, 0.71–1.07; *P*=0.18). Although a better outcome was suggested in patients with larger (≥15 mL) than those with smaller (<15 mL) baseline hematomas who received mannitol (odds ratio, 0.52 [95% confidence interval, 0.35–0.78] versus odds ratio, 0.91 [95% confidence interval, 0.72–1.15]; *P* homogeneity <0.03 in propensity score analyses), the association was not consistent in analyses across other cutoff points (≥10 and ≥20 mL) and for differing grades of neurological severity. Mannitol was not associated with excess serious adverse events.

Conclusions—Mannitol seems safe but might not improve outcome in patients with acute intracerebral hemorrhage.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00716079.

(*Stroke*. 2015;46:2762-2767. DOI: 10.1161/STROKEAHA.115.009357.)

Key Words: blood pressure ■ cerebral hemorrhage ■ clinical trial ■ mannitol ■ propensity score

Mannitol is frequently used in the management of patients with spontaneous intracerebral hemorrhage (ICH),[1] particularly in China[2] and India.[3] It is an intravascular osmostic agent that establishes an osmotic gradient between plasma and neurons, thereby drawing water from the cerebral extracellular space into the vasculature to reduce cerebral edema.[4] Mannitol also increases cardiac preload and cerebral perfusion pressure, which contributes to a decrease in intracranial pressure through cerebral vasoreactivity. Although guidelines recommend using mannitol where there is increased intracranial pressure in ICH,[5] uncertainty exists over the magnitude of potential benefit, with various observational studies,[6,7] clinical

Received March 7, 2015; final revision received June 17, 2015; accepted July 10, 2015.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.009357/-/DC1.

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trials,[8,9] and a systematic review,[10] unable to provide evidence of a clear treatment effect of mannitol in acute ICH. The present analysis aimed to determine the impact of use of mannitol on clinical outcome in patients with acute ICH who participated in the main phase Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2). Our hypothesis was that mannitol would improve outcome in patients with more severe ICH.

Methods

Study Design

Details of the INTERACT2 study have been described elsewhere.[11,12] In summary, this was an international, multicenter, open, blinded end point assessed, randomized controlled trial, that involved 2839 adult patients with computed tomography-confirmed spontaneous ICH within 6 hours of onset and elevated systolic blood pressure (SBP, 150–220 mm Hg) randomly assigned to receive intensive (SBP <140 mm Hg within 1 hour) or guideline-recommended (SBP <180 mm Hg) BP-lowering therapy. Exclusion criteria included a clear indication for, or contraindication to intensive BP lowering; low likelihood of benefit because of severe illness, comorbid condition, or high likelihood of death; and early planned surgical intervention. The study protocol was approved by the appropriate ethics committee at each participating site, and written informed consent was obtained from the patient or an appropriate surrogate.

Procedures and Outcomes

Patients allocated to the intensive BP-lowering group commenced a standardized treatment regime involving intravenous and later oral agents, with the goal of achieving a SBP target of <140 mm Hg within 1 hour and to maintain this level for ≤7 days in hospital. Specific treatment protocols were developed for each participating region/site, based on the availability of BP-lowering agents for routine use. For patients allocated to the guideline group, BP-lowering treatment was recommended to achieve a target SBP of ≤180 mm Hg. Data on any use of mannitol within 7 days of ICH were collected.

The primary outcome was death or major disability (defined as a score of 3–6 on the modified Rankin Scale)[13] at 90 days. Secondary outcomes were major disability and death (modified Rankin Scale scores of 3–5, and 6, respectively) at 90 days. The outcome assessment was undertaken by a site investigator, who was not involved in the clinical management of the patient and blind to the randomized treatment allocation.[12]

