ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΕΘΝΙΚΟ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΚΛΙΝΙΚΗ ΚΑΙ ΠΕΙΡΑΜΑΤΙΚΗ ΝΕΥΡΟΧΕΙΡΟΥΡΓΙΚΗ»

ΔΙΠΛΩΜΑΤΙΚΗΕΡΓΑΣΙΑ

INTRATHECAL THROMBOLYTIC THERAPY IN SUBARACHNOID HEMORRHAGE. A SCOPING REVIEW

ΓΕΩΡΓΙΟΣ ΣΑΒΒΑΝΗΣ

ΑΘΗΝΑ

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ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ

ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ του Μεταπτυχιακού Φοιτητή Γεωργίου Σαββανή

Εξεταστική Επιτροπή

● Σταυρινού Λάμπης, Επιβλέπων
●Στράντζαλης Γεώργιος
● Καλαματιανός Θεοδόσης

Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε από την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της .....για την αξιολόγηση και εξέταση του υποψηφίου κου Γεωργίου Σαββανή, συνεδρίασε σήμερα ...../...../.....
Η Επιτροπή διαπίστωσε ότι η Διπλωματική Εργασία του κου Γεωργίου Σαββανή
Με τίτλο: Intrathecal thrombolytic therapy in subarachnoid hemorrhage, a scoping review, είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη. Η εξεταστική επιτροπή αφού έλαβε υπ' όψη το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή στον παραπάνω Μεταπτυχιακό Φοιτητή την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's). Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους....., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ....., και για τον βαθμό «ΚΑΛΩΣ» ψήφους ..... Κατά συνέπεια, απονέμεται ο βαθμός «.....».

Τα Μέλη της Εξεταστικής Επιτροπής
Σταυρινού Λάμπης Επιβλέπων (Υπογραφή)
Καλαματιανός Θεοδόσης (Υπογραφή)
Στράντζαλης Γεώργιος (Υπογραφή)

Ευχαριστίες

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Intrathecal thrombolytic therapy and subarachnoid hemorrhage: A systematic scoping review

Abstract

Introduction: Subarachnoid hemorrhage causes blood presence outside brain vessels of the circle of Willis and sometimes blood is also found in the ventricular system. Subarachnoid presence of blood is associated with cerebral vasospasm, which may result in secondary neurologic deficits and post-hemorrhagic hydrocephalus. In cases of intraventricular extension, acute obstructive hydrocephalus may occur as well. It therefore makes sense to target subarachnoid and intraventricular blood using thrombolytic agents to reduce such secondary complications. This scoping review aims to assess what has been done in dealing with ways to obtain subarachnoid blood clearance.
Materials and methods: A search was conducted using the Pubmed, Medline, Embase and Cochrane databases. The algorithm used was ((Thrombolysis) OR (thrombolytic therapy)) AND (subarachnoid hemorrhage). Articles were excluded if they were about intravascular thrombolysis. No experimental papers on animals were included. Research was limited to articles where all patients taken into consideration were having aneurysmal subarachnoid hemorrhage due to saccular aneurysms, with possible intraventricular extension, and were treated surgically or endovascularly.
Results: Research in the Pubmed database yielded 399 results. After exclusion criteria were applied, 25 articles were finally selected for elaboration. All studies proved that intrathecal thrombolysis contributes to an earlier intracisternal and/or intraventricular blood clearance. A trend towards clinical amelioration in the thrombolysed patient group was observed in the studies that reported comparisons between treatments.
Conclusion: Intrathecal (intracisternal and intraventricular) thrombolysis is a feasible and effective method for accelerating intracisternal or intra-ventricular blood clots. Further studies on

larger patient series are required to obtain statistically significant conclusions on the clinical outcomes.

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Introduction

Subarachnoid hemorrhage has an incidence of 9 per 100000 person-years. The incidence is higher in women than men 1.24 times. This difference starts at 55 years of age and increases after that. It is a form of stroke that accounts for 2 – 5% of all strokes. It has a 50% mortality rate and only 60% of survivors have an acceptable functionality (Zacharia 2010). Although there have been significant improvements in morbidity and mortality, SAH patients still experience persistent cognitive and functional limitations (Rehman 2022). Intraventricular extension of subarachnoid hemorrhage occurs in approximately 45% of cases. Intraventricular hemorrhage can cause obstructive hydrocephalus. (Rosen 2007). Aneurysms are the underlying cause in 85% of cases of spontaneous subarachnoid hemorrhage. (de Rooij, 2007). The amount of blood in the cisterns and eventually in the ventricles are independent factors of secondary damage such as delayed cerebral ischemia, DCI (Claassen, 2001). Therefore, attempts have been made to dissolve intracisternal and intraventricular blood clots to reduce the probability of DCI and thus ameliorate overall patient outcomes. Since surgical evacuation of intracisternal or intraventricular blood clots is not feasible, thrombolytic agents have been applied to reach this aim (Diringer, 2017, Adams 1997, Adamczyck, 2013)

This scoping review intends to explore the parameters of intrathecal thrombolysis in patients with aneurysmal subarachnoid hemorrhage. These parameters can be clarified by seeking answers to the following Research Questions (RQ).

RQ1: What is the route of administration of intrathecal thrombolysis (intraventricular, intracisternal, lumbar)?

