Cisternal urokinase irrigation for prevention of vasospasm after aneurysmal subarachnoid haemorrhage – a pilot study

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KEY WORDS

cisternal
vasospasm
thrombolysis
urokinase
antibiotic

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ABSTRACT

Background: The optimal treatment for cerebral vasospasm is far from established, despite numerous trials. Intracisternal fibrinolytic therapy after clipping of aneurysm can enhance the clearance of subarachnoid blood and reduce severity of CV. The risk of infection, haemorrhage and lack of proper dosage schedule, however has precluded widespread use of cisternal irrigation. **Purpose:** We present a pilot study conducted to develop a protocol for cisternal irrigation, studying the efficacy and safety of the procedure. **Methods:** Over a period of one year, 25 patients of aneurysmal subarachnoid bleed, having Fisher grade III on CT scan and Hunt and Hess II were subdivided into study and control group. The study group receiving cisternal irrigation consisted of 9 patients and control group 16 patients. Cisternal irrigation was carried in the study group using Urokinase-Ringer lactate (UK-RL) solution (120 IU/ml) at the rate of 30 ml/hr, 12 hours after aneurysm clipping. Cerebral vasospasm was diagnosed using Sasaki's clinical criteria or TCD velocity (>120cm/second) in the middle cerebral artery. Surgical outcome at discharge and six months were assessed using Glasgow outcome scale. **Results:** The incidence of symptomatic vasospasm was 44.1% in the study group and 68.8% in the control group. Based on the TCD criteria, cerebral vasospasm occurred in 44.4% in the study group and 60% in the control group. The cisternal drainage duration ranged from 2 to 5 days. Total amount of drained equivalent blood was 8-155 ml. Two patients in the study group developed fatal meningitis. None of the patients developed haemorrhagic complications. **Conclusion:** The study revealed that cisternal irrigation remains an alternative technique to combat cerebral vasospasm. Overzealous use of antibiotics, especially with neurotoxic preservatives may be counter-productive.

doi : 10.5214/ans.0972.7531.2010.170106

Introduction

Cerebral vasospasm (CV) after aneurysmal subarachnoid haemorrhage remains a major cause of death and disability.[1] Upto 15% patients suffer from ischaemic neurological deficits or death due to cerebral vasospasm inspite of maximal therapy.[2] Over the past three decades, despite numerous studies on aneurysmal cerebral vasospasm, optimal treatment is far from established.[3] Experimental and clinical evidence suggest that the risk of developing cerebral vasospasm correlates with the amount of cisternal blood and may be related to the degradation products including oxyhaemoglobin.[4] Early aneurysm clipping is advocated to prevent rebleeding and to remove the subarachnoid blood.[5] However, complete clot removal may not be feasible.[5] Intracisternal fibrinolytic therapy may enhance the clearance of subarachnoid haematoma, reducing the severity of cerebrovascular vasospasm.[6] Both the urokinase[7] and tissue plasminogen activator[8] (tPA) have been used to clear the residual subarachnoid clot. Cisternal irrigation has not been a common practice due to feared complications of meningitis and haemorrhage.[2,9]

In the present study, we describe the role of cisternal irrigation with urokinase, its efficacy and safety in preventing vasospasm and the clinical outcome at 6 months.

Methods

Patients selection

Twenty-five patients having aneurysmal subarachnoid haemorrhage were selected over the span of 6 months. Inclusion criteria were ;

1) Patients with Fisher grade III on the presenting CT scan5
2) Patients between 18 and 75 years of age
3) Pre-operative Hunt and Hess grade II.[10]

Twenty-five patients, included in the study were divided into study and control group(9 in the study and 16 in the control group). Exclusion criteria for patients in the study group included ;

1) pregnant and post partum females
2) known history of bleeding disorder.

Informed consent was obtained from each patient's authorized representative. All patients in the study and control group received hypertension, haemodilution and hypervolaemic (HHH) therapy and oral nimodipine as per routine protocol of the department.

