Clinical research

Postoperative patient-controlled epidural or intravenous pain treatment after one-stage unilateral hybrid atrial fibrillation ablation surgery?

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Submitted: 13 June 2019
Accepted: 24 October 2019

Arch Med Sci Aging 2019; 2: e1–e9
DOI: https://doi.org/10.5114/amsa.2018.90062

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Abstract

Introduction: Finding the best pain treatment approach after one-stage hybrid AF ablation surgery is difficult as cardiac, thoracic and diaphragmatic nerve endings are sensitized. We hypothesized that patient-controlled postoperative epidural pain treatment with high thoracic (T4) epidural ropivacaine (EA) would provide superior pain relief when compared with an intravenous patient-controlled piritramide pump (IA).
Material and methods: This prospective study in 69 consecutive patients compared postoperative pain report, pain location and breathing mode. A standardized combined anesthesia method with inotropic support (if requested) was used during surgery. The simultaneous thoracoscopic and endovascular ablation surgery consisted of a stepwise ablation protocol. EA consisted of ropivacaine 2 mg/ml set at 4 ml/h with a patient-controlled EA regimen of: 2 ml/30 min. The IA group received a PCA regimen of 2 mg of piritramide every 7 min with 30 mg/4 h maximal dose. Parameters assessed after surgery were pain with VAS scores, pain locations, breathing frequency and mode, sleep, duration of drain and hospital stay. To ease pain patients also received: paracetamol, diclofenac (when possible), morphine, colchicine and aspirin (pericarditis suspicion).
Results: Fifty patients with refractory AF were recruited. Similar peak dynamic pain scores and referred pain localizations, but lesser initial respiratory comfort and sleep recuperation and a tendency to more PONV were observed in IA patients. Postoperative suspected ablation pericarditis incidence was high.
Conclusions: Both postoperative EA or IA pain treatments are valuable options yielding no differences in pain report after surgery. But EA may initially improve the patient's respiratory ease.

Key words: epidural anesthesia, opioids, radiofrequency catheter ablation, hybrid procedure, pain after surgery, persistent atrial fibrillation.

Introduction

The postoperative pain treatment after one-stage hybrid surgery for atrial fibrillation (AF) presents interesting challenges for the pain physi-

Table I. Sensitized nerves during the hybrid ablation procedure (Vaitkevicius R, Heart Rhythm 2009) [18]

Phrenic nerves (left and right)
Epicardial nerve fibers
Pericardio-phrenic nerves
Intrinsic cardiac nerves:
Superior left atrial plexus (superior veno-atrial junction)
Posterolateral plexus (lateral atrial wall and left inferior veno-atrial junction)
Posteromedial plexus (right veno-atrial junctions or concentrations of ganglionated nerves at the inferior surfaces of both inferior pulmonary veins).
Epicardial nerves penetrating PV walls transmurally and forming a neural network beneath the endothelium of the pulmonary veins

cian as several nerve endings of the pleural cavity, the heart, the esophagus and the throat are sensitized during surgery, which in turn may trigger postoperative pain [1] (Table I). To our knowledge, prospective studies in this field are not reported. We therefore prospectively investigated whether patient-controlled thoracic epidural anesthesia with ropivacaine or the intravenous opioid piritramide patient-controlled approach is more appropriate to treat immediate postoperative pain after one-stage hybrid surgery in patients with atrial fibrillation (AF). Postoperative pain characteristics (intensity, localization and type, peak pain), breathing (frequency and mode) and sleep were compared between the two pain treatment options. In the background a multimodal approach for general anesthesia was used: ropivacaine infiltration at the thoracoscopic incision places, systemic administration of paracetamol, non-steroidal anti-inflammatory drugs when possible, and eventually felt necessary systemic opioids, while also enhancing postoperative nutrition intake and quick mobilization.

