Spontaneous Nonaneurysmal Subarachnoid Hemorrhage: Review of 75 Cases

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The primary objective of this study was to describe the clinical, radiological, and transcranial Doppler (TCD) ultrasonography characteristics of patients with spontaneous, nonaneurysmal subarachnoid hemorrhage (SNSAH), and analyze their short- term outcome at discharge. The secondary objective was to determine their risk factors for the development of vasospasm.

Seventy-five patients with SNSAH were analyzed in terms of clinical, radiological, and TCD parameters, as well as Glasgow Outcome Scale (GOS) at discharge. The patients were then divided into two groups based on whether or not they developed vasospasm by TCD ultrasonography. Twenty of 75 patients (26.7%) had vasospasm by TCD criteria. Age, sex, cigarette smoking, hypertension, clinical Hunt and Hess and World Federation of Neurological Surgeons (WFNS) grading, Fisher's grade on computerized tomography (CT) scan, or discharge GOS score did not correlate with the development of vasospasm. Hydrocephalus, identified in 11 (14.7%) patients upon admission, was significantly more common in patients with vasospasm ($p< 0.0001$). Patients with vasospasm stayed in the hospital significantly longer than those without vasospasm ($P<0.001$).

Vasospasm in SNSAH is more prevalent than previously thought. There is no statistical correlation between the incidence of vasospasm in patients with SNSAH and age, sex, smoking, hypertension, and different admission clinical and Fisher's grades. However, the presence of hydrocephalus at admission correlated significantly with the development of vasospasm. Despite the high incidence of vasospasm, there is no difference in short-term clinical outcome at discharge between the patients with and without vasospasm.

Key words: angiography, subarachnoid hemorrhage, transcranial Doppler ultrasonography, vasospasm

Every year approximately 30,000 people suffer from subarachnoid hemorrhage (SAH) in the United States.[17] Approximately 15% of these patients have no identifiable cause to account for the hemorrhage on initial 4-vessel cerebral angiography.[25] Subsequent angiography reveals an identifiable cause in 2-24% of cases.[25] It is generally agreed that delayed ischemic neurological deficit (DIND) due to vasospasm in this population is largely responsible for unfavorable outcomes.[2,14] SNSAH, especially perimesencephalic nonaneurysmal SAH has long been known to have a low incidence of vasospasm and a more favorable outcome compared to patients with aneurysmal bleeds. [4,14,25] It is reasonable to propose that if vasospasm were detected early, timely institution of therapy might make a difference in final outcome.[1,9] With its introduction in 1982, TCD ultrasonography rapidly became a popular tool to assess cerebral vasospasm because of its noninvasive nature. Several studies have documented the accuracy of

TCD ultrasonography to detect and monitor vasospasm.[9,11,29,33] In this study, clinical, radiological and TCD characteristics of all patients admitted with the diagnosis of SNSAH were analyzed.

Materials and Methods

Seven hundred and sixty four patients with symptoms of spontaneous subarachnoid hemorrhage confirmed by CT scan of the head and/or positive lumbar puncture were admitted to Harborview Medical Center between January 1998 to July 2002. Six hundred eighty seven patients were diagnosed to have aneurysms or arteriovenous malformations (AVM) as the cause of bleeding. The remaining 77 patients were found to have SAH without any intracranial identifiable cause on cerebral angiograms. Hospital charts, imaging studies and transcranial Doppler studies of 77 patients were reviewed in detail. Two patients were excluded from the study due to an incomplete TCD evaluation secondary to poor temporal acoustic windows. Thus 75 patients with detailed clinical, radiological and TCD studies constitute the basis of this study. We described the following parameters in this patient population: age, sex, history of hypertension and smoking, Hunt and Hess and world federation of neurological surgeons (WFNS) scales on admission, presence or absence of hydrocephalus at admission, admission CT Fisher grade, location of blood, rebleeding rate, length of hospital stay, and Glasgow outcome scale at discharge from hospital. The patients were subsequently divided into two groups; Group I contained patients who developed vasospasm, and Group II, patients who did not develop vasospasm.

