Reduced length of hospital stay for cardiac surgery implementing an optimized perioperative pathway: prospective evaluation of an Enhanced Recovery After Surgery Program designed for Mini-Invasive Aortic Valve Replacement.

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Introduction

Remarkable anesthetic and surgical advancement have been achieved in the field of cardiac surgery within the last 3 decades[1,2]. Although cardiac fast-track protocols aiming to extubate cardiac patients after surgery at an early stage have been implemented successfully, postoperative morbidity continues to be frequent[1]. Moreover, mini-invasive cardiac surgical approaches have been described to reduce the surgical stress response, but few objective advantages have been demonstrated and equivalent postoperative outcomes have been reported when compared to traditional techniques[2]. The surgical stress response is considered as the principal and most frequent factor leading to postoperative morbidity[3]. To blunt this response causing a systemic release of stress hormones and inflammatory mediators Enhanced Recovery After Surgery (ERAS) program have been developed showing outstanding results[4]. The ERAS concept is based on a multidisciplinary approach, which aims to create a synergistic effect applying several evidence-based perioperative elements[5]. This strategy has been implemented effectively improving outcomes in colorectal, orthopedic, urologic gynecology and breast surgery[6]. Unfortunately, only a few trials have assessed the effectiveness of an ERAS program for cardiac surgery[7-9]. In addition, most of these trials were retrospective and none have been conducted in a population undergoing a mini-invasive aortic valve replacement (MIAVR).

Therefore, the objective of this trial was to determine prospectively the clinical effectiveness of an ERAS protocol specifically designed for MIAVR at a tertiary medical centre. We tested the hypothesis that adoption of an ERAS pathway for MIAVR reduces hospital length of stay (LOS) and improve outcomes when compared with traditional care.

Methods

This human research, prospective, observational, single-centre study was conducted in the Department of Cardiac Anesthesia and Critical Care at the Bordeaux University Hospital (Service d'Anesthésie-Réanimation GH Sud, CHU Bordeaux, France) from September 2014 to November 2015. Before starting the study, the research protocol was approved by the Research Ethics Boards of the Bordeaux University Hospital (N° DC:2014/91). Agreement from the "Commission Nationale de l'Informatique et des Libertés" was also obtained before commencing the study (registration number 1791818 v 0).

Study Design

The present trial was a comparative effectiveness study using a 'before-after' approach, with a nonrandomized, pre-implementation and post-implementation of the ERAS protocol, data collection scheme. This study follows the guidelines and the checklist of the STROBE statement[10]. Data collected before the implementation stage occurred from September 2014 to December 2014. During this period, data from patients undergoing aortic valve replacement via a mini-sternotomy following the traditional perioperative care were collected prospectively. Meanwhile, several meetings were scheduled with a multidisciplinary team during which a team-based approach allowed agreeing on the evidence-based medicine elements incorporating the final protocol (Table 1). To ensure both a good communication between every care providers and the adherence to the elements encompassed in the program, the official implementation of the ERAS pathway started after a 4-month period. Data obtained were collected from May to November 2015 once the ERAS protocol was fully implemented. The Ethics Boards authorized a waiver of the written informed consent because data were collected

according to the standard practice of care of our institution, which consists in applying evidence-based perioperative principles to patients[4]. Thus, this study was not registered on a clinical trial registry.

Study participants

Patients were enrolled in the study if they were older than 18 years old and were scheduled to undergo an elective aortic valve replacement via a mini-sternotomy. Exclusion criteria included patients scheduled for an aortic valve replacement with a full sternotomy or scheduled for other cardiac surgeries than aortic valve replacement, patients who underwent a previous sternotomy, patients with dementia, patients presenting with endocarditis and patients with chronic renal failure.

Demographic and outcomes data collected before and after the implementation of the dedicated ERAS pathway designed for a MIAVR procedure were compared. The preoperative data collected were: anthropomorphic data, NYHA functional status, additive EuroSCORE, medical history and preoperative left ventricular ejection fraction estimation. The intraoperative data collected were: duration of surgery, cross-clamp time, duration of cardiopulmonary bypass (CPB), number of patients transfused with red blood cells and proportion of patients converted full sternotomy. Other data collected were: proportion of adhesion to each item of the ERAS pathway, consumption of morphine, time to first flatus, proportion of patients re-operated, proportion of patients that contracted an infection, proportion of patients that developed an acute myocardial infarction, proportion of patients that developed a stroke, proportion of patients that developed acute kidney injury (AKI) according to the KDIGO criteria[11], proportion of patients that required renal replacement therapy, proportion of patients reintubated for respiratory failure, length of Intensive Care Unit (ICU) stay, length of hospital stay, all-

cause ICU readmission before hospital discharge, all-cause readmission rate at 30-day, hospital mortality rate and mortality rate at 30-day.

Study groups

Traditional MIAVR group

The traditional perioperative protocol of care is described in Table 1.

