HHS Public Access

Author manuscript

J Stroke Cerebrovasc Dis. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

J Stroke Cerebrovasc Dis. 2021 March ; 30(3): 105540. doi:10.1016/j.jstrokecerebrovasdis.2020.105540.

Impact of Intracranial Pressure Monitor-Guided Therapy on Neurologic Outcome After Spontaneous Nontraumatic Intracranial Hemorrhage

Sarah T. Menacho, MD[1], **Ramesh Grandhi, MD**[1], **Alen Delic, MS**[2], **Mohammad Anadani, MD**[3], **Wendy C. Ziai, MD, MPH**[4], **Issam A. Awad, M.D.**[5], **Daniel F. Hanley, MD**[4], **Adam de Havenon, MD**[2]

[1]Department of Neurosurgery, University of Utah, Salt Lake City, Utah, USA

[2]Department of Neurology, Clinical Neurosciences Center University of Utah, Salt Lake City, Utah, USA

[3]Department of Neurology, Washington University, St. Louis, Missouri, USA

[4]Department of Neurosurgery, The University of Chicago School of Medicine, Chicago, Illinois, USA

[5]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Objective: Intracranial pressure (ICP) monitors have been used in some patients with spontaneous intracranial hemorrhage (ICH) to provide information to guide treatment and prevent uncontrolled intracranial hypertension. However, the evidence for use of ICP monitors in patients with ICH is largely drawn from the literature on patients with traumatic brain injury. We sought to assess the impact of ICP monitor placement, including external ventricular drains and intraparenchymal monitors, on neurologic outcome among patients with spontaneous nontraumatic ICH.

Methods: In this secondary analysis of the Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation III (MISTIE III) trial, the primary outcome was poor outcome (modified Rankin Scale score 4–6) and the secondary outcome was death, at 1 year from onset. We compared outcomes in the subgroups of patients with or without an ICP monitor using unadjusted and adjusted logistic regression models. We repeated the analyses in a balanced cohort created with propensity score matching.

Results: Out of a total of 494 patients with complete data, 70 underwent placement of an ICP monitor and 424 did not. Poor outcome was seen in 77.1% of patients in the ICP monitor subgroup compared with 53.8% in the subgroup without ICP monitors ($p<0.001$). Of patients in the ICP monitor subgroup, 31.4% died, compared with 21.0% in the subgroup without ICP monitors ($p=0.053$). In multivariate models, ICP monitor placement was associated with a more than

Corresponding Author: Sarah T. Menacho, MD, Department of Neurosurgery, Clinical Neurosciences Center, University of Utah, 175 North Medical Drive East, Salt Lake City, UT 84132, Phone: 801-581-6908; Fax: 801-581-4385, neuropub@hsc.utah.edu.

twofold increased risk of poor outcome (odds ratio 2.76, 95% CI 1.30–5.85, p=0.008), but not with death (p=0.652). Our findings remained consistent in the propensity score matched cohort.

Conclusion: These results question whether the placement of ICP monitors in patients with spontaneous nontraumatic ICH improves outcome. Further work is required to define the causal pathway in these preliminary findings and improve identification of patients that might benefit from invasive ICP monitoring.

Keywords

intracranial pressure monitoring; spontaneous intracranial hemorrhage; neurologic outcome

Introduction

Spontaneous intracerebral hemorrhage (ICH) affects more than 2 million adults worldwide every year. Forty percent of these patients die within a month, and there is substantial morbidity among survivors.[1–4] The Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation III (MISTIE III) trial studied the potential benefit of surgical clot evacuation.[5] It has been established that intracranial hypertension in patients with spontaneous ICH is a negative prognostic factor;[6] however, prior research has not fully evaluated whether the placement of intracranial pressure (ICP) monitors, including external ventricular drains (EVD) and intraparenchymal monitors (IPM), and treatment of elevated ICPs lead to improved outcomes in this patient population. Current guidelines for placement of ICP monitors in patients with spontaneous ICH are derived from the traumatic brain injury literature and data supporting whether these two patient populations are similar enough to share recommendations is lacking.[7,8] In MISTIE III, the decision to place an ICP monitor was at the discretion of the treating physician. Our objective was to examine the impact of ICP monitoring on neurologic outcome among the well characterized MISTIE III trial cohort.

