The effect of ICP monitoring in severe traumatic brain injury: a propensity score–weighted and adjusted regression approach

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OBJECTIVE The use of intracranial pressure (ICP) monitoring has been postulated to be beneficial in patients with severe traumatic brain injury (TBI), although studies investigating this hypothesis have reported conflicting results. The objective of this study was to evaluate the effect of inserting an ICP monitor on survival in patients with severe TBI.

METHODS The Oslo University Hospital trauma registry was searched for the records of all patients admitted between January 1, 2002, and December 31, 2013, who fulfilled the Brain Trauma Foundation criteria for intracranial hypertension and who survived at least 24 hours after admission. The impact of ICP monitoring was investigated using both a logistic regression model and a multiple imputed, propensity score–weighted logistic regression analysis.

RESULTS The study involved 1327 patients, in which 757 patients had an ICP monitor implanted. The use of ICP monitors significantly increased in the study period ($p < 0.01$). The 30-day overall mortality was 24.3% (322 patients), divided into 35.1% (200 patients, 95% confidence interval [CI] 31.3%–39.1%) in the group without an ICP monitor and 16.1% (122 patients, 95% CI 13.6%–18.9%) in the group with an ICP monitor. The impact of ICP monitors on 30-day mortality was found to be beneficial both in the complete case analysis logistic regression model (odds ratio [OR] 0.23, 95% CI 0.16–0.33) and in the adjusted, aggregated, propensity score–weighted imputed data sets (OR 0.22, 95% CI 0.15–0.35; both $p < 0.001$). The sensitivity analysis indicated that the findings are robust to unmeasured confounders.

CONCLUSIONS The authors found that the use of an ICP monitor is significantly associated with improved survival in patients with severe head injury.

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KEYWORDS traumatic brain injury; Glasgow Coma Scale; ICP monitoring; intracranial pressure

THE incidence of traumatic brain injury (TBI) is increasing worldwide, and there is an urgent need for both preventative measures and better treatment.²² Clinical trials of new measures to reduce the extent of primary injury in TBI have so far been largely futile.¹⁶

It has been postulated that the treatment of patients with severe head injury is facilitated by intracranial pressure (ICP) monitoring.⁵ The literature, however, contains

conflicting reports. Some studies suggest no, or even detrimental, effects of using ICP monitors, while others indicate a positive effect of ICP monitoring on outcome.^{7,9,15,23} Common to these studies is the observational design and limited adjustment for variables known to be associated with a poor outcome. In 2012, Chesnut et al. published a randomized controlled trial that included patients with TBI from Bolivia and Ecuador.⁶ This trial reported a non-

ABBREVIATIONS AIS = Abbreviated Injury Scale; ASA = American Society of Anesthesiologists Physical Status Classification; BEST-TRIP = Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure; BTF = Brain Trauma Foundation; CI = confidence interval; CPP = cerebral perfusion pressure; EVD = external ventricular drain; GB = generalized boosting; GCS = Glasgow Coma Scale; ICP = intracranial pressure; ISS = Injury Severity Score; OR = odds ratio; OUH-U = Oslo University Hospital, Ullevål; TBI = traumatic brain injury.

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significant difference in outcome between an ICP-monitored group and a control group monitored by clinical examination and serial CT, suggesting that the use of ICP monitors is unnecessary in the treatment of TBI. Objections to the study include the external validity of the findings, that it was underpowered, and that the control arm in the study could reflect a trial effect.¹² Therefore, it is still unclear whether patients with severe TBI benefit from ICP monitoring.

In this study we investigated the effect of ICP monitoring on 30-day survival. We tried to overcome some of the limitations of earlier retrospective studies by utilizing a propensity score-weighted analysis of data from a prospectively maintained registry at a level I trauma hospital, thus ensuring good face validity and a relevant clinical setting for our population.

Methods

Study Population

Oslo University Hospital, Ullevål (OUH-U) is the major trauma-care facility in the South-Eastern Norway Regional Health Authority. The neurosurgical department at OUH-U treats all severe neurotrauma within this region, covering a population of approximately 2.8 million people in a geographical area of 110,000 km².²¹

Jones et al. have previously described the trauma registry and trauma logistics at OUH-U.¹³ Briefly, trauma patients with severe injuries and patients with suspected isolated severe neurotrauma are transported and admitted directly to OUH-U from the entire health region. Patients with less severe injuries are admitted to other acute care hospitals but transferred to OUH-U later if necessary. The modes of transportation between the scene of an accident and referring hospitals and OUH-U are helicopters manned with anesthesiologists or ground ambulances manned with paramedics.

