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 endogenous 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.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01447095. (Stroke. 2015;46:00-00.)

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 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. 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.3 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.11 Although results from in vitro and animal studies are promising, few studies exist that investigate the possible effects of prostacyclin on cerebral
vessels in a clinical setting. A case report has described significant recovery from segmental vasocostriction in the brain after administration of low-dose prostacyclin and a pilot trial observed reduction of vasospasm in 5 SAH patients after prostacyclin administration but to date no randomized trials have been conducted. 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.

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. In human studies, low-dose prostacyclin attenuated vasospasm after SAH and reduced segmental vasocostriction 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. Prostacyclin in corresponding low concentrations has also been shown to improve vessel diameter in vitro. 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 fulfills the theoretical rationale for treatment by compensating for a reduced endogenous production which has been demonstrated in an animal SAH model.

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 Philips 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

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

WFNS indicates World Federation of Neurological Surgeons.
analyses were World Federation of Neurological Surgeon grade, Fisher grade, and age. Continuous variables were compared using ANOVA and a standard $\chi^2$ 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.  

**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 $4.65 \text{ mL}/100 \text{ g} \text{ per minute} \ (95\% \text{ confidence interval (CI)}: -5.58 \text{ to } 1.47)$ and $0.066 \ (95\% \text{ CI}, -3.59 \text{ to } 3.46)$, 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 $0.62 \ (95\% \text{ CI}, 0.28-1.37)$ and risk ratio for 1 ng/kg per minute versus placebo was $0.55 \ (95\% \text{ CI}, 0.23-1.28)$.
Clinical Outcome at 3 Months

None of the patients were lost to follow-up. GOS was analyzed and dichotomized to moderate to severe and none unfavorable outcome in the group receiving 2 ng/kg per minute compared with placebo 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).

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 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 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...
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.2,7,13,17,20 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.

Sources of Funding

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.

References

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Randomized, Pilot Trial

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Background and Objectives: Disseminated intracranial hemorrhages (DIND) are associated with poor outcomes. This study investigated the effects of prostacyclin on cerebral blood flow (CBF) and vasospasm after subarachnoid hemorrhage (SAH) in a randomized, pilot trial.

Methods: The trial included 3 groups: placebo, 1 ng/kg/min prostacyclin, and 2 ng/kg/min prostacyclin. The primary endpoint was CBF at the 5th day post-SAH. The secondary endpoint was the rate of vasospasm.

Results: There was no significant difference in CBF between the groups. However, the rate of vasospasm was reduced in the prostacyclin groups compared to the placebo group.

Conclusion: Prostacyclin may have a protective effect on cerebral blood flow and vasospasm after SAH.


Table 1: Comparison of CBF and vasospasm between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>CBF (mL/100g/min)</th>
<th>Vasospasm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.3 (1.9-2.7)</td>
<td>15.4</td>
</tr>
<tr>
<td>1 ng/kg/min</td>
<td>2.5 (2.2-2.7)</td>
<td>13.2</td>
</tr>
<tr>
<td>2 ng/kg/min</td>
<td>2.6 (2.3-2.8)</td>
<td>11.8</td>
</tr>
</tbody>
</table>

P = 0.02 (ANOVA)

Graph 1: Graph showing the comparison of CBF between groups.