

Effect of opioid-free anaesthesia on post-operative period in cardiac surgery: a case-control study

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Abstract

Background No study has demonstrated feasibility and improvement of opioid free anaesthesia in cardiac surgery. The objective of the present study was to evaluate the effect of opioid-free anaesthesia (OFA) on post-operative morphine consumption and the post-operative course. **Methods** We performed a retrospective matched cohort study (1:1) in cardiac surgery with cardiopulmonary bypass. Patients were divided into two groups: OFA or opioid anaesthesia (OA). The main outcome was the cumulated total morphine consumption during the 48 post-operative hours. The secondary outcomes included rescue analgesics, a major adverse event composite endpoint, and the length of stay (LOS) in the ICU and in hospital. **Results** 110 were matched (OFA: n=55; OA: n=55). On inclusion, OFA and OA groups did not differ significantly in terms of demographic and surgical data. The total morphine consumption was higher in the OA group than in the OFA group (15 (6-34) mg vs 5 (2-18) mg, p=0.001). Analgesic rescue did not differ between the two groups. The pain score during the first 48 post-operative hours did not differ between the two groups. Incidence of the composite endpoint was lower in the OFA group (25 patients (43%) vs 38 patients (68%), p=0.021) in relation to lower use of non-invasive ventilation (15% vs 49%, p=0.032). The time to extubation and the ICU stays were shorter in the OFA group (3 (1-5) vs 5 (3-6) hours, p=0.001 and 2 (1-3) vs 3 (2-5) days, p=0.037). **Conclusion** The use of an OFA was associated with a decreased consumption of morphine and shorter ICU stays. Further randomized studies are needed to confirm these results.

Background

Since the 1960s, the systematic administration of opioids has been considered one of the pillars of modern anaesthesia. The use of opioid analgesics has become widespread with the development of administration systems based on "target concentration", and the development of new opioid agents [1]. However, the principle underlying the administration of opioids during anaesthesia has never been called into question [2]. The concept of opioid free anaesthesia (OFA) is based on the fact that in an anesthetised patient a sympathetic reaction marked by hemodynamic changes does not systematically reflect a painful phenomenon. In addition, a painful phenomenon in a sleeping patient may not be memorized, while hormonal stress as well as sympathetic and inflammatory reactions can be controlled by therapeutic classes other than opioid agents [3]. In non-cardiac surgery, an increasing amount of literature has been published on OFA, demonstrating a decrease of post-operative morphine consumption and improvement of postoperative well being [4–7]. Several OFA protocols have been published [8]. The most commonly used agents are lidocaine, [dexmedetomidine](#), corticoid, and ketamine. All these agents have been separately studied in cardiac surgery in the context of their cardioprotective and/or neuroprotective effects with conflicting results [9–11]. Studies on lidocaine demonstrated a cardioprotective effect with a decrease of rhythmic disorders, and a neuroprotective effect with a non-constant improvement in postoperative cognitive functions. All these studies were performed with opioid anaesthesia (OA). In non-cardiac surgery, OFA was demonstrated to be associated with better intraoperative hemodynamic stability, lower post-operative opioid use, and better respiratory recuperation

[4–7]. In cardiac surgery, no studies have evaluated the feasibility and the effect of OFA on morphine consumption and the post-operative course. Since 2017, our institution regularly performs OFA using lidocaine, ketamine and dexamethasone.

The main objective of the present study was to demonstrate that compared with OA, OFA lowers morphine consumption. In addition, we evaluated the effect of OFA on operative hemodynamic stability, postoperative complications assessed by a composite criterion and the length of stay (LOS) in the ICU and in hospital.

Methods

Patients

We performed a retrospective, open-label, matched (1:1), single-centre study in a tertiary university medical centre (Dijon, France) between 2018 and 2019 (ClinicalTrials.gov Identifier: NCT02479529). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. As the study was observational, and used existing, routinely collected data, informed consent was not required from the subjects. The present report was drafted in line with the STROBE statement [12].

