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Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study

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Abstract

Delirium and transient neurologic dysfunctions (TND) often complicate the postoperative course after surgery for acute type-A aortic dissection (AAD). We evaluated the role of clonidine on neurological outcome and respiratory function in 30 consecutive patients undergoing surgery for AAD. Patients were prospectively randomized to receive either clonidine (0.5 μg/kg bolus, followed by continuous infusion at 1–2 μg/kg/h) or placebo (NaCl 0.9%) in on starting and throughout the weaning period from the mechanical ventilation. Incidence of delirium and TND, Delirium Detection Score (DDS), weaning parameters [respiratory rate to tidal volume ratio – f/VT; pressure–frequency product (PFP); partial pressure of arterial oxygen to fractional inspired oxygen concentration (PaO_2/FiO_2); partial pressure of carbon dioxide ($PaCO_2$)], weaning duration and intensive care unit (ICU) length of stay were recorded. The two groups were similar for preoperative and operative variables and also for the incidence of postoperative complications. DDS was lower in the clonidine group ($P<0.001$). Patients weaned with clonidine showed lower f/VT and PFP, higher PaO_2/FiO_2 and $PaCO_2$, lower DDS, weaning period and the related ICU length of stay ($P<0.001$). This was further confirmed in patients developing delirium/TND. Intravenous clonidine after surgery for AAD reduces the severity of delirium, improves the respiratory function, shortens the weaning duration and the ICU length of stay.

Keywords: Acute aortic dissection; Neurological complications; Postoperative care

1. Introduction

Cerebral protection is a primary concern during operations on the aortic arch, particularly in case of acute type-A aortic dissection where neurological complication rates are described in 2–40% of cases [1]. However, despite deep hypothermic circulatory arrest (DHCA) with selective antegrade cerebral perfusion (SACP) reduced the risk for perioperative stroke, the incidence of delirium and other transient neurological dysfunctions (TND) – with resolution of symptoms before discharge – remains as high as 12–37% in different reports [1, 2]. Such accidents negatively impact the weaning from mechanical ventilation, delay the extubation time, and further complicate the postoperative course [3]. Therefore, it is recommended that all intensive care unit (ICU) patients would be monitored using a validated delirium assessment instrument [4].

Recent studies demonstrated alpha-2 adrenergic agonists, such as clonidine or deximeditomidine, to have a beneficial effect on neurological recovery and the related weaning from mechanical ventilation in patients developing withdrawal symptoms after interruption of sedation [5]. However, deximeditomidine is not available commercially in Europe, therefore, it cannot be used for clinical purposes. Consequently, clonidine was the only alpha-2-adrenergic agonist selected for this study. Despite such reports, few studies addressed the role of alpha-2-adrenergic agonists, and in particular of clonidine, on the neurologic outcome and the related weaning from mechanical ventilation of patients undergoing surgery for acute type-A aortic dissection (AAD). Therefore, we reported here our preliminary results of a pilot study on the effects of intravenous clonidine administration in this particular subset of patients.

2. Materials and methods

2.1. Patients

From January 2004 to January 2009, 30 consecutive patients undergoing surgery for AAD were prospectively enrolled in the study after Institution's Ethical Committee/Institutional Review Board approval. If the patients arrived at the hospital conscious and in stable haemodynamic conditions, they were informed about the high-risk proce-

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dure they were to undergo and about the incidence of postoperative complications that could prolong ICU stay and the opportunity to improve postoperative weaning by use of appropriate postoperative procedures. Therefore, if they accepted the protocol and the randomization, they expressed their written informed consent.

2.2. Anaesthesia

Anaesthetic technique was standardized: induction of anaesthesia consisted of intravenous propofol bolus for the initial dose, followed by the infusion at 3 mg/kg/h combined with fentanyl administration (bolus for the initial dose 5–7.5 γ/kg followed by the infusion at 1.5–3.5 γ/kg/h). Neuromuscular blockade was achieved by an initial dose of *cis*-atracurium at 0.2 mg/kg followed by maintenance boluses of 0.05–0.08 mg/kg. Lungs were ventilated to normocapnia with air and oxygen (45–50%). The alpha-stat method was the standard practice in blood gas management.

