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NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Incidence and Effect of Diabetes Insipidus in the Acute Care of Patients with Severe Traumatic Brain Injury

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Abstract

Background: Literature on diabetes insipidus (DI) after severe traumatic brain injury (TBI) is scarce. Some studies have reported varying frequencies of DI and have showed its association with increased mortality, suggesting it as a marker of poor outcome. This knowledge gap in the acute care consequences of DI in severe TBI patients led us to conceive this study, aimed at identifying risk factors and quantifying the effect of DI on short-term functional outcomes and mortality.

Methods: We assembled a historic cohort of adult patients with severe TBI (Glasgow Coma Scale ≤ 8) admitted to the intensive care unit (ICU) of a tertiary-care university hospital over a 6-year period. Basic demographic characteristics, clinical information, imaging findings, and laboratory results were collected. We used logistic regression models to assess potential risk factors for the development of DI, and the association of this condition with death and unfavorable functional outcomes [modified Rankin scale (mRS)] at hospital discharge.

Results: A total of 317 patients were included in the study. The frequency of DI was 14.82%, and it presented at a median of 2 days (IQR 1–3) after ICU admission. Severity according to the Abbreviated Injury Scale (AIS) score of the head, intracerebral hemorrhage, subdural hematoma, and skull base fracture was suggested as risk factors for DI. Diagnosis of DI was independently associated death (OR 4.34, CI 95% 1.92–10.11, $p = 0.0005$) and unfavorable outcome (modified Rankin Scale = 4–6) at discharge (OR 7.38; CI 95% 2.15–37.21, $p = 0.0047$).

Conclusions: Diabetes insipidus is a frequent and early complication in patients with severe TBI in the ICU and is strongly associated with increased mortality and poor short-term outcomes. We provide clinically useful risk factors that will help detect DI early to improve prognosis and therapy of patients with severe TBI.

Keywords: Craniocerebral trauma, Head injuries, Closed, Diabetes insipidus, Neurogenic, Hypernatremia, Critical care, Brain Injuries, Traumatic, Diabetes Insipidus

Introduction

Traumatic brain injury (TBI) is a major cause of death and lifelong disability worldwide [1]. Some estimates show that TBI accounts for 9% of deaths around the world and represents a threat to health in every country [2]. Although causes of TBI vary depending on income and region, the high direct and indirect costs that it generates are common to all countries, and make it a socioeconomic issue of increasing importance. It is often

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referred to as "the silent epidemic," given its continuous rise in incidence and its concomitant burden across high-, middle-, and low-income countries [3].

A recent comprehensive model by Dewan et al. [4] has estimated all-cause, all-severity TBI global incidence at 79 Mio. cases every year (939 cases per 100.000). According to this model, 11% of TBIs are moderate [Glasgow Coma Scale (GCS) score of 9–12] and 8% severe (GCS < or = 8); roughly 6.3 Mio. severe cases per year, of which around 10% die due to primary injury alone. For the remaining, effects of secondary injury contribute to the high mortality and long-term disability that characterizes severe TBI. As such, outcomes of patients with severe TBI are strongly related to its many potential complications during intensive care unit (ICU) stay, which may arise from the pathophysiologic processes triggered by primary and secondary injury [5].

Among these complications, disorders of salt and water are the most commonly recognized during the immediate post-TBI period, and have been previously suggested as markers of poor outcome [6]. Diabetes insipidus (DI) is one of such disorders, for which the causes and mechanism of disease are widely discussed in academy. Surprisingly, the evidence regarding its frequency and effects during the first days after trauma is scarce, and although it is generally considered a transient condition, little has been studied regarding its implications on short-term outcomes [7].

Heterogeneity in the diagnostic criteria of studies assessing DI has made its incidence and prevalence difficult to estimate. It is known that when DI ensues, the systematic loss of diluted water typically leads to hypovolemic hypernatremia, and along with ensuing hypotension, hypoxemia, and the resulting brain water shift, it is likely to further aggravate secondary injury. Hypernatremia from DI also limits the use of solutions like hypertonic saline, and thus hinders the management of intracranial hypertension, another high-value therapeutic target in these patients.