Statistical Analysis

Because of significant variability in baseline covariates between patients treated with and without mannitol, we used propensity scores (PS) analyses and multivariable models to reduce imbalance. Predictors of mannitol treatment and the primary outcome among the baseline characteristics of participants were determined by a χ^2 test for binary measures, *t* test for approximately normally distributed variables, and Wilcoxon signed-rank test for skewed continuous variables. A multivariable logistic regression model, including all univariate significant predictors of mannitol treatment and the primary outcome, and other clinically important factors (sex and randomized BP-lowering treatment), was constructed to produce estimates of the treatment effect of mannitol (Tables I and II in the online-only Data Supplement).[14,15] On the basis of coefficients from this model, we generated a PS[14,16] for each patient. Only patients with complete data were included in the analyses to maximize balancing of the PS analysis with the largest number of variables and to avoid the need to impute data. As the variable, China region (for patient recruitment) was both associated with mannitol treatment and the primary outcome; it was not included in the PS building model because it was so closely matched with mannitol use as to be insensitive as a discriminator of mannitol-related outcomes.

Various methods were used to account for the nonrandom allocation of mannitol to show consistency of the results. We used optimal matching 1:1 without replacement, with an initial caliper width matching algorithm that equates to 0.19 (20% of the SD of the logit of the PS).[14] A smaller caliper of 0.1 was also used to potentially provide better balancing of covariate imbalances. Generalized estimating equations were used to test the effect of mannitol on primary and secondary outcomes, accounting for matching in the PS-matched subpopulation.[15] We next estimated the impact of mannitol using inverse probability of treatment weighting (IPTW). Stabilized weights were used to reduce variance of the estimated effect of mannitol and were incorporated into a logistic regression model that only included the mannitol variable.[17] We also conducted an analysis that was stratified across fifths of the PS. A summary estimate was calculated using unadjusted logistic regression stratified by PS strata.[17] Finally, PS was used as a covariate in the logistic model to assess the impact of mannitol treatment. Effects of mannitol on outcomes were also estimated in multivariable logistic regression models with the same covariates as PS. The model was further adjusted by significant medical and surgical treatment factors at 7 days (admission to an intensive care unit, prophylactic treatment for deep venous thrombosis, hemostatic therapy, and any surgical intervention) to reduce management bias.

Subgroup analyses were also undertaken by key demographic variables (age <65 versus ≥65 years; sex) and clinical severity (defined by baseline hematoma volume <15 versus ≥15 mL; and National Institutes of Health Stroke Scale [NIHSS] scores <15 versus ≥15 points). Consistency of any association of mannitol and outcome according to severity of ICH was assessed in sensitivity analyses using lower (<10 versus ≥10 mL) and higher (<20 versus ≥20 mL) cutoff points for ICH volume and at lower (<10 versus ≥10) and higher (<20 versus ≥20) NIHSS score thresholds for stroke severity. We assessed the heterogeneity of association in subgroups by adding an interaction term in the models.

As it was not possible to adjust for China region in analyses because of manniol use in these participants, the data were stratified by China and non-China region to assess the consistency of any association in these broadly different populations using the same PS and multivariable modeling approaches. However, we were not able to adjust for unaccounted bias, including differences in background care. Thus, we used the modified ICH score,[18] which has been shown to provide high discrimination for 90-day poor outcome when compared with other popular prognostic scales,[19] to help interpreting this comparison. Data were presented with odds ratios (ORs) and 95% confidence intervals (CI). A 2-sided $P<0.05$ was set as the level for statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

After excluding patients with missing data on the outcome or any covariates, 2526 (89%) patients were included in these analyses. A total of 1678 patients (839 mannitol users and 839 nonmannitol users) were PS matched. Table 1 shows the baseline characteristics of patients according to mannitol use; with all baseline variables included in the multivariable model to generate PS. Table 1 also shows improved balance in the distribution of covariates by mannitol use in the PS-matched and IPTW subpopulations. However, the 2 groups of patients were treated differently over the first 7 days post randomization, and the medical and surgical treatment variables were not evenly distributed in PS analyses. The distribution of PS is shown in Figure I in the online-only Data Supplement.

