Original Research Article
Factors associated with enlargement of hematoma in patients with primary intracranial hemorrhage

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ARTICLE INFO
Article history:
Received 31-10-2019
Accepted 16-11-2019
Available online 14-12-2019

Keywords:
Hematoma enlargement
National Institute Stroke Scale score
Glasgow Coma Scale

ABSTRACT
Introduction: This study is done to evaluate the role of different clinical factors in hematoma enlargement, especially severe hypertension during the early phase of spontaneous ICH.

Materials and Methods: All patients with spontaneous intracranial hematoma who were of > 18 years in age, presented within 24 hour of onset, were enrolled for this study. Repeat CT scan was done within 24 - 48 hours after 1st scan.

Results: 88 patients were enrolled and among them, 11 (12.5%) had >20% enlargement in the size of the hematoma on the second CT. The Mean increase in the size of hematoma was 19.8 ± 11.4 ml (47.3 ± 27.2 %). Progression of symptom after onset and after admission, lower GCS (< 8) at admission, time from onset to CT < 6 hrs, higher NIHSS at admission and midline shift were significantly associated with the enlargement of the hematoma. Mean systolic BP at admission > 200 mm Hg was present in a higher proportion of patients with hematoma enlargement.

Conclusion: The present study showed that patients of spontaneous ICH presenting within 6 hours with higher NIHSS, low GCS (GCS <8), larger hematoma volume and midline shift, had increased risk of hematoma enlargement. SBP >200 mm of Hg at admission may be a potential risk factor.

( Hematoma enlargement, NIHSS = National Institute Health Stroke Scale score, GCS = Glasgow Coma Scale, MAP = mean arterial pressure)

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1. Introduction

Stroke is a major cause of morbidity and mortality, especially among the elderly population. Stroke is 4th leading cause of death in India and 3rd in the USA.¹,² among all kinds of stroke intracranial hemorrhage contributes to 15 -30% case.³ ICH is more common in Asian and black populations than the western population.³ The case fatality of ICH ranges from 17-58%.¹,²,⁴ Till now supportive medical care is the only mainstay of treatment.⁵,⁶

Historically, ICH bleeding was considered to be a monophasic event that stopped quickly as a result of clotting and by surrounding brain tissue. Now in recent years, few studies have shown that an increase in the size of spontaneous hematoma may occur even after few hours of onset, can lead to clinical deterioration, increased morbidity and mortality.⁷–¹⁰ In cases of spontaneous ICH, early deterioration occurs within few hours or a day of onset, usually because of hematoma enlargement while delayed deterioration occurs because of edema associated with hematoma.¹¹ More recently, prospective and retrospective CT-based studies have demonstrated that hematoma growth occurs in up to 35% of patients initially scanned within 3 hours of onset, even in the absence of coagulopathy. In a prospective study, substantial growth (>33%) in the volume of parenchymal hemorrhage occurred in 26% of the 103 study patients between the baseline CT (within 3 hours of onset) and 1-hour CT scans. An additional 12% of patients
had substantial growth between the 1- and 20-hour CT scans.\(^2\)

Still role of different clinical factors in hematoma enlargement is doubtful, especially severe hypertension during the early phase of ICH. While some studies found high BP at admission was associated with hematoma enlargement\(^13\text{-}15\) other studies did not find the significant role of high BP in hematoma growth\(^12\text{-}16\text{-}19\) Identifying risk factors for hematoma enlargement can help us to plan a strategy to prevent hematoma enlargement and reducing morbidity and mortality.

Objectives of this prospective observational study were to find out

1. Proportion of patients of primary ICH who have hematoma enlargement as measured by serial CT scan repeated 24 hours after the 1st CT scan
2. Correlation of trends in BP over first the 24 hours of ICH with hematoma enlargement

Methods

Period and place of study The subjects for this study were enrolled from patients who presented with a spontaneous intracranial hematoma in the emergency department and got admitted to the Department of Neurology, GSVM Medical College, Kanpur, India. This study was performed between September 20 17 to August 20 18 at the GSVM Medical College, Kanpur. Ethical clearance was taken from the institutional ethical committee.

Inclusion criteria All patients with spontaneous intracranial hematoma who were of >18 years in age, presented within 24 hr of onset and had provided informed consent were included in the study.

