

Sonography Assisted Clot Evacuation in Early Intracerebral Haemorrhage

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LIST OF ABBREVIATIONS

1.	CT	COMPUTED TOMOGRAPHY
2.	DALY	DISABILITY ADJUSTED LIFE YEAR
3.	GCS	GLASGOW COMA SCORE
4.	ICH	INTRACEREBRAL HEMORRHAGE
5.	MRS	MODIFIED RANKIN SCALE
6.	MRI	MAGNETIC RESONANCE IMAGING
7.	NH DU	NEUROSURGICAL HIGH DEPENDANCY UNIT
8.	OR	ODDS RATIO
9.	SPSS	STATISTICAL PACKAGE FOR SOCIAL SCIENCE
10.	USB	UNIVERSAL SERIAL BUS
11.	USG	ULTRASONOGRAPHY

ABSTRAK

Latar Belakang dan Objektif

Pendarahan intraserebral spontan (ICH) adalah keadaan yang semakin kerap serta mendatangkan morbiditi dan mortaliti. Pembedahan awal untuk ICH *supratentorial* spontan tidak terbukti bermanfaat secara konsisten dari pelbagai kajian. Kami menyiasat keberkesanan pembedahan awal ICH *supratentorial* spontan berpandukan *ultrasound* dari segi kelengkapan darah beku dikeluarkan melalui evaluasi radiologi.

Kaedah

Kami meninjau secara prospektif 58 pesakit yang dibentangkan ke pusat pakar bedah saraf di Malaysia dalam tempoh 48 jam untuk ICH *supratentorial* spontan dan menjalani pembedahan pembuangan darah beku antara bulan Jun 2017 hingga Februari 2019. Pesakit secara rawak digolongkan untuk pembedahan membuang darah beku sama ada dengan atau tanpa bimbingan *ultrasound* intraoperatif dalam nisbah 1:1. Imej otak CT yang sebelum dioperasi dan langsung selepas dioperasi dibandingkan. Hasil utama adalah kelengkapan darah beku dikeluarkan yang diukur melalui formula $(a \times b \times c)/2$. Pesakit atau keluarga mereka menjalani temuduga telefon 3 bulan selepas pembedahan untuk menilai hasil neurologi.

Keputusan

29 pesakit secara rawak digolongkan kepada kedua-dua kumpulan pembedahan awal membuang darah beku dengan dan tanpa bimbingan *ultrasound* intraoperatif. Semua pesakit diikuti pada 3 bulan. Pesakit dalam kumpulan pembedahan dengan bimbingan *ultrasound* intraoperatif dan tanpa bimbingan *ultrasound* intraoperatif mempunyai pengurangan *median* jumlah beku sebanyak 87.9% dan 93.1% masing-masing. Kedua-

dua kumpulan mempunyai *mean* pengurangan sebanyak 88.7% dan 86.9% masing-masing, yang secara statistiknya signifikan, nilai $p = 0.022$. Kadar kematian pada 3 bulan bagi kedua-dua kumpulan adalah 10.3% dan 20.1% masing-masing. (OR 2.3, 95% CI 0.51 hingga 10.08; $p = 0.285$).

Kesimpulan

Pembedahan pembuangan ICH *supratentorial* spontan berpandukan *ultrasound* meningkatkan kelengkapan pembuangan darah beku melalui evaluasi radiologi.

ABSTRACT

Background and Objective

Spontaneous intracerebral haemorrhages (ICH) are an increasingly common condition that leads to severe morbidities and mortality. Early surgical evacuation of spontaneous supratentorial ICHs has not consistently been proven to be beneficial from multiple studies. We investigate the effectiveness of ultrasound guided early surgical evacuation of spontaneous supratentorial ICHs with respect to the completeness of evacuation on radiological evaluation.

Methods

We prospectively recruited 58 patients who presented to a tertiary Neurosurgery centre in Malaysia within 48 hours of ictus for a spontaneous supratentorial ICH and underwent surgical evacuation of clot between June 2017 to February 2019. The patients were randomly assigned to surgical evacuation of clot with or without intraoperative ultrasound guidance in 1:1 ratio. Pre operative and immediate post operative CT brain images were compared. The primary outcome was the completeness of clot evacuation measured via the $(a \times b \times c)/2$ formula. The patient or their family underwent a telephone interview 3 months post surgery to assess neurological outcome.

