Intraoperative neuroprotective drugs without beneficial effects?
Results of the German Registry for Acute Aortic Dissection Type A (GERAADA)

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Abstract

OBJECTIVES: Cerebral protection during acute aortic dissection Type A (AADA) surgery may be affected by perfusion strategies and ischaemic protective drugs.

METHODS: We analysed the impact of intraoperative barbiturate, steroid and mannitol use and adjunctive cerebral perfusion (CP), on 30-day mortality and new postoperative mortality-corrected permanent neurological dysfunction (PNDmc) in the German Registry for Acute Aortic Dissection Type A.

RESULTS: Two thousand one hundred and thirty-seven AADA patients were registered over a 4-year period. The overall 30-day mortality was 16.9%, and the overall rate of PNDmc was 10.0%. A total of 48% of patients received no neuroprotective drugs (control group), steroid monotherapy was used in 11.2% of patients, barbiturates in 8.4%, mannitol in 7.3% and the remainder (25.1%) received a combination of these drugs. The PNDmc rate was 10.6% in the control group and lower (7.1%) in the steroid group (adjusted odds ratio [OR] 0.50; 95% confidence interval [95% CI] 0.24–0.96; P = 0.049). No PNDmc reduction was observed for mannitol or barbiturates. Thirty-day mortality was 18.7% in the control group and with 8.9% lower (P = 0.003) in the mannitol group (adjusted OR 0.58; 95% CI 0.19–1.49; P = 0.295). Hypothermic circulatory arrest that exceeded 30 min was associated with an increased 30-day mortality rate (31.4%) compared with patients who received adjunctive CP >30 min during aortic arch intervention (21.4%) (P = 0.04). We were unable to demonstrate a significant protective effect of any neuroprotective drug on 30-day mortality, or PNDmc rates during prolonged (≥30 min) cerebral ischaemia.

CONCLUSION: Mannitol may be associated with decreased mortality in patients undergoing AADA surgery. Steroid administration may be associated with improved neurological outcomes, but more investigation is required.

Keywords: Aortic dissection · Aortic operation · Cerebral protection · Pharmacology · Neurology/Neurological · The German Registry for Acute Aortic Dissection Type A · Registry

INTRODUCTION

Acute aortic dissection Type A (AADA) is associated with major morbidity and mortality. Because neurological morbidity is a risk associated with both the disease process itself and the required emergency surgery, effective neuroprotection is an often-discussed theme for AADA patients. The effects of different perfusion strategies on hypothermic circulatory arrest (HCA) and various methods of cerebral perfusion (CP) have been studied extensively [1–5]. Comparably less is known about the efficacy of neuroprotective drugs and their clinical benefits in AADA surgery. There is no consensus about which drugs, if any, are useful, and there are large differences among the clinical practice patterns of various cardiac centres. In addition to others, the most commonly used neuroprotective drugs during AADA surgery are barbiturates, mannitol and steroids [6, 7].

The German Registry for Acute Aortic Dissection Type A (GERAADA) is a prospective database from 50 cardiac surgery centres in Germany, Austria and Switzerland that was founded in 2006. We analysed this database in order to determine the effect of intraoperative administration of barbiturates (mainly thiopental), mannitol and steroids as neuroprotective agents during AADA surgery. The endpoints of interest were 30-day mortality and new postoperative permanent neurological dysfunction.
PATIENTS AND METHODS

Study design

The current study is an observational registry survey. No randomization or matching was performed. Patients were treated according to the individual cardiac centres’ protocols, which were not influenced by the study protocol. The registry itself and all of its studies were approved by a central ethics committee (No. 7293; Landesarztekammer Rheinland-Pfalz, Mainz, Germany). Patients’ written informed consent was not obligatory because this is a non-interventional study.