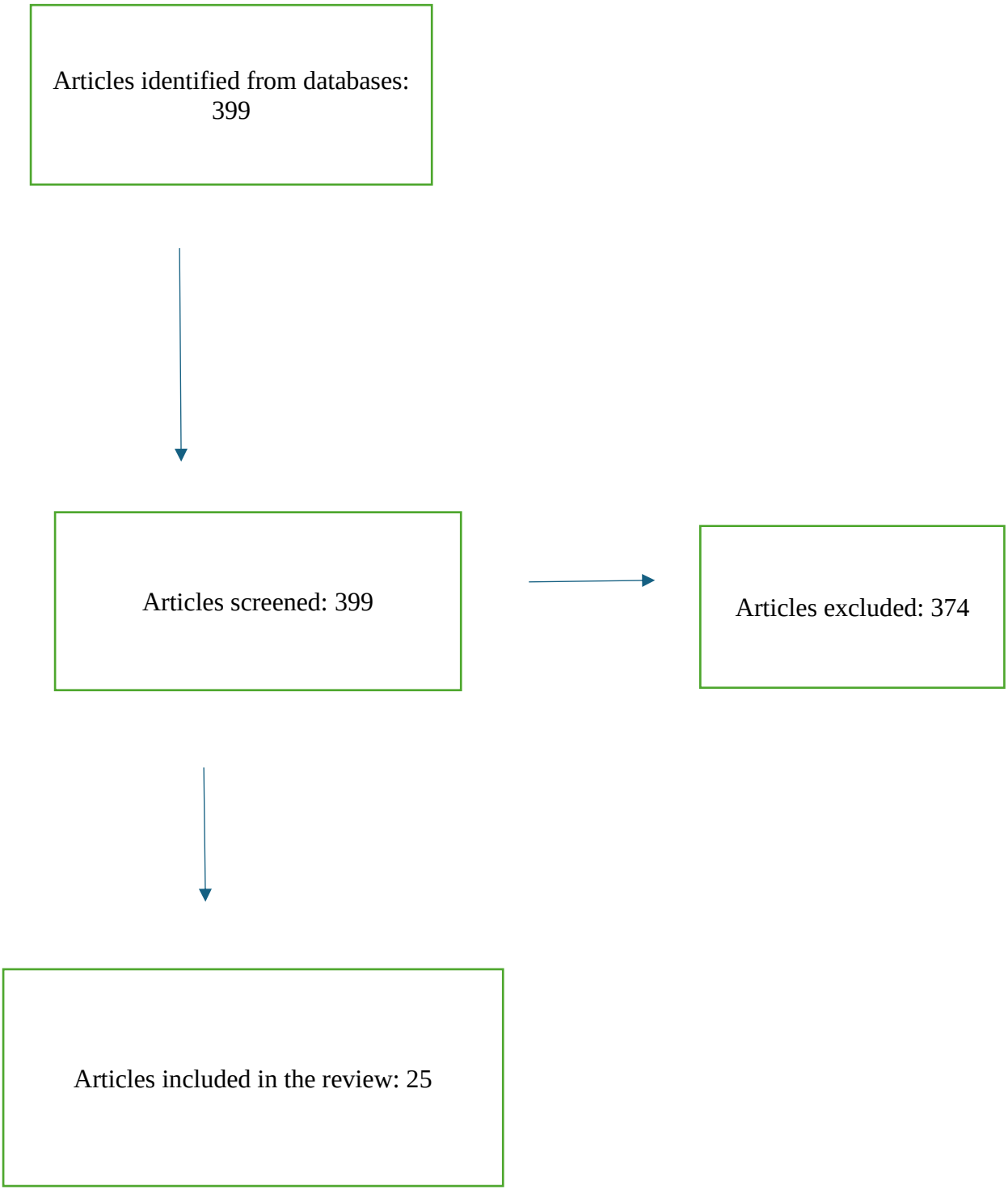
RQ2: What thrombolytic agent is used during intrathecal thrombolysis?

RQ3: What is the dosage of the administered agent?

Search strategy

Protocol: This scoping literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-SCCR) guidelines (Page, 2021) to examine the ways available for dealing with presence of blood in the subarachnoid and intraventricular compartments in patients with aneurysmal subarachnoid hemorrhage.
The review process consists of six stages. Specifically, (i) stating the research questions, (ii) research and identification of the appropriate studies, (ii) evaluating and screening of the identified studies, (iv) data extraction, (v) elaboration of the data extracted, (vi) summarizing and presenting the results.
Eligibility criteria:
Studies such as case reports, observational studies, comparative studies, prospective randomized studies, and randomized control trial studies were included in this review. The studies included were written in English. No restriction was made concerning their publication date. They had to involve human patients. Reviews and meta-analyses were excluded. The research was conducted on April 30, 2024.
Information sources: As information sources, PubMed and Scopus were used.
Conducting the search: The algorithm used was ((Thrombolysis) OR (thrombolytic therapy)) AND (subarachnoid hemorrhage).
Results: Research in the PubMed database yielded 399 results. After exclusion criteria were applied 25 articles were finally selected for elaboration.

Flowchart illustrating the search strategy applied:



Results

The articles taken into consideration are summarized in table 1.