Results

29 patients were randomly assigned to both early surgical evacuation of clot with and without intraoperative ultrasound guidance. All patients were followed up at 3 months. Patients in the surgical evacuation with intraoperative ultrasound guidance and without intraoperative ultrasound guidance had mean reductions of 88.7% and 86.9% respectively, which was statistically significant, p value = 0.022. Mortality rate at 3

months for both groups was 10.3% and 20.1% respectively. (OR 2.3, 95% CI 0.51 to 10.08; $p = 0.285$).

Conclusion

Ultrasound guided evacuation of spontaneous supratentorial ICHs increases the completeness of clot evacuation via radiological evaluation.

1. INTRODUCTION & LITERATURE REVIEW

Intracerebral haemorrhages presents as a significant proportion of patients who result with poor outcomes(1). Large volume of intracerebral clots will exhaust the displacement capacity of cerebrospinal fluid and venous blood rapidly, hence expediting the process of cerebral herniation(2). The process of clot expansion and perilesional oedema formation occurs early in the disease process and further contributes to the mass effect from the original insult(2-4). Direct compression and shearing forces by the clot and its formation onto the surrounding tissue causes disruption of nervous cellular architecture(2,4).

On a molecular level, thrombin release, erythrocyte breakdown and inflammatory processes further contribute to pathology of ICH. Thrombin released as a response to ICH leads to direct damage of neurons and astrocytes, disruption to blood brain barrier, activation of microglia and Src kinase(2,4-6). Erythrocyte lysis releases haemoglobin which is then degraded into iron, carbon monoxide and bilirubin(2,4). These erythrocyte breakdown products are strongly cytotoxic, pro-oxidative and pro-inflammatory towards viable brain cells(5,6).

There exists a region of decreased cerebral perfusion surrounding the clot as well as in the ipsilateral cerebral hemisphere in the initial period after the onset of ICH(2-4,8). Studies have shown that removal of intraparenchymal clot is associated with normalization of cerebral perfusion and improved outcomes(3,8,9).

However, current evidence only suggests a vague benefit for surgical evacuation of the intraparenchymal clot in a specific cohort of patients(10). The marginal benefit is likely due to both the underlying pathology of intracerebral haemorrhage as well as

complications that may arise from the surgery itself. Residual haematoma that is left behind after surgery also contributes to this. Prior studies have shown that incomplete evacuation of haematoma leads to increased perilesional oedema, further secondary brain injury and poorer outcome(11-13).

Intraoperative ultrasonography has been available as an intraoperative imaging modality since beyond the past decade(14). Its efficacy in aiding the resection of brain tumours has already been proven(15-20). Despite the ability to delineate intracerebral haemorrhages and surrounding structures adequately, minimal research has been performed to look into its benefits as an intraoperative modality.

The objective of this study was to determine if use of intraoperative ultrasonography would result in more complete evacuation of spontaneous supratentorial ICHs.

2. STUDY PROTOCOL

This was a prospective randomized controlled trial on patients who were admitted to Hospital Umum Sarawak between June 2017 to February 2019 for a spontaneous supratentorial intracerebral haemorrhage and underwent clot evacuation. Hospital Umum Sarawak is a tertiary training Neurosurgery center with neuroimaging modalities comprising of USG, CT, MRI, angiogram and management modalities for Neurosurgery including a dedicated Neurosurgical High Dependency Unit (NHDU). Patients who fulfilled the inclusion criteria stated below were enrolled.

The analysed parameters are shown below in Table 1.

The inclusion criteria were:

- Patients of all ages who were admitted within 48 hours of ictus with evidence of spontaneous intracerebral haemorrhage on CT scan
- Best Glasgow Coma Scale (GCS) score of at least 8
- Location of intracerebral haemorrhage 1cm or less from the cortical surface of the brain with volume of haemorrhage between 30-100 mL on CT scan

The exclusion criteria were:

- Clear evidence that the haemorrhage is due to an aneurysm or angiographically proven arteriovenous malformation
- Intracerebral haemorrhage secondary to tumour or trauma
- Cerebellar or brainstem haemorrhage or extension of haemorrhage into any of these regions
- Severe pre-existing physical or mental disability or severe co-morbidity which might interfere with assessment of outcome

- If the haematological effects of any previous anticoagulants are not completely reversed
- If patient or primary caretakers of patient refuse surgical intervention

Sample Size

For the completeness of clot evacuation, a sample size of 27 for each group was required to detect a mean difference of 25% with a power of 0.80 (80%) and an alpha at 0.05. The sample size was calculated based on a sample size calculator(21). Universal selection was employed.

