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Clinical Analysis for Stereotatic Aspiration and Thrombolysis of Spontaneous Intracerebral Hemorrhage

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자발성 뇌출혈 환자에서 뇌 정위적 혈종 배액술 및 용해술에 대한 임상적 분석

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목 적 : 저자들은 자발성 뇌출혈 환자에서 뇌 정위적 혈종 배액술 및 용해술의 경험을 분석하여 이 방법의 유용성, 안전성 및 예후인자 등을 평가하고자 한다.

방 법 : 기질적인 원인 혹은 혈액 응고성 질환이 없으면서 천막상부 자발성 뇌출혈 용량이 25ml이상 되는 11명의 환자를 대상으로 하였다. 이 중 글라스고우 혼수계수가 5이하인 환자는 대상에서 제외하였다. 컴퓨터 전산촬영 유도하에 카테터를 자발성 뇌출혈에 정위적으로 유치하고, 유로키나제를 주입한 후 혈종을 흡인하여 제거하였다. 이 과정은 처음 혈종 용량의 절반 이하가 될 때까지 6시간 간격으로 반복하였다. 예후인자를 분석하기 위하여 환자를 두 개의 집단 즉, 글라스고우 결과계수가 4이상의 양호한 집단과 글라스고우 결과계수가 4이하의 불량한 집단으로 나누어 서로 비교분석 하였다.

결 과 : 환자들의 평균연령은 59.8세이고, 초기 혈종의 용량의 범위는 15에서 72ml였다. 혈종 용량의 감소비율은 평균 74.2%였다. 시술 후 6개월 추적관찰결과, 56(50.9%)명의 환자는 양호한 회복을 보였고, 29(26.3%)명의 환자는 의존적인 상태였으며, 10(9.0%)명의 환자는 식물인간상태로 유지되었다. 그리고, 15(13.6%)명의 치료도중 사망하였다. 주요한 중요 예후인자는 젊은 나이, 적은 혈종용량, 높은 글라스고우 혼수계수 및 재출혈, 기존질환, 합병증이 없는 경우였다.

결 론 : 자발성 뇌출혈 환자에서 뇌 정위적 혈종 배액술 및 용해술이 혈종의 용량을 감소에는 안전하고 효율적인 방법임을 알 수 있었다. 그리고, 불량한 예후인자를 가지고 있는 자발성 뇌출혈 환자는 주기적인 방사선학적 검사와 더욱 세심한 시술이 필요할 것으로 사료된다. 그리고, 앞으로 연구는 적절한 용해제 용량의 평가와 치사율과 장해율을 감안한 정밀한 비교분석이 있어야 한다고 생각된다.

중심 단어 : 자발성 뇌출혈 · 정위적 흡인술 · 용해술.

Introduction

Spontaneous intracerebral hemorrhage (ICH) is one of the most serious types of stroke. The majority of cases are associated with arterial hypertension and/or elderly age, and the most common sites of hemorrhage are the

striatum, cerebellum, thalamus, and pons. The 30-day mortality rate is 35% to 50%, and most survivors are typically left severely disabled[2)5)14)].

Current treatment strategies are aimed toward reducing intracranial pressure (ICP) and maintaining adequate cerebral perfusion. While many authors agree that cerebellar and superficial lobar hematomas should be evacuated if the lesions are causing symptomatic mass effect, surgical evacuation as a treatment option for ICH is typically reserved for a minority of cases, typically younger patients with large lobar hemorrhages who are at risk for or who are already suffering brain herniation. A nonsurgical management stance has in part been supported by the results of several randomized, controlled clinical trials that failed to demonstrate improved outcomes with surgery compared with medical therapy alone[4)9)].

The authors report experience with consecutive cases of ICH treated by stereotactic CT-guided aspiration and thrombolysis with urokinase. Our aim in this study is to assess the feasibility and safety of the technique, including refinement of the clinical protocol, procedure-related complications, clinical outcome, and radiological results. And, we also analyzed the prognostic factors related to this technique.

Clinical Material and Methods

From March 1999 to March 2001, 110 patients were treated and are reviewed in this report. The patients were treated according a standardized protocol as illustrated in Fig. 1. Eligibility criteria for this protocol consisted of supratentorial ICH without brain stem extension, clinical onset <48 hours before intervention, age >20 years, hematoma volume >15 ML, GCS score >5 at admission, no signs of transtentorial herniation, no suspected underlying structural etiology to account for the hemorrhage, no systemic bleeding diathesis, and no severe concurrent illness with life expectancy <6 months.