Methods

Cohort

This is a secondary analysis of MISTIE III (clinicaltrials.gov identifier NCT01827046) using a deidentified publicly available dataset obtained from the National Institute of Neurologic Disorders and Stroke at https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets. MISTIE III was an open-label, blinded-endpoint, phase III trial that enrolled 506 patients with nontraumatic supratentorial ICH of ≥30 mL who were randomized to either minimally invasive catheter evacuation with thrombolysis or standard of care. Additional MISTIE III inclusion criteria included a Glasgow Coma Scale (GCS) score ≤14 or a National Institutes of Health Stroke Scale (NIHSS) score ≥6, symptoms for <24 hours before the diagnostic computed tomography (CT) scan, a second “stability” CT scan at least 6 hours after the diagnostic CT that showed <5 mL of ICH growth, and ability to randomize between 12 and 72 hours after diagnostic CT. Key exclusion criteria were intraventricular hemorrhage (IVH) requiring treatment (although external ventricular drains were allowed for ICP monitoring),

supratentorial ICH with midbrain extension, inability to maintain an international normalized ratio <1.4, and GCS score ≤4. We included patients from the study population with outcome data at 1 year from randomization.

Exposure and Outcomes

The exposure of interest was the placement of an ICP monitor, including EVDs and IPMs, which we used to create two subgroups: patients with an ICP monitor and those without an ICP monitor. In MISTIE III, the decision to place an ICP monitor was at the discretion of the treating physician. The trial protocol stated "placement of an ICP monitor is recommended for subjects demonstrating obtundation, which we define as GCS ≤8 on a minimum of two observations over eight hours. The goals of ICP management are to sustain intracranial pressure below 20 mmHg and to improve the patient's level of consciousness."[5] The protocol specified that placement of an ICP monitor had to be followed by a new CT scan of the brain to monitor for ICH stability and any new areas of hemorrhage.[5] Patients with obstructive hydrocephalus were ineligible for enrollment. We also compared patients with an EVD to patients without an ICP monitor and patients with an IPM to patients without an ICP monitor.

The primary outcome for our analysis was an mRS score of 4–6 at 1 year from enrollment, which we termed "poor outcome." The adjudication of mRS in MISTIE III had particular rigor, with both local and central reviewers and the use of archival video recordings of individual patients to allow additional reviewers in cases of disagreement. We utilized the adjudicated mRS in this analysis. The secondary outcome was death within 1 year.

Statistical Analysis

Subject characteristics at randomization are summarized by the full cohort and stratified by ICP monitor versus no ICP monitor. Categorical data are presented as proportions, normally distributed continuous data as mean with standard deviation, and nonnormally distributed continuous data as median with interquartile range. We tested for intergroup differences with Student's t-test or ANOVA for continuous variables, the chi-squared test for categorical variables, and the Wilcoxon Rank Sum or Kruskal-Wallis test for ordinal variables. We fit logistic regression models to our outcomes with the primary predictor of our exposure of interest: ICP monitoring. Model 1 was unadjusted; Model 2 was adjusted *a priori* for patient age, baseline GCS score, sex, white race, current smoking, premorbid mRS score, history of diabetes, prerandomization systolic blood pressure, mechanical ventilation, end-of-treatment (EoT) ICH and IVH volume, deep vs. lobar, ICH location (basal ganglia, frontal, occipital, parietal, temporal, or thalamic), MISTIE randomization arm, and the following adverse events during the trial: ischemic stroke, brain infection, worsened or new intracranial hemorrhage (including intraparenchymal, subarachnoid, subdural, epidural, and ventricular hemorrhages), seizure, and subarachnoid hemorrhage; and Model 3 was adjusted for all baseline covariates from Table 1 with $p<0.05$ after stepwise backwards selection. To limit multicollinearity, we confirmed that all models had a variance inflation factor that was less than 10.

To further account for potential selection bias in patients who received an ICP monitor, we created a propensity score to match patients with an ICP monitor to those without. We matched on the following variables: mechanical ventilation, stability scan and EoT IVH volume, EoT ICH volume, male sex, prior history of diabetes, ICH location, current smoking, prerandomization systolic blood pressure, premorbid mRS, MISTIE III randomization arm, white race, age, deep vs. lobar, and GCS. The resulting decrease in bias after propensity score matching is shown in Figure 1. The logit of the propensity score for the cohort was taken, and a 0.2 standard deviation of the logit propensity scores was used as the caliper distance for propensity score estimation with a radius matching option. The final propensity-matched models took into account the propensity score weights and modelled the outcomes with the exposure of interest. The average effect of the treatment on the treated (ATT) and its odds ratio for our outcomes was calculated. The ATT measures the difference in mean (average) outcomes between patients assigned to the treatment (ICP monitor) and patients assigned to the control (no ICP monitor).