Both the epidural and the intravenous postoperative pain techniques lessen pain after surgery and are linked with advantages but also shortcomings. For instance, a high thoracic epidural anesthesia technique in cardiac surgery induces a segmental temporary sympathetic block [2], decreases the risk of atrial fibrillation or supraventricular tachycardia [3–6], and improves distribution of coronary blood flow and the quality of postoperative analgesia [7], and respiratory function [8–10]. Besides its sympathetic block, ropivacaine has intrinsic anti-inflammatory effects on neutrophils and endothelial cells [11]. Conversely, the epidural approach carries the feared risk of epidural vessel puncture and bleeding and hypotension [12]. This bleeding risk may be increased in AF patients as they are often treated before surgery with anticoagulants to reduce generation of thrombi in the left appendix. To obtain a window of surgical opportunity, anticoagulant intake is interrupted before surgery. The aim is to find a subtle compromise between surgery bleeding risk and generation of thrombi in the left atrial appendix, which is mobilized during surgery and ultimately clipped. Another side effect of the thoracic epidural is hypotension, but its incidence is minimized by avoiding epidural bolus administration, using low doses of local anesthetics, judiciously giving fluids and appropriate vasopressor dosing [12].

The use of a patient-controlled intravenous opioid technique is initially efficacious but may lead to postoperative emesis or nausea (PONV), respiratory depression, or possibly, when given for more than 48 h, to opioid tolerance [13]. Additionally, a paradoxical risk of inducing opioid-induced hyperalgesia in those patients – if requesting higher opioid doses – is also possible.

Material and methods

This retrospective pain study included, after prior approval by the ethical committee (BUN 143201213077) of the Universitair Ziekenhuis Brussel, 69 consecutive patients scheduled for unilateral, one-stage hybrid radiofrequency ablation of atrial fibrillation. Briefly, the patients selected had atrial fibrillation that was refractory to medical treatment, cardioversion or endovascular ablation. All patients were informed of the study before surgery at the anesthesia consultation clinic. Moreover, the evening before their surgery the operating anesthesiologist reviewed and re-explained the study purposes, advocating a shared-decision pain protocol with precise explanations about the postoperative pain course and of the potential risks and benefits of their epidural and intravenous patient-controlled treatments and how to report their pain after surgery. Following their signed informed consent to participate in the study, the patient received for treating their postoperative pain either a patient-controlled thoracic epidural pump with ropivacaine or an intravenous piritramide-dehydrobenzperidol pain pump.

Excluded from study participation were opioid-naïve adults who refused to give their consent, patients with a history of chronic pain or pain drug treatment abuse, depression, psychiatric morbidity or maladaptive coping behavior, severe anxiety or other mental ailment, taking drugs affecting their capacity to assess pain, chronic or acute skin infection of the back, hypersensitivity to local anesthetics or the used products or patients with severe hepatic or renal disease. Also

admitted were patients with previous lumbar back surgery or patients where withholding anticoagulant administration was not possible, due to increased risk of thrombus generation. These patients received the most secure option: the intravenous regimen

Anesthetic perioperative protocol

The surgical procedure has been described [1] and was performed under general anesthesia with an endobronchial blocker under fiberscopic control for selective lung ventilation. Anesthesia was induced with sufentanil (0.1–0.2 µg/kg), propofol 1–2 mg/g and vecuronium 0.6 mg/kg and maintained with inhalation sevoflurane anesthesia (end tidal sevoflurane range (0–3%)), sufentanil (range: 20–100 µg) and rocuronium supplements. Monitoring consisted of radial artery blood pressure and arterial blood gas monitoring and right jugular vein catheter insertion for eventual administration of vasopressors and central venous pressure monitoring, transesophageal echocardiography of the left atrial appendix to exclude thrombus presence, oropharyngeal temperature and hourly urinary output. All patients were kept normothermic with a Bair Hugger. Antibiotic prophylaxis consisted of an initial cefazolin 2 g dose or its equivalent if allergy was suspected or known.

The patients' options to treat their postoperative pain were either an epidural pump with ropivacaine (EA) or an intravenous piritramide pump (IA).

Patients receiving the thoracic epidural catheter anesthesia regimen (EA) received their thoracic epidural catheter 40 min before anesthesia induction. A single needle puncture was performed at the T5-T6 level and the catheter tip was inserted up to the T4 level. A test dose consisting of 3 ml of lidocaine 2% with 1/200 000 of epinephrine was given to test appropriate catheter location and to exclude the intravascular position before anesthesia induction. The initial epidural regimen – consisting of a ropivacaine 2 mg/ml solution – was started at 4 ml/h during thoracoscopic skin closure. Patient-controlled top-ups after awakening in case of residual pain were possible with a 2 ml dose given every 30 min.