Intraoperative anesthesia management and surgical technique:

A total intravenous anesthesia was administered using target-controlled infusion with either sufentanil or remifentanil for analgesia and propofol for hypnosis via a peripheral intravenous catheter. Cisatracurium was used to facilitate endotracheal tube insertion. Then a continuous infusion of cisatracurium was started and stopped at the end of the surgery. Intraoperative fluid delivery before and after CPB was based on changes in hemodynamics (central venous pressure (CVP) and arterial blood pressure) and urine output. After induction of anesthesia, fluid loading was administered to obtain and keep a CVP between 6 and 15 mmHg. Once the latter was obtained a vasoconstrictor was delivered if the mean arterial pressure was below 60 mmHg. Priming varied at the discretion of the anesthesiologist in charge and ranged from 800 ml to 1300 ml of balanced crystalloid solution (PlasmaLyte VIAFLO, BAXTER S.A.S, Guyancourt, France). After separation from CPB, administration of fluid loading and or furosemide based on the urinary output also varied at the discretion of the attending anesthesiologist. Postoperative analgesia was administrated during the sternum closure using morphine 0.2 $mg.kg^{-1}$, 1 g of acetaminophen and 0.3 $mg.kg^{-1}$ of nefopam when not contraindicated. In a surgical standpoint, an upper hemi-sternotomy was performed in a J-shaped fashion at the 4^{th} intercostal space to replace the native aortic valve. Both, the arterial and the venous cannulation were carried out centrally through the main surgical site. At this point,

anterograde cold blood cardioplegia was administered through the aortic root. Then, the aorta was cut in a hockey stick shape. The calcified aortic valve was removed in the same way as for an ordinary aortic valve replacement. Finally, the aorta was closed suturing in a standard fashion under direct vision without endoscopic camera.

All patients were transferred intubated in ICU and were extubated following a traditional fast-track cardiac recovery protocol[1].

Postoperative management:

Upon arrival in the ICU, sedation was stopped and endotracheal extubation was allowed within 6 hours from the end of the surgery, when patients met the modified Reyes' extubation criteria[12]. After extubation, patients were allowed to breath spontaneously through a facemask with 6 $l.min^{-1}$ of O_2. Postoperative acute pain was treated with Patient-Controlled Analgesia (PCA) morphine (containing 0.05 mg of droperidol for each mg of morphine), and nefopam 65 $\mu g.kg^{-1}.h^{-1}$ for the first 48 postoperative hours, or until discharge from ICU. When patients were discharged from ICU, ketoprofen 100 mg was prescribed twice a day with breakthrough tramadol 100 mg every 4 to 6 hours, as required. The central venous line and the bladder catheter were removed on POD3 on the surgical floor. Patients were mobilized from bed to chair on POD3 when the tubes and catheters were removed. Patients were offered a fluid meal on POD3 and a solid meal on POD4. The intensivist in charge decided that patients were eligible to be discharged to the surgical floor when the following criteria were met: nasal administration of O_2 with a flow lower than 3 $l.min^{-1}$ and a respiratory rate lower than 25 per min and higher than 10 per min with blood gas analysis showing a PaO_2 superior than 9 kPa and a $PaCO_2$ lower than 6.5 kPa; no evidence of myocardial ischemia, no on-going infarction nor unstable

hemodynamic dysrhythmia, no catecholamine infusion, no major neurologic complication and a urinary output higher than 0.5 $ml.kg^{-1}.h^{-1}$.

MIAVR-ERAS group

The key supplementary perioperative ERAS elements implemented at the University hospital of Bordeaux are summed up in Table 1.

Pre-operative management:

On average, 4 to 5 weeks before the surgery, patients met with a surgeon (P.O), an anesthesiologist, an intensivist, a nurse, a physiotherapist and a nutritionist. Every stakeholder explained what it would do perioperatively and what he expect his patient to do in order to involve and engage him in adhering to the ERAS pathway. The physiotherapist thought how to perform postoperative respiratory exercises efficiently. The nutritionist assessed patients' nutritional status measuring the levels of serum blood albumin, prealbumin and C-reactive protein. A tailored diet was prescribed preoperatively if judged necessary.

Intraoperative anesthesia management and surgical technique:

A total intravenous anesthesia was administered using target-controlled infusion with remifentanil for analgesia and propofol for hypnosis. To facilitate endotracheal tube insertion, 1.2 $mg.kg^{-1}$ of rocuronium was administered with no subsequent continuous infusion. A pre-emptive multimodal analgesic strategy was implemented at induction and consisted in boluses of ketamine 0.5 $mg.kg^{-1}$, dexamethasone 0.15 $mg.kg^{-1}$ and magnesium 50 $mg.kg^{-1}$. Patients were ventilated according to a multimodal protective lung ventilation management. Ventilation was maintained during CPB with 3 $ml.kg^{-1}$ of ideal bodyweight, with a PEEP of 5 cmH_2O, and with a FiO_2 of 0.35. In this group the surgical technique used was the same except for one change, which was the systematic

