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ORIGINAL ARTICLE

Hematoma Expansion Differences in Lobar and Deep Primary Intracerebral Hemorrhage

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Abstract

Background: Hematoma expansion (HE) after intracerebral hemorrhage (ICH) is associated with worse outcome. Lobar ICHs are known to have better outcomes compared to deep ICH; however, it is unclear whether there are HE differences between these locations. We sought to investigate the hypothesis that lobar ICH has less HE compared to deep ICH.

Methods: Primary ICH patients admitted between 2009 and 2016 were included in a prospective single-center ICH cohort study. Patients with preceding anticoagulant use, coagulopathy on admission labs, or presenting after 24 h from symptom onset were excluded. Lobar and deep ICH patients with baseline and follow-up computed tomography (CT) (within 24 h of admission CT) were evaluated. HE was defined primarily as relative growth > 33% given expected baseline hematoma volume differences between locations. Other commonly utilized definitions of HE: > 6 mL, and > 33% or > 6 mL, were additionally assessed. Multivariable logistic regression was used to assess the association of ICH location with HE while adjusting for previously identified covariates of HE.

Results: There were 59 lobar and 143 deep ICH patients analyzed. Lobar ICH patients had significantly larger baseline hematoma volumes, lower admission systolic blood pressure, and longer times to admission CT compared to deep ICH. Multivariable logistic regression revealed an association of lobar ICH with lower odds of HE (> 33%) [odds ratio (OR) 0.32; 95% confidence interval (CI) 0.11–0.93; $p = 0.04$] compared to deep ICH after adjusting for baseline ICH volume, blood pressure, and time to CT. Secondary analysis did not identify an association of lobar ICH with HE defined as > 6 mL (adjusted OR 1.44; 95% CI 0.59–3.50; $p = 0.41$) or > 33% or > 6 mL (adjusted OR 0.71; 95% CI 0.29–1.70; $p = 0.44$).

Conclusion: We identified less HE in lobar compared to deep ICH. The use of absolute growth thresholds in defining HE may be limited when assessing groups with largely different baseline hematoma sizes. Further study is required to replicate our findings and investigate mechanisms for HE differences between lobar and deep ICH locations.

Keywords: Intracerebral hemorrhage, Hematoma expansion, Lobar, Deep

Introduction

Hematoma expansion (HE) is well known to be associated with worse outcomes after intracerebral hemorrhage (ICH) [1]. Subsequently, rapid coagulopathy reversal is viewed as critical in efforts to prevent HE and improve outcomes [2]. Current paradigms utilize functional coagulation tests and anticoagulant medication history to identify and treat coagulopathy. However, it is increasingly recognized that ICH is a heterogeneous disease and it is unclear how to identify HE risk in ICH patients without overt medication

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or laboratory coagulopathy which risks both over- and under-treating these patients.

Recent studies have shown outcome heterogeneity between lobar and deep ICH [3–5], specifically better outcomes in lobar ICH, not thought to be driven by functional coagulation or HE differences. When using traditional definitions of HE, presence of relative or absolute HE: > 33% or > 6 mL [6], most studies have not consistently found differences between lobar and deep ICH [7, 8]. Subsequently, current ICH trials and ICH treatment paradigms assume similar risks of HE among both these locations. However, the inclusion of absolute HE thresholds (> 6 mL) in the majority of these studies may limit HE comparisons between groups with different baseline hematoma volumes, specifically lobar ICH where volumes are significantly larger compared to deep ICH [9]. Additionally, these studies included patients on anticoagulant medications, making it difficult to assess coagulopathy differences between ICH locations alone.

We investigated whether there would be differences in HE, using the most common relative HE threshold: > 33%, in primary lobar ICH compared to deep ICH in the absence of anticoagulant medication use or admission laboratory coagulopathy. Exploratory analysis was performed on the association of ICH location and HE on outcomes.