Patients receiving the patient-controlled intravenous analgesia regimen (IA) had a patient-controlled analgesia (PCA) piritramide and droperidol pump set initially at 2 mg bolus/7 min, 30 mg/4 h limit.

To reduce immediate pain after extubation and to allow smooth awakening, all patients were given 20 ml of ropivacaine 7.5 mg/ml wound infiltration of their intercostal thoracoscopic wounds by the surgeon just before skin closure. As a complement to ease unsatisfactory pain relief, patients

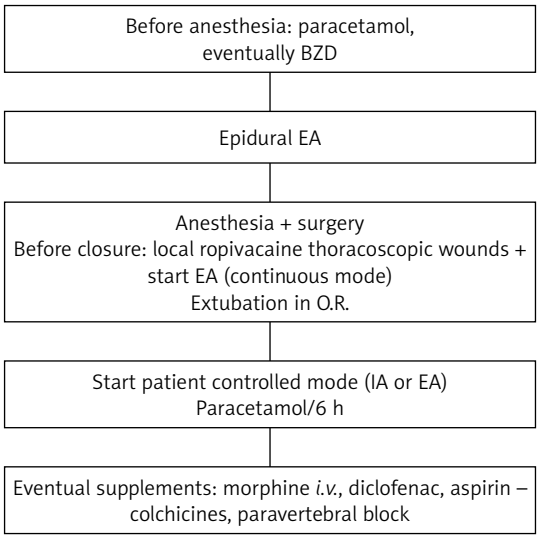

Figure 1. Pain protocol

received, irrespectively of their group allocation, 1 g of intravenously paracetamol up to 4 times/day (i.e. in patients with normal transaminase levels) with a starting dose of 1 g given 1 h before anesthesia induction. Postoperatively, in cases of suspicion of pericarditis, intravenous diclofenac 75 mg or aspirin 1000 mg supplemented later with oral colchicine tablets of 1 mg and morphine supplements (in the ICU) were given when requested or pericarditis suspected. In cases of intractable postoperative pain, an ultrasound-guided left paravertebral block (PVB) was provided as a rescue (Figure 1).

Study measurements tools included: for pain intensity assessment, visual analog scale (VAS) scores (0 = no pain, 10 worst pain ever) at rest or while coughing and moving were evaluated at 2 h and at 6 h after surgery or more when judged necessary. After day 2, VAS scores were taken twice daily unless considered insufficient. Maximal VAS scores were also recorded. The localization of pain was specifically asked for. The non-limited localization options we gave for their pain were: precordial, dorsal, epigastric, thoracic, throat, shoulder and neck. Patients could point out several areas of pain. The pain type was assessed as continuous or intermittent, breathing- or movement-related. Possible side effects of pain treatment such as nausea, vomiting, sedation, respiratory depression, urinary retention, hypotension, epidural catheter kinking, disconnection, or pump failures were recorded.

Hourly respiratory frequency and 6 h evaluation of the breathing mode were also evaluated. The anesthesiologist or intensivist had four options for breathing mode assessment: shallow or superficial breathing, deep or diaphragmatic breathing, tense breathing with eventual grimacing and eventual use of secondary breathing muscles or

normal. The breathing mode was observed for the first 24 h starting 2 h after ICU installation. Arterial blood gases were taken 2 and 6 h after ICU arrival or when deemed necessary. Sleep duration before surgery and the cumulative sleep hours the first night after surgery (taking the average from the ICU nurses' estimation and the patient's estimation) were recorded. The patient was asked to give a sleep quality score of the first ICU night after the night with two options: good recuperating night or bad night.

Daily changes in C-reactive protein levels were compared between the two groups. Preoperative Apfel scores and postoperative nausea or vomiting events as well as preventive administration of anti-emetic drugs in patients with previous PONV or when explicitly requesting PONV preventive treatment (ondansetron 4 mg, dexamethasone 5 mg, droperidol 2.5 mg and/or metoclopramide 10 mg) were noted.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics 25. Continuous variables (VAS, respiratory frequency, LOS, ICU stay, drain duration, CRP, sleeping hours) were compared using the non-parametric Mann-Whitney *U* test. For categorical data (breathing mode, pain localization, pain type, sleep quality) a χ^2 analysis with Yates correction was performed. Significance was considered for *p*-value levels < 0.05. Continuous data are presented as mean ± standard deviation and categorical data as absolute values or %.