We also evaluated the rate of neurologic adverse events in our subgroups and, because they were not balanced, we performed mediation analysis to determine whether this could account for differences in our outcomes. To test the possibility of a variable being a mediator, we performed mediation tests proposed by Baron and Kenny[9] for continuous and ordinal variables and by Iacobucci[10] for categorical variables. Through a series of linear and logistic regressions, depending on the level of the variables, model coefficients were used to calculate a test-statistic that was tested against a standard normal at the alpha 0.05 level. If a test-statistic was significant, we estimated the total, direct, and indirect effects of the variable.

Results

Table 1 shows baseline demographics of the full cohort (n=494). Overall, 424 (85.8%) patients did not have an ICP monitor and 70 (14.2%) had an ICP monitor, of which 49/70 (70.0%) had an EVD and 21/70 (30.0%) had an IPM. Patients who had ICP monitors placed were younger (57.4±11.0 vs. 61.9±12.5 years, p=0.005), had a lower median admission GCS score (8 vs. 11, p<0.001) and higher NIHSS score (23 vs. 19, p<0.001), were more likely to require mechanical ventilation (75.7% vs. 36.6%, p<0.001), and had hemorrhages in deep as opposed to superficial (lobar) locations (78.6% vs. 58.7%, p=0.002). Other premorbid factors, such as race, sex, diabetes, hypertension, illicit drug use, and anticoagulation and antiplatelet use, were not significantly different between the two groups, nor was randomization to the surgical arm of the MISTIE trial (47.1% vs. 51.9%, p=0.462).

Prior to randomization, mean IVH volume was higher in the ICP monitor cohort (6.6±9.2 vs. 2.1±4.6 mL, p<0.001). At the EoT, both the residual ICH and IVH volumes remained higher in the ICP monitor cohort as compared with patients without ICP monitors (EoT ICH volume 38.2±25.3 vs. 30.0±21.2 mL, p=0.004; EoT IVH volume 3.7±5.5 vs. 1.4±3.3 mL, p<0.001). On average, patients with ICP monitors spent 11 more days in the ICU and acute care than patients without ICP monitors (31.5±33.4 vs. 20.5±16.4, p<0.001) and required 29 more days from the onset of hemorrhage to disposition home (n=321, 107.2±70.1 vs. 78.1±69.3, p=0.023).

Of the 70 patients with an ICP monitor, 54/70 (77.1%) had a poor outcome (mRS score 4–6) at the 1-year follow-up compared with 228 (53.8%) of the 424 patients in the cohort that did not have ICP monitors ($p<0.001$). In the ICP monitor cohort, 22/70 patients (31.4%) were dead at 1 year compared with 89/424 (21.0%) in the cohort that did not have ICP monitors placed ($p=0.053$). The rate of death at 180 days was significantly higher in patients with ICP monitors (28.6% vs. 17.9%, $p=0.039$), but by one year the difference was not significant.

Table 2 shows the results of logistic regression models fit to the primary and secondary outcomes. In the unadjusted Model 1, patients who had ICP monitors were more likely to have poor outcome [odds ratio (OR) 2.90, 95% confidence interval (CI) 1.61–5.23], and there was a trend towards a higher rate of the secondary outcome of death (OR 1.73, 95% CI 0.99–3.01) compared with patients without ICP monitors. In the *a priori* adjusted Model 2, patients with ICP monitors were still more likely to have a poor outcome (OR 2.76, 95% CI 1.30–5.85), but the difference in the rate of death at 1 year lost significance (OR 1.19, 95% CI 0.56–2.55). In Model 3, adjusted for covariates identified with stepwise backwards selection, patients who had ICP monitors placed were more likely to have a poor outcome (OR 2.37, 95% CI 1.15–4.86), but were not more likely to die (OR 1.32, 95% CI 0.68–2.60).

The analyses where we separated out the ICP monitors into EVDs and IPMs are shown in Table 3. The comparison between patients with an EVD (n=49) versus those without an ICP monitor (n=424), showed that EVD placement was associated with poor outcome (ORs 3.82, 3.92, and 3.63 for Models 1, 2, and 3; $p<0.01$ for all), but not death (Table 3). The comparison between patients with an IPM (n=21) versus those without an ICP monitor (n=424), showed the same direction of effect for the association with poor outcome (ORs 1.72, 1.61, 1.10; $p>0.05$ for all), but it failed to achieve significance. However, there was a stronger trend towards an association between having an IPM and death (ORs 2.32, 3.04, 2.47; $p=0.071$, 0.069, 0.105).