Data collection

In 2005, the German Society for Thoracic and Cardiovascular Surgery (GSTCVS) initiated the GERAADA in order to collect data about real-world AADA surgery in central Europe [8]. Fifty cardiac surgery centres in Germany, Austria and Switzerland have submitted data through a web-based system since 2006. The only inclusion criterion was the presence of a surgically treated AADA. The web-based questionnaires included over 90 items addressing perioperative, demographic, aetiological and outcome parameters. The final clinical assessment was carried out on the 30th postoperative day. Ventilator times and length of stay in the intensive care unit and hospital that were longer than 30 days were recorded. Contributing centres were instructed to document all consecutive AADAs treated surgically. All datasets were checked for completeness and plausibility by an independent database-monitoring centre and, if necessary, double checked with the documenting hospital. The data collection for the present study was completed in June 2010, at which time 2137 patients had been included. The methods and definitions of the registry have been reported elsewhere in detail [9].

Study groups

The patients were grouped according to the administration of intraoperative neuroprotective agents: no agents (control group, n = 1025), barbiturates (n = 179), steroids (n = 239), mannitol (n = 157) or combinations of the aforementioned drugs (n = 537). Subgroups were analysed according to individual perfusion strategies: cardiopulmonary bypass (CPB) without circulatory arrest (CPB group, n = 135), aortic arch surgery under HCA without CP (HCA group, n = 482) and aortic arch surgery with adjunct CP (CP group, n = 1520). Adjunct CP was defined as any strategy of selective brain perfusion during circulatory arrest, irrespective of the technical approach (i.e. unilateral antegrade, bilateral antegrade or retrograde application). The influence of prolonged HCA and CP time (≥ vs <30 min) on outcomes was also analysed. The use of HCA or adjunctive CP was performed at the discretion of the operating surgeon.

Endpoints

Primary endpoints were 30-day mortality, rate of new postoperative permanent neurological dysfunction (PND) and rate of mortality-corrected permanent neurological dysfunction (PNDmc).

Thirty-day mortality included any death occurring from the intraoperative period until the 30th postoperative day. Adopted from Ergin et al. [10], PND was defined as the ‘presence of permanent neurological deficits that were focal (stroke) or global (parkinsonism, coma and gait disturbance) in nature and persisting at discharge from the hospital’. Only new postoperative neurological deficits that had not been documented preoperatively were included. To estimate the true burden of chronic neurological impairment, as described before [3], we corrected the PND rate for mortality. Patients who were neurologically impaired soon after surgery and then died were excluded from the PNDmc rate.

Such a definition was chosen in order to: (i) avoid the possibility of a single patient accounting for both—the neurological and the mortality endpoints, (ii) achieve both endpoints (30-day mortality and PNDmc) being independent from each other and mutually exclusive and (iii) provide a best possible approximation of the postoperative chronic neurological disability rate. PNDmc provides the percentage of all surgically treated patients with new and persisting deficits who survived beyond day 30 but with neurological dysfunction.

Statistics

Statistics were summarized as total numbers, percentages and 95% confidence intervals (95% CIs) for categorical variables, means with standard deviations for normally distributed continuous variables and median with first and third quartiles (Q1 and Q3) for non-normally distributed continuous variables. Patient groups were compared with the χ² test for categorical variables and the unpaired t-test for normally distributed continuous variables. Non-normally distributed continuous variables were analysed using the Wilcoxon–Mann–Whitney test. Statistics were analysed using only cases with no missing values (complete case analysis). The influence of pharmacological neuroprotection on 30-day mortality, PND and PNDmc was analysed with multiple logistic regression in which the covariables age at surgery, gender, preoperative neurological deficit, malperfusion syndrome, haemodynamic instability, surgery >24 h after symptom onset, aortic regurgitation ≥II°, operation time, extracorporeal circulation (ECC) time, cross-clamp time, circulatory arrest time and CP time were included. The results of the logistic regressions are presented as odds ratios (ORs) with 95% CI. Because this is an explorative study, the term ‘statistically significant’ should be interpreted with caution. There was no formal adjustment for the number of tests performed.

