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Original Article

Safety and efficacy of sildenafil citrate in reversal of cerebral vasospasm: A feasibility study

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Abstract

Objective: Cerebral vasospasm is the commonest cause for mortality and morbidity in patients following clipping of a ruptured aneurysm. Selective phosphodiesterase (PDE) inhibitor like sildenafil acts as a vasodilator. The objective of this study was to evaluate the safety and feasibility of oral sildenafil citrate in patients with symptomatic refractory vasospasm.

Methods: A total of 832 patients with aneurysmal subarachnoid bleed were operated in 4 years. Two hundred and seventy-three patients had vasospasm. Of these, 72 patients had refractory cerebral vasospasm. Vasospasm was defined as "refractory" when institution of "HHH" failed to reverse the transcranial Doppler (TCD) values even after 24 hours. Computed tomography (CT) scan showed no infarct, hematoma, or hydrocephalus, and the serum electrolytes were within normal limits. They received 100–150 mg of sildenafil every 4 hours. Response was evaluated by 2-hourly TCD.

Results: Eight patients had sustained (TCD values normal for >48 hours) and four had temporary relief in vasospasm, as suggested. Four patients developed complications significant enough to terminate the therapy.

Conclusions: Sildenafil citrate may be effective in patients with refractory symptomatic vasospasm. It calls upon the pharmacologists and scientists to discover newer supraselective PDE inhibitors, specific to PDE receptors in brain vessels.

Key Words: Sildenafil citrate, subarachnoid hemorrhage, vasospasm

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INTRODUCTION

Vasospasm is a common complication after subarachnoid hemorrhage (SAH) and influences both mortality and morbidity. Conventionally, the management of symptomatic vasospasm is based on (hypertension, hypervolemia, hemodilution) HHH therapy and nimodipine.[5,11] Papaverine, nimodipine, and magnesium sulfate are some of the available chemotherapeutic agents used in clinical practice. However, the results of these therapies are not always satisfactory.[12] Sildenafil is a selective oral phosphodiesterase (PDE) inhibitor that has a vasodilator effect and has never been tried in humans with cerebral vasospasm.

The objective of this study was to evaluate the safety and efficacy of sildenafil citrate in humans with symptomatic refractory vasospasm.

MATERIALS AND METHODS

The study was started in October 2006 after obtaining clearance from the institute ethics committee. All patients underwent cerebral digital subtraction angiogram before surgery. They underwent pterional craniotomy, trans-sylvian approach, and clipping of aneurysm. The inclusion criteria were the following: 1) Patients older than 18 and less than 60 years of age 2) Case of intracranial aneurysm operated within 72 hours of SAH. 3) Clinically symptomatic vasospasm was defined as a patient who after surgery worsened neurologically as compared to the preoperative grade. The worsening was either in sensorium or a new focal deficit. Clinically symptomatic refractory vasospasm was defined as no improvement after 24 hours following HHH therapy. The HHH therapy constituted of hypertension, hemodilution, and hypervolemia. The hypervolemia and hemodilution were achieved by giving crystalloids to maintain a central venous pressure of 12–14 cm of saline . The systolic blood pressure was maintained around 180 mm Hg by adding dopamine or dobutamine if necessary Other causes of deterioration as mentioned in point 5 (*vide infra*) were ruled out. All the patients were deemed to have vasospasm based on transcranial Doppler (TCD) and none were subjected to a repeat Digital Subtraction Angiogram (DSA). Vasospasm was defined as "refractory" when institution of HHH failed to reverse the TCD values (increased flow velocities) even after 24 hours. 4) Vasospasm was corroborated on TCD velocity middle cerebral artery (v-MCA) >120 cm/s. The TCD was done using 2 MHz probe through the temporal bone window. 5) Computed tomography (CT) scan showed no infarct, hematoma, or hydrocephalus, and the serum electrolytes were within normal limits. Nimodipine (60 mg 4 hourly per orally) was given to all patients with aneurysmal SAH. Dexamethasone, nimodipine, low–molecular-weight dextran and HHH were continued in all, as this has been the protocol of our center. This protocol was not changed as per the ethics committee directive. Consequently, these confounding factors were not eliminated from this study. None of the patients underwent intracranial pressure monitoring.

A total of 832 patients with aneurysmal subarachnoid bleed were operated from October 2006 to September 2010. Two hundred and seventy-three patients had vasospasm in the postoperative period. Seventy-two patients of these 273 patients had clinically refractory symptomatic vasospasm and were included in the study group. The clinical, radiological, and operative details are detailed in Table 1. They were given sildanefil. The dose was 100 mg every 4 hours for patients weighing up to 70 kg and 150 mg every 4 hours for those weighing more. The route of administration for all was enteral. It was given through the nasogastric tube in patients who were not conscious. TCD was done every 30 minutes for 8 hours and then every 2 hours till the end point. Insonation of both ipsilateral and contralateral internal carotid artery (ICA), MCA, and anterior cerebral artery (ACA) was tried, but only ICA and MCA were utilized for measurement.