We explored major adverse neurological events for the entire cohort and for patients with and without an ICP monitor (Table 4). Overall, patients who had an ICP monitor had a higher incidence of new or worsened intracranial hemorrhage (41.4% vs. 22.9%, $p=0.001$) along with a higher likelihood of an intracranial infection (7.1% vs. 1.7%, $p=0.006$). Comparing the subgroups of ICP monitor types to those without an ICP monitor, patients with an EVD had a higher rate of infection (10.2% vs. 1.7%, $p<0.001$) and patients with an IPM had a higher rate of new or worsened intracranial hemorrhage (57.1% vs. 22.9%, $p<0.001$). The rates of seizures, ischemic stroke, and subarachnoid hemorrhage were not statistically different between patients with ICP monitor versus without one (Table 4) and in the EVD versus IPM comparisons (data not shown).

We performed mediation analysis to determine whether the higher rate of new or worsened intracranial hemorrhage, intracranial infection, or number of days spent in acute care occurred contemporaneously with increased likelihood of poor outcome in patients with an ICP monitor. New or worsened intracranial hemorrhage and intracranial infection were not significant mediators (test statistic: $p=0.92$ and 0.73, respectively), but the longer time spent in acute care, either intensive care or inpatient hospitalized care, for patients with an ICP

monitor was a significant mediator in the pathway between ICP monitor and poor outcome (OR=1.17, 95% CI 1.04–1.53, 21.66% mediated, p=0.027).

We used propensity score matching to minimize the presence of bias in the two cohorts (Figure 1). After matching, the balanced cohort had 413 individuals, 70 with ICP monitors and 343 without ICP monitors. When we examined the propensity score–matched cohort ATT results for the primary endpoint of poor outcome (Table 5), the ATT log odds estimate was −0.24, with an OR of 0.79 (95% CI 0.70–0.88, p<0.001), indicating a significantly higher propensity for poor outcome in patients with ICP monitors. For the secondary outcome of death at 1 year, the ATT log odds estimate was 0.09 with a non-significant ATT OR of 1.10 (95% CI 0.84–1.17, p=0.124), consistent with the primary analysis results.

Discussion

The placement of ICP monitors for patients with spontaneous, nontraumatic supratentorial ICH was associated with a negative effect on functional outcome at one year, although we did not find that it was associated with an increase in the risk of death. Of note, intracranial hypertension (defined as an ICP ≥20 mm Hg) has been observed in up to 70% of patients in whom ICP monitors are placed for spontaneous ICH.[11] Increased ICP is thought to be more common in younger patients and in patients with supratentorial ICH.[11] However, we found that even in age and ICH location adjusted models there was no functional outcome benefit for ICP monitor placement. In the MISTIE III trial, ICP elevation was less common in the MISTIE intervention cohort than in the cohort assigned to standard medical care.[5] ICP elevations ≥20 mm Hg occurred in 26% of MISTIE patients and 58% of the cohort assigned to standard medical care (p=0.007). We do not comment on this aspect of ICP monitoring, because the elevated ICPs were not analyzed for association with poor outcome in our analysis or the MISTIE III primary outcome publication.[5] Nonetheless, the hypothesis-generating result of our analysis questions the utility of ICP monitors in this patient population, irrespective of the ICP values.

Guidelines for the management of spontaneous ICH have addressed the use of ICP monitors.[12] The current recommendations for placement of an ICP monitor represent Class IIb evidence and define the patient population as those with a GCS score ≤8, evidence of transtentorial herniation, or significant IVH or hydrocephalus.[7,8] Because there are limited data regarding monitoring and treatment of elevated ICP in ICH, these recommendations are largely borrowed from the existing body of literature on patients with severe traumatic brain injury. The question remains whether these two patient populations are similar enough to share management guidelines.

Our results are in accordance with other recently published literature on ICP monitoring in patients with spontaneous ICH. Chen et al.[13] recently demonstrated higher infection rates and longer hospital stays in their ICP monitoring cohort. The primary outcome of 90-day mortality was similar between patients with and without an ICP monitor. When patients with IVH were excluded from their analysis, the cohort with ICP monitors had a lower rate of mortality at 90 days: 23% vs. 36% (OR 0.54, 95% CI 0.302–0.975, p=0.041), but patients with ICP monitors also had a lower rate of good outcome (defined as functional

independence) at 90 days: 14% vs. 29% (OR 0.416, 95% CI 0.203–0.813, p=0.010). Our finding that patients with spontaneous ICH who underwent ICP monitoring placement experienced higher rates of poor neurologic outcome at the 1-year mark are similar, but we were able to further demonstrate that even after propensity score matching, patients who had ICP monitors placed in the context of spontaneous ICH were more likely to have a poor outcome at 1 year.

