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Sedatives during circulatory arrest are not necessary for aortic arch repair in acute type A aortic dissection

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The standard protocol to maximize cerebral protection during open aortic arch surgery in acute type A aortic dissection (ATAAD) generally involves a combination of two perioperative strategies including hypothermic circulatory arrest (HCA) and cerebral perfusion in conjunction with pharmacologic agents (*eg*, barbiturates) as adjuncts for additional cerebral protection.[1-3] Pharmacologic agents are routinely used as an adjunct intraoperatively in a majority of cases despite minimal evidence supporting their use for incremental neurological protection.[1,3,4] Our study aims to evaluate the cerebral protection that intraoperative administration of adjunctive sedatives provides in aortic arch surgery with HCA and antegrade cerebral perfusion (ACP) in ATAAD. We hypothesize that adjunctive sedatives would not provide additional cerebral protection in aortic arch surgery with HCA and ACP, but would prolong patients' wake-up and intubation time due to its sedative effect.

This study was approved by the Institutional Review Board at the University of Michigan, Michigan Medicine (IRB No. HUM00111673), and was in compliance with Health Insurance Portability and Accountability Act regulations. A waiver of informed consent was obtained. Between September 2011 and January 2018, 120 acute type A aortic dissection patients underwent aortic arch surgery with HCA and ACP by a single surgeon (Yang). Patients were divided into groups based on whether or not additional intraoperative sedatives were used during HCA. The sedative used in this study was phenobarbital. Phenobarbital was used from September 2011 to January 2015 ($n = 53$) and no adjunctive sedatives were used from February 2015 to January 2018 ($n = 67$). In order to eliminate the variation of surgeons and strategy of cerebral protection, we only included patients operated upon by a single surgeon with the same strategy of cerebral protection. No patients were excluded.

Society of Thoracic Surgeons (STS) data were obtained from the University of Michigan Cardiac Surgery Data Warehouse to identify the cohort and to determine preoperative, operative, and post-operative characteristics. Medical record review was utilized to supplement data collection. The National Death Index database was used for long-term survival through December 31, 2015 and supplemented with medical record review after 2015.

The primary outcomes were immediate stroke, in-hospital stroke, and operative mortality while secondary outcomes were wake-up and intubation time. Immediate stroke was defined as: (1) stroke immediately identified as the patient woke up from anesthesia in the intensive care unit (ICU), or (2) patient never woke up from anesthesia and stroke was confirmed by imaging. In-hospital stroke was defined as any stroke which occurred after the operation and before discharge of the patient, including immediate stroke and late stroke. The wake-up time was defined as the time between sedation cessation and signs of waking up in the ICU (*eg*, wakeful eye and extremity movement as well as possessing the ability to follow commands). Intubation time was defined as the time from arrival in the ICU to extubation.

The aortic arch was replaced as either a hemiarch replacement or zone 1/2/3 arch replacement. Indications for zone 1–3 arch replacement were: arch aneurysm >4 cm or intimal tear located in the arch while arch aneurysm or intimal tear could not be resected by a hemiarch replacement, or dissection of arch branch vessels with malperfusion. Arch branch vessels were resected and replaced if they were significantly thrombosed due to dissection. Separate incisions were made at the neck to replace the whole

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common carotid arteries if the false lumen of the common carotid arteries was thrombosed and the arteries were severely stenotic or occluded. A frozen elephant trunk (cTAG-10 cm, manufactured by Gore [Newark, DE, USA]) was placed into the true lumen of the descending thoracic aorta distal to the left subclavian artery if the intimal tear was found in the proximal descending aorta to cover the intimal tear or a narrow true lumen was found in the distal thoracic or abdominal aorta on computed tomography (CT) angiogram to prevent lower body malperfusion.

ACP was used for all cases, and was either unilateral (94/120, 78%) or bilateral (26/120, 22%). The unilateral ACP (uni-ACP) was achieved through an 8 mm chimney Dacron graft sewn to the innominate, intrathoracic right subclavian, right axillary, or right common carotid arteries. The right axillary artery was the preferred site for arterial cannulation in the early stage of the study. Lately, to avoid an additional incision, the arterial cannulation site has been migrated to the innominate artery, and more recently to the intrathoracic right subclavian artery with a chimney graft (8 mm Dacron graft). When uni-ACP was used, the left common carotid artery was always clamped to prevent stealing of cerebral perfusion. If there was minimal back bleeding from left common carotid artery or unilateral (the left) cerebral saturation measured by near-infrared spectroscopy (NIRS) dropped significantly (30%) during HCA, then another cannula was inserted directly into the left common carotid artery for bilateral ACP. Moderate hypothermia (bladder temperature 24–28°C) was used during HCA. The blood temperature for ACP during HCA was 18–24°C in order to further cool the brain. Topical cooling was achieved with ice packs around the head. Mannitol (25 mg) and solumedrol (1 gram) either with phenobarbital (2.5 mg/kg) or without any adjunctive sedatives were administrated prior to the onset HCA as a single dose.

Descriptive statistics were computed for the study cohort. Continuous variables were summarized by median (interquartile range [IQR]) and categorical variables were reported as *n* (%) in frequency tables. Univariate comparisons across different treatment groups were performed using Wilcoxon-Mann-Whitney *U* test for continuous variables, Chi-square test for categorical data (expected cell count ≥5), and Fisher exact test was implemented for categorical variables (expected cell count <5). Multivariable logistic regression was used to calculate the odds ratios (OR) of post-operative stroke by adjusting for group (phenobarbital group), age, gender (male), and HCA time. Kaplan-Meier survival analysis was done to estimate short-term survival of all patients undergoing aortic arch surgery with HCA and ACP. All statistical calculations used SAS 9.4 (SAS Institute, Cary, NC, USA) with a significance level of $P < 0.05$.