Results

Of the 69 AF patients selected, 50 were included in the study. Patients who refused to participate (n = 6) or with missing data (n = 5) were withdrawn from the study. Similarly, patients in the EA group with inadequate epidural anesthesia (n = 5) due for instance to patch block, catheter kinking or connection leakage or hypotension or for patients in the IA group pump failure (n = 3) were removed.

The population demography of both groups was comparable in gender, age, height, weight and ASA physical class, previous gastrointestinal impairment and/or anticoagulants drug intake (Tables I and II).

We observed differences between groups in VAS scores and peak dynamic VAS scores (EA 40 ±25, IA 45 ±25). The patient's referred pain localization in both EA and IA groups was often multifocal, not always isolated. Notwithstanding

Table II. Demographic variables (data are mean ± standard deviation)

Parameter	EA (n = 25)	IA (n = 25)
Age [years]	64 ±11	65 ±9
Height [cm]	172 ±11	173 ±11
Weight [kg]	84 ±19	82 ±18
No./ASA physical class	II: n = 3; III: n = 22	II: n = 3; III: n = 22
Gender, balance	14 M/11 F	16 M/9 F
Previous GI impairment	3	6
Treatment:		
Blood-diluting drugs (new oral coagulant, oral anti-coagulant, low molecular weight heparin, aspirin or other):		
NOAC	18	13
OAC	1	4
LMWH	1	1
Aspirin, others	3	4
Other treatments (anti-arrhythmic (AA), anti-hypertensive (HTN), proton pump inhibitor (PPI), statin, other, before surgery:		
AA, HTN	22	19
PPI	6	9
Statin	3	6
Others	15	11

a similar thoracic drain stay in both groups, the IA group patients had more thoracic pain complaints than the EA group. No differences in pain localization were reported between groups for the precordial, dorsal, neck, shoulder, throat or epigastric areas. Both groups had equivocal (and sometimes persisting) complaints of dorsal, precordial or shoulder pain. Pain- mode perception differences observed were: the IA group complained more of a continuous pain sensation related to breathing than the EA group, which referred more often to an intermittent pain not related to breathing. Pain levels decreased after thorax drain removal in both groups although some patients still had some persisting pain grievances after drain removal. A tendency to reduced IA pain treatment duration was observed in comparison to the EA treatment, which was weaned more progressively from the patient than IA treatment (Table III).

Patients' breathing rates were similar in both groups. However, patients under IA treatment breathed more superficially or tensely than EA patients. We observed in patients under IA treatment higher peak arterial carbon dioxide levels

Table III. Pain and respiratory parameters

Parameter	EA	IA
Dynamic VAS (max score 48 h)	40 ±18	45 ±20
Pain localization (first 48 h):		
Thoracic	13/25	19/25
Precordial	15/25	13/25
Back thoracic	16/25	12/25
Epigastric	2/25	1/25
Shoulder	8/25	8/25
Neck	5/25	4/25
Throat	1/25	2/25
Pain type:		
Intermittent	12/25	6/25
Continuous	5/25	19/25*
Movement-related	22/25	23/25
Breathing related	5/25	22/25*
Duration IA or EA treatment [days]:	2.57 ±0.78	1.75 ±0.95
Other analgesic agents:		
Paracetamol	25/25	25/25
NSAID	4/25	1/25
Morphine	18/25	20/25
Colchicine	9/25	16/25
Aspirin	11/25	19/25
Respiration-related parameters:		
Maximal breathing frequency observed 1st 24 h	24 ±6	24 ±4
Breathing pattern:		
Shallow, superficial	8/25	15/25*
Tense	5/25	12/25*
Normal	12/25	4/25
Maximal arterial CO_2 levels [mm Hg]	42 ±5	45 ±4*
Removal of thorax drain [days]	1.1 ±0.3	1.3 ±0.5

Table IV. Miscellaneous parameters

Parameter	EA	IA
ICU stay [day]	1.37 ±0.74	1.16 ±0.41
Hospital stay [day]	5.6 ±2.3	6.2 ±3.3
Apfel score	2.5 ±0.9	2.4 ±0.8
PONV incidence (*N*/%)	24%	40%
CRP – before surgery	2.6±3.6	2.3±2.2
CRP-maximal level	157 ±72	153 ±99
Sleep quantity:		
Sleep before surgery [h]	6.6 ±1.1	6.7 ±0.9
Sleep first night after intervention	3.9 ±1.2	3.5 ±1.8
Sleep quality report 1st night ICU:		
Good	15/25	3/25
Bad	10/25	22/25

in the first 24 h when compared to the EA group (Table III).