Exclusion criteria included ICH due to trauma, suspected ruptured aneurysm, Arterio-venous malformation, tumor, anticoagulants or antiplatelet agents. Patients having subarachnoid hemorrhage and isolated intraventricular hemorrhage were excluded. Patients who died before the second CT or 2nd CT could not be done because of homodynamic instability were excluded. Patients who underwent surgical intervention before 2nd CT were also excluded.

A definite time of onset was documented for all pts. The time of onset for patients who woke up with a stroke was taken as they were last seen awake and without symptoms.

Study protocol upon arrival to the emergency department, each patient underwent a baseline CT head and a clinical evaluation. Baseline clinical data were recorded which included age, sex, family history of stroke, previous stroke, history of current smoking classified as current smoker /non- smoker, history of alcohol consumption classified as a cons umer (≥ twice/week irrespective of the quantity or type) or non -consumer and presence of known cardiac disease. Patients were noted to have history of hypertension if they met either or all criteria [1] history of being on antihypertensive medication, regular or irregular,
secondly it would eliminate the chances of a false increase due to different positioning and angles of the CT slice imaging.

1.2. Statistical analysis

Data were entered into Microsoft office excel worksheet and was analyzed by SPSS software. On the basis of serial CT head finding, patients were divided into 2 groups, pt who had hematoma enlargement and those who didn’t. Univariate analysis was done to assess risk factors associated with hematoma enlargement based on the chi-square test for a categorical variable like sex, past history of stroke, etc. Continuous variable was assessed by t-test including Age, BP (Systolic, Diastolic, Mean arterial pressure at admission & at 24 hours, average systolic BP, etc. Some continuous variable was dichotomized and assessed using chi-square test, including Systolic blood pressure at admission, MAP at admission, etc. The P-Value <0.05 was taken as statistically significant. Multivariate logistic regression analysis was done for variables with p<0.05 or which appeared clinically significant.

Results In this study total 88 patients were enrolled. Baseline characteristics are given in Table 1. The mean age was 59.4±12.9 years. 67 % of all the patients were male. A previous history of stroke was present in 12.5 % of patients, of which infarct was more common than the hemorrhage. A family history of stroke was present at 34.5 %. 41.4 % of patients were smoker s and 23 % were alcohol consumers. History of hypertension before ictus was present in 74.7% of patients. H/o diabetes was present in 12.6 % and cardiac disease (ischemic cardiac disease) was present in 5.7 %.

88.5 % of the patients were awake when they had a stroke. 54 % had vomiting and 46 % patients had a headache during the initial 2 hours. 2.3 % had seizures at onset. 58.6 % developed loss of consciousness at onset while 34.9 % had the progression of symptoms after onset.

The average systolic, diastolic and mean arterial pressures at admission were 191.9 ± 32.3, 110 ± 17.8 & 137.3 ± 21.3 mm of Hg respectively. (Table 2) The average systolic, diastolic and mean arterial pressures during the first 24 hours were 163.7 ± 20.9, 96.6 ± 10.7 & 113.1 ± 17.1 mm of Hg respectively. Mean max systolic blood pressure during 1st 24 hours after 1st CT was 199.8 ± 26.6 mm of Hg respectively. Mean GCS at admission, at 12 hours and after 24 hours were 9.32 ± 4.1, 9.28 ± 4.0 & 8.9 ± 4.0. The mean NIHSS score at admission was 22 ± 9.2. LVH in ECG done at the time of admission was present in 52.3% of patients.

At admission, the right- sided hematomat was found in 44.8 % of patients while left in 44.8 % of patients. Lesion was considered to be bilateral in 10.4 % of patients. Anintraventricular extension was found in 49 % of patients and midline shift was observed in 44.3 % of patients. Putamen was the most common site of hematoma (57.9%) while thalamic was the 2nd (26.1%). In 7.9% of patients, brain stem hematoma was present. Mean ICH volume was 34.6 ± 29.1 ml on 1st CT and 37.3 ± 32.3 ml in CT done after 24 hours. 11 out of 88 patients (12.5%) had >20% the enlargement in size of the hematoma on the second CT. The m en arterial pressure at admission, NIHSS at admission, volume on 1st CT, hemorrhage type, GCS at admission, at 12 hours and max SBP during the 1st 24 hours did not show any trend towards significance. The volume of hematoma was dichotomized to (≤ 15 ml). (Table 5)Time from onset to 1st CT was categorized in to 2 categories (≤ 6 hours vs. > 6 hours). BP was dichotomized into systolic BP <200/ ≥ 200 mm of Hg, MAP <130/ ≥ 130 mm of Hg because patients with BP of more than these values were treated with rescue medications. GCS was dichotomized into GCS < 8/ ≥ 8. After analysis statistically significant association of hematoma enlargement was observed with GCS < 8 scale s at admission (RR 4.67; p = 0.007) & time to 1st CT < 6 hours (RR 3.83;p 0.048), while trend towards significance was observed in systolic BP at admission, (RR 1.27;p 0.68). MAP at admission and max SBP during 1st 24 hours did not show any trend towards significance.