Table 2 shows significantly fewer serious adverse events over 90 days in mannitol-treated patients. There were 775 (50.6%) patients in the mannitol treatment group than 566 (57%) of those in the nonmannitol treatment group, who were dead or had major disability at 90 days (crude OR, 0.77; 95%

Table 1. Distribution of Patient Characteristics by Mannitol Treatment in Overall, PS-Matched, and IPTW Populations

	Overall		PS Matched		IPTW*	
	Nonmannitol (n=993)	Mannitol (n=1533)	Nonmannitol (n=839)	Mannitol (n=839)	Nonmannitol (n=993)	Mannitol (n=1533)
Demographic						
Age, y	67 (13)	61 (12)*	66 (13)	64 (13)	63.0 (15)	64.0 (12)
Male	612 (62)	952 (62)	520 (62)	504 (60)	791.4 (63)	786.1 (62)
Clinical features						
NIHSS≥15	293 (30)	421 (28)	244 (29)	237 (28)	367.8 (29)	367.2 (29)
Time to randomization, h	3.6 (2.7–4.6)	3.8 (2.8–4.8)	3.6 (2.7–4.6)	3.8 (2.9–4.8)	3.8 (2.8–4.7)	3.7 (2.9–4.7)
Systolic BP, mm Hg	179 (17)	179 (17)	179 (17)	179 (17)	179.1 (19.1)	179.1 (15.2)
Prior intracerebral hemorrhage	65 (7)	134 (9)†	61 (7)	71 (9)	99.3 (8)	96.0 (8)
Prior ischemic/undifferentiated stroke	89 (9)	197 (13)†	76 (9)	77 (9)	144.9 (12)	143.0 (11)
Heart disease	160 (16)	114 (7)†	86 (10)	79 (9)	137.1 (11)	145.3 (12)
Diabetes mellitus	153 (15)	121 (8)†	105 (13)	80 (10)	134.1 (11)	158.2 (13)
Antihypertensive therapy	533 (54)	605 (40)†	399 (48)	359 (43)†	577.4 (46)	589.1 (47)
Use of warfarin anticoagulation/aspirin	224 (23)	85 (6)†	97 (12)	76 (9)	152.5 (12)	178.9 (14)
Use of statin/other lipid-lowering agent	147 (15)	39 (3)†	52 (6)	38 (5)	93.0 (7)	118.6 (9)
Deep location of hematoma‡	820 (83)	1295 (85)	690 (82)	697 (83)	1044.4 (83)	1045.7 (83)
Left hemisphere site of hematoma	493 (50)	779 (51)	424 (51)	414 (49)	629.7 (50)	651.2 (51)
Hematoma volume at baseline, mL	8.9 (4.3–17.1)	12.1 (6.7–19.9)†	9.3 (4.5–17.9)	10.3 (5.8–18.0)	10.3 (5.4–20.5)	10.8 (5.9–18.7)
Intraventricular extension	274 (28)	422 (28)	234 (28)	244 (29)	357.7 (28)	353.5 (28)
Randomized intensive BP lowering	504 (51)	765 (50)	434 (52)	428 (51)	634.2 (50)	627.9 (50)
Medical and surgical treatment						
Intubation	67 (7)	108 (7)	58 (7)	57 (7)	100.4 (8)	94.9 (8)
Admission to an intensive care unit	297 (30)	660 (43)†	266 (32)	373 (45)†	417.1 (33)	576.0 (45)†
Thromboembolism prophylaxis	503 (51)	72 (5)†	398 (47)	45 (5)†	601.2 (48)	99.4 (8)†
Hemostatic therapy§	56 (6)	32 (2)†	31 (4)	18 (2)	48.5 (4)	28.5 (2)†
Any surgical intervention	37 (4)	105 (7)†	31 (4)	55 (7)†	51.6 (4)	84.3 (7)†
Withdraw active care	58 (6)	53 (4)†	45 (5)	31 (4)	60.6 (5)	47.4 (4)

Data are n (%), mean (SD), or median (interquartile range). BP indicates blood pressure; IPTW, inverse probability of treatment weighting; NIHSS, National Institutes of Health stroke scale; and PS, propensity score.

*Synthetic n values derived from weights.

†$P<0.05$.

