**Sedation Patterns and Hyperosmolar Therapy in Emergency Departments were Associated with Blood Pressure Variability and Outcomes in Patients with Spontaneous Intracranial Hemorrhage**

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**Abstract**

**Background:** Spontaneous intracranial hemorrhage (sICH) is associated with high initial mortality. Little information exists to guide initial resuscitation in the emergency department (ED) setting. However, blood pressure variability (BPV) and mechanical ventilation (MV) are known risk factors for poor outcome in sICH. **Objectives:** The objective was to examine the associations between BPV and MV in ED (EDMV) and between two ED interventions – post-MV sedation and hyperosmolar therapy for elevated intracranial pressure – and BPV in the ED and in-hospital mortality. **Methods:** We retrospectively studied adults with sICH and external ventricular drainage who were transferred to a quaternary academic medical center from other hospitals between January 2011 and September 2015. We used multivariable linear and logistic regressions to measure associations between clinical factors, BPV, and outcomes. **Results:** We analyzed ED records from 259 patients. There were 143 (55%) EDMV patients who had more severe clinical factors and significantly higher values of all BPV indices than NoEDMV patients. Two clinical factors and none of the severity scores (i.e., Hunt and Hess, World Federation of Neurological Surgeons Grades, ICH score) correlated with BPV. Hyperosmolarity therapy without fluid resuscitation positively correlated with all BPV indices, whereas propofol infusion plus a narcotic negatively correlated with one of them. Two BPV indices, i.e., successive variation of blood pressure (BPsv) and absolute difference in blood pressure between ED triage and departure (BPdeparture − Triage), were significantly associated with increased mortality rate. **Conclusion:** Patients receiving MV had significantly higher BPV, perhaps related to disease severity. Good ED sedation, hyperosmolar therapy, and fluid resuscitation were associated with less BPV and lower likelihood of death.

**Keywords:** Blood pressure variability, hyperosmolar therapy, postmechanical ventilation sedation, spontaneous intracranial hemorrhage

**INTRODUCTION**

Patients with spontaneous intracranial hemorrhage (sICH) have a mortality rate as high as 40%.¹,² Factors predicting poor outcome include blood pressure variability (BPV)³⁻⁷ and the need for invasive mechanical ventilation (MV).² BPV is defined as the average of absolute differences between consecutive blood pressure measurements (successive variations of blood pressure [BPsv]) or variations in blood pressure during a period of time (standard deviation [BPsd]) or coefficient of variation (BPcv).³

Neurologic deterioration among patients with sICH and elevated intracranial pressure (ICP) is common in the emergency department (ED)⁹ as well as during transfer to

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a tertiary care center. These patients frequently require invasive MV in the ED (EDMV) for airway protection. Initial resuscitation for these sICH patients included MV for airway protection while reducing ICP to maintain adequate cerebral perfusion. An endotracheal tube is a noxious stimulus, and patients frequently require adequate sedation. Hyperosmolar agents, mannitol, and hypertonic saline are administered to patients with intracranial hypertension to reduce ICP. Mannitol, in particular, is a diuretic and may be associated with hypovolemia and fluctuations of patients’ blood pressure. We hypothesized that patients requiring MV in the ED, in addition to having higher clinical severity, have higher BPV than those who are not intubated in the ED (NoEDMV).

Previous studies suggested that sedation of EDMV patients lowered their mortality rate and that the level of sedation influenced catecholamine production, which affects blood pressure. We further hypothesized that two practices in the ED – adequate post-MV sedation and administration of hyperosmolar therapy in EDMV patients with fluid resuscitation – would both be associated with lower BPV and mortality for patients with sICH and elevated ICP.

Overall, we sought to study whether BPV occurs in patients who have sICH and are suspected to have elevated ICP during their ED stays. We hypothesized that BPV during ED stay would be associated with the outcomes and two ED interventions, as stated above, would be associated with less BPV in this group of patients prior to transfer.

**Methods**

**Study settings**

We retrospectively reviewed the charts of adults with sICH and elevated ICP who were transferred to an academic quaternary center from another hospital and received an external ventricular drain (EVD) for intracranial hypertension. The transfers occurred between January 1, 2011, and September 30, 2015. Patients were identified by codes of 430.XX and 431.XX of the International Classification of Disease, version 9, and procedure code 02.2. The study was approved by the institutional review board at the university with which the authors are affiliated.

We excluded patients who presented initially to our academic center, patients who were not directly transferred from any referring ED, and patients not accompanied by records from transferring EDs. Patients who were admitted initially to our academic ED were excluded because of (1) our institutional practice: patients who arrive in our ED and are admitted to an inpatient service such as the neurologic critical care unit are not actively managed by the ED providers unless their condition deteriorates; therefore, management of the admitted patients being boarded in the ED does not reflect care from the clinical staff and (2) we focused on the patients being transferred from another hospital. We also excluded trauma patients and patients whose hemorrhage was secondary to other pathologies, such as a tumor or arteriovenous malformations, because common neurosurgical severity scores were neither designed for, nor validated, in these patient populations.