Management Protocol

Each patient with suspected SAH was evaluated by the neurosurgical team in the emergency room. Clinical grading of patients was performed using Hunt and Hess[10] and WFNS scales[3] at the time of admission. A noncontrast CT scan followed by an infusion CT scan of head were obtained routinely in all patients and amount and distribution of blood in the subarachnoid space was assessed using Fisher's Grading scheme.[6] We divided the location of blood into following types: 1) *Perimesencephalic group (PNSAH)*, satisfying the following criteria as suggested by Rinkel, et al.;[20] *a)* center of hemorrhage located immediately anterior to the midbrain, with or without extension of blood to the anterior part of the ambient cistern or to the basal part of the sylvian fissure; *b)* no complete filling of the anterior interhemispheric fissure and no extension to the lateral sylvian fissure, except for minute amounts of blood; c) absence of frank intraventricular hemorrhage 2) *'Aneurysmal'*, pattern and location of blood in the cisterns or fissures suggestive of aneurysmal bleed e.g. blood entirely or predominantly in the sylvian fissure, 3) *Other variety* e.g. convexity sulcal blood, 4) *No intracranial blood*. All patients subsequently underwent 4-vessel cerebral angiography. If angiogram revealed aneurysm or AVM, the patient was excluded from this study. A diagnostic lumbar puncture was performed in patients with a strong clinical suspicion for SAH and a negative CT scan. If an aneurysm was not detected on the first cerebral angiogram, a repeat angiogram including external carotid runs was performed in 7-10 days. The patients were routinely admitted to the neurosurgical intensive care unit (ICU) and routinely underwent daily TCD evaluation of their internal carotid (ICA), middle cerebral (MCA), anterior cerebral (ACA), posterior cerebral (PCA), basilar (BA) and vertebral arteries (VA). TCD studies were continued on a daily basis until two consecutive studies were normal. Additional angiography was performed for potential angioplasty if there was a high suspicion for clinical vasospasm along with concomitant TCD changes or a positive Single Photon Emission Computerized Tomography (SPECT) scan.

Artery	Mean Blood Velocity	EICA/MCA Ratio (for MCA)
Vertebral artery	>80 cm/sec	
Basilar artery	>95 cm/sec	
Posterior cerebral artery	>110 cm/sec	
Anterior cerebral artery	>130 cm/sec1	
Middle cerebral artery		
Mild	120-149 cm/sec	3-5.99
Severe	>200 cm/sec	>6.00

Table 1. Parameters to diagnose and grade vasospasm by TCD.

TCD Protocol

Methods for assessing vasospasm by TCD ultrasound have been discussed in detail elsewhere.[7] Routine mean blood velocity, Pulsatility Index and extracranial ICA/MCA mean velocity ratio were recorded using a 2-MHz probe. Based on the parameters obtained, criteria as shown in **Table 1** were used to diagnose and grade vasospasm.[26,28,34]

Onset, duration and severity of vasospasm determined by TCD ultrasonography were recorded in all patients. Clinical vasospasm as defined by a decline in the level of consciousness or a new neurological deficit from days 3-11, not explained by a concurrent CT scan or biochemical abnormality, was noted. Presence or absence of vasospasm on angiography was also noted. The short-term neurological outcome was assessed using Glasgow outcome scale (GOS)[13] at the time of hospital discharge or death.