Ventriculostomy was performed in case with poor GCS who had hydrocephalus from ventricular extension of hemorrhage. Ventricular drainage was weaned while intracranial pressure was monitored.

A baseline CT scan was obtained in all patients with axial images at 0.5−1.0 cm slice thickness, and the di-

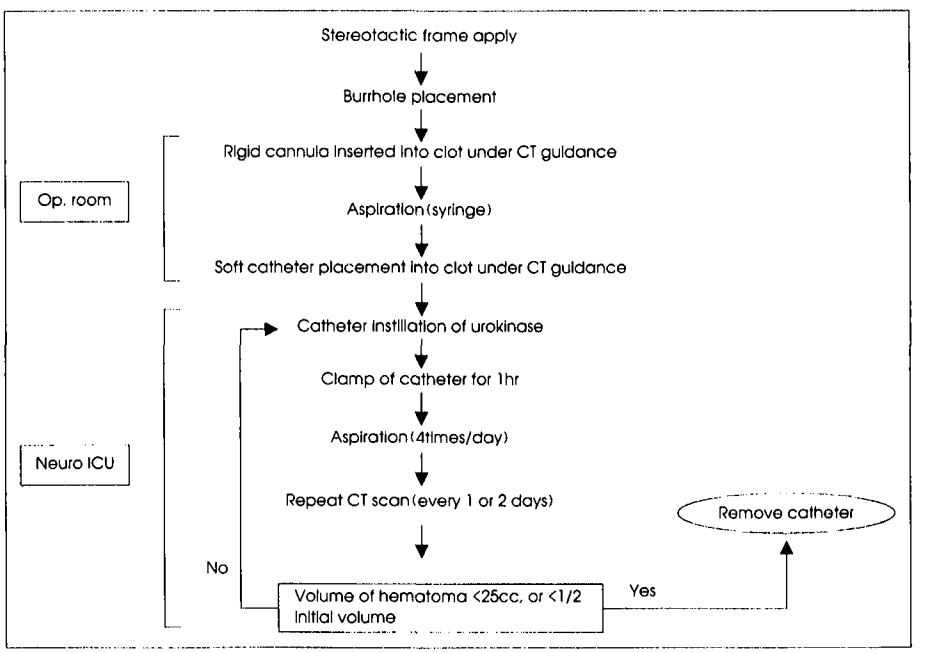

Fig. 1. Management protocol for computed tomography-guided stereotactic aspiration and thrombolysis. Urokinase protocol consisted of catheter injection of 6000IU preceded by hematoma aspiration every 6 hours. The protocol of aspiration, computed tomography scan, and urokinase instillation was repeated as necessary until the final hematoma volume was <25mL or less than half of its initial volume (ICU : Intensive care unit).

mensions of the hematoma were assessed. Volume of the ICH in milliliters was estimated on the basis of approximate ellipse volume with the AxBxC/2 formula, where A represents the largest diameter of the hematoma on axial CT cuts in centimeters, B the diameter of hematoma perpendicular to A on the same cut, and C the number of CT slices in which hematoma is visible multiplied by the slice thickness in centimeters. For the purpose of this calculation we did not count the highest or lowest CT slices in which hematoma was first and last visualized. Intravenous contrast was administered to assess for any enhancement that would be suspicious for an underlying structural lesion. Patients aged <60 years or with abnormal contrast enhancement on CT scan underwent digital subtraction angiography before hematoma aspiration and thrombolysis to exclude an underlying vascular anomaly.

1. Operative technique

All operations were performed under local anesthesia and intravenous sedation unless the patient was already intubated for medical or neurological indications independent of the procedure. In this series, initial localization of the hematoma and catheter placement was performed with the aid of a Fisher stereotactic system (Leibinger, Germany). An ipsilateral frontal standard burr hole location (3cm lateral to mid-line and just anterior to the coronal suture) was typically used for capsular and thalamic hemorrhages. If the hematoma was lobar in location or extended to the cortical surface, the burr hole was localized over the hematoma. A 3F to 5F rigid metal catheter was placed with the introducer cannula into the clot via CT guidance. Careful manual hematoma aspiration was attempted using a syringe. The rigid cannula was removed and replaced by a soft ventriculostomy catheter (15 cm long and 1 to 2 mm internal diameter) with perforations spanning the center of the clot. Catheter placement was adjusted under CT guidance as necessary. After satisfactory placement within the hematoma, the catheter was tunneled subcutaneously and the exit site was covered with antibiotic ointment. The catheter was connected to a single port and capped, and a sterile dressing was applied. The patient was maintained on intravenous antibiotic prophylaxis until the brain catheter was removed.

