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The Effect of Very Early Cisternal Irrigation on Basilar Artery Spasm After SAH in the Rat Model

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Summary

The authors have investigated the effect of very early irrigation of the cerebrospinal fluid (CSF) space in the haemorrhage rat model of vasospasm. Fifteen rats had basilar cistern irrigation with physiological saline for 3 hours after subarachnoid haemorrhage (SAH), and fifteen control rats had subarachnoid haemorrhage without irrigation of clot.

The changes in basilar arteries diameters were determined by angiograms obtained from the rats. The post haemorrhage angiograms showed significant basilar artery spasm in both groups ($P \leqslant 0.0005$, t-test). However in the last angiogram the basilar artery diameter was found to have the same value measured before subarachnoid haemorrhage in the irrigation group whereas no obvious change was observed in the control group. In the irrigation group the mean diameter of the basilar artery in the last angiogram was 0.412 mm. (0.30 mm to 0.50 mm). None of the animals, treated by cisternal irrigation, showed angiographic vasospasm while the latter group did ($P \leqslant 0.0005$). Animals treated with physiological saline irrigation had a median clot grade of 0.40 (range grade 0 to 2); control rats had a median grade 2.86 (range grade 1 to 4, $P < 0.001$, Mann-Withney U test), on the brain stem, indicating significant reduction of clot by lavage.

In conclusion, performance of experimental physiological saline irrigation at a very early time after subarachnoid haemorrhage prevents the arteriographic and morphological changes of both acute and late vasospasms.

Keywords: Cerebral vasospasm; subarachnoid haemorrhage; cisternal irrigation; rat.

Introduction

The clear-cut relationship between the amount of blood in the basal cisterns and the incidence and severity of arterial spasm has been demonstrated by clinico-radiological studies using data from computed tomographic (CT) examinations as well as by recent experimental investigations [2, 7, 15, 20, 21, 22].

These findings have led to endeavours to remove the blood from the cerebral cisterns around the vessels in order to inhibit the accumulation of high concentrations of spasmogenic agents produced by blood clot lysis. There is general agreement about the fact that post-haemorrhagic clot lysis within the subarachnoid space with consequent release of spasmogenic metabolites, derived from breakdown products of blood, plays a pivotal role in the development of cerebral vasospasm [4, 5, 8, 9, 10, 21, 22, 27].

It was our assumption that cisternal irrigation with saline at a very early period after haemorrhage would be a suitable mode of spasm prevention and treatment.

The following experiments were performed in order to examine the efficacy of very early cisternal irrigation to prevent the development of angiographic vessel narrowing in a rat model of cerebral vasospasm.

Material and Method

In this study, 30 ZBZ Cara rats were used, each weighing approximately 350 grams. The rats were anaesthetized by an intramuscular injection of 0.1–0.2 ml/100 gr of Innovar-Vet (Cilag AG Schaffhausen-Switzerland) containing 0.4 mg Fentanyl and 20 mg Droperidol per miligram and anaesthetization was continued by giving very small dozes. The animals were laid down in supine position on a standard rat operation board and fixed by the tails, legs, and teeth.

The abdomen was opened by vertical incision. The aorta was dissected under the operating microscope and catheterized distal to the renal artery origin. The catheter was pushed towards the level of the arch of the aorta. The panangiography was performed by injecting 1–2 ml of Urographine of 60% (Schering AG Berlin Bergkamen, W. Germany) through catheter. With the completion of this process, the rats were turned into prone position and their heads were slightly flexed downwards. Following the microsurgical dissection of the atlanto-occipital membrane, the cisterna magna was punctured and 0.1 ml CSF was withdrawn. After withdrawal of autologous arterial blood from the aortic catheter, CSF and nonheparinized blood were mixed to prevent premature clotting and 0.1 ml

of the mixture was injected over a period of one minute into the cisterna magna. After blood injection, the operation table was tilted 30° down to promote the distribution of blood within the basal cisterns.

After about ten minutes, a second panangiography was performed to demonstrate basilar and vertebral arteries. Then 15 rats were spared to evaluate the effects of cisternal irrigation and another 15 used for control.