No significant differences were observed in duration of ICU stay. IA and EA groups had similar Apfel scores. Notwithstanding former PONV treatment with ondansetron and dexamethasone in high PONV risk groups, a tendency (p = 0.22) to more PONV was observed in the IA group (40%) versus the EA group (24%). Peak CRP levels were similar in the two groups. Although more patients in the EA group reported a good night than a bad night, sleeping hours on the first night after surgery were similar (Table IV).

Discussion

Pain

No evidence seems to favor one analgesic technique over the other for video-assisted thoracoscopic surgery [14]. To a certain extent, this also applies for this study: the epidural and the systemic opioid pain approach did not show different pain scores. The objective assessment of pain by isolated VAS scores is not always satisfactory. The intensity, the duration, the location and type of pain and previous nerve sensitization are important pain determinants. But often a myriad of other factors may alter pain perception and reporting (Figure 2) [15–17]. As stated before, pain should rather be viewed as a dynamic spatiotemporal signature of brain network communications representing the integration of all cognitive, affective and sensory-motor aspects [18]. This reasoning is also valid after one-stage hybrid AF treatment where some small observations can make the difference. To reduce anxiety over surgery, we optimized communication and attention time to our patients. They were repeatedly informed at the consultation clinic and the evening before their surgery of their expected pain course and treatment options, possible peak pain moments, pain location and type of pain. We observed patient variability in reporting postoperative peak dynamic VAS pain scores but globally no differences between EA and IA groups were seen.

A subtle breathing mode difference with less superficial respirations in favor of the EA group was probably related to the continuous ropivacaine epidural infusion in comparison to the IA group, which only received a patient-controlled opioid bolus but without a continuous background infusion. This is probably related to the irritant presence of a thoracic drain and the on-demand character of the patient-controlled opioid pump versus the epidural group, which relied on both a continuous background epidural and a patient-controlled bolus ropivacaine infusion.

Another difference observed between the pain treatments was a tendency, notwithstanding similar Apfel scores in both groups, of more PONV in IA patients. As several anti-emetic drugs alter the QT interval, we did not treat systematically patients preventively for PONV. We opted for preventive anti-PONV treatment only for patients who requested it after repeated previous PONV episodes. The respiratory comfort difference observed in the EA group is related to an efficacious blunting of the drain presence by the epidural ropivacaine infusion. Irritation of autonomic cardiac nerve endings [19] (Table I) induced by the radiofrequency ablation often generated a less specific, delayed, localized dull or sharp pericardial pain sensation in both groups around the heart. The equal ratio of precordial, back pain or shoulder complaints (30–40%) observed in both the EA and the IA groups suggesting radiofrequency-induced pericarditis-like pain did not deliver complete pain relief even when the EA or the IA treatment was set at higher levels. Only the administration of an non-steroid anti-inflammatory drugs (NSAID), or when not indicated, the combination of aspirin and colchicine associated with a proton pump inhibitor combined with intravenous opioids decreased complaints of this tenacious pericarditis pain. Remarkably, several clinical graduations of pericarditis ranging from the clinical full picture – ECG-tracing alterations, troponin increases, retrosternal chest and/or thoracic back pain and echocardiographic imaging [20] – to milder forms with delayed cardiac, shoulder, thoracic or back pain and small troponin increases were observed.

