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SURGERY FOR SPONTANEOUS INTRACEREBRAL HAEMORRHAGE IN BRUNEI DARUSSALAM: SURVIVAL AND LONG-TERM FUNCTIONAL OUTCOMES.

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ABSTRACT

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Keywords: Craniotomy, Cerebral haemorrhage, Functional Status, Hospital mortality, Intracranial haemorrhage.

INTRODUCTION

Spontaneous intracerebral haemorrhage (SICH), with an annual incidence of 24.6 per 100 000, is a significant cause of stroke.[1] It has been found to account for 10% of stroke in high- income countries and 20% in low- and middle-income countries.[2] Despite the advances in diagnostic and therapeutic interventions, SICH is associated with a higher mortality rate and greater loss of health quality compared to ischaemic stroke.[3] Thirty-day mortality in these patients can be as high as 40% and survivors are usually devastated by significant neurological disability.[1] Surgery,

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which includes open and minimally-invasive haematoma evacuation, remains a mainstay of the management for a subset of patient with SICH.[4-8] In theory, surgical intervention aims to reduce intracranial pressure, prevent herniation, and to evacuate haematoma for reduction of secondary neuro-inflammatory effect and cellular toxicity of blood products on surrounding brain tissue. In clinical practice, the role of surgery for most patients with SICH remains controversial.[9] Randomised trials comparing surgery to conservative management have not demonstrated a clear benefit for surgical intervention.[10, 11] However, the generalisability of these trials remains unclear as patients at risk for herniation were likely excluded and there were also high rates of treatment group crossover from conservative management to surgery.

At present, the outcomes of patients with SICH who underwent surgery locally is unknown. Thus, this study aim to evaluate the survival as well as the long-term functional outcomes and the factors associated with better outcomes of surgery for SICH in Brunei Darussalam.

METHODS

A retrospective study of patients who underwent surgery for SICH at the Raja Isteri Pengiran Anak Saleha Hospital (RIPASH) between January 2015 and December 2018 was performed. Study inclusion criteria were all patients admitted to the Department of Neurosurgery at the RIPASH who have undergone surgery for evacuation of SICH during the study period. Patients with isolated intraventricular haemorrhage, secondary causes of intracerebral haemorrhage, incomplete data and those with data less than 30 days due to lost of follow up were excluded (Figure 1). Approval for this study was obtained from the Medical and Health Research and Ethics Committee, Mnistry of Health [Reference: MHREC/MOH/2019/12(1)].

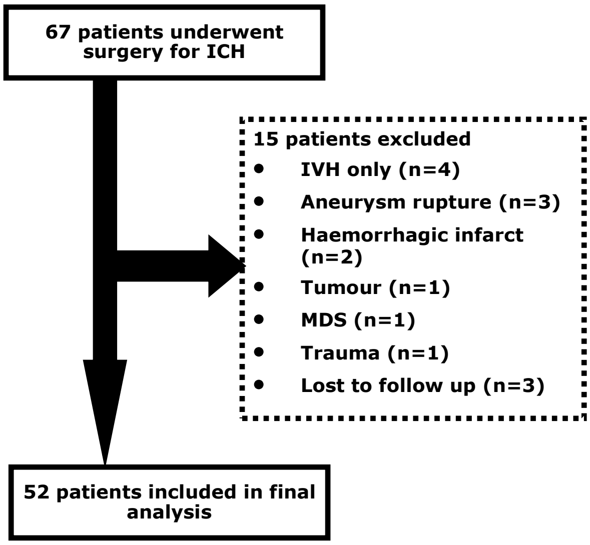

Figure 1: Flow chart of inclusion of patients with ICH who underwent surgery. ICH: Intracerebral haemorrhage; IVH: intraventricular haemorrhage; MDS: myelodysplastic syndrome.