The animals in the cisternal irrigation group were treated by a cisternal lavage 3 hours later by withdrawing 0.1 ml of CSF and injecting 0.1 ml physiological saline. This fluid exchange was repeated several times at intervals of 15–30 minutes until the CSF was clear. A third angiogram was taken to observe especially the basilar artery diameter when the CSF was clear enough to demonstrate no blood elements.

Following the third angiography all the animals were sacrified and their brains were taken out for morphological evaluation.

Examinations of the changes in the angiographic diameter of the basilar artery were made using a Zeiss stereo microscope with 10-fold magnification. The diameter of the basilar artery was measured at three corresponding locations along the course of the vessel. Statistical evaluation of the changes in the angiographic diameter of the basilar artery was performed using student's t test.

The amount of clot present in brains was graded on a scale of 0 to 4 according to the method described by Alexander *et al.*[1], and statistically evaluated by Mann-Withney U test.

The animals with respiratory dysfunction and those which did not survive for different reasons were discarded and replaced by new ones. Only four of them had tracheotomy during the study.

Results

Angiography

In both groups, following the cisternal blood injection, it was observed that the basilar artery diameter was remarkably narrowed. The paired student's t test between first two angiograms of cisternal irrigation and control groups gave value of t = 7.953 and 8.458 respectively which are statically significant ($P < 0.0005$) (Fig. 1).

In the third angiograms made after three hours of subarachnoidal haemorrhage, the vasospasm had clearly disappeared in the irrigation group, whereas the degree of basilar artery spasm was increased in the control group ($P \leqslant 0.0005$) (Fig. 2). Table 1 shows the comparison of changes in the diameter of the basilar artery between cisternal irrigation and control groups. There was a mean reduction of 0.007 mm in basilar artery diameter in rats with irrigation, compared to a 0.133 mm reduction in control rats.

Morphological Changes

The morphological changes around the ventral brain stem and cisterns of the clots present in each of

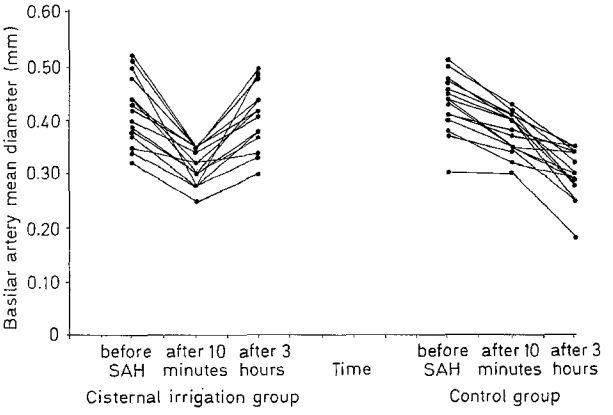

Fig. 2. Graphic presentation of the changes in the diameter of basilar artery. Comparison of cisternal irrigation and control groups. Changes of the vessel diameter in the control group are statistically significant ($P < 0.0005$)

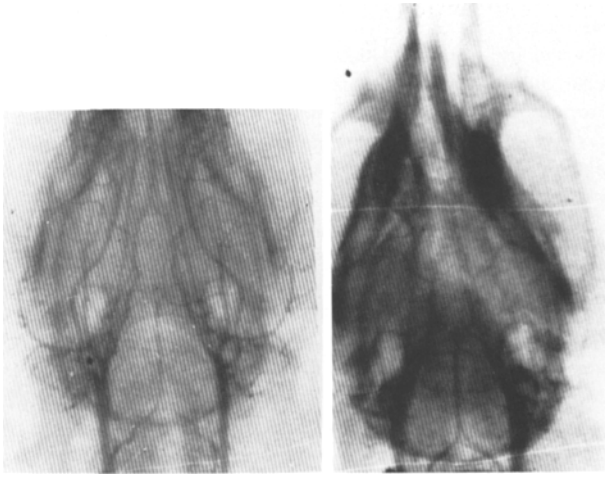

Fig. 1. Angiographic presentation of basilar arteries in irrigation (right) and control group (left)