Table 1. articles taken into consideration

Author, year	Study design	Key findings
Eicker SO, (2012).	prospective randomized phase II study	a combination of intraventricular thrombolysis and lateral rotational therapy is not associated with a higher complication rate. Furthermore, the therapy leads to a significant acceleration of the clot clearance rate.
Ohman J, 1991	Prospective study	Reduction of blood and angiographic vasospasm in the treatment group
Moriyama E, 1995	Comparative study	Reduction of blood and symptomatic

		vasospasm in the treatment group
Gerner ST, 2014	Comparative,study	Intarathecal thrombolysis haw established effects on reducing blood clot but not significant effects on shunt dependency and functional outcome.
Litrico S, 2013	Randomized control study	Intraventicular fibrinolysis accelerates blood clot dissolution. Non statistically significant improvement in mortality
Etminan N, 2013	Randomized, open – label phase II study	Concomitant intaventricular fibrinolysis and low frequency head rotation. Higher clotclearance rates but not significant difference in outcome.
Yamamoto T, 2010	Randomized, control study	Intracisternal thrombolysis is effective in reducing clot clearance, neurologic outcome

		and ischemic lesions, especially if given in an intermittent pattern
Hänggi D, 2009	Prospective randomized study	Intrathecal thrombolysis in combination with intrathecal lavage with nimodipine and kinetic therapy proved effective against vasospasm and ameliorated outcome
Hall B, 2005	Case report	Safe intraventricular thrombolysis after coiling of an aneurysm
Findlay JM, 2004	Observational study	Intraventicular thrombolysis assists in clearance of intaventricular clot, normalizing intracranial pressure, and reducing ventricular catheter obstruction
Azmi-Ghadimi H, 2002	Case report – technique presentation	Intraventricular thrombolysis assists in blood clot clearance and functional outcome
Kinugasa K, 1995	Observational study	Intraventricular thrombolysis helps in clearing intraventricular blood clot

Schmidt JH 3rd, 1994	Observational study	Intraoperative intracisternal thrombolysis is an adjunctive treatment with questionable benefit
Usui M, 1994	Comparative study	postoperative intrathecal thrombolytic therapies, are effective in lysing subarachnoid clot and preventing vasospasm and infarction .
Seifert V,1994	Comparative study	Intrathecal thrombolysis prevents delayed neurologic deficits
Tomasello F, 1993	Case report	Intracisternal thrombolysis after surgery clipping results in earlier blood clot clearance.
Stolke D, 1992	Observational study	Single intracisternal bolus of rt -PA accelerates blood clot lysis
Zabramski JM, 1991	Phase I trial	Intra cisternal rt-PA ameliorates vasospasm and blood clot clearance
Hamada et al, 2000	Observational study	Intra cisternal urokinase ameliorates

		vasospasm and blood clot clearance
Sasaki et al 1994	Phase II clinical trial	Intrathecal administration of rt-PA is useful in vasospasm prevention
Varelas et al,2005	Prospective study	Intraventricular thrombolysis is feasible without complications and may be associated with better outcomes.
Ramakrishna, 2010	Prospective controlled study	Intraventricular rt-PA reduces the need for angioplasty for vasospasm and reduces the need for shunt placement in patients with SAH.
Kinouchi H, 2004	Prospective study	intraoperative cisternal irrigation with tPA combined with cisternal drainage is a safe and effective method for the prevention of symptomatic vasospasm in patients with SAH.
Kramer 2014	Prospectve, randomized placebo controlled pilot trial	Intraventricular rtPA accelerates blood clot lysis in patients with SAH.

Mizoi K, 1993	Prospective study	Intracisternal injection of 2 mg rtPA daily is an effective way of preventing vasospasm

Table 2. Intraventicular vs intracisternal thrombolysis

intraventricular	intacisternal	Intraventricular and intracisternal	lumbar	Intraventricular and lumbar
Eiker 2012	Ohman 1991	Seifert 1994	Häng gi et al, 2009	Kinugasa 1995
Gerner 2014	Moriyama 1995			
Litrico 2013	Yamamoto 2010			
Etminan 2013	Schmidt 1994			
Hall 2005	Tomasello 1993			
Findlay 2004	Stolke 1992			
Azmi-Ghadimi 2002	Zabramski 1991			
Varelas 2005	Usui 1994			
Ramakrishna 2010	Hamada 2000			
Kramer 2014	Sasaki 1994			
	Mizoi 1993			
	Kinouchi 2004			

Ten articles reported thrombolysis via an intraventricular catheter. In all of them rt-PA was used as a thrombolytic agent. Twelve articles reported use of intracisternal thrombolysis. In three of

them (Moriyama 1995, Hamada 2000, Hanggi, 2009) urokinase was used, while in the remaining nine, rt-PA was used. All the patients in whom intracisternal thrombolysis was used were treated surgically and the cisternal drainage was placed at the end of the operation of surgical clipping, except the patients in one article (Hamada 2000), who were treated endovascularly. In one article, where both intraventricular and intracisternal ways were followed (Seifert 1994), rt-PA was used. Finally, rt-PA was used in case of lumbar, or intraventricular plus lumbar thrombolysis (Hanggi 2009, Kinugasa, 1995) (Tables 2 and 3).

Table 3. rt-PA vs Urokinase

rt-PA	Urokinase	rt-PA and urokinase
Eiker 2012	Moriyama 1995	Usui 1994
Ohman 1991	Hänggi 2009	
Litrico 2013	Hamada 2000	
Etminan 2013		
Yamamoto 2010		
Hall 2005		
Findlay 2004		
Azmi-Ghadimi 2002		
Kinugasa 1995		
Schmidt 1994		
Seifert 1994		
Tomasello 1993		
Stolke 1992		
Zabramski 1991		
Gerner 2014		
Sasaki 1994		
Varelas 2005		
Ramakrishna 2010		
Kramer 2014		

Mizoi 1993		
Kinouchi 2004		

Eiker et al, in 2012 investigated the effect of intraventricular thrombolysis in combination with low – frequency head motion in the clot clearance rate, vasospasm and clinical outcome. They also searched for eventual complications of this therapy. As thrombolysis agent they used intraventricular application of rt-PA (Actilyse(®)) bolus 5 mg every 12 h, while clot clearance rate was evaluated based on computed tomography. Delayed cerebral ischemia and early clinical outcome of patients were also determined. The conclusions were that there were no complications associated with this therapy, and there was a significant acceleration of the clearance rate of the subarachnoid blood clot (Eiker, 2012).

