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ARTICLE

# Clinical characteristics and outcomes of methamphetamine-associated intracerebral hemorrhage

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## Abstract

### Objective

To compare the clinical characteristics and outcomes of primary intracerebral hemorrhage (ICH) with and without methamphetamine exposure.

### Methods

We performed a retrospective analysis of patients diagnosed with spontaneous, nontraumatic ICH over a 3-year period between January 2013 and December 2016. Demographics, clinical measures, and outcomes were compared between ICH patients with positive methamphetamine toxicology tests vs those with negative methamphetamine toxicology tests.

### Results

Methamphetamine-positive ICH patients were younger than methamphetamine-negative ICH patients (52 vs 67 years, $p < 0.001$). Patients with methamphetamine-positive ICH had higher diastolic blood pressure (115 vs 101, $p = 0.003$), higher mean arterial pressure (144 vs 129, $p = 0.01$), longer lengths of hospital (18 vs 8 days, $p < 0.001$) and intensive care unit (ICU) stay (10 vs 5 days, $p < 0.001$), required more days of IV antihypertensive medications (5 vs 3 days, $p = 0.02$), and had more subcortical hemorrhages (63% vs 46%, $p = 0.05$). The methamphetamine-positive group had better premorbid modified Rankin Scale (mRS) scores ($p < 0.001$) and a greater change in functional ability as measured by mRS at the time of hospital discharge ($p = 0.001$). In multivariate analyses, methamphetamine use predicted both hospital length of stay (risk ratio [RR] 1.54, confidence interval [CI] 1.39–1.70, $p < 0.001$) and ICU length of stay (RR 1.36, CI 1.18–1.56, $p < 0.001$), but did not predict poor outcome (mRS 4–6).

### Conclusions

Methamphetamine use is associated with earlier age at onset of ICH, longer hospital stays, and greater change in functional ability, but did not predict outcome.

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**Editorial**
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## Glossary

**AVM** = arteriovenous malformation; **DBP** = diastolic blood pressure; **GCS** = Glasgow Coma Scale; **ICD** = International Classification of Diseases; **ICH** = intracerebral hemorrhage; **ICU** = intensive care unit; **IRB** = institutional review board; **IVH** = intraventricular hemorrhage; **LOS** = length of stay; **MAP** = mean arterial pressure; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **SAH** = subarachnoid hemorrhage; **THC** = tetrahydrocannabinol.

The use of methamphetamine is on the rise globally, with an estimated 35 million users worldwide.[1,2] In addition to an increasing incidence of use, methamphetamine carries a high global burden of disease, with approximately 2.6 million disability-adjusted life years lost due to amphetamine-class dependence.[3] Methamphetamine is a highly addictive drug of abuse and is associated with serious health conditions including neuropsychiatric toxicity, cardiovascular disease, and cerebrovascular disease.[4–6] One potentially devastating risk associated with methamphetamine use is stroke, especially in the young.[6–11] While an uncommon occurrence, stroke in young adults is on the rise.[12] The increasing incidence of stroke in the young is an important public health concern because it leads to disproportionately higher loss of life-years, labor productivity, and lifetime health care costs.[13,14]

Intracerebral hemorrhage (ICH) is the deadliest form of stroke, and most survivors have substantial disability.[15,16] Methamphetamine use has been associated with ischemic and hemorrhagic stroke, including both subarachnoid hemorrhage (SAH) and ICH.[6,8,10,17] Methamphetamine use increases the risk of hemorrhagic stroke by 2–5 times that of the baseline population, with most hemorrhagic strokes attributed to ICH.[6,8] While the epidemiologic risk of hemorrhagic stroke due to methamphetamine is well-established, whether methamphetamine-associated primary ICH manifests with unique clinical characteristics or leads to different functional outcomes is unclear. The objective of this study was to compare the clinical characteristics and outcomes of primary ICH with and without methamphetamine exposure.

