Cerebroprotective Effect of Preoperative Dual Antiplatelet Therapy in Patients Undergoing Coronary Bypass Surgery

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Objectives: Reduction of cognitive function is a possible side effect after coronary artery surgery using cardiopulmonary bypass (CPB). We investigated the effect of single versus dual antiplatelet therapy on cognitive performance in patients undergoing coronary artery bypass grafting (CABG) with CPB.

Methods: 50 consecutive CABG patients with preoperative intake of aspirin were compared to 49 consecutive patients with aspirin and clopidogrel. Six neuropsychological subtests from the Syndrom Kurz Test and the Alzheimer’s Disease Assessment Scale were performed preoperatively and on the third postoperative day. To assess the overall cognitive function and the degree of cognitive decline across all tests after surgery we combined the six test-scores by principal component analysis.

Results: Patients had a mean age of 66.1 ± 9.3 years, received a mean of 2.8 ± 1.0 bypasses within an average of 87 ± 31 minutes on cardiopulmonary bypass. These parameters as well as the preoperative combined neurocognitive score were not significantly different between the groups. After the operation there was a significant deterioration of the combined neuropsychological score in both groups (single: preop −0.2 ± 1.5 vs. postop −1.8 ± 1.7, p = 0.000 and dual: preop 0.2 ± 1.5 vs. postop −0.5 ± 2.1, p = 0.004). However, the patients operated under dual antiplatelet therapy showed a significant less decline of overall cognitive function compared to the single antiplatelet therapy patients (dual: 0.7 ± 1.5 vs single: 1.6 ± 1.6, p = 0.004).

Conclusion: Dual antiplatelet therapy has a cerebroprotective effect in patients undergoing coronary artery bypass surgery. Compared to single antiplatelet therapy it reduces an early postoperative substantial decline of neuropsychological abilities.

Keywords: dual antiplatelet therapy, coronary artery bypass surgery, cardiopulmonary bypass, cognition disorders

Introduction

CABG to treat coronary artery disease is the most common operation in the cardiac surgical field and is increasingly performed in patients under single and dual antiplatelet therapy. Although CABG is a relatively safe and effective procedure, relevant cognitive impairments can be observed in a significant amount of patients after the operation.1) Different perioperative factors are accused to cause the cognitive decline after CABG like microembolism, hypoperfusion or drug interaction.2,3) Possible
microemboli in CABG operations with the use of CPB can be platelet aggregates. Platelet aggregation inhibitors might avoid or decrease this problem. Dual antiplatelet therapy is favoured in many critical thrombogenic situations and might be also superior over single platelet aggregation inhibitor therapy regarding a reduction of microemboli during CABG with CPB and a better preservation of cognitive function. Therefore we investigated the effect of single versus dual antiplatelet therapy on cognitive performance in patients undergoing coronary artery bypass with the use of the heart-lung-machine.

**Methods**

**Study design/protocol**

Patients who had an indication for elective isolated CABG and had been preoperatively set on single or dual antiplatelet therapy were included if they gave their written informed consent. Patients with any known neuropsychological diseases were excluded. Fifty CABG patients operated under aspirin were compared to 49 patients operated under aspirin and clopidogrel. The medication was prescribed by the referring cardiologist before surgical admission. Medication was started at least 48h before the operation. All patients received the medication until the day of surgery. The Study was conducted in a blinded fashion. Cognitive function was evaluated the day before surgery and on the third postoperative day.

**Neuropsychological assessment**

Patients were examined with a neuropsychological tests battery for memory and attention lasting approximately 20 minutes and consisting of the following 6 subtests of SKT (Syndrome Kurz Test) and ADAS (Alzheimer’s Disease Assessment Scale). Assessment took place at patient’s bedside without any distraction.

- **S₃** delayed pictured object recall
  - patient is asked to remember as many as possible of 12 previously shown pictures after a delay of 10 minutes
- **S₆** delayed picture recognition
  - patient is asked to recognize as many as possible of 12 previously viewed pictures after a delay of 15 minutes

Except for test **S₃** and **S₄** lower scores mean poorer performance. The tests were performed in two parallel forms in order to minimize practice effects at the postoperative retest.