replacement of the native aortic valve with a rapid deployment bioprosthesis. A TEE allowed hemodynamic assessment and goal-directed therapy (GDT) optimizing fluid filling. The GDT strategy consisted in delivering fluid challenge of 3 $ml.kg^{-1}$ of a balanced crystalloid (PlasmaLyte VIAFLO, BAXTER S.A.S, Guyancourt, France) until a steady stroke index was reached (the GDT protocol is described in Figure 1). If a steady state was reached but the stroke volume index was below 35 $ml.min^{-1}$ and the blood pressure was not within 20% of the base line, a continuous infusion of inotropic agent was started when the cardiac index was below 2.5 $l.\ min^{-1}.m^{-2}$. In contrast, when the cardiac index was above 2.5 $l.\ min^{-1}.m^{-2}$, a bolus followed by a continuous infusion of norepinephrine was delivered. The volume loading was reassessed every 5-10 minutes throughout the procedure. This protocol was applied before and after CPB until completion of the dressing.

To limit discomfort and facilitate early mobilization two small drainage-tubes were inserted through little incisions made above the mini-sternotomy. After sternum closure, wound infiltration with a total of 20 mL of 0.75% ropivacaine was applied along with administration of a multimodal analgesia encompassing acetaminophen, 1 g, ketoprofen, 100 mg, nefopam, 0.3 $mg.kg^{-1}$ and morphine, 0.1 $mg.kg^{-1}$. Patients were extubated either on the operating table or in ICU as soon as the ultrafast-track criteria were met[4].

Postoperative management:

From patients' arrival in ICU to the morning after the surgery, prophylactic Non Invasive Ventilation (NIV) was prescribed according to specific criteria previously described[4]. For the first 48 postoperative hours, or until discharge from ICU, pain was managed with both PCA morphine and nefopam 65 $\mu g.kg^{-1}.h^{-1}$ and pregabalin (150 mg) once a day for the first five postoperative days. When patients were discharged from ICU, they received

the same pain management protocol as in the MIAVR group. In ICU, volume status was assessed by transthoracic echocardiography. When patients were intubated, a bolus of 5 $ml.kg^{-1}$ of Plasma-Lyte solution was delivered when respiratory variations of the maximal Doppler velocity in the left ventricular outflow tract were found[13]. In spontaneously breathing patients, the same fluid loading was administered if respiratory variations of the inferior vena cava diameter were detected[14] and/or the result of a positive passive leg rising test[15]. If urinary output was less than 0.5 $ml.kg^{-1}.hr^{-1}$ and associated with hypovolemia, a bolus of 5 $ml.kg^{-1}$ of Plasma-Lyte was infused. On the contrary, if urinary output was less than 0.5 $ml.kg^{-1}.hr^{-1}$ and associated with hypervolemia, diuretics were prescribed. Four hours after extubation and when they had a PaO_2/FiO_2 ratio > 250, an O_2 saturation >92%, a MAP was > 60 mmHg with dose of norepinephrine below 0.1 $\mu g.kg^{-1}.min^{-1}$ without increment from the endotracheal tube removal, patients were invited to sit on a chair. From the moment patients were sit, they were asked to start incentive spirometry exercises. Nurses and physiotherapists were instructed to stop every activity of the ERAS protocol in case of hemodynamic instability occurrence (new onset of Atrial fibrillation, heat rate > 150, systolic blood pressure > 180 mmHg or < 85 mmHg) and call the attending intensivist. When patients were mobilized, we have applied the latest nonpharmacologic guidelines suggested to prevent postoperative delirium[16]. Patients were given oral fluid and offered a fluid meal 6-hour after extubation and a solid meal on postoperative day (POD)1 if tolerated. Urinary catheter and central venous line were removed on POD1. Until POD4, only a peripheral IV cannula was left in situ with no drip. Patients were discharged to the surgical floor as soon as they met the same criteria described in the MIAVR group. On POD1, patients were encouraged walking in their bedroom along with the presence of a physiotherapist. From POD2, patients were invited

walking in the corridor of the surgical ward along with a physiotherapist. From POD3, patients were invited to climb flight of stairs twice a day along with a physiotherapist.

Hospital discharge

For both groups the criteria for hospital discharge were: presence of sinus rhythm or persistence of the same rhythm traced by the EKG preopeartively, absence of infection, no rise in body temperature, hemoglobin greater than 8 $g.dl^{-1}$, normal white blood cell count, normal serum creatinine and electrolytes, unremarkable chest X-ray, unremarkable EKG, unremarkable transthoracic echocardiography, as well as having recovered an adequate mobility according to the physiotherapist. The same surgeon (P.O.) was responsible for discharging patients from hospital.

