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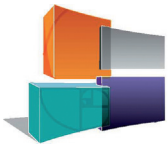

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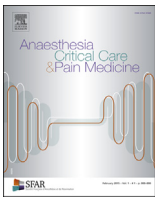

Original Article

# Effect of opioid-free anaesthesia on postoperative epidural ropivacaine requirement after thoracic surgery: A retrospective unmatched case-control study

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ABSTRACT

*Introduction:* Patients undergoing thoracic surgery are at risk of severe postoperative pain. Post-thoracotomy pain relief is usually provided with thoracic epidural analgesia (TEA). Intraoperative use of opioids may result in hyperalgesia and increase analgesics consumption. We investigated the effect of opioid-free anaesthesia (OFA) on epidural ropivacaine requirement after thoracotomy.
*Methods:* This retrospective study compared postoperative epidural ropivacaine requirement of patients undergoing open thoracotomy and receiving either opioid-based anaesthesia (OBA group) or a non-opioid regimen including clonidine, ketamine and lidocaine (OFA group). All patients received postoperative multimodal analgesia including both epidural analgesia and intravenous analgesics. The primary outcome was the cumulative first 48 postoperative hours epidural ropivacaine consumption. Secondary outcomes included postoperative pain scores, requirement for postoperative morphine titration, total opioid analgesics consumption within the first 48 postoperative hours, incidence of nausea and vomiting, intraoperative haemodynamic.
*Results:* From January 2015 to February 2018, 50 patients received an OBA and 25 received an OFA. The cumulative first 48 postoperative hours epidural ropivacaine consumption was significantly higher in the OBA-group (919 ± 311 mg versus 693 ± 270 mg, $P = 0.002$). Numerical Rating Scale at 6 and 24 h were significantly lower in the OFA-group (1[0–2] versus 3 [1–5], $P = 0.0005$ and 1[0–2] versus 3.5 [1–5], $P = 0.001$). In post-anaesthesia care unit, the proportion of patients requiring morphine was significantly higher in the OBA-group (42% versus 4%, $P < 0.001$). During anaesthesia, the OBA-group required more vasopressor support, while there were more hypertensive events in the OFA-group.
*Conclusion:* OFA might reduce ropivacaine consumption, early postoperative pain scores and requirement for morphine titration after thoracotomy.


## 1. Introduction

Pain following thoracic surgery is often severe and its inadequate management results in increased postoperative morbidity, especially pulmonary complications (atelectasis, pneumonia, respiratory failure). Chronic pain after thoracotomy is also common, especially in patients who experienced severe acute post-thoracotomy pain [1]. Therefore, management of postoperative pain is still a challenge. Thoracic epidural analgesia (TEA) is one of the available analgesic techniques for pain relief following thoracic surgery [2]. It offers the possibility of reducing opioid requirements and their side effects [3]. This is particularly interesting in thoracic surgical patients with frequent respiratory comorbidities in whom opioids could lead to respiratory depression. Moreover, opioid can also cause acute

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tolerance and hyperalgesia [4]. Besides, malignant lung disease remains the main indication for lobectomy. Recent findings from retrospective clinical trials, as well as experimental studies strongly suggest that opioids may inhibit cellular immunity, stimulate angiogenesis and accentuate cancer cell growth. Hence, perioperative use of opioids might affect long-term oncological outcomes in the cancer surgical patients [5]. This explains the current trend to use non-opioid drugs as an alternative to opioids for pain management during the perioperative period.

Opioid-Free Anaesthesia (OFA) is a procedure that avoids opioid use during anaesthesia. A combination of several drugs including alpha-2-agonist, low-dose of N-Methyl-D-Asparate (NMDA) antagonist and lidocaine are added to usual hypnotic drug. Modulating peripheral afferent noxious stimulation, these agents may potentiate analgesic effects of opioid. Interestingly, additive analgesic effects of dexmedetomodine [6], as well as ketamine [7] to epidural analgesia have been also previously reported. In patients undergoing renal surgery, low-dose of ketamine potentiates the analgesic effect of epidural thoracic analgesia [8].

In the present investigation, the authors tested the hypothesis that OFA based on alpha-2 agonist, NMDA antagonist and lidocaine could enhance pain relief after open thoracotomy. Therefore, we compared postoperative pain relief of thoracic surgical patients receiving either OFA or opioid-based anaesthesia (OBA) in which a TEA was systematically used.