## Methods

Patients who presented to the emergency department at University of California Davis Medical Center with spontaneous ICH between January 2013 and December 2016 were identified using ICD codes (ICD-9 431 and ICD-10 161) for nontraumatic ICH. We excluded patients with suspected ICH etiologies of trauma, tumor, encephalitis, ischemic stroke with hemorrhagic transformation, aneurysm, and arteriovenous malformation (AVM), as their clinical course is different from that of primary ICH, making direct comparisons difficult.

Demographic information, social history, admission blood pressure, length of intensive care unit (ICU) stay, and duration of use of IV antihypertensive medications were collected through chart review. Standardized clinical instruments (Glasgow Coma Scale [GCS], NIH Stroke Scale [NIHSS], and ICH score) were calculated on admission and abstracted from the clinical notes. Methamphetamine exposure was ascertained by urine toxicology screening on admission or by explicitly recorded history, positive or negative, of illicit drug use. The ICH characteristics of methamphetamine users and nonusers were measured using the ICH score[18] and its various components: ICH volume, location, and presence of intraventricular hemorrhage (IVH). Structural and vascular neuroimaging were analyzed for hematoma size, expansion within 24 hours, and vascular malformations. A premorbid modified Rankin Scale (mRS) score was calculated for each patient, as was an mRS score at the time of hospital discharge. These measures were abstracted from the admission history and physical, discharge summaries, and assessments from physical therapy and social work notes. Hospital discharge destination (e.g., rehabilitation, home) and whether the patient was transferred from an outside facility were also collected.

Statistical analyses were performed using R v3.4 (R Foundation for Statistical Computing, Vienna, Austria). Continuous numbers were compared with $t$ test when data followed a normal distribution and the Mann-Whitney $U$ test when 2 groups were expected to not follow a normal distribution. Fisher exact test and $\chi^2$ test were used when appropriate for categorical data. A logistic regression analysis of poor outcome (mRS 4–6) was performed. Poisson regression was performed to predict variables contributing to hospital length of stay (LOS) and ICU LOS. Variables were selected by forming an initial model that included all variables associated with univariate significance of $p < 0.2$ and employing a backward selection algorithm to produce parsimonious models.

### Standard protocol approvals, registrations, and patient consents

This study was approved by the University of California Davis institutional review board (IRB). The IRB issued an exemption for patient consent given the retrospective chart review design of the study.

### Data availability

De-identified patient data will be made available by request to qualified investigators for the purpose of replicating the validity of this study.

## Results

We identified 250 patients with primary ICH who met the inclusion criteria, of whom 41 (16.4%) tested positive for

**Table 1** Demographics of methamphetamine-positive vs methamphetamine-negative intracerebral hemorrhage patients

| | Meth+ (n = 41) | Meth− (n = 201) | *p* Value |
|---|---|---|---|
| **Age, y** | 52 ± 10 | 67 ± 15 | <0.001 |
| **Sex** | | | 0.53 |
| **Male** | 25 (61) | 109 (54) | |
| **Female** | 16 (39) | 92 (46) | |
| **Race** | | | |
| **White** | 23 (56) | 94 (47) | 0.16 |
| **Black** | 3 (7) | 21 (10) | |
| **Hispanic** | 11 (27) | 34 (17) | |
| **Asian** | 3 (7) | 39 (19) | |
| **Unknown** | 1 (2) | 13 (6) | |
| **Location** | | | 0.74 |
| **Rural** | 15 (37) | 82 (41) | |
| **Urban** | 26 (63) | 119 (59) | |
| **NIHSS** | 19 ± 13 | 15 ± 13 | 0.06 |
| **GCS** | 10 ± 5 | 11 ± 5 | 0.60 |
| **MAP, mm Hg** | 144 ± 31 | 129 ± 25 | 0.01 |
| **SBP, mm Hg** | 199 ± 42 | 188 ± 36 | 0.10 |
| **DBP, mm Hg** | 115 ± 28 | 101 ± 23 | 0.003 |
| **Use of antihypertensive** | | | |
| **Infusions, d** | 5 ± 4 | 3 ± 3 | 0.02 |
| **Length of stay, d** | 18 ± 27 | 8 ± 8 | <0.001 |
| **ICU length of stay, d** | 10 ± 8 | 5 ± 5 | <0.001 |
| **Outside hospital transfer** | 16 (39) | 101 (50.2) | 0.25 |

Abbreviations: DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; ICU = intensive care unit; MAP = mean arterial pressure; NIHSS = NIH Stroke Scale; SBP = systolic blood pressure.
Vales are mean ± SD or n (%).