Procedure of cisternal irrigation in the study group

Cisternal irrigation therapy was performed only from the operated sylvian fissure, irrespective of the location of subarachnoid hematoma. After aneurysm clipping, irrigation tubes were inserted in the sylvian fissure (as the inlet for irrigation) and in pre-pontine/chiasmatic cistern (as the outlet). At scalp, the drain sites were painted with 10% povidone-iodine solution and covered with sterile gauze dressings. Chhabra

external ventricular drainage tubes (Surgiwear, India) were used as irrigation tubes. Drained irrigation fluid (DIF) was collected in the drainage bag. Cisternal irrigation solution contained urokinase in ringer lactate (UK-RL) solution (KD-Unase, Keystone pharmaceuticals Inc, USA) at the concentration of 120 IU/ml. No antibiotic was used in the RL-UK solution in Patients 1 and 2. Gentamicin with a preservative was added to the irrigation fluid at a dose of 60 mg/500 ml (120 μg/ml) in Patient 3 and 4. The concentration was 4 mg/500ml without preservative (8 μg/ml) of UK-RL solution in patients 5 to 9. After surgery, RL solution without UK was infused for the first 12 hours at a rate of 30 ml/hr and a CT scan was done to rule out postoperative haematoma. After 12 hours of aneurysm clipping, cisternal irrigation with UK-RL solution was continued at the rate of 30 ml/hr. The total volume of the infused and Drainage irrigation fluid (DIF) were measured regularly to avoid excessive infusion.

Drainage irrigation fluid (DIF) parameters

DIF was collected daily until the termination of irrigation. The various parameters examined after the fluid had accumulated for 24 hours were – red blood cell (RBC) count, total drained volume, fibrinogen degradation product (FDP) level, white blood cell (WBC) count, glucose, protein, gram stain and bacterial culture. Total drained blood volume was calculated from red blood cell count and supernatant haemoglobin.

Peripheral blood parameters

The safety of therapy was investigated by examination of peripheral blood parameters, like RBC count, haemoglobin, fibrinogen, prothrombin time, activated partial prothombin time (aPTT), FDP, D-dimers, WBC count and platelet count.

Termination of irrigation was determined on the basis of following DIF parameters - RBC count $<10,000/mm^3$; FDP levels <10 μg/ml and 5 days of irrigation.

Occurrence of cerebral vasospasm

Both the control and study groups were assessed for the occurrence of vasospasm using several criteria. The presence of symptomatic vasospasm was clinically based on Sasaki's criteria[9]–insidious onset of confusion, drowsiness or focal deficits occurring from days 4-14 after SAH; 2) negative CT findings to rule out rebleeding, hydrocephalous or infarct; 3) no other identifiable causes of neurological deterioration such as electrolyte disturbance, hypoxia or seizure. The changes lasting for a minimum of 8 hours were considered.[9]

The first CT scan was performed within 24 hours of surgery and then post operatively when the patient's neurological condition worsened. All patients underwent alternate day transcranial Doppler (TCD) ultrasound, mean flow velocity of >120 cm/sec in the middle cerebral artery was taken as TCD evidence of CV.[11]

Definition of complications

The safety of cisternal irrigation therapy was investigated for the occurrence of complication like haemorrhage or infection (meningitis). Septicemia was diagnosed if patients had features of Systemic inflammatory response syndrome (SIRS) with a positive bacterial culture.[12] Gentamicin neuronal toxicity due to overdose or use of preservative was considered in patients who showed neurological deterioration in the absence of CV, infection, haemorrhage (intracranial) or electrolyte abnormalities. The outcome was studied at 6 months by using Glasgow outcome scale (GOS).[13]

Results

The details of all patients in the study group are given in table 1.

Table 1: Details of patients in study group
(GOS=Glasgow outcome scale)

	Age/ sex	Irrigation days Vasospasm	Drained Blood volume			GOS	Cause of death
			TCD	Clinical	(ml)		
1.	45/F	3	+	+	56	death	meningitis
2.	28/F	3	+	+	21	death	meningitis
3.	36/M	2	-	-	8	V	
4.	40/M	3	+	+	11	death	gentamicin toxicity
5.	70/F	3	-	+	29	V	
6.	35/M	5	-	-	155	V	
7.	30/F	3	-	-	18	V	
8.	40/F	5	+	-	103	V	
9.	24/M	5	-	-	45	V	

Occurrence of cerebral vasospasm (CV)

Symptomatic vasospasm using clinical criteria occurred in 44.4% in the study group A and in 68.8% in group B (control group). Using Trans-Cranial Doppler evidence of velocity in MCA >120 cm/sec, vasospasm occurred in 44.4% in group A and 60% in group B.