All patients were managed in a dedicated neurovascular intensive care unit, where subsequent thrombolysis and clot aspiration were performed using sterile technique. Urokinase 6000IU (Green Cross Biotech., South Korea) in 3ML of normal saline was injected into the catheter if the CT scan revealed a residual hematoma volume of >25ML. The catheter was flushed with 2mL of normal saline. After clamping of catheter for 1hour, manual aspiration of lysed clot was attempted, and the aspirated volume was recorded. A CT scan was repeated at least every second aspiration. If the volume of residual hematoma remained >25 mL, catheter instillation of urokinase was repeated. The protocol of aspiration, CT scan, and urokinase instillation was repeated as necessary until less than half of its initial volume, or arbitrarily after 4 catheter aspirations of urokinase instillations per day. The catheter was removed under sterile technique, and a single suture was placed at its exit site and covered with an occlusive dressing.

2. Evaluation of prognostic factors

Follow-up clinical information was obtained on all patients 6 months after the procedure. Clinical outcomes were graded according to the GOS, ranging from grade 5 (good recovery) to grade 1 (dead), by a single investigator not involved in the patients' clinical management. For analysis of prognostic factors, we classified two groups ; good prognosis group (GOS grade 4, 5) and bad prognosis (GOS grade 1, 2, 3) at the time of 6 months' follow-up. We performed comparative analysis between two groups in aspect of all possible relating factors of this procedure.

Unpaired Student t tests were used for the statistical analysis. The value of statistically significance means less than 0.05.

Results

1. Clinical outcome assessment

The Table 1 summarizes clinical and radiographic data in the 110 cases treated during the course of 3 years. The mean age of treated patients was 59.8 years (range 36 to 85 years), and there were 66 males and 44 females. There were 59 right side lesions, and 51 left side lesions. Forty-

Table 1. Patients summary

Characteristic	Value
No. of patients	110
Mean age (year)	59.8 (36–85)
Sex (No. of male/female)	66/44
Underlying disease	
No. of HTN	47
No. of DM	30
No. of HTN+DM	22
Location	
No. of lobar ICH	18
No. of ganglionic ICH	92
Caudate-putamen	84
Thalamus	8
Median initial GCS score	10 (5–15)
Mean initial hematoma volume (ml)	32 (15–72)
Average time to procedure (hour)	4.1 (2– 7)
Average No. of urokinase instillation	13 (4–28)
Average total amount of blood aspirated (ml)	51 (22–85)
Average reduction of ICH volume (%)	74.2 (25–88)
Average final hematoma volume (ml)	8.2 (2–32)
Mortality (No)	
Cardiac problem	2
Respiratory failure	13
Complications during procedure (No)	
Ventriculitis	5
Rebleeding	10
Outcome at 6 months' follow-up (No)	
Good recovery :	56 (51%)
GOS 4	24
GOS 5	32
Bad recovery (N=54, 49%)	54 (49%)
GOS 3	29
GOS 2	10
GOS 1	15

HTN : hypertension, DM : diabetes mellitus, ICH : intracerebral hemorrhage, GCS : glasgow coma scale, No : number, GOS : glasgow outcome scale

seven patients (42.7%) had a prior history of arterial hypertension, and thirty patients (27.2%) had a diabetes mellitus. And, twenty-two patients (20%) had both arterial hypertension and diabetes mellitus. There were 18 lobar and 92 ganglionic ICHs. Among the latter, the epicenter of ICH was in the caudate-putamen in 84 cases and in the thalamus in 8 cases. All patients had spontaneous, nontraumatic ICH. Median initial GCS score was 10 (range 5 to 15). All patients had some degree of neurological deficit such as contralateral hemiparesis, hemiplegia, and dysphasia.

The mean initial hematoma volume was 32mL (ranging from 15 to 72mL). Hematoma aspiration via the inserted catheter was easily achieved in 100 patients. In 10 patients, uncomplicated repositioning of the catheter was necessary after initial placement for optimal positioning within the hematoma before thrombolysis.