Statistical Analysis

We used Fisher's exact test using a standard software (StatXact 4 (version 4.01), Cytel Software Corporation, Cambridge, MA, 2000) to relate categorical factors to the occurrence of vasospasm. For characteristics that were significantly related, logistic regression analysis was used to calculate the odd's ratio and 95% confidence interval (LogXact 4 (version 4.1), Cytel Software Corporation, Cambridge, MA, 1999). Mann- Whitney test was used to evaluate relationship with continuous variables. P values of less than 0.05 were considered significant. We considered

Parameters	Total patients (% out of 75)	Group I (% out of 20)	Group II (% out of 55)
Total Number	75	20	55
Age (mean)	48.5	49.5	48.1
Sex ratio (M: F)	40:35	11:9	29:26
Smoking	14 (18.6%)	5 (25.0%)	9 (16.3%)
Hypertension	20 (26.6%)	6 (30.0%)	14 (25.4%)

Table 2. Demographics of patients

the effects of age, sex, smoking, hypertension, Hunt-Hess grade and WFNS grade at the time of admission, presence of hydrocephalus, Fisher grade, and location of blood on the propensity to develop vasospasm, and compared the length of hospital stay and short-term outcome in patients with SNSAH with and without vasospasm**.**

Results

A total of 77 (10.1%) patients were found to have SNSAH of 764 patients admitted with spontaneous SAH. Two patients were excluded from the study for the reason previously mentioned. Therefore, 75 patients were selected for further analysis. Sixty-five patients underwent two cerebral angiograms. A single angiogram was obtained in the remaining 10 patients due to death, medical instability, or lack of informed consent for the second angiogram.

Demographics

Age of the patients ranged from 15-80 years with a mean of 48.5±13 years and there was no sex predilection (M: F 40:35) (**Table 2**). In total, smoking and hypertension were found in 14 (18.7%) and 20 (26.7%) patients respectively. In patients with vasospasm smoking and hypertension were found in 25.0% and 30.0% respectively, whereas in patients without vasospasm, nine (16.3%) smoked and 14 (25.4%) had hypertension. The difference in the two groups was not statistically significant.

Imaging

Admission scales (H&H and WFNS) and blood on CT according to Fisher's criteria are depicted in **Table 3**. Most patients were good grades (60 (80.0%) patients in I and II in H&H, 62 (81.3%) in I and II in WFNS schemes) at presentation whereas 46 (61.3%) patients had thick layer of subarachnoid blood on CT scan (Fisher's group III). Statistical analysis failed to show any significant correlation between particular grades and the development of vasospasm. **Figure 1** shows the pattern and location of blood on CT. Forty six (61.3%) patients had classic perimesencephalic hemorrhage whereas 19 (25.3%) and five (6.7%) patients had 'aneurysmal' and 'other' types of hemorrhages respectively. Five patients (6.7%) did not have blood in the intracranial subarachnoid space on CT scan. Of these, three had CT done on the same day of ictus, whereas two had their CT on days four and six. All patients had xanthochromia and/or RBC count of greater than 2000/microL. Comparison of groups I and II did not show any significant difference.

Vasospasm

Twenty patients (26.7 %) had vasospasm on TCD. A total of 47 vessels were affected by vasospasm. MCA (46.8%) was the commonly involved vessel followed by ACA (23.4%), as summarized in **Figure 2.** Four patients had severe vasospasm. Two of these patients underwent angiography with angioplasty of the left MCA. Vasospasm was detected as early as, on day two, though most patients (six (30.0%) out of 20)) had vasospasm start on day four as shown in **Figure 3**. In nine(45.0%) of 20 patients vasospasm remained only for one day **(Figure 4).** Four patients had clinical vasospasm. Angiographic vasospasm was detected in five patients.

Hydrocephalus and Vasospasm

Eleven (14.7%) patients were noted to have hydrocephalus upon admission requiring placement of a ventriculostomy. Three patients subsequently required a ventriculoperitoneal shunt. Further analysis showed that eight (40.0%) patients from the vasospasm group had hydrocephalus as opposed to three (5.4%) from the group without vasospasm. This difference was statistically significant ($P<0.0001$).