We found that patients who had an ICP monitor placed had significantly longer time spent in ICU and acute care, nearly double the rate of new or worsened intracranial hemorrhage, and a fourfold higher rate of intracranial infection. However, our mediation analysis showed that new or worsened intracranial hemorrhage and intracranial infection did not account for their higher rate of poor outcome, while the longer time spent in ICU and acute care was a significant mediator. This suggests either that ICP monitor placement leads to additional complications that we were not able to measure or that patients with ICP monitors had higher disease severity, which could independently create additional complications and longer length of ICU and acute care. With the current data, we cannot measure if adverse events were the reason for or cause of ICP monitor placement. Without this information, the causal influence of the adverse events on ICP monitor placement cannot be known. Nonetheless, mitigation of complications with stringent ICP monitor placement protocols including attention to sterile technique, review of coagulation parameters, and administration of antibiotic prophylaxis prior to placement may represent an important strategy for achieving a meaningful improvement in morbidity and mortality among patients with spontaneous ICH undergoing ICP monitor placement.

To date, surgical intervention has not been shown to improve outcome in patients with spontaneous ICH.[13,14] This remained true for patients in the MISTIE III trial, although there was a significant benefit in patients who achieved a reduction in their ICH volume to ≤15 mL via the MISTIE procedure. The literature shows that patients with spontaneous ICH who undergo ICP monitor placement are more likely to undergo surgical evacuation of their ICH.[15,16] These data raise the question of whether patients with spontaneous ICH with concomitant ICP monitor placement are being “overtreated” without Class I evidence of significant benefit. Although there is some evidence that elevations in ICP, even transient, in patients with ICH may lead to worse short-term outcomes, associations with long-term poor outcomes are more variable.[17–19] Furthermore, a randomized controlled trial in patients with severe TBI done by Chesnut et al, comparing outcomes between a protocol involving empiric placement of ICP monitors versus treatment based on imaging and clinical examination, did not show a benefit from the empiric use of ICP monitors.[18] This implies that, even in patients with severe TBI, placement of ICP monitors to guide acute management may not result in improved outcomes and therefore cannot be extrapolated to patients with spontaneous ICH.

Limitations

The main limitation of our analysis is that this is a secondary analysis of a clinical trial that was not designed to answer this question and, thus, the subgroups are not balanced. Although we tried to reduce that bias with adjusted models and a propensity score matched

cohort, it remains a major limitation. In addition, the number of patients in MISTIE III that underwent placement of an ICP monitor and had complete data was small (n=70). It is possible that a benefit associated with ICP monitor placement would be shown with a larger number of patients. Because MISTIE III was a protocolized clinical trial, we were unable to explore the question of whether ICP monitors guide decisions about, or timing of, surgical interventions in this patient population. We did not have full data on the adverse events, such as timing and exact location of new or worsened intracranial hemorrhage. In future research on this topic, adverse events should be fully adjudicated and classified as "related to ICP monitor placement" or "indication for ICP monitor placement." We also did not have data on the indication for ICP monitor, placement location, or the duration of the monitoring, which could have produced analyses pointing to specific subgroups or protocols that have benefit.

We were also underpowered to study the different types of ICP monitors. While the direction of effect was consistent for patients with an EVD or IPM, we could not fully explore differences between them. Finally, we were unable to explore the effect of ICP or cerebral perfusion pressure (CPP) in this cohort and whether patients benefited from ICP and CPP directed care. Ziai[18] performed a randomized trial of intraventricular thrombolysis in 100 patients with IVH and ICH <30 mm^3 and demonstrated that, although initial ICPs were >20 mm Hg upon insertion of a ventricular catheter, ICP was not frequently elevated during the monitoring period. However, it is also important to note that elevated ICP, which can lead to inadequate CPP, was predictive of higher short- and long-term mortality in patients with hypertensive intraventricular hemorrhage that were enrolled in the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) trial.[19]