The median age was 59 (52, 67) years. The demographics and preoperative conditions were not significantly different between the phenobarbital and no-sedatives groups ($P > 0.05$) [Supplemental Table 1, http://links.lww.com/CM9/A394]. There were no significant intraoperative differences between the two groups other than a shorter HCA time, higher bladder temperature at HCA and less intraoperative blood transfusion in the no-sedatives group [Supplemental Table 2, http://links.lww.com/CM9/A394].

There were no significant differences in the postoperative rates of immediate, in-hospital, or permanent strokes between groups; the in-hospital and operative mortality (including the in-hospital and 30-day mortalities) were also similar between groups [Supplementary Table 3, http://links.lww.com/CM9/A394]. However, wake-up time (6 [3, 11] h *vs.* 7 [4, 17] h, $P = 0.083$) and intubation time were significantly shorter in the no-sedatives group than those in the phenobarbital group (19 [9, 59] h *vs.* 29 [16, 84] h, $P = 0.048$) respectively [Supplementary Table 3, http://links.lww.com/CM9/A394]. Age, gender, HCA time, and absence of intraoperative sedatives were not significant risk factors for post-operative in-hospital stroke based on the multivariable logistic model [Supplemental Table 4, http://links.lww.com/CM9/A394]. The mean follow-up time was 21.6 months. One-year survival was similar between phenobarbital and no-sedatives groups (92% *vs.* 90%, $P = 0.795$) (Supplemental Figure 1, http://links.lww.com/CM9/A394).

Intraoperative neurological injury would usually be reflected by immediate stroke. In the no-sedatives group, 2 out of 67 patients had immediate stroke [Supplementary Table 5, http://links.lww.com/CM9/A394]. One of these patients (Patient 2) had an ATAAD with cardiac tamponade and cardiogenic shock while also undergoing a salvage open repair. Furthermore, this patient had severe (70−99%) left carotid artery stenosis and intraoperative hypotension, which likely explains the stroke in this scenario. The other patient (Patient 3) had an ATAAD and ruptured ascending aorta, and the immediate stroke was likely due to intraoperative hypotension. Based on this information, we contend that these two cases were not related to the lack of intraoperative sedatives. Two additional patients suffered delayed in-hospital ischemic strokes due to clear hypotensive episodes at postoperative days 7 and 9. Again, we contend that these in-hospital cases were likely not related to intra-operative management. Overall, we observed a low incidence of immediate stroke after ATAAD repair without phenobarbital and no significant differences in immediate stroke between the phenobarbital and no-sedatives groups [Supplementary Table 3, http://links.lww.com/CM9/A394]. This suggests that phenobarbital may not provide additive neuroprotection, which is consistent with the observation from Krüger *et al*,[1] utilizing the German registry for acute aortic dissection type A (GERAADA) Registry.

What are the disadvantages of administering barbiturates during aortic arch surgery with HCA and ACP? We report prolonged wake-up time and significantly longer intubation time. Prolonged intubation could increase the cost of care for just being on the ventilator despite the length of ICU/hospital stay, and increase the risk of complications associated with ventilation, such as ventilator-associated pneumonia and/or extended ICU/hospital stay. Phenobarbital has been traditionally used at our institution and has a relatively long half-life compared to other sedatives. Sedatives with a shorter half-life may not have such adverse effects on prolonged waking-up time or intubation

time. The HCA time in the no-sedatives group was 6 minutes shorter and the lowest bladder temperature was 3°C higher compared with the phenobarbital group. These factors might also have some contribution to the shorter wake-up/intubation time and the neurological outcome in the no-sedatives group. However, if aortic arch surgery in ATAAD with moderate HCA and ACP alone could achieve low stroke rates and no significant differences compared with patients treated with intraoperative phenobarbital, then adjunctive sedatives should be avoided. Our institution has eliminated the administration of any barbiturates or adjunctive sedatives during aortic arch surgery with HCA and ACP since concluding this study at our institution. Besides delayed awakening, Hirotani *et al*[5] also found a myocardial depression effect from barbiturates. Taken together, this study provides preliminary rationale in support of avoiding intraoperative adjunct sedatives during HCA and ACP to reduce intubation time for ATAAD patients undergoing aortic arch repair.

This study has limitations as a retrospective, non-randomized, single-center study. The sample size was small and the incidence of stroke was low. However, if we only focus on the outcome of the no-sedatives group; we can confidently say that without intraoperative adjunctive sedatives, the neurological outcome was still very good in arch surgery with HCA and ACP. We used a historical control group, however, there was no significant change in practice by the surgical team over a 6-year time period except we stopped the use of intraoperative phenobarbital. The diagnosis of stroke is a clinical diagnosis but not a radiographic diagnosis, since we do not routinely obtain a CT of the brain after HCA if there is no neurological deficit; this could have underestimated the subclinical stroke rate. Additionally, we acknowledge that the data presented were derived from the cases of a single surgeon and at a single institution. This could also be a strength of this study, however, since it eliminates the variation in management of HCA among different surgeons and institutions.

In conclusion, in ATAAD patients undergoing aortic arch repair with HCA and ACP, excellent neurological outcomes were achieved in the absence of intraoperative adjunctive sedatives administration during HCA with ACP for aortic arch repair. Intraoperative adjunctive use of sedatives led to prolonged wake-up and intubation time. We do not recommend adjunctive sedatives for aortic arch repair with HCA and ACP in ATAAD patients.

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Conflicts of interest

None.

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