**Data collection and management**

**Data collection**

The principal investigator of this study (QKT) taught the process of extracting data from patient records to six of the investigators (PC, SH, TN, CPM, CO, and KP), who were blinded to the study’s hypotheses. Data were extracted into a standardized Microsoft Access database (Microsoft Corp., Redmond, WA, USA). To minimize bias, the investigators also collected data in sections and independently from each other. For example, severity scores for subarachnoid hemorrhage (SAH) (derived using the Hunt and Hess Scale [H and HS], the World Federation of Neurological Surgeon Scale [WFNSS]) and intracerebral hemorrhage (the Intracerebral Hemorrhage Score [ICH]) were collected independently by AW and MK, who did not have access to other data or outcomes. The data were compiled, and their quality was assessed by JS. Once all anomalies were resolved, another investigator (KP) validated up to 40% of the data, such as intracranial opening pressure (OP) and blood pressure, to maintain interrater agreement of at least 90%. The group met every 3 months to discuss issues regarding data interpretation, data extraction, and data adjudication until this phase of the study was complete.

**Patient selection and data collection**

Each patient’s data were obtained from multiple sources: records from the referring ED, transport team documentation, and flow sheets from the receiving intensive care unit (ICU). Demographic data included date and time of ED triage and departure from the referring ED, age, and gender. Clinical data included vital signs, Emergency Severity Index (ESI) and Glasgow Coma Scale (GCS) scores at triage and ED departure, the occurrence of seizure prior to arrival at the ED or during the ED stay, and the date and time that MV was initiated. We also documented emergency care providers’ interventions after invasive MV (i.e., type of sedation) and elevated ICP (i.e., dose of hyperosmolar therapy and volume of intravenous crystalloids). We documented the use of a medication if its administration was indicated in the ED records, by a transport team, or by a receiving ICU team. A medication that was ordered but not documented as given to the patient was not recorded.

From the admission ICU teams’ documentation, we collected patients’ presenting GCS score and intracranial OP from EVD placement. In addition, GCS score at hospital day 5 (HD5GCS), which is significantly associated with the 90-day posthospital discharge functional outcome, was collected.

Outcome data regarding mortality and discharge directly to home were extracted from our electronic medical records.

**Blood pressure variability**

Blood pressure measurements were recorded in the charts at the referring EDs in accordance with physicians’ practices. As ED staff members do not record blood pressure measurements
regularly or hourly, we extracted measurements at four clinically meaningful points, as previously used in another study.\(^{[23]}\) at ED triage (BP\(_{\text{triage}}\)) and at ED departure (BP\(_{\text{depart}}\)) and then the highest one (BP\(_{\text{high}}\)) and the lowest one (BP\(_{\text{low}}\)) during the ED stay. If the BP at triage or departure happened to be the highest or lowest value, then the next higher or lower value during the ED stay was extracted.

The magnitude of change of systolic blood pressure (SBP) during the ED stay (BP\(_{\text{Depart} - \text{triage}}\)) was calculated as previously described.\(^{[5,24]}\)

\[
\sqrt{(BP_{\text{depart}} - BP_{\text{triage}})^2}
\]

The magnitude of absolute change between the high and low SBPs (BP\(_{\text{High} - \text{Low}}\)) was calculated as BP\(_{\text{High} - \text{Low}}\) = (SBP\(_{\text{High}}\) − SBP\(_{\text{Low}}\)).

Different indices of BPV were calculated as described earlier.\(^{[24-26]}\) Standard deviation of BP (BP\(_{\text{SD}}\)) was calculated as:

\[
(\frac{1}{n-1}) \int_{i=1}^{n} (BP_i - BP_{\text{mean}})^2
\]

The coefficient of variation of BP (BP\(_{\text{CV}}\)) was calculated as:

\[
\left(\frac{\text{SD}_{\text{mean}}}{\text{BP}_{\text{mean}}}\right) \times 100
\]

BP\(_{\text{sv}}\) were calculated with the following equation:

\[
\sqrt{\frac{1}{(n-1)} \int_{i=1}^{n} (SBP_{i+1} - SBP_i)^2}
\]

Management of sedation

To analyze the effect of post-MV sedation on BPV, we divided our patient population into groups according to the type of sedation they received. Patients who did not require MV in the ED (NoEDMV) and thus did not receive sedation constituted the control group. The EDMV patients were divided into subgroups that received no sedation (NoSedation), only benzodiazepine (OnlyBenzo), propofol infusion (OnlyProp), or propofol infusion, and an opioid (Prop + Pain). A patient who received any intravenous push (IVP) doses of benzodiazepine in addition to propofol by infusion was classified as receiving propofol infusion (OnlyProp). A patient who received a few doses of IVP propofol and continuous infusion of benzodiazepine was considered as receiving only benzodiazepine (OnlyBenzo). A patient who received both IVP benzodiazepine and IVP propofol was categorized in our OnlyBenzo group due to propofol’s short half-life compared with that of benzodiazepine. We did not record the dosages of sedative medications. Infusion was defined as a rate of administration >30 min; IVP administration took <30 min.