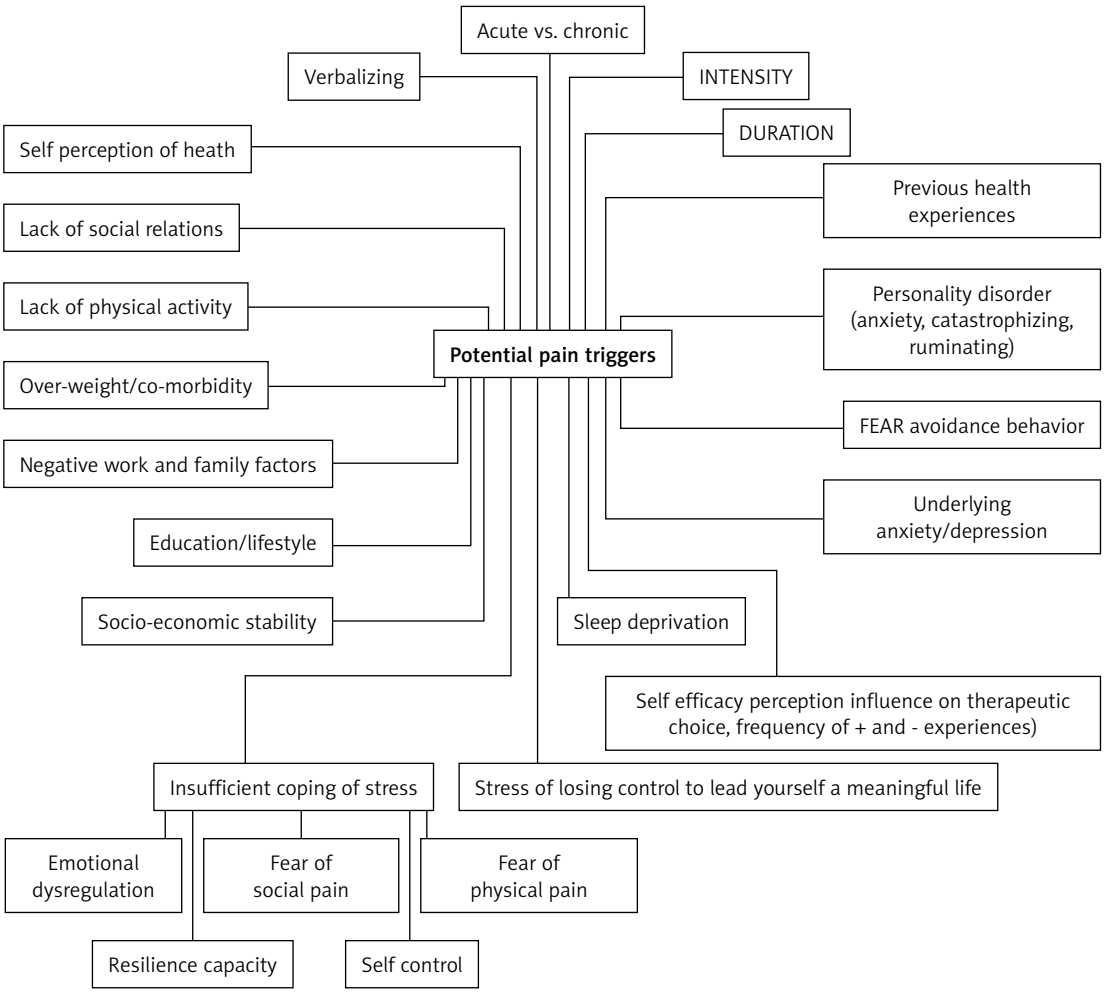

Figure 2. Postoperative pain triggers

Risk/benefit of epidural anesthesia

Epidural catheterization in AF patients treated with anticoagulants – notwithstanding their interrupted intake several days before surgery – may threaten patient safety. The exact incidence of epidural hematoma and the potential for neuraxial complication for hybrid cardiac surgery patients after thoracic epidural catheter insertion is unknown. Estimations for cardiac surgery patients with a 95% confidence interval range from 1 : 1000 to 1 : 400 [21–23]. This incidence is probably overestimated as our patients were not fully heparinized during the procedure. Besides, our AF patients had their anticoagulant treatment stopped several days before their intervention. Moreover, a rebound thrombotic effect after stopping anticoagulants and a pro-inflammatory state induced by surgery may counterbalance the bleeding risk [24, 25]. We undertook preventive measures to minimize bleeding risk. For instance, we repeatedly checked the strict adherence to the suggested last anticoagulant intake. For dubious cases coagulation was repeatedly checked the evening or the morning before surgery, eventually supplemented with a rotational thromboelastometry (ROTEM) analysis. Older female patients and renal dysfunction with increased risk were given more careful attention. Patient contact, information exchange, recruitment and thoracic epidural treatment were also performed by the same experienced anesthesiologist. A single epidural puncture and catheter insertion was performed. Patients with presence of bleeding from the epidural needle or catheter, or in the airways during endobronchial tube insertion for selective right lung ventilation were removed from the study. At the end of the 90 to 200 min long intervention surgery, all patients were immediately awakened and monitored for signs of neurological impairment. We believe that the strict adherence to these safety measures permitted ethical committee approval, facilitated patient recruitment and prevented iatrogenic epidural complications. Fortunately, no patient in our study presented clini-