The main inclusion criteria were as follows: age 18 or over, cardiac surgery with the use of cardiopulmonary bypass (CPB) (coronary artery bypass grafting (CABG), the surgical correction of valve disease (aortic, mitral), combined surgery (CABG and valve disease), aorta ascendant disease, and left ventricular assist device implantation). The main non-inclusion criteria were off pump cardiac surgery, preoperative painkiller use, gabapentin use, antidepressive therapy and preoperative cognitive dysfunction.

Operative management

Maintenance or withdrawal of preoperative medications followed international guidelines. Anaesthesia and cardiopulmonary bypass procedures were standardised for all patients. At induction all patients received ketamine (0.3–0.5 mg kg⁻¹). In the OA group, anaesthesia was induced with propofol (0.4–2 mg kg⁻¹) and sufentanil (0.5 ng ml⁻¹) until the loss of eyelash reflex. Sufentanil was continuously administered using the Schnider target-controlled infusion model. In the OFA group, anaesthesia was induced with dexamethasone (0.1 mg kg⁻¹), lidocaine (1.5 mg kg⁻¹ bolus 15 minutes before the start of propofol) and propofol (0.4–2 mg kg⁻¹) until the loss of eyelash reflex. Lidocaine was continuously administered at 1.5 mg kg⁻¹ h⁻¹. In both group, tracheal intubation was facilitated with cisatracurium (0.15 mg kg⁻¹). Sufentanil and lidocaine were stopped at the end of the surgery. In both groups, anaesthesia was maintained by target-controlled infusions of propofol (started at 2–4 ng ml⁻¹). Titration of sedation was based on the bispectral index (Covidien, Boulder, CO, USA), and aimed to obtain a value between 40

and 60. Arterial hypertension (systolic arterial pressure > 140 mmHg) was treated with esmolol in case of tachycardia (heart rate >80 bpm) or urapidil/nicardipine in case of heart rate < 80 bpm.

Cardiopulmonary bypass with a heart-lung machine (Stockert Sorin S5 Heart Lung, Milan, Italy) was performed at a target blood flow of $2.4 \text{ l min}^{-1} \text{ m}^{-2}$. The mean arterial blood pressure (MAP) was maintained at more than 65 mmHg by increasing the pump flow rate or, if then required, by administering a bolus of phenylephrine (100 mg) or norepinephrine (5 mg). The priming fluid of the CPB circuit contained 1500 ml crystalloids (Plasma-Lyte®; Baxter, Lessines, Belgium) and 5000 ui of heparin. After systemic heparinization (300 UI kg^{-1}) to obtain a hemocron level of 400 sec, median sternotomy or thoracotomy, aortic and right auricular cannulations were started. Myocardial protection was ensured with multidose intermittent antegrade cold blood cardioplegia (via the aortic root every 15 minutes), or custodiol or Delnido. During aortic cross clamp, moderate hypothermia ($32\text{-}34^{\circ}\text{C}$) was maintained. Normoglycemia (arterial blood glycemia < 10 mmol^{-1}) was maintained using intravenous insulin (intravenous bolus of 5-10 ui) if necessary. Homologous red blood cell transfusions were given to patients with a haemoglobin value below 8 g dl^{-1} . Heparin was reversed with protamine on a 1:1 ratio. All OA patients had loco-regional analgesia by serratus anterior plane block (thoracotomy, levobupivacaine 0.125 mg ml^{-1} , 0.5 ml kg^{-1}) or a parasternal continuous infusion of a local anaesthetic (sternotomy, levobupivacaine 0.125 mg ml^{-1} continuous infusion 8 ml h^{-1} during 48 hours). ICU management

At the end of surgery, all patients were sedated and the lungs were mechanically ventilated until haemodynamic stability and normothermia were obtained and blood loss was considered acceptable (less than $1 \text{ ml kg}^{-1} \text{ h}^{-1}$). Tracheal extubation was carried out according to the French guidelines [13]. Patients were treated by physicians trained in postoperative cardiac surgical care, including a cardiologist. Circulatory support was guided by institutional protocols to achieve predefined end-points: mean arterial pressure more than 65 mmHg, cardiac index more than $2.2 \text{ l min}^{-1} \text{ m}^{-2}$, and urine output more than $0.5 \text{ ml kg}^{-1} \text{ h}^{-1}$.