Hyperosmolar therapy

We divided intubated patients into three groups: (1) patients who did not receive any hyperosmolar therapy (no hyperosmolar), (2) patients who received either mannitol or hypertonic saline without fluid resuscitation (HyperosmolarOnly), and (3) patients who received hyperosmolar agents and intravenous fluid (hyperosmolar + IVF). We recorded the dosage of mannitol and volume of hypertonic saline as they were recorded in the chart. We also recorded the rate at which mannitol was administered.

Outcomes

The primary outcome was the difference in BPV indices between nonintubated patients (NoEDMV) and intubated patients (EDMV). Secondary outcomes were BPV indices between groups receiving different types of sedation and groups receiving hyperosmolar therapy with or without IVF. Other outcomes included in-hospital mortality, HD5GCS, and percentage of patients who were discharged directly to home.

Data analysis

Descriptive analyses involving demographic and clinical data were compared for intubated patients versus nonintubated patients. The distributions of continuous data were assessed with the —Shapiro–Wilks test and expressed as mean (SD) or median with interquartile range when appropriate. Chi-square analysis with Yates correction was used to compare categorical data. The Student’s t-test or Mann–Whitney U test was used to compare continuous data when appropriate. Normally distributed data between three or more groups were compared with analysis of variance and post hoc Holm–Sidak corrections.

We performed backward step-wise multivariable linear regressions to assess correlation between clinical variables and each dependent variable (each component of BPV and HD5GCS). Clinical variables with \(P \leq 0.10\) in bivariate analyses were included in the model to avoid inclusion of irrelevant independent variables.\(^{[27]}\) Similarly, we specified the criteria for elimination in our step-wise elimination multivariable linear regression to be \(>0.10\). Goodness of fit of our models was assessed via adjusted R\(^2\).

Multivariable logistic regressions with backward step-wise elimination were used to assess associations between clinical variables and two dependent variables: mortality and discharge home. Criteria for inclusion into the model and elimination in our step-wise regression were similar to procedures in multivariable linear regression. Prior to performing the logistic regression, we decided to include age, which was considered clinically significant, to our model. Goodness-of-fit of our logistic regression models was assessed by the deviance, Pearson’s, and Hosmer–Lemeshow tests. Models with \(P > 0.05\) for all the three tests were considered good fit.

All two-sided \(P < 0.05\) was considered statistically significant. Statistical analyses were performed using MiniTab 18 (Minitab, Inc., State College, PA, USA) and SigmaPlot 13.5 (Systat Software, San Jose, CA, USA).

Results

Patient characteristics

We analyzed the records of 259 patients with sICH meeting the inclusion criteria for our study [Figure 1]. Two-thirds
**Table 1: Characteristics of patients with spontaneous intracranial hemorrhage (n=259)**