Before hypothermic circulatory arrest was established, methylprednisolone sodium succinate (SoluMedrol; Upjohn, Kalamazoo, MI) at dosage of 1000 mg and Pentothal Sodium (ABBOTT SpA, Campoverde di Aprilia – Latina) at a dosage of 3 mg/kg were administered intravenously. The head was packed in ice to maintain low brain temperature. Before the re-establishment of cardiopulmonary bypass (CPB), 1–2 g/kg of mannitol 18% and 0.5 mg/kg of furosemide were administered intravenously to promote diuresis and free radical scavenging.

2.3. Surgical technique and CPB

CPB and surgical techniques were standardized and did not change during the study period. CPB was established via the right atrium and the right axillary artery. Myocardial protection was always achieved with antegrade cold Custodiol cardioplegia. Cooling was limited to 26 °C rectal temperature. Total CPB flow was maintained at 2.6 l/min/m^2 during normothermia and progressively reduced to a minimum of 2.2 l/min/m^2 before starting SACP. When the aortic arch was opened, the epiaortic vessels were snared with vessel loops and the left carotid artery cannulated with a retrograde cardioplegia cannula to accomplish SACP together with the right axillary artery.

2.4. Weaning protocol

Anaesthesiologists and cardiac surgeons caring for the patients during the intraoperative course were blinded towards the postoperative group assignment. At ICU admission, patients were randomized by envelope into two groups: 15 patients (Group A) received a bolus of 0.5 μg/kg of clonidine immediately at the beginning of the weaning, followed by continuous infusion at 1–2 μg/kg/h all over the weaning phase whereas the other 15 (Group B) received placebo (NaCl 0.9%) at the same time points.

At the admission to the ICU, every patient was ventilated in assisted-controlled ventilation (ACV) mode to maintain pH between 7.35 and 7.45, $PaCO_2$ between 35 and 45 mmHg and PaO_2 between 90 and 100 mmHg with an arterial SO_2 $>$95%. The weaning protocol has been previously described [6].

If patients showed signs or symptoms of neurological complication before or after surgery, brain computed tomography (BCT) examination was executed, and only those without any lesion at BCT were definitively enrolled. Accordingly, one patient showing preoperative stroke at BCT was excluded prior to randomization on an intention-to-treat basis as well as two patients with postoperative stroke at BCT were excluded after enrollment.

An awake and compliant extubated patient, with stable haemodynamic parameters, and absence of bleeding indicated the discharge from the ICU to the ward.

2.5. Weaning parameters

The weaning parameters were recorded from the Evita 4® Ventilator – Dräger Medical AG and Co. Respiratory rate to tidal volume ratio (f/VT – breaths/min/l), pressure–frequency product (PFP – $cmH_2O \times$breaths/min), partial pressure of arterial oxygen to fractional inspired oxygen concentration (PaO_2/FiO_2 – mmHg), partial pressure of carbon dioxide ($PaCO_2$ – mmHg) were recorded at the same time in the two groups 30 min after the beginning of the weaning protocol. Successful extubation (SE) was defined as the ability to maintain spontaneous breathing for 48 h. Perioperative complications, need for re-exploration for bleeding, transfusions, length of weaning and of ICU stay were also recorded. Mean arterial pressure as well as need and doses of catecholamine were recorded for the two groups.

2.6. Complications

TND was defined as a temporary non-focal deficit including obtundation, seizures, confusion, or psychosis. Delirium was defined as a disturbance of consciousness and cognition that develops over a short period of time (hours to days) and fluctuates over time, without neurologic sequelae, according to the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM) – IV [7]. The severity of delirium was estimated by the Delirium Detection Score (DDS) 30 min after the beginning of the weaning phase [8]. DDS was always administered by the same anaesthesiologist (SC).