Study Criteria

All patients with Injury Severity Scores (ISSs) ≥ 10 admitted to OUH-U within 24 hours of the trauma, patients with penetrating injuries to the torso, patients with injuries proximal to the knees and elbows, and all cases admitted by the trauma team are included in the trauma registry.³ Two registrars, both nurse anesthetists with trauma team experience and with formal education in injury classification according to the Abbreviated Injury Scale (AIS 90, update 98), prospectively update the registry.² The treatment of patients with TBI at OUH-U has gradually improved during the study period, consistently conforming to the Brain Trauma Foundation (BTF) guidelines.⁵

Although the indications for inserting an ICP monitor have been rooted in the BTF guidelines, the ultimate decision was made at the discretion of the attending neurosurgeon. The changes in trauma team factors, neurosurgical presence and competence, and neurointensive care systems at OUH-U have recently been published by Søvik et al.²⁵ Briefly, the goals of TBI treatment have been to maintain ICP at < 20 mm Hg and the cerebral perfusion pressure (CPP) at > 60 mm Hg. A staircase-protocolled approach using sedation, osmolar therapy, normothermia,

CSF drainage, barbiturates, and hemicraniectomy was utilized to fulfill the ICP and CPP goals.²⁶

In this study, our prospective registry was searched for the records of all patients admitted with either Glasgow Coma Scale (GCS) scores < 9 or head AIS scores ≥ 2 over 12 years (January 1, 2002, to December 31, 2013). We retrieved the records of 6936 patients. Risk factors for intracranial hypertension are either GCS scores 3–8 and an abnormal CT scan (here defined as head AIS score ≥ 3), or GCS scores 3–8 with a normal CT scan, but with two or more of the following factors: age > 40 years, motor posturing, or systolic blood pressure < 90 mm Hg.⁴ Hence, we filtered the 6936 patients according to these risk factors to define a population with a high risk of intracranial hypertension where it is most likely to detect a benefit of ICP monitoring. This filtering resulted in 1509 patients. Patients deemed unsalvageable were removed, by deleting those who died within 24 hours of admittance ($n = 177$). Patients with a maximum head AIS score equal to 6 were also discarded due to poor prognosis ($n = 6$). We retrieved information about the resulting patients on 53 different variables (the full list is available upon request). The most salient variables included information on demographics (age, sex), trauma (date, time, first hospital, ISS), physiological parameters on admission (blood pressure, oxygen saturation, heart rate, preinjury comorbidity scoring according to The American Society of Anesthesiologists Physical Status Classification [ASA] score), brain trauma (GCS score including component scores; maximum head AIS score; ICD-10 diagnoses; and operations according to the Nordic Medico-Statistical Committee classification of surgical procedures), and outcome (date of death, survival at 30 days [yes/no]).

In our department we have routinely utilized a parenchymal ICP probe (Codman Microsensor ICP transducer) in managing patients with TBI. External ventricular drains (EVDs) were inserted only if medical therapy failed to control ICP and/or ventriculomegaly was present on the CT scans. Thus, if an EVD was inserted, the drain was used for therapy, not monitoring, and the patient was monitored concurrently with a parenchymal ICP probe.

Before data extraction, all data elements were thoroughly screened for inconsistencies and nonlogical values, in compliance with the OUH-U trauma registry data validation protocol.

Statistical Analysis

First, the data set was described in two groups according to whether the patient had an ICP monitor inserted or not, using the Wilcoxon test for continuous data and the Pearson chi-square test for categorical data. A proportional odds model was used to check for differences in ordinal data.

There were missing data for the oxygen saturation, heart rate, and systolic blood pressure variables (8.9%, 4.9%, and 4.3% of variables, respectively). Full information on all variables was present in 1186 patients (89.4%). The pattern of missingness was evaluated and found to be reasonably missing at random. In order not to remove these patients from the analysis and consequently reduce the power of the analysis and possibly increase bias, we

imputed a total of 10 data sets using multiple imputation.²⁸ The uncertainty of the imputed value is reflected by the range of imputed values over the 10 data sets and is accounted for in the final analysis.