|                               | EDMV (n=143) | No EDMV (n=116) | P    |
|-------------------------------|--------------|-----------------|------|
| Age (years), mean±SD          | 58±14        | 58±13           | 0.89 |
| Gender                        |              |                 | 0.39 |
| Female, n (%)                 | 79 (55)      | 71 (61)         |      |
| Male, n (%)                   | 64 (45)      | 45 (39)         |      |
| Hospital teaching status      |              |                 | 0.98 |
| Teaching, n (%)               | 53 (36)      | 45 (37)         |      |
| Nonteaching, n (%)            | 94 (64)      | 77 (63)         |      |
| Ground distance (km), mean±SD | 29±44        | 31±36           | 0.72 |
| Mode of transport             |              |                 | 0.37 |
| Ground, n (%)                 | 92 (64)      | 83 (72)         |      |
| Air, n (%)                    | 51 (36)      | 33 (28)         |      |
| Type of intracranial hemorrhage, n (%) | | | |
| IPH                           | 60 (43)      | 25 (22)         | 0.004|
| SAH                           | 83 (57)      | 91 (78)         |      |
| Severity score                |              |                 |      |
| ESP, median (IQR)             | 2 (1-2)      | 3 (2-3)         | <0.001|
| Hunt-Hess scale*, median (IQR)| 4 (3-5)      | 2 (2-3)         | <0.001|
| WFNSS*                        | 4 (4-5)      | 2 (1-2)         | <0.001|
| ICH score*, mean±SD           | 3±1          | 2±1             | <0.01 |
| Clinical seizure prior or during ED, n (%) | | | |
| No                            | 125 (85)     | 116 (95)        | 0.01 |
| Yes                           | 22 (15)      | 6 (5)           |      |
| Anticoagulation, n (%)        | 11 (8)       | 10 (9)          | 0.79 |
| Antiplatelet, n (%)           | 23 (16)      | 18 (16)         | 0.89 |
| Any antihypertensive medication, n (%) | 76 (53)    | 55 (47)         | 0.42 |
| Labelatol IVP, n (%)          | 33 (23)      | 27 (23)         | 0.90 |
| Nicardipine infusion, n (%)   | 34 (24)      | 21 (18)         | 0.34 |
| Other, n (%)                  | 9 (6)        | 7 (6)           | 0.86 |
| Triage GCS, median (IQR)      | 9 (5-13)     | 15 (14-15)      | <0.001|
| Triage SBP (mm Hg), mean±SD   | 183 (41)     | 170 (35)        | 0.003|
| Departure SBP, mean (SD)      | 147 (28)     | 152 (23)        | 0.13 |
| Duration of MV in ED (min), mean±SD | 106 (71) | NA              | NA   |
| Sedation management, n (%)*   |              |                 |      |
| No sedation                   | 41 (29)      | NA              | NA   |
| Benzodiazepine only           | 37 (26)      | NA              | NA   |
| Propofol infusion only        | 50 (35)      | NA              | NA   |
| Propofol infusion + narcotic pain medication | 15 (10)      | NA              | NA   |
| Hyperosmolar therapy**        |              |                 |      |
| Mannitol                      | 38 (26)      | NA              | NA   |
| 3% hypertonic saline          | 2 (2)        | NA              | NA   |
| Hyperosmolar interventions*   |              |                 |      |
| No hyperosmolar               | 103 (72)     | NA              | NA   |
| Hyperosmolar without IVF      | 27 (19)      | NA              | NA   |
| Hyperosmolar with IVF         | 13 (9)       | NA              | NA   |
| ED LOS (min), median (IQR)    | 173 (130-213) | 208 (141-345)  | <0.001|
| ICU GCS, median (IQR)         | 7 (4-8)      | 14 (12-15)      | <0.001|
| ICU SBP, at arrival, mean±SD  | 145±25       | 149±25          | 0.08 |
| Opening ICP (cmH₂O), mean±SD  | 22±7         | 22±7            | 0.62 |
| BP<sub>sys</sub>, mean±SD     | 39±22        | 19±13           | <0.001|
| BP<sub>dia</sub>, mean±SD     | 48±21        | 31±18           | <0.001|
| BP<sub>mean</sub>, mean±SD    | 32±13        | 20±12           | <0.001|
| BP<sub>interp-triage</sub> mean±SD | 45±34    | 26±21           | <0.001|
| BP<sub>high-low</sub> mean±SD | 58±38        | 28±21           | <0.001|
| HD5 GCS, median (IQR)         | 10 (5-13)    | 15 (11-15)      | <0.001|

Contd...
of them \(n = 174, 67\%\) had SAH and one-third \(n = 85, 33\%\) had intraparenchymal hemorrhage. One hundred and forty-three \(55\%\) patients received MV in the ED [Table 1]. Patients in our study had elevated ICP, with a mean OP of 20 (SD 7). The mean age of the intubated patients and nonintubated patients was similar at 58 (SD 14) years. The intubated group had significantly higher care intensity, as measured by ESI at the referring EDs, and higher neurological severity scores (H and HS, WFNSS, and ICHS) [Table 2]. Intubated patients had a lower median triage GCS score \(9 [5–13] vs. 15 [14–15] [P < 0.001]\) and a lower median HD5GCS \(10 [5–13] vs. 15 [11–15] [P < 0.001]\) [Table 2]. In addition, intubated patients had a higher mortality rate \(33\%\) vs. \(9\%\), 95\% confidence interval [CI] 2.4, 9.8 \([P < 0.001]\) and a lower rate of being discharged home \(10\%\) vs. \(36\%\), 95\% CI 0.07, 0.3 \([P < 0.001]\).

The percentage of any antihypertensive medications was similar between the intubated patients \(53\%\) and nonintubated patients \(47\%, P = 0.42\) [Table 1]. Similarly, the patterns of antihypertensive medication such as IVP labetalol and nicardipine infusion were also similar between both groups [Table 1].