## 2. Material and methods

### 2.1. Study design

This observational, retrospective study was conducted in a single regional hospital. Patients undergoing elective open thoracotomy with a TEA from January 2015 to February 2018 were included. This study compared the cumulative first 48 postoperative hours epidural ropivacaine consumption, between patients receiving a general opioid-based anaesthesia (OBA-group) and those receiving a non-opioid based one (OFA-group). Data were collected using DxCare, Clinisoft and eXacto software programs. Exclusion criteria were failure, refusal or contraindication for TEA, surgery for pneumothorax and missing data. Data were collected and analysed confidentially assigning to each patient an identifying number. Our team started to implement an OFA strategy in patients undergoing elective open thoracotomy from May 2016. Consequently, between May 2016 and February 2018 an increased number of thoracic surgical patients received an OFA. In practical terms, OFA administration was totally left at the discretion of the attending anaesthetist regardless of patient's co-morbidities and his surgical risk. Therefore, we were able to assess the effects of an OFA strategy on epidural local anaesthetic requirement through the current observational retrospective study. Based on the power analysis (see below), a 3-year period (from January 2015 to February 2018) was necessary to conduct an unmatched case-control retrospective study with a 2:1 controls to cases ratio trial in which all consecutive patients who underwent thoracic surgery were screened for eligibility. The current trial was approved by the research ethics board of the University of Bordeaux (Registration number CE-GP-2018/07; Chairperson – Dr T. Haaser). We started to collect data from March 2018 (M.B. and S.O.). Agreement of the *Commission Nationale de l'Informatique et des Libertés* was also obtained (registration number 2183760v0). The present investigation being retrospective, an authorisation was granted to waive written informed consent.

### 2.2. Anaesthesia management

Patients did not receive any oral premedication and were monitored using an electrocardiogram, a pulse oximetry and a non-invasive blood pressure measurement. TOF-Watch Neuromuscular Monitor was used to guide muscle relaxant infusion. Patients were also monitored by bispectral index (BIS), when available. The postoperative nausea and vomiting (PONV) risk was estimated using the Apfel's simplified risk score. Patients presenting one risk factor received intravenous (IV) dexamethasone (4 to 8 mg after induction of anaesthesia). Patients with two or more risk factors also received an intravenous injection of droperidol (0.625 mg/30 min before the end of surgery). A Thoracic epidural catheter was inserted preoperatively in a sitting position at the T4/5 or T5/6 interspace using a midline approach. A dose test of 3 mL of lidocaine 1% (30 mg) with epinephrine (30 μg) was administered through the catheter to rule out inadvertent intratechal or intravascular placement. In all patients, TEA was used for intraoperative analgesia using 0.2% ropivacaine (from 4 up to 6 $mL.h^{-1}$), without any adjuvant or bolus. The continuous infusion rate was titrated to reach patient's comfort and haemodynamic stability.

In the OBA-group, a total intravenous anaesthesia with target-controlled infusion (TCI) of propofol and remifentanil was used for induction and maintenance of anaesthesia. Neuromuscular blockade was ensured in both groups using rocuronium given intermittently to reach adequate muscle relaxation. At induction, a single low-dose bolus of ketamine (up to 0.25 $mg.kg^{-1}$) could be given depending on the anaesthetist in charge.

In patients who received OFA, a pre-induction single-dose of IV clonidine (75 to 150 μg) was administered. Once patients arrived in the operating room, a single intravenous dose of lidocaine (1.5 $mg.kg^{-1}$) was administered. A bolus of ketamine (0.25 to 0.5 $mg.kg^{-1}$) was followed by continuous infusion (0.25 $mg.kg^{-1}.h^{-1}$), which was stopped at wound closure. A total intravenous anaesthesia with TCI of propofol was used for induction and maintenance of anaesthesia. Neuromuscular blockade was obtained with rocuronium as described above.

All patients in both groups were intubated with a double-lumen endotracheal tube and were mechanically ventilated. All patients received paracetamol intraoperatively (1000 mg), which could have been associated with nefopam (20 mg), tramadol (50 mg) or ketoprofene (100 mg). According to the anaesthetist in charge, patients could have received pre-emptive intravenous morphine at wound closure. The double-lumen endotracheal tube was removed in post-anaesthesia care unit (PACU) after neuromuscular blocking reversal. In PACU, postoperative pain was managed with an intravenous morphine titration to keep Numerical Rating Scale (NRS) Score $\leq 3$. Patients were discharged from PACU to postoperative intensive care unit once Aldrete scoring criteria were appropriate.