Analgesia was standardized and comprised of intravenous paracetamol (1 g every 6 hours) and patient controlled morphine analgesia. Before extubation, all patients received 1 g of acetaminophen and titration of intravenous morphine with a bolus of 2 to 3 mg until a pain visual analogue scale below 3 was achieved. Then patient controlled analgesia morphine was set up with the following parameters: 1 mg bolus, refractory period of 7 min, maximum dose of 20 mg every 4 h and without continuous infusion. The use of complementary analgesics was left to the discretion of the physician. Complementary analgesia comprised the use of ketoprofen (50 mg), tramadol (50 mg), and nefopam (20 mg). Pain was assessed every 4 hours during the ICU stay by using the pain visual analogue scale. The patients' electrocardiogram, pulse oxygen saturation and central venous blood pressure were continuously monitored. The scheduled blood tests included arterial/venous blood gas measurements on admission to the ICU, and then several times a day on request by the attending physician.

All data was continuously recorded in the institutional data base. The following variables were recorded: age, gender, body weight, height, personal medical history, ASA score, EuroSCORE2, Euroscore, type of cardiac surgery, the preoperative left ventricular ejection fraction, the duration of CPB, the duration of aortic clamping, the need for intraoperative blood transfusion, norepinephrine, dobutamine, the use of an antihypertensive agent (nicardipine, urapidil), the use of a short acting beta-blocker (esmolol), troponin values, creatinine value, time to extubation (hours), any occurrence of complications during the stay in the ICU or in the hospital, and the LOS in the ICU.

The primary endpoint was total cumulated morphine dose during the first 48 hours in milligrams. The secondary endpoints were: analgesic rescue, a composite endpoint of major adverse events (new onset of atrial fibrillation or flutter, second or third atrio-ventricular blockade, stroke, acute renal failure, confusion, reintubation, non-invasive ventilation support, and death in hospital), fluid expansion (ml), total propofol dose (mg), antihypertensive agent use, vasoplegic syndrome, catecholamine use, troponin Ic (ng ml⁻¹), creatinine (mmol l⁻¹), length of stay in ICU (in days), and length of stay in hospital (in days). The secondary composite endpoint was assessed during the hospital stay. All data was extracted from our institutional data base and collected by a physician (Alexandra Spitz) not working in the cardiac surgery anaesthesia-critical care department.

Statistical analysis

The trial was designed to investigate the potential superiority of OFA in terms of morphine consumption. According to the studies of Berthoud et al, we calculated that 55 patients per group would be able to demonstrate a difference of 10 mg of morphine consumption (with a mean consumption of 18 mg) with a power of 0.8 and an alpha risk of 0.05 [14, 15]. Based on known factors associated with postoperative pain and operative course, the database was matched (1:1) on age, body mass index, Euroscore 2, and type of surgery (sternotomy/thoracotomy) [16, 17]. The normality of the data distribution was assessed using the Shapiro-Wilk test. Data are expressed as the median (interquartile range). For comparisons of matched continuous variables, the Wilcoxon test was used. For comparisons of categorical variables, the Cochran-Mantel-Haenszel test with odds ratio (OR) [15]. The threshold for statistical significance was set to $p < 0.05$. Statistical analyses were performed with SPSS 24 (IBM, France).

Results

Of the 931 patients operated during the study period, 110 were matched and analysed (Figure 1). The intervention and control groups did not differ significantly in their demographic characteristics and cardiac surgery type (Tables 1 and 2). In the overall study population, the mean age was 69 (63-74) years (males: n= 78), the median EuroSCORE2 was 1.6 (0.89-3.01) and the median EuroScore 6 (4.9-8.3).

Analgesia evaluation

The postoperative total morphine dose differed between the two groups: 5 (2 to 18) mg vs 15 (6-34) mg, $p = 0.001$ (Table 3). Complementary analgesia did not differ between the two groups: ketoprofen (18% vs

16%, OR=1.136, p=1), nefopam (20% vs 13%, OR=1.714, p=0.441), and tramadol (31% vs 31%, OR=1, p=1) were used in equal measure in both groups. The pain score did not differ between the two groups (Table 3).