The average time from symptom onset until first aspiration was 4.1hours (ranging from 2 to 7hours). The hematoma catheter was in place for a median duration of 5 days (range 2 to 8 days). During this time the average number of urokinase instillations was 13 (range 4 to 28 times), and the amount of blood plus saline aspirated averaged 51mL (range 22 to 85mL). Initial ICH volume was reduced by an average of 74.2% (range 65% to 88%) and the average final hematoma volume was 8.2mL (range 2 to 24mL).

Ventriculitis developed during procedure in 5 patients, and this complication was probably related to catheter instillation for long periods. And, there were instance of local rebleeding in originally presented sites developed in 10 patients. Repeat brain CT image performed after the first urokinase instillation revealed hematoma size increased, and the patients became less responsive. They remained severely disabled (GOS 3, 4 patients) in 4 patients, 4 patients remained vegetative (GOS 2), and 2 patients died (GOS 1) at 6 months' follow-up. However, systemic hemorrhage related to procedure was not encountered in any patient. There were no instances of late clinical deterioration from mass effect or edema associated with residual hematoma.

Fifteen patients (14%) died before hospital discharge (2 from cardiac problems and 13 from respiratory failure). At 6 months' follow-up, 56 patients (51%) had achieved good recovery (24 patient GOS 4, and 32 patients GOS 5), 29 patients (26%) were severely disabled (GOS 3), and 10 patient (8%) remained vegetative (GOS 2). The 18 patients who achieved good recovery harbored lobar hematomas. They returned to premorbid level of function, being completely independent. However, two of the 18 patients, one patient had a rebleeding during procedure

Table 2. Investigated prognostic factors

Prognostic factors	Mean		p-value
	*Group A	**Group B	
Sex (M/F ratio)	.58	.63	.566
Age (years)	58.1	63.5	.033
Pre vol. (ml)	25.1	45.9	.000
Post vol. (ml)	6.4	11.9	.000
Pre GCS (score)	10.9	7.7	.000
Post GCS (score)	12.8	8.1	.000
Time to procedure (hr)	4.2	3.9	.154
Total instillation vol. (ml)	81.6	82.1	.940
***IVH	.32	.77	.000
***No. of rebleeding	.11	.39	.000
***Underlying disease (HTN+DM)	.19	.44	.004
***Pneumonia	.14	.50	.000

*Group A : (good prognosis group) : GOS 4, 5(N=56), **Group B : (bad prognosis group) : GOS 1, 2, 3 (N=36), ***Event(+) : 1 point, Event(−) : 0 point, Statistical analysis was performed by independent t-test. GOS : glasgow outcome scale, GCS : glasgow coma scale, M : male, F : female, Pre : preoperative, Post : postoperative, vol. : volume, hr : hours, HTN : hypertension, DM : diabetes mellitus, IVH : intraventricular hemorrhage

and another patient had a complication of pneumonia, were severely disabled (GOS 3) at 6 months' follow-up. On the contrary, forty-one of 92 patients (44.5%) with ganglionic ICH achieved independence at 6 months (23 patient GOS 4, and 18 patients GOS 5), and all had reached that level of function by 6 months after the procedure. The other patients reached below GOS 3 [27 patients were severely disabled (GOS 3), or 10 patients remained vegetative (GOS 2), or 15 patients died (GOS 1)]. Of 92 patients with ganglionic ICH, there were 8 patients with thalamic ICH. They have relatively achieved bad recovery [2 patients were moderate disabled (GOS 2), 2 patients were severely disabled (GOS 3), or 2 patients remained vegetative (GOS 2), or 2 patients died (GOS 1)].

2. Evaluation of prognostic factors

Significant good prognostic factors for this procedure of ICH were found in our study to be young age, small pre-and-postoperative volume, low pre-and-postoperative GCS, absence of intraventricular hemorrhage (IVH), absence of rebleeding, absence of underlying disease, and absence of complication of pneumonia after procedure. The other factors such as sex, time to procedure, total instillation volume, and total number of instillation were not meaningful prognostic factors in our study (Table 2).