‡Deep location refers to location in the basal ganglia or thalamus.

§The use of fresh frozen plasma, vitamin K, and recombinant tissue factor VIIa.

CI, 0.66–0.91; $P<0.01$; Figure 1). However, the association was no longer significant after adjustment for baseline imbalances (OR, 0.87; 95% CI, 0.71–1.07; $P=0.18$), and further with the addition of treatment imbalances (OR, 1.02; 95% CI, 0.81–1.30; $P=0.86$). These neutral results were confirmed by PS analyses: matching (OR, 0.90; 95% CI, 0.75–1.09; $P=0.30$), IPTW (OR, 0.97; 95% CI, 0.83–1.14; $P=0.72$), summary stratified (OR, 0.91; 95% CI, 0.77–1.08; $P=0.30$), and covariate adjustment using PS (OR, 0.92; 95% CI, 0.77–1.10; $P=0.35$). The PS-matched analysis with the smaller caliper of 0.10 showed a similar result (OR, 0.89; 95% CI, 0.73–1.09; $P=0.26$). There was no association with the separate outcomes of death and major disability (data on request) and no heterogeneity according to sex and age (Figures II and III in the online-only Data Supplement, respectively).

Our primary subgroup analysis by severity of ICH showed an association of mannitol and reduced poor outcome in patients with larger (≥15 mL) when compared with smaller (<15 mL) hematomas (OR, 0.52; 95% CI, 0.35–0.78 versus OR, 0.91; 95% CI, 0.72–1.15; P homogeneity 0.02 in PS-matched analysis; Figure 2). The association was also significant in IPTW, summary stratified, and covariate adjustment using PS analyses, but not either in multivariable-adjusted analyses or in other sensitivity analyses of different cutoff points (10 and 20 mL; Tables III and IV in the online-only Data Supplement, respectively), despite favorable trends in the point estimates. Associations for mannitol use by degree of neurological impairment were not consistent across analyses: whereas a better outcome was seen for mannitol use in those with greater clinical severity (NIHSS≥15) in PS-matched analysis, summary stratified, and covariate adjustment using PS analyses (all P heterogeneity $P<0.05$), no significant heterogeneity was evident in the adjusted models, IPTW, and also in other sensitivity analyses of different cutoff points (10 and 20; Figure 3, Tables V and VI in the online-only Data Supplement, respectively). Moreover, subgroup

Table 2. Safety Outcomes by Mannitol Treatment

	Nonmannitol (n=993)	Mannitol (n=1533)	*P* Value
Neurological deterioration in first 24 h	161 (16)	216 (14)	0.12
Non-fatal serious adverse events*	312 (31)	295 (19)	<0.01
Direct effects of the primary ICH event	31 (3)	60 (4)	…
Cardiovascular disease	44 (4)	26 (2)	…
Recurrent ICH	2 (0.2)	5 (0.5)	…
Ischemic or undifferentiated stroke	10 (1)	4 (0.4)	…
Acute coronary event	4 (0.4)	3 (0.3)	…
Other cardiovascular disease	30 (3)	15 (1)	…
Noncardiovascular disease	136 (14)	150 (10)	…
Renal failure	7 (1)	5 (0.5)	…
Respiratory infections	53 (5)	48 (3)	…
Sepsis (includes other infections)	28 (3)	10 (1)	…
Nonvascular medical	44 (4)	17 (1)	…

Data are numbers (%). ICH indicates intracerebral hemorrhage.
*One patient could have >1 event.

analyses of patients with both large hematomas (≥15 mL) and greater clinical severity (NIHSS≥15) and of younger patients (age <65 years) with either large hematoma (volume ≥15 mL) or more severe (NIHSS≥15) showed no clear association of mannitol and outcome (Tables VII–IX in the online-only Data Supplement, respectively).