Secondary endpoints

Operative data differed in terms of vasopressor use, antihypertensive drug use, and total fluid infused (Table 2). The time to extubation was shorter in the OFA group (3 (1-5) vs 5 (3-6) hours, p=0.001) (Table 3). The OFA group differed in terms of the composite endpoint incidence (25 patients (43%) vs 38 patients (68%), OR= 0.373, p=0.021) with a lower use of non-invasive ventilation (27% vs 49%, OR=0.389, p=0.032). Incidence of cardiac and renal outcomes did not differ between the two groups. The OFA group had shorter ICU stays (2 (1-3) vs 3 (2-5), p=0.037) whereas the length of the hospital stay did not differ (8 (7-15) vs 10 (8-14), p=0.790).

Discussion

The main results of the present study are: (1) OFA was associated with lower morphine consumption; (2) OFA was associated with a higher operative use of vasoactive agents (antihypertensive and vasopressor); (3) OFA was associated with a decrease of orotracheal intubation time and the use of non-invasive respiratory support; (4) OFA was associated with shorter ICU stays.

To date, no study on OFA in the cardiac surgery area has been published. Only two case reports, and one retrospective study in thoracic surgery have been published [5, 18, 19]. In non-cardiac surgery, studies have already demonstrated decreased postoperative pain scores and opioid consumption with OFA [4, 6, 7]. In cardiac surgery, only studies evaluating loco-regional analgesia have demonstrated a decrease in morphine consumption [20]. Despite its retrospective design, the present study confirmed the feasibility of OFA in cardiac surgery. Because OFA is based on the avoidance of opioids by a multimodal analgesic treatment, it is associated with lower postoperative morphine consumption. The pain score did not differ between the two groups, which shows that analgesia was equivalent between OA and OFA. One question remains: what is the analgesic effect of OFA during surgery [21]? When we began using OFA in our institution, we monitored analgesia by measuring pupillary reflex dilatation. We noted that in most cases, patients had low values during nociceptive stimulus.

We performed OFA by using lidocaine, ketamine, dexamethasone and rescue therapy with beta-blockers (esmolol) and/or antihypertensive agents (urapidil, nicardipine). The choice of lidocaine was based on the literature published since the 1990s. It appears that lidocaine administered during cardiac surgery may have several effects, the most relevant being; (a) an anti-inflammatory effect; (b) the improvement of the cardioprotective effect of cardioplegia; (c) the decrease of arrhythmia; and (d) the decrease of early postoperative cognitive dysfunction by decreasing brain inflammation [9–11]. These effects may depend on the total dose with detrimental effects of high doses of lidocaine [22]. To date, we have not observed clinical signs of local anaesthetic toxicity with our protocol, which confirms existing data on lidocaine

plasma level. One patient suffered a seizure in relation to a stroke. We did not use dexmedetomidine in our protocol because this agent is not available in our operating room. The use of an α_2 agent may have several advantages. The combination of dexmedetomidine with lidocaine was demonstrated to provide better postoperative pain relief than the use of each agent alone [23]. In cardiac surgery, a recent meta-analysis confirmed the benefit of dexmedetomidine on hemodynamic stability during surgery with less tachycardia and arterial hypertension [24]. Moreover, studies suggest a positive effect on confusion and atrial fibrillation, with a shorter time to extubation and shorter ICU length of stay [25, 26]. According to the literature, the combination of lidocaine and dexmedetomidine should improve hemodynamic stability and decrease the use of antihypertensive agents.

We demonstrated lower intubation time and use of non-invasive ventilation. Respiratory effects may be explained by the avoidance of opioids and better pain relief. In our experience, patients anesthetized with OFA have a shorter period of respiratory inhibition during surgery than patients anesthetized with opioids. Spontaneous breathing returns sooner with OFA, and patients seem more quickly vigilant after orotracheal extubation than patients treated with OA. Oxygen requirements and non-invasive ventilation was lower in the OFA group. These effects may be in relation with the depressive effects of opioids on respiratory and cognitive functions that are well studied and known [6, 27].