Data were collected from patients' electronic medical records in Brunei Health Information Management System (Bru-HIMS), which included age at the time of SICH presentation, gender, co-morbidities, preoperative blood investigations (full blood count, renal panel, clotting profiles), blood pressure and Glasgow Coma Scale (GCS) on arrival in emergency department, and computed tomography and/or magnetic resonance imaging findings. Haematoma volume was calculated using the ABC/2 method. Individual patient's intracerebral haemorrhage (ICH) score was calculated based on presentation clinical and radiological parameters.[12] Operative data such as type of surgery performed and associated post-operative complications were also collected. Outcomes including 30-day and overall in-hospital mortality related to SICH presentation, and functional status using Modified Rankin Score (MRS) at 6 and 12 months were also assessed.

All statistical analyses were performed with SPSS version 20 (IBM Corporation, Armonk, New York, USA). The X^2 test, Student t-test, and the Mann-Whitney U test were performed for nominal, normally, and nonnormally distributed variables, respectively. Potential predictors of 30-day and overall in-hospital survivability were screened using univariate analyses. Variables that fulfilled the cutoff of P ≤ 0.1 in the univariate analyses were entered into a multivariate logistic regression with forward selection (conditional). In the final model, predictors for 30-day and overall in-hospital survivability were identified based on P < 0.05.

RESULTS

Our cohort consisted of 52 patients (33 men and 19 women) with a median age of 50 years (interquartile range (IQR), 39-58) who had undergone surgery for SICH. The demographic, clinical and radiological variables are summarised in Table I. The most common comorbidities was hypertension (69.2%). 86.6% of patients presented with abnormal GCS of less than 12. Median systolic and diastolic blood pressure at presentation were 204 and 114 mmHg respectively. Location of SICH was supratentorial in the majority of patients (90.4%) and most common site was the basal ganglia (59.6%). 73.1% of patients had SICH extending into the ventricles. Majority of patients (78.8%) presented with ICH score 2 and 3.

Twenty-seven (51.9%) patients underwent decompressive craniectomy with haematoma evacuation compared with 13 (25.0%) who had craniotomy with haematoma evacuation. Eleven (21.2%) patients had external ventricular drain insertion and one patient (1.9%) had decompressive craniectomy only. The median haematoma volume at presentation was 55 ml (IQR, 34-80ml). The median haematoma volume evacuated during surgery was 33.6 ml (IQR, 4.7 – 57.2 ml). The percentage of total haematoma volume evacuated after surgery was 69.1% (IQR, 29.3% – 91.2%) and only a third of patients had ≥ 80% of haematoma evacuated at time of surgery.

Mortality and Survival outcomes.

Fourteen patients died within 30 days of presentation resulting in a 30-day mortality of 26.9%. The 30-day mortality based on ICH score is summarised in Table II. The overall in-hospital mortality was 38.5% (20/52). The 30-day mortality and overall in-hospital mortality for patients with dialysis dependent end-stage renal failure was 28.6% (2/7) and 100% (7/7) respectively. All patients with dialysis dependent end-stage renal failure were never discharged from hospital and died within the year of their SICH presentation (median 92 days, minimum 3 days, and maximum 254 days).

Patients on pre-operative anticoagulant was significantly associated with higher 30-day mortality outcome after surgery (Table I: *p=0.017*), while patients who had ≥ 80% of haematoma evacuation was significantly associated with better 30-day survivability (Table I: *p=0.017*). Multivariate analysis (Table III) showed that patients with haematoma evacuation ≥ 80% was the only factor significantly associated with 30-day survival, odds ratio (OR) 9.46 (95% confidence interval (CI), 1.12 – 79.84; *p=0.039*) and overall in-hospital survival, OR 7.94 (95% CI, 1.58 – 40.03; *p=0.012*).

Functional outcome

Twenty-nine patients (three foreign patients were discharged and repatriated to their respective countries) were available for functional outcome assessment. The overall 6- and 12- month functional outcomes are summarised in Table II. Four patients (13.8%) achieved good favourable functional outcome (MRS ≤ 3) at 6 and 12 months.