Conclusion

To date, there is no medical or surgical intervention shown to benefit patients with spontaneous ICH on primary outcome analysis. Additionally, there is no published evidence showing that monitoring of ICP or management of elevated ICP in patients with spontaneous ICH leads to improved neurologic outcomes. Our study demonstrates that in patients with spontaneous ICH who have ICP monitors placed there is an association with poor neurologic outcome at one year that remains significant despite multiple strategies to minimize bias. This is an association study and is hypothesis generating. It cannot imply causality or any treatment recommendations regarding placement of ICP monitors in this population. Current management principles for the placement of an ICP monitor in ICH are largely extrapolated from the literature on patients with severe traumatic brain injury, but these patient populations are distinct and should be treated as such, particularly from the standpoint of ICP monitor placement. Further studies are needed to confirm our preliminary findings and determine which patients with spontaneous ICH require ICP monitoring.

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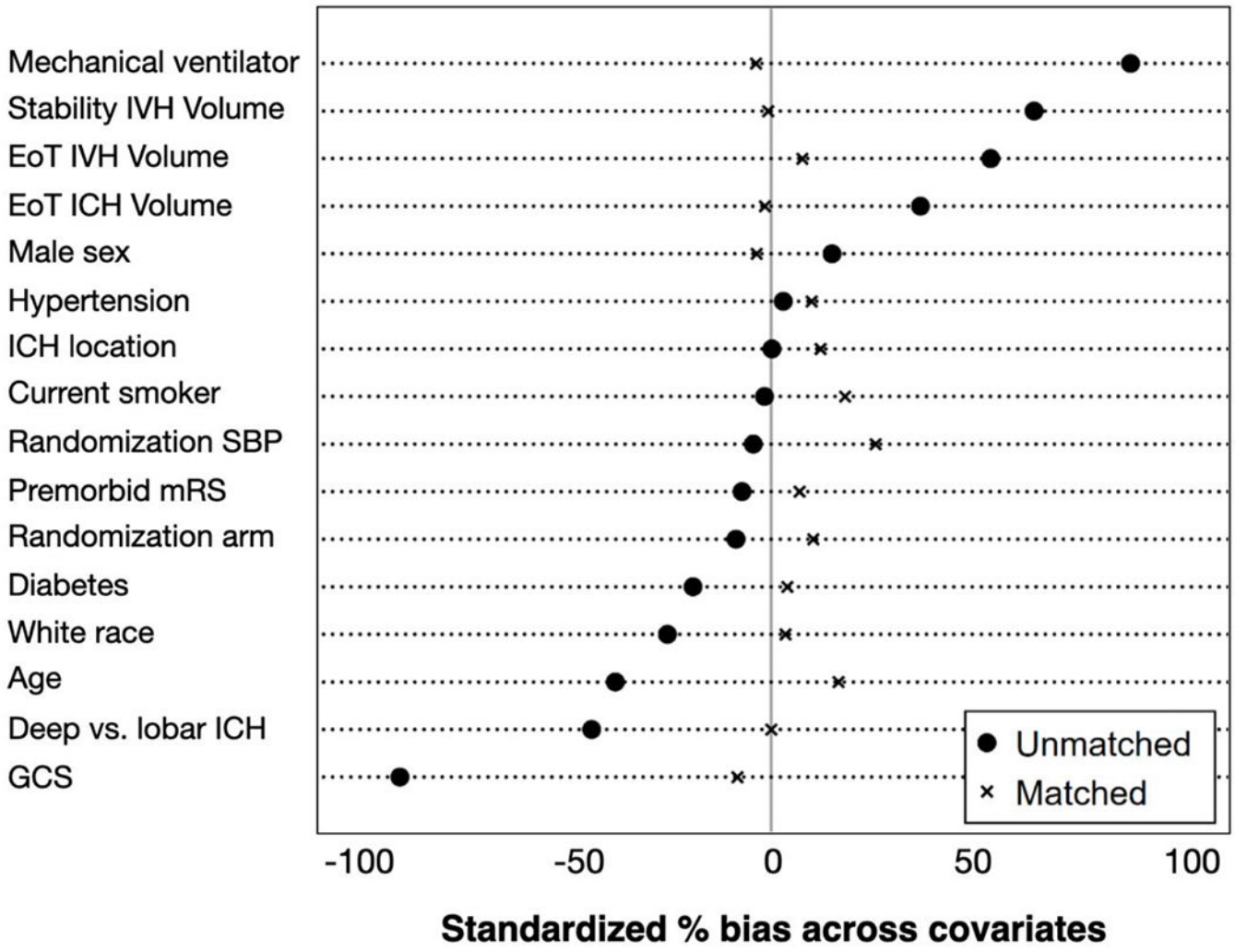

Figure 1.

