Original Paper

Local Fibrinolysis in Spontaneous Supratentorial Hematomas: Comparison with Surgical and Medical Treatment

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Key Words

Supratentorial spontaneous intracerebral hemorrhage · Local fibrinolysis · Minimally invasive surgery · Craniopuncture · Craniotomy · Conservative management

Abstract

Objective: To evaluate the effectiveness of minimally invasive craniopuncture with local fibrinolysis in the management of supratentorial spontaneous intracerebral hemorrhage (SICH). **Methods:** The study included 218 consecutive patients with supratentorial SICH who were assigned to one of three groups: treated with minimally invasive craniopuncture with local fibrinolysis, treated with craniotomy or other minimally invasive techniques without local fibrinolysis, or receiving conservative management alone. **Results:** Minimally invasive craniopuncture with local fibrinolysis was associated with a lower rate of assisted ventilation, a shorter period of in-hospital stay, a more frequent initiation of early rehabilitation, and a lower mortality rate at all periods of assessment. The overall mortality at 12 months was 19.4% (vs. 50.0 and 33.3% in the two other therapy groups). Lobar (subcortical and cortical) SICHs treated with local fibrinolysis had an overall mortality of 4.8% (vs. 43.5 and 41.7% in the two other therapy groups). On the other hand, SICHs having mixed (basal ganglia and lobar) locations treated with medical therapy alone had an overall mortality of 28.6%, while associated surgery with or without local fibrinolysis increased the overall mortality to over 65%. **Conclusions:** The study demonstrated the applicability of minimally invasive craniopuncture with local fibrinolysis for the management of supratentorial SICHs and the advantages it may have in certain categories of patients. The method proved particularly useful in lobar SICHs, being associated with the lowest mortality. Mixed SICHs do not represent a predilection for surgical interventions; however, the results related to mixed supratentorial locations need confirmation in larger cohorts.

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Introduction

Spontaneous intracerebral hemorrhage (SICH) remains a major public health problem and a significant cause of morbidity and mortality throughout the world [1, 2]. The incidence in low- to middle-income countries is almost twice the incidence in high-income countries, which might be related to differences in the exposure to environmental risk factors, particularly arterial hypertension and smoking [3]. Despite active research, it is still the least treatable cause of stroke [2]. Different surgical options have been evaluated; however, the role of surgery for most patients with SICH remains controversial [1, 4]. The effectiveness of minimally invasive clot evacuation, utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage, is considered investigational [5], and various studies addressing this topic are still underway. The Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator (MISTIE) II trial, a rigorous multicenter, randomized, prospective trial sponsored by the National Institutes of Health, found that hematoma evacuation was associated with significant reduction in perihematomal edema [1, 6, 7]. A randomized phase 3 clinical trial of minimally invasive hematoma evacuation aiming to investigate clinical outcome and safety in a larger population of 500 patients from about 100 medical centers around the world (MISTIE III) is still ongoing [1, 6]. In the current study, we report the results of 218 consecutive patients with SICH who underwent surgical treatment with or without local fibrinolysis or conservative management alone.

Methods

Study Population

The study was approved by the institutional ethics committee and included 218 consecutive patients with supratentorial SICH admitted to the Institute of Neurology and Neurosurgery and to the Neurosurgical Unit of the Institute of Emergency Medicine during the period 2011–2014. The clinical services at these two hospitals act as referral stroke centers in Moldova. Informed consent was obtained from all individual participants included in the study. The inclusion criteria were as follows: (a) supratentorial SICH with a volume ≥ 30 ml confirmed by head computed tomography (CT), (b) age between 18 and 90 years, and (c) a Glasgow Coma Scale (GCS) score ≥ 8 points on admission. Exclusion criteria included previous SICH with known residual neurological deficits, intracerebral hematomas related to known or identifiable secondary etiologies such as traumas or tumors, as well as patients in coma on admission (GCS score ≤ 7) and/or unable to give informed consent.