**Coronary artery bypass grafting**

Patients were premedicated with benzodiazepines. General anaesthesia was conducted using propofol or isoflurane, opiates and muscle relaxants. Median sternotomy and full heparinization was performed and the bypass grafts were harvested. The pericardium was opened, the ascending aorta and right atrium were cannulated and normothermic cardio-pulmonary bypass was started. A heart lung machine with roller pumps (System1, Terumo®) and a pre-bypass filter were used in any case. The aorta was cross clamped, cardioplegic solution infused and the distal anastomoses performed on the arrested heart. After release of the aortic cross clamp the heart usually started beating spontaneously and the proximal anastomoses were sutured. Ventilation was started and the patient was weaned from CPB. The chest was closed and the patient transferred to the ICU.

**Statistics**

Statistical analysis was done using SPSSS 19.0 (SPSS Inc., Chicago, USA). The level of significance was \( \alpha = 0.05 \).

To assess the overall cognitive function and the degree of cognitive decline across all tests after surgery we combined the six test-scores by principal component analysis.

\[
S_{pre} = 0.29* z_{1,pre} + 0.24* z_{2,pre} - 0.22* z_{3,pre} \\
- 0.25* z_{4,pre} + 0.26* z_{5,pre} + 0.22* z_{6,pre} 
\]

is the first principal component of the standardized scores before operation (baseline), i.e.

\[
z_{i,pre} = \frac{S_{i,pre} - \mu(S_{i,pre})}{\sigma(S_{i,pre})}, \quad i = 1, \ldots, 6.
\]
with \( \mu(S_{i,pre}) \) and \( \sigma(S_{i,pre}) \) the mean and standard deviation of \( S_{i,pre} \).

The same transformation was applied to the scores \( S_{1,post}, \ldots, S_{6,post} \) after operation.

\[
S_{post} = 0.29* z_{1,post} + 0.24* z_{2,post} - 0.22* z_{3,post}
\]
\[
- 0.25* z_{4,post} + 0.26* z_{5,post} + 0.22* z_{6,post}
\]

with

\[
z_{i,post} = \frac{S_{i,post} - \mu(S_{i,pre})}{\sigma(S_{i,pre})} i = 1, \ldots, 6.
\]

Note, the mean \( \mu(S_{i,pre}) \) and standard deviation \( \sigma(S_{i,pre}) \) of the pre-operative scores are used in the transformation formula for the \( z_{i,post} \).

Association of cognitive change with age, number of bypasses, CPB time and therapy group was examined by a general linear model (Table 1).

Comparison of age, CPB time and number of bypasses between the groups was done by Mann-Whitney-U test (Table 2). Changes in the scores (preop - postop) were also compared by Mann-Whitney-U test and comparisons of preoperative with corresponding postoperative scores within the treatment groups were conducted by Wilcoxon tests for paired samples (Table 3).

Results

99 patients were included into the study with a mean age of 66.1 ± 9.3 years. An average of 2.8 ± 1.0 bypasses were constructed using a mean time on cardiopulmonary bypass of 87 ± 31 minutes. No postoperative TIA or CVA occurred. Reexploration for bleeding rate and 30d-mortality was 0%. Single and dual antiplatelet therapy groups were comparable in terms of age, number of bypass grafts and CBP time indicating a homogenous study sample (see Table 2).

CPB time and preoperative dual platelet inhibitor intake were the variables having an impact on the cognitive development (see Table 3).