During Intensive Care Unit (ICU) stay, paracetamol (1 g) was given every 6 hours during the first 48 hours in both groups. TEA was maintained via a patient-controlled epidural analgesia device (PCEA) for 48 hours, using ropivacaine 0.2% with sufentanil (0.25 $\mu g.mL^{-1}$) as adjuvant, independently of the group. PCEA settings were as follow: continuous infusion of 5 $mL.h^{-1}$ (10 $mg.h^{-1}$), bolus of 5 mL (10 mg) with a lockout interval of 20 min. Background infusion was increased in case of inadequate sensory block level up to 6 $mL.h^{-1}$. Intravenous rescue analgesia was administrated if the NRS Score was $> 3$ despite the presence of a functioning TEA, using nefopam, tramadol, ketoprofene or morphine patient-controlled analgesia (PCA).

### 2.3. Outcomes

The primary outcome was the cumulative first 48 postoperative hours epidural ropivacaine consumption. Secondary outcomes included the level of postoperative pain at rest (measured using the NRS Score) in PACU, at 6-hour, 24-hour and 48-hour postoperatively, the incidence of moderate-to-severe pain (defined as NRS $>$ 4), the requirement for morphine titration in the PACU, the total opioid analgesics intake within the first 48 hours, the incidence of intraoperative hypertension (systolic blood pressure $>$ 150 mmHg), the vasopressor use (ephedrine and/or phenylephrine), the atropine use, the incidence of PONV and the incidence of postoperative complications.

### 2.4. Statistical analysis

Continuous variables are expressed as mean $\pm$ SD or median (interquartile range, 25th to 75th percentile) according to the variable distribution. Categorical variables are presented as number (percentage of patients). The sample size was determined from a preliminary retrospective analysis including 10 patients receiving an opioid-based anaesthesia. In these patients the mean postoperative consumption of ropivacaine was 946 $\pm$ 249 mg. Considering a 25% decrease in patients with OFA as clinically relevant, a sample size of 25 patients per group was necessary to show a statistical difference with a power of 90% and a two-sided type I error of 0.05. Based on a 2:1 control to case ratio, 75 patients were needed to conduct the present investigation. A Shapiro-Wilk test was used to test the normality of the distribution using. Two-sided Student's t-tests were used for normally distributed data. Mann–Whitney U-test was performed to compare non-normally distributed data and Fischer's exact test was used to compare categorical data. Two-sided *P*-values of less than 0.05 were considered to indicate statistical significance.

## 3. Results

From January 2015 to February 2018, a total of 101 consecutive patients were screened for eligibility. Among them, 75 patients were included: 50 patients in the OBA-group (control group) and 25 patients in the OFA-group (case group). The flow chart of the study is displayed in Fig. 1. The same surgeon operated all patients. The most common operation was lobectomy, which was performed in 57 patients (76%). Sixty-three patients (84%) were operated for lung cancer. Patient characteristics are summarised in Table 1. Both groups were globally comparable at baseline except for age, which was significantly higher in the OFA-group.

Intraoperative anaesthetic management, length and type of surgery are detailed in Table 2. Seventeen patients (34%) in the OBA-group received ketamine intraoperatively but only one of those patients received a continuous infusion intraoperatively. In the OFA-group, all patients received a ketamine bolus followed by a continuous infusion. Therefore, the OFA-group received a significantly higher intraoperative total dose of ketamine (71 $\pm$ 20 mg versus 24 $\pm$ 11 mg, $P < 0.05$). Two patients in the OFA-group received dexmedetomidine as an alpha-2-agonist instead