2.7. End-points of the study

The primary endpoints of the study were the incidence of delirium and TND, the severity of delirium (DDS), and the related differences in the weaning parameters (f/VT, PFP, PaO_2/FiO_2, $PaCO_2$). Duration of the weaning, prevalence of successful extubation, and the ICU length of stay were secondary endpoints.

2.8. Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (S.D.), and categorical variables are presented as absolute numbers and proportions. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired

t-test, whereas the Mann–Whitney *U*-test was used for those variables not normally distributed. Categorical variables were analyzed using the χ^2-test or Fisher's exact test.

All statistical analyses were considered significant if $P<0.05$ and were performed with the SPSS statistical package 13.0 (SPSS Inc, Chicago, IL, USA).

3. Results

Patients were similar for preoperative and intraoperative variables (Table 1) as well as for mean arterial pressure throughout the study period (Table 2). However, the use of catecolamines throughout the ICU stay was similar between the two groups (mean norepinephrine dosage: clonidine group 0.10 ± 0.04 μg/kg/min vs. placebo group 0.07 ± 0.02 – $P=0.624$; mean dobutamine dosage: clonidine group 8.5 ± 1.2 μg/kg/min vs. placebo group 6.9 ± 2.2 – $P=0.762$).

No differences were recorded in the two groups in terms of length of sedation in ICU before starting the weaning protocol (Group A: 11.2 ± 3.1 h vs. Group B: 10.8 ± 3.2; $P=0.685$). Five patients (33.0%) in the clonidine group and six (40.0%) in the placebo group ($P=0.705$) complicated with TND. However, all of them recovered before discharge from the ICU. Nonetheless, neurological recovery proved shorter in patients undergoing i.v. clonidine (20.2 ± 10.7 h vs. placebo: 60.6 ± 17.3; $P=0.001$). When delirium was considered, six patients in the clonidine group (40.0%) and five patients in the placebo group (33.0%; $P=0.705$) demonstrated delirium postoperatively. However, DDS proved lower in patients weaned with clonidine compared to those treated with placebo ($P=0.001$, Table 3). As already reported, all these patients underwent BCT-scan without any evidence of focal brain lesion. As already reported, three patients developing perioperative stroke at CT-scan evaluation during the study period were excluded from the study on an intention-to-treat basis.

Table 1
Preoperative, intraoperative and postoperative demographics

	Group A	Group B	*P*-value
ASA score 3/4	9/6	5/10	0.143
Female/Male	5/10	7/8	0.456
Uncontrolled hypertension	6	9	0.273
COPD	5	8	0.269
Age (years)	63.9 ± 8.9	61.3 ± 6.3	0.377
BMI	28.2 ± 2.8	28.7 ± 2.5	0.636
LVEF (%)	52.8 ± 4.6	51.7 ± 3.9	0.476
Operation time (min)	439.7 ± 81.2	473.7 ± 97.0	0.061
CPB time (min)	143.9 ± 35.7	144.9 ± 42.6	0.767
AoX time (min)	83.3 ± 16.6	86.0 ± 27.0	0.326
DHCA time (min)	26.7 ± 8.4	26.1 ± 9.2	0.778
Intervention			
Bentall	1	1	
AoV + AscAo repl	5	7	
AscAo repl	5	3	0.999
ElephTrunk	1	1	
AoV pl + AscAo repl	3	3	
Exitus	2	1	0.543
Pneumonia	1	1	0.543
Renal failure requiring dialysis	3	3	>0.999
Bleeding requiring reintervention	2	3	0.624
Transfusion/patient	8.7 ± 4.4	9.2 ± 4.6	0.779

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; BMI, body mass index; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; AoX, aortic cross-clamp; DHCA, deep hypothermic circulatory arrest; AoV, aortic valve; AscAo, ascending aorta; repl, replacement; pl, plasty; ElephTrunk, elephant trunk.