After admission, the patients were assigned to one of the three study groups (fig. 1). Group I received initial conservative treatment consisting of minimally invasive craniopuncture with local fibrinolysis (67 patients), group II received initial conservative treatment consisting of other minimally invasive procedures or conventional craniotomy without local fibrinolysis (70 patients), and group III received conservative treatment alone according to standard protocols (81 patients). Allocation to a therapy group was performed randomly, with the exception of patients requiring emergency decompression craniotomy (large hematomas with rapid clinical deterioration, elevated intracranial pressure refractory to medical management, etc.), who were assigned to group II.

Age ranged from 24 to 89 years, with a mean value of 57.9 ± 1.1 years for group I, 59.0 ± 1.4 years for group II and 59.3 ± 1.0 years for group III ($p > 0.05$). Females represented 43.1% (range 40–45% in all groups) and males 56.9% (range 55–60% in all groups). All patients underwent a detailed medical and neurological examination on admission. Focal neurological deficits were detected in most patients, with no significant difference between groups. Thus, motor deficits were revealed in at least 97% of patients; of these, over 1/2 had plegia and over 1/3 presented various degrees of paresis (table 1). Arterial hypertension was detected in over 90% of subjects. Other risk factors such as obesity, smoking, excessive alcohol intake, diabetes mellitus, dyslipidemias and cardiopathies were encountered in over 50% of cases. It is noteworthy that all subjects presented one or more risk factors, with no significant differences between groups. Commonly used baseline severity scores such as the GCS score, the intracerebral hemorrhage grading scale score, the

Fig. 1. Schematic representation of the study groups and assigned patients.

intracerebral hemorrhage score for predicting 30-day mortality, and the FUNC score (for risk stratification and functional outcome at 90 days after stroke) were also obtained as part of the initial evaluation [8–10], the mean values being presented in table 1.

Neuroimaging

A head CT scan was performed on admission in all patients. Relevant details related to CT findings in the study groups are provided in table 1. Other imaging modalities such as CT angiography, contrast-enhanced CT or MRI were also employed in selected patients depending on the suspected pathology (hematoma expansion, underlying vascular malformations, associated brain pathology, etc.). Repeat CT scans were obtained at various intervals to evaluate hematoma dynamics depending on the study group, administered local fibrinolysis and clinical condition. The imaging results were reviewed independently by a radiologist and by a neurologist or neurosurgeon. Any potential differences were reviewed until a consensus was reached.

Management

Medical management was initiated immediately and continued in the stroke unit according to the European Stroke Organisation and the American Heart Association/American Stroke Association guidelines for the management of SICH [1, 5, 6]. Although the therapy was individualized, it also addressed a number of general principles such as cardiorespiratory and blood pressure control, reversal of coagulation defects, management of cerebral edema and elevated intracranial pressure, glycemic control, seizure management, neuroprotection, controlling the risk factors and associated medical conditions, deep venous thrombosis prophylaxis, etc.

The minimally invasive craniopuncture with local fibrinolysis employed in group I included several steps: (1) applying a burr hole according to the automatically calculated puncture site and catheter trajectory based on CT data, (2) guiding the puncture cannula into the hematoma cavity according to the calculated trajectory, and (3) aspiration of the liquid part of the hematoma and application of a special catheter in the hematoma cavity for subsequent infusion of thrombolytic agents to enhance clot drainage. In some cases, a real-time 3D intraoperative imaging system with integrated navigation (SonoWand and Medtronic, USA) was used. The system allowed operating with a higher precision during the entire surgery and proved particularly useful for accessing relatively small SICHs located deep within the basal ganglia. The fibrinolytic agent we used was Hemase, a recombinant urokinase, administered to the hematoma cavity at a dose of 1,000 IU every 8 h. A head CT was performed 12, 24, 48 and 72 h after the first dose of Hemase. If the hematoma volume had decreased by at least 2/3 compared to the initial CT scan, the local fibrinolysis was stopped; otherwise a new dose of 1,000 IU Hemase was administered every 8 h for a total of 72 h. Given the associated risk of infections and the subsiding effects of local fibrinolysis after 72 h, the fibrinolytic therapy was not extended beyond this period.