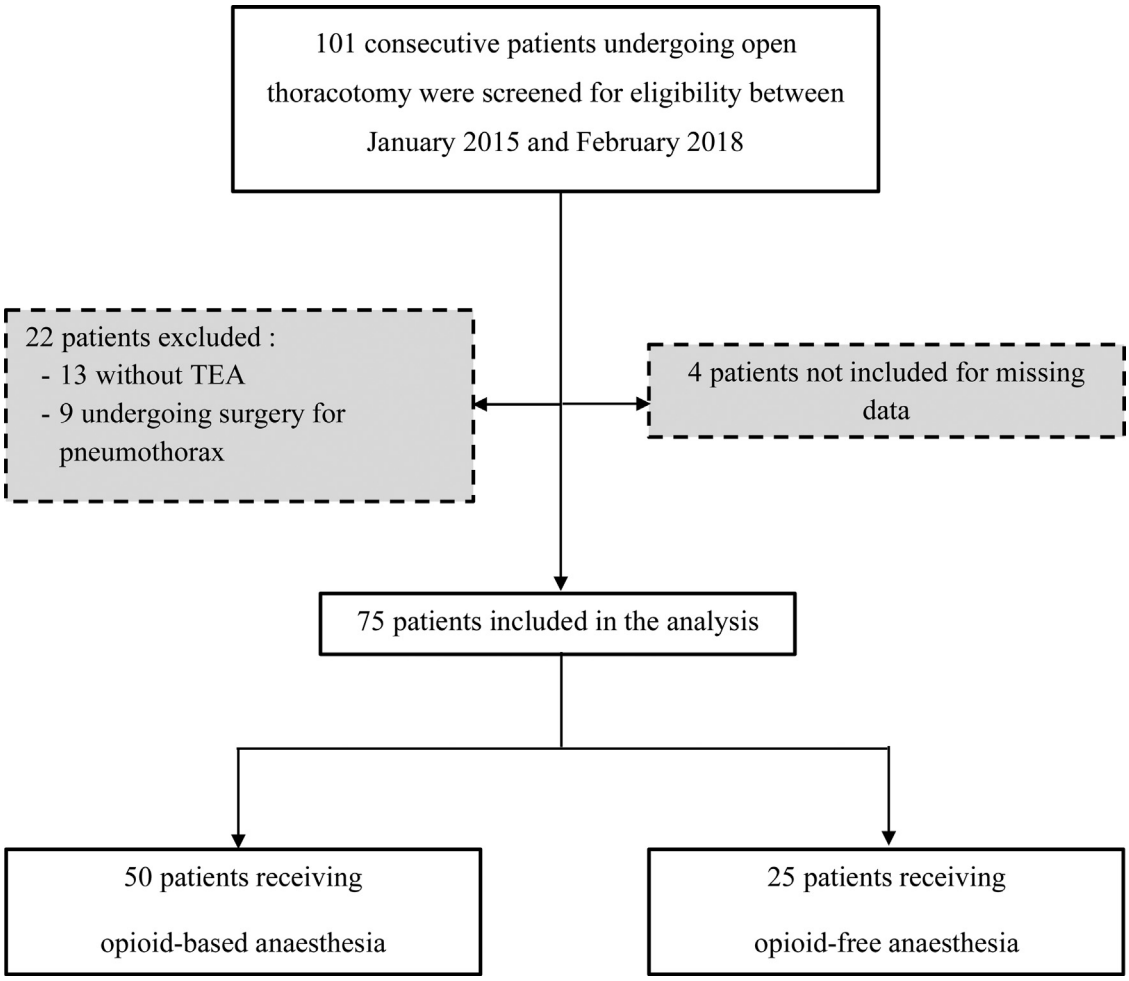


**Fig. 1.** Flow chart of the study.

**Table 1**
Baseline characteristics of patients receiving opioid-based anaesthesia (OBA) and opioid-free anaesthesia (OFA).

| Variables | OBA ($n$ = 50) | OFA ($n$ = 25) |
|---|---|---|
| Age (year) | 64 [54–67] | 67 [63–72][a] |
| Male/female | 37/13 (74%/26%) | 20/5 (80%/20%) |
| BMI, kg.m$^{-2}$ | 24 [20–28] | 25 [23–27] |
| ASA | | |
| ASA I-II | 30 (60%) | 17 (68%) |
| ASA III-IV | 20 (40%) | 8 (32%) |
| Apfel score | 2 [2–2] | 2 [2–2] |
| Comorbidity | | |
| Smoking history | 44 (88%) | 23 (92%) |
| COPD | 21 (42%) | 16 (64%) |
| OSAS | 3 (6%) | 1 (4%) |
| Arterial hypertension | 17 (34%) | 12 (48%) |
| Ischemic heart disease | 5 (10%) | 4 (16%) |
| Cancer history | 15 (30%) | 8 (32%) |
| Chemo/radiotherapy history | 9 (18%) | 5 (20%) |
| Depressive disorder | 13 (26%) | 5 (20%) |
| Long-term opioid therapy | 1 (2%) | 0 (0%) |
| Alcohol abuse | 7 (14%) | 2 (8%) |
| Type of disease | | |
| Lung cancer | 42 (84%) | 21 (84%) |
| Metastatic lung tumor | 6 (12%) | 3 (12%) |
| Other | 2 (4%) | 1 (4%) |