Outcome data

The primary outcome was postoperative hospital LOS, which was defined as the number of days spent in the hospital after surgery. Secondary outcomes were percentage of patients adhering to the protocol, number of patients extubated on the operating table, time to extubation after the last skin suture, reintubation for respiratory failure, postoperative pain scores, morphine consumption during the first two postoperative days, time to first flatus, postoperative infection, postoperative complication, all-cause ICU readmission, all-cause 30-day readmission, and intra-hospital death. Pain intensity was assessed using the Visual Analogue Scale (VAS) every 6 hours as long as patients were in ICU and then twice a day at rest and on coughing when transferred to the surgical ward. PCA morphine consumption was recorded every 6 hours as long as patients were in ICU. Patients were diagnosed having in-hospital urinary tract infection and surgical site infection according to international guidelines[17,18]. A postoperative bronchial congestion

clinically significant requiring a treatment with antibiotics by the attending intensivist was considered as a bronchopulmonary infection.

Statistical analysis

The sample size was calculated to detect a reduction of patients LOS scheduled to undergo an aortic valve replacement via a mini-sternotomy. In our institution, the average hospital stay for patients undergoing an aortic valve replacement via a mini-sternotomy was on average 10 days. Twenty-three patients per group would be necessary to detect a 30% reduction of the LOS in the ERAS group with a type-1 error of 5% and a power of 80%. All data collected were inserted in a private computer database. Data were then transferred to the XLSTAT for analysis (Addinsoft, XLSTAT Version 2016.02.27444, Paris, France). Results are presented as mean standard deviation (SD) when normally distributed, as median and [interquartile range] for nonparametric data and as proportions (%) for categorical data. Student's t test, Mann- Whitney U test, and Fisher's exact test were used according to their distribution and their scale. A *P*-value below 0.05 was considered statistically significant. Demographic and clinical variables were compared between the two groups. To control for the potential confounding effect all independent variables statistically significant in bivariate analysis were forced into a multivariable linear regression model to study the effect of such covariates on the primary endpoint.

Results

Twenty-three consecutive patients scheduled to undergo an aortic valve replacement via a mini-sternotomy were included in the "MIAVR traditional protocol of care" group and twenty-three consecutive patients were included in the "MIAVR-ERAS" group after a 4-month period of protocol implementation. The same surgeon (P.O.) performed all the mini-sternotomies. The cardiac anesthesia and intensive care clinicians in charge of patients during the study period remained unchanged. Patients' demographic and preoperative data were similar between the two groups except for a higher body mass index in the MIAVR group and more female in the MIAVR-ERAS group (Table 2). There was no significant difference in the mean surgical time, CPB time or aortic cross-clamp time between the two groups (Table 2).

Protocol compliance.

Each patient in the accelerated recovery pathway received counseling session with every stakeholder of the protocol and was able to watch the video describing the arrival in the OR. In contrast, no patient had counseling session in the traditional patient care protocol. Every patient in the traditional MIAVR group received a multimodal analgesia. However, only 3 out of the 8 agents integrating the multimodal analgesic ERAS protocol were used in the MIAVR group. The proportion of patient adhering to each items of the multimodal analgesia varied considerably (Table 3). Overall, adherence to the ERAS elements of the pathway were statistically more frequent in the MIAVR-ERAS group except for 5 out of the 19 items described in Table 3. Those five elements that did not reach a statistical difference between the two groups, were not consequent to poor protocol adherence but because it was already part of the common practice of some anesthesiologists before

implementation of the ERAS protocol. Five out of 14 patients (36%) and 9 out of 13 (69%) received preventive postoperative NIV in the MIAVR and in the MIAVR-ERAS group, respectively ($P = 0.180$).

Primary clinical outcome

Hospital LOS was significantly shorter in the MIAVR-ERAS group compared to the traditional MIAVR care group with 7 [6.5-8] days and 10 [9-13.5] days, respectively ($P < 0.001$). In the model built to adjust for possible confounding factors we found that significant covariables were the followings: patients with no postoperative infection (shorter stay, $P=0.002$) and patients adhering to the ERAS bundles adherence (shorter stay, $P=0.005$) (table 5).

Secondary clinical outcomes

Time to extubation was not significantly different between the two groups. However, it seems that there was a trend toward a faster extubation time in the MIAVR-ERAS group ($P=0.083$). Thirteen patients (57%) were extubated on the operating table in the MIAVR-ERAS group. During the postoperative ICU stay, morphine consumption in the MIAVR group was 7 [3–12] mg compared with 2 [0-12] mg in the MIAVR-ERAS group, ($P=0.090$) (Table 4). The highest median pain score tended to be higher in the MIAVR-ERAS group ($P=0.068$). However, the median average ICU pain was statistically greater in the MIAVR group ($P=0.030$) (table 4). No difference in the median pain score on the surgical ward was detected between the two groups. Time to first flatus was significantly shorter in the MIAVR-ERAS group compared to the MIAVR group with a median of 1[1-1.5] day and 1[1-2] day, respectively ($P = 0.035$). One patient was converted to full sternotomy during the surgical procedure in the MIAVR group. Another patient in the MIAVR group was brought back to the OR during his ICU stay because of significant

postoperative bleeding. No acute myocardial infarction, no stroke, no renal replacement therapy nor reintubation for respiratory failure was reported in any of the groups. Postoperative complication rates were similar between the two groups (Table 4). Taking into account only the pulmonary infection the difference between the two groups almost reached the statistical difference (P=0.060). Intensive Care Unit LOS was significantly shorter in the MIAVR-ERAS group compared to the other group (P=0.003). In the MIAVR group, 2 patients have been readmitted in ICU for respiratory failure secondary to cardiogenic pulmonary edema that did not require re-intubation. Two patients in the MIAVR group developed AKI stage 1. No patient has been readmitted in ICU in the MIAVR-ERAS group and none developed AKI. One patient died during the hospital stay in the MIAVR group (septic shock) and two patients were re-hospitalized before 30-day postoperatively in the MIAVR group for drainage of a pericardial effusion. There was no 30-day mortality and no 30-day hospital re-admission in the MIAVR-ERAS group.