Ohman J et al, 1991 studied the effect of intrathecal thrombolysis on clot lysis and vasospasm in patients with aneurysmal subarachnoid hemorrhage. Thirty patients with an aneurysmal subarachnoid hemorrhage were selected. Selection criteria were: operation performed by day three of the hemorrhagic event, single or multiple aneurysms secured at the same operation, and blood presence only in the basal cisterns. At the end of the operation for aneurysm clipping a catheter was placed in the basal cisterns and continuous irrigation of physiological saline was performed. After closing the dura, 5 to 10 ml of rinsing solution was aspirated, and rt-PA solution was injected via the catheter. After additional rinsing of 5 ml of saline, the catheter was removed. Three groups of ten were established each receiving a single intracisternal injection of 3, 10, or 13 mg of rt-PA. Parameters assessed were outcome at three months, using the Glasgow Outcome Scale, effect on angiographic vasospasm, which was assessed by performing a control angiography on the operative side between days 7 and 9 after the event of subarachnoid hemorrhage, and effect on Computed tomography findings. Computed tomography findings

were assessed by comparing CT scans performed on the day after the operation, in case of clinical worsening, and as a follow-up examination, after three months of the operation. No difference in overall outcome between groups was observed. In all groups reduction of subarachnoid blood was observed in post-operative CT scans. Significant differences were found in the reduction of SAH grade between groups 10 mg and 13 mg rt-PA. The difference in angiographic vasospasm between groups 3 mg rt-PA and 13 mg rt-PA was also significant (Ohman, 1991)

Moriyama et al, 1995 reported on the combined cisternal drainage and intrathecal urokinase injection for the prevention of vasospasm in patients with aneurysmal subarachnoid hemorrhage. Sixty patients were selected, of whom in 16 no cisternal drainage was placed, in 34 cisternal drainage alone was placed, and in 10 of them cisternal drainage was placed and urokinase injection was performed through it. Cisternal drainage was placed in the chiasmatic or prepontine cistern before dural closure after aneurysm surgery. Analysis of patients without postoperative cisternal drainage demonstrated that the amount of subarachnoid blood on the initial computed tomographic scan was closely related to severe vasospasm. In patients with cisternal drainage, the amount of bloody cerebrospinal fluid (CSF) drained during the 10 days after surgery and the duration of drainage placement were determining factors in preventing vasospasm. A greater quantity of CSF drainage reduced the incidence of permanent neurological deficits caused by vasospasm, but significantly increased the incidence of hydrocephalus requiring shunt procedures. Urokinase was injected in a dose of 60,000 U in a sterile saline solution and the drainage was occluded for 1 hour. The procedure was repeated two to four times over 2-3 days. Urokinase injection achieved a further reduction in the occurrence of severe vasospasm. The authors concluded that intrathecal thrombolytic therapy after aneurysmal surgery is an effective method for severe vasospasm and delayed neurologic deficit prophylaxis, and CSF drainage (> 1500 ml for 10 days) enhances these effects (Moriyama 1995).

Gerner et al, in 2014 investigated the effects of intraventricular fibrinolysis in a series of 88 patients with subarachnoid hemorrhage. Inclusion criteria were intraventricular extension, requiring external ventricular drainage in the first 48 hours, and endovascular coiling of the underlying aneurysm. They used rt-PA as fibrinolytic agent in 14 of them. Intraventricular fibrinolysis was not commenced before six hours after placement of the external ventricular drainage, and not before 24 hours after endovascular coiling. If other non secured endovascularly aneurysms were present, no intraventricular fibrinolysis was applied. The dosage of rt-PA was 1 mg or 2x 0,5 mg in case of bilateral external ventricular drainage, every eight hours until the achievement of clot clearance in the third and fourth ventricles, as assessed by CT scans performed. They performed routinely CSF cell counts after 24- 72 hours and administered antibiotics in case of diagnosis of infection. Assessment of vasospasm was made using transcranial Doppler. The endpoints investigated were shunt dependency and overall outcome. Although they found significant improvement in blood clot dissolution, they found no significant difference in functional outcome and shunt dependency between groups (Gerner 2014).

Litrico et al 2013 aimed to assess the safety and efficacy of intraventricular fibrinolysis in patients with aneurysmal subarachnoid hemorrhage with intraventricular extension. Patients were randomly assigned into two groups: those treated with external ventricular drainage alone (eight patients), and those treated with external ventricular drainage and intraventricular thrombolysis (eleven patients). Recombinant tissue plasminogen activator (rt-PA) was used as a thrombolytic agent. A review of the then-existing literature was also performed. Mortality at 30 days was lower in the thrombolysis group but not statistically significant. Clearance of the blood clot was earlier in the thrombolysis group. This result was statistically significant. No statistically significant complications were found between groups. Similar results (longer survival in the thrombolysis group but not statistically significant) were found in the literature review. The authors concluded that intraventricular thrombolysis is as safe as external ventricular

drainage alone and accelerates intraventricular clot resolution. It also seems to improve survival (Litrico 2013).