Outcome and Length of Stay

At discharge, 64 (85.3%) patients had favorable outcome (good and minor disability) and mortality was 8.0% **(Figure 5).** All patients who died either came to the hospital in a neurologically poor condition or suffered a significant preexisting medical condition. Some of these patients were on anticoagulation therapy; others had poor cardiac reserve, or suffered a nosocomial pneumonia ultimately leading to death. There was no significant difference between the two groups of patients in their Glasgow outcome scale. Total

Grades	Total patients (% out of 75)	Group I (% out of 20)	Group II (% out of 55)
H&H Grade			
I	17 (22.7%)	1 (5.0%)	16 (29.1%)
II	43 (57.3%)	13 (65.0%)	30 (54.5%)
III	5 (6.7%)	1 (5.0%)	4 (7.3%)
IV	8 (10.7%)	4 (20.0%)	4 (7.3%)
V	2 (2.7%)	1 (5.0%)	1 (1.8%)
WFNS Grade			
I	49 (65.3%)	8 (40.0%)	41(74.5%)
II	12 (16.0%)	6 (30.0%)	6 (10.9%)
III	3 (4.0%)	1 (5.0%)	2 (3.6%)
IV	5 (6.7%)	2 (10.0%)	3 (5.5%)
V	6 (8.0%)	3 (15.0%)	3 (5.5%)
Fisher's Group			
I	5 (6.7%)	1 (5.0%)	4 (7.3%)
II	20 (26.7%)	4 (20.0%)	16 (29.1%)
III	46 (61.3%)	12 (60.0%)	34 (61.8%)
IV	4 (5.3%)	3 (15.0%)	1 (1.8%)

Table 3. Clinical and Fisher's CT grades of SAH at admission.

length of stay for all patients in this series was 10.3±9 days. Patients with vasospasm stayed in the hospital significantly longer than patients without vasospasm (15.1±nine days vs. 8.6±9.7 days, P<0.001).

Discussion

At our institution, SNSAH was found in 10.1 % of all patients admitted with spontaneous SAH, which is consistent with previously published reports ranging from 7.2% to 23%.[2, 7, 23, 24]

Demographics and Risk Factors

The demographic characteristics of this study population were very similar to those observed in other series of patients with SNSAH.[12,16,21] There is no age predilection for this disease though most of the patients tend to be younger.[16,21] The youngest patient reported with SNSAH was three years.[22] Similarly, there is no definite trend in the sex incidence among the series published previously.[12,21] Hypertension and cigarette smoking have been shown to correlate with the development of vasospasm in patients with SNSAH, although not as strongly as in patients with aneurysmal SAH.[15,31] Our study, however, did not show that cigarette smoking or hypertension influenced the development of vasospasm.

Grading

Patients with SNSAH generally present in good clinical grades.[12,16,31,32] Our results corroborate with previous studies since most patients presented with good grades. Loiseau, et al.,[16] in their review of 65 patients with SAH and negative angiography found patients in Hunt Hess grade I and II in 69.0% of cases. Ildan, et al.,[22] in their analysis of 84 patients found 78.7 % of patients in grade I or II. Analysis of our data failed to show any relationship between the development of vasospasm and the clinical grade upon admission.

Imaging

Forty-six (61.3%) patients had thick clot in the subarachnoid cistern (Fisher's group III). However in contrast to SAH due to aneurysmal rupture,[6] it was not a significant factor for the development of vasospasm. Blood in the perimesencephalic cistern on CT was the most common

