Original Contribution

Effects of Prostacyclin on Cerebral Blood Flow and Vasospasm After Subarachnoid Hemorrhage

Randomized, Pilot Trial

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Background and Purpose—Delayed ischemic neurological deficits (DINDs) are a major contributing factor for poor outcome in patients with subarachnoid hemorrhage. In this trial, we investigated the therapeutic potential of prostacyclin, an endogen substance with known effect on vascular tone and blood flow regulation, on factors related to DIND.

Methods—This trial is a single-center, randomized, blinded, clinical, pilot trial with 3 arms. Ninety patients were randomized to continuous infusion of prostacyclin 1 ng/kg per minute, prostacyclin 2 ng/kg per minute, or placebo. The intervention was initiated day 5 after subarachnoid hemorrhage and discontinued day 10. Primary outcome was the difference in change from baseline in global cerebral blood flow. Secondary outcome measures were occurrence of DIND, angiographic vasospasm, and clinical outcome at 3 months.

Results—No statistically significant difference in change of global cerebral blood flow was found between the intervention groups. The observed incidence of DIND and angiographic vasospasm was markedly higher in the placebo group, although this difference was not statistically significant. No statistically significant differences in safety parameters or clinical outcome were found between the 3 groups.

Conclusions—Administration of prostacyclin to patients with subarachnoid hemorrhage may be safe and feasible. Global cerebral blood flow after subarachnoid hemorrhage is not markedly affected by administration of prostacyclin in the tested dose range. It may be possible that the observed reduction in the point estimates of DIND and vasospasm in the prostacyclin groups represents an effect of prostacyclin as this trial was not powered to investigate the effect of prostacyclin on these outcomes.

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Key Words: epoprostenol ■ subarachnoid hemorrhage ■ vasospasm, intracranial

Subarachnoid hemorrhage (SAH) accounts for only 5% of strokes. Nevertheless, because of the poor prognosis and lower patient age for patients with SAH, the subsequent loss of productive life years is similar to that of ischemic stroke.[1] One of the main causes of poor outcome after SAH is the development of delayed ischemic neurological deficit (DIND).[2] The presumed course of DIND is cerebral vasospasm although a simple causality has been challenged lately. DIND and vasospasm is a transient condition and only about half of the DIND incidences lead to permanent brain damage. The condition may manifest itself anytime within the first 2 weeks after SAH but most incidences happen between days 5 and 10 with peak incidence around day 8.[3] The pathophysiology behind the development of DIND and vasospasm remains poorly understood but factors related to the vascular endothelium and the smooth muscle cell is thought to play an important role.[4] Several intervention options including triple-H therapy (induction of hypertension, hypervolemia, and hemodilution) and angioplasty have been used to prevent or treat vasospasm and DIND, but treatments with convincing effects are lacking.

Prostacyclin is an endogenous substance released from the vascular endothelium. It is a potent vasodilator and inhibitor of leukocyte activation, platelet aggregation, and leukocyte–endothelial interactions, all of which are properties with a hypothetical impact on the development of DIND.[5] Animal studies and in vitro studies have demonstrated positive effects of prostacyclin on cerebral blood flow (CBF) and vasospasm,[6–10] and an imbalance in the prostacyclin–prostaglandin ratio has been proposed as a cause of vasospasm.[6,11] Although results from in vitro and animal studies are promising, few studies exist that investigate the possible effects of prostacyclin on cerebral