**Table 2** Intracerebral hemorrhage (ICH) characteristics of methamphetamine-positive vs methamphetamine-negative ICH patients

| | Meth+ (n = 41) | Meth− (n = 201) | *p* Value |
|---|---|---|---|
| **ICH volume, mL** | 25 ± 31 | 22 ± 30 | 0.29 |
| **ICH score** | 1.73 ± 1.4 | 1.76 ± 1.4 | 0.93 |
| **ICH location** | | | 0.05 |
| **Subcortical** | 26 (63) | 93 (46) | |
| **Lobar** | 10 (24) | 67 (33) | |
| **Brainstem** | 4 (10) | 13 (7) | |
| **Cerebellum** | 1 (2) | 28 (14) | |
| **IVH** | 18 (44) | 80 (40) | 0.75 |

Abbreviation: IVH = intraventricular hemorrhage.
Vales are mean ± SD or n (%).

methamphetamine by urine toxicology screening on presentation. There were 8 patients who presented with ICH and had a positive drug screen for cocaine (6) or heroin (2); these patients were not included in the study because there were too few for meaningful analysis. Of the 41 methamphetamine-positive patients, 4 of them tested positive for a second drug: opioid (3) and cocaine (1). Since tetrahydrocannabinol (THC) is not routinely included in our institution's drug screen, the effect of THC was not assessed. During this same time period, 201 patients were identified with primary ICH and negative drug screens on admission, determined either by urine toxicology screen (130) or history (71).

Baseline demographics of methamphetamine-positive and methamphetamine-negative ICH patients are shown in table 1. Methamphetamine-positive ICH patients were a mean of 15 years younger than methamphetamine-negative ICH patients (52 ± 10 [median 52] vs 67 ± 15 [median 68], $p < 0.001$). There were no differences between the groups in terms of sex ($p = 0.53$), race ($p = 0.16$), whether they lived in a rural or urban location ($p = 0.74$), or if they were transferred from an outside hospital ($p = 0.25$). Methamphetamine-positive patients had higher diastolic blood pressure (DBP) (115 vs 100.8, $p = 0.003$) and mean arterial pressure (MAP) (144 vs 129, $p = 0.01$) at the time of hospital presentation. Systolic blood pressure, while higher in methamphetamine-positive patients (199 vs 188), was not statistically relevant ($p = 0.10$, table 1). Relatedly, methamphetamine-positive patients required a longer duration of IV antihypertensive medications (5 days vs 3 days, $p = 0.02$) and had longer ICU stays (10 days vs 5 days, $p < 0.001$) and a longer hospital LOS compared to methamphetamine-negative ICH patients (18 days vs 8 days, $p < 0.001$). In terms of the hemorrhage characteristics, there was a notable difference in hemorrhage location, with subcortical hemorrhages being seen more commonly in association with methamphetamine ($p = 0.05$), whereas there were no differences in other severity-related measures, including NIHSS, GCS, hematoma volume, or proportion with IVH (table 2).

Methamphetamine-positive patients had less premorbid disability as measured by mRS ($p < 0.001$), but no difference in mRS at discharge or in discharge disposition (table 3). The overall change in functional ability pre-ICH vs post-ICH was notably different in methamphetamine-associated ICH, with methamphetamine-positive patients having a greater change in functional ability post-ICH ($p = 0.001$). Of the patients who died during their hospitalization, the decision to withdraw care was made in 83% of the methamphetamine-positive