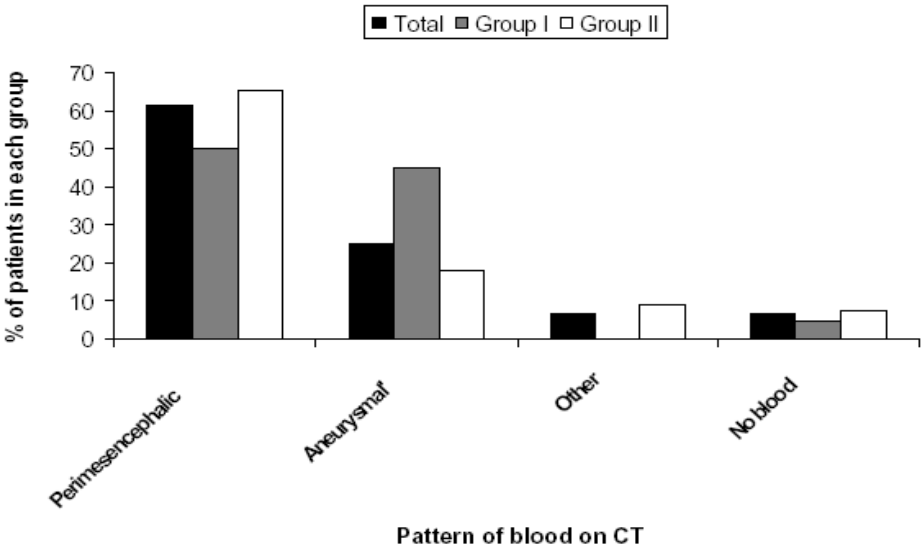

Figure 1. Bar graph showing the pattern and location of blood on CT scan in each group of patients.

location observed in this series, which is consistent with previous reports.[20,32] However, there was no statistical correlation between the location of blood and development of vasospasm. Van Gijn,et al., in the original paper described PNSAH in 13 of 28 patients whereas an 'aneurysmal' pattern of bleeding was noted in Seven of 28 patients.[32] Though they speculated that patients might develop an aneurysmal pattern of bleeding due to thrombosed aneurysm, no subsequent data exists to confirm this theory. Ildan, et al., noted 34.5% of patients in the PNSAH group, 35.7% in the "aneurysmal" group, and 9.7% of patients, in a group characterized on CT scan as "no blood".[12] In Schwartz, et al.'s series, 7 (26.2%) of the 24 patients had PNSAH.[24]

Vasospasm

We found a relatively high incidence of vasospasm in patients with SNSAH (26.7%) by TCD criteria. Schaller, et al.,[21] in their review of 16 patients noted moderate and severe vasospasm on TCD associated with symptomatic vasospasm in six patients (37.4%). Most other reports

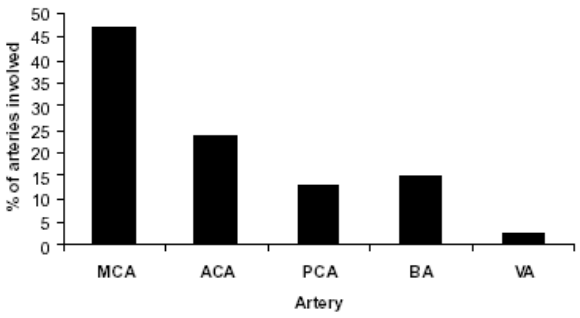

Figure 2. Bar graph showing the distribution of different vessels affected by Vasospasm by TCD in a total of 47 vessels (MCA= middle cerebral artery, ACA= anterior cerebral artery, BA= basilar artery, PCA= posterior cerebral artery, VA= vertebral artery).

describing the incidence of vasospasm have not included TCD criteria.[23,27] Vasospasm in nearly half of our patients (45.0%) lasted for one day only.

In our series, the MCA was the most commonly affected artery by vasospasm. There are very few reports assessing all the accessible arteries by TCD ultrasonography. One series reported vasospasm to be most common in the vertebrobasilar system which would be the expected vessel of involvement in close proximity to the hemorrhage.[16] It is difficult to explain why the MCA, which is away from the actual location of blood was most commonly affected by vasospasm in our series.