Table 3
Weaning parameters

	Group A	Group B	*P*-value
f/VT (breaths·min^{-1}/l)	38.6 ± 5.2	68.1 ± 9.4	<0.001
PFP (cmH_2O·breaths/min)	204.0 ± 22.4	313.4 ± 49.4	<0.001
PaO_2/FiO_2 (mmHg)	315.8 ± 28.0	233.7 ± 48.4	<0.001
$PaCO_2$ (mmHg)	38.4 ± 2.8	31.0 ± 2.5	<0.001

f/VT, respiratory rate to tidal volume ratio; PFP, pressure–frequency product; PaO_2/FiO_2, partial pressure of arterial oxygen to fractional inspired oxygen concentration; $PaCO_2$, partial pressure of carbon dioxide.

The two groups behaved differently in terms of weaning parameters. In particular, patients receiving clonidine showed higher PaO_2/FiO_2 and $PaCO_2$ ($P<0.001$) and lower f/VT and PFP ($P<0.001$) (Table 3). However, successful extubation could be achieved in all patients except for three patients (20%) in group A and four patients (26.7%) in group B ($P=0.666$). Furthermore, none of the extubated patients belonging to clonidine group needed re-intubation (0%), which was necessary in four patients (26.7%) of the placebo group ($P=0.05$). Patients who received intravenous clonidine required also a shorter period of weaning and showed a shorter ICU length of stay ($P<0.001$, Table 4).

Finally, when the subgroup of patients developing postoperative TND and/or delirium was considered, those receiving intravenous clonidine showed significantly better PaO_2/FiO_2, $PaCO_2$, f/VT, PFP, DDS, weaning duration and ICU length of stay (Table 5).

4. Discussion

Despite DHCA with SACP and pharmacological neuroprotection reduce cerebral injury, these protocols do not completely avoid neurological complications, ranging from

Table 2
Mean arterial pressure (mmHg)

	Preoperative	ICU admission	6 h after ICU admission	30 min after the beginning of weaning	*P*-value[b]	*P*-value[c]
Group A	74.2 ± 7.3	69.1 ± 7.6	69.9 ± 9.8	73.1 ± 3.3	0.732	
Group B	74.5 ± 5.3	70.2 ± 7.1	66.5 ± 4.9	77.9 ± 8.3	0.678	0.675
P-value[a]	0.942	0.815	0.536	0.6421	–	

[a]*P*-value for comparison at specific time points; [b]group·time *P*-value (within group); [c]*P*-value for comparison between groups.
ICU, intensive care unit.

Table 4
Incidence of delirium and length of stay

	Group A	Group B	*P*-value
DDS	0.6±0.7	1.8±0.8	<0.001
Weaning duration (days)	1.4±0.3	2.2±0.4	<0.001
ICU stay (h)	31.4±28	35.9±35.4	<0.001

DDS, delirium detection score; ICU, intensive care unit.

Table 5
Subgroup analysis of patients developing TND

	Group A	Group B	*P*-value
f/VT (breaths·min^{-1}/l)	39.0±6.6	68.2±10.0	<0.001
PFP (cmH_2O·breaths/min)	217.6±28.5	303.3±51.3	0.009
PaO_2/FiO_2 (mmHg)	309.0±21.5	238.8±51.3	0.019
$PaCO_2$ (mmHg)	39.2±2.9	31.5±2.5	0.001
DDS	0.3±0.4	1.8±0.8	0.002
Weaning duration (days)	1.6±0.3	2.3±0.4	0.001
ICU stay (h)	41.2±27.6	53.6±19.2	0.001

TND, transient neurologic dysfunctions; f/VT, respiratory rate to tidal volume ratio; PFP, pressure–frequency product; PaO_2/FiO_2, partial pressure of arterial oxygen to fractional inspired oxygen concentration; $PaCO_2$, partial pressure of carbon dioxide; DDS, delirium detection score; ICU, intensive care unit.

stroke to TND, generally manifested with psychosis, delirium, and other psychological disturbances [2, 9]. Therefore, supplementary neuroprotective strategies should be continued during the postoperative assistance. The patients enrolled in the present study shared the same perioperative management, and did not differ significantly in terms of length of DHCA and of CPB (Table 1). Moreover, patients developing focal brain injury at CT-scan analysis were excluded on an intention-to-treat basis.