The outcome was measured in the form of survival and death. Death as outcome was found to be significantly more common in patients with hematoma enlargement. (72.7% vs 37.7 %, p = 0.028).

Multiple logistic regression analysis was done to look for risk factors associated with hematoma enlargement. Variables that were found to be significant on univariate analyses but occurred as a consequence of hematoma enlargement were removed including progression after onset, progression after admission, headache in 2 hrs. GCS at admission, NIHSS at admission, volume on 1st CT, Systolic BP at admission and mean arterial pressure at 12 hours (which was found significant in bivariate analysis) were tested on linear regression analysis. Statistically significant positive correlation observed with Volume of hematoma on 1st CT (p = 0.012, f3 coefficient 0.509) and negative correlation mean arterial pressure at 12 hours
Table 1: Base line characteristics of patients.

|                              | n (total =88) | Percent |
|------------------------------|---------------|---------|
| Male: female                 | 59:29         | 67:33   |
| Previous stroke              | 11            | 12.5    |
| Previous infarct             | 9             | 10.2    |
| Previous ICH                 | 2             | 2.3     |
| Hypertension                 | 65            | 74.7    |
| On regular treatment         | 12            | 14.1    |
| Irregular treatment          | 53            | 61.5    |
| Diabetes                     | 11            | 12.6    |
| Cardiac disease              | 5             | 5.7     |
| Family history of stroke     | 30            | 34.5    |
| Smoking                      | 36            | 41.3    |
| Alcohol intake               | 20            | 23      |
| Awake at onset               | 77            | 88.5    |
| Progression after onset      | 30            | 34.9    |
| Headache in 2 hours          | 40            | 46.0    |
| Vomiting                     | 47            | 54      |
| Loss of consciousness at onset| 51           | 58.6    |
| Progression after admission  | 14            | 15.9    |
| Level of consciousness at admission | 44  | 50.50     |
| Unarousable Arousable/ awake | 44  | 50.50     |
| LVH in ECG                   | 46            | 52.3    |
| Side of lesion Rt Lt b/I     | 39  | 44.8 10.4 |
| Site of lesion               | 51  | 79.25 5.7 |
| Putamen Thalamic Pontine     | 23            | 26.1    |
| Cerebellum Combined          | 7             | 8.5     |
| Midline shift                | 39            | 44.3    |
| IV extension in 1st CT       | 47            | 49      |

(p=0.010, 13 coefficient -0.639). Systolic BP was not found to be significant.

* The number of patients for these variables is 11, while 88 for other factors.

2. Discussion

The present study was done to obtain information regarding expansion of primary spontaneous intracerebral bleed within 1st 24 hours. We found that 12.5% of patients with primary spontaneous intracerebral hemorrhage showed enlargement of hematoma documented by serial CT head done apart 24 hours. This observation is similar to that found in a retrospective study, Fuji et al 14%14 but was less than prospective study by Brott et al12 38%, which is because in that study all patients underwent 1st CT within 3 hours (mean ictus to 1st CT time 1.3 hours). In a study by Jinjin et al,19 it was 21.3%, which can be explained by early 1st CT time < 6 hr. In our study, only 32.2% of patients underwent 1st CT in 3 hours (which contributes to lesser chances to pick up hematoma enlargement) out of which 7(25 %) patients had hematoma enlargement. Other retrospective studies showed that hematoma enlargement in patients in whom 1st CT was done within 24 hours, ranging from 10.4%- 37%. 7,9,13,15–18

A higher proportion of patients with hematoma enlargement had their 1st CT done within 6 hours of the symptom as compared to patients without hematoma enlargement (81.8% vs. 50 %). This finding was found to be statistically significant. Time from onset to 1ST CT was less in patients with hematoma enlargement as compared to patients without it. Incidence of hematoma enlargement as compared to patients without it. Incidence of hematoma growth in patients with 1St CT done in 3 hours, >3-6 hours and >6-24 hours were 21.4%, 15.8 % & 5 % respectively. This finding was similar to few of earlier studies.12,13,19