Vasospasm started as early as on day two from the onset of symptoms, although the majority developed vasospasm by day three and four. Vasospasm lasted for only one day in 45% of the patients with vasospasm. This could well be due to the fact that vasospasm in patients with SNSAH runs a benign course. Alternatively, the early and aggressive institution of hypervolemia, hemodilution and hypertension (popularly known as triple-H) therapy and daily TCD surveillance could also have played a role. Severe vasospasm of the MCA was noted in four patients. In our series, angiographic vasospasm was found in five cases and clinical vasospasm was noted in only four patients. Sheehan, et al.,[27] reported symptomatic and angiographic vasospasm in a patient with perimesencephalic nonaneurysmal SAH although no TCD information was included in that paper. Angiographic vasospasm is considered to be much higher in patients with aneurysmal SAH.[2] Loiseau, et al.,[16] in their review of 65 patients with angiographically negative SAH noted angiographic vasospasm in 52.0% of the cases, although symptomatic vasospasm was noted in only two (3.0%) patients. We did not find any reports of angioplasty for severe vasospasm in patients with SNSAH. Two of our patients of 'aneurysmal' pattern of hemorrhage had severe vasospasm by TCD criteria. Both of these patients had clinical vasospasm and

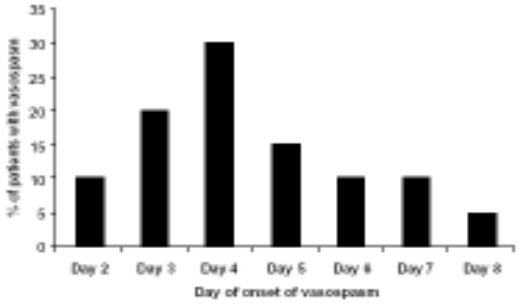

Figure 3. Bar graph showing the day of onset of vasospasm from the day of ictus.

underwent a SPECT scan, which confirmed decreased perfusion in the left MCA territory. Subsequent angiography confirmed severe vasospasm for which the patients underwent angioplasty successfully. This stresses the fact that severe vasospasm does occur in the setting of SNSAH.

Hydrocephalus

Hydrocephalus was detected in 11 patients and all required placement of a ventriculostomy upon admission. Three patients required a ventriculoperitoneal shunt. Strikingly, eight (40.0%) patients with vasospasm had hydrocephalus compared to three patients without vasospasm. This difference was found to be statistically significant. Ildan et al in their series of 84 patients noted hydrocephalus only in four patients.[12] Loiseau, et al., noted acute hydrocephalus in 17.0 % of patients in a series of 65 patients.[16] Rinkel, et al., in their series of 65 patients with perimesencephalic nonaneurysmal SAH noted hydrocephalus in three (5.0%) patients, two of whom ultimately required a ventriculoperitoneal shunt.[19]

Rebleeding

Patients with angiographically negative SAH have been found to have low rebleeding rates.[12,18,25] None of our patients developed rebleeding during hospitalization. This could well be due to the short follow-up period. In Loiseau, et al.,'s series, no rebleeding was reported in 65 patients with SNSAH who review of 65 patients with SNSAH also did not report any rebleeding.[19] In contrast**,** Giombini, et al., reported a rebleeding rate of 6.8 % in the first six months in patients with SAH and negative angiography.[8]

Outcome

Patients with vasospasm had significantly longer length of stay than patients without vasospasm (P<0.001). This shows the economic implication of vasospasm in patients with SAH.

In this series, the overall short-term outcome of patients with SNSAH was favorable; 85.3% had good or minor disability at the time of discharge. These data are consistent with the reported literature.[8,16,30,32] Van Gijn, et al., in their original article reported good outcomes in angiographically negative SAH.[32] No deaths were reported and all patients returned to work within three months. Giombini et al reported a favorable outcome in 89.0% of patients in a series of 58 patients.[8] Similarly, Van Calenberg et al reported excellent outcome in 88.0% patients with negative angiography.[30] Loiseau, et al., noted an initial mortality of 3.0% in a series of 65 patients with SAH and negative angiography.[16]

The development of vasospasm in patients in our series did not influence their final outcome. This could be due to several factors: a) most patients had mild vasospasm that was very short-lived; b) the treatment of vasospasm (triple H therapy for mild and cerebral angioplasty for severe vasospasm) early in its course may have effectively improved the prognosis.