Drainage irrigation fluid (DIF) parameters

The number of days of irrigation ranged from 2-5 days (mean 3.5 +/- 1 day) Total amount of blood drained ranged from 8 to 155 ml. Of the 9 patients who received intracisternal irrigation, total amount of blood volume drained was <50 ml in 6 patients, 50-100 ml in 1 patient and >100 ml in 2 patients.

Over the irrigation period, the mean value of daily WBC count ranged from 75 to 198 per mm^3; mean daily glucose ranged from 34 to 56.3 mg/dl and protein from 155 to 275.3 mg/dl. The WBC counts in the drainage fluid were high in many patients. The counts started falling by day 3 of irrigation and had returned to normal value by the end of the irrigation.

Occurrence of complications

Two patients (16.7%) who did not have antibiotic in the irrigating fluid developed meningitis in the study group A. Bacterial culture of cisternal fluid showed growth of *E.coli* in the first patient on second day of irrigation. Irrigation was continued for 3 days with intravenous antibiotics as per sensitivity report. Another patient showed growth of *klebsiella pneumoniae* from cisternal fluid and blood. Intravenous antibiotics were given and drains were removed by day 3 of irrigation. Both the patients died inspite of receiving intravenous antibiotics. There was no incidence of intracranial bleeding. Following these complications, gentamicin was added to irrigation fluid. There was no

incidence of meningitis in patients receiving gentamicin in the cisternal irrigation fluid. However, gentamicin toxicity could have occurred in 2 of the patients one of whom died (even though he received gentamicin in the irrigation fluid) at the concentration of 60 mg/500 ml of RL-UK solution (120 μg/ml) either due to preservative methyl paraben or dosage of the drug. No adverse effect was noted in cisternal irrigation of 5 patients who received preservative free gentamicin at a lower concentration of 4 mg /500 ml (8μg/ml) of RL-UK solution. There was no case of meningitis in the control group B.

In the control group B, 5 patients (31.2%) developed evidence of septicemia while three patients (33%) showed evidence of septicemia in the study group A.

Outcome

Out of 9 patients in the study group, 3 patients (33.3%) died while 6 (66.7%) patients had good clinical outcome. In the control group, out of 16 patients, 1 patient (43.7%) died during the hospital stay while one (5.3%) had permanent neurological deficit and eight (50%) had good clinical outcome.

The first two deaths occurred primarily due to infection through cisternal irrigation leading to meningitis. The third death could have occurred due to high dose of gentamicin or methylparaben. The last 5 patients had good outcome following cisternal irrigation.

Discussion

CV after aneurysmal subarachnoid haemorrhage(SAH) continues to be a major cause of death[1] and disability since its original description by Robertson.[14]

Clinical and experimental studies suggest that the risk of developing vasospasm is related to the amount of blood in the basal cistern. Previously reported that vasospasm was found in almost all cases with a thick and widespread subarachnoid clot on CT scan (grade III according to their grading scale). Hence, the most appropriate method to prevent CV, would demand early and complete removal of the clot.

Experimental studies demonstrated that intracisternal fibrinolytic therapy can enhance the clearance of blood from subarachnoid space and reduce the severity of vasospasm.[6] Irrigation therapy with urokinase(UK) was first reported by Yoshida *et al,*[16] in 1983. Since then, both UK and tissue plasminogen activator (tPA) have been used to clear the residual clot. However, an established method has not evolved due to the differences in the dosage, the application methods and the rate of haemorrhagic complications associated with tPA.[1] Haemorrhagic complications with tPA have been reported to be 20.5% (55/268)[1] and 1.9% with UK.[2]

The impact of any therapy on CV is confounded due to difficulty in estimating its true incidence. Incidence of vasospasm ranges from 19 to 97%2. Based on angiography, the incidence has ranged from 40 to 97%2. The reported incidence of CV, based on TCD velocity, is 43.3%2. Delayed ischaemic deficits, based on clinical parameters, are reported between 5-90% (average incidence is 32.4%).[1]

