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Opioid-free general anaesthesia for transthoracic oesophagectomy: does it improve postoperative analgesia and other recovery criteria? A prospective randomised study

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Abstract

Background: Side effects related to intraoperative opioid administration are well known. Recently, it was found that opioids may inhibit cellular immunity through their effects on natural killer cell activity, stimulate angiogenesis and accentuate cancer cell growth. Hence, peri-operative use of opioids might affect long-term oncological outcomes in cancer surgical patients. Opioid-free anaesthesia (OFA) is a methodology that dodges narcotic use during anaesthesia by using blends of several drugs added to common anaesthetic agents.
The study aims to test the impact of OFA in transthoracic oesophagectomy in comparison with opioid-based anaesthesia technique (OBA) on postoperative analgesia and recovery criteria (hemodynamics, respiratory rate and haemoglobin oxygen saturation).

Results: The postoperative VAS was significantly lower in OFA group (A) than OBA group (B) in the measured time points (immediate postextubation, 30 min, 2 and 4 h postoperative) with *P* values 0.001, 0.001, 0.0012 and 0.0065 respectively. The time passed till first rescue analgesia requested was significantly longer in OFA group (A) than OBA group (B) and the total dose of rescue analgesia given to the patients were significantly higher in group B than group A. The recorded postoperative respiratory rate was significantly faster in OBA group (B) than OFA group (A), and the haemoglobin oxygen saturation (SPO_2) showed statistically significant lower values in the OBA group (B) than the OFA group (A).

Conclusions: We emphasise the perioperative safety and efficacy of the opioid-free anaesthesia techniques provided for transthoracic oesophagectomy with better postoperative analgesia and other post recovery criteria.

Trial registration: We carried out our trial at Ain-Shams University Hospitals, Cairo, Egypt, between June 2020 and November 2020. The study was approved by the Research Ethics Committee at the Faculty of Medicine, Ain Shams University and then registered in the Pan African Clinical Trials Registry (https://pactr.samrc.ac.za/) with the following ID (PACTR202010907549506).

Keywords: Transthoracic oesophagectomy, Opioid-free anaesthesia, Dexmedetomidine, Ketamine, Lidocaine, Opioid-based anaesthesia

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Background

Transthoracic oesophagectomy (Ivor Lewis oesophagectomy) is a surgical procedure in which part of the oesophagus is excised through combined abdominal and right thoracotomy incisions for benign and/or malignant oesophageal lesions. Although oesophageal malignancy is a highly fatal cancer, ranked as the sixth highest cancer-related death rate worldwide, yet limited available research data compared to other malignancies (Enzinger & Mayer, 2003; Zhang, 2013).

In the past two decades, there was super-sized utilisation of opioids, especially by the anaesthesiologists that led to actual 'opioid crisis', particularly obvious in the USA (Kharasch & Brunt, 2016; Kamdar et al., 2017; Steyaert & Lavand'homme, 2013). The well-known side effects related to intraoperative opioid administration include neuroadaptation, and activation of pronociceptive processes named 'opioid-induced hyperalgesia' which interferes with opioids' ability to provide long-term analgesia (Minkowitz et al., 2014; Simonnet & Rivat, 2003; Rivat & Ballantyne, 2016). Even hyperalgesia in other parts of the body that have not been operated upon was increasingly noticed with opioids (Lavand'homme & Steyaert, 2017).

Recent findings from retrospective, and experimental clinical trials, strongly suggest that opioids may inhibit cellular immunity through their effects on natural killer cell activity, stimulate angiogenesis and accentuate cancer cell growth. Thus, the opioids used peri-operatively might affect long-term oncological outcomes in oncological patients. This illustrates the current increase in using non-opioid medications as an alternative to opioids for pain relief during the perioperative time (Byrne et al., 2016).