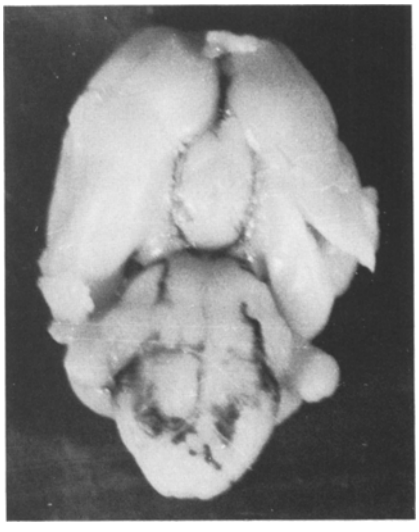

Fig. 3. Postmortem brain specimens in control group

Table 1. *The Comparison of Changes in the Diameter of the Basilar Artery Between Cisternal Irrigation and Control Groups*

	Cisternal irrigation group				Control group			
Pat. number	Diameter of basilar artery							
	before SAH	after 10 minutes	after 3 hours	difference: before SAH to after 3 hours	before SAH	after 10 minutes	after 3 hours	difference: before SAH to after 3 hours
	A 1	A 2	A 3		B 1	B 2	B 3	
1	0.44	0.32	0.42	−0.02	0.41	0.37	0.35	0.06
2	0.37	0.28	0.38	+0.01	0.40	0.35	0.30	0.10
3	0.35	0.32	0.34	−0.01	0.44	0.40	0.25	0.19
4	0.52	0.35	0.50	−0.02	0.48	0.40	0.30	0.18
5	0.34	0.28	0.33	−0.01	0.51	0.42	0.32	0.19
6	0.42	0.35	0.44	+0.02	0.50	0.43	0.34	0.16
7	0.44	0.30	0.44	0.00	0.44	0.35	0.34	0.10
8	0.50	0.28	0.49	−0.01	0.47	0.41	0.28	0.19
9	0.48	0.35	0.48	0.00	0.38	0.32	0.29	0.09
10	0.40	0.34	0.41	+0.01	0.30	0.30	0.18	0.12
11	0.43	0.35	0.42	−0.01	0.43	0.35	0.29	0.14
12	0.39	0.30	0.38	−0.01	0.45	0.40	0.28	0.17
13	0.32	0.25	0.30	−0.02	0.46	0.41	0.35	0.11
14	0.38	0.30	0.37	−0.01	0.41	0.38	0.34	0.07
15	0.51	0.35	0.48	−0.03	0.37	0.34	0.25	0.12
Mean	0.419	0.315	0.412	0.007	0.430	0.375	0.297	0.133

The paired student's t test between A 1 and B 1 gave a value of t = 0.497 and had P 0.375. On the other hand the difference between A 3 and B 3 is very significant. (t = 5.749, P < 0.0005).

the control and cisternal irrigation groups are shown in Table 2. In the control group, postmortem inspection of the brain stem under the operating microscope magnification, cisterns and basilar artery revealed in all rats, blood clots filling the cisterna magna with blockage of the fourth ventricle. The basilar artery was embedded in thick subarachnoid blood collections of different grades which could be removed by microsurgical dissection (Fig. 3). In contrast, in the cisternal irrigation group, no relevant subarachnoid clot collections either within the cisterna magna or along the course of basilar artery could be detected (Mann-Withney U test, u = 2, z = -4.583, P < 0.001) (Fig. 4).

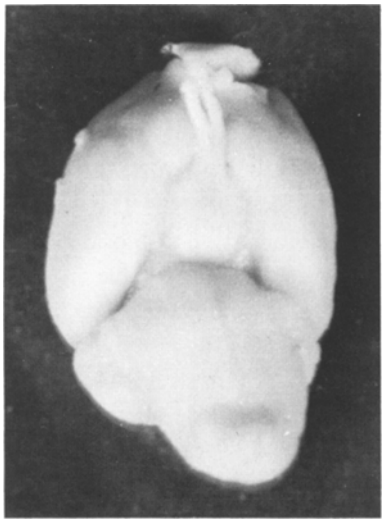

Fig. 4. Postmortem brain specimens in cisternal irrigation group

Discussion

The well-founded correlation between the presence and amount of clot in the subarachnoid cisterns and the occurence of vasospasm as well as the consequent suggestion that components of blood are responsible for the induction of vasospasm have led to extensive efforts either by surgical and/or pharmacological means to evacuate the subarachnoid clot from basal cisterns in order to prevent the development of ischaemic deficits [1, 18, 20, 21, 22, 24, 30].