Data are expressed as median [25–75th percentile] or $n$ (% of patients). OBA: opioid-based anaesthesia; OFA: opioid-free anaesthesia; BMI: body mass index; COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome.
[a] $P < 0.05$ versus OBA-group.

of clonidine (loading dose of 1.4 μg.kg$^{-1}$ over 20 min followed by a continuous infusion of 0.4 μg.kg$^{-1}$.h$^{-1}$). Its administration was stopped at wound closure. The proportion of patients requiring intraoperative use of ephedrine was comparable in both groups (Table 2). However, the median intraoperative dose used was higher in the OBA-group ($P < 0.001$). In addition, more patients in the OBA-group required phenylephrine to treat intraoperative hypotension ($P < 0.01$). Intraoperative hypertension occurred more frequently in the OFA-group and occurred exclusively during the insertion of the double lumen tube ($P < 0.001$).

More patients received tramadol for preventive analgesia in the operating room in the OFA-group, while patients in OBA-group received more frequently pre-emptive morphine. In PACU, a larger proportion of patients in the OBA-group required morphine titration (42% versus 4%, $P < 0.05$). The total dose of morphine administered for titration was also higher in the OBA-group ($P < 0.001$). The perioperative analgesia profile is summarised in Table 3.

In the OBA-group, postoperative morphine requirement was similar regardless of ketamine administration (data not shown). Eleven patients (22%) in the OBA-group and 5 patients (20%) in the OFA-group received epidural sufentanil started postoperatively at their arrival in ICU.

**Table 3**
Perioperative pain management patients receiving opioid-based anaesthesia (OBA) or opioid-free anaesthesia (OFA).

| Variables | OBA ($n$ = 50) | OFA ($n$ = 25) |
|---|---|---|
| Preventive analgesia drug started in the operative room | | |
| Paracetamol | 48 (96%) | 23 (92%) |
| Ketoprofene | 21 (42%) | 9 (36%) |
| Nefopam | 6 (12%) | 2 (8%) |
| Tramadol | 2 (4%) | 6 (24%)[a] |
| Morphine | 25 (50%) | 2 (8%)[a] |
| Postoperative analgesia in PACU | | |
| Patients requiring morphine titration | 21 (42%) | 1 (4%)[a] |
| Total dose morphine (preventive and titration) | 7 [0–10] | 0 [0–0][a] |
| PONV | 2 (4%) | 0 (0%) |
| Postoperative analgesia in ICU within the first 48 h | | |
| Paracetamol | 48 (96%) | 25 (100%) |
| Ketoprofene | 2 (4%) | 2 (8%) |
| Nefopam | 12 (24%) | 5 (20%) |
| Tramadol | 36 (72%) | 18 (72%) |
| Patients requiring morphine PCA | 11 (22%) | 3 (12%) |
| Cumulative morphine dose (mg) | 9 [0–15] | 0 [0–0][a] |
| PONV | 6 (12%) | 3 (12%) |

Data are expressed as median [25–75th percentile], mean ± standard deviation or $n$ (% of patients). OA: opioid anesthesia; OFA: opioid-free anesthesia; PACU: post-anaesthesia care unit; PONV: postoperative nausea and vomiting.
[a] $P$-value $< 0.05$ versus OA-group.

**Table 2**
Intraoperative characteristics of patients receiving opioid-based anaesthesia (OBA) or opioid-free anaesthesia (OFA).

| Variables | OBA ($n$ = 50) | OFA ($n$ = 25) |
|---|---|---|
| Time length of surgery (min) | 180 [150–210] | 180 [150–210] |
| Type of surgery | | |
| Lobectomy | 38 (76%) | 19 (76%) |
| Pneumonectomy | 8 (16%) | 3 (12%) |
| Segmentectomy | 2 (4%) | 1 (4%) |
| Wedge resection | 2 (4%) | 2 (8%) |
| Hypertension occurrence | 2 (4%) | 16 (64%)[a] |
| Ephedrine use | 44 (88%) | 19 (76%) |
| Ephedrine consumption (mg) | 27 [12–33] | 12 [6–18][a] |
| Phenylephrine use | 20 (40%) | 2 (8%)[a] |
| Atropine use | 4 (8%) | 2 (8%) |
| Remifentanil use | 50 (100%) | 0 (0%)[a] |
| Ketamine use | 17 (34%) | 25 (100%)[a] |
| Total intraoperative dose of ketamine (mg) | 24 ± 11 | 71 ± 20[a] |
| Lidocaine use | 0 | 25 (100%)[a] |
| Clonidine use | 0 | 23 (92%)[a] |
| PONV prophylaxis | 10 (20%) | 10 (40%) |
| Complications | 3 (6%) | 3 (12%) |
| Surgical complications | 0 (0%) | 1 (4%) |
| Non surgical complications | 3 (6%) | 2 (8%) |

