

MANAGEMENT OF VASOSPASM IN A NEUROSURGICAL CENTER

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ABSTRACT

Background: Cerebral vasospasm after subarachnoid hemorrhage remains a major source of morbidity and mortality. Various agents have come into vogue to deal with this complication but none has shown any absolute results. We conducted this study to assess the effectiveness of intracisternal lavage of papavarine both prophylactically and therapeutically in a simple cost effective way.

Methods: This is a retrospective analysis of patients who were admitted at our institution between January 2002 and July 2003. Eightyfive patients with anterior circulation aneurysmal bleed who underwent microsurgical clipping were divided into two groups. **Group A** - patients who received papavarine through a reservoir and **Group B** - patients who did not receive papavarine. The location of aneurysm, timing of surgery, incidence and outcome of vasospasm were assessed in the patients in two comparable groups.

Results: 13% of patients in Group A developed vasospasm whereas 38% of patients in Group B developed vasospasm. Symptoms of vasospasm reversed in all patients in Group A. There were 3 deaths in Group A but none were attributed to vasospasm. Four of seven deaths in Group B were attributed to consequence of vasospasm. Eleven patients who survived in Group B in spite of vasospasm had significant morbidity at the time of discharge.

Conclusion: Intracisternal lavage with papavarine both prophylactically and therapeutically can prevent and reverse vasospasm and this can be achieved by installing a simple reservoir. It is a cost effective and rapid bedside procedure for dealing with vasospasm.

Key words: Subarachnoid haemorrhage, Vasospasm, Papavarine, Reservoir.

INTRODUCTION

Vasospasm after aneurysmal subarachnoid haemorrhage (SAH) continues to be a major source of morbidity and mortality even though the treatment modalities are consistently improving. The incidence remains 30% to 70% in most of the series. Various theories have been put forward as the pathogenesis of vasospasm but till date no absolute cause has been identified.

The main stay of therapy for post SAH vasospasm remains 'Triple H' therapy in most of the centers. It remains a gamble as it works in some

but remains ineffective in other cases. Research is on going with various agents to deal with this post subarachnoid vasospasm. Agents like papavarine, nitroprusside, nicardipine and fibrinolytic agents have shown promising results but more trials are required to define it as a treatment option. The goal of our study was to report a cost effective way of dealing with this dreaded complication in a set up which caters to patients with economic restraints. We report our experience with prophylactic and therapeutic intracisternal lavage of papavarine for prevention of vasospasm.

MATERIALS & METHODS

This is a retrospective analysis of patients who received intracisternal papavarine therapy through a reservoir placed during the time of clipping for

management of vasospasm between January 2002 and July 2003.

All patients admitted with a diagnosis of subarachnoid haemorrhage following a rupture of intracranial aneurysm were considered in the analysis. Eighty five cases of anterior circulation aneurysmal bleed that underwent treatment were included in our study. All the patients in this study group underwent microsurgical clipping. These patients were divided into two groups:

Group A: Patients who received papaverine post surgery (n = 46)

Group B: Patients who did not receive papaverine (n = 39)

Management protocol

All patients who were referred with a diagnosis of SAH to this tertiary level institution were assessed clinically, evaluated with a CT scan and four vessel angiogram. They were categorized according to World Federation of Neurologic Surgeons (WFNS) grading clinically and Fisher grading on CT scan.

Standard medical management was used including administration of nimodipine, treatment of hydrocephalus by CSF drainage, anticonvulsants and maintenance of hypervolaemia and a haematocrit value of $33\% \pm 2\%$ and optimization of patients medical and general status.

On confirmation of an aneurysm, treatment options are provided to the relatives of the patients for microsurgical clipping or embolisation if indicated. On obtaining consent for microsurgical clipping patients are taken to operation theatre usually within 24 hours of admission. A standard pterional or fronto-temporal craniotomy is used as decided by the operating surgeon. Clipping of the aneurysm to the surgeon's satisfaction and removal of intracisternal clot is done. Irrigation of the cisterns with one ml of papaverine is done. A catheter is placed into the cistern around the aneurysm (Fig. 1). The reservoir is placed through the posterior burr hole. The reservoir is further filled with one ml of papaverine after dural closure. Patients belonging to Group B had only irrigation with papaverine in the vicinity of clipped aneurysm before closing the dura.