**Table 3** Clinical outcomes of methamphetamine-positive vs methamphetamine-negative intracerebral hemorrhage patients

| | Meth+ (n = 41), n (%) | Meth− (n = 201), n (%) | *p* Value |
|---|---|---|---|
| **mRS prehospital** | | | <0.001 |
| **0** | 36 (88) | 127 (63) | |
| **1** | 2 (5) | 28 (14) | |
| **2** | 3 (7) | 11 (5) | |
| **3** | 0 | 25 (12) | |
| **4** | 0 | 8 (4) | |
| **5** | 0 | 3 (2) | |
| **6** | 0 | 0 | |
| **mRS at discharge** | | | 0.55 |
| **0** | 2 (5) | 3 (2) | |
| **1** | 5 (12) | 18 (9) | |
| **2** | 2 (5) | 10 (10) | |
| **3** | 4 (10) | 27 (13) | |
| **4** | 12 (29) | 45 (22) | |
| **5** | 4 (10) | 20 (10) | |
| **6** | 12 (29) | 69 (34) | |
| **Withdraw of care** | 10 (83) | 64 (93) | 0.36 |
| **Disposition** | | | 0.85 |
| **Home** | 10 (24) | 52 (26) | |
| **Rehabilitation** | 8 (20) | 27 (13) | |
| **Nursing home** | 9 (22) | 37 (18) | |
| **Dead** | 12 (29) | 69 (34) | |
| **Transferred to outside hospital** | 2 (5) | 16 (8) | |

Abbreviation: mRS = modified Rankin Scale.

patients vs 93% of the methamphetamine-negative patients ($p$ = 0.36). Other causes of fatality included brain death (methamphetamine-positive patients 2, methamphetamine-negative patients 4) and a single incidence of cardiac death (methamphetamine-negative patient) following hemorrhagic shock secondary to a gastrointestinal bleed.

A sensitivity analysis was performed excluding methamphetamine-negative ICH patients without a confirmed negative drug toxicology screen to assure the validity of our results. The majority of our measured parameters remained the same. Age, MAP, DBP, use of antihypertensive infusions, hospital LOS, ICU LOS, and change in functional ability all remained significant. The previously noted difference in ICH location was no longer significant (table 4).

In multivariate analysis, age, premorbid mRS, NIHSS, hematoma volume, and days on antihypertensive transfusions were independently predictive of poor mRS (table 5). Methamphetamine use showed no association with outcome in univariate analysis ($p$ = 0.98) and was not included in the model. Methamphetamine use was predictive of both hospital LOS ($p$ < 0.001) and ICU LOS ($p$ < 0.001) (table 5).

## Discussion

We found that ICH patients with recent methamphetamine exposure were younger, had a different distribution of hemorrhage location, required more critical care interventions to control blood pressure, had longer hospital stays, and had a greater decrease in functional ability following ICH as compared to patients without recent exposure. Methamphetamine is a powerful psychostimulant that promotes release and blocks the reuptake of dopamine, norepinephrine, and serotonin in the brain.[19] By stimulating the release of catecholamine, methamphetamine exerts an α- and β-adrenergic agonist effect leading to elevated heart rate, blood pressure, and hyperpyrexia, which in turn may cause widespread organ toxicity.[5,20] The exact mechanism of methamphetamine's role in ICH is unknown, but acute spikes in blood pressure caused by methamphetamine ingestion may cause hemorrhage by similar mechanisms as hypertension-associated ICH.[4,6,9] Some authors have proposed a vasculitic process as a possible etiology of methamphetamine-associated ICH based on autopsy findings in case series and case reports; however, this has not been verified.[21–24]

Our study supports the previously reported association between methamphetamine use and ICH in the young, and aids in defining the clinical course of methamphetamine-associated ICH.[8,10] The reason for longer ICU stays is likely multifactorial, stemming from the sympathomimetic effects of methamphetamine intoxication and subsequent withdrawal. One contributing factor in increased ICU stays among methamphetamine-positive patients was a longer need for IV antihypertensive infusions, suggesting a higher degree of resistant hypertension in this population. In addition to having longer ICU stays, methamphetamine users had longer overall hospital stays. Longer ICU care duration likely contributed. In addition, acute withdrawal from methamphetamine is a protracted process, lasting as long as 14 days, with symptoms including anhedonia, hypersomnia, irritability, anxiety, and aggression.[25] Any of these withdrawal symptoms could affect the length of hospital stay.

