Surgical intervention for prevent post-stroke malignant cerebral edema, clinical beneficial outcome aspects.

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Abstract

Background: Acute ischemic strokes can develop post-stroke malignant cerebral edema. Surgical intervention known as decompressive craniectomy (DC) can decrease mortality but there is not evidence support for clinical beneficial outcome. The aim of this study assess beneficial outcome in surgical intervention for prevent post-stroke malignant cerebral edema.

Methods: Non-randomized, prospective, observational cohort study from 2016 to 2021 in 243 Subjects with acute ischemic stroke involving the middle cerebral, internal carotid artery, or both. Analyses of parameters affecting clinical beneficial outcome according to the modified Rankin Scale (mRS) at 3 and 6 months follow up were performed.

Results: Risk factors after multivariate analysis were onset to DC, tobacco use, NIHSS at admission, peripheral arterial occlusive disease, diabetes mellitus, body mass index (BMI), coronary artery disease, age more than 70 year and left side large-territory infarction. Age ≤ 71 year (AUC=0.955, p-value <0.001 accuracy 89.7%), onset to DC ≤ 9 hours (AUC =0.824, p-value <0.001 accuracy 78.8%), volume of infarction ≤ 155 cm^3 (AUC =0.939, p-value <0.001 accuracy 93.6%) and ASPECT score ≥ 6 (AUC = 1, p-value <0.001 accuracy 100%) were significantly parameters affecting clinical beneficial outcome.

Conclusion: Surgical intervention for prevent post-stroke malignant cerebral edema, age ≤ 71 years, onset to DC ≤ 9 hours, volume of infarction ≤ 155 cm^3 and ASPECT score ≥ 6 associated with clinical beneficial outcome.

Keywords: Malignant cerebral edema, Acute ischemic strokes, decompressive craniectomy, modified Rankin Scale (J Thai Stroke Soc. 2022;21(1):5-25)

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การศึกษาการผ่าตัดเปิดกะโหลกเพื่อลดความดันในกะโหลกศีรษะภายในระยะเวลา 48 ชั่วโมงเพื่อป้องกันการขยับเลื่อนที่ของเนื้อสมองไปกดก้านสมองในแง่ค่าพารามิเตอร์ที่เป็นปัจจัยที่มีผลต่อผลลัพธ์ของการรักษาทางคลินิกที่ดี

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บทคัดย่อ

ความเป็นมา ผู้ป่วยโรคหลอดเลือดสมองที่มาด้วยภาวะสมองขาดเลือดขนาดใหญ่จะมีการพัฒนาไปสู่ภาวะสมองบวมที่ไม่สามารถควบคุมได้และมีความเสี่ยงที่จะเกิดภาวะ การกดเบียดเนื้อสมองข้างเคียงและการขยับเลื่อนที่ของเนื้อสมองไปกดก้านสมอง การผ่าตัดเปิดกะโหลกเพื่อลดความดันในกะโหลกศีรษะภายในระยะเวลา 48 ชั่วโมง สามารถลดอัตราการเสียชีวิตของผู้ป่วยที่มีภาวะสมองขาดเลือดขนาดใหญ่และมีการพัฒนาไปสู่ภาวะสมองบวมที่ไม่สามารถควบคุมได้อย่างมีนัยสำคัญ แต่ในแง่ของคุณภาพชีวิตเมื่อติดตามการรักษาหลังการผ่าตัดเปิดกะโหลกเพื่อลดความดันในกะโหลกศีรษะภายในระยะเวลา 48 ชั่วโมงและการฟื้นฟูสภาพทางระบบประสาทที่ดีเมื่อติดตามการรักษายังไม่มีหลักฐานทางการแพทย์ที่เป็นที่ประจักษ์และในปัจจุบันยังไม่มีการศึกษาใดที่ศึกษาถึงปัจจัย และค่าพารามิเตอร์ที่เหมาะสมที่มีผลต่อการฟื้นฟูสภาพทางระบบประสาทที่ดีหลังการผ่าตัด การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาหาค่าพารามิเตอร์ที่เหมาะสมและปัจจัยที่ส่งผลต่อผลลัพธ์ของการรักษาทางคลินิกที่ดีในผู้ป่วยโรคหลอดเลือดสมองที่มีภาวะสมองขาดเลือดเป็นบริเวณกว้างและได้รับการผ่าตัดเปิดกะโหลกเพื่อลดความดันในกะโหลกศีรษะภายในระยะเวลา 48 ชั่วโมง

รูปแบบการวิจัย non-randomized, prospective และ observational cohort study

วิธีการศึกษา เก็บข้อมูลในช่วงตั้งแต่เดือนธันวาคม 2559 จนถึงมิถุนายน 2564 ในผู้ป่วยโรคหลอดเลือดสมองที่มีภาวะสมองขาดเลือดขนาดใหญ่ ครอบคลุมบริเวณที่เลี้ยงด้วยเส้นเลือด middle cerebral, internal carotid artery หรือทั้งสองเส้น ใช้วิธีการทางสถิติ เพื่อหาค่าพารามิเตอร์ที่เหมาะสมและปัจจัยที่ส่งผลต่อผลลัพธ์ของการรักษาทางคลินิกที่ดีตาม modified Rankin Scale (mRS) ที่ 0 ถึง 3 ที่ระยะเวลาติดตามการรักษาที่ 3 และ 6 เดือน

ผลการศึกษา ในผู้ป่วย โรคหลอดเลือดสมอง ที่มีภาวะสมองขาดเลือดขนาดใหญ่ 243 ราย พบว่าปัจจัยที่ส่งผลต่อผลลัพธ์ของการรักษาทางคลินิกที่ดีอย่างมีนัยสำคัญทางสถิติ ได้แก่ อายุน้อยกว่าหรือเท่ากับ 71 ปี, ระยะเวลาตั้งแต่เริ่มมีอาการจนถึงได้รับการผ่าตัดไม่เกิน 9 ชั่วโมง, ปริมาตรของสมองที่ขาดเลือดไม่เกิน 155 ลูกบาศก์เซนติเมตร และ ASPECT score ที่มากกว่าหรือเท่ากับ 6