Discussion

Optimal treatment of ICH remains a complex and controversial issue[20)24)]. Application of stereotactic surgery and minimally invasive therapies to cerebrovascular surgery has led investigators to utilize such techniques toward the goal of reducing hematoma volume in the treatment of ICH. Recently, ICH is more often operated on by stereotactic surgery instead of conventional open surgery, and many authors have stressed the usefulness of this procedure[6)10)15)18)20)]. Stereotactic surgery has the following advantages over open surgery: it is a simple and less traumatic method for removing the ICH, and can be done under local anesthesia[10)]. Early attempts aimed at simple clot aspiration as well as more ingenious means of mechanical evacuation have failed to accomplish satisfactory volume reduction of ICH[12)]. This has led to the adjunct use of fibrinolytic agents as a means of enhancing clot lysis and catheter drainage. Since the first report by Doi et al[6)], in which direct instillation of urokinase was used after stereotactic aspiration to liquefy the hematoma, several reports have followed that have favorably reported its usefulness in ICH volume reduction[6)11)15)17-19)]. Most of the randomized controlled trials have failed to demonstrate a superiority of craniotomy for ICH evacuation over medical therapy, especially after 24 hours from the onset of symptoms[4)9)16)18)].

The rationale for evacuation of ICH is that reduction of clot volume may indeed improve neurological recovery and clinical outcome. Removal of focal mass effect may improve perfusion of compromised brain parenchyma and prevent intracranial hypertension[1-3)]. It also may enhance the clearance of blood breakdown products, hence preventing secondary brain edema and other potential neurotoxicity. Animal studies have in fact demonstrated that edema is diminished with the early evacuation of intracerebral clot[25)]. Pang et al[21-23)]. speculated that intraventricular fibrinolytic treatment might prove useful for infants with perinatal IVH and older patients with IVH whose spe-

cific lesions have been definitively treated. Other previous experimental studies have shown that infusion of urokinase promotes clot lysis and restoration without producing neurotoxicity, histopathological alterations, or recurrent bleeding[2)8)17)19)21-23)26)].

Eligibility criteria of ICH volume are more controversial. The recent open surgery trial by Morgenstern et al included ICH volumes of >10 ml (20 ml in patients with GCS 15)[18)]. The trial by Auer et al[3)]. also considered a threshold volume of >10ml for treatment, although therapeutic benefit appeared to be limited to lobar cases with larger ICH volume. Other studies enrolled only patients with larger ICH volumes (15 to 30mL)[15)]. We limited enrollment in this study to cases with ICH volume >25mL, with the major aims of verifying procedure safety and feasibility of reduction of ICH volume. It is possible that more favorable clinical outcomes may have been accomplished if patients with smaller ICH volumes had been included. It is not likely that smaller volumes of ICH will benefit from the procedure, as most such patients have a favorable outcome without intervention and the technique rarely succeeds at complete evacuation of ICH below such residual threshold.

According to Hokama's[16)] reports, absolute indication the patients could be operated on by conventional open surgery with indications that is, moderate-sized hematoma with a volume of 40−60ml, moderate neurological grade, and no severe general complications. This group is best treatment option for stereotactic surgery at an optimal time. Aggressive indication in this group, stereotactic surgery is performed in order to achieve early rehabilitation with a chance to regain higher cerebral function. This group included patients with small hematoma under 40ml with mild neurological deficit. Passive indication patients in this group have large hematoma over 60ml with severe neurological deficit, and the patient's age is over 70 years, and they may have severe general complications[10)].

Other variables in treatment protocol include the surgical technique, thrombolytic agent, dosage, frequency, and end point of aspiration. Most reported studies of thrombolytic aspiration of ICH have used frame-based stereotaxy, often with general anesthesia. We have used urokinase in view of the reported case experience with this agent for more than a decade. We sought to adapt the most frequently used dosages (6000IU) and aspiration parameters, although it is clear that these were empirically derived and largely arbitrary. In more recent cases we escalated dosage of urokinase (5000IU to 10000IU) and the frequency of aspiration from every 8 to every 6 hours.

Mortality has been the primary end point of therapeutic studies in most published studies, and it has ranged from 30% to 70%[9)18)24)]. This reflects in part patient inclusion and exclusion criteria, and to a lesser extent the treatment rendered in individual studies. In our series, there was 14% mortality at 6 months among patients with relatively large hematoma volume (>25mL). These were admittedly selected, excluding deeply comatose patients. The postoperative mortality rate has varied from 20% to 80%, with some patients, such as those in deep coma or those with thalamic hemorrhage, having a mortality rate as high as 90%[12)].