The OFA group was associated with higher hemodynamic events, especially a higher use of vasoactive agents. We observed a trend to higher use of norepinephrine, especially during CPB. These findings were not associated with an increase of fluid infusion or a higher incidence of post-operative vasoplegic syndrome. On contrary, the amount of fluid infused was lower in the OFA group. These observations may be explained by two main factors: the half-life of urapidil/nicardipine (mostly used before CPB), and the vasoactive effect of lidocaine. None of the published studies on lidocaine during cardiac surgery have reported hemodynamic alteration. Lidocaine is known to have a concentration dependent biphasic effect on vascular smooth muscle; with vasoconstrictive effects at low concentration and vasodilation effects at high concentration [28, 29]. Based on literature, the dosage regimen of the present study may be associated with low to moderate plasma values of lidocaine [22]. Because blood pressure may be high, physicians frequently use anti-hypertensive agents that may increase vasopressor use during the CPB. As explained above, adding dexmedetomidine could limit the use of anti-hypertensive agents.

In summary, we demonstrated the feasibility of OFA with a decrease in opioid consumption. Keeping in mind the retrospective nature of the study, we were able to demonstrate OFA as an alternative technique associated with improvement of the postoperative course (analgesia, respiratory function, and ICU stays). Nevertheless, OFA was associated with a higher use of vasoactive agents during surgery.

The present study had several limitations. Firstly, our study was a single retrospective study with all the limitations of such a design. Despite protocol management for sedation and analgesia, bias could be introduced by the attending physician and nursing staff. The same limitations exist for non-invasive ventilation. Only controlled prospective randomized studies can confirm the present results. Moreover, further studies are needed to determine optimal association, dosages, and modality of infusion during

cardiac surgery. Secondly, the relatively small number of patients might also limit our study's external validity. Nevertheless, we calculated a sample size basing on morphine consumption because it has been demonstrated to be associated with OFA. Thirdly, we included a mixed cardiac surgery population. We believe our results demonstrate the feasibility of OFA in several cardiac surgery subtypes. Our team daily performs OFA in cardiac surgery without any restrictions other than contraindications to lidocaine use.

Conclusions

The present study demonstrated the feasibility of OFA in cardiac surgery with CPB. The use of OFA was associated with a decrease of postoperative morphine consumption, and shorter ICU stays. Our results provide clinical evidence for potential additional positive effects of OFA on the post-operative course following cardiac surgery with CBP. Further randomized studies are need to confirm these results.

Abbreviations

CPB; cardiopulmonary bypass, LOS; lenght of stay, MAP; mean arterial pressure, OA; opioid anesthesia, OFA; opioid free anesthesia, ICU: intensive care unit

Declarations

Acknowledgements

None

Competing interest

The authors declare that they have no competing interests. Pr Guinot Pierre-Grégoire works as associated editor member for BMC anesthesiology.

Authors contribution

Study design: PGG. Data acquisition: AS. Data analysis: PGG, MN. Data interpretation: PGG, OE, VB, MR, TC, AM, JBA, JPP, JPM. Manuscript preparation: PGG, MN, BB, NN. Manuscript revision: all authors. Final approval: all authors.

All authors read and approved the manuscript.

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Ethics Approval and Consent to Participate

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. As the study was observational, retrospective, and used existing, routinely collected data, informed consent was not required from the subjects. According to French Law, we did not need ethic approval (Loi Jardé 5 mars 2012), and we have followed the MR004 (méthodologie de référence 004). The study was recorded to clinical trial gov as ***NCT03816592***.

Availability of data and materials

All data and related metadata underlying the findings reported in our study are provided as part of the submitted article. Additional data is available on reasonable request from the corresponding author.

Consent for publication

NA

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Tables

Table I. Demographic characteristics. Data are expressed as median (25th to 75th percentiles), or number (%).
The p-value always refers to comparison between the OFA group and the OA group.

