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Outcome analysis of intraventricular thrombolytic therapy for intraventricular haemorrhage

對腦室內出血施行溶解血栓療法的結果分析

Objectives. To evaluate the outcome of intraventricular thrombolytic therapy for intraventricular haemorrhage and to formulate a safe and effective regimen.
Design. Retrospective study.
Setting. Regional neurosurgical centre, Hong Kong.
Patients. Twenty-nine consecutive adult patients who presented from November 1995 to November 1998 with non-traumatic intraventricular haemorrhage (Graeb score, ≥7) with no active rebleeding risks from vascular abnormalities.
Interventions. Fourteen consecutive patients received intraventricular streptokinase via the external ventricular drainage, and 15 consecutive patients received intraventricular urokinase treatment.
Main outcome measures. Patient demographics, Glasgow coma scale score, Graeb score, mortality rate, shunt rate, fever response, infection rate, catheter blockage rate, and local and systemic bleeding tendency.
Result. The mean age of the 16 men and 13 women was 59 years (range, 14-76 years). The median Graeb score for cases of intraventricular haemorrhage was 10 (range, 7-12). There was no significant difference in terms of the Graeb score distribution, total dosage, and duration of treatment between the streptokinase and urokinase groups. More cases of fever were observed in the streptokinase group, which could be due to its antigenicity. The infection rate of the central nervous system was 3%, and the shunt rate was 24%. The overall 1-month postoperative mortality was 10%, which was related to a low preoperative Glasgow coma scale score (≤4). No local rebleeding, systemic coagulopathy, or catheter blockage occurred.
Conclusions. Intraventricular thrombolytic therapy is a safe and effective method of managing intraventricular haemorrhage. We suggest instilling 20 000 units urokinase intra-operatively, followed by 20 000 units daily for about 3 days, except in cases of vascular abnormality, bleeding tendency, and trauma.

目的：評估腦室內溶解血栓治療腦室內出血的成效，以制定安全有效的治療方案。
設計：回顧研究。
安排：香港的分區神經外科中心。
患者：在 1995 年 11 月至 1998 年 11 月期間，連續 29 位出現非創傷性腦室內出血(Graeb score ≥7)的成年病者，這些病者沒有由於血管異常而引致再次大量出血的危險。
療法：以體外腦室引流對14位患者施用鏈激酶，另15位接受腦室內尿激酶治療。
主要結果測量：患者的人口學數據、格拉斯哥分值、 Graeb 分值、死亡率、分流率、發熱反應、感染率、導管阻塞率、原位或系統性出血的比率。
結果：16位男患者和13位女患者的平均年齡為59歲(分佈域：14至76歲)。腦室內出血病例的Graeb分值中位數為10(分佈域：7至12歲)。分別接受鏈激酶或尿激酶治療的兩組患者，在 Graeb 分值的分佈、藥物總用量、治療期長短上沒有明顯差別。施用鏈激酶一組出現發熱的患者人數較多，這可能是抗原能力所致的。中央神經系統的感染率為 3% ，分流率為 24% 。術後一個月整體死亡率為 10% ，這和術前偏低的格拉斯哥分值(≥4)有關。患者並無出現原位再出血、系統性的凝血病症或導管阻塞。
結論：腦室內溶解血栓療法是治理腦室內出血一個安全有效的療法。我們建議手術期間滴注 20 000 單位的尿激酶，之後每天 20 000 單位，用藥大約三天；但對於血管異常、出血機會大、或受創傷的患者則不適宜。

Key words:
Cerebral ventricles;
Drainage;
Intracranial hemorrhages;
Thrombolytic therapy;
Tomography, X-ray computed

關鍵詞：
腦室；
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Introduction

Intraventricular haemorrhage (IVH) is a strong independent indicator of poor functional outcome and mortality.[1] In addition to the initial insult to the brain, various mechanisms contribute to brain damage. For example, an intraventricular blood clot may hinder effective circulation of the cerebrospinal fluid (CSF), leading to obstructive hydrocephalus and raised intracranial pressure. The blood clot may distend the ventricle walls, thereby damaging the periventricular neural and vascular structures. Breakdown products of the blood clot may also cause adhesive arachnoiditis, or blockage of arachnoid granulations, thereby leading to delayed communicating hydrocephalus.[2,3]