Recently, alpha-2 adrenergic agonists have been suggested to be useful adjuvants to the common postoperative management since they induce sedation and maintain stable systemic blood pressure and low heart rate [10]. Myles et al. reported a beneficial effect of postoperative clonidine administration following vascular or coronary bypass surgery, particularly improving myocardial protection, haemodynamics and organ function [11]. Moreover, clonidine has been suggested as an alternative to opioids and other sedatives to help alleviate withdrawal symptoms [5]. Clonidine in conjunction with an opioid allows a significant reduction of opioid dosage and may facilitate weaning from mechanical ventilation [5]. However, if the use of clonidine would be beneficial also in neurological dysfunction developing after surgery for acute aortic dissection has not been investigated until now. Our preliminary data seem to favour i.v. infusion of clonidine during the weaning phase, given the better combined neurological and respiratory outcome.

Delirium and psychosis – which can often complicate the postoperative course of type-A aortic dissection – are common manifestations of acute brain dysfunction in critically ill patients, and correlate with poor short-term outcomes and adverse sequelae [4]. The administration of alpha-2-adrenergic agonists can reduce anaesthetic requirements after surgery decreasing the risk of postoperative delirium and psychosis. Therefore, it could be expected that clonidine infusion would improve the postoperative course for at-risk patients [12]. In the present study, DDS was significantly improved by clonidine administration ($P=0.001$). Furthermore, patients developing TND showed significantly better DDS, which resulted in improved weaning from the mechanical ventilator, as demonstrated by lower f/VT, PFP, higher PaO_2/FiO_2 and $PaCO_2$, and by shorter weaning duration and ICU length of stay (Table 5). These data confirm those of a previous trial on the prevention of the occurrence of delirium and psychosis after surgery in patients treated with clonidine [12].

In particular, different functional parameters have been suggested to predict successful weaning from mechanical ventilation. In particular, Cohen showed that f/VT is predictor of successful extubation [13]. Additionally, Mekontso-Dessap et al. proved that patents undergoing a successful weaning from mechanical ventilation had lower PFP values [14]. Furthermore, McCartney and Boland demonstrated that the delirious patient cannot cooperate with weaning [15]. Accordingly, Girard et al. proved that delirium is associated with multiple complications and adverse outcomes, including self-extubation and removal of catheters, failed extubation, prolonged hospital stay and increased mortality [4]. Therefore, delirium control could be associated to improved early hospital outcome [4]. Our results confirm those of previous studies since we found that patients receiving clonidine showed lower f/VT and PFP with higher PaO_2/FiO_2 and $PaCO_2$ (Table 3). That is, patients treated by postoperative clonidine had a better compliance to mechanical ventilation and a better response to spontaneous breathing trial.

However, despite such findings, we failed to demonstrate any amelioration of perioperative morbidity and mortality. This can be the result of the limited number of patients enrolled, or to the multifactorial aetiology responsible for perioperative morbidity and mortality in the setting of aortic dissection.

5. Conclusions

Our preliminary experience showed that the use of clonidine during the weaning period after surgery for AAD reduced the severity of postoperative TND and delirium in the absence of focal brain lesion at BCT. These results correlate with an improved quality of the weaning and lowered the weaning duration and ICU length of stay. Further studies on a higher number of patients or in patients with focal neurological lesions will be able to clarify these topics.

6. Limitation of the study

The main limitation of the study is the limited number of patients enrolled. Moreover, this study was not designed to ascertain differences in haemodynamic stability with the use of clonidine, although it is well known that alpha-2-adrenergic agonists induce a stable systemic blood pressure and reduce heart rate [11]. However, the criteria to begin the weaning protocol included stable haemodynamics. Therefore, the two groups could be considered similar according to this parameter. All these limitations stem from the single-centre design of the study, which, on the other hand, guarantees uniformity of the perioperative manage-

ment of the patient population throughout the study. Certainly, further randomized studies with more patients enrolled and followed-up for a longer period are necessary.

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