Variables	OFA group (n=55)	OA group (n=55)	P-value
Age, (years)	69 [62-74]	69 [65-74]	0.066
Gender (M), n (%)	43 (78)	35 (64)	0.115
Body mass index (kg m ⁻²)	26 [24-30]	26 [23-30]	0.162
ASA, n (%)			
2	3 (5)	7 (12)	
3	41 (75)	38 (69)	
4	11 (20)	10 (19)	
EuroSCORE II (%)	1.51 [0.98-3.1]	1.69 [0.87-3.01]	0.805
Euroscore (%)	6 [5-9]	6 [3-8]	0.238
Medical history, n (%)			
Coronary disease	31 (56)	27 (49)	0.571
Arrhythmia	8 (14)	13 (24)	0.332
Dyslipidaemia	31 (56)	34 (62)	0.556
Smoking history	23 (42)	19 (35)	0.556
High blood pressure	42 (76)	43 (77)	1
Diabetes	15 (27)	15 (27)	1
Chronic renal insufficiency	12 (22)	7 (13)	0.276
Stroke	4 (7)	4 (7)	1
Obstructive sleep apnoea	7 (13)	7 (13)	1
Treatment, n (%)			
Beta blocker	34 (62)	34 (62)	1.00
Calcic channel blocker	9 (16)	6 (11)	0.581
Aspirin	32 (58)	28 (49)	0.596
Clopidogrel	2 (4)	6 (11)	0.261
Angiotensin enzyme converting inhibitor	21 (38)	23 (42)	0.832

Statin	32 (58)	34 (62)	0.832
Diuretics	21 (38)	19 (35)	0.850
Left Ventricular Ejection Fraction (%)	60 [51-65]	60 [50-65]	0.278
Creatinine (mmol l ⁻¹)	83 [72-96]	84 [70-98]	0.558

Table 2. Operative characteristics. Data are expressed as median (25th to 75th percentiles), or number (%). *The p-value always refers to comparison between the OFA group and the OA group.*

Variables	OFA group (n=55)	OA group (n=55)	OR (CI _{95%})	P-value
Type of surgery				
Valvular surgery	20 (34)	22 (38)		0.806
Coronary artery bypass graft	11 (22)	9 (19)		0.845
Combined	21 (38)	21 (38)		1
Ascending aorta	1 (2)	1 (2)		1
LVAD	2 (4)	2 (4)		1
Sternotomy/thoracotomy	40/15	39/16		1
Urgent, n (%)	13 (23)	10 (18)		0.641
Anaesthesia time (min)	303 [268-360]	308 [288-360]		0.409
Cardiopulmonary bypass time (min)	118 [102-148]	119 [101-149]		0.505
Aortic cross clamp time (min)	84 [66-119]	94 [72-114]		0.383
Cardioplegia, n (%)				
<i>Blood</i>				
<i>Delnido</i>	29 (54)	25 (46)	1.338 (0.632-2.832)	0.569
<i>Custodiol</i>	15 (27)	17 (31)	0.838 (0.368-1.911)	0.834
	8 (14)	10 (18)	0.766 (0.277-2.115)	0.798
Propofol (mg)	1351 [922-1840]	1145 [740-1634]		0.008
Sufentanil (gamma)	0	89 [75-120]		0.0001
Anti hypertensive agents, n (%)				
<i>Urapidil</i>				
Median dose (mg)	28 (50)	12 (22)	3.716 (1.620-8.522)	0.003
<i>Nicardipin</i>				
Median dose (mg)	15 (10-20)	10 (5-15)		0.713
	6 (11)	10 (18)	0.551 (0.185-1.639)	0.419
	1.5 (1-2)	1 (0.5-2.5)		0.157
Vasopressor, n (%)				
Ephedrine				

<i>Median dose (mg)</i>	28 (51)	40 (73)	0.389 (0.176-0.861)	0.032
<i>Phenylephrine</i>				
<i>Median dose (mg)</i>	15 (9-28)	26 (15-30)		0.130
<i>Norepinephrine</i>				
<i>Median cumulated dose (mg)</i>	36 (67)	31 (56)	1.467 (0.679-3.168)	0.588
	0.275 (0.15-0.5)	0.35 (0.2-0.55)		0.272
	40 (73)	30 (55)	2.222 (1.002-4.927)	0.076
	1.24 (0.35-2.4)	1.34 (0.41-2.46)		0.092
Esmolol, n (%)	11 (20)	1 (2)	13.5 (1.677-108.652)	0.006
<i>Median dose (mg)</i>	30 (10-46)	73 (73-73)		
Dobutamine, n (%)	7 (13)	8 (15)	0.857 (0.288-2.551)	1
Total fluid administration				
<i>Cumulated in ml</i>				
<i>Cumulated in ml kg⁻¹</i>	1250 [1000-1500]	1500 [1000-2000]		0.060
	15.2 [10.7-21.4]	21.4 [12.5-27.7]		0.015
Transfusion, n (%)	13 (24)	13 (24)	1 (0.439-2.277)	1