Several experimental and clinical studies have shown that intraventricular thrombolytic therapy (ITT) may hasten the resolution of IVH.[4-9] This treatment can shorten the duration of external ventricular drainage needed, thereby leading to a decreased infection rate,[10,11] a decreased rate of catheter blockage, and a reduced incidence of delayed hydrocephalus and reduced requirement for permanent shunting procedure. Consequently, the overall outcome is improved and hospital stay shortened. Intraventricular lysis is an effective and safe procedure, but there is wide variation in the literature regarding the length and dosage of the ITT. In this study, we evaluate the outcome of ITT for IVH and formulate a safe and effective regimen.

Methods

Since 1995, we have been giving intraventricular thrombolytic agents—streptokinase or urokinase—and using external ventricular drainage in the Department of Neurosurgery, Pamela Youde Nethersole Eastern Hospital, for IVH. Recombinant tissue plasminogen activator has not been used because it was relatively expensive.

Table 1. System for grading severity of intraventricular haemorrhage

Score*	Characteristic
Lateral ventricles†	
1	Trace of blood or mild bleeding
2	Less than half of the ventricle filled with blood
3	More than half of the ventricle filled with blood
4	Ventricle filled with blood and expanded
Third and fourth ventricles	
1	Blood present, ventricle size normal
2	Ventricle filled with blood and expanded

* Maximum total score is 12
† Each lateral ventricle is scored separately

Between November 1995 and November 1998, 29 consecutive patients were operated on in our department after computed tomography findings showed IVH; treatment consisted of urgent external ventricular drainage and ITT. Surgery was indicated if IVH was massive and involved the third and fourth ventricles (Graeb score[12] ≥7, on a scale of 1-12) [Table 1, Fig 1]. Patients with a poor premorbid state were treated conservatively, and thrombolytic agents were not given to patients with suspected bleeding cerebral aneurysm or injury due to trauma.

We instilled 20 000 units urokinase in 2 mL warm Hartman's solution to the external ventricular drainage system, followed by 2 mL warm Hartman's solution, all under aseptic conditions. The drainage system was then kept clamped for 1 hour before free drainage at ear level. Because a large intraventricular infusion volume (>10 mL) is associated with headache and profuse sweating,[7] ITT was stopped and the drainage system removed when the third and fourth ventricles were cleared of blood and the Graeb score for the IVH was 1 or less (Fig 2).

We reviewed all the medical records and computed tomography films. We particularly searched for potential complications, such as infection, local rebleeding,