RESULTS

Study population

From July 2006 to July 2010, 2137 AADA patients were included in the GERAADA. Table 1 shows the demographics of the study population. The overall 30-day mortality in this population was 16.9% (95% CI 15.3–18.5%), and 12.9% (95% CI 11.5–14.3%) of patients experienced new postoperative neurological dysfunction (PND). Death occurred in 22.5% of PND patients within the perioperative period, resulting in an overall PNDmc rate of 10.0% (95% CI 8.7–11.3%).

No intraoperative administration of neuroprotective drugs was documented in 48.0% of the patients, and this population...
formed the control group. Steroid, barbiturate (mainly thiopental) and mannitol monotherapy were used in 11.2, 8.4 and 7.3% of patients, respectively, and 25.1% received more than one drug. Preoperative risk factors are summarized in Table 2, and the peri- and intraoperative data are displayed in Table 3. Compared with the control group, significant differences existed for the following variables: shorter operation, ECC and cross-clamp times but longer CP and circulatory arrest times (all \( P < 0.05 \)) in the barbiturates group; more preoperative neurological deficits (\( P = 0.04 \)) and aortic valve insufficiency (\( P = 0.02 \)) and longer intraoperative times (all \( P < 0.05 \)) in the steroids group; shorter ECC times (\( P < 0.05 \)) and more haemodynamic instability (\( P = 0.003 \)) but less catecholamine therapy (\( P = 0.049 \)), compared with the no-pharmacological- and barbiturate (10.1%, \( P = 0.005 \)) groups.

The multivariate analysis (Table 4) revealed just an insignificant OR of 0.58 for the mannitol group, and neither steroid nor barbiturate therapy showed any effect on 30-day mortality.

### Hypothermic circulatory arrest, cerebral perfusion and pharmacological neuroprotection

We also sought to assess the effects of CP and interactions with neuroprotective agents in the current study. The majority of our patients, 71.1% (1520 patients), received adjunctive CP according to the individual institutional protocols, while 22.6% (482 patients) underwent surgery under HCA alone, and 6.3% (135 patients) were managed with CPB alone.

The overall PNDmc rates in the HCA and CP groups were 10.0 (95% CI 7.3–12.6%) and 10.1% (95% CI 8.6–11.6%), respectively. We observed a similar rate of 30-day mortality in the CP group (16.6%, 95% CI 14.8–18.5%) and in the HCA-alone group (19.1%, 95% CI 15.6–22.6%). It should be noted, however, that the CP time (median = 30 min, Q1–Q3 22–42 min; mean = 35.1 min) in the CP group was significantly longer than the circulatory arrest time in the HCA-only group (median = 20 min, Q1–Q3 12–29 min; mean = 21.6 min, \( P < 0.001 \)). In the small group of patients undergoing surgery with CPB alone, the PNDmc rate was 9.6% (95% CI 4.7–14.5%), and the 30-day mortality rate was 12.6% (95% CI 7.1–18.1%).

CP group patients were more likely to have received pharmacological neuroprotection. In the CP group, 10% of patients

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### Table 1: Demographic variables

<table>
<thead>
<tr>
<th>No drugs</th>
<th>Barbiturates</th>
<th>Steroids</th>
<th>Mannitol</th>
<th>Combined drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (N)</td>
<td>1025</td>
<td>179</td>
<td>239</td>
<td>157</td>
</tr>
<tr>
<td>Age at surgery (mean ± standard deviation)</td>
<td>60.1 ± 13.8</td>
<td>61.2 ± 12.7</td>
<td>60.5 ± 12.7</td>
<td>61.1 ± 13.4</td>
</tr>
<tr>
<td>Male gender (n, %)</td>
<td>638 (62.2%)</td>
<td>103 (57.5%)</td>
<td>154 (64.4%)</td>
<td>93 (59.2%)</td>
</tr>
<tr>
<td>Surgery within 24 h (n, %)</td>
<td>672 (65.6%)</td>
<td>99 (55.3%)</td>
<td>172 (72.0%)</td>
<td>55 (35.0%)</td>
</tr>
</tbody>
</table>