The end points of this therapy were: 1) no response for 48 hours, i.e. if the fall of TCD values was less than 40 cm/s; 2) normalization of TCD values for 2 days or 1 week after clipping, whichever occurs later; and 3) adverse reaction (defined as any new symptom, including increase in severity of headache or deficits after starting sildenafil in whom no obvious organic cause like infarct, hematoma, hydrocephalus, metabolic disturbance was found).

Sustained reversal of vasospasm was defined as decrease of TCD values by more than 40 cm/s for more than 48 hours and it was transient if there were intermittent readings of vMCA of fall less than 40 cm/s interspersed with readings of fall more than 40 cm/s.

RESULTS

Sustained reversal was seen in eight patients (TCD values normal for >48 hours) and transient reversal in four patients [Table 2]. Of the eight patients who developed sustained relief, seven had vMCA >200 cm/s and one patient had vMCA between 120 and 200 cm/s. All the eight patients had a Lindegaard ratio of >3. On the other hand, all four patients with transient reversal had velocities between 120 and 200 cm/s and Lindegaard ratio of <3.

Four patients developed side effects severe enough to terminate the therapy. One patient had severe hypotension (possibly due to dehydration and concomitant dehydration), two patients had severe headache, and one patient had visual obscuration. The patient who developed hypotension was found to have a central venous pressure of 0–2 cm suggestive of significant volume depletion. This was despite giving HHH therapy. The patient with severe visual obscuration would complain of visual blurring lasting for several minutes with no other features of raised intracranial pressure.

The milder side effects were headache in 12, flushing in 7, and abnormal vision in 1 patient. Any complaint of headache was attributed to sildenafil. The mild abnormality of vision was manifested as seeing colored halo around light source.

Table 1: Preoperative and operative details of patients with refractory vasospasm in whom the therapy was instituted

Hunt and Hess or Fisher grade	Number of preoperative patients in that H&H grade	Number of preoperative patients in that Fisher grade	Number of patients in each Hunt and Hess grade at the time of instituting sildenafil
I	16	1	
II	34	16	
III	22	43	34
IV	0	12	38
			Vasospasm detected on DSA preoperatively (number of patients)
Ictus–surgery interval	**Number of patients**		**Focal vasospasm**	**Diffuse Vasospasm**
<24 hours	06		3	0
24–48 hours	22		8	1
>48 hours	44		6	5
Site of aneurysm				
Anterior communicating artery	46			
Middle cerebral artery bifurcation	18			
Posterior communicating artery	6			
Internal carotid artery bifurcation	1			
Anterior choroidal artery	1			
Temporary clipping time (rescue)				
≤5 minutes	6			
6–10 minutes	1			
>10 minutes	1			
Temporary clipping time (elective)				
<5 minutes once	1			
<5 minutes twice	1			
9 minutes once	1			

DISCUSSION

With early recognition and clipping of aneurysms, cerebral vasospasm has become the most feared acute complication following the rupture of an aneurysm. Vasospasm pathophysiology is complex and not fully understood.[8] Delayed ischemic neurological deficit secondary to vasospasm represents a frequent cause of disability and death. Without a proper therapy, cerebral vasospasm is associated with a 34% permanent disability and 30% mortality.[5,6] Papaverine is a nonspecific phosphodiesterase (PDE) inhibitor that has been used in vasospasm when applied topically during surgery. When given intra-arterially, it effectively dilates the spastic arteries. However, the effect is short-lived and vasospasm usually recurs.

Nitric oxide (NO) is a primary endogenous vasodilator that affects smooth muscle relaxation. NO regulates the relaxation of vascular smooth muscle cells through activation of soluble guanylate cyclase. The cyclase converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP) in the cells of cerebral arteries. Accumulation of cGMP relaxes the smooth muscles and its reduction leads to vasoconstriction. On the contrary, PDE hydrolyzes cGMP and cyclic adenosine monophosphate (cAMP). Type 5 PDE isoenzyme causes vasoconstriction. Thus, the amount of cGMP in the vascular smooth muscle cells is influenced by both NO and PDE.[3]

Currently, 11 families of PDEs have been identified in humans. PDE1 and PDE5 are present in vascular smooth muscle cells. Brain tissue has PDE1, PDE2, PDE4, and PDE10.[2] Sildenafil has good selectivity for PDE5, but the selectivity is not exclusive as it has some action on PDE1, PDE2, and PDE4. The selectivity ratio for PDE5 to PDE1, PDE2, and PDE4 is 1:80:19,000:2057, respectively.[4]

