Original Research Article

Admission leukocytosis and its implications on intracerebral haemorrhage

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ABSTRACT

Background: Intracerebral haemorrhage is one amongst the most common subtype of stroke. It is a catastrophic disease with significant rate of mortality and may lead to severe disabilities. Immediate and effective treatment is a prime requisite of ICH, as rapid mortality occurs within first 24 hours. Definitive diagnosis of ICH is difficult as its symptoms are similar to ischemic stroke. Aim of current investigation was to establish a relationship between intracerebral haemorrhage and leukocytosis and to use it as an early tool for detecting haematoma expansion for prognostication and developing newer drugs using a suitable therapeutic target.

Methods: Current investigation was an observational study carried out on 100 patients with intracerebral haemorrhage. Differential counts were studied with respect to influence of particular subtypes on hematoma expansion. Follow up NCCT was done after 48 hours of the event.

Results: Results of present investigation revealed that mean age of the patients was 56 years, 82% were males and all the patients were hypertensive. It was observed that majority of patients with neutrophilic leukocytosis, did not show hematoma expansion and neutrophilic leukocytosis was preferentially present in patients with higher initial bleed volumes. Significant association was observed between monocytosis and haematoma expansion and association between lymphocytosis and volume expansion was observed to be non-significant.

Conclusions: Current study findings can aid in early risk stratification and prognostication of ICH patients and can also provide a tool for identification of new therapeutic targets for controlling haematoma expansion.

Keywords: Intracerebral haemorrhage, Leukocytosis, Haematoma expansion

INTRODUCTION

Bleeding in intracranial vault, including the brain parenchyma or surrounding meningeal spaces can be referred as intracranial hemorrhage, which is considered as one of the bad prognostic variants of stroke and accounts for 10-20% of all cerebrovascular accidents.1,2 There are four types of intracranial haemorrhage including: subdural haemorrhage, extra-dural haemorrhage, sub-arachnoid haemorrhage and intra-cerebral haemorrhage with or without intra-ventricular extension.3 Intracerebral hemorrhage (ICH) is considered as a catastrophic disease with overall worldwide incidence ratio of 24.6 per 100,000 people.4 The mortality rate due to ICH ranges from 35% to 52% and only 20% of survivors are reported to have full functional recovery after 6 months.4,5 ICH is reported to be more frequent in low-to-middle income countries compared to high-income countries. In majority of ICH cases mortality occurs within the first 24 hours, hence early and effective treatment in the emergency department is critically important for ICH patients.6 The most important risk factors for ICH include cerebral amyloid angiopathy (CAA) and hypertension (HTN).7 Other risk factors for ICH include; alcohol intake, cholesterol, genetics, anticoagulation and drug abuse.7,8

ICH is typically a small vessel disease caused by mechanical disruption of glia and neurons and followed by
Aim and objectives

Aim of the current study was to establish a relationship between intra-cerebral haemorrhage and leukocytosis that occurs at the face of it, with due focus on leukocyte subtype and its influence on hematoma expansion. Objective of current study was to use the investigated findings as an early tool for detecting hematoma expansion which further can be used both in prognostication and in developing newer drugs using a suitable therapeutic target.

METHODS

Study design, population, place and duration

Current investigation was an observational study carried out on patients with intra-cerebral haemorrhage admitted at Institute of Internal Medicine, Madras medical college and at Rajiv Gandhi Government general hospital, Chennai, for the period of one year from April 2018 to April 2019.

Sample size

Sample size was computed using the χ² tests, Goodness of fit tests and contingency tables using the parameters listed in (Table 1). 100 patients admitted with diagnosis of intra cerebral haemorrhage were enrolled in the study.

Table 1: Sample size determination parameters.

| Parameters                          | Values    |
|-------------------------------------|-----------|
| Input                               |           |
| Effect size; w                       | 0.3       |
| α error probability                  | 0.05      |
| Power (1-β error probability)        | 0.85      |
| Degree of freedom                    | 1         |
| Output                              |           |
| Non-centrality parameter λ           | 9.00      |
| Critical χ²                          | 3.8414588 |
| Total sample size                    | 100       |
| Actual power                         | 0.850838  |

Inclusion criteria

Inclusion criterion for the patients to be enrolled in current study were; diagnosis of spontaneous intracerebral brain hemorrhage (ICH) on non-contrast CT scan within 48 hours from onset, available follow up noncontrast head CT (NCCT) and complete blood count performed within 48 hours of admission.