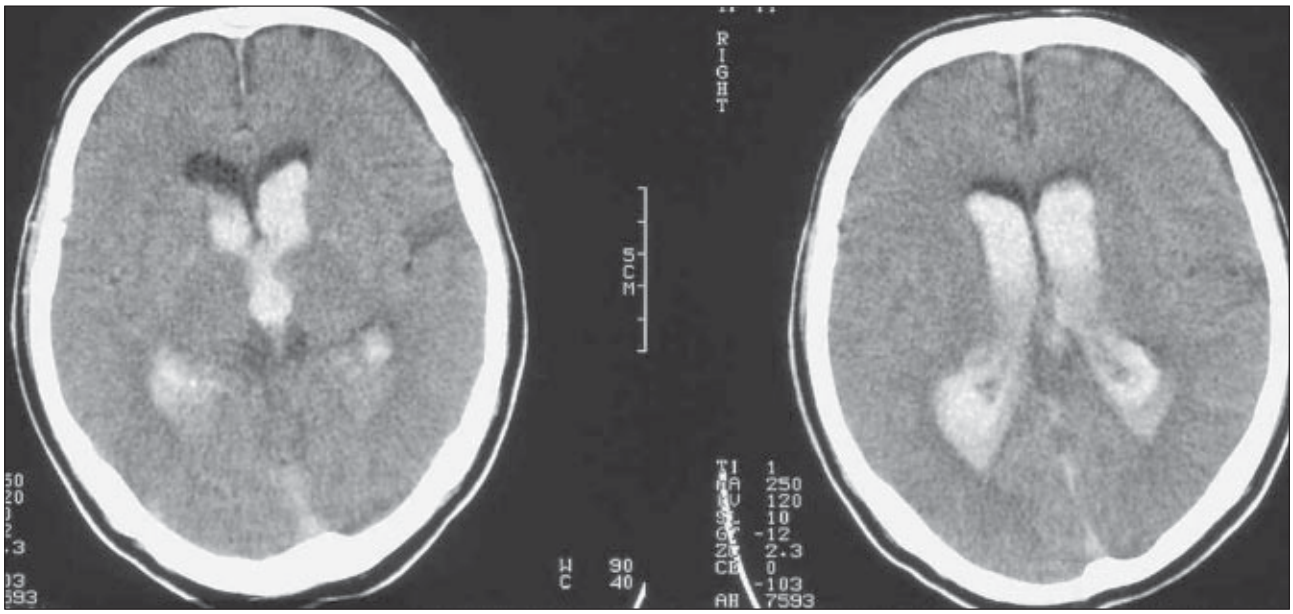

Fig 1. Computed tomography scans showing massive intraventricular haemorrhage at the third and fourth ventricles

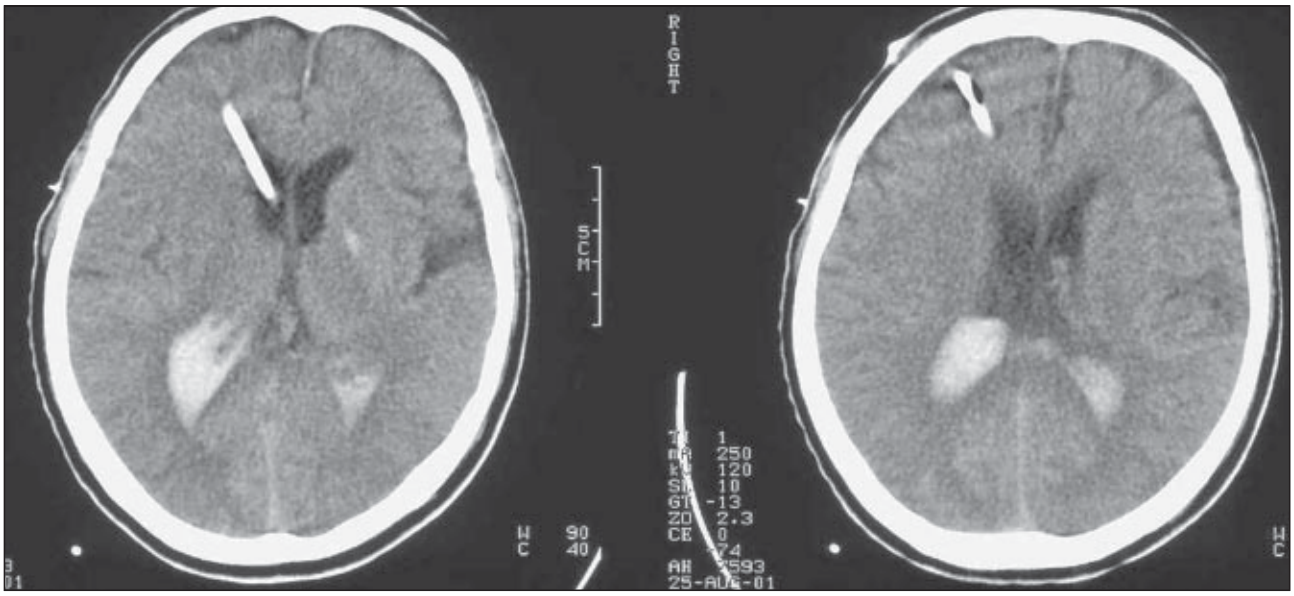

Fig 2. Computed tomography scans showing the third and fourth ventricles are cleared of blood

generalised bleeding tendency, catheter obstruction, headache, sweating, transient confusion, allergic reactions, and fever. For all patients, the systemic clotting profile was monitored and the CSF in the drainage system was routinely sent for Gram stain analysis, culture, and biochemical tests; the ventricular catheter tip was sent for culture.