In a prospective study, Brott et al,12 in which base line CT was done within 3 hours of ictus and subsequent 2 & 3 scans were done 1 hour and 20 hours after 1st scan. This study showed that 26% of patients had hematoma enlargement between base line and 1st- hour scan while an additional 12% of patients had hematoma growth between 1st and 20 hours scan. So ICH growth was found in 38% of patients who se 1st scan was done within 3 hours of onset. Mean time of ictus to 1st CT in that study was 1.3 hours. There are few retrospective studies showing that hematoma enlargement is common in the first 6 hours of onset.18,19,24

In a retrospective study by Fuzi, 14% hematoma growth was observed in patients in whom 1st CT was done within 24 hours.14 Incidence of hematoma growth in patients in whom 1st CT done within 0 - 1, 1 - 2, 2 - 4, 4 - 6, and >6 hours after onset was 21.4%, 16.9%, 14.0%, 6.8%, and 1.9%, respectively. Similar kind of observation was seen in other study S Kauzi,13 41/204 patients (20%) had hematoma expansion which was greatest among those who underwent the initial CT scan early [36% (27/74) patients. at 3 hours] and progressively declined as the time to initial scan was delayed [7/45 patients (16%) at 3 -6 hours; 5 /33 patients (15%) at 6 -12 hours; 2 /34 patients (6%) 12-24 hours; and
Table 2: Base line findings of patients on admission.

|                                | Mean (SD) | Max | Mm |
|--------------------------------|-----------|-----|----|
| Age (years)                    | 59.4 (12.9)| 96  | 28 |
| SBP at admission (in mm of Hg) | 191.9(32.3)| 290 | 90 |
| DBP at admission (in mm of Hg) | 110 (17.8) | 160 | 70 |
| MAP at admission (in mm of Hg) | 137.3 (21.3)| 193 | 76 |
| Max SBP during 1st 24 hrs (in mm of Hg) | 199.8 (34.2)| 290 | 140 |
| GCS at admission               | 9.32 (4.1)  | 15  | 3  |
| GCS AT 12 Hrs                  | 9.28 (4.0)  | 15  | 3  |
| GCS AT 24 Hrs                  | 8.9 (4.0)   | 15  | 3  |
| NIHSS at admission             | 22 (9.2)    | 38  | 4  |
| Volume of bleed 1st CT (in ml) | 34.6 (29.1) | 110 | 3  |
| Volume of bleed 2nd CT (in ml) | 37.3 (32.3) | 120 | 3  |
| Size increase b/w 1st and 2r CT * (in ml) | 19.8 (11.4)| 48  | 10 |
| % increase b/w 1st and 2nd CT * | 47.3 (27.2) | 110 | 22.3 |
| Time from onset of symptom to 1st CT (in hours) | 7.23 (5.6)  | 24  | 1.2 |
| Time b/w 1st and 2nd CT (in hours) | 29.6 (6.8)  | 46.3 | 23 |

Table 3: Categorical variables: bivariate analysis for risk factors for hematoma enlargement in patients with primary ICH

