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Original Research Article

Admission leukocytosis and its implications on intra cerebral 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 intra-cerebral 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 intra-cerebral 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

mechanical deformation causing oligaemia, neuro-transmitter release, mitochondrial dysfunction, and membrane depolarization.[9] Chronic hypertension may lead to hypertensive vasculopathy causing microscopic degenerative changes in the walls of small-to-medium penetrating vessels, known as lipohyalinosis and is one of the major cause of ICH.[10] CAA which is characterized by the deposition of amyloid-beta peptide (Aβ) in the walls of small leptomeningeal and cortical vessels may lead to ICH as it results in degenerative changes in the vessel wall, which are characterized by the loss of smooth muscle cells, wall thickening, luminal narrowing, microaneurysm formation and microhemorrhages.[11-13] In both the cases following initial vessel rupture, the hematoma causes direct mechanical injury to the brain parenchyma leading to perihematomal edema within the first 3 hours. Blood and plasma components mediate secondary injury through inflammatory response, activation of the coagulation cascade, and iron depositions from hemoglobin degradation leading to continuous expansion of hematoma.[14] Acute ICH is difficult to distinguish from ischemic stroke due to similar symptoms like; headache, nausea, seizures and focal or generalized neurologic symptoms. Although investigational findings such as coma, vomiting, neck stiffness, seizures and increased diastolic blood pressure are indicatives of ICH, but only neuroimaging can provide a definitive diagnosis.[14,15] As ICH volume and location are determined upon presentation, hematoma expansion is considered as a potential and only modifiable predictor of ICH.[16] Hematoma expansion is defined as absolute increase of initial bleed volume by 6 ml or 30% due to ongoing bleeding from secondary sites adjacent to the initial site.[17] Therapies preventing expansion are considered to decrease the final volume, thus several clinical trials are focused on limiting expansion, using approaches such as recombinant factor VIIa (rFVIIa) or aggressive blood pressure reduction.[18,19]

Acute leukocytosis is also considered as a potential indicator of intracerebral haemorrhage.[21] Leukocytosis is a common lab finding commonly observed in conditions like infections and inflammation.[22] Bone marrow in response to infection and inflammation increases the number of leukocytes especially polymorphonuclear neutrophils (PMNs).[23] Although the relationship between acute inflammation and pathology of intra-cerebral haemorrhage is complex, leukocytes via its interaction with platelets, endothelium may shift the balance in favour of coagulation and may therefore play a role in arrest of bleeding after an intracerebral haemorrhage.[24] Counts higher than 1 lakh/mm3 is itself a medical emergency due high risk of CNS haemorrhage.[22,24]

Thus the current investigation was carried out to study the relation between hematoma volume expansion and intra-cerebral haemorrhage and to test the hypothesis; that whether acute leucocytosis limits extent of the bleeding following intra-cerebral haemorrhage or not.

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 χ^2 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 χ^2	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 0.8x109 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 (103/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 (105/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	.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
	>6	59.23	62.50	10.14	45.00	74.00	29.00	20.50
Total count (10^3/µl)	<6	12.71	12.35	5.52	5.00	24.50	19.50	7.83
	>6	12.84	12.35	2.75	8.75	17.20	8.45	5.25
Neutrophils (%)	<6	76.15	82.00	12.84	51.20	90.00	38.80	21.00
	>6	73.50	74.50	7.56	62.00	85.00	23.00	15.18
Monocyte (%)	<6	4.98	5.00	1.48	0.70	7.70	7.00	2.00
	>6	9.36	10.00	1.99	5.00	12.00	7.00	1.25
Platelet count (10^5/µl)	<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
INR	<6	1.10	1.10	0.08	1.00	1.30	0.30	0.20
	>6	1.06	1.05	0.07	1.00	1.20	0.20	0.10
First CT (ml)	<6	10.96	10.00	7.62	1.70	29.00	27.30	11.83
	>6	14.64	15.00	7.76	0.60	29.00	28.40	7.25
Repeat CT (ml)	<6	10.14	8.75	8.03	0.80	30.00	29.20	11.93
	>6	25.95	26.00	7.21	11.00	38.00	27.00	6.00
Volume exp (ml)	<6	-0.69	-0.25	2.58	-8.00	4.00	12.00	1.23
	>6	11.27	10.50	3.26	6.00	16.00	10.00	5.88

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	92.3	16	72.7	88	88		
Yes /CKD	6	7.7	3	13.6	9	9	12.058	0.002
Yes old CVA	0	0	3	13.6	3	3		

Continued.