Discussion

To the best of our knowledge, our trial is the first prospective investigation demonstrating that patients undergoing a MIAVR coupled with an ERAS pathway is feasible and could shorter both ICU LOS and hospital LOS. Although the postoperative recovery program started the same day of the surgery with early mobilization, incentive spirometry and respiratory exercises, patients following the accelerated recovery program had less postoperative pain. Also, patients in the MIAVR-ERAS group followed a trend toward earlier extubation time as well as a trend toward less postoperative all-cause infections.

Fast-track protocols in cardiac surgery aiming to extubate patients at an early stage postoperatively have been described since the early 1980's. The most recent meta-analysis including a total of 28 trial with more than 4400 patients did not demonstrate better postoperative outcome, shorter ICU LOS nor hospital LOS[19]. In light of the strong data showing the benefit of ERAS programs for patient outcome for many surgeries[20], it could be advocated that the cardiac fast-track protocol lacks postoperative advantages because no dedicated multidisciplinary perioperative pathways have been implemented. Therefore, after the extubation, this period of 'therapeutic silence' that does not incorporate early physiotherapy, early oral nutrition, early mobilization and early tube/line removal might explain why these cardiac fast-track protocols have failed to show any postoperative potential patients' benefit[21]. It has to be underlined that the implementation of an ERAS program for cardiac surgery is challenging considering the important heterogeneity of institutional practice and the unique sequence of the procedure requiring a CPB with an aortic cross-clamping. However, recent trials suggest that such

implementation is feasible and carries substantial postoperative advantages in terms of patient outcome[7,8]. Based on our previous experience in cardiac surgery[4], the key to success in implementing ERAS elements was building the program with a trans-disciplinary participation. Another fundamental feature of our protocol favoring an early postoperative recovery was to avoid benzodiazepine premedication, which could trigger delirium postoperatively[7]. Our preoperative anxiolytic strategy was rather based on preoperative patient counseling and education with video material coupled with tailored patient communication seems to reduce anxiety and also improve outcome after cardiac surgery[22,23]. We also used pregabalin for this purpose[24]. It seems that pregabalin could act as a sparing opiate agent after cardiac surgery[25,26] and has an antiemetic drug [27], which is an essential facet to help starting efficiently and rapidly the postoperative protocol.

The backbone of the pathway established during the preoperative period was strengthened pharmacologically and surgically during the intraoperative phase. Our results are in line with a recent trial analyzing specifically how a multimodal strategy could help to implement the other ERAS elements such as ultrafast-track extubation, reduced postoperative opiate consumption and shorter hospital stay[8]. However, in this trial, the average postoperative morphine consumption in the ERAS group was almost 15-fold higher than the average noted in our MIAVR-ERAS group. This noteworthy difference could be explained by our more extensive multimodal analgesia protocol but also by the association with a mini-invasive surgical technique to decrease significantly postoperative pain[28]. Nevertheless, how the minimally invasive cardiac surgical procedure could modulate the recovery process is still unknown[7]. To lower the inflammatory cascade, particular intraoperative elements were incorporated in the present ERAS cardiac bundle. First, we used a mini extracorporeal circuit, which has been shown

to be an independent predictor of early recovery after coronary artery bypass graft ABG with less blood transfusion, shorter duration of inotropic support and fewer AKI[29]. Second, ventilation with small tidal volume was maintained during CPB. This strategy seems to reduce the inflammation preventing alveolar collapse, atelectasis, and hypoxemia[30]. Another crucial element of our intraoperative ERAS bundle was the pre-emptive goal-directed fluid therapy echo-guided, which seems to reduce postoperative morbidity and hospital LOS in patients undergoing cardiac procedures[31].

Our findings suggest that the preoperative and intraoperative elements of our ERAS protocol offer appropriate conditions to start early mobilization, early feeding, and early physiotherapy compared to the standard protocol. As suggested by recent trials conducted in the cardiac setting[7-9], it is likely that the postoperative ERAS bundle established favored the earlier ICU discharge, the earlier hospital discharge as well as the trend toward less postoperative infections. Early mobilization is a fundamental element for fast recovery[32]. A recent randomized control trial conducted in patients undergoing major abdominal cancer surgery suggests that mobilization is an independent factor helping early functional capacity recovery[33]. On the other hand, our opioid-sparing approach in combination with early mobilization and early hospital discharge might have helped to diminish both delirium and postoperative cognitive dysfunction[34].