Table 3: Post-operative course. Data are expressed as median (25th to 75th percentiles), or number (%). *The p-value always refers to comparison between the OFA group and the OA group.*

Variables	OFA group (n=55)	OA group (n=55)	OR (CI _{95%})	P-value
Total morphine consumption (mg)	5 (2-18)	15 (6-34)		0.001
Additional analgesic (n, %)				
<i>Tramadol</i>	17 (31)	17 (31)	1 (0.445-2.245)	1
<i>Total median dose (mg)</i>	150 (50-262)	125 (50-263)		1
<i>Ketoprofen</i>	10 (18)	9 (16)	1.136 (0.422-3.056)	1
<i>Total median dose (mg)</i>	100 (50-150)	100 (50-150)		0.441
Nefopam	11 (20)	7 (13)	1.714 (0.611-4.812)	0.317
<i>Total median dose (mg)</i>	40 (20-100)	20 (20-33)		
Visual analog score				
<i>Extubation</i>	0 (0-2)	0 (0-3)		0.324
<i>12 hours after ICU admission</i>	0 (0-0)	0 (0-1)		0.777
<i>First postoperative day</i>	0 (0-2)	0 (0-2)		0.665
<i>Second postoperative day</i>	0 (0-2)	0 (0-2)		0.874
Vomiting (n, %)	5 (9)	9 (16)	0.511 (0.160-1.637)	0.393
Creatinine (mmol l ⁻¹)				
<i>at admission to ICU</i>	83 [72-106]	76 [64-91]		0.105
<i>on first postoperative day</i>	80 [66-115]	77 [69-95]		0.284
Troponin Ic (ng ml ⁻¹)				
<i>at admission to ICU</i>	6.2 [3.7-10]	7.5 [2.9-20]		0.091
<i>24 hours after surgery</i>	4.7 [2.6-8.2]	7 [3.1-16]		0.091
PaO ₂				
<i>at admission to ICU</i>	162 [113-195]	155 [114-181]		0.479
<i>24 hours after surgery</i>	99 [83-122]			0.084

FiO ₂		115 [89-138]		
<i>at admission to ICU</i>	50 [30-60]			0.005
<i>24 hours after surgery</i>	28 [25-32]			0.018
PaO ₂ /FiO ₂ ratio		50 [50-60]		
<i>at admission to ICU</i>	357 (275-458)	32 [30-36]		0.006
<i>24 hours after surgery</i>	355 (261-420)	290 (213-372)		0.919
		322 (265-435)		
Time to extubation (hours)	3 [1-5]	5 [3-6]		0.001
Catecholamine use, n (%)				
<i>Norepinephrine</i>	26 (32)	31 (38)	0.694 (0.328-1.471)	0.447
<i>Dobutamine</i>	9 (16)	9 (16)	0.766 (0.277-2.115)	0.798
Transfusion, n (%)				
<i>Red blood cell</i>	16 (29)	18 (33)	0.843 (0.375-1.895)	0.837
Endpoint composite score, n (%)	25 (43)	38 (66)	0.373 (0.171-0.813)	0.021
<i>Confusion</i>	4 (7)	10 (19)		0.151
<i>Stroke</i>	1 (2)	0	0.353 (0.103-1.204)	1
<i>Seizure</i>	1 (2)	0		1
<i>Atrial fibrillation,</i>	15 (27)	22 (40)		0.228
<i>Ventricular tachycardia or fibrillation</i>	1 (2)	3 (5)	0.563 (0.252-1.254)	0.599
<i>Atrio-ventricular block requiring pacemaker implantation</i>	2 (4)	1 (2)		1
<i>Acute renal failure</i>			0.315 (0.032-3.125)	
<i>Reintubation</i>	12 (22)	14 (26)	2.038 (0.179-23.151)	0.823
<i>Non-invasive ventilation</i>	1 (2)	3 (6)		0.612