**Blood pressure variability as outcome**

All the five indices of BPV were significantly higher among intubated patients than that in the nonintubated group [Table 1],
who need neither sedation nor hyperosmolar therapy. Table 2 shows different indices of BPV in relation to the types of sedation. Approximately 29% of the intubated patients received no sedation. They had the highest values for all the five indices of BPV, and those values were significantly higher than those of the nonintubated patients. One BPV index (BP\textsubscript{High−Low}) was significantly higher than these values for patients receiving propofol and any opioid pain medication (Prop + Pain) (67 [SD 40]) versus 39\textsuperscript{23} (P = 0.023). Furthermore, patients receiving propofol and any opioid pain medication had lower BPV, which reached nonsignificant difference to values for the nonintubated group (BP\textsubscript{SV, CV}, BP\textsubscript{Depart−Triage*} and BP\textsubscript{High−Low}) [Table 2].

Thirty-eight patients (26%) received mannitol and two (1%) received hypertonic saline [Table 1]. The mean dose of mannitol was 0.76 g/kilogram (g/kg) body weight [Appendix 1]. Among the patients receiving any hyperosmolar and any amount of IVF (hyperosmolar + IVF), the mean volume of IVF administered was 19 ml/kg [Appendix 1]. Table 3 shows that all five indices of BPV among patients receiving hyperosmolar therapy without any IVF (hyperosmolar only) were significantly higher than those of the nonintubated group, for whom hyperosmolar therapy was not administered. The administration of IVF reduced the BPV of patients effectively so that the five indices of BPV in the group receiving both hyperosmolar and IVF were significantly lower than that in the patients given hyperosmolar therapy without fluid. Furthermore, four BPV indices (BP\textsubscript{SV, CV, Depart−Triage*}, BP\textsubscript{High−Low}) of the group receiving both hyperosmolar therapy and IVF were lower and were nonsignificantly similar to those of the nonintubated patients.

Multiple linear regressions showed that none of the severity scores correlated with BPV [Table 4]. Only two clinical factors, i.e., triage SBP and triage GCS score, correlated with BPV. Triage SBP positively correlated with all the five indices of BPV, whereas triage GCS score negatively correlated with one

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**Table 2: Blood pressure variability in patients according to the type of sedation**

| BPV components, mean±SD | No EDMV (n=116) | EDMV (n=143) | P |
|-------------------------|-----------------|--------------|---|
|                        | Group A         | Group B (n=15) | Group C (n=41) | Group D (n=50) | Group E (n=37) | A versus B | A versus C | B versus C |
| GCS at ICU arrival, median (IQR) | 14 (12-15) | 7 (3-8) | 7 (4-9) | 7 (5-8) | 6 (3-7) | <0.001 | <0.001 | 0.99 |
| BP\textsubscript{SV} | 19 (13) | 31 (18) | 41 (22) | 37 (23) | 41 (20) | 0.133 | <0.01 | 0.33 |
| BP\textsubscript{SD} | 31 (18) | 49 (21) | 54 (21) | 44 (21) | 50 (18) | 0.006 | <0.01 | 0.67 |
| BP\textsubscript{CV} | 20 (11) | 31 (13) | 35 (14) | 28 (14) | 32 (12) | 0.07 | <0.01 | 0.66 |
| BP\textsubscript{Depart−Triage*} | 26 (21) | 39 (38) | 54 (39) | 40 (32) | 45 (29) | 0.431 | <0.01 | 0.38 |
| BP\textsubscript{High−Low} | 28 (21) | 39 (23) | 67 (40) | 57 (41) | 58 (36) | 0.52 | <0.01 | 0.023 |

*Patients were either not intubated (NoEDMV) or intubated (EDMV) and received propofol infusion + any amount of narcotic pain medication (Prop + Pain), no sedation (NoSedation), propofol infusion only (OnlyProp), or any amount of benzodiazepine (OnlyBenzo). BP\textsubscript{SV, CV, Depart−Triage*}: Absolute change in blood pressure between departure from the ED and triage, BP\textsubscript{high−low}: Absolute difference of high and low SBP during ED stay, BPEDM: Standard deviation of blood pressure, Depart: Departure from emergency department, ED: Emergency department, GCS: Glasgow Coma Scale, ICU: Intensive care unit, SD: Standard deviation, EDMV: Invasive mechanical ventilation in the ED