Analysis of patients recruited from China (Table X in the online-only Data Supplement) showed a similar neutral association of mannitol and outcome as seen for the whole population. However, use of mannitol was associated with an increased risk of death or major disability in non-Chinese patients (Table XI in the online-only Data Supplement). There was no association in Chinese patients with larger ICH (Table XII in the online-only Data Supplement). The disparities in associations between Chinese and non-Chinese patients might be explained by differences in characteristics, management, and prognosis that were not fully accounted for in analyses (Tables XIII–XV in the online-only Data Supplement), which was supported by a lower proportion of poor outcome in Chinese patients with the same baseline modified ICH score as in non-Chinese patients (Table XVI in the online-only Data Supplement).

Discussion

This is the largest study to investigate the impact of mannitol in patients with acute ICH. Overall, there was no significant difference in frequency of the conventional poor outcome of death or major disability at 90 days between mannitol and non–mannitol-treated patients independent of other prognostic factors assessed across a variety of analyses that took account of significant imbalances in baseline and management covariates. Although there was an apparent benefit of mannitol in patients with larger hematomas (≥15 mL), this was not consistent in analyses across other cutoff points (≥10 and ≥20 mL) and for differing grades of neurological impairment (NIHSS score cut points of 10, 15, and 20). Moreover, the impact of mannitol was not consistent between Chinese and non-Chinese patients, but this could be because of other diseases and management factors because patients with similar predicted prognosis had different outcomes between the 2 groups. Finally, there was no evidence that mannitol use was associated with any clear harms such as an increase in renal or cardiac complications, or of neurological deterioration, that may have occurred from rebound intracranial hypertension.[20–23]

Few studies have investigated the effects of mannitol in acute ICH. An observational study[6] of 111 consecutive patients within 72 hours of ICH found no association of mannitol on survival. Similarly, 2 small randomized controlled trials of 21 ICH patients with medium- or small-sized hematomas,[8] and

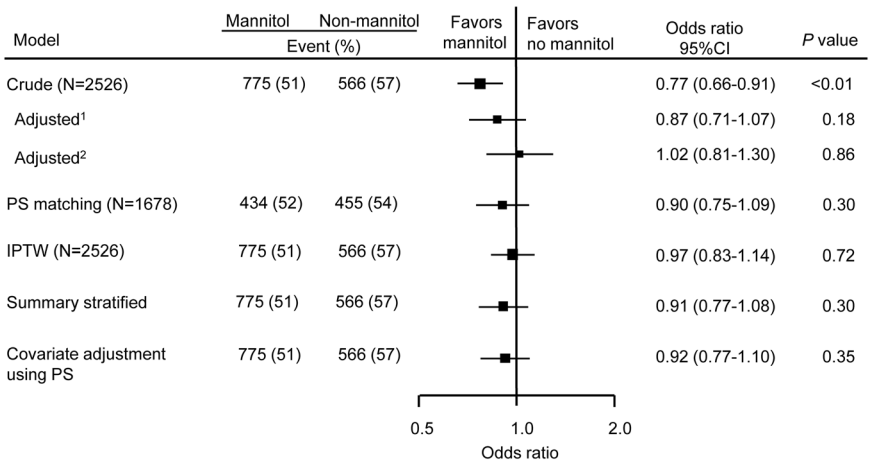

Figure 1. Association of mannitol treatment on death or major disability at 90 days. Solid boxes represent estimates of treatment effect on the risk of outcomes. Centers of boxes are placed at the estimates of the effect; areas of the boxes are proportional to the reciprocal of the variance of the estimates. Horizontal lines represent 95% confidence intervals (CIs). Adjusted model 1: adjusted by age, sex, National Institutes of Health Stroke Scale ≥15, time to randomization, systolic blood pressure (BP), prior intracerebral hemorrhage, prior ischemic or undifferentiated stroke, heart disease, diabetes mellitus, current use of antihypertensive therapy, use of warfarin anticoagulation or aspirin, use of statin or other lipid-lowering agent, deep location of hematoma, left hemisphere site of hematoma, log-transformed baseline hematoma volume, intraventricular extension, and randomized BP-lowering treatment. Adjusted model 2: model 1+admission to an intensive care unit, prophylactic treatment for deep venous thrombosis, hemostatic therapy, and any surgical intervention. IPTW indicates inverse probability of treatment weighting; and PS, propensity score.