Results

Among the 29 patients, 14 consecutive patients received intraventricular streptokinase, and 15 consecutive patients received intraventricular urokinase (Table 2). The ages of the 16 men and 13 women ranged from 14 to 76 years (mean, 59 years). The Graeb scores for the IVH ranged from 7 to 12 (median, 10), with no significant difference between the two treatment groups (P=0.88, two-tailed Mann-Whitney *U* test). The causes for the IVH were parenchymal putaminal and thalamic haemorrhage (52%), primary vascular abnormalities (28%), including arteriovenous malformation (AVM) and Moyamoya disease (17%), as well as generalised bleeding tendency such as thrombocytopenia (3%).

Only one patient (patient 28) had a positive result from culture testing (3%): the ventricular catheter tip grew methicillin-resistant *Staphylococcus epidermidis*. The patient had diabetes mellitus and suboptimal control of serum glucose level. She was treated with a course of intravenous vancomycin and had no long-term sequelae. Another patient (patient 3) had unexplained transient low glucose content in the CSF but had negative cultures in the CSF and the drainage system.

One patient (patient 27) had transient coagulopathy after surgery, with coffee-ground vomiting, oozing over wounds, and gross haematuria, even before intraventricular instillation of urokinase. He had a history of alcoholic liver disease with preoperative thrombocytopenia (platelet count, 103 x 10^9 /L [reference range, 150-450 x 10^9 /L]) and abnormal clotting (international normalised ratio, 1.3). He was treated conservatively with one episode of fresh frozen plasma transfusion and had a smooth recovery. Intraventricular urokinase was given under close monitoring once the clotting was normalised; therapy lasted for 8 days in total. For all other patients, their clotting profiles remained normal after ITT. No local rebleeding, catheter obstruction, headache, sweating, or transient confusion was noted in any patients.

All 14 patients had a high swinging fever (>38.5°C) after streptokinase treatment, irrespective of whether they had foci of infections. In contrast, seven of the 15 patients who received urokinase treatment remained afebrile.

For the streptokinase group, the total dosage ranged from 25 000 to 275 000 units (mean, 91 214 units). The duration ranged from the intra-operative time to 11 postoperative days (mean, 3.8 days). For the urokinase group, the total dosage ranged from 40 000 to 300 000 units (mean, 103 666 units). The duration ranged from the intraoperative time to 13 postoperative days (mean, 4.5 days).

The operative mortality of external ventricular drainage for ITT was approximately 10% within 1 month postoperatively. All three patients who died had preoperative Glasgow coma scale score of 4 or lower, with fixed and dilated pupils. Sixty-six percent (19/29) of patients had good outcome, with preoperative Glasgow coma scale scores of 5 to 15 (median, 9); they all regained full consciousness postoperatively. The overall shunt rate was 24% (7/29) and the duration between the shunting procedure and external ventricular drainage ranged from 1 week to 1 month.

Discussion

Among the patients who had ventriculostomy for ITT in this series, the central nervous system (CNS) infection rate

was approximately 3%. This rate was about three times that among patients with ventriculostomy alone.[13] This difference was compatible with the finding of prospective studies that IVH per se is related to a higher infection rate.[14,15] Whether this association is due to increased handling of the external ventricular drainage system is still debatable. Incidences of CNS infection during ventriculostomy alone can range from 0% to 40%,[14-19] but are most commonly 10% to 17%. Because no catheter obstruction was encountered among the patients in our series, ITT may be preferable to ventriculostomy alone in the management of IVH.