cal signs suggestive of epidural hematoma or of neuraxial damage.

Should we investigate systemic local anesthetics or paravertebral block in future clinical trials?

As part of the observed pain benefits of the EA group may be related to local anesthetic anti-inflammatory and anti-apoptotic effects on neutrophils [26, 27] it could be suggested, similarly to abdominal surgery patients [28, 29], to include a treatment arm with systemic local anesthetics. The previous rationale was that systemic local anesthetics reduce opioid-related side effects, avoid the potential shortcomings of thoracic epidural catheterization and were more easily implemented, while the feared cardiac or pulmonary lidocaine toxicity risks for colon surgery seemed not to be justified [30]. Whether this deduction might be valid for our AF patients remains questionable as systemic lidocaine infusion may add unwanted arrhythmic lidocaine effects on heart' Purkinje cells affected by epicardial and endocardial radiofrequency ablation. A postoperative inflammatory state and the previous one-lung ventilation possibly delaying lidocaine lung metabolization are also to be feared.

The epidural approach is still considered as the gold standard for unilateral video assisted lung surgery [14] but the paravertebral block thoracoscopic surgery is becoming more popular. As postoperative pain treatments, both the thoracic epidural and the paravertebral block seem to offer similar relief. Inclusion of a postoperative PVB group may prove useful and a suggestion for a future trial.

In conclusion, for patients undergoing unilateral one-stage hybrid atrial fibrillation surgery we observed no differences in pain report or hospital length of stay when comparing a systemic opioid to thoracic epidural ropivacaine. An improved recuperation profile with fewer respiratory complaints with a feeling of better nighttime rest during the first 24 h, and a tendency of less postoperative nausea or emesis incidence in the first postoperative days were observed after thoracic epidural ropivacaine administration when compared to systemic opioid infusion. These advantages should however be balanced against the potential risk of epidural catheterization. Pericarditis-related pain complaints after surgery are an important issue after unilateral one-stage hybrid AF surgery equally present after local anesthetic epidural or systemic opioid patient-controlled approaches.

Acknowledgments

This study, evaluating differences in postoperative pain with patient-controlled epidural or intravenous pain treatment after one-stage unilateral hybrid atrial fibrillation surgery, did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. No funding was received from the involved UZ Brussel hospital's departments of the University (Vrije Universiteit Brussel).

Conflict of interest

Mark La Meir (Atricure consultant) and Carlo de Asmundis (Medtronic consultant) might have financial interests in this publication. However, the contents of this clinical study do not interfere with their consultancy.