Several treatment strategies have emerged due to increased understanding of CV. In a review of literature of over 30,000 cases, Dorsch[1] reported the incidence of CV in patients receiving triple H therapy as 17.5% . The incidence of CV after prophylaxis with triple H therapy is reported as 14.3%. With triple H therapy, deaths occurred in 17.5%, permanent deficits in 28.4% and good outcome in 54.4%.[2] In patients receiving nimodipine, there were 18% deaths (80/443), 31% permanent disability and good outcome in 51% patients.[1]

Kodama *et al* reported 217 patients of Fisher grade III,[2] in whom cisternal irrigation therapy with UK in ringer lactate (UK-RL) solution with ascorbic acid at a concentration of 120 IU/ml was used. The average amount of total blood volume drained was 113.7 ± 12 ml. Average duration of cisternal irrigation was 9.9 days (2 to 18 days). Seizures occurred in 0.9%, meningitis in 0.9% and intracranial haemorrhage in 1.9%. Symptomatic vasospasm was observed in 6 cases(2.8%).[6]

Sasaki *et al* [9] reported 28 cases who received cisternal irrigation with RL-UK solution at the concentration of 30, 60 and 120 IU/ml of RL solution. Cerebral vasospasm occurred in 10.7% patients. It was shown that UK, at the concentration of 120 IU/ml, was highly effective in dissolution of the clot and was free of haemorrhagic complications. Meningitis occurred in 3.6% patients.[15]

Using tPA for dissolution of clot, CV occurred in 10% (11/268) patients.[1] The principal complication noted was haemorrhage, which occurred in 0-70%.[1] Furthermore, the optimum dosage of tPA remains under investigation. Continuous irrigation is considered to be more beneficial than intermittent irrigation. Studies remain limited due to higher risk of haemorrhagic complications and non-availability of its safe concentration levels.

Cisternal irrigation therapy caused complications in 4 of our patients (4/9). However, none of the patients had haemorrhagic complications. WBC level in DIF showed an increase till day 3 of irrigation and gradually, returned to normal levels. Persistence of raised WBC counts raises doubt about meningitis.

The risk of infection remains formidable in cisternal irrigation therapy. The first two patients suffered meningitis leading to their death inspite of systemic antibiotics. Strict maintenance of aseptic precautions and painting of the drain site with povidone-iodine have been recommended to prevent sepsis. Use of intrathecal gentamicin has been considered safe[17] but the dosage and the concentration remain debatable. Kawamoto *et al,*[18] reported use of tobramycin in Ringer lactate irrigating fluid at a concentration of 0.12 mg/ml. They reported bacterial meningitis in eight patients (8/49). Watanabe *et al,*[19] reported occurrence of neurotoxicity following intraventricular administration of gentamicin. Ventriculitis has been noted to occur at the intraventricular concentration of gentamicin between 50-150 μg/ml.[20] Intraventricular aminoglycosides can cause abrupt release of inflammatory cytokines, that may lead to enhanced neurological damage.[21] In our study group, the concentration of gentamicin used in the first four patients was 120 μg/ml, which was further reduced to 8 μg/ml in order to avoid probable

complication of ventriculitis.[20] Intracisternal gentamicin induced neuronal toxicity has not been reported earlier. Intracisternal gentamicin, especially with preservative, at the concentration of 120 μg/ml, may have caused neuronal toxicity in two of our patients, which stopped after decreasing the concentration. It is also important to use gentamicin free of methyl paraben as preservative which is neurotoxic.

The results suggest that cisternal irrigation therapy with UK can be used and is effective in prevention of occurrence of CV. The use of gentamicin in cisternal irrigation fluid may reduce the incidence of meningitis. However, it should be used in safe concentration (<50 μg/ml) and without preservative.[13]

Conclusion

This is a prospective controlled study to evaluate the efficacy of intracisternal irrigation to prevent CV and to develop a protocol for cisternal irrigation. No such previous study has been conducted to determine the efficacy as well as safety of cisternal irrigation using study and control arms.[6,8,9,15] Cisternal irrigation therapy is effective method to reduce incidence of CV but is not free of complications.

Meningitis remains an important complication and may outweigh the advantages of irrigation. Hence, cisternal antibiotics such as gentamicin may be of help in reducing risk of infection. It is recommended that gentamicin used should be preservative free and the dose used should be 4 mg/500 ml RL-UK solution to prevent neuronal toxicity.

The small sample size of the study and control groups remains the limitation and a larger prospective and randomized trial is warranted.