The documented mortality among patients receiving ITT is 32% compared with 67% among the control group,[20] and the mortality among those with ventriculostomy alone ranges from 36% to 83%.[21] Our 10% 1-month operative mortality was thus considerably lower. This finding may be accounted by our lower CNS infection rates and better patient selection. Patients

Table 2. Patient characteristics

Patient No.	Sex/Age (years)	Past health	Graeb score*	Cause of IVH†	Cerebral angiography	Total dose (mega units)
1	M/74	Hypertension	3,3,2,2(10)	Right caudate ICH‡	No	SK¶ 25
2	M/62	Hypertension, chronic obstructive airway disease	1,4,2,2(9)	Primary§	No	SK 85
3	M/48	-	4,2,1,2(9)	Moyamoya disease	Yes	SK 60
4	M/42	Intravenous drug use	4,4,2,2(12)	Thrombocytopenia	No	SK 25
5	F/48	-	4,4,2,2(12)	Left thalamic ICH	Yes	SK 60
6	M/67	Hypertension	2,4,2,2(10)	Left capsular ICH	No	SK 85
7	F/64	-	3,3,1,1(8)	Primary	Yes	SK 25
8	F/69	Hypertension, ischaemic heart disease	4,3,2,2(11)	Right thalamic ICH	No	SK 275
9	F/36	-	3,3,1,1(8)	Right cerebellar AVM‖	Yes	SK 25
10	M/69	Diabetes mellitus	3,4,2,2(11)	Left parietal ICH	No	SK 50
11	M/68	-	3,4,2,2(11)	Left parietal ICH	No	SK 115
12	M/68	Hypertension	3,4,2,1(10)	Primary	No	SK 250
13	F/14	-	3,4,2,2(11)	Left occipital AVM	Yes	SK 65
14	F/52	-	4,3,1,1(9)	Primary	Refused	SK 130
15	F/70	Hypertension	3,3,2,2(10)	Primary	No	UK** 80
16	F/76	Hypertension, previous cerebrovascular accident, lung metastases	3,2,2,2(9)	Right thalamic ICH	No	UK 110
17	F/62	Hypertension, asthma	3,2,1,1(7)	Left thalamic ICH	No	UK 70
18	M/74	-	3,4,2,2(11)	Left thalamic ICH	No	UK 130
19	F/72	Hypertension	4,4,2,2(12)	Primary	No	UK 50
20	F/39	-	4,2,1,1(8)	Right parietal AVM	Yes	UK 60
21	M/65	Hypertension	4,3,2,2(11)	Primary	No	UK 300
22	M/46	Hypertension	4,3,2,2(11)	Right capsular ICH	No	UK 60
23	F/72	Previous cerebrovascular accident	4,2,2,2(10)	Right thalamic ICH	No	UK 40
24	M/75	Hypertension	4,2,1,1(8)	Right capsular ICH	No	UK 125
25	M/62	-	2,4,2,2(10)	Left capsular ICH	No	UK 180
26	M/45	-	4,4,2,2(12)	Left parietal AVM	Yes	UK 50
27	M/57	Chronic alcohol use	2,3,2,2(9)	Left thalamic ICH	No	UK 190
28	F/63	Diabetes mellitus, gastrointestinal bleeding	4,2,2,2(10)	Primary	No	UK 65
29	M/45	Hypertension	4,3,2,2(11)	Right frontal ICH	No	UK 45

* Scores are in the following sequence: right lateral, left lateral, third ventricle, fourth ventricle (total)
† IVH intraventricular haemorrhage
‡ ICH intracerebral haemorrhage
§ Primary refers to the idiopathic spontaneous intraventricular haemorrhage
‖ AVM arteriovenous malformation
¶ SK streptokinase
** UK urokinase
†† GCS Glasgow coma scale; E denotes eye response, M motor response, and V verbal response, (total); PFAD denotes pupils fixed and dilated
‡‡ MSSA methicillin-sensitive *Staphylococcus aureus*
§§ MRSE methicillin-resistant *Staphylococcus epidermidis*

with a poor premorbid condition were treated conservatively. In addition, patients with suspected bleeding cerebral aneurysm and haemorrhage due to trauma did not receive ITT. In our view, conservative management should be used for patients with poor preoperative Glasgow coma scale score (≤4) and with fixed and dilated pupils, even if they are relatively young.