A 10-day length of stay might appear long compared to other institutions[35]. However, there are several reasons why our findings could be applicable to other centres. First, a 10-day length of stay after an open-heart surgery is the average in France. This average is similar to the one reported by a large cohort study conducted in a university hospital in Denmark that recorded a median length of stay of 9 days[36]. Second, there are centres reporting an average hospital length of stay greater than 14 days in octogenarians

undergoing coronary artery bypass graft surgery[37]. Our data are striking in that respect. Indeed, the median age of the patients in the MIAVR-ERAS group was 80 year-old, which was 7 years older than the patients in the MIAVR group. Thus, it could be advocated that our protocol is applicable for octogenarians scheduled for open-heart surgeries. On the other hand, it could be claimed that the length of hospital stay might depend on institutions practice, discharge location to dedicated post-acute care, procedure type and patients' age[37,38]. Independently of these considerations, implementing a cardiac ERAS protocol could be an essential asset to meeting hospital discharge criteria at an earlier stage in every institution and for every patient. Finally, ERAS protocols have been shown to reduce the hospital length of stay but also to lower significantly rates of postoperative complication and readmission[39]. The present investigation was not powered to find differences in that matter but we found a trend. Thus, our protocol could be applicable in other centres also for this purpose.

There were several limitations. The present study is a nonrandomized-controlled trial and the ERAS bundles were implemented concomitantly. Thus, it is difficult to define which elements of the protocol were responsible for the positive outcome reported in the MIAVR-ERAS group. However, no improvements of the scale presented in the current study have been implemented during the study period for the other cardiac surgery not even for aortic valve replacement performed via a full sternotomy using or not a rapid deployment aortic bioprosthesis. Therefore, it could be advocated that a quality of care improvement during the present trial is possible but unlikely. In fact, during the study period patients' average length of hospital stay undergoing all other cardiac surgery without an ERAS protocol did not change. It could be claimed that the

quality of care found only in our study population compared to the other patients operated during the same time frame is the result of the "aggregation of marginal gains" as described elsewhere[40]. In addition, prospective auditing is considered to be more prone to demonstrate efficacy than randomized investigations, which are impossible to blind and claimed to be unethical[5]. Nevertheless, randomized clinical trials have been conducted in the cardiac setting[9]. Another limitation is that the Hawthorne effect[5] might have affected the time of discharge from both ICU and hospital in the MIAVR-ERAS group. However, the discharge criteria were the same between the two groups. Also, implementation and adherence to the present ERAS program encompassing many elements required an increased workload from all the stakeholders. Conversely, it is possible to claim that a shorter ICU stay and shorter hospital stay could lower the cost related to the surgical procedure. The lower incidence of postoperative complications found in the MIAVR-ERAS group could also lower indirectly the cost related to the intervention. Despite not being strictly in line with the definition of a bronchopulmonary infection, our definition considered the present major public health issue represented by antibiotic resistance[41]. Hence, whether the infection was documented or not, the necessity to use antibiotics was deemed clinically more relevant than the occurrence of a documented infection per se. Furthermore, it is our intention to complement our protocol with new elements such as preoperative use of iron or rhEPO in anemic patients, shorten the fasting time, allow carbohydrate beverage intake 2-hour before anesthesia induction, implement a postoperative antiarrhythmic protocol and implement a goal direct perfusion strategy during CPB.

In conclusion, we showed a significant reduction in hospital length of stay after implementation of a dedicated cardiac enhanced recovery pathway for minimally

invasive aortic valve replacement. The present study suggests that this type of protocol for such intervention is feasible and could enhance the benefit of this surgical approach sublimating patient outcome. In the future, a MIAVR procedure associated with a dedicated ERAS protocol should be considered as a treatment option for high/intermediate risk patients considered in the grey zone between TAVI and surgery.

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Legend for Figure

Figure 1: Perioperative goal-direct fluid therapy protocol implemented in the MIAVR-ERAS pathway.

Fluid challenge with 3 $ml.kg^{-1}$:
Is there an increase in the left ventricular
outflow tract velocity time integral value greater than 10% ?
(Maintenance with crystalloid infusion at 2 $ml.kg^{-1}.Hr^{-1}$)

No

Yes

Is stroke volume index
> 35 $ml.m^{2-1}$?

Repeat fluid challenge

No

Yes

Is blood pressure
within 20% of base line value?

Reassess the volume loading every 5-10 minutes
throughout the procedure
(except during cardiopulmonary bypass)

No

Yes

Is cardiac index above
2.5 $l.min^{-1}.m^{2-1}$?