There were no significant differences of preoperative test results in all subtests between the groups. Preoperative overall cognitive function was similar in both groups (single: -0.2 ± 1.5 vs. dual: 0.2 ± 1.5, p = 0.27). Comparison of postoperative testing with preoperative testing revealed a significant decline of overall test results in both groups (single: preop -0.2 ± 1.5 vs. postop -1.8 ± 1.7, p < 0.0005 and dual: preop 0.2 ± 1.5 vs. postop -0.5 ± 2.1, p = 0.004). However, patients of the dual antiplatelet therapy group showed only in two of six subtests significant worse postoperative results compared to the baseline whereas single platelet inhibitor results decreased in five of six subtests (Fig. 1). Moreover, comparison of the overall postoperative performance of both groups showed significant better results in the dual antiplatelet therapy patients (dual: -0.5 ± 2.1 vs. single: -1.8 ± 1.7, p = 0.002). Analysis of the cognitive change (preop-postop) revealed that patients who had dual platelet inhibitor therapy preoperatively had significant less decline of overall function (dual: 0.7 ± 1.5 vs. single: 1.6 ± 1.6, p = 0.004), see Table 3, Fig. 2.

Discussion

Cognitive impairments were frequently detected after coronary bypass surgery with CPB\(^1\) and are of clinical relevance.\(^7\)–\(^9\) Genesis of neuropsychological deficits is most likely multifactorial. Hypoperfusion states during the operation particularly in the presence of a cerebral vascular disease, toxic influence of narcotics and microemboli from either atherosclerotic debris or the extracorporeal circuit including the pump heads are involved in the cognitive changes.\(^2,3\) We evaluated the cognitive impact of preoperative single versus dual platelet inhibitor therapy because it is known that platelets aggregates are CPB associated microemboli.\(^5\) Patients operated with a dual antiplatelet therapy had a significant smaller decline of overall cognitive function compared to the patients who received only one platelet inhibitor. To our knowledge this is the first study demonstrating a cognitive advantage of dual antiplatelet therapy in patients undergoing coronary bypass surgery.

Dual antiplatelet therapy is evidence-based recommended for all patients presenting with all types of acute coronary syndromes as well as for patients presenting with percutaneous coronary interventions (PCI) for any indication.\(^5\) As a result almost all PCI-patients of the Syntax-trial received dual antiplatelet therapy up to one year after the intervention whereas only 15% of the Syntax CAGB patients had two antiplatelet drugs.\(^10\) This might be an explanation why CAGB patients suffered from significantly more strokes within the first 12 months

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### Table 1 Association with cognitive change

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.165</td>
</tr>
<tr>
<td>Number of bypasses</td>
<td>0.102</td>
</tr>
<tr>
<td>CPB time</td>
<td>0.044</td>
</tr>
<tr>
<td>Therapy group (Single vs. Dual)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
after the operation. The CHARISMA trial\textsuperscript{11} assessed the effect of dual antiplatelet therapy with clopidogrel and aspirin in patients at risk of atherothrombotic events. There was no benefit from dual antiplatelet therapy in the overall cohort of patients ($n = 15603$) at 28 months. However there was a benefit in the subgroup of patients with known cardiovascular disease. In these group ($n = 12153$) the primary end point (combined incidence of myocardial infarction or stroke, or death from cardiovascular causes) was reached in 6.9% of patients treated with clopidogrel vs. 7.9% with placebo ($p = 0.046$). Similar to this CHARISMA subgroup all of our study patients suffer from cardiovascular disease. They also benefit from dual antiplatelet therapy which preserved their neurocognitive abilities early after the operation.

Apart from the type of antiplatelet therapy, duration on cardiopulmonary bypass had also a significant impact on the postoperative cognitive change in this study. This can be explained with the larger amount of platelet aggregates formed during longer times of extracorporeal circulation resulting in more cerebral microembolism.\textsuperscript{12} It has been assumed that complete avoidance of CPB would yield to better cognitive results.\textsuperscript{2,13,14} However, preservation of cognitive function is as important as achieving the main goal of coronary surgery namely complete and accurate revascularization which is definitely more difficult to achieve with off-pump bypass surgery.

Beside the efforts to eliminate the causative mechanisms of cognitive decline, attempts were also undertaken to directly protect the brain. Different potentially cerebroprotective substances, like piracetam, which proved to be effective in CABG patients, have been evaluated to lower the cognitive changes associated with cardiopulmonary bypass.\textsuperscript{15,16} Patients that received a single dose of 12 g Piracetam i.v. at the beginning of the operation performed significantly better early after the operation.