สรุป ในผู้ป่วย โรคหลอดเลือดสมอง ที่มีภาวะสมองขาดเลือดขนาดใหญ่ที่มีอายุน้อยกว่าหรือเท่ากับ 71 ปี, มีระยะเวลาตั้งแต่เริ่มมีอาการจนถึงได้รับการผ่าตัดไม่เกิน 9 ชั่วโมง, มีปริมาตรของสมองที่ขาดเลือดไม่เกิน 155 ลูกบาศก์เซนติเมตร และ ASPECT score ที่มากกว่าหรือเท่ากับ 6 มีผลลัพธ์ของการรักษาทางคลินิกที่ดีหลังผ่าตัดเปิดกะโหลกเพื่อลดความดันในกะโหลกศีรษะภายในระยะเวลา 48 ชั่วโมงสามารถนำไปใช้ประกอบการตัดสินใจในการพิจารณาให้การรักษาและอธิบายญาติผู้ป่วยได้

คำสำคัญ: ภาวะสมองบวมที่ไม่สามารถควบคุมได้, ภาวะสมองขาดเลือดขนาดใหญ่เฉียบพลัน, Modified Rankin Scale, ปัจจัยที่ทำนายผลลัพธ์ของการรักษาทางคลินิก (J Thai Stroke Soc. 2022;21(1):5-25)

Introduction

Acute large-territory cerebral infarction can progress to refractory brain swelling increase morbidity and death although decompressive craniectomy (DC) was performed. Refractory cerebral edema was associated with subfalcine herniation and increased the risk of death. Survival rates of malignant middle cerebral artery (MCA) infarction was quite fair after DC was done. Previously studies have showed high mortality rates, and most patients were post-operative disabled. However, conservative management for malignant MCA infarction almost ineffective then patients always proceed to DC. Recent pool data analysis[1] proved that DC reduced death or disability, defined as modified Rankin Score (mRS) ≤ 3. Compared to conservative therapy in addition DC significantly reduced mortality although it was potentially many cost and post-operative outcome was worse functional disability.[2] Acute malignant cerebral infarction involves more than two-thirds of MCA territory.[3] Early clinical deterioration or involvement of complete MCA territory terms were reported as malignant large cerebral infarction.[4] DC for malignant large cerebral infarction was performed for increase survival and life-saving procedure. Due to the fact that increased interest in DC as a result of studies showing mortality reduction, there might also be a chance for improve functional outcome.[5] However, more predicting factors affecting the outcome after DC have been postulated and it is also important to realize that most of the published data comes from western populations where long-term stroke rehabilitation facilities exist and more stroke units are well-established and continued development. Timing of surgery is another crucial factor for DC in malignant large cerebral infarction. there is a benefit associated with early DC. Early DC markedly reduced volume of infarcted brain tissue and mortality. We aimed to assess beneficial outcome in surgical intervention for prevent post-stroke malignant cerebral edema.

Materials and Methods

The objective of this study was to assess beneficial outcome in surgical intervention for prevent post-stroke malignant cerebral edema. We performed non-randomized, prospective, observational cohort study conducted between December 2016 and June 2021 at Phramongkutklao hospital, Thailand. The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants. All Participants with malignant large cerebral infarction indicated to undergo surgical intervention for prevent post-stroke refractory cerebral edema on the basis of National Institute of Health Stroke Scale [NIHSS], Glasgow coma scale [GCS]) and neuroimaging (computed tomography, CT) were prospectively enrolled. Patients who died within 24 hours of presentation, those with dilated and fixed pupils at presentation, GCS < 6, mRS ≥ 3 prior to the acute ischemic stroke and alteration of consciousness from extracranial causes were excluded to reduce the risk of bias.The diagnosis of stroke was established clinically and confirmed by neuroimaging (non-contrast CT (NCCT) head). Details of demographics including age, sex, address, contact number, body mass index[BMI (kg/m^2)], detailed history of event, presenting symptoms and signs, risk factors for stroke, blood pressure (BP), GCS and NIHSS score, laboratory parameters, imaging findings (type of stroke, arterial territory involved, ASPECT score, volume of infarction (cm^3) and midline shift), onset to DC (hr), intracranial pressure (ICP) at operative field and post-operative events such as surgical site infection and post-stroke hydrocephalus were noted. Western Aphasia Battery was used to record the severity of aphasia. Aphasia quotient (AQ) was calculated by kerrtesz formula; a score ≤ 93.8 was taken as cut off for defining aphasia. [6] DC in our patients consisted of creation of a large fronto-parieto-temporal free bone flap and duraplasty. No intervention on brain tissue was performed. Details of DC including time of onset of symptoms to DC, duration of surgery, blood loss, post-operative complications and intensive care unit (ICU) stay and status at discharge was noted. Functional outcome at the time of discharge was measured using Glasgow coma outcome scale (GCOS), NIHSS and mRS score. Aphasia testing using western aphasia battery was done on follow-up visits in the stroke clinic. By acute stroke trials in 2005 [7], mRS of ≤ 3 was taken as a good outcome. Statistical methods during out-patient department (OPD) visits in the stroke clinic at 3 and 6 months.