### Table 2: Preoperative risk factors (n, %)

<table>
<thead>
<tr>
<th>No drugs</th>
<th>Barbiturates</th>
<th>Steroids</th>
<th>Mannitol</th>
<th>Combined drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative neurological deficit</td>
<td>185 (18.0%)</td>
<td>34 (19.0%)</td>
<td>57 (23.8%)</td>
<td>29 (18.5%)</td>
</tr>
<tr>
<td>Preoperative malperfusion syndrome</td>
<td>345 (33.7%)</td>
<td>51 (28.5%)</td>
<td>89 (37.2%)</td>
<td>55 (35.0%)</td>
</tr>
<tr>
<td>Haemodynamic instability</td>
<td>562 (54.8%)</td>
<td>87 (48.6%)</td>
<td>131 (54.8%)</td>
<td>106 (67.5%)</td>
</tr>
<tr>
<td>Catecholamine therapy</td>
<td>219 (21.4%)</td>
<td>30 (16.8%)</td>
<td>56 (23.4%)</td>
<td>13 (8.3%)</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>195 (19.0%)</td>
<td>37 (20.7%)</td>
<td>43 (18.0%)</td>
<td>39 (24.8%)</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation</td>
<td>62 (6.0%)</td>
<td>14 (7.8%)</td>
<td>9 (3.8%)</td>
<td>6 (3.8%)</td>
</tr>
<tr>
<td>Intubated</td>
<td>149 (14.5%)</td>
<td>30 (16.8%)</td>
<td>28 (11.7%)</td>
<td>15 (9.6%)</td>
</tr>
<tr>
<td>Aortic regurgitation ≥II*</td>
<td>420 (41.0%)</td>
<td>67 (37.4%)</td>
<td>118 (49.4%)</td>
<td>62 (39.5%)</td>
</tr>
</tbody>
</table>
received barbiturate monotherapy, 10% received mannitol monotherapy, 13% received steroid monotherapy and 25% received some form of combined therapy. Only 42% of the CP patients did not receive any of these medications, compared with 59% in the HCA-alone group.

Pharmacological neuroprotection in the subpopulation of cerebral perfusion patients

The univariate results for the subgroups of pharmacological neuroprotection within the CP cohort (Fig. 2) were similar to those of the complete study population.

The PNDmc rate (dark blue column) in the CP patients who did not receive any neuroprotective drugs was 10.6%. Steroids and mannitol led to insignificant reductions in the PNDmc rate. The 30-day mortality rate (red column) for the CP patients who did not receive neuroprotective drugs was 20.0%. Lower mortality rates were found in the CP patients who received neuroprotective drugs: 30-day mortality was 11.5% for the barbiturate patients \( (P = 0.01) \), 13.6% for the steroid patients \( (P = 0.05) \) and 8.1% for the mannitol patients \( (P = 0.001) \).

In the multivariate analysis of the CP subgroup, an insignificant trend towards lower mortality (OR 0.48, \( P = 0.21 \)) was found for mannitol, and a trend towards lower PNDmc rate for steroids (OR 0.54, \( P = 0.09 \)). However, the multivariate analysis did not reveal any statistically significant protective effects of any of the neuroprotective agents (data not shown).

Arch intervention time and pharmacological neuroprotection

Figure 3 illustrates outcomes in the entire HCA and CP groups, as well as for the CP subgroups receiving neuroprotective drugs, according to the length of aortic arch intervention.