Bias present in the cohorts of intracranial pressure (ICP) monitor vs. no ICP monitor shown as standardized percentage before propensity score matching (circle). The change in bias is shown by an x. IVH, intraventricular hemorrhage; EoT, end-of-treatment; ICH, intracerebral hemorrhage; GCS, Glasgow Coma Scale.

Table 1.

Baseline demographics of the MISTIE III trial patients stratified by ICP monitor versus no ICP monitor placement.

Variable	Full cohort (n=494)	ICP monitor (n=70)	No ICP monitor (n=424)	p value*
Age (years)	61.3±12.4	57.4±11.0	61.9±12.5	0.005
Male	303 (61.3)	47 (67.1)	256 (60.4)	0.282
White	372 (75.3)	48 (68.6)	324 (76.4)	0.046
Hispanic	68 (13.8)	13 (18.6)	55 (13.0)	0.208
Diabetes	141 (28.5)	15 (21.4)	126 (29.7)	0.155
Hypertension	478 (96.8)	68 (97.1)	410 (96.7)	0.846
Hyperlipidemia	194 (39.3)	24 (34.3)	170 (40.1)	0.357
Cardiovascular disease	74 (15.0)	12 (17.1)	62 (14.6)	0.584
Current smoker	87 (17.6)	12 (17.1)	75 (17.7)	0.912
Cocaine abuse	19 (3.9)	2 (2.9)	17 (4.0)	0.642
Alcohol abuse	68 (13.8)	8 (11.4)	60 (14.2)	0.540
Antiplatelet medication	146 (29.6)	19 (27.1)	127 (30.0)	0.633
Anticoagulant medication	36 (7.1)	7 (10.0)	28 (6.6)	0.305
Premorbid mRS score = 1	36 (7.3)	4 (5.7)	32 (7.6)	0.585
Surgical arm of MISTIE III	253 (51.2)	33 (47.1)	220 (51.9)	0.462
Admission GCS score	10, 8–13	8, 7–10	11, 9–13	<0.001
Admission NIHSS score	19, 15–23	23, 18–27	19, 15–23	<0.001
Prerandomization SBP (mm Hg)	139.6±12.1	139.2±12.1	139.7±13.1	0.740
Prerandomization DBP (mm Hg)	70.0±11.3	71.7±12.1	69.7±11.1	0.171
Deep (vs. lobar) location of ICH	304 (61.5)	55 (78.6)	249 (58.7)	0.002
Right hemisphere location	243 (49.2)	37 (52.9)	206 (48.6)	0.508
Mechanical ventilation	208 (42.1)	53 (75.7)	155 (36.6)	<0.001
Enrollment in US	389 (78.7)	57 (81.4)	107 (78.7)	0.554
Ictus to site arrival (hours)	7.4±8.0	8.5±8.3	6.4±7.7	0.036
Prerandomization ICH volume	49.0±18.0	53.3±21.1	48.3±17.3	0.29
Prerandomization IVH volume	2.7±5.7	6.6±9.2	2.1±4.6	<0.001
EoT ICH volume (mL)	31.2±22.0	38.2±25.3	30.0±21.2	0.004
EoT IVH volume (mL)	1.7±3.8	3.7±5.5	1.4±3.3	<0.001
Percent change of ICH volume at EoT (%)	−36.5±36.8	−29.2±34.4	−37.7±37.0	0.071
Percent change of IVH volume at EoT (%)	−4.1±116.7	−30.2±65.5	0.2±122.6	0.044
Days hospitalized in ICU and acute care	22.1±20.0	31.5±33.4	20.5±16.4	<0.001
Days from onset to disposition home (n=321, 33 vs 288 patients)	81.1±69.8	107.2±70.1	78.1±69.3	0.023
Poor outcome (mRS score 4–6)	282 (57.1)	54 (77.1)	228 (53.8)	<0.001
Dead	111 (22.5)	22 (31.4)	89 (21.0)	0.053

Categorical variables presented as number (percentage); ordinal variables presented as median, IQR; continuous variables presented as mean±SD.

* P values calculated with the Chi-squared test for categorical variables, the Wilcoxon Rank Sum test for ordinal variables, and Student's t-test for continuous variables.

ICP, intracerebral pressure; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS; Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; EoT, end of treatment

Table 2.