Participants

Acute ischemic stroke patients in medical stroke unit and surgical intensive care unit (ICU), Phramongkutklao hospital, Bangkok, Thailand from December 2016 to June 2021 were monitored invasive arterial blood pressure, peripheral O_2 saturation (SpO_2), and electrocardiogram (ECG). All patients were measured for Oxygenation, arterial blood pressure, glucose. The inclusion criteria were age more than 18-year-old, diagnosis malignant large cerebral infarction involved ≥ two-thirds of the middle cerebral artery (MCA) territory on cranial CT or magnetic resonance imaging (MRI) within 48 hours after symptoms onset (Meanwhile, the score of National Institutes of Health Stroke Scale (NIHSS) item 1a which reflected consciousness needed to be ≥1), DC was operated within 48 hours of onset and the exclusion criteria were large volume hemorrhagic transformation, malignant herniation, severe coagulopathy, severe infection, patients refusal to treatment, patients who died within 24 hours of presentation, those with dilated and fixed pupils at presentation, GCS < 6, mRS ≥ 3 prior to the current stroke and alteration of consciousness from extracranial causes were excluded to reduce the risk of bias.

Standard medical therapy

All patients were admitted to a stroke unit or intensive care unit in the department of neurology and neurosurgery. The patient's head was kept elevated by 30°. All patients were kept in a mild fluid restriction state with 1800 ml of daily fluid in the first week. Intravenous antihypertensive agents were administered when blood pressure was higher than 220/120 mmHg. Body temperature was kept below 38°C and blood glucose level was maintained at less than 180 mg/dl. Endotracheal intubation was performed to maintain adequate tissue oxygenation in patients with clinical deterioration or signs of respiratory insufficiency. Hyperventilation was used only in an emergency with the target level of $PaCO_2$ of 30–35 mmHg. Osmotherapy with Mannitol or glycerol launched when there was an evidence of mass effect. Mannitol was administered with the dosage of 0.25–0.5 g/kg body weight bolus. During osmotherapy, blood osmolarity was maintained at approximately 300–320 mOsm/l. Oxygenation, blood pressure, glucose were sustained at appropriate level. Early enteral nutrition was given. Pneumonia and deep venous thrombosis were monitored and well treated. For hemodynamic monitoring, Radial arterial catheter and central venous catheter was linked to a bedside monitor on one side and to a specific transducer (Philips Intellivue Philips MX600, USA) for blood pressure and central venous pressure (CVP) monitoring. If patients have unstable hemodynamics value of cardiac output (CO) and Stroke volume (SV) were estimated from pulse contour analysis (EV1000 clinical platform, Edwards advanced hemodynamic monitoring tools for an integrated Edwards Critical Care System, USA).

Surgical treatment

Surgical intervention for prevent post-stroke malignant cerebral edema was carried out within 48 hours of onset. It consisted of a craniectomy with dimensions of at least 12 cm in the anteroposterior and 10 cm in the superoinferior direction which was large enough to match the infarcted area. Additional temporal bone removal was performed so that the floor of the middle cerebral fossa can be fully explored and decompressed. The dura was opened and an augmented patch was inserted to further relief the high intracranial pressure. Those surgical survivors received a secondary operation of cranioplasty three months after surgical intervention.

Analyses of outcome predictors of surgical intervention for prevent post-stroke malignant cerebral edema and the impact of surgical intervention (early DC) on clinical beneficial outcome aspects

Various variables including demographic (age and gender), body mass index [BMI (kg/m^2)], detailed history of event, presenting symptoms and signs, risk factors for stroke, blood pressure, GCS and NIHSS score, laboratory parameters, imaging findings (type of stroke, arterial territory involved, ASPECT score, volume of infarction (cm^3) and midline shift), onset to DC (hr), intracranial pressure (ICP) at operative field and post-operative events such as surgical site infection and hydrocephalus were recorded and was evaluated as outcome predictors. Univariate analysis proceeded first to assess each factor. Those factors with statistically significant difference in the first stage were subsequently adopted for the multivariate analysis to identify the independent outcome predictors. The impact of early DC on outcome was further analyzed in good survival, poor survival, and mortality, respectively.

Outcome assessment

Outcome was assessed with mRS at 3 and 6 months follow-up. It was dichotomized into good outcome (mRS 0 to 3) and poor outcome (mRS 4 to 6) in order to compare and contrast survivors' functional outcome in early DC.

Statistical analysis

Results were expressed as mean ± SD if data were normally distributed or median and interquartile range (IQR) if not. A p-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS version 23.0. Primary outcome was cut off parameters associated beneficial outcome in surgical intervention for prevent post-stroke malignant cerebral edema and secondary outcome were clinical variables in relationship to functional outcome according to mRS, the sample size estimation showed 243 patients were required to evaluate ability.

Ethics approval and consent to participate

Institutional Review Board Royal Thai Army Medical Department Ethics Committee approved this study on December 8, 2016. Research no.R102h/59 followed Council for International Organization of Medical Science (CIOMS) Guidelines 2012 and Good Clinical Practice of International Conference on Harmonization statement no.IRBRTA1731/2559.

Results

Baseline characteristics

243 patients with malignant large cerebral infarction involved ≥ two-thirds of the middle cerebral artery (MCA) territory on cranial CT or magnetic resonance imaging (MRI) within 48 hours after symptoms onset included in our analysis. Most of the patients were male (80.7%) with average ages of 65 years. The most frequent coexisting disease was hypertension (HT) (88%). There were 153 (63%) patients with left-side territory ischemic stroke and 90 (37%) patients were right-side territory ischemic stroke. Among these patients, Mean range of NIHSS and GCS at admission were 21 and 9 (9.5 ± 3) respectively. Mean Onset to DC from time of onset of symptoms was 10 hour (10.41 ± 5.96). Mean ICP at operative field was 19 mmHg (19.32 ± 8.6). Mean volume of infarction was 135 cm^3(135.19 ± 51.1). Mean ASPECT score was 5 (5.77 ± 2.41). There were 6 (2.5%) patients with post-operative surgical site infection and 23 (9.5%) patients were post-operative hydrocephalus. (Table 1) and Outcome was assessed with GCOS, NIHSS, Modified Barthel Index at 3 and 6 months follow-up was showed in Table 3.

