A Randomized Controlled Trial of Prophylactic Intra-aortic Balloon Counterpulsation in High-Risk Aneurysmal Subarachnoid Hemorrhage

Diederik Olivier Bulters, FRCS(SN); Anthony A. Birch, PhD; Edward Hickey, FRCS(C); Ian Tatlow; Karen Sumner, BNS(Hons); Robert Lamb, FRCS; Dorothy Lang, FRCS

Background and Purpose—To assess whether prophylactic postoperative intraaortic balloon counterpulsation (IABC) reduces the risk of poor outcome because of vasospasm following aneurysmal subarachnoid haemorrhage relative to conventional hypervolemic therapy (HT).

Methods—This was a single-center, parallel group randomized controlled trial. Patients suffering a subarachnoid hemorrhage at high risk of vasospasm were eligible. Patients were randomly allocated to receive prophylactic IABC (n=35) or HT (n=36). The primary end point was Glasgow Outcome and SF-36 scores assessed at 6 months by a blinded and independent observer and analyzed by intention to treat. Secondary analysis of physiological parameters was by treatment performed.

Results—Twenty-seven patients in each arm had a good outcome (P=0.55). There was no statistical difference in mean SF-36 score (t=0.39, P=0.70). There were no long-term complications secondary to IABC. There were no differences in preload (pulmonary artery wedge pressure, P=0.97) or afterload (mean arterial pressure, P=0.97). IABC was associated with a lower cardiac output (P=0.002) and higher systemic vascular resistance (P=0.005), although for both groups mean cardiac output was >6 L/min. Cerebral blood flow was not different between groups: HT=41.5 (SD 7.2), IABP=44.9 (SD 8.6) mL/100 g/min (P=0.14).

Conclusions—In this study, prophylactic IABC did not improve perfusion indices or confer any clinical benefit following subarachnoid haemorrhage in patients with normal cardiac function. The study was small, however, and cannot be extrapolated to patients with cardiac failure and medically refractory symptomatic cerebral vasospasm.

Key Words: cerebral blood flow ■ intraaortic balloon pumping ■ intracranial aneurysm ■ outcome ■ randomized controlled trial ■ subarachnoid hemorrhage ■ vasospasm

Surgical and endovascular treatment of aneurysms have significantly reduced rebleeding following subarachnoid hemorrhage. Delayed ischemic neurological deficits (DIND) because of vasospasm, however, remain a major cause of death and disability.

The mainstays of treatment are hypervolemic therapy (HT) and hypertension, hypervolemia and hemodilution therapy (HHH). This is based on opinion and case series. The only two randomized studies were negative, and neither actually achieved an improvement in cerebral blood flow (CBF). It is, therefore, possible that a strategy more effective at increasing CBF would have an effect on outcome.

Intraaortic balloon counterpulsation (IABC) has been extensively used in cardiogenic shock. It results in elevated mean diastolic (coronary perfusion) pressure, reduced end diastolic pressure (afterload), and overall increased cardiac output. It has been shown to increase cerebral perfusion pressure (CPP) and CBF in healthy dogs and in humans with a failing heart. In a pilot study, we observed that IABC increased CBF and was associated with a reversal of DIND in the setting of subarachnoid hemorrhage without heart failure.

Our objective was to assess whether prophylactic postoperative IABC reduced the risk of poor outcome following subarachnoid hemorrhage.

Materials and Methods

All spontaneous subarachnoid haemorrhages referred to the Wessex Neurological Centre aged between 16 and 70 years were screened. High-risk patients based on blood load on CT and best neurological grade within 72 hours were eligible for inclusion. Exclusion criteria included unprotected additional aneurysms, peripheral vascular disease, pregnancy, and mechanical ventilation.
Patient Management
All patients underwent surgical clipping. During surgery, patients were assigned to postoperative HT or IABC by random allocation. If assigned IABC, a balloon catheter was implanted at the end of the procedure.

The protocol for postoperative fluid management in the first 5 days is in Figure 1. This was continued beyond day 5 if there was evidence of ongoing vasospasm and a reversible DIND. Inotropes were only employed if patients developed a DIND.

Outcomes
The primary end point was Glasgow Outcome and SF-36 score at 6 months assessed by two independent blinded investigators and analyzed by intention to treat.

A secondary analysis of physiological parameters achieved was analyzed by treatment performed to clarify the mechanisms underlying the actions of IABC. Further details of the methodology can be found in the online supplement.

Results
Patient recruitment is illustrated in Figure 2. There were no significant differences in patient age, sex, aneurysm location, WFNS grade, or time to surgery between groups (online supplement).