Exclusion criteria

Patients with history or evidence traumatic intracranial, vascular or neoplastic cause of bleeds, venous haemorrhages, haemorrhagic transformation of ischemic strokes and primary intraventricular hemorrhage (IVH)
due to difficulty in assessing expansion were excluded from the study.

**Procedure**

After obtaining clearance and approval from the institutional ethics committee, 100 patients were selected as per inclusion and exclusion criteria. Leukocytosis as defined by WBC count was measured within 24-48 hours of the ICH event. Differential counts were studied with respect to influence of particular subtypes on hematoma expansion. Monocytosis was defined by monocytes >8% or absolute monocyte count of 0.8×10⁹ per mm³ and neutrophilic leucocytosis was defined by neutrophils more than 70%. Follow up NCCT was done after 48 hours of the event. Hematoma expansion was defined by absolute increase of 6 ml or 30% of initial ICH volume.

**RESULTS**

In current study 100 patients admitted with ICH were studied. Investigation results revealed that mean age of the patients was 56 years, 82% were males and all the patients who participated in the study were hypertensive (Table 2).

**Table 2: Descriptive study results for all patients of volume expansion.**

| Parameters                      | Mean   | Median  | SD    | Minimum | Maximum | Range | Interquartile range |
|---------------------------------|--------|---------|-------|---------|---------|-------|---------------------|
| Age (years)                     | 56.4700| 55.0000 | 9.82828| 28.00   | 74.00   | 46.00 | 15.00               |
| Total count (10^3/µl)           | 12.7365| 12.3500 | 5.02598| 5.00    | 24.50   | 19.50 | 6.80                |
| Neutrophil count (%)            | 75.5670| 78.5000 | 11.89458| 51.20  | 90.00   | 38.80 | 20.75               |
| Monocyte (%)                    | 5.9450 | 5.6500  | 2.42180| 0.70    | 12.00   | 11.30 | 2.00                |
| Platelet count (10^5/µl)        | 2.2411 | 2.2000  | 0.47137| 1.00    | 3.50    | 2.50  | 0.60                |
| INR                             | 1.0900 | 1.1000  | 0.08087| 1.00    | 1.30    | 0.30  | 0.11                |
| First CT (ml)                   | 11.7730| 11.0000 | 7.76404| 0.60    | 29.00   | 28.40 | 13.70               |
| Repeat CT (ml)                  | 13.6230| 12.7500 | 10.22082| 0.80   | 38.00   | 37.20 | 19.38               |
| Volume exp (ml)                 | 2.0580 | 0.0000  | 5.63530| -8.00   | 16.00   | 24.00 | 4.80                |

**Table 3: Descriptive study results for two groups of volume expansion.**

| Parameters                      | Volume expansion groups | Mean   | Median  | SD    | Minimum | Maximum | Range | Interquartile range |
|---------------------------------|-------------------------|--------|---------|-------|---------|---------|-------|---------------------|
| Age (years)                     | <6                      | 55.69  | 55.00   | 9.66  | 28.00   | 73.00   | 45.00 | 13.25               |
| Total count (10^3/µl)           | >6                      | 59.23  | 62.50   | 10.14 | 45.00   | 74.00   | 29.00 | 20.50               |
| Neutrophils (%)                 | <6                      | 12.71  | 12.35   | 5.52  | 5.00    | 24.50   | 19.50 | 7.83                |
| Monocyte (%)                    | >6                      | 12.84  | 12.35   | 2.75  | 8.75    | 17.20   | 8.45  | 5.25                |
| Platelet count (10^5/µl)        | <6                      | 76.15  | 82.00   | 12.84 | 51.20   | 90.00   | 38.80 | 21.00               |
| INR                             | >6                      | 73.50  | 74.50   | 7.56  | 62.00   | 85.00   | 38.00 | 23.00               |
| First CT (ml)                   | <6                      | 4.98   | 5.00    | 1.48  | 0.70    | 7.70    | 7.00  | 2.00                |
| Repeat CT (ml)                  | >6                      | 9.36   | 10.00   | 1.99  | 5.00    | 12.00   | 7.00  | 1.25                |
| Volume exp (ml)                 | <6                      | 2.24   | 2.20    | 0.50  | 1.00    | 3.50    | 2.50  | 0.60                |
|                                  | >6                      | 2.25   | 2.20    | 0.35  | 1.70    | 3.00    | 1.30  | 0.48                |