Data are expressed as median [25–75th percentile], mean ± standard deviation or $n$ (% of patients). OBA: opioid-based anaesthesia; OFA: opioid-free anaesthesia; PONV: postoperative nausea and vomiting.
[a] $P < 0.05$ versus OBA-group.

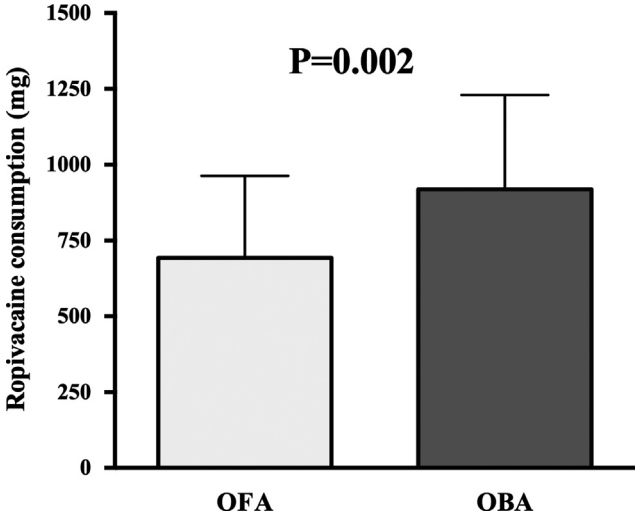


**Fig. 2.** Cumulative 48-hour epidural ropivacaine consumption (mg) in patients receiving opioid-free anaesthesia (OFA, $n$ = 25) and opioid-based anaesthesia (OBA, $n$ = 50). Results are expressed as mean ± SD. P value refers to between groups comparison.

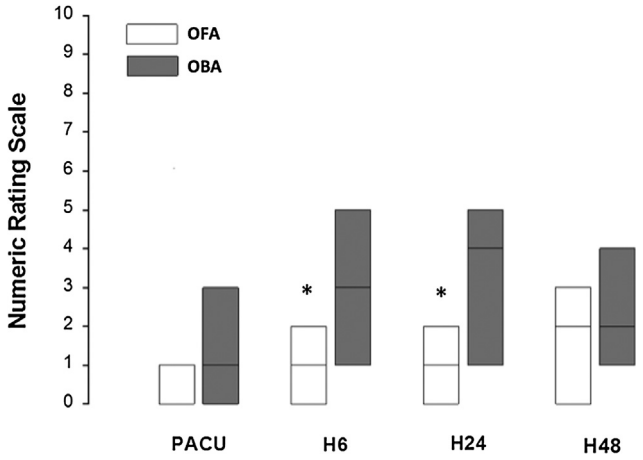


**Fig. 3.** Numeric Rating Scale in the PACU and at 6, 24 and 48 hours after surgery in patients receiving opioid-free anaesthesia (OFA, $n = 25$) and opioid-based anaesthesia (OBA, $n = 50$). Lines within boxes represent median values. Upper and lower lines of boxes represent 25th and 75th percentiles, respectively. *: $P < 0.05$ versus OBA. PACU: post-anaesthesia care unit.

Within the first 48 postoperative hours, the cumulative epidural ropivacaine *consumption* was significantly higher in the OBA-group ($P = 0.002$) (Fig. 2). There was a trend toward less morphine PCA requirement in ICU in the OFA-group. However, the cumulative postoperative morphine consumption was lower in the OFA-group ($P = 0.01$). NRS scores were significantly lower in the OFA-group at 6- and 24-hour after surgery (Fig. 3). Seven patients (28%) in the OFA-group and 33 (66%) in the OBA-group had a NRS $> 4$ within the first 48 hours after discharge from PACU ($P = 0.003$). The incidence of PONV, as well as the incidence of intraoperative complications (two bronchospasms and one episode of bradycardia in the OBA-group, one difficult intubation, one case of bradycardia and one bleeding in the OFA-group) were similar between the two groups. The rate of postoperative complications was also similar between the two groups (40% in the OFA-group versus 42% in the OBA-group, $P = 0.8$). The incidence of respiratory complications between the two groups was also similar (20% in the OFA-group versus 26% in the OBA-group, $P = 0.8$). The most frequent complications were cardiac arrhythmias (seven cases) and atelectasis (eight cases). None of the patients after an OFA regimen reported recall of intraoperative events and/or complained about any side effects that may be related to local anaesthetics delivery (cardiac arrhythmia, perioral numbness, metal taste, tinnitus and visual disturbance).