Parameters	Volume expansion groups				Total		Pearson Chi-Square coefficient	P value
	<6		>6					
	N	%	N	%	N	%		
Diabetes								
No	51	65.4	13	59.1	64	64	0.295	0.587
Yes	27	34.6	9	40.9	36	36		
Gender								
Female	18	23.1	0	0	18	18	6.191	0.013
Male	60	76.9	22	100	82	82		
PMN group (neutrophils)								
<70%	18	62.07	11	37.93	29	100	6.014	0.014
>70%	60	84.51	11	15.49	71	100		
Monocytes group								
>8%	0	0	19	8.6	19	19	83.165	<0.0001
<8%	78	100	3	13.6	81	81		
Drug use								
Aspirin	3	3.8	3	13.6	6	6	2.916	0.088
No	75	96.2	19	86.4	94	94		
First CT group (ml)								
<10	38	48.7	4	18.2	42	42	6.569	0.010
>10	40	51.3	18	81.8	58	58		
Repeat CT group (ml)								
<10	42	53.8	0	0	42	42	20.424	<0.001
>10	36	46.2	22	100	58	58		
Total leukocyte count (10^3/µl)								
<5000	1	1.3	0	0	1	1	3.815	0.282
5001-10000	31	39.7	5	22.7	36	36		
15001-20000	23	29.5	11	50	34	34		
Above 20000	23	29.5	6	27.3	29	29		

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 monocytes defined by monocytes value>8%.

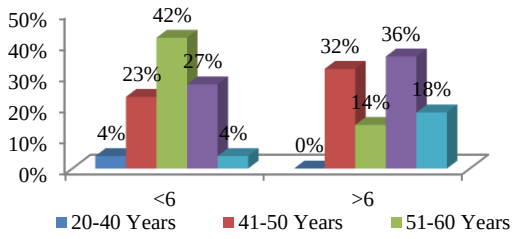

Figure 1: Distribution of volume expansion groups based on age (Pearson chi-square=10.854, p=0.028).

Total 22 patients experienced significant hematoma expansion defined by absolute increase in hematoma volume by 6 ml (30%) of initial bleed volume (Table 4). After adjustment for established predictors of hematoma expansion, like hypertension it was found that higher WBC count on admission was associated with reduced risk of hematoma expansion. On further analysis, it was observed that neutrophilic leukocytosis (pmn>70%) was significantly less associated with hematoma expansion and was independent of other risk factors (p=0.014). Out of 71 patients with neutrophilic leukocytosis, 60 patients did not show hematoma expansion as opposed to 11 out of 29 patients who did not have neutrophilic leukocytosis. It was also statistically proven (p<0.001) that neutrophilic leukocytosis was preferentially present in patients with higher initial bleed volumes (>10 ml). Significant association was observed between monocytosis (>8%) and hematoma expansion, as 19 patients who had monocytosis had significant volume expansion (p<0.0001) (Table 5). No significant association was established between lymphocytes and volume expansion.

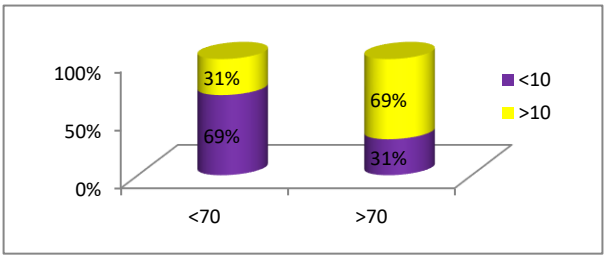

Figure 2: Comparison of first CT of neutrophilic leukocytosis group (Pearson chi-square=12.192, p<0.001).

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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