This study was conducted over a period of 21 months from the 1st of June 2017 till the 28th of February 2019. The flow of the study is as shown in Figure 1.

Data analysis was performed with the use of SPSS statistical software. Descriptive statistics of proportion and mean was used to describe the patient's demographic data. Independent group t-test was used to analyse the post operative difference in clot volume between both cohorts. Univariate and multivariate logistic regression analysis was used to adjust for age, GCS and volume of clot.

Declaration of Interest Conflict

There are no additional side effects on the participants from this study as use of intraoperative ultrasonography are routine in this centre. The study does not present any known direct benefit to the participants. However, any benefit determined from this study may be used in the future.

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki (2013) and the Malaysian Good Clinical Practice Guideline (2016). Approval was obtained prior to the initiation of this study. Written consent was obtained prior to enrolment into the study.

Names of subjects will be kept on a password-protected database and will be linked only with a study identification number during this research. The patient identification number instead of patient identifiers will be used on data sheets. All data will be entered into a computer that is password protected. Names of patients will not be disclosed, and all will be changed into identification number instead. On the completion of study, data in the computer will be copied to a USB drive and other softcopies will be erased while the hardcopy data will be kept and locked in the office cabinet located in the Department of Neurosurgery, Hospital Umum Sarawak for 2 years, after which, the data will be removed permanently.

TITLE PAGE

Sonography Assisted Clot Evacuation in Early Intracerebral Haemorrhage

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3.2 Abstract

Background and Objective

Spontaneous intracerebral haemorrhages (ICH) are an increasingly common condition that leads to severe morbidities and mortality. Early surgical evacuation of spontaneous supratentorial ICHs has not consistently been proven to be beneficial from multiple studies. We investigate the effectiveness of ultrasound guided early surgical evacuation of spontaneous supratentorial ICHs with respect to the completeness of evacuation on radiological evaluation.

Methods

We prospectively recruited 58 patients who presented to a tertiary Neurosurgery centre in Malaysia within 48 hours of ictus for a spontaneous supratentorial ICH and underwent surgical evacuation of clot between June 2017 to February 2019. The patients were randomly assigned to surgical evacuation of clot with or without intraoperative ultrasound guidance in 1:1 ratio. Pre operative and immediate post operative CT brain images were compared. The primary outcome was the completeness of clot evacuation measured via the $(a \times b \times c)/2$ formula. The patient or their family underwent a telephone interview 3 months post surgery to assess neurological outcome.

Results

29 patients were randomly assigned to both early surgical evacuation of clot with and without intraoperative ultrasound guidance. All patients were followed up at 3 months. Patients in the surgical evacuation with intraoperative ultrasound guidance and without intraoperative ultrasound guidance had mean reductions of 88.7% and 86.9% respectively, which was statistically significant, p value = 0.022. Mortality rate at 3

months for both groups was 10.3% and 20.1% respectively. (OR 2.3, 95% CI 0.51 to 10.08; $p = 0.285$).

Conclusion

Ultrasound guided evacuation of spontaneous supratentorial ICHs increases the completeness of clot evacuation via radiological evaluation.

Keywords

Intracerebral haemorrhage; ultrasound; surgical evacuation;

3.3 Introduction

An intracerebral haemorrhage (ICH) is defined as a blood clot within the brain parenchyma that occurs spontaneously and not as a result of surgery or trauma(22). They can be divided by their underlying causes into two groups: Primary and Secondary. Primary ICH occurs as a result of hypertension or amyloid angiopathy leading to the rupture of small intracerebral vessels. Congenital and acquired conditions are the causes of Secondary ICH and these include vascular anomalies, coagulopathies and tumours.

Intracerebral haemorrhage remains a significant global health problem, that is more prevalent in Asian populations(23,24). The incidence of ICH continues to increase in developing countries such as ours(24). In Malaysia, the incidence of ICH stands at 21.07 per 100,000 population in 2014, which is more than 2 times the number in 2010(25). Intracerebral haemorrhages accounts for 15-36% of all strokes in our country, which is higher than the global average(26-29).