Due to covariate imbalance between the two groups (with or without an ICP monitor), the analysis with regard to ICP monitoring could be biased. Consequently, we used different propensity score methods to determine if we could achieve balance in the distribution of covariates between the two groups. Briefly, the probability of receiving treatment is modeled based on the other covariates. This probability can be calculated from a logistic regression model or from machine-learning algorithms. We fitted both a logistic regression model and a generalized boosting (GB) model using the twang package in R with 15,000 iterations to define the probability of treatment. All variables in Table 1 were used to predict treatment, apart from the “dead within 30 days” variable.

This probability of treatment was subsequently used for matching.²⁷ The following approaches were investigated for matching the propensity score derived from both logistic regression and the GB model: full matching, nearest neighbor matching, genetic matching, subclassification, and weighting. The GB method with a weighted analysis outperformed the other approaches using the metric of standardized differences in means between the two groups (data available upon request).

The final effect of ICP monitoring on survival was calculated using weighted uni- and multivariate regression on each of the imputed data sets. The aggregated coefficients from the 10 data sets were obtained by using a cluster approach detailed in the survey package and by using Rubin’s rule adapted in the MItools package. The results from these different methods were compared and found to be similar. Furthermore, a weighted Kaplan-Meier curve is presented. For reference, uni- and multivariate logistic regression models were calculated using only the patients from the original sample with complete information.

Propensity-score weighting can primarily adjust for observed variables. Unobserved variables are only accounted for to the extent that they are correlated with the observed variables.²⁷ A sensitivity analysis can indicate the amount of hidden bias from unobserved variables necessary to invalidate the findings from the propensity-score weighted analysis. We performed a sensitivity analysis for binary responses in each of the imputed data sets according to Rosenbaum’s method. The genetic matching procedure performed marginally poorer than the weighted matching method, but was used due to the convenience of the binares function in the Rbouds package.

The statistical program R was used for all analyses (version 3.2; <http://www.R-project.org>). A p value < 0.05 was considered statistically significant.

Ethics

The Oslo University Hospital Data Protection Officer, in this matter representing the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Protection Authority, considered the study exempt from patient consent requirements.

TABLE 1. Patient characteristics

Variable	No. of Patients	ICP Monitor		p Value
		No (n = 570)	Yes (n = 757)	
GCS score	1327			0.247
3		44.1% (164)	55.9% (208)	
4		30.4% (41)	69.6% (94)	
5		40.3% (71)	59.7% (105)	
6		45.7% (107)	54.3% (127)	
7		46.0% (87)	54.0% (102)	
8		45.2% (100)	54.8% (121)	
Admission	1327			0.554
Primary		43.6% (348)	56.4% (450)	
Secondary		42.0% (222)	58.0% (307)	
Age (yrs)*	1325	22.2/41.4/64.2	23.4/38.1/56.6	0.014
Sex	1327			0.146
Female		46.3% (161)	53.7% (187)	
Male		41.8% (409)	58.2% (570)	
Year	1327			<0.001
2002		72.2% (83)	27.8% (32)	
2003		71.7% (66)	28.3% (26)	
2004		51.4% (57)	48.6% (54)	
2005		45.4% (59)	54.6% (71)	
2006		39.8% (45)	60.2% (68)	
2007		39.4% (56)	60.6% (86)	
2008		31.4% (33)	68.6% (72)	
2009		32.1% (35)	67.9% (74)	
2010		41.2% (33)	58.8% (47)	
2011		33.0% (38)	67.0% (77)	
2012		30.2% (32)	69.8% (74)	
2013		30.3% (33)	69.7% (76)	
Epidural hematoma	1327			<0.001
No		44.3% (544)	55.7% (685)	
Yes		26.5% (26)	73.5% (72)	
Subdural hematoma	1327			<0.001
No		47.1% (520)	52.9% (585)	
Yes		22.5% (50)	77.5% (172)	
Contusion	1327			<0.001
No		44.5% (554)	55.5% (692)	
Yes		19.8% (16)	80.2% (65)	
Penetrating injury	1327			0.313
No		43.1% (564)	56.9% (744)	
Yes		31.6% (6)	68.4% (13)	
Cranial fracture	1327			<0.001
No		44.7% (552)	55.3% (684)	
Yes		19.8% (18)	80.2% (73)	