Following surgery patients are monitored aggressively for any evidence of neurological deterioration. A high index of suspicion is kept for detection of clinical vasospasm. Symptoms of headache, speech disturbance, increasing irritability or additional neurological deficits were con-

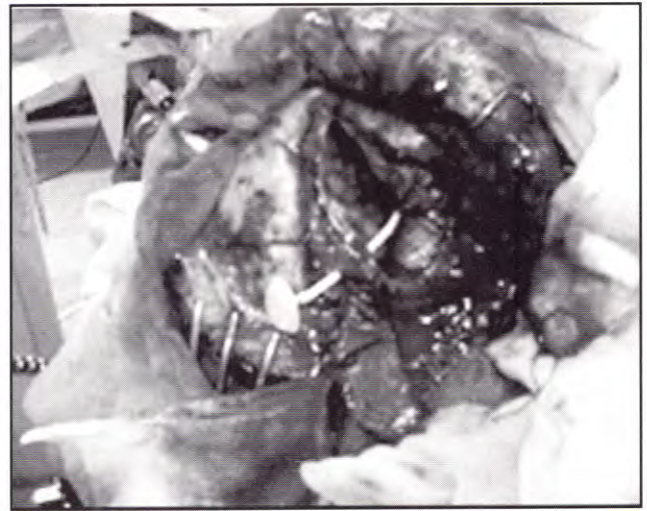


Fig. 1. Catheter tip placed around the clipped aneurysm.

sidered as vasospasm. The patient is immediately evaluated with a CT scan to rule out any ischaemic event. If the CT scan is negative for any ischaemic features then papaverine is injected into the reservoir in Group A patients using the following protocol. Papaverine injection was in addition to standard Triple "H" therapy instituted for both group of patients.

Papaverine protocol

Once ischaemic deficits has been ruled out, 30 mg of papaverine is injected in the reservoir (Fig 2) as a bedside procedure under aseptic precautions. Papaverine is injected every 12 hours if deficits are not reversed. Post clipping angiograms were not done due to financial limitations.

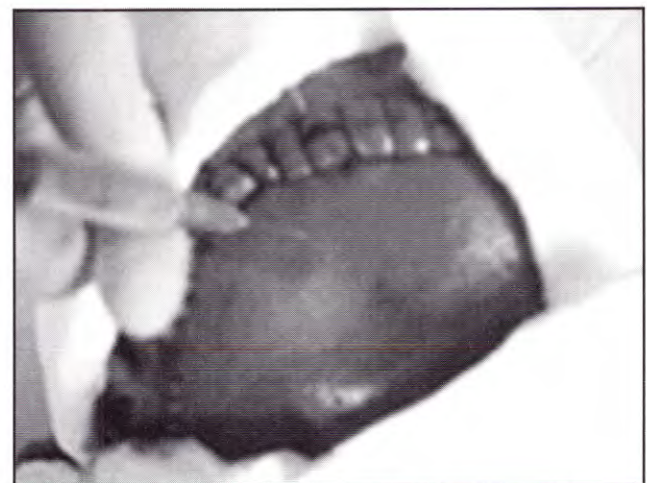


Fig. 2. Papaverine being injected in the reservoir bedside.

Study analysis

Study analysis was performed by reviewing the case files, operation notes, neurointensive care records and patient follow up book. Statistical analysis was done using the Chi-square test to find the comparative outcome between the two groups.

RESULTS

This study consisted of eighty five patients who had anterior circulation aneurysm and who were microsurgically clipped. Table 1 describes the demographic features and location of aneurysm in Group A and Group B.

Fifty three aneurysms were clipped in this group. The location of aneurysms was 30 A.com, 12 MCA aneurysms, 8 ICA and 3 distal ACA aneurysms (Table 1). There were multiple aneurysms in 6 cases. The WFNS grade at the time of admission for this group is depicted in Table 2. The Fischer grade at the time of admission was 0 in Grade I, 21 in Grade II, 21 in Grade III and 4 in Grade IV (Table 3).