Out of 100 patients 36 were diabetics, 9 patients exhibited chronic kidney disease, 5 patients were on maintenance dialysis, 3 patients had previous H/O ischemic stroke and 6 patients were on aspirin prior to the episode. The mean and median leukocyte count of the population was observed to be 12.7×10³ per µl and 12.3×10³ per µl respectively (Table 3).
Table 4: Results of distribution study of patients based on different parameters.

| Parameter                  | Frequency | Percent |
|----------------------------|-----------|---------|
| **Age group (years)**      |           |         |
| 20-40                      | 3         | 3.0     |
| 41-50                      | 25        | 25.0    |
| 51-60                      | 36        | 36.0    |
| 61-70                      | 29        | 29.0    |
| 71-80                      | 7         | 7.0     |
| **Hypertension**           |           |         |
| Yes                        | 88        | 88.0    |
| Yes /CKD                   | 9         | 9.0     |
| Yes old CVA                | 3         | 3.0     |
| **Diabetes**               |           |         |
| No                         | 64        | 64.0    |
| Yes                        | 36        | 36.0    |
| **Gender**                 |           |         |
| Female                     | 18        | 18.0    |
| Male                       | 82        | 82.0    |
| **Volume expansion group** |           |         |
| Insignificant expansion    | 6         | 6.0     |
| No expansion               | 72        | 72.0    |
| Significant expansion      | 22        | 22.0    |
| **PMN group (neutrophils)**|           |         |
| <70%                       | 29        | 29.0    |
| >70%                       | 71        | 71.0    |
| **Monocytes group**        |           |         |
| >8%                        | 19        | 19.0    |
| <8%                        | 81        | 81.0    |
| **Drug use**               |           |         |
| Aspirin                    | 6         | 6.0     |
| No                         | 94        | 94.0    |
| **First CT group (ml)**    |           |         |
| <10                        | 42        | 42.0    |
| >10                        | 58        | 58.0    |
| **Repeat CT group (ml)**   |           |         |
| <10                        | 42        | 42.0    |
| >10                        | 58        | 58.0    |
| **Volume expansion group (ml)** |     |         |
| <6                         | 78        | 78.0    |
| >6                         | 22        | 22.0    |
| **Total leukocyte count (10^3/µl)** | | |
| <5000                      | 1         | 1.0     |
| 5001-10000                 | 36        | 36.0    |
| 15001-20000                | 34        | 34.0    |
| Above 20000                | 29        | 29.0    |

Table 5: Distribution of volume expansion groups based on different parameters.

| Parameters     | Volume expansion groups | Total | Pearson Chi-Square coefficient | P value |
|----------------|-------------------------|-------|--------------------------------|---------|
|                | <6          | >6          | N  | %  | N  | %  | N  | %  |                |
| **Hypertension** |           |              |    |    |    |    |    |    |
| Yes            | 72         | 16           | 88 | 88 | 12.058 | 0.002 |
| Yes /CKD       | 6          | 3            | 9  | 9  |                |
| Yes old CVA    | 0          | 3            | 3  | 3  |                |