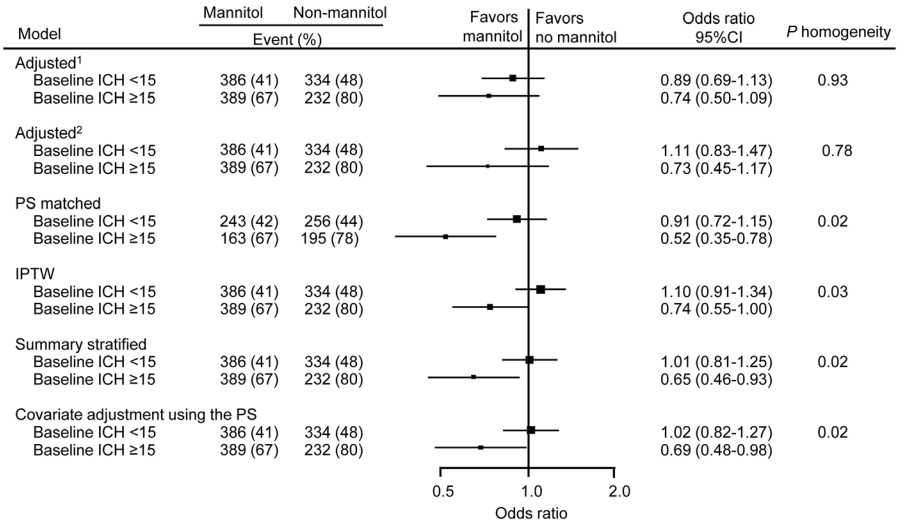

Figure 2. Association of mannitol treatment on death or major disability at 90 days by baseline hematoma volume. Solid boxes represent estimates of treatment effect on the risk of outcomes. Centers of boxes are placed at the estimates of the effect; areas of the boxes are proportional to the reciprocal of the variance of the estimates. Horizontal lines represent 95% confidence intervals (CIs). Adjusted model 1: adjusted by age, sex, National Institutes of Health Stroke Scale ≥15, time to randomization, systolic blood pressure (BP), prior intracerebral hemorrhage, prior ischemic or undifferentiated stroke, heart disease, diabetes mellitus, current use of antihypertensive therapy, use of warfarin anticoagulation or aspirin, use of statin or other lipid-lowering agent, deep location of hematoma, left hemisphere site of hematoma, intraventricular extension, and randomized BP-lowering treatment. Adjusted model 2: model 1+admission to an intensive care unit, prophylactic treatment for deep venous thrombosis, hemostatic therapy, and any surgical intervention. ICH indicates intracerebral hemorrhage; IPTW, inverse probability of treatment weighting; and PS, propensity score.

128 ICH patients within 6 days after onset,[9] found no effect of mannitol on early mortality. A Cochrane review of the topic concluded with uncertainty over whether mannitol is beneficial in this clinical setting.[10] The much larger data set of >2500 patients provided by the INTERACT2 study also indicates that mannitol has no effect in this population of predominantly mild to moderate severity of ICH.

Strengths of this study include the large heterogeneous sample of patients recruited from a diverse range of hospitals and healthcare settings, who were assessed according to a