Sildanefil was originally used for angina and later for erectile dysfunction. It has been used in pulmonary hypertension, Raynaud's phenomenon and vertebro-basilar insufficiency.[3,17]

The bioavailability is approximately 40% and the peak level is usually reached in 30–120 minutes. The terminal half-life is 4 hours. Considering the bioavailability and the half-life, 100 mg every 4 hours was the dose given to

Table 2: Details of patients who responded to sildenafil therapy

	Fisher grade	Hunt and Hess at presentation	Hunt and Hess at administration of sildenafil	TCD values for MCA at the time of administration of sildenafil (cm/s)	Ictus–surgery interval	Site of aneurysm	Pre-op spasm on DSA
Sustained responders							
Patient 1	2	I	IV	>200	B	ACom	N
Patient 2	3	II	IV	>200	B	ACom	N
Patient 3	2	I	IV	120–200	C	ACom	D
Patient 4	2	I	IV	>200	C	MCA	Focal
Patient 5	3	I	IV	>200	C	ACom	Focal
Patient 6	3	II	III	>200	B	ACom	Focal
Patient 7	4	III	IV	>200	B	ACom	D
Patient 8	4	III	IV	>200	B	MCA	N
Transient responders							
Patient 1	2	III	IV	120–200	C	MCA	Focal
Patient 2	3	I	IV	120–200	B	MCA	N
Patient 3	3	I	III	120–200	C	ACom	D
Patient 4	3	I	III	120–200	C	ACom	N

B: 24–48 hours, C: 48–72 hours, ACom: Anterior communicating artery aneurysm, MCA: Middle cerebral artery aneurysm, N: None, D: Diffuse

patients weighing less than 70 kg and 150 mg was given every 4 hours for persons weighing more.

The mechanism of action of sildenafil may be more complex. Rats administered sildenafil in the lateral ventricles had remarkable tachycardia without significant change in basal arterial pressure.[7] Sildenafil elicited an increase in sympathetic nerve activity that is not baroreflex mediated, suggesting that this drug is able to elicit an autonomic imbalance of central origin.

Certain clinical studies and reports, however, have revealed contrary results. Sildenafil administration in stroke patients showed significantly more areas with diminished perfusion compared to baseline.[13] Our results are contrary to these. Though a perfusion study was not carried out in our patients, we presume that sildenafil administration may have improved the cerebral blood flow in responders. SAH has also been reported after usage of sildenafil.[9]

A critical review of the clinical data supports the conclusion that nimodipine decreases the severity of neurologic deficits and improves outcome after SAH. All our patients received nimodipine. One may argue that nimodipine *per se* would have helped in overcoming vasospasm. The mechanisms by which mortality and morbidity are reduced are still controversial. First, the frequency of vasospasm is not altered. Second, the consistent reversal of vasospasm once present has not been demonstrated either angiographically or by noninvasive cerebral blood flow studies. These observations suggest that there is either modification of microcirculatory flow (i.e., dilation of pial conducting vessels or decreased platelet aggregation) or a direct neuronal protective effect. Thus, nimodipine is unlikely to cause the improvement in the flow velocity on TCD.[14]

Natural resolution of vasospasm over a period of time or delayed response to HHH (>24 hours) cannot be ruled out, as there was no control group.

It has been shown that inhibitors of PDE 2, PDE4, PDE5, PDE9, and PDE10 improve a wide range of cognitive processes, including information processing, attention, learning, memory, executive functioning, and response inhibition, in various behavioral models within different species. It is argued that it is unlikely that blood flow is the mechanism underlying these procognitive effects. It is felt that long-term potentiation appears to be a better substrate for the cognition-enhancing properties of PDE inhibitors.[16]

Nitrates, which increase cGMP by increasing NO, have been used in cerebral vasospasm by intrathecal and intraventricular routes.[10,15] The approach is invasive with accompanying complications and infection. Administering oral PDE inhibitor in the form of sildenafil is a novel approach. It is easier to administer with less side effects. Sildenafil citrate is documented to be useful to treat cerebral vasospasm in animal studies.[1] This is the first human study, though there are a few limitations. It lacks outcome measures and there is no control group. Larger studies may be carried out to find out the efficacy of sildenafil in refractory vasospasm.

CONCLUSIONS

In this report, we present our initial results on the use of oral sildenafil in cerebral vasospasm. It may be useful in severe refractory vasospasm. Till date, no human trials have been published. This is a feasibility study and opens up the possibility of further trials in humans. Also, it calls upon the pharmacologists and scientists to discover newer supraselective PDE inhibitors specific to PDE receptors in brain vessels.