Table 1. Patient details on admission for the three study groups

	Group I	Group II	Group III
Admitted within 24 h from onset	20.9%	54.3%	35.8%
Admitted after 24 h from onset	79.1%	45.7%	64.2%
GCS score	12.0±0.2	11.2±0.3	12.6±0.2
ICH-GS score	6.7±0.1	7.4±0.2	6.4±0.2
ICH score for predicting 30-day mortality	30.9±2.6	35.8±2.4	29.2±1.4
FUNC score	6.9±0.2	6.1±0.2	6.9±0.2
Motor deficits	97.0%	98.6%	100.0%
Plegia	62.7%	54.3%	55.6%
Paresis	34.3%	44.3%	44.4%
Severe	22.4%	30.0%	27.1%
Light or moderate	11.9%	14.3%	17.3%
Subcortical SICH	31.3%	33.8%	29.6%
Basal ganglia SICH	59.8%	57.4%	61.8%
Mixed (subcortical and basal ganglia) SICH	8.9%	8.8%	8.6%
Intraventricular eruption of ICH	19.4%	17.1%	21.0%
Superficial (≤2 cm from cortex) SICH	79.1%	79.7%	79.0%
Deep (>2 cm from cortex) SICH	20.9%	20.3%	21.0%
Right hemisphere hematomas	52.2%	58.0%	57.0%
Left hemisphere hematomas	47.8%	42.0%	43.0%
Hematoma volume, ml	50.4±1.9	64.8±2.5	48.0±1.9
Cerebral midline shift, mm	6.3±0.4	7.1±0.3	4.9±0.3

Values are presented as mean ± standard error of the mean or as percentage.

Group I: craniopuncture with local fibrinolysis; group II: surgical evacuation without fibrinolysis; group III: standard medical treatment.

ICH = Intracerebral hemorrhage; ICH-GS = intracerebral hemorrhage grading scale.

In group II, conventional craniotomy was performed in 40 (57.1%) patients and minimally invasive surgery was used in 30 (42.9%). Standard medical treatment was also administered; however, no local fibrinolysis was used in this group. All surgical procedures in groups I and II were carried out under general anesthesia and endotracheal intubation, with the exception of one patient in group I, who underwent a minimally invasive procedure under local anesthesia supplemented by intravenous sedation.

After discharge, all patients underwent periodic assessments at 1, 3, 6 and 12 months for detailed evaluation of their functional status, interval response to therapy and for preventing recurrences by controlling risk factors and associated diseases. Their functional status was assessed using scales such as the Glasgow Outcome Score (GOS) for assessing the final state after acute brain disease, the modified Rankin score for measuring the degree of disability or dependence in daily activities, and the Barthel index for evaluating basic activities of daily living [11, 12].

Statistical Analysis

All data were analyzed using SPSS® v. 21.0 (SPSS Inc., Chicago, Ill., USA) and MedCalc statistical software v. 12.5.0 (MedCalc Software, Ostend, Belgium). Categorical variables were tested for statistical significance using the χ^2 test. For comparing small samples (any expected frequency <1 or 20% of expected frequencies ≤5), Fisher's exact test for small samples was used. Continuous variables (for functional scores, hematoma volume, etc.) were expressed as the mean ± standard error of the mean and tested for normal distribution. After the assumption had been met, a pooled t test was used to compare the values between the groups. Otherwise a nonparametric (Mann-Whitney) test was used. A p value <0.05 was considered significant for all tests. Survival analysis using Kaplan-Meier survival plots was also performed.