**Table 3: Blood pressure variability in patients receiving hyperosmolar therapy**

| No EDMV | Yes hyperosmolar | EDMV | P |
|---------|------------------|-----|---|
|          | Group A (n=116) | Group B (n=13) | Group C (n=27) | Group D (n=106) | A versus B | A versus C | B versus C |
|          | OP, cmH\textsubscript{2}O, mean±SD |               |               |               |               |               |               |
| Indices of BPV, mean (SD) |               |               |               |               |               |               |               |
| BP\textsubscript{SV} | 19 (13) | 32 (16) | 55 (28) | 36 (20) | 0.032 | <0.01 | 0.01 |
| BP\textsubscript{SD} | 31 (18) | 41 (17) | 58 (19) | 47 (21) | 0.161 | <0.01 | 0.036 |
| BP\textsubscript{CV} | 20 (12) | 27 (11) | 37 (13) | 30 (14) | 0.159 | <0.01 | 0.035 |
| BP\textsubscript{Depart−Triage*} | 25 (21) | 32 (39) | 60 (36) | 43 (31) | 0.501 | <0.01 | 0.011 |
| BP\textsubscript{High−Low} | 28 (20) | 45 (29) | 81 (35) | 54 (39) | 0.114 | <0.01 | 0.002 |

*Patients who were intubated in the ED were divided into groups according to the patterns of hyperosmolar therapy: those who did not receive hyperosmolar therapy (No hyperosmolar), patients who received hyperosmolar therapy but without IVF (HyperosmolarOnly) versus those receiving hyperosmolar therapy and intravenous fluid (hyperosmolar + IVF). BP\textsubscript{SV, SD, CV, Depart−Triage*}: Absolute change in blood pressure between departure from the ED and triage. ED: Emergency department, BP\textsubscript{high−low}: Absolute difference of high and low SBP during ED stay, these values are different from values at triage or departure, BP\textsubscript{SD, CV, Depart−Triage*}: Standard deviation of blood pressure.
index (BP_{Depart − Triage}). Administration of hyperosmolar agents without fluid resuscitation correlated positively with all the five BPV indices [Table 4]. One type of sedation management, propofol infusion + any pain medication, was negatively associated with one BPV index, BP_{High−Low} (correlation coefficient [corr. coeff.], −4.2, *P* = 0.019) [Table 4]. In multiple linear regression using HD5GCS as the dependent variable, high BP_{Depart − Triage} (corr. coeff. −0.02, *P* = 0.022), age, H and HS, and ICHS negatively correlated with HD5GCS [Table 4]. Contrarily, ED triage GCS and ICU GCS positively correlated with HD5GCS [Table 4].

**Secondary outcome: Mortality and discharge home**

In our multivariable logistic regressions, two indices of BPV were associated with patients’ mortality [Table 5]. Each unit increase of BP_{sy} (odds ratio [OR], 1.03; 95% CI, 1.004, 1.05, *P* = 0.013) and BP_{Depart − Triage} (OR, 1.02; 95% CI, 1.001, 1.03, *P* = 0.029) was associated with an increased likelihood of in-hospital mortality. Higher H and HS score, older age, and longer ED length of stay were also associated with increased mortality [Table 5]. This model passed all the three goodness-of-fit tests: deviance test (*P* = 0.96), Pearson’s test (*P* = 0.27), and Hosmer–Lemeshow test (*P* = 0.85).

In another multivariable logistic regression with discharge home as the dependent variable, older age (OR 0.96, 95% CI, 0.94, 0.99, *P* = 0.003) and receiving MV in the ED (OR, 0.36; 95% CI, 0.16, 0.82, *P* = 0.011) were associated with a lower likelihood of being discharged home. Higher ED triage GCS (OR 1.16, 95% CI, 1.03, 1.31, *P* = 0.009) [Table 5] was associated with higher likelihood of being discharged home [Table 5]. This model also passed all the three goodness-of-fit tests: deviance test (*P* = 0.86), Pearson’s test (*P* = 0.25), and Hosmer–Lemeshow (*P* = 0.53).

**Discussion**

Our study demonstrated that patients with SICH who require invasive MV in an ED have higher BPV than those who do not. Only two clinical factors, triage SBP and triage GCS, and none of the severity scores significantly correlated with BPV. However, receiving hyperosmolar therapy without IVF (HyperosmolarOnly) positively correlated with all the indices of BPV, and administration of propofol infusion and opioid (Prop + Pain) negatively correlated with one BPV index. The two components of BPV, BP_{sy} and BP_{Depart − Triage}, were associated with increased odds of death.

Approximately 30% of patients with sICH requiring MV in our study did not receive any sedatives. The practice of not administering sedatives was not because patients were comatose nor having poor GCS. The GCS of these subgroups of mechanically ventilated patients were similar at ICU arrival [Table 2]. We assumed that it was because of variation among emergency providers’ practice regarding sedation of mechanically ventilated patients, although we could not ascertain the providers’ hospitals’ protocols regarding sedation. This finding was consistent with the observations...