Table 1. Demography of patients in Group A and Group B

	Group A (Reservoir with papavarine)	Group B (No reservoir)
No. of patients	46	39
Sex (male: female)	22:24	19:20
Type of Aneurysm		
A Com	30	16
MCA	12	12
ICA	8	13
Distal ACA	3	1
Median Age	50	40

Table 2. Comparative WFNS Grade in Group A & Group B

	Group A (Reservoir with papavarine)	Group B (No reservoir)
Grade 1	33	18
Grade 2	7	15
Grade 3	4	5
Grade 4	2	1

Table 3. Comparative Fischer Grade in Group A & Group B

	Group A (Reservoir with papavarine)	Group B (No reservoir)
Grade 1	0	0
Grade 2	21	14
Grade 3	21	14
Grade 4	4	11

All these patients received 1 ml of papavarine immediately after clipping. Of these 46 patients, 6 patients developed clinical symptoms of vasospasm. In all these cases CT scan was done immediately after detection of vasospasm. None of these cases had any evidence of ischaemic changes. In one case the onset of vasospasm was on the 2nd post operative day and in rest of the five cases the onset of vasospasm was on the third post operative day. All these 6 cases required only one dose of papavarine. Clinical improvement was seen by one day in one patient and in rest of the five patients improvement was seen on the second day. 5 cases had A.com aneurysm and one case had a left MCA bifurcation aneurysm. In these 6 patients the window period between ictus and treatment was 4 days in two patients, 6 days in two, 12th day in one and 13th day in another patient. All these 6 cases were in WFNS Grade I at the time of admission and also remained the same at the time of discharge. The Fischer grade was II in 3 patients and grade III in rest of the 3 patients. The mean post operative hospital stay in these 6 patients was 15 days (11 to 26 days).

The median post operative hospital stay for all the patients in Group A was 11 days (4 to 45 days). The mortality in this group was 6%. None of the three deaths which occurred in this group was attributed to vasospasm. One patient had an associated abdominal aneurysm which ruptured on the 5th post operative day. Another patient had a bilateral ACA territory infarct immediately post operatively who died on the 6th post operative day. This patient was in WFNS Grade III at the time of presentation. The third patient succumbed to severe chest infection on the 10th post operative day. The details of the patients who developed vasospasm in this group is given in (Table 4).

In Group B there were 39 patients of whom 19 were male and 20 were female. The median age for this group was 40 years (7 to 67 years). 41 aneurysms were clipped in group B. The location of aneurysms was 16 A.com, 12 MCA and 13 ICA

Table 4. Characteristics of patients who developed vasospasm in Group A (Reservoir with papavarine)

Location of aneurysm	Onset of vasospasm/papavarine given (post op day)	Fischer Grade at admission	Papavarine (frequency)	Papavarine (Duration)	Improvement (in days)	Ictus to Treatment (in days)	WFNS (Admission)	WFNS (Discharge)	Post op Hospital Stay (in days)
A. Com	3 rd	III	1 dose	Single day	2	6	I	I	13
Left MCA bifurcation	3 rd	II	1dose	Single day	1	6	I	I, Rt. Hemiparesis, Broca's aphasia.	11
A. Com	2 nd	II	1 dose	Single day	2	12	I	I	12
A. Com	2 nd	III	1 dose	Single day	2	13	I	I	11
A. Com	3 rd	II	1 dose	Single day	2	4	I	I	21
A. Com	3 rd	III	1 dose	Single day	2	4	I	I	26, Chest MRSA infection

in its various segments (Table 1). The WFNS grade at the time of admission was 18 with Grade I, 15 with Grade II, 5 with Grade III and 1 with Grade IV (Table 2). The Fischer Grade at the time of admission was 0 in Grade I, 14 in Grade II, 14 in Grade III and 11 in Grade IV (Table 3).

Fifteen of these 39 patients developed vasospasm. 5 had A.com aneurysm, 5 had MCA aneurysm, 2 had P.Com, 2 had anterior choroidal aneurysm and 1 patient had an A.com along with DACA aneurysm. The onset of vasospasm was on the 2nd post operative day in 1 patient, 3rd postoperative day in 7 cases, 4th day in 2 patients 5th day in 3 patients and 6th day in another two cases. The window period between ictus and treatment was a mean of 6 days in these 15 patients. The median post operative hospital stay in these cases was 11 days (3 to 47 days). Seven out of these 39 patients died i.e. a mortality of 17%. Of these 7 patients who died, 4 cases (66%) were due to effects of vasospasm and in 3 other cases the cause was due to infection in the post operative period. The details of the patients who developed vasospasm in Group B is given in Table 5. Comparing the results in group A and Group B (Table 1,2,3,4) patients whose characteristics were similar, it is clearly evident that Group A patients benefited from injection of papavarine both in terms of morbidity and mortality.