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TABLE 1. Patient characteristics

Variable	No. of Patients	ICP Monitor		p Value
		No (n = 570)	Yes (n = 757)	
Max head AIS score	1327			<0.001
2 & 3		66.3% (185)	33.7% (94)	
4		36.9% (117)	63.1% (200)	
5		36.7% (268)	63.3% (463)	
ISS (points)*	1327	17/26/34	26/29/38	<0.001
ASA	1320			0.032
1		41.2% (333)	58.8% (475)	
2		40.4% (112)	59.6% (165)	
3		50.5% (104)	49.5% (102)	
4		55.2% (16)	44.8% (13)	
Systolic blood pressure (mm Hg)*	1269	105/130/150	105/122/140	0.054
Oxygen saturation (%)*	1208	97/99/100	97/99/100	0.066
Heart rate (beats/min)*	1262	72.0/85.0/105.0	71.0/85.0/103.5	0.690
Dead within 30 days	1327			<0.001
No		36.8% (370)	63.2% (635)	
Yes		62.1% (200)	37.9% (122)	

* Data given as lower quartile/median/upper quartile.

Results

We retrieved the records of 1327 patients fulfilling the inclusion criteria of having sustained a severe TBI and surviving ≥ 24 hours. The overall mortality rate in our cohort was 24.3% (322 patients). Patients in the ICP-monitored group tended to be younger ($p = 0.01$). Furthermore, there was a clear tendency for increasing use of ICP monitors in the time period from 2002 to 2013 ($p < 0.001$). Patients with more severe anatomical head injuries were also more likely to have an ICP monitor inserted ($p < 0.001$). Further information about the study population is provided in Table 1.

The weights from the GB model were calculated and the balance between the ICP-monitored and non-ICP-monitored group was investigated and found to be within 0.2 standardized means of each other in all 10 imputed data sets (Fig. 1 left). Furthermore, the relative influences of the different variables in predicting whether an ICP monitor was inserted or not in the GB models were calculated (Fig. 1 right). Age, year, ISS sum, systolic blood pressure on admission, maximum AIS head score, and heart rate accounted for 86% of the cumulative influence in predicting whether the patient received an ICP monitor or not.

The GB-weighted Kaplan-Meier curve for the aggregated 10 imputed data sets demonstrated improved survival in patients who had an ICP monitor inserted (log-rank test, $p < 0.001$). The 30-day mortality rate was 35.1% (200

patients, 95% confidence interval [CI] 31.3%–39.1%) in the group without ICP monitors and 16.1% (122 patients, 95% CI 13.6%–18.9%) in the group with ICP monitors (Fig. 2).

The impact of ICP monitors on 30-day mortality was found to be beneficial for the adjusted analyses in both the complete case data set (odds ratio [OR] 0.23, 95% CI 0.16–0.33) and the aggregated, multiple imputed, propensity-weighted data set (OR 0.22, 95% CI 0.15–0.35; both $p < 0.001$). Moreover, decreasing maximum AIS head scores were associated with reduced 30-day mortality compared to maximum AIS head scores of 5 (all $p < 0.001$). Likewise, decreasing ASA scores were associated with reduced odds of 30-day mortality, compared to an ASA score of 4 (all $p < 0.05$). Epidural hematomas and increasing oxygen saturation were also associated with reduced odds of 30-day mortality ($p < 0.01$). Increasing age was the only factor, identified in both the complete case analysis and in the imputed data set with propensity-score weighted analysis, found to be associated with increased odds of 30-day mortality (all $p < 0.001$). For further details and the coefficients, see Fig. 3.

The sensitivity analysis for the different imputed propensity-weighted models ($n = 10$) demonstrated that a median gamma of 2.41 (range 2.08–2.69) is needed to invalidate the beneficial effect of inserting an ICP monitor. This implies that to attribute the improved survival rate in the group with an ICP monitor due to an unobserved covariate, rather than to the ICP monitor, the unobserved covariate would need to account for a 2.41 increase in the odds of receiving an ICP monitor.

Discussion

The results from our study indicate a clear survival benefit of using ICP monitors in patients with severe brain injury who survive the first 24 hours after injury. The adjusted ORs for 30-day mortality in both the complete case analysis and in the imputed data set with propensity score-weighted analysis were 0.23 (95% CI 0.16–0.33) and 0.22 (95% CI 0.15–0.35), respectively (both $p < 0.001$).