Disability levels among surviving patients may be more relevant in assessment of management outcome. It is not clear from countless cases in published uncontrolled series whether ICH evacuation in fact enhances functional recovery. In our study, forty-one of 92 patients (44.5%) with ganglionic ICH in this study achieved independence at 6 months (23 patient GOS 4, and 18 patients GOS 5), and all had reached that level of function by 6 months after the procedure. Such outcome assessment should be supplemented by documentation of quality of life domains relevant to patient and family, and these should be compared among treated and untreated cases. It may be advantageous to minimize stay in critical care unit and acute hospital settings even if eventual survival or disability level are not significantly altered by treatment. The state of consciousness is the best indicator of survival and that deficit of consciousness are not always a good indicator of functional prognosis. And, the factor most heavily influencing the functional prognosis is hemiplegia[20)]. In light of the fact that, in the overall results, the percentage of patients with good result (GOS 4, 5) was 51%, we concluded that stereotactic aspiration should have a definite place in the neurosurgeon's battery of therapeutic technique.

Cases of lobar ICH with a preoperative good grade recovered to better than that of ganglionic ICH. In our study, the 18 patients who achieved good recovery (GOS

4 or 5) harbored lobar hematomas. They returned to premorbid level of function, being completely independent. However, two of the 18 patients, one patient had a rebleeding during procedure and another patient had a complication of pneumonia, were severely disabled (GOS 3) at 6 months' follow-up.

Several authors reported the rebleeding rate in CT-guided stereotactic surgery to be 3% to 16%[10)12)15)20)]. The factors contributing to recurrent hemorrhage include excessive hematoma aspiration, intraoperative or postoperative hypertension, and a bleeding tendency. Because of the rebleeding risk that could potentially be increased by early aspiration suggest not to do the stereotactic aspiration before 6 to 24 hours after onset[8)15)20)]. Hondo et al[11)]. reported a rebleeding risk of only 4% when aspiration had been carried out between 5 and 48 hours after the hemorrhage. However, from our result, rebleeding after procedure seems to be not related to early aspiration. Even if the average time from symptom onset until first aspiration was 4.1 hours (ranging from 2 to 7 hours), the rebleeding risk cannot potentially be increased in our study (9%). Kandel et al[12)]. developed a method of preventing recurrent bleeding after hematoma evacuation. After removal of the hematoma, the balloon catheter with a metal shift inside is introduced through the cannula into the cavity. Inflation continues until the pressure inside the balloon equals the pressure in the contralateral ventricle.

It is not clear whether the incidence of expanding hematoma in these above series represents any added risk from thrombolytic therapy. During the early period of time after ictus, hematoma may cause neurological deterioration as a result of an increasing mass effect caused by surrounding edema, and this mass effect may last up to 4 weeks after bleeding, even with decreasing density of clot. The risk of hematoma expansion during treatment must be closely monitored in future studies, including any associated untoward clinical sequelae, but this should also be compared with the substantial risk of spontaneous hematoma expansion in the first day among untreated patients[13)].

Volume of ICH is consistently shown to be a powerful predictor of poor outcome regardless of clot location, patient age, and neurological condition[4)5)]. Most postoperative complications were seen in older patients and in those with severe neurological deficit or chronic disease. Factors contributing to poor outcome are as follows : age over 70 years, large hematoma, bad neurological grading. Stereotactic surgery is effective in regaining higher cerebral function in patients with a small hematoma less than 40ml in volume, and with minor neurological deficit[10)]. Larger hematomas result in more profound and longer-lasting alterations in adjacent brain parenchyma, attributed in part to mass effect and focal edema. The main prognostic factors affecting the outcome are clinical state of a patient on admission, the size of hematoma, and the presence of intraventricular hematoma (IVH)[9)]. The level of consciousness, intraventricular extension of blood, volume of hematoma, and age are related well with bad outcome[14)]. And, many reports have agreement that ICH with IVH results in high mortality and morbidity[7)20)23)].

No differences were found from our study. Significant good prognostic factors for this procedure of ICH were found in our study to be young age, small preoperative and postoperative volume, low pre-and-postoperative GCS, absence of intraventricular hemorrhage (IVH), absence of rebleeding, absence of underlying disease, and absence of complication of pneumonia after procedure. However, the other factors such as sex, time to procedure, total instillation volume, and total number of instillation were not meaningful factors in our study.

Conclusion

The procedure appears effective at decreasing ICH volume and is not associated with significant management morbidity. Patients of ICH presenting with bad prognostic factors should require frequent radiological investigation and more meticulous procedure. Further studies must assess optimal thrombolytic dosage, frequency, and timing of urokinase instillation for safety and effectiveness and must include controlled comparisons of mortality disability outcome, quality of life, time until convalescence, and cost of care in treated and untreated patients.

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