Opioid-free anaesthesia (OFA) is a method that dodges narcotic use during anaesthesia with a blend of several drugs including alpha-2-agonist (dexmedetomidine), low-dose of N-Methyl-D-Aspartate (NMDA) receptor blockers (ketamine) and lidocaine to common anaesthetic agents. Reducing peripheral afferent noxious stimulation, these agents may potentiate the efficacy of opioids, besides the analgesic potentiality of dexmedetomidine and ketamine (Bugada et al., 2016).

Aim of the work

The study aims to test the impact of OFA in transthoracic oesophagectomy in comparison with opioid-based anaesthesia technique (OBA) on postoperative analgesia and recovery criteria (hemodynamics, respiratory rate and haemoglobin oxygen saturation).

Methods

This prospective, randomised, double-blind study was carried out after taking local ethical committee approval. A patient's written informed consent was got from all the candidates scheduled for transthoracic oesophagectomy. Patients' inclusion criteria included age between 18 and 64 years, BMI ≤ 35 $kg.m^{-2}$ at the initial hospital visit and forced vital capacity (FVC) or forced expiratory volume 1 (FEV1) ≥ 60% of the predicted values.

Exclusion criteria included class 2 obesity with BMI ≥ 35 $kg.m^{-2}$ at the initial hospital visit, history of thoracic trauma, FVC or FEV1 < 60% of predicted values, history of obstructive sleep apnea or need for a home CPAP mask, severe uncontrolled hypertension ≥ 180/110, uncontrolled diabetes mellitus, severe cardiovascular, renal or hepatic diseases, history of analgesic administration or intake during past 24 h, pregnant females and history of relevant drug allergy.

Current study included thirty patients that were randomly classified into 2 equal groups based on computer-generated random number tables prepared by a statistician not part of the study. We assigned the first group of patients to opioid-free general anaesthesia (group A), and the second group of patients to opioid-based general anaesthesia (group B). An anaesthesia resident who was neither involved nor interested by any means in the study performed the group assignment, preparation and administration of drugs. Blind grouping kept to all including the patients themselves, until the completion of the study. The study drugs were prepared, as described later, by one researcher and handed over inside sealed envelope to the anaesthesia resident attending the procedure who was neither interested nor involved in the study. Data collection was done by other anaesthesiologists who were blinded to the given medication during the study and not included in the research team. Consort chart of anaesthetic management is shown in Fig. 1.

We subjected all patients to a thorough medical history, physical examination with thorough airway assessment, laboratory investigations (complete blood count, fasting blood sugar, kidney, liver function tests, serum electrolytes, coagulation profile, arterial blood gases (ABG) and electrocardiogram), chest X-ray and respiratory function tests preoperatively. We counselled all the participants about the anaesthetic management and potential complications of both surgery and anaesthesia, and the explanations of visual pain analogue scale (VAS) from 1-10, we documented all these data.

Anaesthetic protocol

All participants were admitted to operating theatre (OR) induction area where patient identification was confirmed and an 18-gauge intravenous cannula inserted to all participants. The participants in group A received dexmedetomidine 1 μg/kg diluted in 20 ml saline 0.9% over 10 min immediately before induction of anaesthesia. The participants in group B received fentanyl 1 μg/