Clinical Outcomes
There was no difference in Glasgow Outcome scores ($\chi^2=2.13$, $P=0.55$; Table 1) or mean SF-36 scores at 6 months: HT 460.7 and IABC 437.7 ($t=0.39$, $P=0.70$). There was no difference in the incidence of DIND: HT 24 patients and IABC 22 patients ($\chi^2=0.11$, $P=0.74$). Five patients in each arm had evidence of infarction on CT scan ($\chi^2=0.002$, $P=0.96$).

Three complications attributable to IABC were observed. Two patients had bleeding from the insertion site without any clinical consequences. One further patient suffered a thromboembolism necessitating femoral embolectomy with no long-term sequelae.

Physiological Outcomes
Systemic Hemodynamic Parameters
Cardiac output was lower ($P=0.002$) and systemic vascular resistance higher ($P=0.005$) in patients receiving IABC versus HT throughout treatment. None of the other trends in systemic hemodynamic parameters measured showed a significant difference between groups (mean arterial pressure $P=0.51$, heart rate $P=0.31$, pulmonary artery wedge pressure $P=0.97$, central venous pressure $P=0.27$, stroke volume $P=0.12$).

<p>| Table 1. Glasgow Outcome Scores at 6 Months |
|-------------------------------|---------|--------|</p>
<table>
<thead>
<tr>
<th>GOS</th>
<th>Outcome</th>
<th>HT</th>
<th>IABC</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>Good</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Moderate</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Poor</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Vegetative</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Dead</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
Cerebral Perfusion Indices
There was a trend for CPP and CBF to be higher in the IABC patients during the first 2 days of treatment. Thereafter, there were no noticeable differences between the two treatment groups. The trend in CBF on the first postoperative day was not significant. HT=41.5 (SD 7.2), IABP=44.9 (SD 8.6) mL/100g/min (P=0.14). However, the difference in CPP was significant (P=0.038).

Discussion
This study has demonstrated no improvement in perfusion indices and no clinical benefit from the prophylactic use of IABC in patients with no preexisting cardiac disease.

Limitations
Our power calculation was based on a 40% poor outcome in the control arm. Although this came from a comparable cohort of patients, in this series the HT arm only had a 20% incidence of poor outcome. These surprisingly good outcomes mean the study would only be able to detect a very large difference between management regimens.

Following concerns of fluid overloading in our pilot study, we relaxed central venous pressure and pulmonary artery wedge pressure targets for the IABC group in this trial. However, actual central venous pressure and pulmonary artery wedge pressure achieved were the same in both arms, and this is, therefore, unlikely to have masked a difference between treatments.

Generalizability
Prophylactic Versus Selective Treatment
This trial was prophylactic and cannot be extrapolated to treatment of symptomatic vasospasm. There was some suggestion of an early and fast effect on blood pressure and cerebral perfusion pressure on the first day of treatment. Although such an early effect would have no benefit to the patient in a prophylactic situation, it may have a theoretical advantage in the treatment of symptomatic vasospasm.

Healthy Myocardium Versus Cardiac Impairment
This study constitutes the first reported series of patients receiving IABC without cardiac failure. Although isolated empiric applications solely for cerebral indications have been reported, they are untested anecdote. All previous understanding of these devices comes from patients with cardiac impairment in whom increased myocardial oxygen delivery and reduced myocardial oxygen consumption lead to greater stroke volume and cardiac output. Unfortunately, in this series of patients with good cardiac function the same did not hold true, and it cannot, therefore, be extrapolated to patients with a failing heart.

Partial Transitory Aortic Obstruction
Partial transitory aortic obstruction (NeuroFlo™; CoAxia, MN) aims to improve cerebral perfusion by diverting flow of blood into the cerebral vasculature. Similar to IABC, animal studies have shown that it increases CBF, and small case series in symptomatic vasospasm have suggested clinical efficacy. It currently has FDA approval to treat cerebral vasospasm that has failed maximal medical management. Although our data cannot be extrapolated to this device, our experience reiterates the need to replicate pilot data.

Conclusions
This randomized controlled trial has shown no improvement in CBF and no clinical benefit of prophylactic IABC over HT in patients who have suffered SAH and are at high risk of DIIND but do not have any cardiac impairment. IABC did not cause any long-term complications. It may, therefore, still play a role in patients with concomitant cardiac failure or medically refractory symptomatic vasospasm.

Sources of Funding
This trial was funded by a charitable donation from the Medlock family. Datascope provided equipment free of charge. The company did not have any involvement in the trial design, the conduct of the trial, the data analysis, or the writing and approval of the report.

Disclosures
None.

References
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Supplemental Material

Materials and Methods

The study was approved by the local research ethics committee. Consent was obtained from all patients or their relatives.