## 4. Discussion

The principles findings of the present retrospective study are that OFA in patients undergoing open thoracic surgery could enhance postoperative pain relief and thus reduce significantly:

- cumulative ropivacaine consumption administered through a PCEA within the first 48 postoperative hours;
- postoperative morphine consumption and;
- postoperative pain scores.

To the best of our knowledge, our study is the first to investigate the feasibility of OFA for thoracic surgery. We have chosen as primary outcome the cumulative first 48 postoperative hours epidural ropivacaine consumption. The majority of studies investigating the effect of OFA on postoperative pain relief choose postoperative opioid requirement as primary outcome. If this outcome appears to be relevant for general surgery, it seems to be less adapted for patients receiving thoracic epidural analgesia. Indeed, in thoracic surgical patients receiving thoracic epidural analgesia, it has been clearly demonstrated that the postoperative morphine requirement is already dramatically reduced [9,10]. Moreover, most of these thoracic surgical patients do not require opioids after surgery. For instance, in Wahlander's study [6], every patient receiving a thoracic epidural analgesia did not require IV opioids after thoracic surgery. We confirmed these findings previously reported in our study. Indeed, the median cumulative consumption of morphine over the first 48 postoperative hours was low in our control group. Moreover, in this group, a large proportion of control patients ($n = 39$, 78%) did not require opioids during the first 48 postoperative hours. These findings could be easily explained by the use of thoracic epidural analgesia, the most efficient method for pain relief after open thoracic surgery [2]. Considering these findings, we believe that postoperative morphine requirement should not be considered as a clinically pertinent outcome to evaluate the potential positive effects of OFA in thoracic surgical patients receiving postoperative TEA. Bearing in mind that alpha-2 agonist, NMDA antagonist and lidocaine [7,11] may potentiate the analgesic effect of TEA, we preferred to test the scientific hypothesis that OFA might reduce postoperative local anaesthetics consumption. The hypothesis that OFA could reduce the cumulative first 48 postoperative hours epidural ropivacaine consumption has been already tested and confirmed in patients undergoing renal surgery but never after thoracic surgery [8]. It should be pointed out that other authors did not find any interest in adding ketamine to epidural analgesia in thoracic surgery [12]. Similarly, some authors found modest benefit of intravenous dexmedetomidine to epidural analgesia after thoracotomy [6]. In our study, the avoidance of remifentanil use, drug known to trigger acute opioid tolerance and hyperalgesia [4], may also have had an impact on postoperative pain relief and analgesics consumption.

We found that OFA lower postoperative pain scores after open thoracic surgery. These findings are consistent with those previously reported in general low-risk surgery excluding thoracic surgical patients [13,14]. In addition, cumulative postoperative morphine consumption was lower in the OFA-group. Again, these results are congruent to those of other studies, in which patients receiving OFA needed fewer postoperative opioids to achieve a pain-free recovery [13–16]. These results can be due to perioperative opioid-induced hyperalgesia and acute opioid tolerance, attenuating the effectiveness of morphine to relieve postoperative pain in patients who received opioids intra-operatively. The epidural analgesia solution injected must be taken into account to interpret correctly our findings. Some patients (about 20% in each group) received postoperative epidural sufentanil. Opioid epidural administration provides pain relief after thoracic surgery. It is thus likely that the additional sufentanil administration has been a bias resulting in better pain relief in patients who received ropivacaine-sufentanil mixture.

A previous study reported a reduction of PONV in bariatric surgery due to avoidance of opioid use during anaesthesia [17]. Our findings did not show such decrease despite the opioid-sparing effect of OFA. The PONV incidence may be underestimated due to the retrospective nature of the study. Indeed, nausea may not have been reported whereas only vomiting and antiemetic rescue medications were described in the patients' chart.