It was only with the increasing use of early operative intervention for cerebral aneurysm clipping in recent

Table 2. *Amount of clot Present around the Brain Stem at Sacrifice*

Pat. number	Clot grade	
	cisternal irrigation group	control group
1	0	2
2	0	2
3	0	3
4	1	3
5	0	3
6	1	4
7	0	3
8	1	4
9	0	3
10	0	2
11	0	3
12	1	3
13	0	3
14	2	2
15	0	3
Mean	0.40	2.86

Grading scale system (1).

Grade 0: Total absence of clot.

Grade 1: Trace amount of clot present.

Grade 2: Minimal clot present (that is, two to six areas of clot, no more than 2 to 4 mm across, randomly distributed over the ventral brain stem without predilection for the basilar artery).

Grade 3: Moderate clot present (that is, more and/or larger areas of clot, with greater involvement of the basilar artery).

Grade 4: Brain stem and basilar artery essentially encased in clot.

Mann-Withney U test is used for comparison of two groups, and a very significant difference was found ($u = 2, z = -4.583, P < 0.001$).

years that the idea of aggressive intra-operative surgical lavage of cisterns was reinstituted and a concept of "Scavenger Surgery" was proposed [6, 11, 12, 23].

Experimental studies substantiated the fact that wash out of blood clots was supposed to be effective only when performed within a time limit of 48 hours after aneurysm rupture [5, 16]. Despite the fact that, in a number of clinical studies the efficacy of cisternal irrigation to prevent the development of vasospasm at least during early cerebral aneurysm surgery could be demonstrated [3, 6, 14, 15, 19, 25], the blood clots around cerebral vessels at the base of brain are sometimes so adherant that clot removal is not possible [17, 20, 21, 22]. However, Alexander *et al.* reported that this clot removal had no significant effect on the neuroradiological course or degree of angiographic spasm on day 8 [1]. Similarly, almost all of the morphological changes associated with chronic vasospasm in both autopsy and experimental reports were uneffected by delayed lavage [13, 15]. On the other hand, Alexander *et al.* reported that cisternal lavage 24 hours after haemorrhage has no effect on the angiographic vasospasm in spite of evidence of clot removal as seen at sacrifice [1].

The acute spasm is maximal at ten minutes and the late spasm is maximal at two days after subarachnoid haemorrhage. The time course of spasm is shorter in the rat as compared to other species [24]. Wilkins and Levitt did not see an acute phase in their canine blood injection model [29]. Also the acute phase does not seem to occur in humans [26, 28]. However, the longer the period after the haemorrhage is, the more unsatisfactory will be the wash out of the clot around the basilar cistern and basilar artery and its branches. Additionally, the important perforating arteries may be damaged. The most effective metabolites in vasospasm pathogenesis are produced by blood clot lysis. Such events may occur one after another following the bleeding, but with very early cisternal irrigation, such undesirable conditions may be prevented at the very beginning, and the blood elements around arteries and cisterns may be cleaned easily before clotting. We found that vasospasm had largely disappeared, when cisternal irrigation was initiated within 15 minutes and continued until clear CSF was obtained and that no blood clot elements were observed either in the basal cisterns or around the arteries in the postmortem inspection. But in the control group, the arterial spasm continued or the basilar artery grew more spastic (Mean difference = 0.133, $t = 5.749$, $P < 0.0005$), and the basal cisterns were largely covered with blood clot ($u = 2, z = 4.583, P < 0.001$). The general constriction ratio was 0,0167 in the irrigation group while it is 0,309 in the control group.

Although it has been stated that, the reduction of gross clot after lavage was associated with decreased endothelial desquamation and platelet adherence, with a trend toward reduced intimal fibroplasia, the relative roles of gross clot and adventitial blood cells in the genesis of vasospasm were not clear [16, 26]. The present study shows that complete evacuation of blood clot at 3 hours after haemorrhage is very effective in preventing vasospasm in the rat model.

In conclusion, we can say that the clots which are presumably the source of vasoactive substances, can easily be cleaned before getting more sticky by employing cisternal irrigation in the very early period of experimental subarachnoid haemorrhage. It should also be possible to avoid acute vasospasms and so to prevent the development of ischaemic deficits.

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