Table 1. *Demographic data of 243 patients with large-territory ischemic strokes undergoing early DC.*

Variables	N = 243
Male, n (%)	196 (80.7%)
Age (year)	64.82 ± 14.81
Body mass index, BMI (kg/m^2)	29.14 ± 6.2
Diabetes mellitus	186 (76.5%)
Hypertension	214 (88.1%)
Tobacco use	126 (51.9%)
Old cerebrovascular accident	87 (35.8%)
History of ipsilateral TIA	22 (9.1%)
Hypercholesteralemia	167 (68.7%)
History of angina pectoris	87 (35.8%)
Coronary artery disease	116 (47.7%)
Atrial fibrillation	116 (47.7%)
Peripheral arterial occlusive disease	48 (19.8%)
Position of large-territory infarction	
left	153 (63%)
Right	90 (37%)
bilateral	0 (0%)
Onset to DC (hour)	10.41 ± 5.96
GCS at admission	9.5 ± 3
NIHSS at admission	21.44 ± 9.64
ICP at operative field	19.32 ± 8.6
Volume of infarction(cm^3)	135.19 ± 51.1
ASPECT score	5.77 ± 2.41
Post-operative surgical site infection	6 (2.5%)
Post-operative hydrocephalus	23 (9.5%)

Value presented as mean ± SD

Table 3. *Outcome was assessed with GCOS, NIHSS, Modified Barthel Index at 3 and 6 months follow-up in early DC.*

Variables	**Baseline***	**3 Month**	**6 Month**
GCOS			
Death	7 (2.9%)	7 (2.9%)	7 (2.9%)
Persistent vegetative state#	90 (37%)	52 (21.4%)	52 (21.4%)
Severe disability	85 (35%)	54 (22.2%)	54 (22.2%)
Moderate disability	61 (25.1%)	110 (45.3%)	13 (5.3%)
Good recovery	0 (0%)	20 (8.2%)	130 (53.5%)
NIHSS	21.95 ± 8.89	19.51 ± 9.46	18.47 ± 9.58
Modified Barthel Index	29.56 ± 31.75	51.8 ± 33.96	66.4 ± 34.73
No symptoms	0 (0%)	0 (0%)	0 (0%)
No significant disability	0 (0%)	0 (0%)	0 (0%)
Slight disability	0 (0%)	60 (24.7%)	113 (46.5%)
Moderate disability	4 (1.6%)	68 (28%)	16 (6.6%)
Moderate to severe disability	85 (35%)	4 (1.6%)	1 (0.4%)
Severe disability	147 (60.5%)	104 (42.8%)	94 (38.7%)
Death	7 (2.9%)	7 (2.9%)	19 (7.8%)

Values presented as frequency (%) and mean ± SD.

Baseline* was post-operative 6 week

Persistent vegetative state# define as timing of after 6 week post-operative

Factors affected functional outcome

Functional outcome measured by dichotomized mRS at 0-3 was showed. Risk factors after univariate analysis were male, age, body mass index, BMI (kg/m2), diabetes mellitus (DM), hypertension, Tobacco use, history of cerebrovascular accident (CVA), angina pectoralis, hypercholesterolemia, coronary artery disease (CAD), atrial fibrillation (AF), peripheral arterial occlusive disease (PAD), Left side large-territory infarction, Onset to DC, GCS, NIHSS at admission, volume of infarction, ASPECT score and surgical site infection. (Table 2)

Table 2. Univariate analysis factor affected outcome

Variables	Modified Rankin Scale	
	r	***p-value***
Male	0.288	<0.001
Age (year)	0.608	<0.001
Body mass index, BMI (kg/m^2)	0.436	<0.001
Diabetes mellitus	0.432	<0.001
Hypertension	0.266	<0.001
Tobacco use	0.757	<0.001
Old cerebrovascular accident	0.633	<0.001
History of ipsilateral TIA	0.259	<0.001
Hypercholesteralemia	0.395	<0.001
History of angina pectoris	0.218	<0.001
Coronary artery disease	0.405	<0.001
Atrial fibrillation	0.430	<0.001
Peripheral arterial occlusive disease	0.518	<0.001
Left side large-territory infarction	-0.464	<0.001
Onset to DC (hour)	0.413	<0.001
GCS at admission	-0.740	<0.001
NIHSS at admission	0.842	<0.001
Volume of infarction(cm^3)	0.613	<0.001
ASPECT score	0.783	<0.001
Post-operative surgical site infection	0.225	<0.001
GCOS Scale Baseline (post-operative 6 week)	-0.757	<0.001
GCOS Scale 3 Month	-0.724	<0.001
GCOS Scale 6 Month	-0.797	<0.001
NIHSS baseline (post-operative 6 week)	0.838	<0.001
NIHSS 3 month	0.864	<0.001
NIHSS 6 month	0.877	<0.001
Post-operative Hydrocephalus	-0.003	0.960

Value presented as mean ± SD. or n (%). *p-value* corresponds to Independent-t test andFisher's exact test

Clinical outcomes data in post-operative hydrocephalus

In patients with malignant large cerebral infarction involved ≥ two-thirds of the middle cerebral artery (MCA) territory undergo DC with post-operative hydrocephalus, we found that correlation between post-operative hydrocephalus and clinical outcome (mRS 0 to 3) at 6 months follow-up showed no significant differences were observed between good and poor outcome. It was concluded that post-operative hydrocephalus was not affected clinical outcome (Table 4). Risk factors after multivariate analysis were onset to DC, tobacco use, NIHSS at admission, PAD, DM, BMI, CAD, Age ≥ 70 yr and Left side large-territory infarction (Table 5).