This is in contrast to the randomized controlled BEST-TRIP (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure) trial, in which the effect of ICP monitoring was insignificant.⁶ The BEST-TRIP trial was designed to compare the effect of ICP monitoring to best clinical monitoring. Best clinical monitoring entailed looking for signs indicating increased ICP clinically or radiologically. Hence, BEST-TRIP was a trial comparing ICP read by an ICP monitor to clinical and radiological proxy signs of increased ICP. Thus, the concept of ICP in the treatment of severe TBI was not investigated. In the event of clinical or radiological signs of increased ICP, adjunctive ICP-lowering treatment measures were started. Such treatment measures were utilized to a larger extent in the clinically monitored group underscoring the implicit focus on ICP, even in the non-ICP-monitored group.

The clinical examination, monitoring, and documentation of the patients were probably more comprehensive than standard clinical practice. Consequently, by providing more vigilant clinical monitoring, the non-ICP-moni-

FIG. 1. The *left panel* demonstrates the effect of weighting the propensity score obtained from the GB model on standardized differences between the ICP-monitored and -nonmonitored groups. The different points indicate the different results from the 10 imputed data sets. The *right panel* indicates the relative influence of the variable on the final multivariate model from the GB model. BP = blood pressure; fx = fracture.

tored arm in the BEST-TRIP trial could detect more detrimental episodes of increased ICP than were detected in the non-ICP-monitored group in our cohort. Thus, the BEST-TRIP trial could have reduced the relative impact of the ICP monitor on outcome by providing excellent clinical monitoring.

Cremer et al. compared outcomes between two centers in Holland, in which one of the centers subscribed to the tenets of the BTF guidelines (211 patients) while the other center used clinical monitoring in the treatment of severe TBI (122 patients).⁷ These investigators failed to detect a significant difference with respect to outcome between these centers, thus agreeing with the results from BEST-TRIP and maintaining the external validity for industrialized countries. Likewise, Shafi et al. analyzed the National

Trauma Data Bank run by The American College of Surgeons in the time period from 1994 to 2001.²³ Of almost 500,000 trauma victims, they identified 1646 meeting the BTF criteria for ICP monitoring. Only 43% received an ICP monitor (708 patients). In the ICP-monitored group they found a 45% reduction in survival (OR 0.55, 95% CI 0.39–0.76, $p < 0.001$). Head AIS score and the use of craniotomies were significantly higher in the ICP-monitored group, and GCS score at the scene of the accident was significantly lower. Although they used multivariate techniques that to a certain extent can adjust for group differences, we believe their findings also could be due to confounding by indication.

Our results are compatible with findings in other observational studies, indicating that ICP monitoring is benefi-

FIG. 2. A weighted Kaplan-Meier curve (using the aggregated, propensity score, multiple-imputed data set) demonstrating improved survival in the ICP-monitored cohort.

cial for patients with severe TBI fulfilling the BTF criteria for ICP monitoring.^{1,8,14,17,30,31} Moreover, in a recent meta-analysis of both observational and randomized controlled trials, the use of ICP monitors was found to be beneficial.²⁴

The heterogeneity in the effect of ICP monitors on outcome in the observational studies is perplexing. However, the definition of a futile prognosis is different among the studies. A study that includes all patients would also include patients defined to be unsalvageable. Unsalvageable patients would not receive an ICP monitor, be assigned to the non-ICP-monitored group, and most likely die. This practice would inflate the ratio of dead patients in the non-ICP-monitored group. Conversely, by defining futility as death several days after admittance, the relative impact of ICP monitoring will be reduced. The findings by Shafi et al. could be consistent with this, as they used a futility cutoff at 48 hours.²³ However, this explanation is contested by the findings of Cremer et al. and Griesdale et al. who both failed to identify a significant effect of ICP monitoring and used futility cutoffs at 24 and 12 hours, respectively.^{7,10}

Strengths and Limitations

A major strength of our study is that it includes 1327 patients meeting the 2007 BTF level II and III criteria for being at high risk of intracranial hypertension.⁴ Thus, by

restricting the study population to the population most likely to develop intracranial hypertension, it can be argued that we increase the power of the study.