In spite of having longer lengths of hospital stay, methamphetamine-positive patients had the same median mRS score (4) as methamphetamine-negative patients at the time of hospital discharge. Although outcomes were similar, the degree of change in functional ability measured by premorbid mRS compared to mRS at hospital discharge was greater in the methamphetamine-positive group. This suggests that the

**Table 4** Sensitivity analysis of the confirmed methamphetamine-negative intracerebral hemorrhage (ICH) patients

| | Meth− (n = 130) | *p* Value |
|---|---|---|
| **Age** | 62 ± 15 | <0.001 |
| **Sex** | | |
| **Male** | 75 (58) | |
| **Female** | 55 (42) | 0.84 |
| **Race** | | 0.62 |
| **White** | 58 (45) | |
| **Black** | 16 (12) | |
| **Hispanic** | 27 (21) | |
| **Asian** | 22 (17) | |
| **Unknown** | 7 (5) | |
| **Location** | | |
| **Rural** | 53 (41) | |
| **Urban** | 77 (59) | 0.72 |
| **NIHSS** | 16 ± 13 | 0.13 |
| **GCS** | 11 ± 5 | 0.66 |
| **MAP, mm Hg** | 132 ± 24 | 0.05 |
| **SBP, mm Hg** | 190 ± 35 | 0.27 |
| **DBP, mm Hg** | 102 ± 22 | 0.01 |
| **Use of antihypertensive drips, d** | 3 ± 3 | 0.04 |
| **Length of stay, d** | 8 ± 8 | 0.003 |
| **ICU length of stay, d** | 5 ± 5 | 0.002 |
| **Outside hospital transfer** | 67 (52) | 0.22 |
| **ICH volume, mL** | 20 ± 28 | 0.23 |
| **ICH score** | 1.65 ± 1.3 | 0.71 |
| **Hematoma location** | | 0.14 |
| **Subcortical** | 66 (51) | |
| **Lobar** | 37 (28) | |
| **Brainstem** | 18 (14) | |
| **Cerebellum** | 9 (7) | |
| **IVH** | 56 (43) | 0.99 |
| **mRS prehospital** | | 0.06 |
| **0** | 94 (72) | |
| **1** | 16 (12) | |
| **2** | 3 (2) | |
| **3** | 11 (9) | |
| **4** | 4 (3) | |
| **5** | 2 (2) | |
| **6** | 0 | |
| **mRS at discharge** | | 0.74 |
| **0** | 2 (2) | |
| **1** | 15 (11.5) | |
| **2** | 14 (10) | |
| **3** | 14 (10) | |
| **4** | 30 (23) | |
| **5** | 11 (9) | |
| **6** | 44 (34) | |
| **Discharge disposition** | | 0.99 |
| **Home** | 35 (27) | |
| **Rehabilitation** | 19 (15) | |
| **Nursing home** | 23 (18) | |
| **Dead** | 45 (34) | |
| **Transferred to outside hospital** | 8 (6) | |

Abbreviations: DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; ICU = intensive care unit; IVH = intraventricular hemorrhage; MAP = mean arterial pressure; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; SBP = systolic blood pressure.
Vales are mean ± SD or n (%).

generally younger methamphetamine-exposed patients experience a greater loss of quality-adjusted life years compared to unexposed patients. Interestingly, studies of methamphetamine-associated SAH and hemorrhagic stroke, where SAH and ICH are combined, have found that methamphetamine use is associated with worse outcomes in comparison to non-methamphetamine-related hemorrhagic stroke.[8,10,17,26] The most likely explanation why our study did not replicate these findings is that we chose to focus on primary ICH as a distinct disease entity and excluded ICH secondary to aneurysm or AVM rupture.