Table 4. *orrelation between post-operative hydrocephalus and clinical outcome (mRS 0 to 3) at 6 months follow-up in early DC*

	Good outcome (n=130)	**Bad outcome (n=113)**	*p-value*
Hydrocephalus	17 (13.1%)	11 (9.7%)	0.831
No Hydrocephalus	113 (86.9%)	102 (90.3%)	

Values presented as frequency (%). p-value corresponds to Pearson chi-square test.

Table 5. *Multivariate analysis factor affected outcome (mRS 0 to 3)*

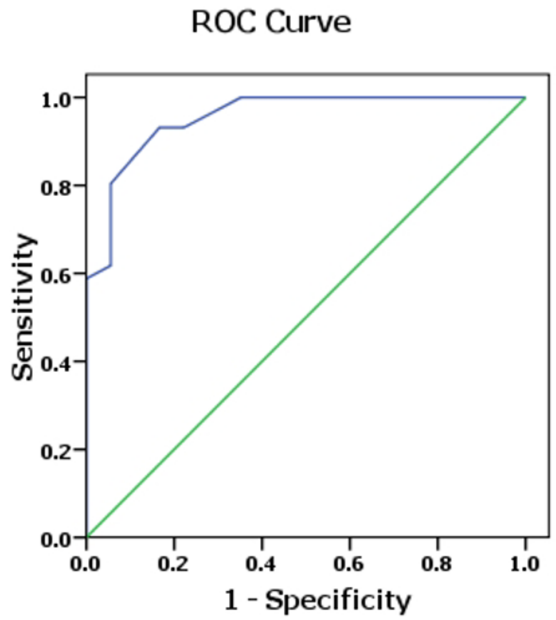
	Beta coefficient	**Std. Error**	***p-value***
(Constant)	4.26	0.52	<0.001
Onset to DC (hour)	-0.05	0.02	0.001
Tobacco use	1.49	0.23	<0.001
NIHSS at admission	0.09	0.01	<0.001
Peripheral arterial occlusive disease	0.95	0.22	<0.001
Diabetes mellitus	0.55	0.19	0.003
Body mass index, BMI (kg/m^2)	-0.11	0.02	<0.001
Coronary Artery disease	-0.35	0.17	0.041
Age ≥ 70 year	0.62	0.32	0.049
Left side large-territory infarction	-0.31	0.19	0.108

Value presented as mean ± SD. or n (%). p-value corresponds to Independent-t test and Fisher's exact test. Multivariate analyses were performed for an array of clinical variables in relationship to functional outcome at 6 months follow-up. Linear regression were performed for an array of clinical variables in relationship to functional outcome.

Outcome predictors of surgical intervention for prevent post-stroke malignant cerebral edema and the impact of surgical intervention (early DC) on clinical beneficial outcome aspects defined as cut off parameters for good clinical outcome in early DC (mRS 0 to 3)

1. Age, study showed that age ≤ 71 year was significantly associated with good clinical outcome in early DC (mRS 0 to 3) AUC =0.955, p-value <0.001 accuracy 89.7%. (Figure 1, Table 6)

***Figure 1**. Age cut off value for good clinical outcome in early DC (mRS 0 to 3)*



ROC Area = 0.955, p-value <0.001

***Table 6**. Age cut off value for good clinical outcome in early DC (mRS 0 to 3)*

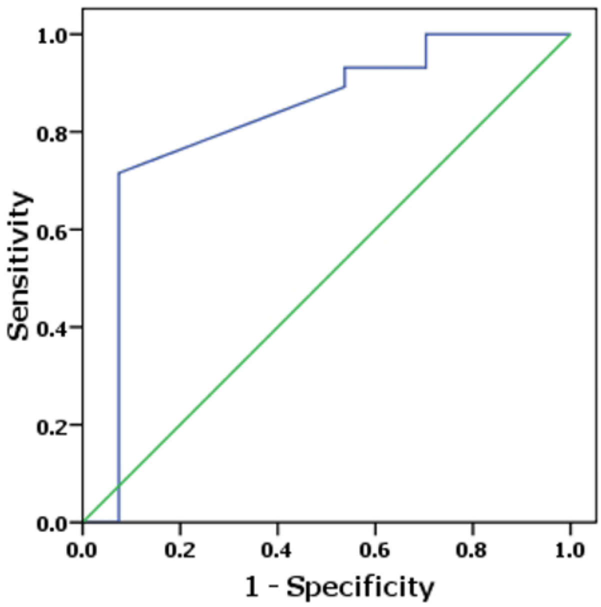
Age cut off	a	b	c	d	Sensitivity	Specificity	PPV	NPV	Accuracy
-84.50	102	48	0	6	100.0%	11.1%	68.0%	100.0%	69.2%
-80.00	102	38	0	16	100.0%	29.6%	72.9%	100.0%	75.6%
-77.50	102	26	0	28	100.0%	51.9%	79.7%	100.0%	83.3%
-76.00	102	19	0	35	100.0%	64.8%	84.3%	100.0%	87.8%
-74.00	99	16	3	38	97.1%	70.4%	86.1%	92.7%	87.8%
-72.50	95	12	7	42	93.1%	77.8%	88.8%	85.7%	87.8%
-71.50	95	9	7	45	93.1%	83.3%	91.3%	86.5%	89.7%
-70.00	82	3	20	51	80.4%	94.4%	96.5%	71.8%	85.3%
-68.50	78	3	24	51	76.5%	94.4%	96.3%	68.0%	82.7%
-65.00	69	3	33	51	67.6%	94.4%	95.8%	60.7%	76.9%
-61.50	63	3	39	51	61.8%	94.4%	95.5%	56.7%	73.1%
-60.50	60	0	42	54	58.8%	100.0%	100.0%	56.3%	73.1%
-59.00	57	0	45	54	55.9%	100.0%	100.0%	54.5%	71.2%