Methods

Consecutive patients admitted and enrolled from 2009 to 2016 in a single-center prospective ICH cohort study: ICH Outcomes Project (ICHOP), were evaluated. ICH was diagnosed via admission non-contrast head computed tomography (CT). CT angiogram and/or digital subtracted angiography was performed when vascular lesions were suspected. Baseline characteristics, neuroimaging, laboratory results, interventions, and discharge/90-day outcomes were collected. Patients under 18 years were excluded. Patients were managed according to American Heart Association guidelines [2] with ICHOP treatment protocols described previously [10]. Patients, or families when appropriate, provided consent. The study was approved by the Columbia University Irving Medical Center Institutional Review Board.

Patient Selection

Primary lobar or deep ICH presenting within 24 h of symptom onset and having both admission and follow-up CT (obtained within 24 h from admission CT) were included for analysis. For patients with unclear time of onset, last time seen normal was used. Lobar and deep ICH were defined as cortical/subcortical or thalamus/basal ganglia locations, respectively. ICH involving both lobar and deep structures or having brainstem/infratentorial locations were excluded. In order to look primarily at location effect on coagulopathy/HE, patients with coagulopathy on admission laboratory testing secondary to anticoagulation medication or systemic disease were identified by SMASH-U criteria [3] and excluded. Patients with known or suspected secondary ICH (malignancy, vascular malformation, aneurysm, ischemic stroke with hemorrhagic transformation), trauma, primary intraventricular hemorrhage (primary intraventricular hemorrhage [IVH]: IVH only without concurrent parenchymal hematoma), and patients receiving neurosurgery prior to follow-up CT were also excluded (eFigure 1). ICH locations were adjudicated by prospective weekly consensus meetings of study physicians.

Neuroimaging/Functional Outcomes

Semi-automatic hematoma size measurements (MIPAV software, NIH, MD) were obtained for all CTs using previously described methods [10, 11] (eFigure 2). Symptom onset to admission CT times was recorded. Per clinical protocol, patients received admission and a stability CT within 24 h. The primary outcome was HE defined as > 33% relative HE. Previously utilized HE definitions were additionally evaluated: > 6 mL alone in addition to traditionally utilized > 33% or > 6 mL HE definitions [6]. Modified Rankin scale (poor 4–6) at discharge and 90 days was obtained via standardized telephone interviews by trained research staff [10].

Analyses

Analyses were performed using SPSS (ver23). Intergroup differences were determined by applying Mann–Whitney *U* or *t* test for continuous variables and χ^2 or Fisher's exact test for categorical variables. We used logistic regression to assess associations of ICH location with HE after adjusting for established covariates of HE: time from symptom onset to admission CT (dichotomized at 6 h according to previous studies [7]), baseline hematoma volume along with systolic blood pressure (SBP) given expected differences between groups. Due to expected differences in baseline hematoma volumes, this was primarily evaluated as a categorical variable dichotomized at the cohort median. Baseline hematoma volumes were additionally entered into the model as a categorical variable defined as: < 30 mL, 30–60 mL, and > 60 mL as per prior studies [7]. Additional differences between lobar and deep ICH thought to potential impact HE were adjusted for in separate sensitivity analysis. Separate logistic regression models were used to assess the association of HE and ICH location with outcome after adjusting for significant intergroup differences thought to impact

outcome and ICH score [12]. Statistical significance was judged at p value < 0.05.

Results

Of 202 ICH patients meeting inclusion criteria, 29% were lobar ($n = 59$) and 71% deep ($n = 143$). Intergroup differences are shown in Table 1. Lobar ICH patients were significantly older, predominantly female, had larger hematoma volumes, lower SBP, less history of hypertension, less IVH, and longer times from symptom onset to admission CT compared to deep ICH. No differences in medical (hyperosmolar or prothrombotic) treatments, do-not-resuscitate, or withdrawal-of-care were seen (data not shown). There was 7% ($n = 14$) loss to 90-day follow-up. No differences in HE or ICH location were seen in patients that were lost to 90-day follow-up.