Adverse events

Four of the patients (7.7%) experienced a surgery related complication - three had bleeding that required a return to operating theatre and one patient had a superficial cranial wound infection (Table IV). Non-surgery

Table I: Patient Demographics and Characteristics.

	Overall (N=52)	30-day survivors (n=38)	30-day non-survivors (n=14)	p
Male gender, n (%)	33 (63.5)	25 (65.8)	8 (57.1)	0.566
Median Age, years (IQR)	50 (39-58)	50 (39-55)	54 (37-64)	0.358
Co-morbidities, n (%)				
Hypertension	36 (69.2)	25 (65.8)	11 (78.6)	0.376
Hyperlipidaemia	12 (23.1)	10 (26.3)	2 (14.3)	0.361
Diabetes mellitus	15 (28.8)	10 (26.3)	5 (35.7)	0.507
Dialysis dependence	7 (13.5)	5 (13.2)	2 (14.3)	0.916
Antiplatelet use	2 (3.8)	1 (2.6)	1 (7.1)	0.453
Anticoagulant use	2 (3.8)	0 (0)	2 (14.3)	***0.017****
Median GCS (IQR)	8 (6-11)	9 (6-11)	8 (6-8)	0.117
3-4, n(%)	7 (13.5)	7 (18.4)	0 (0)	0.084
5-12, n (%)	38 (73.0)	26 (68.4)	12 (85.7)	0.212
13-15, n (%)	7 (13.5)	5 (13.2)	2 (14.3)	0.916
Pupil, n (%)				
Bilateral reactive	41 (78.8)	31 (81.6)	10 (71.4)	0.427
Unilateral dilated	3 (5.8)	2 (5.3)	1 (7.1)	0.797
Bilateral dilated	8 (15.4)	5 (13.2)	3 (21.4)	0.463
Median systolic BP, mmHg (IQR)	204 (169-228)	201 (170-229)	214 (152-225)	0.765
Median diastolic BP, mmHg (IQR)	114 (99-128)	112 (99-122)	117 (92-134)	0.672
Blood investigations, median (IQR)				
Haemoglobin, g/dL	14.0 (12.3-16.0)	14.0 (12.0-16.0)	14.0 (12.5-16.0)	0.770
White blood cell, x 10^3/uL	14.0 (10.3- 17.0)	14.0 (11.0-17.3)	13.0 (9.0-16.3)	0.251
Platelets, x 10^3/uL	286 (231-346)	273 (215-346)	298 (261-347)	0.381
APTT, seconds	30.0 (28.5-32.0)	30.0 (28.7-31.5)	30.4 (25.2-33.5)	0.723
INR	1.00 (0.94-1.06)	1.00 (0.95-1.05)	1.00 (0.92-1.06)	0.992
Sodium, mmol/L	139 (134-140)	139 (136-140)	139 (137-140)	0.992
Potassium, mmol/L	3.6 (3.2-4.2)	3.4 (3.7-4.2)	3.4 (3.1-4.2)	0.139
Creatinine, umol/L	99 (80-145)	97 (79-134)	104 (79-173)	0.613
Urea, mmol/L	7.9 (3.7-9.0)	5.2 (3.6-9.3)	5.8 (3.9-7.7)	0.642
Location, n (%)				
Supratentorial	47 (90.4)	35 (92.1)	12 (85.7)	0.488
Infratentorial	5 (9.6)	3 (7.9)	2 (14.3)	0.488
Left sided	22 (42.3)	15 (39.5)	7 (50.0)	0.496
Site, n (%)				
Thalamus	6 (11.5)	4 (10.5)	2 (14.3)	0.825
Basal ganglia	31 (59.6)	23 (60.5)	8 (57.1)	0.707
Lobar	10 (9.2)	8 (21.1.8)	2 (14.3)	0.583
Cerebellum	5 (9.6)	3 (7.9)	2 (14.3)	0.488
Extension into ventricles, n (%)	38 (73.1)	27 (71.1)	11 (78.6)	0.588
Median ICH volume in ml (IQR)	55 (34-80)	56 (34-81)	54 (40-78)	0.951
< 30, n (%)	8 (15.4)	6 (15.8)	2 (14.3)	0.894
≥ 30, n (%)	44 (84.6)	32 (84.2)	12 (85.7)	0.894
ICH score, n (%)				
1	4 (7.7)	4 (10.5)	0 (0)	0.206
2	18 (34.6)	13 (34.2)	5 (35.7)	0.919
3	23 (44.2)	17 (44.7)	6 (42.9)	0.904
4	4 (7.7)	3 (7.9)	1 (7.1)	0.928
5	3 (5.8)	1 (2.6)	2 (14.3)	0.110
Haematoma evacuation ≥ 80%, n (%)	17 (32.7)	16 (42.1)	1 (7.1)	***0.017****