| Variables                           | Hematoma enlargement grp n(%) | No Hematoma enlargement grp n(%) | Total | Significance p value. |
|-------------------------------------|--------------------------------|---------------------------------|-------|-----------------------|
| Number on patients                  | 11 (9.1)                      | 77 (10.9)                       | 88    | 0.79                  |
| Onset while Sleep                   | 1(9.1)                        | 10(90.9)                        | 11   | 0.79                  |
| Awake                               | 9(11.8)                       | 67(88.2)                        | 77    | 0.70                  |
| Previous stroke Infarct Hemorrhage  | 1(9.1)                        | 1(9.1)                          | 2    | 0.70                  |
| Family h/o stroke                   | 6(54.5)                       | 24(31.6)                        | 30   | 0.13                  |
| Hypertension                        | 7(63.6)                       | 58(76.3)                        | 65   | 0.37                  |
| Diabetes                            | 1(9.1)                        | 10(13.2)                        | 11   | 0.70                  |
| Cardiac disease                     | 1(9.1)                        | 4(5.3)                          | 5    | 0.61                  |
| Smoking                             | 6(54.5)                       | 30(39.5)                        | 36   | 0.34                  |
| Alcohol                             | 2(18.2)                       | 18(23.7)                        | 20   | 0.68                  |
| Progression of symptom after onset  | 7(63.6)                       | 23(30.7)                        | 30   | 0.032                 |
| Headache                            | 8(72.7)                       | 32(42.1)                        | 40   | 0.057                 |
| Vomiting                            | 7(63.6)                       | 40(52.6)                        | 47   | 0.49                  |
| LOC at onset                        | 8(72.7)                       | 43(56.6)                        | 51   | 0.31                  |
| Progression after admission         | 6(54.5)                       | 8(10.4)                         | 14   | <0.001                |
| Level of consciousness at admission | 8(72.7)                       | 3(27.3)                         | 11   | 0.11                  |
| Unarousable Arousable/awake         |                               |                                 |      |                       |
| LVH in ECG                          | 7(63.6)                       | 39(50.6)                        | 46   | 0.42                  |
| Midline shift                       | 9(81.8)                       | 30(39)                          | 39   | 0.007                 |
| IV extension                        | 8(72.7)                       | 33(42.9)                        | 41   | 0.063                 |
### Table 4: Continuous variables: T-test for risk factors for hematoma enlargement in patients with primary ICH

| Variables                          | Hematoma. enlargement grp (n=11) Mean (SD) | No Hematoma enlargement grp (n=77) Mean (SD) | Significance p-value |
|------------------------------------|-------------------------------------------|---------------------------------------------|---------------------|
| Age (years)                        | 58.6(19.3)                                | 59.5(12.2)                                  | 0.84                |
| Systolic BP at admission (mm Hg)   | 197.8(22.3)                               | 191.1(33.6)                                 | 0.52                |
| MAP at admission (mm Hg)           | 140.1(12.9)                               | 136.9(22.3)                                 | 6.65                |
| Diastolic BP at admission (mm Hg)  | 111.3(12.3)                               | 109.87(18.6)                                | 0.81                |
| Mean Systolic BP during 24 hrs (mm Hg) | 161.5(27.4)                | 164(20.1)                                   | 0.71                |
| Mean MAP during 24 hrs (mm Hg)     | 112.3(22.3)                               | 113.2(16.4)                                 | 0.87                |
| Max Systolic BP during 24 hrs (mm Hg) | 200.5(20.8)                       | 199.69(27.5)                                | 0.92                |
| GCS - at admission -at 12 hrs -at 24hrs | 7.82(4.0) 7.73(3.9) 6.45(4.4)  | 9.55(4.1) 9.45(4.2) 9.25(4.4)  | 0.18 0.22 0.033    |
| NIHSS at admission                 | 29.1(8.7)                                 | 21(9.7)                                     | 0.008               |
| Time from onset to emergency (in hours) | 2.8(2.7)                             | 6.9(5.1)                                    | 0.001               |
| Time from onset to 1st CT (in hours) | 4.5 (3.0)                        | 7.6 (5.8)                                   | 0.092               |
| Volume of ICH at admission (in ml) | 47.1(25.8)                                | 32.8(26.1)                                  | 0.063               |
| Admitting blood sugar (mg %)       | 114.4(21.5)                               | 133(59.8)                                   | 0.48                |
| Urea (mg %)                        | 48(22.5)                                  | 42(22.6)                                    | 0.32                |
| Creatinine (rng %)                 | 1.24 (0.46)                               | 1.15(0.66)                                  | 0.20                |
| Na (meq/l)                         | 140 (3.1)                                 | 139 (4.9)                                   | 0.26                |
| K(meq/l)                           | 4.3(0.55)                                 | 4.1(0.56)                                   | 0.10                |

### Table 5: Dichotomized continuous variables: bivariate analysis for risk factors for hematoma enlargement in patients with primary ICH.