<i>Mortality</i>	15 (27)	27 (49)		0.032
	1 (2)	1 (2)	0.817 (0.338-1.974)	1
			0.321 (0.032-3.186)	
			0.389 (0.176-0.861)	
			1 (0.061—16.401)	
ICU stays (days)	2 [1-3]	3 [2-5]		0.037
Hospital stays (days)	8 [7-15]	10 [8-14]		0.790

Figures

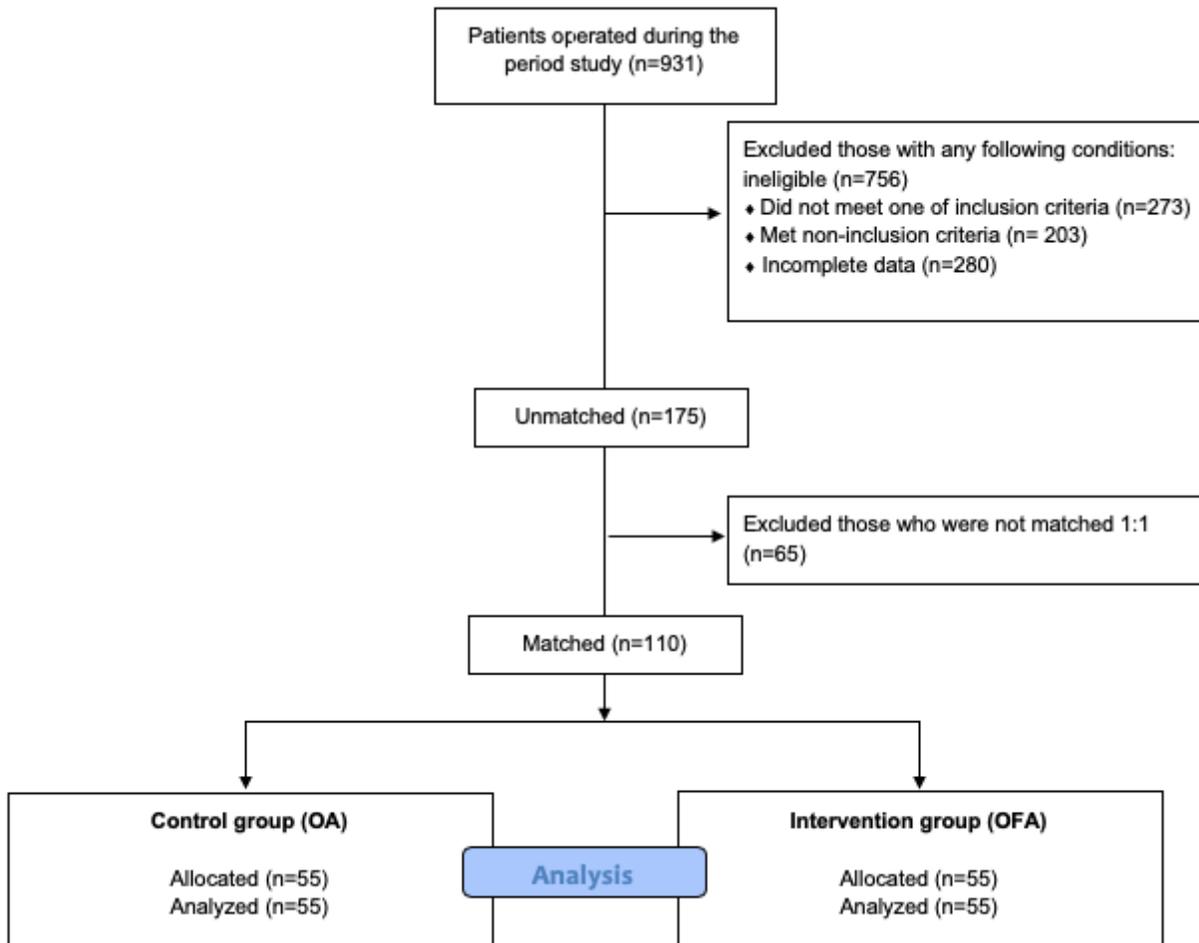


Figure 1

Flow chart diagram

Supplementary Files

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