Our study had several limitations, including being a single-center study and retrospective in nature. Inclusion in the study required that a diagnosis of ICH be made on presentation to the emergency department; it is possible that some patients died en route or in the emergency department prior to receiving this diagnosis, which may have biased our results. Similarly, we did not have information on patients who were found dead and diagnosed with ICH on autopsy. We chose to exclude ICH secondary to AVM or aneurysm rupture, which is a well-documented association with methamphetamine use.[8–11,26] This exclusion may contribute to why our study did not show comparatively worse outcome for methamphetamine users following ICH. Though a sensitivity analysis was done showing continued significance in several of

**Table 5** Multivariate analysis of outcomes

| Variable | OR | 95% CI | *p* Value |
|---|---|---|---|
| **Poor outcome: mRS 4–6** | | | |
| **Age** | 1.03 | 1.00–1.06 | 0.03 |
| **Premorbid mRS** | 2.13 | 1.50–3.17 | <0.001 |
| **NIHSS** | 1.16 | 1.11–1.22 | <0.001 |
| **Hematoma volume, mL** | 1.04 | 1.01–1.22 | 0.03 |
| **Antihypertensive infusions, d** | 1.27 | 1.09–1.50 | 0.003 |
| **Hospital length of stay** | RR | 95% CI | *p* Value |
| **NIHSS** | 1.01 | 1.00–1.02 | <0.001 |
| **GCS** | 1.04 | 1.02–1.06 | <0.001 |
| **ICH score** | 0.92 | 0.87–0.97 | <0.001 |
| **Antihypertensive infusions, d** | 1.16 | 1.15–1.17 | <0.001 |
| **Race: Black** | 1.42 | 1.22–1.65 | <0.001 |
| **Race: Hispanic** | 0.88 | 0.77–1.03 | 0.11 |
| **Race: White** | 0.92 | 0.81–1.05 | 0.38 |
| **Race: Unknown** | 0.90 | 0.72–1.13 | 0.21 |
| **Methamphetamine use** | 1.54 | 1.39–1.70 | <0.001 |
| **ICU length of stay** | RR | 95% CI | *p* Value |
| **Age** | 0.99 | 0.99–1.00 | 0.07 |
| **MAP** | 0.99 | 0.99–1.00 | <0.001 |
| **Antihypertensive infusions, d** | 1.15 | 1.14–1.17 | <0.001 |
| **Premorbid mRS** | 0.95 | 0.90–1.00 | 0.06 |
| **Lobar ICH** | 1.10 | 0.93–1.30 | 0.25 |
| **Subcortical ICH** | 1.22 | 1.06–1.41 | 0.006 |
| **Methamphetamine use** | 1.36 | 1.18–1.56 | <0.001 |

Abbreviations: CI = confidence interval; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; ICU = intensive care unit; MAP = mean arterial pressure; mRS = Modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio.

our measured parameters, urine toxicology test was not uniformly performed on all patients, so some patients assumed to be unexposed might have been misclassified. This shortcoming would bias our results towards the null hypothesis of no effect, rather than the effects that we found. Socioeconomic variables, such as lack of health insurance and poor social support, were not measured but may also explain difference in hospital LOS. The prevalence of methamphetamine varies regionally, and not all medical centers may see such a high proportion of patients with a history of methamphetamine abuse. In our medical center, approximately 3% of emergency department urine toxicology tests are positive for methamphetamine.[27]

This study found that patients with ICH and recent methamphetamine exposure were younger, required more antihypertensive therapy, had longer stays in the ICU and the hospital, and experienced a greater decrease in functional status between baseline and discharge.


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## Disclosure

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## Appendix Authors

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| **David P. Bissig, MD, PhD** | University of California, Davis | Author | Analysis and interpretation of data |
| **Sandeep S. Walia, MD** | University of California, Davis | Author | Acquisition of data |
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| **Matthew B. Maas, MD** | Northwestern University | Author | Interpreted the data, revised the manuscript for intellectual content |
| **Andrew M. Naidech, MD** | Northwestern University | Author | Interpreted the data, revised the manuscript for intellectual content |
| **Kwan L. Ng, MD, PhD** | University of California, Davis | Author | Designed and conceptualized study, interpreted data, revised the manuscript for intellectual content |

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