Etminan et al 2013 sought to investigate the effect of intraventricular fibrinolysis in association with low-frequency head motion therapy in patients with aneurysmal subarachnoid hemorrhage treated surgically or endovascularly. To this end, they randomized sixty patients with aneurysmal subarachnoid hemorrhage with ventricular extension requiring placement of external ventricular drainage into two groups after aneurysm treatment. In the first group of thirty patients, intraventricular recombinant tissue plasminogen activator was applied, associated with lateral rotational therapy of the head. In the other group, no such measures were applied. As a treatment, 5mg of rt-PA diluted in 2ml of NaCl 0,9% was given as an intraventricular bolus every 12 hours for 48 hours. Daily CT scans were performed until a day after treatment, while daily CSF samples were taken until the removal of the ventricular catheter to rule out infection. The primary endpoint was functional outcome measured by Glasgow Outcome Scale (GOS) at discharge and at three-month follow-up. Secondary endpoints were clot clearance rate, radiographic evidence of delayed cerebral ischemia and post-hemorrhagic hydrocephalus. Although there was an earlier clot clearance in the treatment group, no significant differences were found in overall survival, functional outcome, delayed cerebral ischemia and post-hemorrhagic hydrocephalus. It was, however, noted that most patients (78%) had severe subarachnoid hemorrhage (SAH WFNS grade was II to V and Fisher grade was III to IV). So the authors suggested that the severity of the primary brain damage may have not allowed any potential benefits of fibrinolytic therapy to be expressed. (Etminan 2013).

Yamamoto et al, 2010 investigated the effect of intracisternal administration of tissue plasminogen activator for the prevention of cerebral vasospasm after subarachnoid hemorrhage. To this end, they chose sixty patients with aneurysmal subarachnoid hemorrhage after surgical treatment. The sixty patients were

divided into three groups, each consisting of twenty patients. In the control group treatment was with “baseline” treatment, the second group, (“intermittent” group) intermittent administration of rT-PA was performed, and in the third group rt-PA96 IU/ml was infused at 20ml/hr for 48 hours. They found that in the intermittent and continuous groups, the subarachnoid clot was significantly removed compared to the control group. The intermittent group had also better outcomes and also significantly lower ischemic lesions. The authors concluded that cisternal thrombolysis is effective in reducing clot clearance, neurologic outcome and ischemic lesions, especially if given in an intermittent pattern (Yamamoto et al, 2010).

Hänggi et al, 2009 investigated the effect of intracisternal thrombolysis on symptomatic vasospasm in patients with severe subarachnoid hemorrhage. Twenty patients with WFNS grades 2 to 5 were enrolled. Nine of them were treated and eleven served as controls. A ventricular drain was inserted, securing of the aneurysm by a microsurgical or endovascular route was performed, and two lumbar catheters were inserted. Then, intracisternal lysis with urokinase 120 000 IU daily was performed in a continuous infusion for 48 h in the patients of the study group through one lumbar catheter. The urokinase was dissolved in 500 cc of Ringer’s solution. Intrathecal pressure was monitored using the second lumbar catheter. Daily CT scans were performed to monitor blood clot lysis and reveal any potential hemorrhage. After intracisternal lysis, intrathecal nimodipine lavage was applied for the following seven days. For comatose patients, kinetic head-rotation was also performed. No delayed neurologic deficit was found in the study group among the patients who were awake. Two delayed neurologic deficits were found in the control group. The transcranial Doppler evidenced no difference in flow velocities over an average period of fourteen days. Vasospasm-related infarction on CT scan was revealed in two patients of the control group, whereas evident vasospasm on DSA appeared in three patients of the study group and with 7 patients in the control group. However, in two consecutive patients randomized to the study group a

paresis of the lower extremities occurred. Thus, the study was stopped. The authors concluded that trans lumbar lysis in combination with kinetic therapy followed by intrathecal nimodipine lavage gave promising results against cerebral vasospasm and for clinical outcome (Hänggi 2009).

Hall et al 2005 reported on a case of an aneurysmal subarachnoid hemorrhage with intraventricular extension on which, after coiling of the underlying anterior communicating aneurysm, intraventricular thrombolysis using rt-PA was performed. The authors concluded that the administration of intraventricular rt-PA after endovascular coiling of a ruptured cerebral aneurysm was a safe procedure (Hall, 2005).

Findlay et al 2004 reported on a cohort of fifteen patients with aneurysmal subarachnoid hemorrhage with ventricular extension. The aneurysms were treated surgically, and the patients had an external ventricular drainage. rt-PA was used intraventricularly as a single intraoperative injection. The concentration of rt-PA was from 7.5 to 15 mg. The aim was to assess the clot clearance rate. In 14 of those patients, there was partial to complete blood clot removal. No vasospasm was detected in six patients on the follow-up angiography, while moderate vasospasm was detected in the remaining eight patients. The patient who did not have clot lysis developed symptomatic vasospasm and died eight days later. They concluded that Intraventricular thrombolysis with rt-PA assists in, accelerating the clearance of intraventricular blood clots, lowering intracranial pressure, and preventing catheter occlusion (Findlay 2004).

Azmi-Ghadimi et al 2002 reported two cases of massive intraventricular hemorrhage due to aneurysmal subarachnoid hemorrhage. The patients were treated with coiling and then intraventricular tissue plasminogen activator (tPA) was administered. Rapid clot resolution was demonstrated radiographically in both. Both patients survived and had a meaningful functional neurological recovery. The authors

concluded that it was safe to administer intraventricular rt-PA after endovascular coiling in patients with aneurysmal subarachnoid hemorrhage and ventricular extension to accelerate blood clot clearance and ultimately patients treated have better outcomes. (Azmi-Ghadimi et al 2002).