Continued.
Parameters | Volume expansion groups | Total | Pearson Chi-Square coefficient | P value
--- | --- | --- | --- | ---
Diabetes | | | | 0.295 | 0.587
No | N | % | N | % | N | % | 0.295 | 0.587
Yes | 27 | 34.6 | 9 | 40.9 | 36 | 36 | 6.191 | 0.013
Gender | | | | 0.013
Female | 18 | 23.1 | 0 | 0 | 18 | 18 | 6.191 | 0.013
Male | 60 | 76.9 | 22 | 100 | 82 | 82 | 6.014 | 0.014
PMN group (neutrophils) | | | | 0.014
<70% | 18 | 62.07 | 11 | 37.93 | 29 | 100 | 6.014 | 0.014
>70% | 60 | 84.51 | 11 | 15.49 | 71 | 100 | 83.165 | <0.0001
Monocytes group | | | | <0.0001
>8% | 0 | 0 | 19 | 8.6 | 19 | 19 | 2.916 | 0.088
<8% | 78 | 100 | 3 | 13.6 | 81 | 81 | 3.815 | 0.282
Drug use | | | | 0.282
Aspirin | 3 | 3.8 | 3 | 13.6 | 6 | 6 | 3.815 | 0.282
No | 75 | 96.2 | 19 | 86.4 | 94 | 94 | 94 | 2.916 | 0.088
First CT group (ml) | | | | 0.088
<10 | 38 | 48.7 | 4 | 18.2 | 42 | 42 | 42 | 6.569 | 0.010
>10 | 40 | 51.3 | 18 | 81.8 | 58 | 58 | 58 | 20.424 | <0.001
Repeat CT group (ml) | | | | <0.001
<10 | 42 | 53.8 | 0 | 0 | 42 | 42 | 42 | 6.569 | 0.010
>10 | 36 | 46.2 | 22 | 100 | 58 | 58 | 58 | 20.424 | <0.001
Total leukocyte count (10^3/µl) | | | | 0.001
<5000 | 1 | 1.3 | 0 | 0 | 1 | 1 | 1 | 3.815 | 0.282
5001-10000 | 31 | 39.7 | 5 | 22.7 | 36 | 36 | 36 | 3.815 | 0.282
15001-20000 | 23 | 29.5 | 11 | 50 | 34 | 34 | 34 | 3.815 | 0.282
Above 20000 | 23 | 29.5 | 6 | 27.3 | 29 | 29 | 29 | 3.815 | 0.282

Total 68 patients exhibited leukocytosis on admission and 71 patients had neutrophilic leukocytosis which by definition in current study is polymorphonuclear leukocytes >70%. 19 patients exhibited monocytosis defined by monocytes value>8%.

Figure 1: Distribution of volume expansion groups based on age (Pearson chi-square=10.854, p=0.028).

Figure 2: Comparison of first CT of neutrophilic leukocytosis group (Pearson chi-square=12.192, p<0.001).
DISCUSSION

The role of leukocytes in coagulation is an ongoing field of research. The contrasting effect of neutrophils and monocytes is the significant outcome of current study. As per current study findings higher neutrophil count is associated with reduced risk of hematoma expansion as opposed to monocyte counts. Neuroinflammation and leukocyte infiltration of hematoma have been main targets of neuroprotective strategies in ICH. Chronic inflammation is a proven detriment of secondary change in ICH. Presence of neutrophilic leukocytosis in patients with higher initial bleed volumes confirms that neutrophilic leukocytosis is almost always reactive. Acute inflammation though complex and through contrasting effects of neutrophils and monocytes on hematoma expansion can present itself as therapeutic target which can affect the modifiable determinant of ICH which is hematoma expansion. The current study findings are in concordance with study of Morotti et al.25

Limitations

Limitations of current study were; limited sample size due to mortality and follow up hurdles, the results in current study are based on temporal observation of differential count values and hematoma expansion and more scientific approach is essential to study actual sequence of events before it can be used as a therapeutic target.

CONCLUSION

Current study highlights the role of acute inflammation on hematoma expansion in intra-cerebral haemorrhage. Patients with higher monocyte exhibited higher risk of hematoma expansion while patients with higher neutrophil counts were protective against hematoma expansion. Current study findings can aid in early risk stratification and prognostication of ICH patients and can also provide a tool for identification of new therapeutic targets for controlling hematoma expansion.

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