The 8.0% mortality rate in our series warrants clarification. All but one patient had significant comorbid medical conditions. Though we cannot deny the fact that the insult of SAH could well have exacerbated the preexisting conditions, it is hard to justify all deaths due to intracranial insult *per se*. Another confounding factor has been the "withdrawal of care" measures, which was performed in five out of six patients.

Finally, the limitations of our study also deserve mention. This study is retrospective in nature, although data was acquired prospectively, and inherent biases associated with this cannot be ignored. This is also a single institutional study and therefore may not be generalized for other regions. Though we wanted to include as many patients as possible with SNSAH, it is an uncommon disease and the incidence of vasospasm in these patients is relatively infrequent. Therefore, potential introduction of errors due to small sample size cannot be ruled out.

Conclusions

The demographic, clinical, radiological and TCD ultrasonography characteristics of patients with SNSAH have been described in a consecutive series of 75 patients. In addition, we correlated the above characteristics with the development of vasospasm in this patient population. The results demonstrated several important clinical facts, as follows: 1) Incidence of vasospasm in SNSAH is relatively high (26.7%). The time of onset of vasospasm is similar to aneurysmal SAH, although the duration is much shorter. 2)

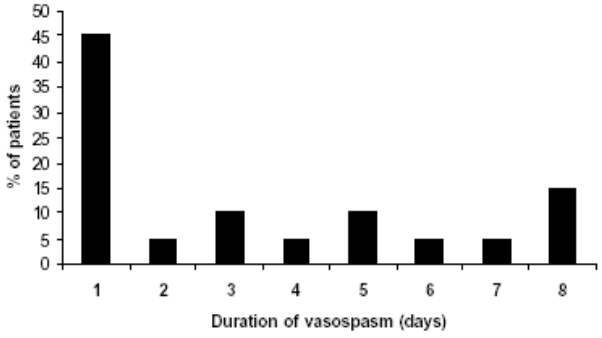

Figure 4. Bar graph showing the duration of vasospasm in 20 patients.

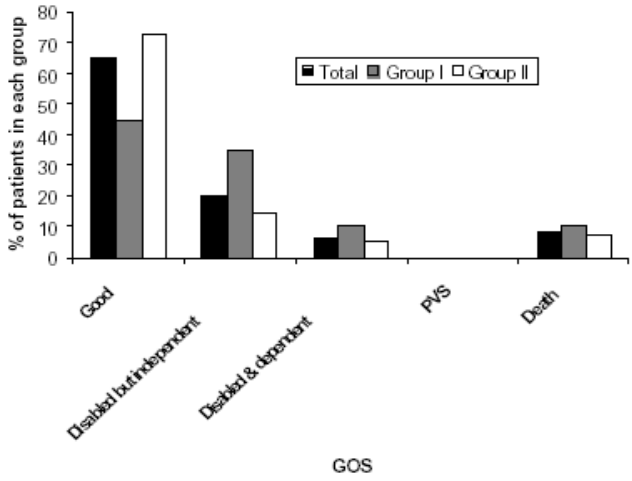

Figure 5. Bar graph showing the GOS score at discharge (PVS= persistent vegetative state) in each group of patients.

There is no statistical correlation between the incidence of vasospasm in patients with SNSAH and age, sex, smoking, hypertension, and different admission clinical and Fisher grades. 3) The presence of hydrocephalus at admission correlates significantly with the subsequent development of vasospasm. 4) Despite the high incidence of vasospasm and increased length of stay for these patients, there is no difference in short-term clinical outcome as determined by GOS scores at discharge between the patients with and without vasospasm.

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