Patient Management

All patients underwent surgical clipping of their aneurysm. During surgery patients were assigned to post-operative HT or IABC by random allocation. If assigned to IABC, a balloon catheter was implanted at the end of the neurosurgical procedure using a sheathless technique via a right transfemoral approach. Position was confirmed by X-ray. IABC was started immediately with a system 97 Datascope Medical Unit, using electrocardiogram triggering and a 1:1 ratio with full balloon inflation. Augmentation and balloon timing were adjusted such that inflation occurred at the dichrotic notch and deflation occurred abruptly immediately prior to systole. Patients were not anticoagulated.

Clinical Outcomes

Patients were assessed at 6 months by two independent blinded investigators. The primary endpoints were Glasgow Outcome and SF36 Scores at 6 months. Patients were also assessed daily by the clinical team for signs and symptoms of DIND. DIND was defined as any neurological deterioration after exclusion of haemorrhage,
hydrocephalus, hyponatraemia, seizures and infection. It was not possible to blind these assessments due to the intrusive nature of the IABC device.

**Physiological Outcomes**

**Systemic Hemodynamic Indices**
Daily measurements of pulmonary artery wedge pressure (PAWP), central venous pressure (CVP), mean arterial pressure (MAP) and heart rate were made in all patients throughout treatment. Cardiac output (CO) was calculated using the thermodilution principle, from which stroke volume (SV) and systemic vascular resistance (SVR) were derived.

**Cerebrovascular Perfusion Indices**
Daily intracranial (ICP) measurements were made from a monitor placed at surgery. This was used to calculate of cerebral perfusion pressure (CPP) concomitant with measurements of systemic indices. ICP monitoring was withdrawn from an increasing number of patients from day two onwards. Removal of the ICP monitor cannot be assumed to be independent of the patient’s condition. Statistical assessment of ICP and CPP has therefore been restricted to the first two days of treatment.

Cerebral flow velocities were determined via trans-cranial Doppler ultrasound (TC-264 : EME, Ueberlingen, Germany or a Multi-Dop-t :DWL Sipplingen, Germany) of the middle cerebral artery, concomitant to cerebral blood flow recordings. Velocities recorded are the time averaged maximum velocity at the depth with the highest recorded velocities.
CBF was measured once prior to surgery and randomization, immediately post-operatively (day 0), and daily during the course of post-operative treatment. Cerebral perfusion studies were performed using a 32c Cerebrograph (Novo Diagnostic System, Hallsund, Denmark) with sixteen detectors recording symmetrically from 8 regions of each cortical hemisphere. Xenon-133 was administered by one-minute inhalation and the washout curves were recorded for the following 10 minutes. Cerebral blood flow (CBF) was determined as the initial slope index as described by Risberg et al\textsuperscript{1}.

**Power Calculation**

Historical data showed 41\% of this select group of patients were expected to have a poor outcome without prophylactic IABC.\textsuperscript{2} Our pilot study demonstrated an improvement of DIND in 5 out of 6 patients.\textsuperscript{3} The aim of the study was to show a reduction to 10\% poor outcome with a power of 80\% and probability of 0.05. A power calculation demonstrated that 33 patients in each arm would be required to achieve this.

**Statistical analysis**

Statistical analysis was performed using SPSS 14.0 (SPSS (UK) Ltd, Woking). In general continuous data were compared using a 2-tailed Student’s test and categorical data with a Chi-squared test. The level for significance was set at 5\%. Comparisons between groups was made with two-tailed independent samples Students t-tests. Differences in trends of hemodynamic parameters between the two patient groups were sought via two-factor mixed design repeated measures analysis of variance.
Where Mauchly’s test indicated that assumption of sphericity had been violated the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. Patients without complete records have been excluded from graphical and statistical analysis. The number of patients included in the analysis is presented whenever more than six (9%) needed to be excluded. Correction for multiple comparisons has not been applied.

**Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>IABC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.4 (25-70)</td>
<td>52.5 (26-69)</td>
<td>0.13</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>16/19</td>
<td>11/25</td>
<td>0.19</td>
</tr>
<tr>
<td>WFNS (1/2/3)</td>
<td>13/20/2</td>
<td>20/14/2</td>
<td>0.28</td>
</tr>
<tr>
<td>Site (Acom/MCA/Pcom/ICA/Post)</td>
<td>17/10/5/1/2</td>
<td>13/7/11/1/4</td>
<td>0.14</td>
</tr>
<tr>
<td>Delay to Surgery (days)</td>
<td>4.97 (1-17)</td>
<td>4.22 (1-9)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Characteristics of the 71 patients recruited between July 1997 and June 1999.

**References**