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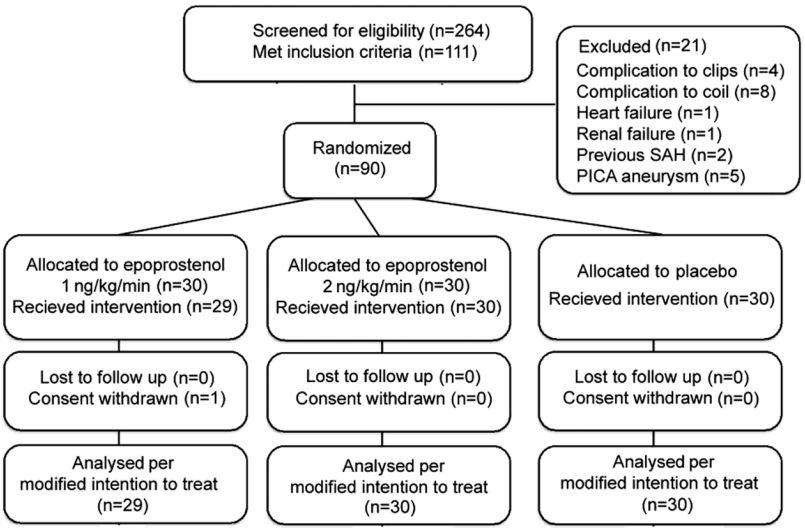

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of inclusion, allocation, and analysis of subjects. PICA indicates posterior inferior cerebellar artery; and SAH, subarachnoid hemorrhage.

vessels in a clinical setting. A case report has described significant recovery from segmental vasoconstriction in the brain after administration of low-dose prostacyclin and a pilot trial observed reduction of vasospasm in 5 SAH patients after prostacyclin administration[12,13] but to date no randomized trials have been conducted.[14] In this randomized, placebo-controlled trial, we investigate the possible pharmacodynamic effects of prostacyclin on the human brain after SAH. The full background and trial protocol have been published previously.[14]

Methods

Overview and Randomization Procedure

This trial is a single-center, randomized, placebo-controlled, parallel group, blinded, clinical, pilot trial. The trial was conducted at Rigshospitalet, Copenhagen University Hospital, Neurointensive Care Unit, Denmark, and was approved by the Danish ethical committee on Human Research (ref No. H-1-2011-087), the Danish Medicines Agency (EudraCT 2011-002798-5), and registered on www.clinicaltrials.gov (ref No. NCT01447095). The inclusion criteria were aneurysmal SAH treated with coiling or surgery, a World Federation of Neurological Surgeons score between 1 and 4 and Fisher grade 3 or 4. Exclusion criteria were previous SAH, pregnancy/lactation, renal failure, heart failure, bleeding diathesis, major complication during endovascular procedure or surgery, or SAH on the basis of posterior inferior cerebellar artery aneurysm. A total of 90 patients were randomized to a continuous infusion of epoprostenol 1 ng/kg per minute, epoprostenol 2 ng/kg per minute, or placebo (drug solvent). Trial medication was initiated day 5 after SAH and discontinued day 10. Concealed allocation was achieved by randomization and allocation by specially assigned nurses not involved in patient care at any circumstance. Randomization was done using a computer-generated allocation list only accessible by the project nurse. When a patient was included the nurse was contacted by telephone and the patient was subsequently randomized. The nurse then prepared the blinded trial medication according to the allocated intervention. Patients or their approved proxy gave informed consent according to a protocol approved by the Ethics Committee. The randomization was not stratified for any baseline characteristics and no interim analysis was performed.

Prostacyclin Dose Rationale

The standard dose of prostacyclin for the frequent clinical indication, hemodialysis, is 4 ng/kg per minute. This dose is associated with a risk of hypotension and local hemorrhage, which is not desirable in SAH patients. However, several human and animal studies have shown hemodynamically beneficial effect of prostacyclin in doses of ≤2 ng/kg per minute. Low-dose prostacyclin improved CBF and reduced the contusion volume in rats after a brain trauma.[9,15] In human studies, low-dose prostacyclin attenuated vasospasm after SAH[13] and reduced segmental vasoconstriction[12] using similar doses as used in the present study. Two microdialysis studies showed improved oxygenation of the penumbra zone with prostacyclin in low doses after a traumatic brain injury.[16,17] Prostacyclin in corresponding low concentrations has also been shown to improve vessel diameter in vitro.[7,8] Thus, a dose of 1 to 2 ng/kg per minute might be effective while the risk of the well-known dose-dependent adverse effects could be minimized. The low-dose prostacyclin used also fulfils the theoretical rationale for treatment by compensating for a reduced endogenous production which has been demonstrated in an animal SAH model.[11]