In our study, the use of an alpha-2-agonist did not seem to be responsible for bradycardia or hypotension. Interestingly enough, hypotension seemed to be even more frequent in the OBA-group as vasopressor use was higher. There is a controversy in the literature concerning alpha-2-agonists' and its effects on haemodynamic. These drugs are known to provoke hypotension and bradycardia. Some authors reported that low-dose clonidine increased the risk of clinically important hypotension and non-fatal cardiac arrest in non-cardiac surgery [18]. Nonetheless, several studies using intraoperative

alpha-2-agonists, although small in size, did not report significant haemodynamic effects [13–15,17,19,20]. Such discrepancy might be due to dosing issue, considering that alpha-2-agonist use in opioid-free regimen is confined to intraoperative period.

In contrast, in our study, more episodes of hypertension were noted in the OFA group. These episodes always occurred at intubation. However, all these episodes were of short duration and no patient required antihypertensive agent. This may be related to clonidine onset of action. Intravenous clonidine, if administered too late, may not have time to provide sufficient autonomic block, so that intubation stimulus is not blunted yet.

In the first place, OFA has been described for bariatric and digestive surgeries [14,15,17,19,21]. Avoiding opioids could provide less respiratory depression, less nausea and vomiting and sedation in this population. Scarce and small studies have reported its use in breast cancer surgery [13], orthopaedics [20], ear, nose and throat surgery [16,22] or neurosurgery [23]. In our trial, both the OBA- and the OFA-group received a thoracic epidural analgesia intra and postoperatively. Our results suggest that OFA provides added values in pain reduction compared to our actual standard of care. These benefits may be due to a multimodal anaesthesia based on analgesic, antihyperalgesic drugs and, also, to opioid avoidance, which prevent postoperative hyperalgesia.

Postoperative complications occurred in about 40% of the patients in both group. This rate seems high but is consistent with another study [24], which collected prolonged air leaks and excessive chest tube drainage as a complication in the same fashion as we did.

Our study did not find any benefit of non-opioid anaesthesia on respiratory complications. Nevertheless, the study was not designed to detect such a difference and was probably underpowered for this purpose. Besides, TEA is known to be effective in preventing such issues [25].

Some limitations should be considered when assessing the clinical relevance of this study. First, the retrospective nature of our study could explain that some data are missing. Consequently, we could not evaluate postoperative ileus duration, postoperative sedation or confusion. In the same way, intraoperative BIS values should have been interesting, particularly during the hypertension observed in OFA-group. However, both groups received the same anaesthesia management except for the drugs studied (remifentanil, NMDA-antagonist, lidocaine and alpha-2-agonist). Postoperative PACU analgesia management, although not protocolised, was also similar between the two groups regarding intravenous analgesics use. Second, patients received intraoperative intravenous lidocaine and epidural ropivacaine. The association of two local anaesthetics is not recommended by all the guidelines published on this topic. Thereby, to limit the risk of toxicity, a single IV bolus of lidocaine was performed at patient arrival in the operating room. The continuous infusion of ropivacaine in the epidural catheter was started without loading dose and only after the appropriate patient positioning was obtained, which was on average 75 minutes after the lidocaine bolus. Hence, considering the pharmacokinetic properties of these local anaesthetics, overdosing is unlikely. Finally, lung cancer surgery might be a special indication for OFA considering the long-term outcomes related to this procedure, such as chronic pain syndromes and opioid-induced immunosuppression and its possible impact on patients' survival [5]. Our study was obviously not designed to assess such issues. These outcomes need further investigations.

## 5. Conclusion

OFA for patients undergoing open thoracic surgery appears to be feasible. Such anaesthetic approach seems to reduce cumulative ropivacaine consumption administered through PCEA within the first 48 hours as well as early requirement of morphine and early postoperative pain scores.

## Ethical statements

The current trial was approved by the research ethics board of the University of Bordeaux (registration number CE-GP-2018/07. Chairperson - Dr T. Haaser). We started to collect data on March 2018 (MB and SO). Agreement of the Commission Nationale de l'Informatique et des Libertés was also obtained (registration number 2183760v0). Because data retrospectively analysed during routine care that conformed to standard procedures currently used in the institution, authorization was granted to waive written informed consent.

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## Authors' contributions

SO, MB, SBC, CZ and AO helped to conceive, design and conduct the study and draft the manuscript. SO and MB helped to supervise data collection. SO, CV and MB helped to collect data. SO and AO supervised the conduct of the trial. SO, SBC and AO helped to analyse and review the data, to provide statistical advice and to perform statistical analyses. AO helped to conceive original artworks. AO gave final approval of the version. All authors read and approved the final manuscript.

### Disclosure of interest

The authors declare that they have no competing interest.

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