Agha et al. [6] published two TBI case series in which prevalence of DI was shown to range from 2.9 to 26% [8]. One prospective study by Hadjizacharia et al. [9] brought light on this matter by finding an association between DI and mortality after severe TBI, thus highlighting the clinical relevance of this syndrome in the critical care setting. This study identified DI as an independent risk factor for death, but its effect on the functional short-term outcome of patients was not assessed. This knowledge gap led us to conceive this study, aimed at measuring the frequency of DI, identifying risk factors for DI development and quantifying its effect on short-term outcomes among patients with severe TBI admitted to the ICU.

Methods

Design and study population

Before conducting this study, we received approval by our institutional biomedical research ethics board. We studied a historic cohort that included patients that presented with severe traumatic brain injury at the emergency department of a tertiary-care university hospital in Cali, Colombia, between January 2011 and December 2016. Inclusion criteria were age over 18 years old and traumatic brain injury with GCS < or = 8 upon arrival. Exclusion criteria were patient deemed unsalvageable in the first 24 h of ICU admission for whom therapeutic effort was redirected to palliative care, and patients with brain death diagnosis in the first 24 h of ICU admission. These exclusion criteria were selected because TBI patients who die early are not at risk of developing DI, and as such should not be considered to measure its frequency during ICU stay.

Data collection

We retrieved electronic clinical records from the described 6-year period. Demographic, clinical, laboratory, and imaging data were extracted. Head Abbreviated Injury Scale (AIS) was used to classify patients according to injury severity. The severity of general trauma was calculated using the Injury Severity Score (ISS), as the sum of squares of the AIS scores for the three most severely injured body regions. We used the definition proposed by Butcher and colleagues [10, 11] [(AIS > 3) for at least two different body regions] to determine polytrauma. Only diagnoses made upon ICU stay were taken into account to assess the presence of the water/salt imbalance syndromes in the study population; no retrospective diagnoses were made. For patients diagnosed with DI, values of serum and urinary osmolarity were collected when available. The test is typically ordered upon suspicion of DI given the presence of hypernatremia and polyuria, and the diagnosis is confirmed by the finding of hypo-osmolar urine (< 300 mOsm/L) output consistent with clinical features.

Outcomes

Mortality was defined as death during hospital stay. Short-term functional outcome was assessed using the modified Rankin scale upon hospital discharge. We defined an *unfavorable outcome* as a modified Rankin scale score (mRs) = or > 4 at hospital discharge (patients dependent on others for basic care). Although less common, this cut-off point for dichotomization is clinically useful, has been previously used in relevant studies [12], and responded to the absence of patients with DI that had mRs = 0–2. Given the poor prognosis typically

associated with severe TBI, we also considered adequate to define mRs = 3 as part of a *favorable outcome.*

Statistical analysis

Results of categorical variables are reported as proportions. Continuous variables are reported as means (± standard deviation) or medians [interquartile range (IQR)], as appropriate. In each group, categorical variables were compared using the Chi-square (χ^2) test, and for continuous variables, we used the *t* test or the Mann–Whitney *U* test, according to variable distribution. We carried out three different logistic regressions models to (1) identify factors associated with and clinical predictors for the development of DI, and (2) estimate the effect of diabetes insipidus and sodium disturbances on mortality, and (3) on short-term functional outcomes.

A purposeful variable selection approach was employed for building the multivariate models. Variables with statistical significance as assessed by the Wald test (p value < 0.25) were selected as candidates for each model. We used an iterative process to remove variables from the model if they were nonsignificant ($p > 0.10$) (according to the LR test) and were not a confounder. We considered that a variable had a confounding effect when change in any estimate was observed to be greater than 20% when compared to the full model. If nonsignificant but acting as a confounder, variables were retained in the model. If nonsignificant and not a confounder, variables were only retained in the model if they were part of the study objective (exposures of interest). Statistical analyses were performed in R studio, Version 1.2.1335 using a 95% confidence level.

Results

Patients baseline and clinical characteristics

A total of 317 patients met criteria for inclusion. Median age was 34 years old (IQR 23–48); 83.6% were male; and 98% had no history of functional limitations (mRs = 0 or 1). Remaining 2% represents three patients with mRs = 2, and three more with mRS = 3; no patient included had severe disability (mRS = 4 or 5) before the traumatic event. These and other baseline characteristics are displayed in Table 1. Table 2 displays relevant therapy received and complications during ICU stay.