Results

The duration of fibrinolytic therapy was between 24 and 48 h in 22.4% of patients and over 48 h in 77.6% of patients. The initial volume removed before starting the fibrinolytic therapy was 2–5 ml in 59.7% of patients, between 5 and 10 ml in 37.3% of patients, and between 10 and 15 ml in 3.0% of patients. After starting local fibrinolysis, the average evacuated volume was 15.3 ± 0.8 ml during the 1st day (limits between 6 and 32 ml), 16.5 ± 0.9 ml during the 2nd day (limits between 4 and 44 ml), and 13.46 ± 1.1 ml during the 3rd day (limits between 0 and 46 ml). On average, 43.5 ± 1.9 ml of hematoma could be evacuated from every subject, the limits varying between 16 and 86 ml. The mean values for residual hematoma represented 35.1 ± 1.8 ml 24 h after commencing local fibrinolysis, 21.6 ± 1.7 ml at 72 h and 13.6 ± 1.8 ml at discharge. When expressed in percentages, this translated into a volume reduction of $37.9 \pm 2.4\%$ at 24 h, $46.1 \pm 2.2\%$ at 72 h and $57.7 \pm 3.9\%$ at discharge, the difference reaching statistical significance between all values ($p < 0.05$).

In the postoperative period, 12 patients treated with local fibrinolysis required assisted mechanical ventilation for a period between 3 and 11 days. The frequency and the overall period of assisted ventilation were significantly lower compared to group II, where 27 patients required assisted mechanical ventilation for a period between 2 and 40 days (table 2). A tracheostomy for assisted mechanical ventilation was performed in 1 patient from group I and in 3 patients from group II. Local postoperative complications such as rebleeding, expanding cerebral edema or local infections were significantly lower in group I (11.9 vs. 27.8%), while general postoperative complications such as pulmonary and renal infections were relatively similar in both groups (15.4 vs. 13.3%). Early rehabilitation that included physiotherapy and kinesiotherapy within the first 48 h could be initiated in 75.8% of patients from group I, the rate being significantly higher compared to the other groups (table 2). The period of in-hospital stay varied between 3 and 32 days in group I, between 2 and 80 days in group II, and between 2 and 30 days in group III, the mean values being significantly higher for group II (table 2).

Overall mortality was 19.4% for group I, 50.0% for group II and 33.3% for group III. The patients from group I also had the lowest in-patient mortality as well as the lowest values at 14 and 21 days, even though statistical significance was reached only against group II (table 2). Mortality analysis depending on hematoma location revealed a higher overall mortality for mixed SICHs (55.0%), followed by thalamic (37.8%), lobar (30.9%) and putaminal (26.8%) locations. Apparent differences were also revealed depending on the therapy administered (fig. 2). Thus, lobar (subcortical and cortical) SICHs treated using minimally invasive craniopuncture and local fibrinolysis had an overall mortality of 4.8%, while lobar SICHs treated with other methods had an overall mortality $>40\%$ ($p < 0.05$). On the contrary, SICHs having mixed (basal ganglia and lobar) locations treated with medical therapy alone had an overall mortality of 28.6%, while associated surgery with or without local fibrinolysis increased overall mortality $>65\%$.

The results of the neurological and functional status scores at discharge and at 1, 3, 6 and 12 months of follow-up are shown in table 2. Patients from group I demonstrated the highest GOS scores at all assessments, the difference reaching statistical significance versus group II at 1 month after discharge. The Rankin score for measuring the degree of disability or dependence in daily activities and the Barthel index for evaluating basic activities of daily living demonstrated relevant improvements during the first year after discharge, with no statistical significance between the therapy groups (table 2). Cumulative survival at 36 months was 75% for group I, 44% for group II and 63% for group III, the difference being statistically significant for group I vs. II and for group II vs. III (table 2, fig. 3).