Logistic regression models fit to primary and secondary outcomes showing odds ratios for having an ICP monitor versus not having an ICP monitor.

	Poor outcome			Death		
	Odds ratio	**95% CI**	**p value**	**Odds ratio**	**95% CI**	**p value**
Model 1 *	2.90	1.61–5.23	0.002	1.73	0.99–3.01	0.055
Model 2 †	2.76	1.30–5.85	0.008	1.19	0.56–2.55	0.652
Model 3 ‡	2.37	1.15–4.86	0.019	1.33	0.68–2.60	0.411

* Model 1 unadjusted.

† Model 2 *a priori* adjusted for patient age, baseline GCS score, sex, white race, current smoking, premorbid mRS score, history of diabetes, prerandomization systolic blood pressure, mechanical ventilation, EoT ICH and IVH volume, deep vs. lobar, ICH location, MISTIE randomization arm, and the following adverse events during the trial: ischemic stroke, brain infection, worsened or new intracranial hemorrhage, seizure, and subarachnoid hemorrhage (n=487).

‡ Model 3 when fit to good outcome is adjusted for baseline covariates selected with backwards stepwise selection set to $p<0.01$, which included patient age, baseline NIHSS score, deep vs. lobar, history of diabetes, MISTIE randomization arm, and EoT ICH volume. Model 3 when fit to death is adjusted for baseline covariates selected with backwards stepwise selection set to $p<0.01$, which included patient age, baseline GCS score, current smoking, and EoT ICH volume (n=487).

Table 3.

Logistic regression models fit to primary and secondary outcomes showing odds ratios for having an EVD or an IPM versus not having an ICP monitor.

Predictor	Model	Poor outcome			Death		
		Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
EVD (n=49) (vs. not having an ICP monitor, n=424)	Model 1 *	3.82	1.81-8.07	0.002	1.51	0.78-2.92	0.226
	Model 2 †	3.92	1.50-10.3	0.005	0.81	0.33-1.97	0.641
	Model 3 ‡	3.63	1.47-9.00	0.005	1.03	0.47-2.24	0.940
IPM (n=21) (vs. not having an ICP monitor, n=424)	Model 1 *	1.72	0.68-4.35	0.252	2.32	0.93-5.76	0.071
	Model 2 †	1.61	0.53-4.89	0.402	3.05	0.92-10.2	0.069
	Model 3 ‡	1.10	0.37-3.32	0.865	2.47	0.83-7.33	0.105

*Model 1 unadjusted.

†Model 2 *a priori* adjusted for patient age, baseline GCS score, sex, white race, current smoking, premorbid mRS score, history of diabetes, prerandomization systolic blood pressure, mechanical ventilation, EoT ICH and IVH volume, deep vs. lobar, ICH location, MISTIE randomization arm, and the following adverse events during the trial: ischemic stroke, brain infection, worsened or new intracranial hemorrhage, seizure, and subarachnoid hemorrhage (n=466 for EVD, n=438 for IPM).

‡Model 3 when fit to good outcome is adjusted for baseline covariates selected with backwards stepwise selection set to $p<0.01$, which included patient age, baseline NIHSS score, deep vs. lobar, history of diabetes, MISTIE randomization arm, and EoT ICH volume. Model 3 when fit to death is adjusted for baseline covariates selected with backwards stepwise selection set to $p<0.01$, which included patient age, baseline GCS score, current smoking, and EoT ICH volume (n=466 for EVD, n=438 for IPM).

Table 4.

Major adverse neurological events

Variable	Full cohort (n=494)	ICP Monitor (n=70)	No ICP Monitor (n=424)	p value*
Worsened or new intracranial hemorrhage	126 (25.5)	29 (41.4)	97 (22.9)	0.001
Brain infection	12 (2.4)	5 (7.1)	7 (1.7)	0.006
Ischemic stroke	101 (20.5)	18 (25.7)	83 (19.6)	0.238
Seizure	70 (14.2)	7 (10.0)	63 (14.9)	0.280
Subarachnoid hemorrhage	26 (5.3)	3 (4.3)	23 (5.4)	0.693

Categorical variables presented as number (percentage)

* P values calculated with the Chi-squared test.

Table 5.

Propensity score-matched cohort ATT results for patients with and without an ICP monitor

Outcome	ATT log odds estimate	ATT OR	95% CI of OR	p value
Poor outcome	0.236	1.5	(1.40-1.75)	< 0.001
Dead	0.096	1.10	(0.84-1.17)	0.124