Diabetes insipidus and water/sodium disturbances

DI was diagnosed in 47 patients (14.82%); 102 patients (32.18%) developed hypernatremia (serum sodium > 155 mEq/L), and DI was the most likely underlying cause of 46% of hypernatremia cases. Patients with DI had a median serum osmolarity of 329 mOsm/L, (IQR = 318 – 339). Urine osmolarity measurements were available in 68% of patients with DI diagnosis; median urine osmolarity was 210 mOsm/L (IQR = 134–290 mOsm/L). Syndrome of inappropriate ADH secretion (SIADHS) was diagnosed in eight patients (2.52%). Only 29 patients (9.15%), including seven patients with SIADHS, developed hyponatremia (serum sodium < 132 mEq/L), all during ICU stay.

Increasing category of head and neck AIS was significantly associated with development of DI (OR 6.04; 95% CI 2.92–12.4). Multivariate analysis also suggested some specific intracranial lesions as risks factors for the development of DI: subdural hematoma (OR 4.31; 95% CI 1.86–10.0), intracerebral hemorrhage (OR 2.72; 95% CI 1.18–6.26), and skull base fracture (OR 2.91; 95% CI 1.33–6.35) (Table 3).

Patients with DI received management with intravenous vasopressin (87.2%) or desmopressin (12.7%) and required vasopressor therapy more frequently that non-DI patients (74.4 vs 38.8%, $p < 0.001$). DI was transient

Table 1 Baseline characteristics in total study population and according to the presence of diabetes insipidus

Characteristic	All patients, *n* (%)	Diabetes insipidus, *n* (%)	
	Total = 317	No = 270	Yes = 47
Age (years)	34 (23–48)*	35 (24–49)*	32 (24.5–44)*
Male gender	265 (83.6)	223 (83.2)	41 (87.2)
Modified Rankin scales prior to TBI			
0	300 (94.6)	253 (93.7)	47 (100)
1	11 (3.5)	11(4.1)	0 (0)
2 or 3	6 (1.9)	6 (2.2)	0 (0)
Penetrating injury	43 (13.6)	31 (11.4)	12 (25.5)
Head AIS			
1. Minor	5 (1.6)	4 (1.5)	1 (2.1)
2. Moderate	22 (6.9)	22 (8.1)	0 (0)
3. Serious	98 (30.9)	97 (35.9)	1 (2.1)
4. Severe	119 (37.5)	110 (40.7)	9 (19.1)
5. Critical	73 (23)	37 (13.7)	36 (76.6)
Polytrauma	204 (64.4)	174 (64.4)	30 (63.8)
Spine trauma	31 (9.8)	28 (10.3)	3 (6.4)
CT findings			
Subarachnoid hemorrhage	214 (67.5)	174 (64.4)	40 (85.1)
Subdural hematoma	129 (40.7)	96 (35.6)	33 (70.2)
Intracerebral hemorrhage	123 (38.8)	97 (35.9)	26 (55.3)
Epidural hematoma	77 (24.3)	65 (24.1)	12 (25.5)
Middle cranial fossa fracture	76 (24)	50 (18.5)	26 (55.3)

AIS Abbreviated Injury Scale, *CT* computed tomography scan, *TBI* traumatic brain injury

* Median and interquartile range

Table 2 Therapy, clinical features, and complications during ICU stay

Variable	All patients = 317 *n* (%)	Diabetes insipidus		OR	*p* value
		No = 270 *n* (%)	Yes = 47 *n* (%)		
Hypertonic saline therapy	87 (27.4)	65 (24)	22 (46.8)	2.77	0.006
Mannitol therapy	76 (23.9)	54 (20)	22 (46.8)	3.52	< 0.001
ICP measurement	68 (21.4)	59 (21.8)	12 (25.5)	1.22	0.75
Vasopressor requirement	128 (40.3)	105 (38.8)	35 (74.4)	4.52	< 0.001
Surgical hematoma drainage	77(24.2)	61 (22.5)	16 (34)	1.74	0.098
Decompressive craniectomy	63(19.8)	47 (17.4)	16 (34)	2.43	0.006
Acute kidney failure	30 (9.4)	26 (8.8)	4 (8.5)	0.87	0.778
Acute kidney failure by AKIN					0.631
1	11 (36.6)	8 (30.7)	3 (75)	–	–
2	10 (33.3)	9 (34.6)	1 (25)	–	–
3	9 (30)	9 (34.6)	0 (0)	–	–
Infectious complications	129 (40.6)	110 (40.7)	19 (40.4)	0.97	0.94
Hypernatremia	102 (32.1)	59 (21.8)	43 (91.4)	38.3	< 0.001
Hyponatremia	29 (9.1)	26 (9.6)	3 (6.3)	0.63	0.395
SIADH	8 (2.5)	8 (2.9)	0 (0)	0	0.611
Death	88 (27.7)	56 (20.7)	32 (68.1)	8.15	< 0.001