Kinugasa et al 1995 reported on twelve patients with subarachnoid hemorrhage of Hunt and Hess neurological Grades III to V who underwent endovascular treatment of the aneurysms within 23 hours of aneurysm rupture. All of them had an intraventricular extension of hemorrhage. After aneurysm treatment, all patients were administered tissue plasminogen activator (TPA) through spinal or ventricular catheters. Ten patients showed complete clearance of the cisternal clot on CT within 72 hours. Seven of these patients had partially thrombosed aneurysms and five had multiple aneurysms that were clipped during delayed surgery. One patient had mild vasospasm on the follow-up angiogram. Eight patients had clinical improvement, two had severe disability, and two died. The authors concluded that endovascular treatment of a ruptured aneurysm followed by immediate post-coiling administration of TPA may be a safe means of preventing vasospasm and improving patient outcome (Kinugasa et al 1995).

Schmidt et al 1994 reported on fifteen patients who had aneurysmal subarachnoid hemorrhage with significant basal cistern blood accumulation. All patients underwent aneurysm clipping within four days after subarachnoid bleeding. Transcranial Doppler performed postoperatively demonstrated reduction of vasospasm in patients treated with rt-PA than in patients managed without the rt-PA treatment. 80% of patients receiving intracisternal rt-PA had good results compared with 78% of another group of patients who also underwent surgery shortly after subarachnoid hemorrhage and were not given rt-PA. The authors concluded that intracisternal rt-PA remains an adjunctive treatment of questionable benefit in the management of patients with aneurysmal subarachnoid hemorrhage (Schmidt et al 1994).

Usui et al 1994 reported the results of early surgery and intrathecal thrombolytic therapy in a retrospective series of 111 patients with aneurysmal subarachnoid hemorrhage. 60 of these patients were treated with urokinase 60,000 IU/d for 7 days, 22 patients were treated with 0.043 to 1 mg tissue plasminogen activator every 6 to 8 hours for five days, and 29 patients received no treatment. All patients underwent surgery for aneurysm clipping within the first 48 hours after the onset of subarachnoid hemorrhage. A catheter was placed in the basal or prepontine cisterns and in the treatment group another catheter was placed in the periphery of the Sylvian fissure or on the convexity of the brain. When indicated, an intraventricular catheter was also placed. Urokinase treatment commenced immediately after clipping with 60000 IU dissolved in 500 ml Ringer's lactate per day. On the contrary, in the rt-PA group, treatment was initiated 24 hours after clipping surgery. rt-PA was administered every six hours for five consecutive days (at least three days). The endpoints investigated were clot clearance, vasospasm evidenced angiographically and symptomatically, cerebral infarction, and overall patient outcome. No differences in overall outcome were observed among the three groups after three months. There was however earlier blood clot lysis in the treatment groups. The severity of angiographic vasospasm and the incidence of infarction were also less frequent in the treatment than in the no-treatment group. The authors concluded that postoperative intrathecal thrombolytic therapies, are effective in lysing subarachnoid clot and preventing vasospasm and infarction (Usui 1994).

Seifert et al 1994, reported a series of patients with aneurysmal subarachnoid hemorrhage in a prospective study. 52 of the patients were treated with intrathecal tissue plasminogen activator (rt-PA). All of these patients were operated within 72 h after SAH. Patients had a SAH according to Fisher's grade III, as a prerequisite for inclusion into the study. In 21 patients intraventricular bleeding was also detectable. 68 patients, which were also treated surgically within 72 h after SAH served as controls. After the aneurysm had been clipped, 10 mg of rt-PA, dissolved in 10 ml of its solution

fluid, were slowly instilled into the basal cisterns in the treatment group. In 15 patients with additional intraventricular bleeding, 5-10 mg of rTPA were injected into the ventricles via an intraventricular catheter at the end of the operation. In two patients with intraventricular hemorrhage, due to complete clotting of the ventricles more intraventricular rtPA was administered on postoperative days 1, 2 and 3. Patients had transcranial Doppler on a daily basis and CT scans were performed on postoperative days 1, 2, 5, and 10. The patients were graded according to the Glasgow Outcome Scale three months after the event. The occurrence of clinical signs of delayed ischaemic deficits (DID), attributable to the occurrence of cerebral vasospasm, was the only defined endpoint of the study. Blood clot removal, was achieved in all patients treated. The authors concluded that that intrathecal thrombolysis is an effective and safe method for removal of intracisternal blood accumulations after SAH, resulting in a significant reduction of symptomatic vasospasm and delayed ischaemic neurologic deficit (Seifert 1994).

Tomasello et al 1993 reported a case of a patient who underwent surgery within 24 hours of aneurysm rupture and was administered recombinant tissue plasminogen activator (rt-PA) directly into the basal subarachnoid cisterns after aneurysm clipping. The patient had diffuse thick subarachnoid blood clots on CT. The rt-PA was given as a single injection of 10 mg. An almost complete clot clearance was demonstrated on CT scans carried out on day 2 and day 4 after surgery. No evidence of vasospasm or delayed cerebral ischemia was detected. The authors concluded that intracisternal thrombolysis with rt-PA can be achieved with relative safety with potential benefits on vasospasm and delayed cerebral ischemia (Tomasello 1993).