| Variables                          | Hematoma enlargement grp n(%) | No Hematoma enlargement grp n(%) | Total n(%) | Significance p-value |
|------------------------------------|-------------------------------|---------------------------------|------------|---------------------|
| Systolic BP at admission           |                               |                                 |            |                     |
| 1) <200 mm of Hg                   | 7(63.6)                       | 44(57.1)                       | 51(58.0)   | 0.68                |
| 2) ≥200 mm of Hg                   | 4(36.4)                       | 37(42.9)                       | 41(42)     |                     |
| MAP at admission                   |                               |                                 |            |                     |
| 1) <130mm of Hg                    | 5(45.5)                       | J 37(48.1)                     | 42(47.7)   | 0.87                |
| 2) ≥130 mm of Hg                   | 6(54.5)                       | L 40(40)                       | 46(52.3)   |                     |
| Max Systolic BP during 24 hrs      |                               |                                 |            |                     |
| 1) <200 mm of Hg                   | 6(54.5)                       | 34(44.2)                       | 40(45.5)   | 0.54                |
| 2) ≥200 mm of Hg                   | 5(45.5)                       | 43(55.8)                       | 48(54.5)   |                     |
| Volume of ICH at admission         |                               |                                 |            |                     |
| 1) ≤15ml 2) >15 ml                 | 1(9.1) 10(90.9)               | 19(24.7) 58(75.3)              | 20(22.7)   | 0.25                |
| Time from onset to CT 1) ≥6 hrs    | 9(81.8) 2(18.2)               | 38(50) 38(50)                  | 47(54)     | 0.048               |
| 2) >6 hrs                          | 8(72.7) 3(27.3)               | 24(31.2) 53(68.8)              | 32(36.4)   | 0.007               |

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Risk factors for hematoma growth This study was done to evaluate clinical demographic factors and their relation to enlargement of the hematoma. Progression of symptom after onset and after admission, lower GCS (< 8) at admission, time from onset to CT < 6 hrs, higher NIHSS at admission and midline shift were significantly associated with enlargement of the hematoma. There were a few factors that showed a trend towards association but not statistically significant. These included headache within 2 hours of hematoma, vomiting, systolic BP at admission (> 200 mm of Hg), presence of intraventricular extension and higher volume of ICH in 1st CT.

Multivariate analysis showed a statistically significant positive correlation with the volume of the hematoma on 1st CT. Systolic BP was not found to be significant. In a prospective study by Brott et al., it was found that hemorrhage growth between the baseline and 1-hour CT scans was significantly associated with clinical deterioration as measured by the change between the baseline and 1-hour GCS and NIH Stroke Scale scores. However, individual patients had significant hemorrhage growth without neurological deterioration. There was a non-significant trend towards poorer functional outcome and higher mortality at 4 to 6 weeks, in patients with hemorrhage growth. They found no significant clinical or CT predictor for hemorrhage growth on serial CTs, although a higher but non-significant growth rate was seen in thalamic hematomas. The only consistently identified risk factor associated with hematoma enlargement in different studies was shorter interval from onset to CT.

Other risk factors that are found to be associated with hematoma growth were alcohol consumption, irregular shape of hematoma, presence of consciousness disturbance, reduced level of fibrinogen, history of cerebral infarction, liver disease and systolic BP >200 mm of Hg in setting of hyperglycemia. The role of high blood pressure in hematoma enlargement has been controversial for a long time. While some studies found high BP at admission was associated with hematoma enlargement, other studies did not find a significant role of high BP in hematoma growth. We found that mean systolic BP at admission was higher in patients with hematoma growth. SBP > 200 mm Hg at admission was present in a higher proportion of patients with hematoma enlargement. But this observation was not found to be significant though it had a trend towards significance, possibly due to the small sample size. Average mean arterial pressures at admission, diastolic BP at admission and maximum SBP during I St 24 hours were not found to be significant.

3. Conclusion

The present study showed that patients of spontaneous ICH presenting within 6 hours with higher NIHSS, low GCS (GCS <8), larger hematoma volume and midline shift, had increased risk of hematoma enlargement. SBP >200 mm of Hg at admission may be a potential risk factor, but it will require a larger study.

4. Acknowledgements

Authors would like to thank Dr. Ashok Verma, Professor, department of radiology, GSVM Medical College, Kanpur for sharing his pearls of wisdom with us during the course of this research. We also thank our colleagues from medicine & SPM dept, GSVM Medical College, Kanpur who provided insight and expertise that greatly assisted the research.

5. Funding

No funding sources

6. Conflict of interest

None declared

7. Ethical approval

The study was approved by the Institutional Ethics Committee.

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Cite this article: Verma A, Agarwal S, Singh M. Factors associated with enlargement of hematoma in patients with primary intracranial hemorrhage. *Indian J Neurosci* 2019;5(4):181-188.