Multivariable logistic regression revealed that lobar ICH was associated with less odds of relative HE (> 33%) compared to deep ICH (adjusted odds ratio [OR] 0.32; 95% confidence interval [CI] 0.11–0.93; $p = 0.04$). Models adjusting for age, sex, hematoma size as a categorical variable (< 30 mL, 30–60 mL, and > 60 mL) and IVH did not change the result. When using a > 6 mL absolute HE definition, lobar ICH more commonly encountered HE compared to deep (20% vs. 13%), but this was non-significant in adjusted multivariable analysis (adjusted OR

Table 1 Lobar versus deep ICH baseline characteristics

	All ICH $N = 202$	Lobar ICH $N = 59$	Deep ICH $N = 143$	*P* value
Age mean (SD)	66 (15)	73 (14)	62 (15)	< 0.001
Female *N* (%)	94 (47)	41 (70)	53 (37)	< 0.001
Race *N* (%)				
White	44 (22)	16 (27)	28 (20)	0.30
Black	65 (32)	19 (32)	46 (32)	
Hispanic	81 (40)	24 (41)	57 (40)	
Other	12 (6)	0 (0)	12 (8)	
Medical history *N* (%)				
Dyslipidemia	52 (26)	18 (31)	34 (24)	0.38
Coronary artery disease	25 (12)	8 (14)	17 (12)	0.82
Atrial fibrillation	10 (5)	3 (5)	7 (5)	1.00
Hypertension	164 (81)	40 (68)	124 (87)	0.003
Diabetes	55 (27)	13 (22)	42 (29)	0.30
Medication history *N* (%)				
Antiplatelet	82 (41)	26 (44)	56 (39)	0.53
Statin	39 (19)	12 (20)	27 (19)	0.85
Clinical/radiographic				
Admit SBP mean (SD)	191 (37)	178 (39)	197 (34)	0.001
Admit DBP mean (SD)	103 (26)	91 (24)	108 (26)	< 0.0001
GCS median (IQR)	11 (7–15)	13 (9–14)	10 (6–15)	0.05
ICH score median (IQR)	1 (1–3)	1 (1–3)	2 (1–3)	0.75
ICH volume (mL) median (IQR)	14 (5–34)	29 (14–47)	10 (4–26)	< 0.0001
IVH *N* (%)	102 (51)	18 (31)	84 (59)	< 0.0001
Intubation *N* (%)	95 (47)	21 (36)	74 (52)	0.04
Symptom onset to baseline CT (h) median (IQR)	5.9 (1.8–11.2)	9.3 (3.8–12.6)	4.7 (1.3–9.3)	0.001
Time between CTs (h) mean (SD)	11.0 (6.6)	10.8 (6.4)	11.1 (6.6)	0.77
Absolute HE (mL) between scans median (IQR)	0.2 (− 0.7 to 2.6)	− 0.4 (− 3.0 to 3.7)	0.3 (− 0.5 to 2.2)	0.18
Laboratory coagulation testing mean (SD)				
Prothrombin time (s)	13.5 (1.4)	13.7 (1.3)	13.4 (1.5)	0.26
Partial thromboplastin time (s)	28.7 (4.5)	28.9 (6.1)	28.7 (3.7)	0.76
International normalized ratio	1.1 (0.2)	1.1 (0.2)	1.0 (0.1)	0.27
Platelet count (10^3/μL)	227 (63)	228 (59)	227 (65)	0.90

CI confidence interval, *CT* computed tomography, *DBP* diastolic blood pressure, *GCS* Glasgow coma scale, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *IVH* intraventricular hemorrhage, *OR* odds ratio, *SBP* systolic blood pressure, *SD* standard deviation

1.44; 95% CI 0.59–3.50; $p=0.41$). There were no significant associations of lobar location with HE when using traditional definitions that combine relative and absolute growth: >33% or >6 mL (adjusted OR 0.71; 95% CI 0.29–1.70; $p=0.44$) (Table 2, Fig. 1).