Stolke et al 1992 reported the use of intracisternal thrombolysis in 20 patients with aneurysmal subarachnoid hemorrhage. All patients underwent operation in the first 72 hours after the stroke. After surgical clipping, a single bolus of 10 mg of recombinant tissue plasminogen activator rt-PA was injected into the basal

cisterns. The endpoints assessed were vasospasm and Glasgow Outcome Scale (GOS). All patients demonstrated radical clot removal. Daily transcranial Doppler detected accelerated blood flow velocity, and thus vasospasm in 16 patients. GOS was grade I and II in 16 patients and III in two patients. Two other patients died, one from bowel perforation and one from delayed ischemic deficits.The authors concluded that intracisternal injection of rt-PA is a safe procedure that accelerates blood clot lysis and reduces delayed cerebral ischemia (Stolke 1992).

Zabramski et al, 1991 reported the results of a preliminary Phase I trial of intracisternal rt-PA in 10 patients with aneurysmal subarachnoid hemorrhage (SAH). Patients were Grade III or IV (according to Hunt and Hess) with (Fisher Grade 3). Ventriculostomy and surgery for securing the aneurysms were performed within 48 hours of hemorrhage. In one of the patients, 10 mg rt-PA was instilled into the subarachnoid cisterns before closing the dura. In the remaining nine patients, a catheter was left in the subarachnoid cisterns and rt-PA (5 mg in four cases or 1.5 mg (0.5 mg every 8 hours for three infusions) in five cases) was instilled 12 to 24 hours after surgery. Analysis of cisternal cerebrospinal fluid samples was made, which revealed thrombolytic tissue plasminogen activator (t-PA) levels for 24 to 48 hours. the authors focused on revealing postoperative vasospasm. To this end cerebral angiographies 7 to 8 days after rupture were performed, which disclosed mild to moderate vasospasm in nine patients, while one patient with posterior inferior cerebellar artery aneurysm had severe non symptomatic focal spasm of the vertebral arteries. The authors concluded that postoperative treatment with rt-PA may be effective in reducing the severity of delayed cerebral vasospasm. (Zabramski 1991)

Hamada et al, 2000 reported the results of urokinase treatment in 15 patients with aneurysmal subarachnoid hemorrhage after endovascular coiling of the aneurysm. At the end of the embolization session, a lumbar catheter was advanced till the

cisterna magna and urokinase 60000 IU were administered for two or three days once or twice daily. In eight of these patients, thrombolytic therapy was administered within the first 24 hours after the ictus, while in the remaining seven thrombolytic therapy was administered 24 to 48 hours after the ictus. In those patients that thrombolytic therapy was administered within the first 24 hours, almost complete clearance of the clot was achieved in the first two days, while in those patients that thrombolytic therapy was administered between 24 and 48 hours after the insult, clearance of the clot was achieved at the latest 4 days after the stroke. None of the patients developed permanent neurological deficit as a result of vasospasm. None of the patients developed hydrocephalus. Glasgow Outcome Scale assessment after three months revealed good recovery in all patients. The authors concluded that administering urokinase via the cisterna magna is a reasonable way of clearing cisternal clots and thus preventing vasospasm and eventually improving overall outcomes (Hamada, 2000)

Sasaki et al, 1994 reported the results of a Phase II clinical trial of intrathecal recombinant tissue-type plasminogen activator for the prevention of vasospasm. The subjects examined were 53 patients with aneurysmal subarachnoid hemorrhage who underwent surgical clipping within the third day after bleeding. The patients were divided into three groups. Tissue-type plasminogen activator was intracisternally administered 24 hours after surgery in doses of 0,1, 0,2 or 0,4, three times daily for 5 days. They observed rapid clot clearance in the three groups, which were characterized as effective or highly effective. The clot-dissolving effect was slightly slower in the 0,4 group. No severe vasospasm was observed. They concluded that repeated intrathecal administration of tissue-type plasminogen activator is useful for preventing vasospasm even in the low dose of 0.1 mg (Sasaki, 1994).

Varelas et al, 2005 reported the results of a clinical trial, in which ten patients with SAH with intraventricular extension received rt-PA therapy via an intraventricular catheter after the aneurysm had

been secured. In four patients the aneurysm was secured surgically while in six patients the aneurysm was coiled. These patients were matched with 10 age-, sex-, and Glasgow Coma Scale score-matched patients who served as controls. Each dose was 2mg lyophilized tPA diluted in 2 ml of sterile water for injection. Patients received three doses of rt-PA (one patient), two doses (three patients), or a single dose (six patients) within the first five days of hospital admission. The primary endpoint was third and fourth ventricle blood clot resolution. rt-PA-treated patients had a, non-statistically significant, shorter length of stay, decreased mortality, and better Glasgow Outcome Scale at discharge. They also showed a reduced need for shunt placement. The authors concluded that intra-ventricular administration of tPA is feasible SAH and may be associated with better outcomes (Varelas, 2005).

Ramakrishna et al, 2010 aimed to assess whether intraventricular administration of tissue plasminogen activator (rt-PA) may result in less vasospasm or less need for cerebrospinal fluid shunting procedures. Their study was a retrospective case-control study. They reported on 41 patients (rt-PA group, Hunt and Hess 3, 4, 5) from 2007 to 2008, who received intraventricular rt-PA and lumbar drainage for a minimum of 5 days (range 5-7 days). A group of 35 patients from 2006 to 2007 (Control, HH 3, 4, 5) served as controls. All patients had an early (within 48 hours) treatment of the aneurysm, either surgically, or intravascularly. All of the patients had intraventricular extension of the hemorrhage requiring ventriculostomy. A lumbar drain was also placed in patients whose post-treatment CT scan showed no risk for herniation. The dosage was 5 mg in 2 ml of normal saline. The next dose was administered 24 hours after the previous one for a total of seven doses, that is seven days. CT scans of the head were performed daily, to rule out hemorrhagic complications. As a means of assessment, neurologic examination (for those who were awake), transcranial Doppler, and neurologic examination at three months were used. Facts recorded were endovascular vasospasm treatments and the numbers of ventriculoperitoneal shunts placed. Patients in the treatment group had lower percentages of shunt placements, angioplasties for

vasospasm treatments, numbers of vessels treated by angioplasty and numbers of days in severe vasospasm as recorded by transcranial Doppler. (Ramakrishna, 2010).