Data Collection and Subject Monitoring

Baseline computed tomography (CT) perfusion was done at day 3±1 day after SAH. The second CT perfusion was done day 8±1 day as the risk of vasospasm and DIND peaks here. In this way the primary outcome was obtained during the prostacyclin infusion and during the period with the highest risk of DIND and vasospasm, thereby optimizing the chances of detecting a difference between the intervention groups. All scans were performed on a Phillips Brilliance scanner covering a 4-cm slab selected at the level of the basal ganglia. Images were stored on a database and

Table 1. Baseline Characteristics of Included Subjects

	Placebo	1 ng/kg per min	2 ng/kg per min
No. of subjects	30	30	30
Mean age (range), y	54 (27–75)	50 (22–71)	56 (35–77)
Women	23 (77%)	24 (80%)	27 (90%)
Clinical condition at admission			
WFNS grade 1	14 (47%)	14 (47%)	21 (70%)
WFNS grade 2	12 (40%)	11 (37%)	5 (17%)
WFNS grade 3	0 (0%)	0 (0%)	0 (0%)
WFNS grade 4	4 (13%)	5 (17%)	4 (13%)
Fisher grade 3	22 (73%)	22 (73%)	23 (77%)
Fisher grade 4	8 (27%)	8 (27%)	7 (23%)
Aneurysm treated with surgery	17 (57%)	18 (60%)	15 (50%)
Aneurysm treated with coiling	13 (43%)	12 (40%)	15 (50%)

WFNS indicates World Federation of Neurological Surgeons.

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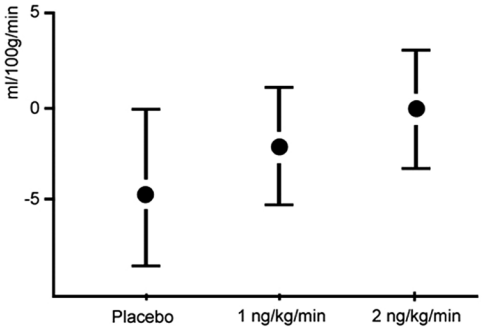

Figure 2. Mean change in global cerebral blood flow from baseline with 95% confidence interval for each of the 3 intervention groups.

subjected to blinded analysis after data collection was completed. For each patient, 6 predefined cortical regions of interest were identified, each being representative of the arterial territory of the anterior, middle, and posterior cerebral artery in both hemispheres. CBF for each regions of interest was calculated using the deconvolution method (Philips Medical Systems, EBW workstation v. 3.5). Global CBF was estimated from the average of these 6 values. In the presence of an intraparenchymal hematoma a software mask was applied to the hematoma itself, thereby excluding it from the CBF calculation. To reduce the risk of outcome evaluation bias, all analyses were performed by 2 independent reviewers and the CBF values used in the final analysis were the average between the values calculated by the 2 reviewers. Consensus reading was done for discordant results (>20% difference in global CBF). CT angiography during intervention was done at day 8±1 day after SAH, 10 minutes after CT perfusion. Images were reviewed by a blinded, experienced neuroradiologist, and vasospasm was qualified as absent, mild, moderate, or severe. All patients were monitored in the intensive care unit and an assessment of neurological performance was done every 4 hours by the nursing staff. The occurrence of DIND as defined by Vergouwen et al[18] was qualified as present or absent daily by the principal investigator. Transcranial Doppler ultrasonography was done daily. All patients were seen in our outpatient clinic after 3 months or contacted by phone and clinical outcome was recorded using the Glasgow Outcome Scale (GOS).

Outcome Measures

The primary outcome was change in global CBF from baseline calculated as CBF during intervention minus CBF at baseline. CBF was chosen as the primary outcome for this pilot, explorative trial as this seems to be a surrogate outcome measure with a possible high biological relevance. Secondary outcome measures were (1) occurrence of ≥1 DINDs during the intervention, (2) cerebral vasospasm qualified as severe, moderate, mild, or absent on a CT angiography, (3) change from baseline in regional blood flow in each of the 6 vascular territories, and (4) GOS at 3 months after SAH. Exploratory outcomes were the occurrence of elevated transcranial Doppler values (>50% from baseline) in the middle cerebral artery and the number of patients receiving endovascular intervention in the attempt to treat vasospasm.