ICP intracranial pressure, *SIADH* syndrome of inappropriate ADH secretion

Table 3 Regression model: factors associated with the development of diabetes insipidus, *n* = 317

Variable	OR	95% CI
Penetrating trauma	0.88	[0.32; 2.40]
Head and neck AIS	6.04	[2.92;12.4]
Subdural hematoma	4.31	[1.86; 10.0]
Intracerebral hemorrhage	2.72	[1.18; 6.26]
Middle fossa fracture	2.91	[1.33; 6.35]

AIS Abbreviated Injury Scale, *95% CI* 95% Confidence Interval

Table 4 Regression model: clinical features associated with death, *n* = 317

Variable	OR	95% CI
Age	1.04	[1.01; 1.06]
Head and neck AIS	1.66	[1.13; 2.48]
GCS—motor score	0.71	[0.58; 0.88]
Middle fossa fracture	4.11	[2.06; 8.31]
Diabetes insipidus	4.34	[1.92; 10.1]
Acute renal failure	4.69	[1.80; 12.8]

AIS Abbreviated Injury Scale, *95% CI* 95% Confidence Interval, *GCS* Glasgow Coma Scale

in 80% of patients that survived up to hospital discharge ($n = 15$), persisting in only three patients upon discharge. Other clinical features and laboratory data are displayed in Table 2 for all patients, and according to the presence of DI.

Mortality

In our study, overall mortality was 27.76%. Specific in-ICU mortality was 23.65%. Multivariate analyses—after controlling for severity of trauma (head and neck AIS score and GCS motor score), and other relevant confounders—showed that diagnosis of DI (OR 4.34, CI 95% 1.92–10.11, $p = 0.0005$) and the presence of acute renal failure (OR 4.69, 95% CI 1.80–12.81, $p = 0.0018$) had a strong association with a fatal outcome. Finding of a middle cranial fossa fracture also had a strong and independent association with death (OR 4.11, 95% CI 2.06–8.31, $p = 0.0007$) (see output from the mortality regression model in Table 4).

Outcomes at discharge

Modified Rankin scale score at discharge presented the following distribution: only four patients had mRs = 0, all in the non-DI (control) group. From total, 28% had mRs = 1 or 2, all in the control group too; there were no patients with diagnosis of DI with mRs = 0, 1, or 2 at discharge. Fifteen percent of patients had mRs = 3 (6.4% in DI group vs 16.6% in control group); 15.1% had mRs = 4 (8.5% in DI group vs 16.3% in control group); and 12.9% had mRs = 5 (17% in DI group vs 12.2% in control group); mRs = 6 (death) was described in detail in the mortality section. Figure 1 shows the proportion