In the literature, the shunt rate among adult patients receiving ITT is 33%.[9] For adults undergoing only ventriculostomy, the shunt rate is 40%.[7] Our 24% shunt rate compared favourably to that documented and supported the finding that ITT can lower the shunt rate.

The differences in the total dosage and duration of ITT were not statistically significant between the streptokinase and urokinase groups. However, there was a statistically significant difference in fever response between the two groups (P=0.003; χ^2=14.1). This result could be due to the

Duration (days)	Preoperative GCS[††] score	GCS score on discharge	1-Year outcome	Postoperative shunting	Comments
1	E4M6V4(14)	15	Good	No	-
4	E1M5V1(7)	15	Good	Yes	-
3	E1M4V1(6)	15	Good	No	Cerebrospinal fluid glucose, 1.6 mmol/L; white blood cells, 0.07 x 10^9/L; culture-negative
1	3,PFAD	Died	Poor	No	Died of septicaemia (MSSA[‡‡]) 1 day postoperatively
3	E2M2V1(5)	15	Good	No	-
3	E2M2V1(8)	E4M6V2(12)	Good	No	-
1	E2M2V1(8)	15	Good	Yes	-
11	E1M5V1(7)	15	Fair	No	-
1	4,PFAD	Died	Poor	No	Died of cerebral oedema 2 weeks postoperatively
2	E4M1V1(6)	15	Good	No	-
5	E3M6V4(13)	15	Good	Yes	-
10	E4M6V3(13)	15	Good	No	-
3	E2M5V2(9)	15	Good	Yes	-
5	E4M6V4(14)	15	Good	No	-
3	E3M6V4(13)	15	Good	No	Deep vein thrombosis
4	E2M5V2(9)	Died	Poor	Yes	Died of pneumonia 39 days postoperatively
3	E2M5V2(9)	15	Good	No	-
6	E1M3V1(5)	E4M4V2(10)	Fair	No	-
3	E1M4V2(7)	15	Good	No	-
3	E3M6V5(14)	15	Good	No	-
14	E1M4V1(6)	15	Good	No	-
3	E2M3V1(6)	E4M4V2(10)	Fair	No	-
2	E2M6V1(9)	Died	Poor	No	Died of pneumonia 6 months postoperatively
6	E2M3V2(7)	E4M6V3(13)	Good	Yes	-
7	E1M5V1(7)	E4M6V3(13)	Good	No	-
1	E1M3V1(5)	E4M6V3(13)	Good	Shunted already	-
8	E2M5V2(9)	15	Good	No	Transient coagulopathy related to alcoholic liver disease
3	15	15	Good	No	Drainage catheter and blood grew MRSE[§§], poor glucose control
2	4,PFAD	Died	Poor	No	Died of pneumonia 15 days postoperatively

allergic response triggered by streptokinase. In view of the possible allergic reactions, we recommend instillation of 20 000 units of urokinase intra-operatively, followed by 20 000 units daily, for about 3 days. Studies have shown that the clot in the third and fourth ventricles should resolve on the third postoperative day.[4,8] However, for patients with IVH due to vascular abnormalities, such as bleeding AVM, caution should be given as the risk of rebleeding in these conditions, which is expected to be high and each case should be considered individually. There were four cases of IVH related to AVM as listed in Table 2 (patients 9, 13, 20, and 26; all were ≤45 years). For patients 9 and 20, the AVMs were embolised before ITT. For patients 13 and 26, external ventricular drainage was inserted but was blocked shortly afterwards (probably related to the extensiveness of IVH—Graeb scores 11 and 12 out of 12, respectively), and ITT was given to maintain the patency of the drainage system. For patients with a suspected bleeding cerebral aneurysm or occult vascular lesion, it is important that cerebral angiography should be performed before the application of thrombolytic agents, irrespective of the presence or absence of subarachnoid haemorrhage. High clinical suspicion is warranted for cases of occult vascular lesion in patients in younger age-groups, such as those aged 45 years or younger.

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