IQR, interquartile range; GCS, Glasgow Coma Scale; BP, blood pressure; APTT, activated partial thromboplastin time; INR, international normalised ratio; ICH, intracerebral haemorrhage. * denotes statistical significance based on univariate analysis.

Table II: Mortality and Functional Outcomes.

Variables	n (%)
30-day mortality	14/52 (26.9)
30-day mortality by ICH score	
1	0/4 (0)
2	5/18 (27.8)
3	6/23 (26.1)
4	1/4 (25.0)
5	2/3 (66.7)
Overall in-hospital mortality	20/52 (38.5)
6-month MRS, n=29	
0	1 (3.4)
1	0 (0)
2	0 (0)
3	3 (10.3)
4	16 (55.2)
5	6 (20.7)
6	3 (10.3)
12 months MRS, n/29	
0	1 (3.4)
1	0 (0)
2	0 (0)
3	3 (10.3)
4	16 (55.2)
5	5 (17.2)
6	4 (13.8)
12 months good outcome (MRS ≤ 3)	4 (13.8)

ICH, intracerebral haemorrhage; MRS, Modified Rankin Scale.

related adverse events were recorded in 21 (40.4%) patients. The most common was pneumonia (16/21, 81.0%). Other complications include acute renal failure, scrotal abscess, upper gastrointestinal bleed and cerebral infarct (Table IV).

DISCUSSION

SICH remains a devastating form of stroke with significant morbidity and mortality. Although the majority of patients present with small haematomas which are readily treated with good medical care, a subset of SICH patients can present in extremis, requiring surgery.[13]

The 30-day mortality rate of 26.9% in this study is comparable to prior findings in the Asian population (28.5%).[14] STICH, a multi-centre and multi-country randomized controlled trial, showed early surgery did not reduce mortality or improve neurological outcome compared with conservative management for supratentorial SICH when the treating neurosurgeon determined that uncertainty of preferred treatment (equipoise) was present.[10] Twenty-six percent of the patients in the surgical arm achieved a favourable outcome compared with 24% in the medical arm. STICH did not find any overall statistically significant difference in either mortality or functional outcome between surgery and conservative groups. However, a crossover of more than a quarter of patients (26%) initially assigned to conservative management to surgery may have affected the final analysis centred on an intention-to-treat basis. Subgroup analyses suggested that patients with lobar haemorrhages within 1 cm of the cortical surface might benefit from surgery and the risk for a poor outcome was increased for patients who presented as comatose (GCS score ≤8). In addition, a meta-analysis of surgical trials reporting on 3366 patients showed a significant advantage for surgery when all patients were considered, but there was significant heterogeneity in the data.[15]

Table III: Multivariate analysis of factors predicting 30-day and overall in-hospital survivability.