Analyzing statistically we found that the incidence of vasospasm in Group B i.e. group not receiving papavarine was significantly higher than in Group A i.e. group receiving papavarine with a p value of 0.007 (Table 6). Statistically we found

that the location of the aneurysm, the WFNS grade or the Fischer grade did not influence the incidence of vasospasm in the two groups. The p value was insignificant for the above parameters. Using the Chi-Square test it was found that the mortality as well as the morbidity was higher Group B in those patients who developed vasospasm with a p value of 0.039.

It was also found that the overall mortality and the morbidity were significantly higher in Group B than in Group A with a significant p value of 0.026.

DISCUSSION

Medical therapies with aggressive critical care management remain the corner stone of therapy for treating cerebral vasospasm¹.

Many drugs other than papavarine has been studied in the management of cerebral vasospasm by various routes. Agents like calcium antagonists², fibrinolytic agents, free radical scavengers³,

Intrathecal sodium nitropruside⁴, milrinone⁵, intracarotid NO donors in primates⁶, steroids and endothelial antagonist have been administered to relax cerebral vasospasm. Agents like Cyclosporine A, Actinomycin D have also been tried^{7,8}. Experiments with fibrinolytic agents are also ongoing. Findlay et al¹ conducted a randomized controlled trial with rtPA as a bolus dose of 10 ml to cistern after clipping. They found a significant decrease in angiographic vasospasm but no improvement of clinical vasospasm. Also they found that the risk of intracranial vasospasm remains

Table 5. Characteristics of patients who developed vasospasm in Group B (without papavarine)

Aneurysm location	Onset of vasospasm Post op day	Fischer Graded (at adms)	WFNS admission	WFNS at discharge Other NL deficits	Ictus to treatment (in days)	Post op hospital stay
Ant. choroidal	3 rd	II	II	I, Left hemiparesis 3/5,	10	14
A. com	3 rd	II	III	II, cognitive impairment	8	14
A. Com	3 rd	III	II	Death on 5 th post op day. HBsAg+, GTCS once.	1	
A. Com	4 th	III	I	I	3	8
A. Com	5 th	III	I	Death	3	47
A. Com + DACA	2 nd	IV	I	Death	4	13
A. Com	5 th	II	I	I	10	9
Ant. choroidal	3 rd	III	II	II, Left UMN facial palsy	3	15
MCA	4 th	III	II	II, Rt. Hemiparesis 4/5	9	17
MCA	3 rd	III	I	III, Left UMN facial	1	7
P. Com	6 th	II	I	III, Rt. Hemiparesis 3/5	2	15
MCA	5 th	IV	I	II, Rt hemiparesis 4/5, Rt. UMN facial	4	15
P. Com	3 rd	IV	II	I	14	15
MCA	6 th	IV	III	III, Aphasia, pseudomeningocele	8	14
MCA	3 rd	III	I	Death	3	3

Table 6. Outcome of vasospasm in Group A and Group B

	Group A (Reservoir with papavarine)	Group B (Without papavarine)
Post operative vasospasm	6/46 (15%)	15/39 (37%)
Outcome of patients having vasospasm		
Mortality	0	4 (10.2%)
Persistent deficit due to vasospasm	1 (2.17%)	8 (20.51%)
Overall outcome		
Mortality	3 (6.52%)	7 (17.94%)
Morbidity	2 (4.34%)	8 (20.51%)

high if aneurysm is incompletely secured. Mizoi et al⁹ and Usui et al¹⁰ also found that bolus tPA intrathecal injection produces marked effect on vasospasm. But the disadvantage remains that tPA has to be given within the first two hours of onset which may not be possible always^{1,10}. Another study by Sasaki et al has shown that repeated tPA administration is useful for reducing vasospasm.

Randomized trial with nicardipine intravenous infusion studied by E.C. Haley Jr. et al² was beneficial but the dose needs to be titrated to individual tolerance level of hypotension, renal

dysfunction and pulmonary oedema. Tirilazad mesylate, a 21-aminosteroid has also been extensively studied but there are controversial reports regarding its benefit^{11,12}.