Stroke represented the second leading cause of death and disability-adjusted life-years (DALYs) worldwide in 2015(30,31). In Malaysia, stroke remains as the third leading cause of death behind ischaemic heart disease and pneumonia, as per their latest available national statistics in 2014(32).

For patients with ICH, national data revealed that poor outcomes (defined as Glasgow Outcome Score of 1-3) are evident in three quarters of the population(1). Mortality rates within this population of patients range from 26-44% (25,26,28), which is similar to rates reported worldwide. The majority of deaths occur within the first 3 weeks of admission with a mean at 4 days after admission(1,26,33).

Theoretically, removal of the intraparenchymal clot would be beneficial due to the multifactorial pathological effects of the clot residing within the cerebral hemisphere(2-7). However, current evidence only suggests a vague benefit for surgical evacuation of the intraparenchymal clot in a specific cohort of patients(10). The marginal benefit is likely due to both the underlying pathology of intracerebral haemorrhage as well as complications that may arise from the surgery itself.

Although current guidelines do not provide definite recommendations, surgery continues to appear beneficial for certain groups of patients(10,34-39). Patient groups with an initial Glasgow Coma Scale (GCS) of 9-12 with supratentorial ICHs of at least 30 mL in volume and less than 1 cm from the cortical surface with no intraventricular haemorrhage appear to benefit the most from surgical evacuation of ICH(34). The average clot size reduction from “open” surgery is 75.02%(11). Incomplete evacuation of haematoma leads to increased perilesional oedema, secondary brain injury and poorer outcome(11-13).

Much of prior medical research focused on the use of ultrasonography in the resection of brain tumours(14-16). Multiple studies have shown that intraoperative use of ultrasonography improves resection rates of brain tumours, with a predilection for higher grade tumours(12,17-20). Intraoperative ultrasonography has also been shown to enable safer resection of brain tumours by delineation of important structures(18,40).

Intraoperative ultrasonography can reliably demonstrate presence of intracerebral blood and surrounding vasculature(16,17,41,42). However, literature regarding ultrasound guided evacuation of intracerebral haemorrhages remains sparse.

Shanley et al reported a case from which localization and subsequent evacuation of an ICH was performed with ultrasonographic guidance(43). Unsgaard et al looked at ultrasound assisted evacuation of deep seated ICHs(15). All reports were consistent in their finding of ultrasonography aiding the evacuation process however none of them performed controlled trials nor did they report on the long term outcomes of their cohorts.

3.4 Methodology

3.4.1 Research design

This was a prospective randomized controlled trial. Approval was obtained from the Medical Research & Ethics Committee of the Ministry of Health Malaysia and registered in the national register for clinical trials. The study aims to compare radiological outcomes between ultrasound guided and non-ultrasound guided evacuation of spontaneous supratentorial ICHs.

3.4.2 Research location and duration

Data was collected from patients who fulfilled the inclusion criteria from Hospital Umum Sarawak and underwent a clot evacuation for a spontaneous supratentorial ICH during the period from 1st June 2017 till 28th February 2019 and analysed

3.4.3 Study population

All patients who sustained a spontaneous supratentorial ICH and underwent a clot evacuation who fulfilled the inclusion and exclusion criteria were included in the study. The inclusion criteria for patients in this study were patients who underwent a clot evacuation for a spontaneous supratentorial ICH who presented within 48 hours of ictus, had a best GCS score of at least 8 and had a supratentorial ICH with a volume of 30-100 mL which was located 1 cm or less from the cortical surface of the brain on CT scan. Patients who had ICHs extending to or involving the cerebellum or brainstem, had evidence that the ICH was due to secondary causes such as vascular anomalies, tumours or trauma, had ongoing haematological effects from previous anticoagulants which were not completely reversed or had primary caretakers who refused surgical intervention were excluded from the study.

3.4.4 Method of research

Patients were randomly allocated to either clot evacuation with or without intraoperative ultrasonography guidance. In either group, surgeons were expected to endeavour to undertake the evacuation of the clot within 12 hours. All patients were given best medical treatment from and throughout admission, as per guidelines(35).