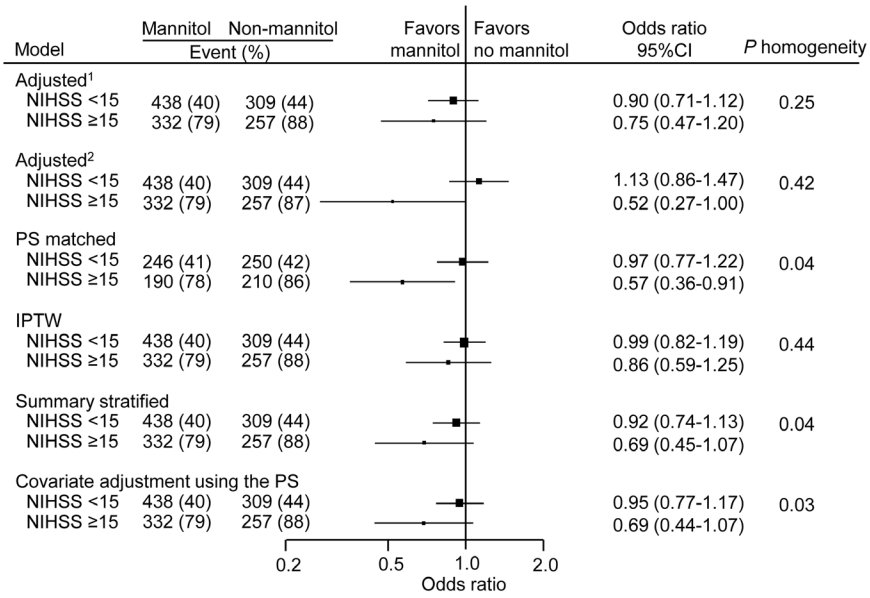

Figure 3. Association between mannitol treatment and death or major disability at 90 days by National Institutes of Health Stroke Scale (NIHSS). Solid boxes represent estimates of treatment effect on the risk of outcomes. Centers of the boxes are placed at the estimates of the effect; areas of the boxers are proportional to the reciprocal of the variance of the estimates. Horizontal lines represent 95% confidence intervals (CIs). Adjusted model 1: adjusted by sex, age, time to randomization, systolic blood pressure (BP), prior intracerebral hemorrhage, prior ischemic or undifferentiated stroke, heart disease, diabetes mellitus, current use of antihypertensive therapy, use of warfarin anticoagulation or aspirin, use of statin or other lipid-lowering agent, deep location of hematoma, left hemisphere site of hematoma, log-transformed baseline hematoma volume, intraventricular extension, and randomized BP-lowering treatment. Adjusted model 2: model 1+admission to an intensive care unit, prophylactic treatment for deep venous thrombosis, hemostatic therapy, and any surgical intervention. IPTW indicates inverse probability of treatment weighting; and PS, propensity score.

standardized protocol and objective measures. We also undertook PS-matched analysis, which allowed us to mimic some of the characteristics of a randomized controlled trial, and the numerous subgroup and sensitivity analyses strengthen the consistency of the findings. Although a benefit of mannitol was suggested in larger hematomas (>15 mL), the absence of a clear dose–response relationship in smaller and larger hematomas indicates that the former was likely to have been a spurious finding. Furthermore, the worse outcome for mannitol use in non-Chinese participants seems to relate more to background differences in prognosis between Chinese and non-Chinese patients rather than from mannitol.

However, there are limitations to our analytic approaches, where mannitol was administered according to the discretion of investigators, with variable doses and duration of treatment that were not captured in this study. Furthermore, mannitol was much more frequently used in China than for the other countries, which could have introduced bias despite our efforts to balance the baseline characteristics of patients. Because these analyses were not prespecified, they are prone to random error and incomplete adjustment for potential confounding, especially because we were unable to address all potential management confounders in analyses. Finally, the data are prone to selection bias by using a clinical trial population, where patients with a poor prognosis because of massive hematoma or deep coma, and those with early surgery, being excluded. Thus, the study sample may have been too small to adequately assess the effects of mannitol in patients with large hematomas.

We conclude that the use of mannitol is safe but might not improve outcome in patients with acute ICH. In the absence of definitive evidence from future randomized controlled trials, these data may serve as a guide in the management of patients.

Sources of Funding

The second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial study was supported by Program (571281) and Project (512402 and 1004170) grants from the National Health and Medical Research Council of Australia. The study was designed, conducted, analyzed, and interpreted by the investigators independent of sponsors.

Disclosures

Dr Anderson reports membership of Advisory Boards for Pfizer and The Medicines Company, and receiving travel reimbursement and honorarium from Takeda China and Covidien. Dr Lavados reports grants from the George Institute for Global Health as a national leader of Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) 2.

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