Age cut off	a	b	c	d	Sensitivity	Specificity	PPV	NPV	Accuracy
-56.00	53	0	49	54	52.0%	100.0%	100.0%	52.4%	68.6%
-53.00	45	0	57	54	44.1%	100.0%	100.0%	48.6%	63.5%
-51.00	39	0	63	54	38.2%	100.0%	100.0%	46.2%	59.6%
-47.50	29	0	73	54	28.4%	100.0%	100.0%	42.5%	53.2%
-43.50	25	0	77	54	24.5%	100.0%	100.0%	41.2%	50.6%
-41.00	19	0	83	54	18.6%	100.0%	100.0%	39.4%	46.8%
-37.50	12	0	90	54	11.8%	100.0%	100.0%	37.5%	42.3%
-33.50	4	0	98	54	3.9%	100.0%	100.0%	35.5%	37.2%
-31.00	0	0	102	54	0.0%	100.0%	#DIV/0!	34.6%	34.6%

ROC Area = 0.955, p-value <0.001

2. Onset to DC, study showed that onset to DC ≤ 9 hours was significantly associated with good clinical outcome in early DC (mRS 0 to 3) AUC =0.824, p-value <0.001 accuracy 78.8%. (Figure 2, Table 7)

***Figure** 2. Onset to DC (hour) cut off value for good clinical outcome in early DC (mRS 0 to 3) (set accuracy more than 70%))*



ROC Area = 0.824, p-value <0.001

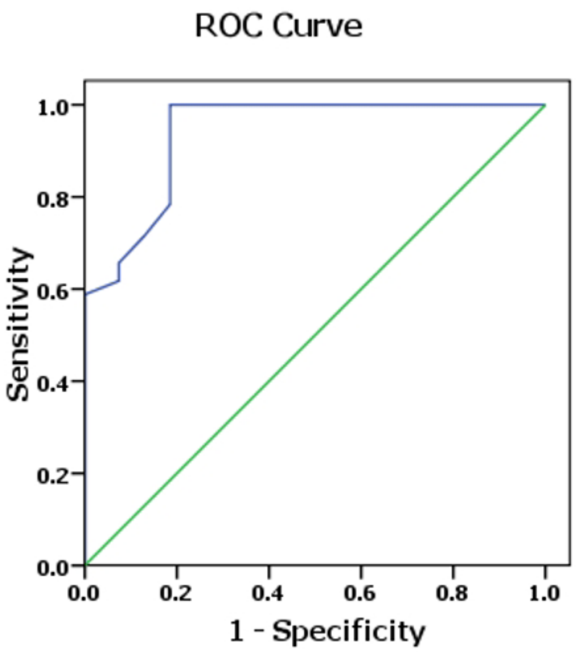
Table *7. Onset to DC (hour) cut off value for good clinical outcome in early DC (mRS 0 to 3) (set accuracy more than 70%)*

Duration cut off	a	b	c	d	Sensitivity	Specificity	PPV	NPV	Accuracy
-22.00	102	38	0	16	100.0%	29.6%	72.9%	100.0%	75.6%
-18.00	99	38	3	16	97.1%	29.6%	72.3%	84.2%	73.7%
-14.50	95	38	7	16	93.1%	29.6%	71.4%	69.6%	71.2%
-12.50	95	35	7	19	93.1%	35.2%	73.1%	73.1%	73.1%
-11.50	95	29	7	25	93.1%	46.3%	76.6%	78.1%	76.9%
-10.50	91	29	11	25	89.2%	46.3%	75.8%	69.4%	74.4%
-9.00	73	4	29	50	71.6%	92.6%	94.8%	63.3%	78.8%
-7.50	63	4	39	50	61.8%	92.6%	94.0%	56.2%	72.4%

ROC Area = 0.824, p-value <0.001

3. Volume of infarction, study showed that volume of infarction ≤ 155 cm^3 was significantly associated with good clinical outcome in early DC (mRS 0 to 3) AUC =0.939, p-value <0.001 accuracy 93.6%. (Figure 3, Table 8)

Figure *3. Volume of infarction (cm^3) cut off value for good clinical outcome in early DC (mRS 0 to 3)*



ROC Area = 0.939, p-value <0.001

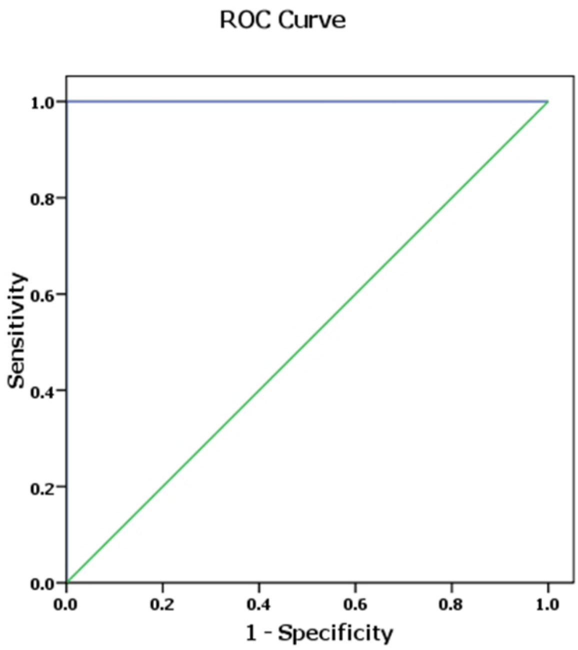
Table 8. Volume of infarction (cm^3) cut off value for good clinical outcome in early DC (mRS 0 to 3)