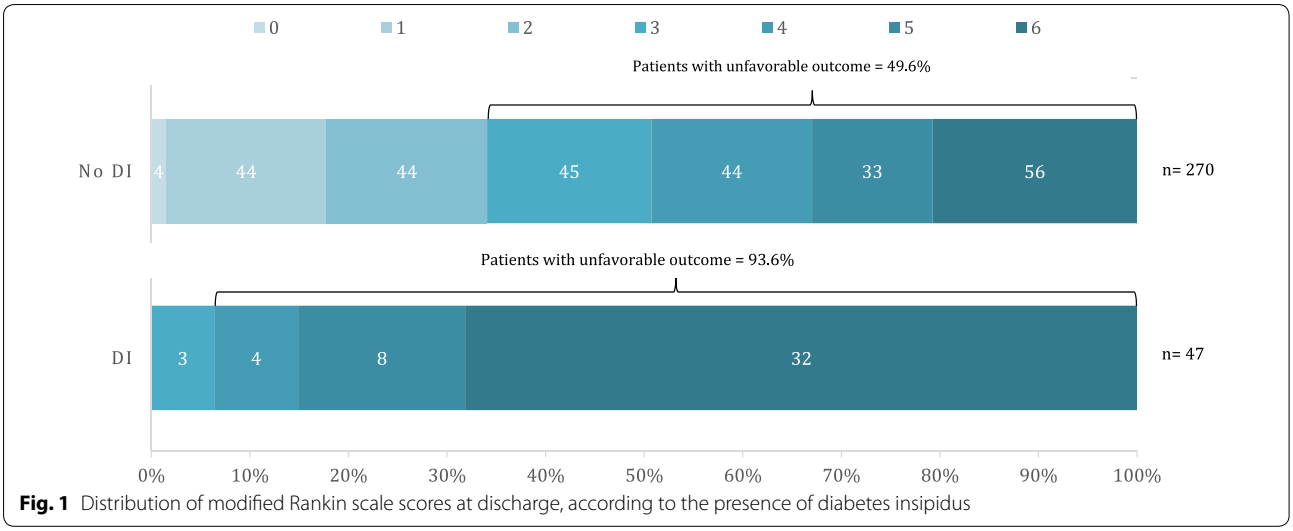

Fig. 1 Distribution of modified Rankin scale scores at discharge, according to the presence of diabetes insipidus

Table 5 Regression model: factors associated with an unfavorable outcome at discharge (mRs = 4, 5 or 6), *n* = 317

Variable	OR	95% CI
Age	1.02	[1.01; 1.04]
Head and neck AIS	2.66	[1.92; 3.77]
GCS motor response	0.71	[0.59; 0.84]
Diabetes insipidus	7.38	[2.16; 37.2]

AIS Abbreviated Injury Scale, *95% CI* 95% Confidence Interval, *GCS* Glasgow Coma Scale

of patients with *unfavorable outcome* upon hospital discharge and the absolute number of patients for each category of the mRs, according to the presence of DI. Our regression model showed, after controlling for severity and types of injury, that diabetes insipidus was strongly associated with an *unfavorable outcome* at discharge (OR 7.38; CI 95% 2.15–37.21, $p = 0.0047$) (see Table 5).

Discussion

Our study was set to investigate the frequency and effects of DI in severe TBI patients. We found an incidence of DI of 14.8% in our historic cohort, and found strong associations of DI with mortality and unfavorable outcomes at discharge.

Our results regarding the frequency of DI after TBI are comparable to reports from similar studies, although given our definition of DI, it might have been underestimated. Variable follow-up times, heterogeneity in diagnosis criteria, and selection of study subjects may account for the wide range of DI incidence reported in the literature [6, 9, 13, 14]. In our study, DI was diagnosed after a median 2 days of ICU admission, making it an early complication of the severe TBI patient. Also, 80% of survivors with DI had transient DI that resolved previous to hospital discharge, suggesting a partial or reversible lesion as a cause for DI in survivors; brain edema and stalk displacement secondary to expanding lesions may be responsible. We did not obtain data on follow-up after discharge, but we found one study reporting that only 6% of all TBI cases have persistent DI after 12 months of follow-up [13].

Factors associated with diabetes insipidus

Previous studies have demonstrated that TBI and SAH may lead to central diabetes insipidus and other forms of neuroendocrine dysfunction [6, 15–18]. To our knowledge, only one study has specifically assessed posterior pituitary dysfunction in an adult population after TBI; the study by Hadjizacharia et al. [9], which suggested that head AIS > 3, GCS < 8, and cerebral edema were strong and independently associated with DI. Some studies have assessed several types of endocrinopathies after TBI, suggesting that penetrating injuries, skull base fractures, diffuse axonal injuries, subarachnoid hemorrhage, increased intracranial pressure, prolonged ICU stay, and brain edema as risk factors [8, 15, 19–22]. In our study, the regression model used to identify risk factors for DI development showed that severity of trauma, subdural hematoma, intracerebral hemorrhage, and skull base fracture was strongly associated with DI development. These data suggest that the presence of one of these lesions should prompt early laboratory tests for detection of DI.