Evacuation of the clot was done as per routine in this centre, which is via craniotomy and “naked eye” assessment by the operating surgeon. The aim of surgery was for complete clot evacuation. Intraoperative ultrasonography was used to determine the shortest cortical distance to reach the clot both prior to and after durotomy and determination of completeness of clot evacuation during and at the end of the evacuation. Intraoperative ultrasonography was performed by a Neurosurgical Resident who had undergone formal training for such procedures. All patients will then have an immediate post operative CT brain done to re-evaluate the volume of residual clot. The pre operative and post operative CT brain images were then compared to determine the completeness of clot evacuation. The volume of pre and post operative clot was calculated using Broderick’s formula: $\text{volume (mL)} = a \times b \times c/2(44)$, where a is the largest diameter (cm) of the clot, b is the diameter (cm) of the clot perpendicular to a , and c is the height (cm) of the clot calculated by multiplying the number of slices involved with the slice thickness. Subsequently, the change in the volume of clot would then be calculated in percentages. An average measurement was obtained from separate readings made by two Neurosurgical residents who were blinded to the final outcome. The same method was applied to both pre and post operative images. Intraclass correlation was used to estimate the inter rater reliability between the two residents. A high degree of reliability was found between their measurements. The average measure of intraclass correlation was 0.917 with a 95% confidence interval from 0.861 to 0.951 (p value <0.001). (Table 2) Information about the premorbid status and pre and post operative progress of all patients (including GCS score, pre and post operative blood pressure, need for re-evacuation of clot and modified Rankin scale) was gathered by the investigator at two weeks, discharge or death, whichever was earliest.

Long term outcome measures was collected via telephone interviews based on the modified Rankin scale (MRS)(45). The MRS (Table 3) is a widely used method to measure the degree of neurological disability in patients and is based on the assessment of patients' ability to carry out their activities of daily living(46).

All the patients were randomized via a validated randomization program to minimize possible sources of bias(47,48). Patients were blinded to whether or not ultrasonography was used during surgery. It was not possible to blind the treating surgeon to whether or not ultrasonography was used. Treatment allocation was masked from the assessors calculating the clot volumes and interviewers conducting the telephone interviews.

The primary outcome was to compare the completeness of evacuation of the intracerebral haemorrhage with and without intraoperative ultrasonography based on pre operative and post operative CT brain imaging. Secondary outcomes were MRS at discharge and 3 months after discharge.

3.4.5 Statistical analysis

Cho et al previously reported a mean reduction of clot volume of 75% when compared to pre operative CT imaging for spontaneous ICHs that were evacuated via craniotomy(49). This value was used as the anticipated mean to calculate the required sample size for this study. A minimum of 27 patients for each group was required to detect a mean difference of 25% with a power of 0.80 (80%) and an alpha at 0.05(21).

The recorded data was analysed using SPSS (version 26, SPSS Inc., IBM, Chicago, IL, USA) statistical software. Descriptive statistics of proportion and mean was

used to describe the patient's demographic data. Independent group t-test was used to analyse the post operative difference in clot volume between both cohorts. Univariate and multivariate logistic regression analysis was used to adjust for age, GCS and volume of clot. Additionally, MRS was also reported by treatment allocation.

3.5 Results

58 patients were randomly assigned between 1st June 2017 and 28th February 2019: 29 to evacuation of ICH without intraoperative ultrasonography and 29 to evacuation of ICH with intraoperative ultrasonography. Table 4 shows the details of the patients' age, sex, previous medical history and neurological status. The two groups were well matched at baseline. 57% of the study population were male and the median age of the patients was 51 years (age range 21-76 years).

The most common comorbidity within the study population was hypertension with 39 patients (67.2%) who were previously diagnosed with the disease. Other comorbidities included diabetes mellitus, 9 patients (15.5%), ischaemic heart disease, 5 patients (8.6%), atrial fibrillation, 3 patients (5.2%), and hyperthyroidism, 1 patient (1.7%).

Average GCS at randomization was 11.8 for the group who underwent clot evacuation without ultrasonography and 12.1 for the group that underwent clot evacuation with ultrasonography. The most common presenting complaint was hemiparesis or hemiplegia, 42 patients (72.4%), followed by loss of or reduced consciousness, 33 patients (55.2%), seizures, 13 patients (22.4%), and headache, 10 patients (17.2%). The