volume of infarction cut off	a	b	c	d	Sensitivity	Specificity	PPV	NPV	Accuracy
−215.00	102	48	0	6	100.0%	11.1%	68.0%	100.0%	69.2%
−205.00	102	45	0	9	100.0%	16.7%	69.4%	100.0%	71.2%
−195.00	102	23	0	31	100.0%	57.4%	81.6%	100.0%	85.3%
−185.00	102	20	0	34	100.0%	63.0%	83.6%	100.0%	87.2%
−170.00	102	14	0	40	100.0%	74.1%	87.9%	100.0%	91.0%
−155.00	102	10	0	44	100.0%	81.5%	91.1%	100.0%	93.6%
−145.00	86	10	16	44	84.3%	81.5%	89.6%	73.3%	83.3%
−130.00	80	10	22	44	78.4%	81.5%	88.9%	66.7%	79.5%
−115.00	73	7	29	47	71.6%	87.0%	91.3%	61.8%	76.9%
−109.50	67	4	35	50	65.7%	92.6%	94.4%	58.8%	75.0%
−104.50	63	4	39	50	61.8%	92.6%	94.0%	56.2%	72.4%
−93.00	60	0	42	54	58.8%	100.0%	100.0%	56.3%	73.1%
−85.50	54	0	48	54	52.9%	100.0%	100.0%	52.9%	69.2%
−83.50	50	0	52	54	49.0%	100.0%	100.0%	50.9%	66.7%
−81.00	46	0	56	54	45.1%	100.0%	100.0%	49.1%	64.1%
−77.50	13	0	89	54	12.7%	100.0%	100.0%	37.8%	42.9%
−72.50	10	0	92	54	9.8%	100.0%	100.0%	37.0%	41.0%

ROC Area = 0.939, p-value <0.001

4. ASPECT score, study showed that ASPECT score ≥ 6 was significantly associated with good clinical outcome in early DC (mRS 0 to 3) AUC = 1, p-value <0.001 accuracy 100%. (Figure 4, Table 9)

Figure 4. *ASPECT score cut off value for good clinical outcome in early DC (mRS 0 to 3)*



ROC Area = 1, p-value <0.001

Table 9. *ASPECT score cut off value for good clinical outcome in early DC (mRS 0 to 3)*

ASPECT score cut off	a	b	c	d	Sensitivity	Specificity	PPV	NPV	Accuracy
-10.00	102	54	0	0	100.0%	0.0%	65.4%	0.0%	65.4%
-8.50	102	23	0	31	100.0%	57.4%	81.6%	100.0%	85.3%
-7.50	102	11	0	43	100.0%	79.6%	90.3%	100.0%	92.9%
-6.00	102	0	0	54	100.0%	100.0%	100.0%	100.0%	100.0%
-4.50	69	0	33	54	67.6%	100.0%	100.0%	62.1%	78.8%
-3.50	47	0	55	54	46.1%	100.0%	100.0%	49.5%	64.7%
-2.00	0	0	102	54	0.0%	100.0%	#DIV/0!	34.6%	34.6%

ROC Area = 1, p-value <0.001

Discussion

Surgical intervention for prevent post-stroke malignant cerebral edema and the impact of surgical intervention (early DC) on clinical beneficial outcome aspects carried on challenging in management of large-territory acute ischemic strokes patients that DC can decrease the mass effect from infarcted brain tissue, preventing brain herniation and death. Risk factors after multivariate analysis were onset to DC, tobacco use, NIHSS at admission, PAD, DM, BMI, CAD, age ≥ 70 yr and left side large-territory infarction. Post-operative hydrocephalus was not affected clinical outcome. Age ≤ 71 year, onset to DC ≤ 9 hours, volume of infarction ≤ 155 cm^3 and ASPECT score ≥ 6 was significantly associated with good clinical outcome in early DC (mRS 0 to 3). Three randomized controlled trials[8-10] have compared decompressive surgery plus medical treatment (DC group) versus medical treatment alone in patients with large-territory ischemic strokes. In stroke guideline 2005[7], inclusion of less severe stroke than previous studies had result in better functional outcome. A recent Cochrane review was concluded that less than equal to 60 years of age suggested that DC reduced the risk of death at the end of follow-up and the risk of poor functional outcome defined as mRS ≥ 4 at 12 months. When apply poor functional outcome as mRS > 3 at the end of follow-up was no different between two groups. Although all the trials were early terminated and potential overestimation of the sample size was showed. In 13 studies of 138 patients, ages more than 50 years old was a great predictor of poor functional outcome after DC. About timing of the operation, side of the infarct and involvement of other vascular territories showed no affected the outcome.[11] Recent studies showed 8% patients older than 60 years old had a favorable outcome after DC, as compared with 54% of younger patients.[12]

In our study, age ≤ 71 year was identified as a predictor of outcome of DC. No studied in malignant MCA infarction about the impact of age on outcome prediction. Recent studied showed poor functional outcome and increased mortality in older patients in DC group.[13-16] In addition, recovery function after strokes generally decreased significantly after the age of 60 years old.[17] Foerch et al. found that age was the factor that effect in predicting functional outcome.[18] Walz et al. proposed the same conclusion that outcome prediction depend on age.[15] Uhl et al. studied in DC patients found that age older than 50 years old patients showed higher mortality and poorer outcome.[19] So age was the most important pretreatment predicting prognostic factor. Our study confirmed that age is a crucial factor for mortality and functional outcome in DC patients and may be the most important factor in deciding which patients should performed DC.

Timing from onset to surgery is important factor for DC in malignant MCA infarction. Recent clinical studies showed benefit in early DC that decreased mortality and volume of infarcted cerebral tissue.[20] Schwab et al. found that DC within 24 hours of onset showed a lower mortality and a mean Modified Barthel Index (BI) score of 68.8. In their series, 84% of patients had a BI ≥ 60. Similar the same results were showed in previous study.[21] DC within 6 hours of ictus was associated with a 8.3% mortality and a mean Modified BI score of 70.0, compared with a 36.7% mortality rate and a mean BI score of 52.8 in patients that DC was performed within 6 hours of ictus. In previous and our study showed onset to DC ≤ 9 hours was significantly associated with good clinical outcome in early DC. We suggested ultra-early DC associated with better benefit in functional outcome.