Lobar ICH was associated with less hospital-mortality (adjusted OR 0.31; 95% CI 0.10–0.98; $p=0.04$) after adjusting for primary ICH score and gender. HE (>33%) was independently associated with increased hospital-mortality (adjusted OR 2.69; 95% CI 1.04–6.95; $p=0.04$) after adjusting for the same covariates. Neither ICH location nor HE was associated with functional outcomes at discharge or 90-day follow-up (Table 2).

Given significantly longer times to admission CT in lobar compared to deep ICH (median: 9.3 vs. 4.7 h), a subgroup analysis was performed excluding patients with delayed times. After excluding 50 patients within the top IQR of symptom onset to admission CT times (>11.2 h),

Table 2 Crude and adjusted multivariable logistic regression analysis assessing association of lobar ICH location with hematoma expansion and neurological outcomes

Outcome	All ICH *N* = 202 *N* (%)	Lobar ICH *N* = 59 *N* (%)	Deep ICH *N* = 143 *N* (%)	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
HE > 33%[a]	43 (21)	7 (12)	36 (25)	0.4 (0.17–0.96)	0.04	0.32 (0.11–0.93)	0.04
HE > 6 mL[b]	30 (15)	12 (20)	18 (13)	1.77 (0.79–3.96)	0.16	1.44 (0.59–3.50)	0.41
HE > 33% or > 6 mL[a]	48 (24)	12 (20)	36 (25)	0.76 (0.36–1.59)	0.46	0.71 (0.29–1.70)	0.44
Hospital mortality[c]	32 (16)	6 (10)	26 (18)	0.53 (0.21–1.36)	0.19	0.31 (0.10–0.98)	0.04
Discharge mRS 4-6[c]	165 (82)	44 (75)	121 (85)	0.62 (0.29–1.33)	0.22	0.39 (0.12–1.24)	0.11
*90-day mRS 4–6[c]	128 (68)	34 (64)	94 (70)	0.78 (0.39–1.53)	0.47	0.65 (0.27–1.54)	0.32

CI confidence interval, *HE* hematoma expansion, *ICH* intracerebral hemorrhage, *mRS* modified Rankin score, *OR* odds ratio

*14 patients lost to 3-month follow-up (percentages in 188 patients: 53 lobar, 135 deep)

[a] Adjusted for baseline ICH volume, time from symptom onset to baseline CT, SBP