Skull base fractures are known to occur after high-energy impact trauma and lead to fronto-occipital displacement of the brain over the skull base. Such a displacement is likely to provoke damage of the infundibular stalk. Furthermore, infarction or hemorrhage of the pituitary and hypothalamus can also occur due to tearing of perforating and portal vessels [23]. These mechanisms may be responsible for DI cases in patients that died or those for whom DI did not resolve. Space-occupying intracranial lesions (intracerebral hemorrhages and subdural hematomas) increase intracranial pressure, exerting pressure upon the stalk [24], which can lead to transient dysfunction, which is most likely responsible for the observed transitory nature of DI in survivors.

Mortality and functional outcomes

It is important to highlight that we excluded patients deemed unsalvageable or with brain death diagnosis during the first 24 h after admission. As such, mortality in our sample can be lower than that in other reports of patients with severe TBI. Patients with DI during ICU stay had an increased risk of death (OR 4.34 95% CI 1.92–10.11, from multivariate analysis). We found only another study assessing posterior pituitary dysfunction in a similar setting, which showed comparable estimates of the association between DI and mortality (OR 3.96; 95% CI 1.65–9.72, from Hadjizacharia et al. [9]).

Neuroendocrine dysfunction may lead to death, sodium disturbances, hypotension, and vasoactive drugs requirement [9]. Furthermore, treatment of DI may worsen outcomes of patients with severe TBI because of the risk of complications like refractory hypernatremia, fluid overload, seizures, and cerebral edema [25, 26]. Hypernatremia and the hyperosmolar state that accompany DI have several physiological implications, which include neuronal shrinkage, muscle weakness, rhabdomyolysis, decreased ventricular contractility, and impairment in glucose utilization, all of which contribute to increased mortality in the ICU [27]. Systematic loss of diluted water leads to hypovolemic hypernatremia, which usually prompts therapy to maintain volume and perfusion, and explains the high frequency of vasopressors used in DI population compared with non-DI patients (72 vs 38%, $p < 0.001$). The described phenomena explain the increased mortality and elevated frequency of poor functional outcomes in the group of patients with DI. Also, hypernatremia can be the result of hyperosmolar therapy and act as a marker of severity, cerebral edema, and/or therapy intensity. Hypernatremia occurred in 52 out of 87 patients (59.8%) that received hypertonic saline therapy, compared to 50 out of 228 (21.9%) that did not receive therapeutic hypertonic saline.

Limitations

This study is limited by its single-center retrospective nature. Given that our measurements relied on clinical records, we consider that diagnosis of DI may have been underestimated in our study. Because DI diagnoses were supported by clinical features and laboratory confirmation of hypernatremia and low urine osmolarity, overestimation was unlikely. This differential misclassification would have bias estimation of the effects of DI on outcomes toward the null. Nevertheless, significant associations between DI and outcomes were identified despite of this differential bias, which supports the validity of our findings. Also, given the exclusion criteria of early death used for this study, our mortality measurements may underestimate the mortality associated with the complete spectrum of severe TBI. Finally, while relevant confounders were identified and incorporated into the study, it is possible that unknown confounders and clinician bias could have impacted our results.

Conclusion

Diabetes insipidus in the ICU is a frequent and early complication in patients with severe TBI, and it seems to account for an elevated number of deaths. In survivors, its association with poor functional outcomes is strong. Our results emphasize the importance of detecting DI promptly. Factors associated with the development of this syndrome should be helpful to improve its diagnosis, therapy, and prognosis among patients with severe TBI in the ICU.

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None.

Author contributions

AG contributed to Protocol and project development, data collection and management, data analysis, manuscript writing and editing. EOG and AHC contributed to Protocol development, data collection, data Analysis, manuscript writing. AMC contributed to Protocol development, data analysis, manuscript editing. JDAM contributed to Protocol/project development, data collection and management, data analysis, manuscript editing. JHMM contributed to Protocol/project development, data management, data analysis, manuscript writing and editing.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical Approval/Informed Consent
Our institutional Research Ethics Committee approved our study protocol, the participation of each author, and oversaw study conduction. No informed consent was required for this study.

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