No

Yes

Begin inotropic agent

Start a continuous infusion of norepinephrine
(to obtain a mean arterial pressure > 65 mmHg)

Table 1: Bordeaux University Hospital MIAV-RERAS protocol

	MIAVR (n=23)	MIAVR-ERAS protocol (n=23)
Preoperative		
Counseling/Education	Absent	a - Meeting with a nurse: screening for tobacco use, comorbidities and explaining the pathway and our expectation regarding patients' involvement and engagement b - Meeting with a physiotherapist: explanation and training how the respiratory exercises are done properly, c - Meeting with a nutritionist: screening for malnutrition (with albumine, pre-albumine and C-reactive protein) and prescription of a diet if deemed necessary d - Booklet describing every step of the protocol to reduce anxiety and stress related to the surgery e - Video describing the patients arrival in the OR reduce anxiety and stress related to the surgery
Premedication	Benzodiazepines or hydroxyzine	No premedication allowed except for pregabalin the night before and on the morning of surgery if no contraindication
Intraoperative		
Multimodal analgesia	Physician's discretion	Protocol associating dexamethasone, acetaminophen, ketoprofen, nefopam, morphine, magnesium, ketamine, pregabalin
Surgical wound infiltration	No	20 mL of Ropivacaine 0.75%
Insertion of a pulmonary artery catheter	Physician's discretion	Exclusion of its usage
Surgical Technique	Mini-sternotomy for aortic replacement	Mini-sternotomy and aortic replacement with rapid deployment valve (INTUITY, Edwards Lifesciences, Irvine, CA, USA).
Type of CPB	No standardization	Minimal Extra Corporeal Circulation
Intraoperative ventilation strategy	No standardization	Protective lung ventilation intraoperatively based on the predicted body weight and during CPB
Intraoperative fluid therapy	Management based on changes in hemodynamics (arterial blood pressure and heart rate) and urine output	Goal directed therapy TEE- guided *
Transfusion threshold	Physician's discretion	Only when hemoglobin is below 7.2g.dl^{-1} during CPB
Postoperative		
Extubation criteria	Fast track criteria	As soon as the ultrafastrack extubation criteria were met**
Non pharmacologic strategies to reduce postoperative delirium	Absent	Application of the best practice statement from the American Geriatric society***
Mobilization	Mobilization on postoperative-day 3.	Mobilization on chair on the same day after surgery
Tubes removal	No protocol, urinary catheter and central venous line usually left at discharge from ICU. Chest tube removed at physician's discretion.	Urinary catheter if the urinary output was above 0.5 ml.h^{-1} for 6 consecutive hours with no diuretic prescribed and central venous line removed at discharge from ICU. Chest tubes removed when collecting less than 100 mL of blood in 8 hrs (no routine chest X-ray after drain removal).

*: See Figure 1

: Zaouter C, Imbault J, Labrousse L, et al. Association of Robotic Totally Endoscopic Coronary Artery Bypass Graft Surgery Associated With a Preliminary Cardiac Enhanced Recovery After Surgery Program: A Retrospective Analysis. *Journal of cardiothoracic and vascular anesthesia* 2015; **29: 1489-97

***: American Geriatrics Society Expert Panel on Postoperative Delirium in Older A. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. *Journal of the American College of Surgeons* 2015; **220**: 136-48 e1

Table 2:

Patients' characteristics and intraoperative data of interest.

	MIAVR (n=23)	**MIAVR- ERAS (n=23)**	**P-value**
Patients' characteristics			
Age, year	73(*68-82*)	80(*74-82*)	0.156
Female gender, n(%)	7(*30*)	14(*61*)	0.038
Body Mass Index, $kg.m^{-2}$	28(*26-32*)	26 (*23-27*)	0.022
Logistic EuroSCORE, %	6(*4-10*)	8(*6-11*)	0.410
History of stroke, n(%)	1(*4*)	2(*9*)	0.550
PVD, n(%)	3(*13.0*)	2(*9*)	0.636
COPD, n(%)	4(*17*)	2(*9*)	0.381
Diabetes, n(%)	7(*30*)	5(*22*)	0.502
Hypercholesterolemia, n(%)	9(*39*)	13(*56*)	0.238
Arterial hypertension, n(%)	18(*78*)	20(*87*)	0.437
History of smoking, n(%)	5(*22*)	7(*30*)	0.502
LVEF, %	60(*50-65*)	60(*58-70*)	0.224
Intraoperative Data			
Duration of anesthesia, (min)	240(*227-277*)	240(*225-260*)	0.494
Cross clamp time, (min)	53(*47-60*)	51(*48-55*)	0.275
CPB time, (min)	80(*73-90*)	81(*75-85*)	0.667
Number of patients transfused with RBC, n(%)	11(*48*)	13(*56*)	0.554

Data are expressed as mean±(Standard Deviation) or median (*interquartile* range) or n (% of patients). The P-value refers to comparison between groups (pre AVRERAS versus AVRERAS).

Abbreviations: MIAVR: mini invasive aortic valve replacement; MIAVR-ERAS: mini invasive aortic valve replacement - enhanced recovery after surgery; PVD: perivascular disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; CPB: cardiopulmonary bypass; RBC: red blood cells.