In patients undergoing HCA alone, the circulatory arrest time did not have a significant influence on the neurological endpoint, but did have an adverse effect on mortality. PNDmc rates were 9.1 (95% CI 5.9–12.3%) and 11.6% (95% CI 4.8–18.4) below and above the 30-min threshold \( (P = 0.48) \). In contrast, 30-day mortality was 16.3% (95% CI 12.2–20.4%) for patients with an HCA time of <30 min, compared with 31.4% (95% CI 21.5–41.3%) for HCA time ≥30 min \( (P = 0.002) \). Just 21%

### Table 3: Intra- and postoperative times (median, first and third quartile)

<table>
<thead>
<tr>
<th></th>
<th>No drugs</th>
<th>Barbiturates</th>
<th>Steroids</th>
<th>Mannitol</th>
<th>Combined drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min)</td>
<td>310 (250–385)</td>
<td>266 (225–310)</td>
<td>337 (282–410)</td>
<td>300 (245–372)</td>
<td>310 (257–290)</td>
</tr>
<tr>
<td>ECC time (min)</td>
<td>177 (136–228)</td>
<td>149 (123–192)</td>
<td>194 (158–237)</td>
<td>159 (120–215)</td>
<td>179 (141–225)</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>94 (70–131)</td>
<td>88 (64–121)</td>
<td>105 (78–137)</td>
<td>84 (65–131)</td>
<td>97 (72–126)</td>
</tr>
<tr>
<td>CP time</td>
<td>25 (15–40)</td>
<td>28 (21–40)</td>
<td>31 (24–50)</td>
<td>26 (21–54)</td>
<td>30 (21–40)</td>
</tr>
<tr>
<td>Respirator time (h)</td>
<td>35 (15–120)</td>
<td>24 (13–95)</td>
<td>32 (14–127)</td>
<td>22 (12–90)</td>
<td>32 (15–96)</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>4 (2–10)</td>
<td>3 (2–7)</td>
<td>5 (3–10)</td>
<td>3.5 (2–8)</td>
<td>5 (2–9)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>13 (8–21)</td>
<td>13 (9–21)</td>
<td>13 (8–21)</td>
<td>11 (8–16)</td>
<td>13 (8–18)</td>
</tr>
</tbody>
</table>

ECC: extracorporeal circulation; ICU: intensive care unit.
of the HCA patients had arrest times ≥30 min, which resulted in subpopulations that were too small to allow meaningful statistical analysis of the impact of the above-mentioned neuroprotective drugs.

In the CP cohort, 47.3% of the patients had CP times ≥30 min.

Thirty-day mortality was 14.7% (95% CI 11.5–17.8%) for patients with CP times <30 min and 21.4% (95% CI 17.8–24.9%) if the CP time was ≥30 min (P = 0.006). Although the mortality associated with prolonged CP times was significantly increased, it was partially attenuated by CP, compared with patients receiving just HCA (30-day mortality 31.4% for circulatory arrest time ≥30 min, P = 0.04).

In the CP subgroups receiving pharmacological neuroprotection, we failed to identify any protective effect on neurological dysfunction or mortality in patients with prolonged CP times.

**DISCUSSION**

Recent improvements in treating patients with AADA have mainly involved advances in surgical techniques and perfusion management. As demonstrated in previous studies, aortic arch surgery under HCA alone may be adequate only for short arch procedures [1, 3, 5]. Selective CP was found to reduce mortality after AADA surgery and to attenuate the significant increase in mortality after 30 min of aortic arch intervention time. CP during AADA surgery has become standard practice in most cardiac centres. Indeed, 71% of the GERAADA patients were managed with CP.

Compared with various CP strategies, the impact of neuroprotective drugs in aortic arch surgery has been poorly investigated. Currently, three groups of drugs with suspected neuroprotective...
effects are frequently used during aortic arch surgery: barbiturates (mainly thiopental), glucocorticosteroids (mainly dexamethasone, methylprednisolone and cortisol) and mannitol [6, 7]. Thus, the use of these drugs was recorded in the GERAADA.

Potential limitations of this study include differences in the treatment protocols of the centres, and the lack of data about the dosing, the timepoint and the route of application of the different drugs. Furthermore, some preoperative items and intraoperative times were unequally distributed between the groups and probably clustered between the treating heart centres. However, all of these limitations are inevitable problems of registry studies and must be weighed against the advantages of this approach, i.e. sufficient patient numbers, multisurgeon and multicentre data.