References

1. Umbrain V, Verborgh C, Chierchia GB, De Asmundis C, Brugada P, La Meir M. One-stage approach for hybrid atrial fibrillation treatment. Arrhythmia Electrophysiol Rev 2017; 6: 210-6.
2. Freise H, Van Alen HK. Risks and benefits of thoracic epidural anaesthesia. Br J Anaesth 2011; 107: 859-68.
3. Bakhtiary F, Therapidis P, Dzemali O, et al. Impact of high thoracic epidural anesthesia on incidence of perioperative atrial fibrillation in off-pump coronary bypass grafting: a prospective randomized study. J Thorac Cardiovasc Surg 2007; 134: 460-4.
4. Pöpping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. Br J Anaesth 2008; 101: 832-40.
5. Pöpping DM, Elia N, Van Aken HK, et al. Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials. Ann Surg 2014; 259: 1056-67.
6. Do DH, Bradfield J, Ajijola OA, et al. Thoracic epidural anesthesia can be effective for the short-term management of ventricular tachycardia storm. J Am Heart Assoc 2017; 6: e007080.
7. Scott NB, Turfrey DJ, Ray DA, et al. A prospective randomized study of the potential benefits of thoracic epidural anesthesia and analgesia in patients undergoing coronary artery bypass grafting. Anesth Analg 2001; 93: 528-35.
8. Stenseth R, Bjella L, Berg EM, Christensen O, Levang OW, Gisvold SE. Effects of thoracic epidural analgesia on pulmonary function after coronary artery bypass surgery. Eur J Cardiothorac Surg 1996; 10: 859-65.
9. Tenling A, Joachimsson PO, Tydén H, Hedenstierna G. Thoracic epidural analgesia as an adjunct to general anaesthesia for cardiac surgery. Effects on pulmonary mechanics. Acta Anaesthesiol Scand 2000; 44: 1071-6.
10. Pöpping DM, Elia N, Marret E, Remy C, Tramèr MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg 2008; 143: 990-9.
11. Blumenthal S, Borgeat A, Pasch T, et al. Ropivacaine decreases inflammation in experimental endotoxin-induced lung injury. Anesthesiology 2006; 104: 961-9.
12. Casalino S, Mangia F, Stelian E, Novelli E, Diena M, Tesler UF. High thoracic epidural anesthesia in cardiac surgery: risk factors for arterial hypotension. Tex Heart Inst J 2006; 33: 148-53.
13. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011; 14: 145-61.

14. Steinthorsdottir KJ, Wildgaard L, Hansen HJ, Petersen RH, Wildgaard K. Regional analgesia for video-assisted thoracic surgery: a systematic review. Eur J Cardiothorac Surg 2014; 45: 959-66.
15. Dimova V, Lötsch J, Hühne K, et al. Association of genetic and psychological factors with persistent pain after cosmetic thoracic surgery. J Pain Res 2015; 27: 829-44.
16. Zunhammer M, Eichhammer P, Busch V. Do cardiorespiratory variables predict the antinociceptive effects of deep and slow breathing? Pain Med 2013; 14: 843-54.
17. Bjørnnes AK, Lie I, Parry M, et al. Association between self-perceived pain sensitivity and pain intensity after cardiac surgery. J Pain Res 2018; 11: 1425-32.
18. Kucyi A, Davis KD. The dynamic pain connectome. Cell 2015; 38: 86-95.
19. Vaitkevicius R, Saburkina I, Rysevaite K, et al. Nerve supply of the human pulmonary veins: an anatomical study. Heart Rhythm 2009; 6: 221-8.
20. Imazio M, Gaita F, LeWinter M. Evaluation and treatment of pericarditis: a systematic review. JAMA 2015; 13: 1498-506.
21. Sanchez R, Nygård E. Epidural anesthesia in cardiac surgery: is there an increased risk? J Cardiothorac Vasc Anesth 1998; 12: 170-3.
22. Ho AM, Chung DC, Joynt GM. Neuraxial blockade and hematoma in cardiac surgery: estimating the risk of a rare adverse event that has not (yet) occurred. Chest 2000; 117: 551-5.
23. Cook TM, Counsell D, Wildsmith JA; Royal College of Anaesthetists Third National Audit Project. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth 2009; 102: 179-90.
24. Van Cleve R. The rebound phenomenon-fact or fancy? Experience with discontinuation of long-term anticoagulation therapy after myocardial infarction. Circulation 1965; 32: 878-80.
25. Agarwal A, Patel A, Mufti O, Jbara Y, Abdul Jabbar A. Rivaroxaban rebound acute coronary event: a post marketing experience. Cardiol Res 2013; 4: 207-10.
26. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? Anesthesiology 2000; 93: 858-75.
27. Poffers M, Bühne N, Herzog C, et al. Sodium channel Nav1.3 is expressed by polymorphonuclear neutrophils during mouse heart and kidney ischemia in vivo and regulates adhesion, transmigration, and chemotaxis of human and mouse neutrophils in vitro. Anesthesiology 2018; 128: 1151-66.
28. Swenson BR, Gottschalk A, Wells LT, et al. Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. Reg Anesth Pain Med 2010; 35: 370-6.
29. Terkawi AS, Tsang S, Kazemi A, et al. a clinical comparison of intravenous and epidural local anesthetic for major abdominal surgery. Reg Anesth Pain Med 2016; 41: 28-36.
30. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. Br J Surg 2008; 95: 1331-8.