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### Table 4: Multiple linear regression to assess correlation between patients’ clinical factors and different indices of blood pressure variability*

| Outcomes (adjusted *R*²) | Clinical factors | Correlation coefficient | *P* |
|--------------------------|------------------|-------------------------|-----|
| BP_{sy} (0.31)           | Hyperosmolar therapy - hyperosmolaronly | 10.9 | <0.001 |
|                          | Triage SBP       | 0.112 | <0.001 |
| BP_{ad} (0.46)           | Hyperosmolar therapy - hyperosmolaronly | 3.7  | 0.027  |
|                          | Triage SBP       | 0.3   | <0.001 |
|                          | EDMV             | 7.9   | 0.013  |
| BP_{cv} (0.47)           | Hyperosmolar therapy - hyperosmolaronly | 2.4  | 0.027  |
|                          | Triage SBP       | 0.19  | <0.001 |
|                          | EDMV             | 5.12  | 0.013  |
| BP_{Depart-Triage} (0.50)| Hyperosmolar therapy - hyperosmolaronly | 5.41 | 0.002  |
|                          | Triage SBP       | 0.49  | <0.001 |
|                          | Triage GCS       | -0.97 | 0.008  |
| BP_{High−Low} (0.27)     | Hyperosmolar therapy - hyperosmolaronly | 10.5 | <0.001 |
|                          | Sedation - prop+pain | -4.2 | 0.019  |
|                          | Triage SBP       | 0.21  | <0.001 |
| HD5GCS (0.49)            | BP_{Depart-Triage} | -0.02 | 0.022  |
|                          | Age              | -0.05 | 0.001  |
|                          | Triage GCS       | 0.22  | 0.001  |
|                          | ICU GCS          | 0.24  | 0.001  |
|                          | Hunt-Hess scale  | -1.06 | 0.001  |
|                          | ICH score        | -0.53 | 0.044  |

*Only factors with significant correlation were reported. ED: Emergency department. BP_{cv}: Coefficient variation of blood pressure. BP_{ad}: Absolute difference of blood pressure between ED departure and triage. BP_{High−Low}: Absolute difference between high and low SBP during ED stay. BP_{sy}: Standard deviation of SBP. BP_{cv}: Successive variation of blood pressure. EDMV: Invasive mechanical ventilation in ED, GCS: Glasgow Coma Scale, SBP: Systolic blood pressure.

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*Nguyen, et al.: Sedation, hyperosmolar therapy, and BPV*
Table 5: Multivariable logistic regressions for association of clinical factors and outcomes*

| Clinical factors | Odds ratio | 95% CI   | P     |
|------------------|------------|----------|-------|
| **Outcome: In-hospital mortality** |            |          |       |
| BP<sub>SV</sub>   | 1.03       | 1.004-1.05 | 0.013 |
| BP<sub>Depart-triage</sub> | 1.02       | 1.001-1.03 | 0.029 |
| Age              | 1.03       | 1.004-1.06 | 0.019 |
| EDLOS            | 1.0024     | 1.0004-1.004 | 0.019 |
| Triage GCS       | 0.90       | 0.82-0.98  | 0.027 |
| Hunt and Hess scale | 2.40     | 1.17-4.87 | 0.011 |
| EDMV             | 4.8        | 1.56-14.6 | 0.004 |
| **Outcome: Discharge home** |            |          |       |
| Age              | 0.96       | 0.94-0.99 | 0.003 |
| Triage GCS       | 1.16       | 1.03-1.31 | 0.009 |
| EDMV             | 0.36       | 0.16-0.82 | 0.011 |

*Only variables with significant association were reported.

Published by Bonomo et al., who reported that patients who require MV in the ED frequently receive inadequate sedatives and analgesia. In that study, 33% of the patients received no sedatives, which is attenuated with continuous propofol infusion. Moreover, patients undergoing MV produce significantly higher level of catecholamines when their sedation is paused, resulting in significantly higher blood pressure and heart rate than during the periods of adequate sedation. As a result, besides their disease severity, patients with intracranial hypertension and who required MV but did not receive sedation were associated with higher BPV. Those patients who required MV and received propofol infusion and intravenous opioid were associated with lower BPV and were almost nonsignificantly similar to those who did not require MV.

Further studies are needed to confirm the relationship between the level of sedation and BPV. Our study, which agreed with a previous study, showed that any sedatives would be associated with less BPV than no sedation in mechanically ventilated patients. Infusion of propofol not only provides comfort for patients but also seems to reduce BPV as discussed above. Although propofol infusion and administration of an opioid were only associated with one BPV index in our study, propofol infusion and administration of an opioid should be considered the first-line sedative for patients requiring MV because this regimen has been recommended by the Society of Critical Care Medicine for pain and sedation management. Administration of benzodiazepines, which are associated with delirium, should not be used as the first-line therapy but can be reserved for other indications (e.g., seizure).