Variables	30-day survival			Overall in-hospital survival		
	OR	CI	p	OR	CI	p
Anticoagulant use			0.058			0.157
ICH score			0.390			0.163
Haematoma evacuation ≥ 80%	9.46	1.12-79.84	***0.039****	7.94	1.58-40.03	**0.012***

ICH, intracerebral haemorrhage. * denotes statistical significance

Table IV: Adverse events (N=52).

Variables	n (%)
Surgery related	4 (7.7)
Haematoma	3 (5.8)
Superficial wound infection	1 (1.9)
Non-surgery related	21 (40.4)
Pneumonia	16 (30.8)
Cerebral infarct	1 (1.9)
Acute renal failure	1 (1.9)
Upper gastrointestinal bleed	1 (1.9)
Scrotal abscess	1 (1.9)

The 30-day mortality in our surgical cohort based on the ICH score 1, 2, 3, 4 and 5 were 0%, 27.8%, 26.1%, 25%, and 66.7%, respectively. Increase survivability in the higher ICH scores, however, did not translate to good functional outcomes as only 13.8% of patient achieve a 12-month MRS ≤ 3. These findings show that the role of surgery for most patients remain life-saving and is unlikely to reverse neurological impairment sustained from the initial bleed. Surgical management of SICH tends to be more aggressive in the local setting where affordable high quality healthcare is readily available. More significantly, the definition of an acceptable neurological recovery locally can be complex. Strong religious and cultural beliefs and family principles, in which the sanctity of life usually take precedence over the quality of life, may define meaningful outcome differently. Therefore, the decision for surgery and a high chance of survivability with unfavourable functional outcomes should be carefully discussed with family members or other proxy decision-makers who are familiar with the patient's values and preference so that they are prepared for the possibility of long-term care required for these dependent patients who are unlikely to return to prior or meaningful function.

All dialysis-dependent patients in our surgical population did not survive beyond one year following surgery for SICH, and all of them were not discharged and died in hospital with poor functional status (MRS 5). Therefore, strong considerations for non-surgery and palliation should be advised for patients with end-stage renal failure requiring dialysis who presents with life-threatening SICH as their prognosis remains guarded even with surgical intervention.

The amount of haematoma evacuation during surgery is important in preventing herniation, reducing intracranial pressure, and decreasing the pathophysiological impact of the hematoma on surrounding tissue by decreasing mass effect or the cellular toxicity of blood products. MISTIE III showed that a lesser amount of residual clot was significantly associated with a greater likelihood of achieving a good functional outcome (10.5% difference in the likelihood of achieving a good functional outcome in 58% of patients with haematoma volume of ≤ 15 ml).[16] At present, three studies (ICH-ENRICH, MIND, and INVEST) evaluating minimally invasive surgical techniques in removing the haematoma and at improving functional outcomes in SICH are ongoing. In this study, haematoma evacuation ≥ 80% was significantly associated with improved 30-day survival and overall in-hospital survival. Therefore, surgeons need to aggressive with haematoma removal and at the same time, balance the benefits of lesser amount of residual clot against the risk of tissue injury and post-operative bleed with aggressive haematoma evacuation.

As this is a retrospective study, limitations, including loss of patient data, are inherent and reported findings should be regarded in this context. These results represent only a single-centre experience. However, minimal patient lost to follow-up and the availability of long term patient follow-up may outweigh our shortcomings. Moreover, as the main tertiary centre, where referral bias is minimal, these findings are a reflection of the "real world" management of SICH in the country.

CONCLUSION

SICH continue to be a devastating condition which is significantly associated with morbidity and mortality. The role of surgery for most patients remains a life-saving measure and the decision for surgery should be weighed against survivability with unfavourable functional outcomes. Patients with end-stage renal failure requiring dialysis who presents with life-threatening SICH should be treated conservatively as their prognosis remains guarded even with surgical intervention. Future research into establishing specific surgical treatments or therapies for enhancing post-haemorrhage recovery is essential for improving outcome from this devastating form of stroke.

DECLARATION OF CONFLICT OF INTEREST

None

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