Statistics

All statistical analyses of outcome variables were performed while preserving the blinding of the investigators for the interventions. Abstract presenting the conclusions was written and approved by the investigators before the blinding was unmasked. The required sample size was originally estimated to 25 patients per intervention arm based on a type 1 error risk of 5%, a type 2 error risk of 20% (a power of 80%), a SD of 35%, and the possibility to detect or reject a 20% difference in the primary outcome of global CBF between the intervention groups. All analyses were conducted according to the modified intention-to-treat principle, and all tests of significance were 2-sided with a maximal type 1 error risk of 5%. The primary analyses were performed without adjustment for baseline covariates; however, adjusted analyses were performed for primary and secondary end points in addition. Predefined variables for the adjusted analyses were World Federation of Neurological Surgeon grade, Fisher grade, and age. Continuous variables were compared using ANOVA and a standard χ^2 test was used to assess the effect of the intervention on binary outcomes. For the primary outcome a P value <0.05 was considered statistically significant. For secondary outcomes P values <0.01 were considered as definitely statistically significant, whereas a P value between 0.01 and 0.05 was considered indicative of statistical significance. All analyses were performed using SAS version 9.4. A detailed statistical analysis plan has been published previously.[19]

Results

Of 264 potentially eligible patients with SAH admitted and screened at our institution, 111 patients met the inclusion criteria. Of these 90 patients were included. The reasons for exclusion are shown in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram in Figure 1. One patient withdrew consent before receiving the intervention and was excluded from the data analysis according to the modified intention-to-treat principle, leaving 89 patients to be included in the main analysis. Baseline characteristics are shown in Table 1.

Primary Outcome

The primary outcome was global CBF quantified during intervention minus baseline CBF.

All baseline and intervention CT perfusion scans were performed for all patients. CT perfusion scans from 3 patients could not be interpreted because of patient head movement during the scanning procedure, leaving 86 patients to be analyzed for the primary outcome. Figure 2 shows the difference between baseline CBF and CBF during intervention for each of the 3 intervention groups. Absolute values of CBF are shown in Table 2. The mean change in CBF for the placebo group was −4.65 mL/100 g per minute (95% confidence interval [CI], −8.64 to −0.17). The mean change in CBF for the groups receiving prostacyclin 1 and 2 ng/kg per minute was −2.05 (95% CI, −5.58 to 1.47) and −0.066 (95% CI, −3.59 to 3.46), respectively. Unadjusted analysis showed no statistically significant difference between the 3 groups (P=0.20). Analysis adjusted for the predefined baseline covariates was also nonsignificant (P=0.21).

Secondary Outcome Measures

Besides global CBF, changes in regional CBF in each of the 6 vascular territories were compared for each intervention group using multiple test of ANOVA. No significant difference was found for change in regional blood flow for any of the territories. Absolute values of regional CBF are shown in Table 2. Table 3 summarizes the results of the remaining secondary outcomes.

Delayed Ischemic Neurological Deficit

The highest incidence of DIND was observed in the placebo group (38%) and the lowest incidence was observed in the group receiving prostacyclin 1 ng/kg per minute (21%); however, the difference between the 3 groups was not statistically significant (P=0.28). Analysis adjusted for baseline covariates was also not statistically significant (P=0.36). Risk ratio for 2 ng/kg per minute versus placebo was 0.62 (95% CI, 0.28–1.37) and risk ratio for 1 ng/kg per minute versus placebo was 0.55 (95% CI, 0.23–1.28).