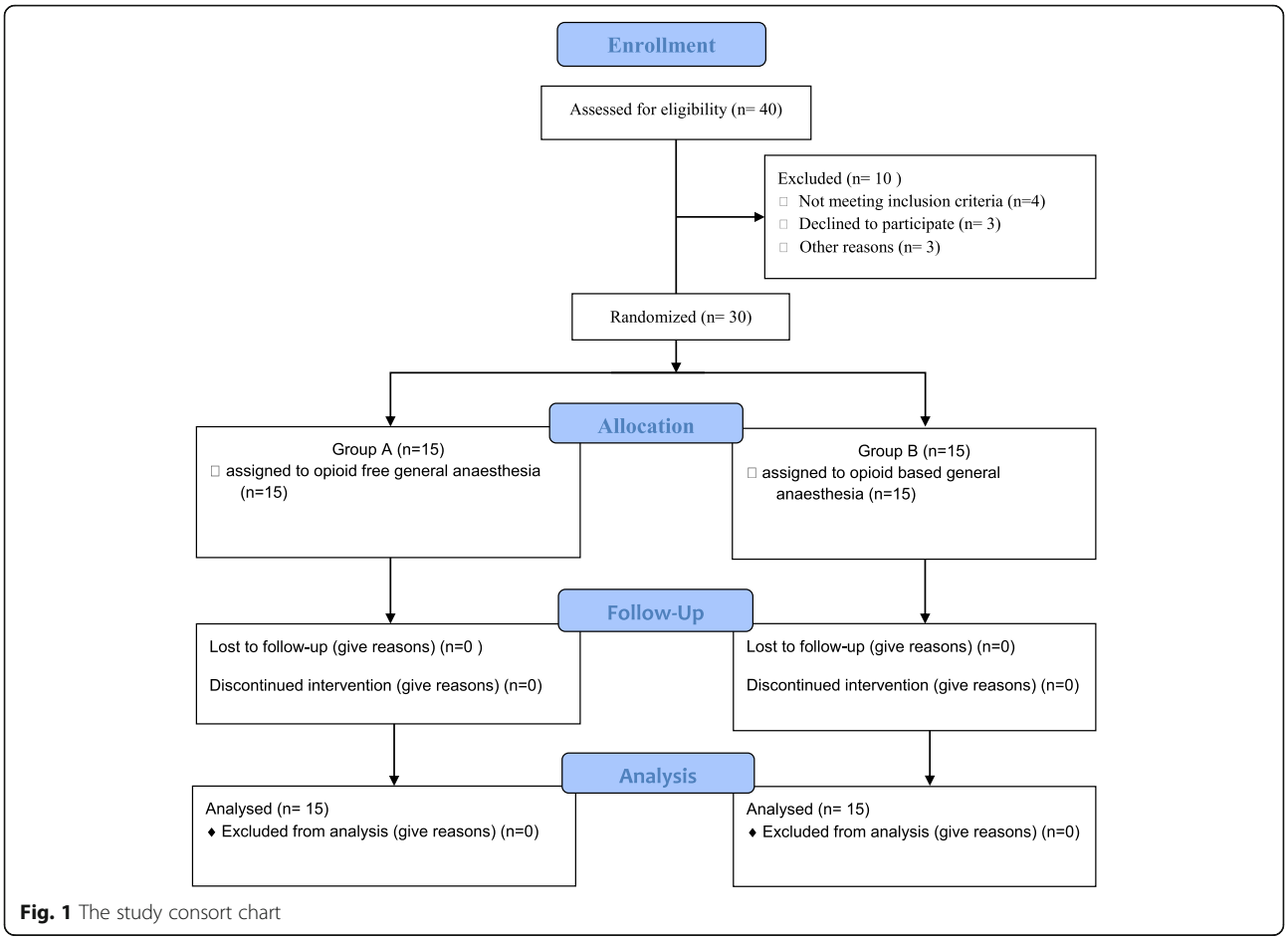

Fig. 1 The study consort chart

kg diluted in 20 ml of saline 0.9% over 10 min immediately before induction of anaesthesia.

General anaesthesia was induced with intravenous propofol 2.0 mg/kg, rocuronium 0.5 mg/kg then the double-lumen endotracheal tube was inserted orally and fixed after confirmation of its place by capnography and auscultation before and after patient positioning. Ultrasound-guided radial arterial cannula and internal jugular venous catheter were inserted, for invasive measurement of the blood pressure and central venous pressure (CVP). All patients were monitored throughout the surgery by standard monitors including continuous 5 lead electrocardiography, the pulse oximeter, non-invasive and invasive blood pressure, capnography, CVP, urine output and bispectral index (BIS).