Kinouchi et al, 2004, investigated the efficacy of intracisternal thrombolysis using rt-PA in patients with aneurysmal subarachnoid hemorrhage. They studied 70 patients with subarachnoid hemorrhage who were treated surgically within the first 48 hours. During the operation, a bolus injection of 1,6 or 3,2 mg or rt-PA was injected in the exposed cisterns. Subsequently, cisternal catheters were placed and kept in place until day 14. If on postoperative CT scan blood clot could be detected, additional rt-PA (0,8mg/day) was injected until high-density areas on CT scans disappeared. This additional rt-PA dose was necessary in four of the 55 patients who received 1,6 mg rt-PA. Three of 70 patients developed vasospasm. They concluded that cisternal irrigation of rt-PA associated with cisternal drainage is a safe and effective way for the prevention of symptomatic vasospasm in patients with subarachnoid hemorrhage (Kinouchi 2004).

Kramer et al, 2014 reported on a group of 12 patients who were randomly allocated to treatment or control subgroups. These patients had aneurysmal subarachnoid hemorrhage treated intravascularly. There was also ventricular extension of hemorrhage, which required external ventricular drainage. rt-PA was used as a thrombolytic agent at a dosage of 2 mg every twelve hours for no more than five doses. The authors were concerned with safety, feasibility, and rate of clearance of intracranial blood clots as primary outcomes, while they were also concerned with radiographic vasospasm, need for ventriculoperitoneal shunt placement, and 6-month neurological status, as secondary outcomes. Intracranial blood clearance was quicker in the treatment group. It was noted that much of the blood clearance was obtained after a single dose. No statistically significant differences were observed in outcome at six months, vasospasm, or the need for shunt placement. The authors concluded that rt-PA thrombolysis was a safe and feasible way of accelerating blood clot

clearance. They also highlighted the need for similar studies on a larger scale (Kramer 2014).

Mizoi et al, 1993 conducted a study reporting on the intracisternal use of rt-PA in patients who underwent aneurysm surgery within 48 hours after the onset of subarachnoid hemorrhage. Intracisternal drainage was placed in all patients after surgery. 105 patients were selected, 30 of them were placed in the treatment group and 75 of them were placed in the control group. The distinction between the two groups was made based on the mean CT density of the blood in the subarachnoid space. Thus, the treatment group had subarachnoid blood clots with mean scores of CT density of more than 75 Hounsfield units. The control group had subarachnoid blood clots with mean scores of CT density of less than 75 Hounsfield units. rt-PA was administered at a dosage of 2 mg daily beginning 24 hours after the operation until all the cisterns were cleared of blood as depicted by low density at CT of the basal cisterns. As monitoring studies for vasospasm and delayed ischemic neurologic deficit (DIND), DSA (Digital Subtraction Angiography) and SPECT (Single Photon Emission Tomography) were used respectively. In none of the 30 patients in the treatment group did SPECT show evidence of cerebral ischemia, although in 4 of them angiography did show angiographic vasospasm (severe vasospasm in one case). In the control group, eleven patients developed vasospasm and in five of them a transluminal balloon angioplasty was performed. The authors concluded that intracisternal injection of 2 mg of rt-PA daily for five days is a feasible and effective means for preventing vasospasm in patients with aneurysmal subarachnoid hemorrhage after the aneurysm has been secured (Mizoi, 1993).

Discussion

Since extravascular blood in the intracranial compartment can cause cerebral vasospasm and delayed cerebral ischemia, it makes sense to try to dissolve this blood by means of thrombolysis. Three ways of administering drugs into the subarachnoid space

have been described: intraventricular, intracisternal and lumbar. Intracisternal administration of drugs can be done before dural closure after surgical clipping of the aneurysm and can be done once (single dose of thrombolytic drug) or an intracisternal tube can be left in place in case of administration of more doses. Intraventricular administration of drugs requires the placement of an external ventricular drainage device, which is routinely placed in case of intraventricular extension of basal ganglia or subarachnoid hemorrhage. Administration of drugs via a lumbar catheter has also been described. All studies show that intracisternal or intraventricular thrombolysis accelerate blood clot clearance. Thrombolysis must be done after the aneurysm has been secured, either surgically or endovascularly. The catheter is placed intracisternally only in case of surgery, before dural closure, while the intraventricular catheter is placed before any treatment as protection from acute hydrocephalus.

Conclusion

The studies analyzed in this review show that intrathecal fibrinolysis can be safely applied in patients with subarachnoid hemorrhage with intraventricular extension after securing of the aneurysm. This treatment does not have hemorrhagic complications, while facilitates blood clot lysis, reduces the incidence of secondary vasospasm, prevents delayed neurologic damage and the need for ventriculoperitoneal shunt placement. It also increases overall survival and ameliorates Glasgow Outcome Scale. Further studies need to be done in larger series of patients for these results to gain statistical significance.

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