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Table 2. Absolute Values of Global and Regional CBF for Each of the 3 Intervention Groups at Baseline and During Intervention

	Placebo	1 ng/kg per min	2 ng/kg per min
Global CBF			
Baseline	43.5 (40.0–46.9)	42.4 (39.1–45.8)	39.1 (35.7–42.6)
Intervention	38.3 (34.8–41.9)	40.3 (37.8–42.8)	39.1 (35.9–42.2)
Regional CBF			
Right AAT baseline	42.0 (38.9–45.1)	41.3 (36.9–45.7)	38.6 (35.6–41.9)
Right AAT intervention	37.3 (33.1–41.4)	39.9 (36.5–43.3)	38.6 (34.8–42.4)
Left AAT baseline	43.7 (40.0–47.3)	42.4 (38.0–46.9)	38.7 (34.6–42.8)
Left AAT intervention	37.5 (33.6–41.4)	39.2 (35.7–42.7)	38.6 (34.0–43.2)
Right MAT baseline	43.9 (40.1–47.6)	43.0 (39.5–46.4)	40.4 (37.1–43.6)
Right MAT intervention	38.5 (34.6–42.4)	40.9 (38.3–43.6)	40.0 (36.7–43.2)
Left MAT baseline	44.7 (40.6–48.7)	43.7 (40.1–47.4)	41.1 (37.5–44.7)
Left MAT intervention	39.0 (35.0–43.0)	39.2 (36.5–41.9)	39.8 (36.2–43.4)
Right PAT baseline	43.1 (38.5–47.6)	41.2 (38.0–44.5)	37.7 (33.9–41.5)
Right PAT intervention	38.5 (34.6–42.4)	41.0 (38.1–43.9)	38.6 (35.0–42.2)
Left PAT baseline	43.6 (39.5–47.6)	42.9 (39.1–46.7)	38.4 (34.3–42.5)
Left PAT intervention	39.3 (34.9–43.6)	41.5 (38.2–44.8)	38.9 (35.8–41.9)

Values are displayed in mL/100 g per minute with 95% confidence interval. AAT indicates anterior artery territory; CBF, cerebral blood flow; MAT, middle artery territory; and PAT, posterior artery territory.

Angiographic Vasospasm

In 3 cases, the quality of the CT angiography was not sufficient for interpretation. All the remaining 86 scans were analyzed and dichotomized to moderate to severe and none to mild vasospasm. Moderate to severe vasospasm was seen in 38% of patients in the placebo group compared with 17% in the group receiving prostacyclin 1 ng/kg per minute; however, both unadjusted and adjusted analyses comparing the 3 groups were not statistically significant (P=0.24 and P=0.15, respectively). Risk ratio for 2 ng/kg per minute versus placebo was 0.81 (95% CI, 0.38–1.71) and risk ratio for 1 ng/kg per minute versus placebo was 0.47 (95% CI, 0.19–1.19).

Clinical Outcome at 3 Months

None of the patients were lost to follow-up. GOS was dichotomized to excellent outcome (GOS, 5) and unfavorable outcome (GOS, 1–4). Outcome at 3 months did not differ significantly between the 3 intervention groups (P=0.46). Analysis adjusted for baseline covariates did, however, show a trend toward unfavorable outcome in the group receiving prostacyclin 2 ng/kg per minute (P=0.18). The risk ratio for an unfavorable outcome in the group receiving 2 ng/kg per minute compared with placebo was 1.50 (95% CI, 0.72–3.14). Overall mortality at 3 months was 3.3% because of 1 fatality in the placebo group and 2 fatalities in the group receiving prostacyclin 1 ng/kg per minute.

Table 3. Secondary Outcomes in Percentage for Each of the 3 Intervention Groups

	DIND*	Vasospasm†	Poor Outcome‡
Placebo	38% (23–56)	36% (22–55)	27% (14–45)
1 ng/kg per min	21% (10–39)	17% (8–35)	28% (15–46)
2 ng/kg per min	23% (12–41)	30% (16–49)	40% (25–58)
P value (χ^2)	0.28	0.24	0.46

All values in percent with 95% confidence interval. DIND indicates delayed ischemic neurological deficit.

*Patients with ≥1 DIND during the intervention.

†Patients with moderate to severe vasospasm days 7 to 9.

‡Patients with unfavorable outcome at 3 months.

Explorative Outcomes

The observed incidence of endovascular intervention in the groups receiving placebo, 1 ng/kg per minute and 2 ng/kg per minute was 23%, 17%, and 27%, respectively. This difference was not significant (P=0.68). No statistically significant difference was found when comparing incidence of elevated Doppler values between the 3 groups (P=0.64).