Likewise, imputation of the missing variables instead of only using a complete case analysis ensures statistical power by not decreasing the effective sample size. The imputation technique also obviates any bias that could have been introduced by a complete case analysis if the missing cases were not missing completely at random.¹¹

In randomized controlled trials, the randomization process conceptually guarantees that all confounders, both observed and nonobserved, will be evenly assigned between the groups. This process thus ensures that the groups only differ with respect to the intervention, allowing causal inferences to be made. Our study consists of an observational cohort stratified by an intervention. The ICP-monitored and -nonmonitored groups are not assumed to be equal with regard to the distribution of confounding factors. Consequently, a causal association between ICP monitoring and survival is difficult to defend. However, we have used a weighted analysis approach based on a propensity score derived from a GB model demonstrating similar covariate distribution between the two groups. This methodology can only account for the observed confounders. However, we argue that many of the observed confounders used in our model are well-established outcome predic-

FIG. 3. Coefficient plot. The unadjusted and adjusted β -coefficients and their associated 95% CIs from the complete case data set using logistic regression are contrasted with the β -coefficients from the imputed, propensity score-weighted logistic regression analysis. The effect of ICP monitor insertion is significant for the adjusted analyses in both data sets (OR 0.23, 95% CI 0.16–0.33, and OR 0.22, 95% CI 0.15–0.35; both $p < 0.001$).

tors.²⁰ Moreover, these well-established prognostic factors are very likely correlated with other unobserved outcome predictors. This correlation mitigates the effect of any unobserved outcome predictors.²⁷ The sensitivity analysis indicates that an unobserved uncorrelated predictor would have to be differentially assigned between the two groups with an OR of 2.41 before the effect of ICP monitoring is insignificant. Finding such a strong uncorrelated outcome predictor is improbable, given that the strongest multivariate predictor in the IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI) study had an OR of 2.23 for CT class (Model A).²⁰ Consequently,

we argue for a causal significant effect of ICP monitoring on outcome despite the shortcomings of an observational cohort.

The propensity score was obtained using both the fitted probabilities from a logistic regression model and from a GB algorithm. The latter technique automatically incorporates the effect of nonlinearity and interactions.¹⁹ These theoretical advantages could improve the model fit in a GB model and contribute to the almost equal distribution of the salient prognostic factors in TBI between the groups with and without an ICP monitor noted in Fig. 1. This distribution of covariates supports the notion that quasi-cau-

sality can be inferred. Furthermore, imputation techniques are often recommended to reduce bias and increase statistical power rather than just analyzing the complete cases.¹¹

A major caveat to appreciate the effect of all types of monitoring on outcome is that the monitor itself cannot be assumed to influence the outcome. Rather, it is the decisions and treatment based on the output from the monitor that is presumed to affect outcome. In this study, as in most other observational studies investigating the effect of ICP monitoring, we have taken the approach that just inserting an ICP monitor could have an impact on outcome. This is a simplistic approach ignoring the extent to which the ICP and CPP values have actually been adequately treated. In contrast, requiring compliance with either the ICP and/or CPP protocol recommendations will effectively make the problem unamenable to scientific scrutiny if the outcome is mortality rate, because a moribund patient with TBI will be in violation of protocols. To circumvent this issue, other studies have reported the proportion of time spent above a certain threshold, amount of ICP-lowering measures used in treatment, and area under the ICP curve.^{6,18,29} However, the effects of the ICP-lowering measures could act through other mechanisms than lowering ICP alone, thus complicating the prospect of establishing causality between ICP and outcome.

Conclusions

ICP monitoring was associated with improved survival in our cohort of patients with severe TBI, even after controlling for baseline severity of the head injury using a propensity score-weighted approach. Our results support the continued use of ICP monitors in patients with severe TBI.

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Disclosures

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Author Contributions

Conception and design: Rønning, Langmoen. Acquisition of data: Skaga. Analysis and interpretation of data: Rønning, Stavem. Drafting the article: Rønning. Critically revising the article: all authors. Reviewed submitted version of manuscript: Rønning, Helseth, Skaga, Stavem. Approved the final version of the manuscript on behalf of all authors: Rønning. Statistical analysis: Rønning, Stavem. Administrative/technical/material support: Helseth, Langmoen. Study supervision: Langmoen.

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