[b] Adjusted for baseline ICH volume, time from symptom onset to baseline CT

[c] Adjusted for sex, ICH score

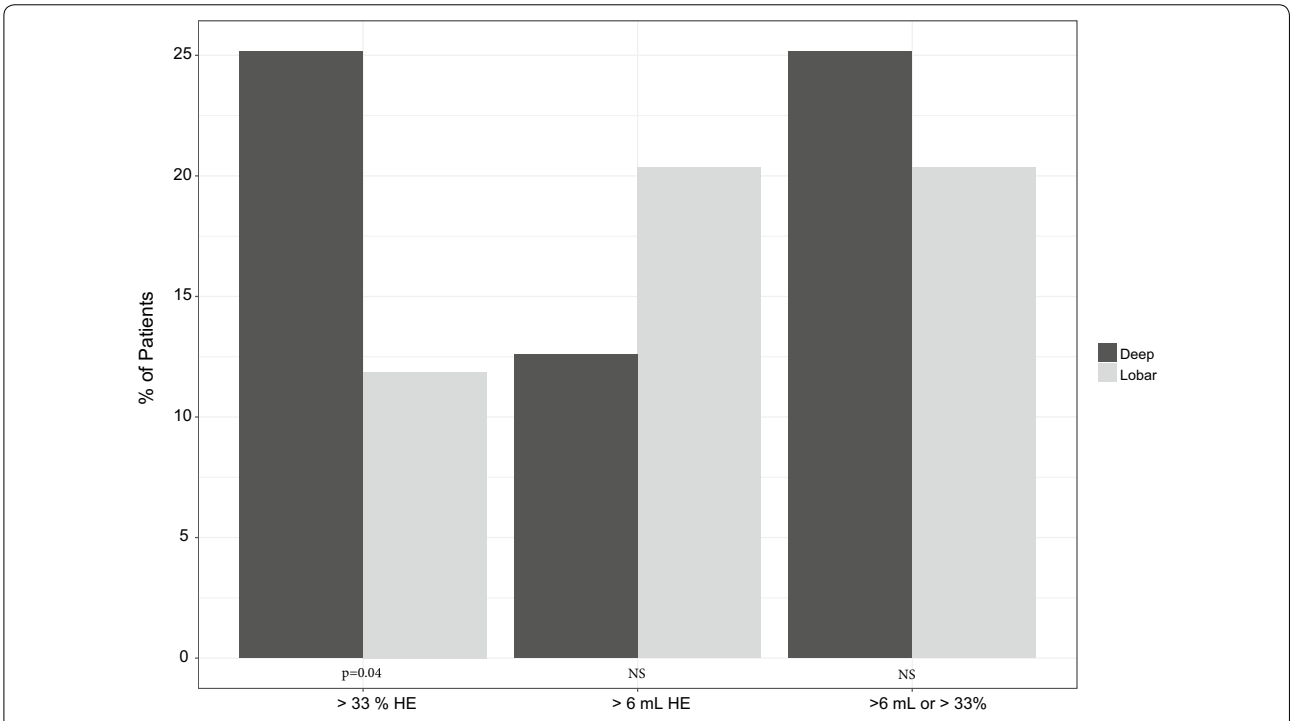

Fig. 1 Hematoma expansion differences in lobar and deep ICH. *Legend*: *HE* hematoma expansion, *ICH* intracerebral hemorrhage, *NS* not significant. Percentage of lobar versus deep ICH patients with HE using previously utilized HE definitions and significance based on adjusted logistic regression

there were no longer significant time differences between lobar ($n=36$) and deep ($n=116$) ICH (median: 4.4 vs. 3.2 h). Baseline differences between groups in the subgroup analysis were similar to the parent study with there being significant differences in baseline hematoma volumes between groups (lobar vs. deep median: 29 vs. 11 mL). There continued to be less relative HE (>33%) in lobar compared to deep ICH (14% vs. 28%), and there was an association of lobar location with less odds of HE on multivariable logistic regression (adjusted OR 0.33; 95% CI 0.10–1.08; $p=0.06$), but this estimate was imprecise after adjusting for ICH volume, time from symptom onset to admission CT and SBP. There also continued to be more absolute HE (>6 mL) in lobar compared to deep ICH (28% vs. 15%); however, this was non-significant in adjusted regression models. No associations were seen with lobar ICH and HE defined traditionally as >33% or >6 mL (Supplemental Table 1).

Discussion

Previously identified factors associated with HE after ICH are larger hematoma volumes, preceding anticoagulation use, and faster symptom onset to admission CT times [7]. ICH location has not been identified as a factor associated with HE. Our analysis excluded patients previously taking anticoagulants, and despite having larger baseline hematoma size, we identified less HE in lobar compared to deep ICH using commonly described relative HE thresholds (>33%) after adjusting for known covariates of HE including time to admission CT.

However, similar to prior studies [7], we did not identify less HE in lobar compared to deep ICH when using HE defined as both relative and absolute hematoma growth: >33% or >6 mL. This may have been due to our lobar ICH patients having more absolute HE (>6 mL) compared to deep ICH. These findings may confirm the prior literature revealing significant associations of lobar ICH with absolute HE >6 mL [13]. The opposite directionality of HE using >6 mL absolute thresholds compared to relative >33% HE thresholds may create limitations when combining these thresholds together to define HE for groups with largely differing baseline hematoma volumes. It is possible that these findings are explained by the significantly larger baseline hematoma volumes in lobar compared to deep ICH, thus making smaller absolute growth more likely in lobar ICH. Conversely, relative thresholds of HE may be much more difficult to achieve in ICH patients with larger baseline hematoma volumes such as those with lobar ICH. In our cohort, HE >6 mL translated to 20% and 60% relative HE for lobar and deep ICH, respectively, and HE >33% translated to 10 mL and 3 mL absolute HE for lobar and deep ICH, respectively. Both deep ICH location and HE were associated with increased hospital-mortality. We did not identify associations of HE or ICH location with functional outcome as seen in prior studies [4, 5], but this was most likely due the limitations of our smaller patient cohort and sicker patient population seen with larger hematoma volumes and longer times to admission.