Barbiturates reduce neuronal activity (burst suppression in electroencephalography), cerebral metabolism and cerebral oxygen consumption. Although a clinically relevant neuroprotective effect has not been convincingly demonstrated [11, 12] and although negative effects such as delayed extubation, greater need for inotropes and even detrimental effects on brain metabolism have been demonstrated [13], thiopental is a popular drug in aortic arch surgery [6]. In the current study, we found no beneficial effect of barbiturates on new postoperative neurological dysfunction. The univariate analysis suggested that barbiturates may have a positive influence on perioperative neurological mortality, but this effect was not supported by the multivariate analysis. The improved mortality probably resulted from the shorter intraoperative times—a marker of less-advanced aortic pathology—observed in the barbiturate group, rather than from any form of neuroprotection.

The rationale for administering steroids in AADA surgery is mainly to prevent severe inflammatory response syndrome, which can lead to vasoplegia, organ malfunction and neurological impairment. In animal models, improved recovery from cerebral ischaemia during circulatory arrest [14] and spinal cord ischaemia during aortic cross clamping [15] has been reported after steroid administration. Furthermore, steroids are known to be neuroprotective in traumatic spinal cord injury [16] and vasogenic, but not cytotoxic, cerebral oedema [17]. Although the potential disadvantages of steroid administration, i.e. immunosuppression, are well known and although there is no direct evidence supporting their use as neuroprotective agents in aortic arch surgery, a survey among anaesthesiologists showed that steroids were frequently judged to be efficient [6]. In the current study, we found a reduction in new postoperative neurological deficits in the steroid group by both univariate and multivariate analyses, despite intraoperative times that were slightly longer than those of the control group. This finding may support a clinically relevant neuroprotective effect of steroids, but further investigations are required. We were unable to demonstrate any effect of steroid administration on perioperative mortality.

Similar to steroids, mannitol is thought to have many potential advantageous effects in aortic surgery. Its nephroprotective capability was discovered decades ago [18], and similarly positive effects on pulmonary function have been reported [19]. Mannitol is also a free-oxygen radical scavenger, which may contribute to its cardioprotective [20] and neuroprotective properties [17]. Furthermore, mannitol may have an antiapoptotic effect in focal cerebral ischaemia [21]. In our study, the univariate analysis revealed a small reduction in the PNDmc endpoint and a significant reduction in the 30-day mortality endpoint for the mannitol group. The multivariate analysis, taking account of the slightly shorter intraoperative times in the mannitol group, also suggested a protective effect on perioperative mortality. It is unclear if the decreased mortality results from the neuro- or the visceral protective effects described above.
Circulatory arrest times, and to a lesser extent CP times, exceeding 30 min were associated with a higher perioperative mortality rate in the current study. Neuroprotective drugs would be expected to have a more distinctive protective effect in high-risk patients, i.e. those with longer aortic arch intervention times. Unfortunately, too few HCA-alone patients received neuroprotective agents in order to make a valid assessment of their effect in prolonged circulatory arrest. In contrast to HCA, the physiological situation during adjunctive CP is distinctly different, with the preservation of residual structural (but not functional) metabolism. This capability may have resulted in our observed attenuation of increased mortality during prolonged arch intervention times. However, we were unable to detect any beneficial effect on mortality or neurological morbidity of any of the neuroprotective agents in patients with prolonged CP times. The lack of an obvious neuroprotective effect in such high-risk patients, despite a relatively large sample size, is somewhat disconcerting and argues against a clinically significant neuroprotective effect of such agents.

Conclusion

We found a strong trend towards improved perioperative survival after the administration of mannitol during surgery for AADA, and steroid therapy may have a positive effect on neurological outcomes, but further investigation is required.

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**REFERENCES**