Transluminal angioplasty, a minimally invasive procedure is definitely showing a good relief of cerebral vasospasm but needs to be very rapidly done following onset.

The best results for treating vasospasm has been if it is treated within 2 hours of onset of vasospasm^{1,9}. Conventional intra arterial papavarine or angioplasty probably takes a longer time at our institution. Hence intracisternal papavarine has been effective in administering within the window period of two hours.

In this series of 85 patients 25% developed vasospasm cumulatively. The group who received papavarine in the cistern, 13% developed vasospasm whereas the group which did not receive vasospasm 38% developed vasospasm. All patients, showed improvement after instillation of papavarine. Papavarine is an alkaloid belonging to the opiod group. It is one of the strongest non specific vasodilator¹² but its exact role is not completely understood. It has a direct action on smooth muscles of blood vessels and is hypothesized to work by inhibition of cAMP and cGMP phosphodiesterase¹². Another mechanism specu-

lated is by blocking the calcium ion channels in the channel membrane and inhibits the release of Ca^{++} from intracellular space⁴ Review of literature reveals data regarding use of papavarine for management of cerebral vasospasm both clinically and experimentally. Various routes are used, viz. intravenous, intraarterial and intrathecal¹³⁻¹⁷. Milburn et al, demonstrated that papavarine causes vasodilatation in proximal, intermediate and distal cerebral arteries¹⁸ and also a consistent decrease in cerebral circulation time and thereby increasing cerebral blood flow¹⁹. Papavarine also has a complementary role with angioplasty for treatment of vasospasm in distal vessels. Intravenous infusion was not effective. Intraarterial route was effective producing significant transient vasodilatation but with moderate hypotension. Subarachnoid injection was more promising. However limited use of intracisternally instilled papavarine in clinical study is due to methodological difficulties and increased risk of infection. Intracranial intracisternal administration of papavarine by means of a prolonged release pellet significantly decreased vasospasm when a high dose pellet containing 25 mg papavarine was given in canine model as studied by Shiokawa et al²⁰ and clinical application by Dalbast et al²¹.

Papavarine is definitely way ahead in this race of various agents and more studies need to be conducted with large number of patients in a randomized controlled trial to come to a conclusion.

This study reports the effect of cisternal lavage with papavarine in a simple cost effective way.

CONCLUSION

Intracisternal lavage with intermittent instillation of papavarine through a simple reservoir prevents and reverses delayed cerebral vasospasm. It is an effective, economical, easy bedside and rapid procedure in dealing with vasospasm and very well suited to deal with poor patients who have limited resources in most of our institutional Indian hospitals.

We recommend further study including larger number of patients in a randomized fashion to come to an absolute conclusion.

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RESUMEN

Introducción. El vasospasmo post hemorragia subaracnoidea constituye una causa importante de morbilidad y mortalidad. Múltiples agentes han sido utilizados para su tratamiento, pero ninguno mostró resultados absolutos. El presente estudio se ha realizado para evaluar la efectividad del uso intracisternal de papaverina utilizado en forma profiláctica y terapéutica.

Material y método. Se efectuó un análisis retrospectivo de los pacientes admitidos en nuestra Institución entre enero 2002 y julio 2003; 85 pacientes con hemorragia aneurismática de la circulación anterior y clipados quirúrgicamente fueron divididos en 2 grupos. Grupo A: pacientes que recibieron papaverina a través de un reservorio y Grupo B pacientes que no recibieron papaverina. Se

evaluó la localización, timing de la cirugía, incidencia y evolución post-vasospasmo en ambos grupos.

Resultados. 13% de los pacientes del Grupo A y 38% del Grupo B desarrollaron vasospasmo. Los síntomas de vasospasmo revirtieron en todos los pacientes del Grupo A mientras que 11 pacientes del Grupo B con vasospasmo presentaron una significativa morbilidad.

Conclusión. La utilización profiláctica terapéutica de papaverina intracisternal puede prevenir y revertir el vasospasmo, pudiendo ser inyectado a través de un reservorio.

Palabras clave. hemorragia subaracnoidea, papaverina, reservorio, vasospasmo