Whether less HE in lobar ICH has pathophysiologic basis requires further study. Inherent limitations with our cohort were the longer times to admission CT in lobar ICH. While these differences were adjusted in all HE models, it is plausible that our findings may merely reflect longer times required for lobar ICH to become symptomatic resulting in longer times to admission CT scans in our cohort rather than functional coagulation differences. However, in efforts to further explore this natural confounder, we performed a subgroup analysis excluding patients with delayed times to admission CT and there continued to be an association, although imprecise, of less HE in lobar ICH. If there are indeed functional coagulation differences between lobar and deep ICH, it is feasible that lobar arterioles rupture under lower pressure than more central lenticulostriate arteries creating less HE or there may be inherent functional coagulation differences between ICH locations not detectable with traditional functional coagulation testing.

Further investigation is warranted to replicate our findings. There is currently growing evidence of outcome heterogeneity among the most common primary ICH locations: lobar versus deep. If there is additional evidence to support radiographic outcome differences between lobar and deep ICH that are either due to functional coagulation differences or merely time to presentation, future ICH clinical trial paradigms may need to either adjust for these differences or even study these locations as separate entities. Whether there are targeted treatment options based on ICH location alone will require future study.

Our study strengths included the prospective collection of data, inclusion of patients regardless of early mortality/withdrawal-of-care, prospective multidisciplinary consensus on neuroimaging characteristics, and relative protocolization of ICH treatment at our center limiting treatment and diagnostic scanning heterogeneity. Inherent limitations included its single-center small sample size, loss to 3-month follow-up, absence of spot-sign testing or hematoma density analysis, limited hyperacute CT scanning in our cohort subjecting our data to ascertainment bias, potential selection bias with patients that were excluded for early surgical intervention, and aforementioned differences in times to admission CT scans between lobar and deep ICH. We did not explore the role of ICH etiology (cerebral amyloid vs. hypertension) in our findings given the inherent interaction between ICH

location and these etiologies. Though this may be a limitation, ICH location may be a more clinically applicable risk factor to identify for hyperacute HE management as opposed to the workup required to identify ICH etiology. However, it is also worth mentioning that the biological mechanism for understanding these potential differences in HE may in fact be underpinned in ICH etiology and warrants exploration in a larger dataset. Lastly, > 33% relative growth as a HE definition may be limited in its association with outcome. There may be different outcome effects using this definition, particularly when being used across different locations compared to prior studies [6]. Because of our limited numbers, we were unable to assess optimal HE thresholds associated with outcome when stratifying by location and this may require further investigation in a larger multi-center cohort.

Conclusion

Further investigation is warranted to confirm our associations of lobar ICH with less odds of HE. This may suggest the importance of accounting for ICH location in future ICH studies and potentially coagulopathy treatment strategies for HE.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-018-00668-2) contains supplementary material, which is available to authorized users.

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DR contributed to project development, data collection, data analysis, and manuscript writing. C-HS contributed to data collection and manuscript writing/editing. SM contributed to project development and manuscript writing/editing. MSVE contributed to project development and manuscript writing/editing. SSB contributed to data analysis. KM contributed to data collection and data analysis. NI contributed to data collection and data management. AB contributed to data analysis. KD contributed to data analysis, data management, and manuscript writing/editing. DW contributed to project development and manuscript editing. HK contributed to project development. SP contributed to data collection, data management, and manuscript editing. SA contributed to data collection, data management, and manuscript editing. ESC contributed to data collection, data management, project development, and manuscript editing. JC contributed to data collection, data management, project development, and manuscript editing.

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Conflicts of Interest
The authors declare that they have no conflict of interest.

Ethical Approval
This study was approved by the Columbia University Institutional Review Board.

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