Competing interests : None, Source of Funding - None
Received Date : 2 December 2009; Revised Date : 30 December 2009
Accepted Date : 12 January 2010

References

1. Dorsch WCN. Cerebral arterial spasm-a clinical review. Br J Neurosurg 1995;9:403-412.
2. Gilsbach JM, Harders AG. Morbidity and mortality after early aneurysm surgery-a prospective study with nimodipine prevention. Acta Neurochir (Wien) 1989;96:1-7.
3. Kodama N, Sasaki T,Kawakami M, *et al.* Cisternal irrigation therapy with UK and ascorbic acid for prevention of vasospasm after aneurysmal subarachnoid hemorrhage. Surg Neurology 2000;52:110-118.
4. Steinberg GK, Vanefky MA, Michael PM, *et al.* Failure of intracisternal tissue plasminogen activator to prevent vasospasm in certain patients with aneurysmal subarachnoid hemorrhage. Neurosurg 1994 ; 34 : 809-814.
5. Saito I, Sano K. Vasospasm after aneurysm rupture : incidence, onset and course, in Wilkins RH (ed), cerebral arterial spasm, Baltimore: Wilkins and Wilkins 1980 ; 294-301.
6. Zabramski JM, Spetzler RF, Stuart LK, *et al.* Phase I tpA for prevention of vasospasm in patients with aneurysmal SAH. J Neurosurg 1991;75:189-196.
7. Yamanobe K. Prevention of vasospasm: Experimental studies on lysis of UK. Fukushima Med J 1987;37:27-39.
8. Shane M Pearce, Melissa A Ramsey, Gurwattan S Miranpuri, *et al.* Regulation and function of matrix metalloproteinases in nervous system injury and neuropathic pain. Annals of Neurosciences 2008;15(4):94-105.
9. Sasaki T, Kodama N, Kawakami M, *et al.* UK arterial irrigation therapy for prevention of symptomatic vasospasm after aneurysmal SAH. Stroke 2000;31:1256-1262.
10. Kosnik EJ, Hunt WE. Prospective hypertension in management of intracranial arterial Aneurysm. J Neurosurg 1976;45:148-154.
11. Boet K, Mee E. Magnesium sulphate in the management of patients with Fisher's grade III SAH ; A pilot study. Neurosurg 2000;47:602-607.
12. Munford R.S. Sepsis and septic shock. In : Fauci A.S, Martin J.B, Braunwald E, *et al.* Harrison's Priciples of internal medicine.McGraw-Hill, 14th edition, 1998:776-780.
13. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480-487.
14. Ecker A, Reimenschneider PA. Arteriographic demonstration of spasm of intracranial arteries with special reference to saccular arterial aneurysm. J Neurosurg 1951;8:600-607.
15. Prabhakar S, Phani V, Sethi S, *et al.* Roche amplicor *Mycobacterium tuberculosis* assay for respiratory specimens detects Tubercular meningitis in CSF revealing preponderance of disease among male patients from lower socio-economic strata of north west. Annals of Neurosciences. India 2009;16(1):10-13.
16. Yoshida Y, Hayashi T, Amot M, *et al.* Postoperative intrathecal irrigation with UK after early stage operation on ruptured cerebral aneurysm. Neurol Med Chir (Tokyo) 1983;23:659-666.
17. Newman RL, Holt RJ. Intrathecal gentamicin in treatment of ventriculitis in children. Br Med J 1967:555-539.
18. Kawamoto S, Tsutsumi K, Yoshikawa G, *et al.* Effectiveness of the head-Shaking method with cisternal irrigation with Urokinase in preventing CV after subarachnoid hemorrhage. J Neurosurg 2004; 100:236-243.
19. Watanabe I, Hodges GR, Dworzack DL, *et al.* Neurotoxicity of intrathecal gentamicin : A case report and experimental study. Ann Neurol 1978;115:79-85.
20. Ross N, Hutchinson PJ, Seeley H, *et al.* Timing of surgery for supratentorial aneurysmal subarachnoid hemorrhage : report of a prospective study. J Neurol Neurosurg Psychiatry 2002;72: 480-484.
21. Pearce SM, Ramsey MA, Miranpuri GS, *et al.* Regulation and function of matrix metalloproteinases in nervous system injury and neuropathic pain. Annals of Neurosciences 2008;15(4):94-105.