Adverse Events and Adverse Reactions

No serious adverse reactions, including bleeding or hypotension, were observed in any patients during administration. The percentage of patients in the placebo group, 1 ng/kg per minute group, and 2 ng/kg per minute group with ≥1 serious adverse events was 43%, 41% and 46%, respectively (P=0.92).

Discussion

This is the first randomized, clinical trial investigating the possible pharmacological effects of prostacyclin on the human brain after SAH. The primary outcome in this trial, global CBF, was not markedly affected by administration of prostacyclin. Thus, prostacyclin in the present doses does not seem to increase the net perfusion of the brain after SAH. This does not rule out possible effects on local perfusion, for example, prevention of hypoperfusion in small areas, which could be of clinical importance. Our CT perfusion technique only allowed us to look at a representative 4-cm slab of the brain and therefore could not monitor the entire brain for possible, minor hypoperfused areas. The present use of CBF as an outcome measure in a DIND trial is novel and its association to long-term outcome after aneurysmal SAH remains unknown.

This trial was a pilot trial designed to investigate the possible pharmacological effect of prostacyclin administration after SAH on the primary outcome of global CBF. The trial does not have power to adequately investigate the effect of prostacyclin on important clinical outcomes. However, an interesting difference in the point estimates with a reduced incidence of clinical symptoms and radiographic vasospasm was observed in both intervention groups compared with placebo. In the group receiving 1 ng/kg per minute only

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approximately half of the DIND incidences and angiographic vasospasm was observed compared with the group receiving placebo. It cannot be ruled out that these observed differences represent an effect of prostacyclin.

The few clinical studies conducted to date investigating the effect of prostacyclin on the brain have done so with doses between 0.5 and 1 ng/kg per minute.[12,13,17,20] In this trial we wished to explore the possible effect of a higher dose as well. Although the group receiving 2 ng/kg per minute had the highest mean global CBF, this difference was modest and not statistically significant. Furthermore, none of the secondary outcomes turned out more favorable in the high-dose group. On the contrary, the observed clinical outcome at 3 months was least favorable in the high-dose group. Thus, the observations in this trial were not supportive of a beneficial dose-dependent effect of prostacyclin in the tested dose range. It must be pointed out that the apparent lack of dose dependency in the low-dose area does not rule out the possibility that even higher doses of prostacyclin could be beneficial. However, an investigation of the possible effects of prostacyclin in this dose range poses a serious risk of adverse effects like hypotension and bleeding diathesis and was beyond the scope of this trial.

It is important to distinguish between trials investigating DIND prevention and trials investigating DIND treatment as it is not possible to sufficiently investigate both the preventative and the therapeutic properties of an intervention within the same trial. This trial was designed to investigate whether administration of prostacyclin could affect relevant factors related to DIND when initiated during the vasospasm phase. Accordingly, it is not primarily a prevention trial, although the preventative properties of prostacyclin were investigated to some degree because the intervention was initiated before the DIND incident rate peaks. To sufficiently investigate a potentially preventative effect of prostacyclin a trial with early intervention start would be required. Furthermore, this trial was not a clear cut therapeutic trial either as all patients received the intervention regardless of development of symptoms. It is possible that a potential effect of prostacyclin would be more pronounced in a trial where only patients with clear signs of vasospasm were included.

Conclusions

Administration of prostacyclin to patients with SAH may be safe and feasible. Global CBF after SAH is not markedly affected by administration of prostacyclin in the tested dose range. This trial was not powered to adequately investigate the effect of prostacyclin on important clinical outcomes. Accordingly, it may be possible that the reduction in the point estimates of DIND and cerebral vasospasm observed in the prostacyclin groups represents an effect of prostacyclin. Future trials investigating low-dose prostacyclin in relation to SAH should consider focusing on doses around 1 ng/kg per minute and should be powered to detect changes in clinical outcome.

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The trial was funded by Copenhagen University Hospital research fund, a nonprofit organization with no influence on the trial protocol, conduct, or analysis.

Disclosures

None.

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