Table 3: Protocol compliance

	MIAVR (n=23)	MIAVR- ERAS (n=23)	P-value
Counseling			
Counseling with all the stakeholders, n(%)	0	23(100)	<0.001
Patients that watched a video describing their arrival in the OR, n(%)	0	23(100)	<0.001
Multimodal analgesic protocol compliance			
Patients that received pregabalin perioperatively, n(%)	2(9)	21(91)	<0.001
Patients that received remifentanil intraoperatively, n(%)	12(52)	17(74)	0.221
Patients that received magnesium intraoperatively, n(%)	0	23(100)	<0.001
Patients that received ketamine intraoperatively, n(%)	3(13)	10(43)	0.020
Patients that received dexamethasone intraoperatively, n(%)	2(9)	8(35)	0.032
Patients that received ketoprofen, n(%)	12(52)	15(65)	0.369
Patients that received nefopam, n(%)	17(74)	22(96)	0.04
Patients that received acetaminophen, n(%)	23(100)	23(100)	1
Patients that received wound infiltration with ropivacaine, n(%)	0	23(100)	<0.001
Other elements compliance			
Patients that received a rapid deployment prosthesis, n(%)	6(26)	23(100)	<0.001
Patients who underwent the CPB with a MECC circuit, n(%)	15(65)	16(70)	0.753
Patients transfused only when Hb level < 7.2 $g.dL^{-1}$during CPB, n(%)	3(13)	10(43)	0.020
Patients ventilated during CPB, n(%)	23(100)	23(100)	1
Patients following a GDT protocol for fluid therapy, n(%)	0	10(43)	0.020
Patients mobilized on chair on POD 0, n(%)	0	11(48)	<0.001
Patients that received their first postoperative meal on POD 0, n(%)	0	7(30)	0.004
Patients that had their transurethral catheter removed on POD 1, n(%)	0	22(96)	<0.001
Patients that had their central venous line removed on POD 1, n(%)	1(4)	17(74)	<0.001

Data are presented as frequency (proportion). The *P*-value refers to comparison between groups (MIAVR versus MIAVR-ERAS). Abbreviations: MIAVR: mini-invasive aortic valve replacement; MIAVR-ERAS: mini-invasive aortic valve replacement - enhanced recovery after surgery; CPB: cardiopulmonary bypass; MECC: minimal extracorporeal circulation circuit; NIV: non invasive ventilation; GDT: goal directed therapy; POD : postoperative day.

Table 4: Patient outcome of interest

Data are presented as median and interquartile range (IQR: 25th – 75th percentiles).
The p-value refers to comparisons between groups (MIAVR versus MIAVR-ERAS). Abbreviations: MIAVR: mini-invasive aortic valve replacement; MIAVR-ERAS: mini-invasive aortic valve replacement - enhanced recovery after surgery; ICU: intensive care unit ; UTI: urinary tract infection; SSI: surgical site infection;

	MIAVR (n=23)	**MIAVR-ERAS (n=23)**	**P-value**
Postoperative opioid consumption and pain scores			
Total postoperative morphine (mg)	7 (3-12)	2 (0-12)	0.090
Highest ICU pain score	4 (2-6)	5 (3-6)	0.680
Average ICU pain score	2 (2-3)	1.4 (0-2)	0.030
Average surgical ward pain score	0.5 (0-1)	0.5 (0-1)	0.320
Postoperative complications			
Overall infections, n(%)	9(39)	4(17)	0.098
UTI	1(4)	1(4)	1
SSI	1(4)	1(4)	1
Pulmonary infection	7(30)	2(9)	0.060
New onset of atrial fibrillation, n(%)	6(26)	9(39)	0.345
ICU Readmission, n(%)	2(9)	0	0.148
Hospital readmission within 30-day of surgery, n(%)	2(9)	0	0.148
Number of patients developing AKI, n(%)	2(9)	0	0.148
Length of stay in ICU and Hospital			
ICU length of stay (hours)	28(25-47)	24(24-28)	0.003
Hospital length of stay (days)	10(9-13.5)	7(6.5-8)	<0.001

Table 5: Multivariate linear regression on Hospital Length of Stay

	Value	Std err	T test	P-value	CI (95%)
Age	0.044	0.169	0.263	0.795	-0.305; 0.394
Patient with infection	0.448	0.177	2.526	0.019	0.081; 0.814
Body Mass Index	-0.100	0.177	-0.566	0.577	-0.466; 0.265
Female gender	0.003	0.156	0.019	0.985	-0.321; 0.326
ERAS bundles adherence	-0.637	0.204	-3.116	0.005	-1.060; -0.214
Early mobilization	-0.200	-0.203	-0.984	0.331	-0.612; 0.212
Early urethral catheter removal	0.330	0.226	1.456	0.159	-0.138; 0.798

Data are presented as Value of the regression coefficient, Standard Error (Std err) of the regression equation, T test of the linear regression model, and the probability (*P*-value) that a linear relation exists between the studied variable and the Hospital Length of Stay.
The relation is said to be significant between the independent variable and the Hospital Length of Stay when the *P*-value is under 0.05.
Abbreviations: MIAVR-ERAS; Mini-invasive Aortic Valve Replacement - Enhanced Recovery After Surgery.