In our study, fluid resuscitation was very effective in reducing BPV in patients receiving mannitol or hypertonic saline. Hyperosmolar therapy was not directly associated with mortality, but it correlated most positively with BPV<sub>SV</sub> [Table 3], which was associated with higher likelihood of mortality.

Hyperosmolar agents, while able to reduce ICP due to their osmotic effects, are potent diuretics. Mannitol inhibits fluid reabsorption at the renal proximal tubules and hypertonic saline inhibits the renin–angiotensin II-aldosterone pathway and increases renal sodium excretion and volume significantly. Patients who experience a sudden increase in blood pressure also experience a significant increase of urinary sodium excretion and volume diuresis, a condition called pressure natriuresis. As a result, these hypertensive sICH patients are usually depleted intravascularly. In addition, when mannitol is used to reduce ICP, it should be infused in <30 min. If the infusion lasts longer, mannitol acts more like a diuretic. Administering a potent diuretic without volume resuscitation causes patients’ volume to be further depleted and thus precipitates more BPV. In our study population, up to 87% of patients who received hyperosmolar therapy were given mannitol for >30 min [Appendix 1]. Although further study is needed to confirm our observation regarding hyperosmolar therapy and BPV due to our small number of patients receiving hyperosmolar therapy, emergency physicians should be cautious when administering hyperosmolar agents. However, to maximize the benefits of hyperosmolar therapy in reducing intracranial hypertension, patients’ volume status should be monitored carefully, and volume replacement should be provided to maintain euvolesia in these critically ill patients. Besides the potential association with BPV, hyperosmolar therapy is also associated with potential issues such as brain shrinkage rebound edema if the hyperosmolar therapy is reversed too rapidly. As a result, emergency providers should be cautious with the use of hyperosmolar therapy.

The effects of BPV on outcome are still unclear. Sykora et al. surmised that BPV promotes peri-hematoma edema; however, Manning et al. concluded the opposite that BPV was not associated with hematoma growth. Our findings are consistent with this observation: the ICH score, which takes into account hematoma volume, did not correlate with any BPV index. Moreover, cerebral perfusion pressure is dependent on SBP and lower blood pressure may directly affect blood flow and decrease brain perfusion, thus exacerbating secondary brain injury. Our data suggested that each unit increase of BP<sub>SV</sub> and BP<sub>Depart-triage</sub> in the ED was associated with 3% and 2% increased likelihood of death, respectively. Emergency physicians should attempt to prevent BPV in patients with sICH and elevated ICP because fluctuations in BP, even during a short ED stay, seem to increase their odds of death.

**Limitations**

Our study has several limitations which may limit its interpretation. We used a retrospective method to evaluate...
clinical practice; therefore, we were limited in our ability to ascertain why patients did not receive fluid resuscitation or a sedative. For example, a patient might have been comatose and was not given sedatives. We did not assess other factors that could have affected BPV such as (a) sedative dosages because they were often not documented in ED records; (b) antihypertensive medications because antihypertensive therapy in patients experiencing a hypertensive emergency is a complex topic, beyond the scope of this study; and (c) other post-MV factors such as tidal volume which have been shown to be associated with BPV.\(^{[23]}\) We also had only four blood pressure measurements as more measurements may affect BPV. Finally, we did not present long-term follow-up data (modified Rankin Scale and Glasgow Outcome Scale) in our study because this information was not collected prospectively and is unreliable when gathered retrospectively.\(^{[24]}\)

**Conclusion**

Patients with SICH and elevated ICP had high BPV; higher BPV values in the EDs were associated with higher likelihood of in-hospital mortality. The combination of hyperosmolar therapy with fluid resuscitation and the administration of propofol infusion and an opioid were associated with less BPV. Emergency care providers should consider sedating sICH patients with a propofol infusion and providing fluid resuscitation when administering hyperosmolar therapy in this particular group of high-risk patients.

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**Conflicts of interest**

There are no conflicts of interest.

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**Appendix 1: Patterns of Mannitol administration**

| Mannitol administration |  |
|-------------------------|--|
| Number of patients, N (%) | 38 (15) |
| Amount of mannitol given, g, mean (SD) | 55 (26) |
| Amount of mannitol per Kg, g, mean (SD) | 0.76 (0.3) |
| Total IVF, mean, ml (SD) | 1300 (750) |
| IVF per kg (ml/kg), mean (SD) | 19 (15) |
| Administration rate, N (%) |  |
| < 30 minutes | 5 (13) |
| 30-60 minutes | 12 (32) |
| > 60 minutes | 21 (55) |

*Percentage was calculated from number of patients receiving mannitol, not from total number of patients. G: Grams; IVF: Intravenous fluid, kg: Kilogram, ml: Millimeter, SD: Standard deviation