Table 2. Results obtained in the three study groups

	Group I	Group II	Group III	p < 0.05
Hospital stay, days	11.9±0.6	17.7±1.8	11.8±0.6	I vs. II, II vs. III
Ventilatory support in postoperative period	18.2%	48.2%	–	I vs. II
Duration of ventilatory support, days	7.0±0.8	12.0±1.7	–	I vs. II
Initiation of early rehabilitation (within 48 h)	75.8%	12.9%	22.2%	I vs. II, I vs. III
Local postoperative complications	11.9%	27.8%	–	I vs. II
General postoperative complications	15.4%	13.3%	–	–
Repeat interventions using craniotomy	4.5%	10.0%	–	–
Overall mortality				
In-hospital	13.4%	45.7%	22.2%	I vs. II, II vs. III
At 14 days	11.9%	30.0%	17.3%	I vs. II
At 21 days	14.9%	37.1%	22.2%	I vs. II
At 12 months	19.4%	50.0%	33.3%	I vs. II, II vs. III
GOS				
At discharge	3.4±0.1	3.2±0.1	3.3±0.1	–
At 1 month	3.7±0.1	3.3±0.1	3.5±0.1	I vs. II
At 3 months	4.2±0.1	4.0±0.1	4.1±0.1	–
Rankin score				
At discharge	5.7±1.3	4.1±0.1	3.8±0.1	–
At 1 month	4.8±1.3	3.8±0.1	4.1±0.6	–
At 3 months	4.3±1.5	3.3±0.1	3.6±0.6	–
At 6 months	2.6±0.2	2.7±0.2	3.4±0.7	–
At 12 months	2.2±0.2	2.1±0.2	2.4±0.2	–
Barthel index				
At discharge	38.4±1.9	39.0±1.7	41.5±1.4	–
At 1 month	46.2±2.1	45.9±2.0	47.2±1.8	–
At 3 months	55.3±2.3	54.4±2.5	55.7±2.1	–
At 6 months	63.9±2.4	63.6±3.2	61.7±2.4	–
At 12 months	72.2±2.9	71.4±3.5	68.3±2.3	–
Cumulative survival at 36 months	75%	44%	63%	I vs. II, II vs. III

Values are presented as mean ± standard error of the mean or as percentage.

Group I: craniopuncture with local fibrinolysis; group II: surgical evacuation without fibrinolysis; group III: standard medical treatment.

Discussion

Surgical evacuation of SICHs is aimed at reducing the mass effect, decreasing intracranial pressure, preventing herniation, improving regional blood flow, minimizing the release of blood degradation products, as well as minimizing cerebral edema and secondary brain injury [1]. Minimally invasive techniques with local fibrinolysis have added new values to surgical management by allowing local instillation of fibrinolytic agents into the hematoma cavity for clot thrombolysis and by circumventing the tissue damage caused by open craniotomy [13, 14]. However, if the indications for surgical evacuation of intracerebral hematomas remain controversial, the means by which to achieve this evacuation are even less well established [5].

The current study demonstrated the applicability of minimally invasive craniopuncture with local fibrinolysis for the management of supratentorial SICHs and the advantages it may have in certain categories of patients. The method was associated with a lower frequency and a shorter period of assisted ventilation, a lower incidence of local postoperative complications and a shorter in-hospital stay compared to patients treated with open craniotomy or other minimally

Fig. 2. Recorded mortality in the three study groups depending on hematoma location. Group I: patients treated with craniopuncture and local fibrinolysis; group II: patients treated with surgical evacuation without fibrinolysis; group III: patients treated with standard medical therapy.

Fig. 3. Cumulative survival in the three study groups.

invasive techniques without local fibrinolysis (group II). It also allowed more frequent initiation of early rehabilitation (within the first 48 h) compared to the two other groups.