### Table 3 Comparison of cognitive test results ($S =$ Single, $D =$ Dual, $ns =$ non significant)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Preop Mean ± SD</th>
<th>Postop Mean ± SD</th>
<th>p value Preop vs. postop</th>
<th>p value Preop-Postop: S vs. D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate pictured object recall</td>
<td>S</td>
<td>5.9 ± 1.5</td>
<td>4.8 ± 1.6</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>6.3 ± 1.6</td>
<td>5.8 ± 2.0</td>
<td>0.072</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>$p$ (S vs D)</td>
<td>0.28</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed pictured object recall</td>
<td>S</td>
<td>3.8 ± 1.7</td>
<td>2.8 ± 1.9</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>4.5 ± 1.9</td>
<td>4.3 ± 2.4</td>
<td>0.634</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>$p$ (S vs D)</td>
<td>0.076</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed picture recognition</td>
<td>S</td>
<td>8.9 ± 2.1</td>
<td>7.2 ± 2.1</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>9.2 ± 1.9</td>
<td>8.7 ± 2.2</td>
<td>0.129</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>$p$ (S vs D)</td>
<td>0.399</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate word recall</td>
<td>S</td>
<td>4.8 ± 1.3</td>
<td>4.6 ± 1.4</td>
<td>0.474</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>4.8 ± 1.5</td>
<td>4.9 ± 1.8</td>
<td>0.478</td>
<td>0.317</td>
</tr>
<tr>
<td></td>
<td>$p$ (S vs D)</td>
<td>0.919</td>
<td>0.377</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter interference</td>
<td>S</td>
<td>31.0 ± 9.4</td>
<td>36.6 ± 12.7</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>30.9 ± 9.2</td>
<td>34.5 ± 10.4</td>
<td>0.002</td>
<td>0.485</td>
</tr>
<tr>
<td></td>
<td>$p$ (S vs D)</td>
<td>0.847</td>
<td>0.724</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>S</td>
<td>19.1 ± 7.7</td>
<td>27.3 ± 9.8</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>18.5 ± 7.1</td>
<td>23.7 ± 9.6</td>
<td>0.001</td>
<td>0.108</td>
</tr>
<tr>
<td></td>
<td>$p$ (S vs D)</td>
<td>0.944</td>
<td>0.041</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cognitive function</td>
<td>S</td>
<td>−0.2 ± 1.5</td>
<td>−1.8 ± 1.7</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.2 ± 1.5</td>
<td>−0.5 ± 2.1</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>$p$ (S vs D)</td>
<td>0.273</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and had less decline of overall cognitive function compared to placebo patients.

Neuropsychological test selection in our study was based on tests procedures that require a minimum of motor activity considering the early postoperative patient situation. A brief battery of neuropsychological tests for verbal and non-verbal short term memory and attention were tested. Other cognitive functions may also be affected by the surgery but because of the limited cooperation of patients, a selection of psychometric instruments had to be made. Most of them were chosen from the repeatable test battery SKT. It is a standardized screening instrument designed to assess cognitive function in a brief administration.

Further work is necessary to identify and reduce factors that negatively influence cognitive function in patients undergoing coronary artery bypass surgery because they reduce patient’s quality of life and complicate their rehabilitation. Moreover they increase in-hospital mortality and length of stay and last but not least the use of resources.

A limitation of the study is that there was no randomization of the patients to the groups because patients received platelet inhibitor therapy already before they were admitted for surgery. However, patients of both groups were well matched concerning age, number of bypasses and duration of CPB. Another limitation is the number of patients included into the study and the follow up time which are probably too small to detect differences in the incidence of major neurologic complications. Postoperative CT or EEG of the study patients would have been interesting. However, we were not able to perform these examinations since there occurred no major neurologic complications like focal deficits, seizures or somnolence.
In summary, preoperative dual antiplatelet therapy has a cerebroprotective effect in patients undergoing coronary artery bypass surgery. Compared to single platelet inhibitor therapy it reduces an early postoperative substantial decline of neuropsychological abilities.

Disclosure Statement

The authors have nothing to disclose and there is no conflict of interest.

References