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Commentary

Reversal of transcranial Doppler vasospasm with sildenafil

Mukherjee and colleagues present a series of 72 patients with aneurysmal subarachnoid hemorrhage (SAH), who deteriorated neurologically days after the hemorrhage.[6] They were treated with sildenafil when they developed increased transcranial Doppler (TCD) flow velocities that persisted despite hemodynamic therapy. Eight (11%) were classified as having a sustained reversal response to sildenafil, with sustained reversal being defined as a decrease in TCD velocity of more than 40 cm/s for more than 48 hours. Four patients (6%) had side effects that may or may not have been related to sildenafil. Hypotension occurred in one patient, severe headache in two patients, and visual obscurations in one patient. These are known but relatively rare side effects of the drug. The response rate is small but potentially important. This small retrospective study suffers from all the limitations of such reports including lack of blinding and of any controls to excludes the possibility of spontaneous regression, variability in TCD, and as such requires confirmation in a more rigorous early phase clinical trial using something other than TCD.

The rationale for using sildenafil rests mostly on its known vascular actions. Normal vascular function relies on, among other things, a balance in the production of vasodilators such as nitric oxide (NO) and vasoconstrictors such as endothelins.[8] In the cerebral and other vasculature, NO produced mainly in endothelial cells activates soluble guanylate cyclase in smooth muscle cells. This enzyme synthesizes cyclic guanosine monophosphate (cGMP) which relaxes smooth muscle and causes vasodilation. The cGMP is metabolized by phosphodiesterases (PDEs). PDEs are now known to include over 100 proteins divided into 11 families.[12] PDE4, 7, and 8 hydrolyze cyclic adenosine monophosphate; PDE5, 6, and 9 hydrolyze cGMP; and PDE1, 2, 3, 10, and 11 hydrolyze both cAMP and cGMP. Thus, inhibition of PDE will generally result in vasodilation.

The history of PDE inhibitors spans centuries. Xanthines, one class of PDE inhibitors, including caffeine, were found to be broncho- and vasodilators about a century ago. Papaverine is perhaps the best known PDE inhibitor. Theophylline has been used since the 1950s, and like many drugs, studied for its effect on angiographic vasospasm, without showing robust effects.[11] Each of these drugs has varying specificities for the different PDE isoforms.[9] PDE3 inhibitors include milrinone, which has positive inotropic effects and less vasodilatory action. The pharmacology is very much more complicated than simple inhibition of one PDE type, for example, cilostazol is a PDE3 inhibitor also, but its principle actions are vasodilation and antiplatelet aggregation. Interestingly, it also has been suggested to have favorable effects against vasospasm after SAH. PDE4 is involved in inflammatory cells and lung vasculature. Sildenafil is an inhibitor of cGMP phosphodiesterase type 5 (PDE5). PDE1 and PDE5 are abundant in the vasculature. PDE6 is important in light perception in the retina, and action of sildenafil on this isoform may explain its visual side effects. Sildenafil is approved for use for erectile dysfunction as well as for primary pulmonary hypertension. The penis and lung arteries possess predominately PDE5.

Alksne and Branson tested nonspecific PDE inhibitors such as phthalazinol for SAH-induced vasospasm in dogs over 30 years ago.[1] Impairment in NO-mediated relaxation of vasospastic arteries was documented in experimental models.[5] One mechanism of this was suggested to be increased metabolism of cGMP by PDE5.[10] Inoha *et al*. demonstrated increased PDE5 expression in vasospastic dog basilar arteries and antivasospastic effects of sildenafil in 2002.[4] Other experimental studies found that sildenafil administered orally starting at the time of SAH prevented angiographic vasospasm in rabbits.[2] Tadalafil, another PDE5 inhibitor, started 12 hours after SAH, also reduced angiographic vasospasm in rabbits.[7]

The other point is that sildenafil has other potentially beneficial effects. As the authors and others note, the brain contains multiple PDE isoforms, including PDE1, PDE2, PDE4, and PDE10.[12] Sildenafil induced neurogenesis and promoted recovery after experimental ischemic stroke.[13] Positive effects on cognition also have been noted.[12] Brain injury after SAH is multifactorial and includes early brain injury as well as microthrombosis, cortical spreading ischemia, angiographic vasospasm, and neuronal injury. Indeed, Han and colleagues reported that sildenafil decreased vasospasm and neuronal death and improved behavior after SAH in mice.[3] Many of these processes at least theoretically could be modulated by PDE inhibition. The report of Mukherjee *et al*. does not contain any clinical outcome, but it is intriguing in view of the above, and the authors are encouraged to continue their studies.

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