A major concern for surgical evacuation of SICH is still related to the prevention of rebleeding once the tamponade effect of the hematoma on the bleeding vessel is lost. For this reason, an important aspect of local fibrinolysis is directed towards gradual removal of hematoma content. Other measures undertaken in this study included catheter positioning in the middle of the hematoma (the bleeding vessel commonly being on the surface) and avoidance of sudden strong aspirations. As a result, rebleeding within the first 30 days was encountered in only 6% of patients, while repeat interventions using open craniotomy were performed in only 4.5% of patients from group I.

A better 3-month neurological outcome in group I was supported by highest GOS scores at all intervals of assessment, the difference reaching statistical significance versus group II

at 1 month after discharge. The relatively higher values of the modified Rankin score for measuring the degree of disability or dependence in daily activities recorded at discharge in groups I and II may be related to a higher degree of perceived disability in the immediate postoperative period. Subsequently, however, the pace of functional recovery proved faster following surgical interventions, the recorded scores at 6 and 12 months being already reversed (i.e. lower for groups I and II compared to group III). Of note is also that in patients who underwent surgical interventions (groups I and II), the modified Rankin score showed a steady decrease following discharge. On the contrary, patients receiving medical treatment (group III) showed an initial increase in the modified Rankin score after discharge, which may have been related to an increasing degree of disability in the home environment during the first month. A similar pattern of the Barthel index for evaluating basic activities of daily living obtained in the three groups following discharge may have similar explanations.

Patients treated with minimally invasive craniopuncture and local fibrinolysis also had the lowest mortality rates at 14 days, 21 days and 12 months as well as the highest cumulative survival at 36 months, even though statistical significance in our study was reached only against group II. Although the technique proved also effective in patients presenting after 24 h from onset of symptoms (almost 80% of patients from group I), the optimal timing of the procedure remains to be established and requires new clinical trials.

Subgroup analysis depending on hematoma location further revealed that minimally invasive craniopuncture with local fibrinolysis is particularly useful in lobar (cortical and subcortical) SICHs, being associated with an overall mortality of only 4.8% in our cohort. Due to the relatively small number of patients with mixed SICHs included in the current study (a total of 6–7 patients in each group), the results related to mixed SICHs need confirmation in larger cohorts for a meaningful evaluation of statistical significance. Nevertheless, the registered mortality of 66.7% (4 from 6 patients) in group I and 71.4% (5 from 7 patients) in group II versus 28.6% (2 from 7 patients) in group III rather suggests that mixed locations of SICHs do not represent a predilection for surgical interventions and are associated with a reserved prognosis when emergency decompression is required as a lifesaving procedure. New multidisciplinary and multicenter studies are also required to further define the guidelines on SICH management.

Study Limitations and Perspectives

Even though every attempt for random selection to a therapy group was made, patients requiring emergency decompression craniotomy after admission were assigned to group II. In an attempt to minimize the number of such patients, those with a GCS score ≤ 7 on admission were not included in this study. Due to the relatively small number of patients with mixed SICHs (a total of 6–7 patients in each group), the results related to mixed SICHs need confirmation in larger cohorts. At its very least, the study provides a valid comparison of minimally invasive craniopuncture with local fibrinolysis versus conservative management, the assignment to these groups having been random without any potential bias associated with worsening clinical status and required emergency decompression craniotomy. The results can also serve as a foreground for further research, including prospective blinded outcome studies involving different surgical approaches.

Conclusions

The study demonstrated the applicability of minimally invasive craniopuncture with local fibrinolysis for the management of supratentorial SICHs and the advantages it may have in certain categories of patients. The technique was associated with a lower rate of assisted

ventilation, shorter in-hospital stay, a lower incidence of local postoperative complications, more frequent initiation of early rehabilitation and a lower mortality rate at all periods of assessment. The method proved particularly useful in lobar SICHs, being associated with the lowest mortality. On the other hand, the study results suggest that mixed locations of SICHs do not represent a predilection for surgical interventions, even though the results related to mixed supratentorial locations need confirmation in larger cohorts.

Disclosure Statement

The authors declare no competing interests. This study received no funding.

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