Although many studies found that clinical signs of herniation are not associated with functional outcome in malignant MCA infarction patients who performed DC. Unequal pupil indicating uncal herniation with progression to ischemia of mesencephalon, brain-stem dysfunction and worse prognosis. Early treatment before the clinical signs of herniation showed better outcome. In our study, poor functional outcome was associated with the presence of clinical signs of herniation before treatment. So we excluded patients who have signs of herniation from study and we suggest that DC was carried out within 6 hours of ictus to prevent herniation syndromes in malignant large cerebral infarction involved ≥ two-thirds of the middle cerebral artery (MCA) territory and hemispheric infarction of the dominant hemisphere was more important to get a better outcome. Theoretically, if there is strong clinical studies to support the high risk of subsequent clinical deterioration, early DC before clinical worsening would be the ideal surgical timing. Some clinical studies had shown several factors in the early prediction of malignant MCA infarction, such as lesion volume more than 145 cm^3 in diffusion weighted imaging study was the outcome predictors of malignant large infarction and the functional outcome of survivals following DC [22] In this study, we found that volume of infarction ≤ 155 cm^3 was significantly associated with good clinical outcome in early DC. For ASPECT score showed that ASPECT score ≥ 6 was significantly associated with good clinical outcome in early DC.

Limitations

This study has some limitations. First, the benefit of surgery in motor and aphasia recovery is progressive and sustained until 1 year. Results of the present study suggests that 3 months or 6 months outcome assessment may be insufficient to know the real benefit of surgical intervention thus 1 year follow-up should be recommended for measuring its functional benefit. Second, our study was conducted in single center. Finally, many exclusion criteria were applied in this study.

Conclusions

Surgical intervention for prevent post-stroke malignant cerebral edema, age ≤ 71 years, onset to DC ≤ 9 hours, volume of infarction ≤ 155 cm^3 and ASPECT score ≥ 6 associated with clinical beneficial outcome.

New explicit knowledge

There was a first study for good predictor outcome after perform early DC in Thai population. As the previous studies for early DC and factor associated with function outcome was mostly from western population and no study performed appropriate cut off value to determine which patients with large-territory ischemic strokes can gain benefit for early DC as the fact that DC can decrease the mass effect resulting from infarcted brain tissue, preventing brain herniation and death. Challenging in management of patients with large-territory ischemic strokes due to the results that age ≤ 71 years significantly associated with good clinical outcome in early DC so age was the most important pre-treatment prognostic factor and crucial factor for mortality and functional outcome in patients undergoing early DC. Age was the most important factor in deciding which patients should undergo early DC.

Onset to DC ≤ 9 hours significantly associated with good clinical outcome in early DC, suggested that ultra-early DC showed good benefit in functional outcome and was crucial factor for early DC. Volume of infarction ≤ 155 cm^3 significantly associated with good clinical outcome in early DC, high lesion volume was very high risk of subsequent clinical deterioration, early surgery before clinical worsening would be the ideal surgical timing, lesion volume was promising parameters in the early prediction of malignant infarction, and ASPECT score ≥ 6 significantly associated with good clinical outcome in early DC, explained that involvement of more than one vascular territory (internal carotid artery infarction) and hemispheric infarction of the dominant hemisphere had poor function outcome

LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AQ	Aphasia quotient
ASPECT	Alberta stroke program early CT score
AUC	Area under the curve
BI	Barthel Index
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CO	Cardiac output
CT	Computer Tomography
CVA	Cerebrovascular accident
CVP	Central venous pressure
DC	Decompressive craniectomy
DM	Diabetes mellitus
DWI	Diffusion weighted imaging
ECG	Electrocardiogram
GCOS	Glasgow Coma Outcome Scale
GCS	Glasgow Coma Scale
HT	Hypertension
ICA	Internal carotid artery
ICP	Intracranial pressure
ICU	Intensive care unit
IV	Intravenous
IQR	Interquartile Range
kg	Kilogram
MCA	Middle cerebral artery
MLI	Malignant large infarction

MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OPD	Out patients department
$PaCO_2$	Partial pressure of carbondioxide
PAD	Peripheral arterial occlusive disease
SD	Standard deviation
SV	stroke volume
SpO_2	Peripheral O_2 saturation

Declarations

Ethics approval and consent to participate:

Institutional Review Board Royal Thai Army Medical Department Ethics Committee approved this study on December 8, 2016. Research no.R102h/59 followed Council for International Organization of Medical Science (CIOMS) Guidelines 2012 and Good Clinical Practice of International Conference on Harmonization statement no.IRBRTA 1731/2559.

Consent for publication: not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interests:

No potential conflict of interest relevant to this article was reported.

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Authors' contributions:

Study concept and design: P. Boontoterm, Phontien, Sakoolnamarka, Udommongkol. Acquisition of data: P. Boontoterm, Udommongkol, Feungfoo. Analysis and interpretation of data: P. Boontoterm, Sakoolnamarka ,D. Panpanich. Drafting of the manuscript: P. Boontoterm, Phontien, Sakoolnamarka, Udommongkol. Critical revision of the manuscript for important intellectual content: P. Boontoterm, Sakoolnamarka, Udommongkol, Feungfoo. Statistical analysis: P. Boontoterm, Sakoolnamarka, D. Panpanich. Administrative, technical, or material support: P. Boontoterm, Sakoolnamarka, Udommongkol. Supervision:S. Sakoolnamarka, Phontien, Udommongkol.

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