In group A, patients received ketamine 0.5 mg/kg and lidocaine 1 mg/kg IV in 10 ml saline 0.9% immediately after intubation, followed by maintenance by continuous infusion of a mixture of 50 μg dexmedetomidine with 50 mg ketamine and 500 mg lidocaine in 50 ml syringe that was infused as maintenance as 1 ml/10 kg/h where the doses were (0.1 μg/kg/h dexmedetomidine, 0.1 mg/kg/h ketamine and 1 mg/kg/h lidocaine) and another 10 ml syringe filled with 100 mg ketamine in 9 ml saline for intraoperative breakthrough pain manifested by tachycardia and/or hypertension. In group B, a bolus of fentanyl 1 μg/kg diluted in 10 cc saline 0.9% immediately after intubation, followed by maintenance by continuous infusion of fentanyl 0.4 μg/kg/h diluted in 50 ml of saline 0.9% and another 10 ml syringe filled with 100 μg fentanyl in 9 ml saline for intraoperative breakthrough pain manifested by tachycardia and/or hypertension.

Anaesthesia was maintained by 2% sevoflurane in oxygen/air mixture 1:1 and then rocuronium 0.1 mg/kg was given for the maintenance of muscle relaxation.

When hypotension (MAP ≤ 60 mmHg) occurred, sevoflurane was reduced keeping the BIS within 40-60; if no response, a bolus of 250 mL ringer acetate with ephedrine 12.5 mg intravenously were given and when there was no response, noradrenaline 4 mg diluted in 50 ml saline IV infusion started by a dose of 50 ng/kg/min and titrated till normalisation of the blood pressure. If both HR and MAP increased over 20% above the baseline, a bolus of 1-2 ml from the pre-prepared 10 ml syringe for breakthrough pain management was given and if no response, sevoflurane concentration was increased to be 2

MAC till both reached the desirable levels; if no response, an extra bolus of 50 mg propofol IV was given to be repeated every 5 min till reaching 200 mg or both variables reached the desirable levels. If the MAP increased only with an acceptable level of BIS and without tachycardia, a bolus of 1-2 ml from the pre-prepared 10 ml syringe for breakthrough pain management was administered and if no response an extra bolus of 50 mg propofol IV was given to be repeated every 5 min till reaching 200 mg; if no response, nitroglycerin infusion was started in a dose 0.5 μg/kg/min to be titrated till normalisation of MAP. If a decrease in heart rate (more than 20% of baseline values) was associated with a decrease in the MAP below desirable values, 0.5 mg atropine was given.

At the end of surgery, the surgeon administered intercostal block at the thoracotomy incision and one space above and below with injection of 5 ml bupivacaine 0.25% at each space, and the attending anaesthetist performed bilateral ultrasound-guided subcostal transversus abdominis plane block with the injection of 20 ml of 0.125% bupivacaine for postoperative analgesia and then stopped the infused analgesic drugs and antagonised the muscle relaxant by sugammadex (Bridion) 2-4 mg/kg IV and then performed awake extubation and transferred the patients to the recovery unit after stable hemodynamics and oxygen saturation had been assured. All patients were transferred to post-anaesthesia care unit (PACU) and upon arrival to PACU, nasal oxygen catheter was applied with a flow of 2-4 L/min and a pulse oximeter and non-invasive blood pressure (NIBP) monitors were attached to the patients. Postoperative analgesia protocol for both groups was accomplished by acetaminophen 1 g given in the PACU to be repeated every 6 h and ketorolac tromethamine 30 mg intravenous slow injection every 8 h starting immediately post-extubation and if postoperative breakthrough pain (VAS ≥ 5), a 0.1 mg/kg mg nalbuphine IV was given and re-assessment of pain severity after that dose by 10 min and increments of the same dose of nalbuphine IV given till pain subsides without exceeding 20 mg every 3 h. Thereafter, all patients were transferred to the surgical ICU after 30 min when modified Aldrete score ≥ 9 was assured.

We assessed the participants for the following:

A. Postoperative pain as a primary outcome which was assessed by visual analogue pain score (VAS) which is a 10 cm line with 0 at one end representing no pain and 10 cm at the other end representing the worst imaginable pain at certain time points started immediately post-extubation, 30 min in the PACU, 2, 4 and 6 h postoperatively. After 6 h postoperatively, the patients had been managed in the surgical ICU according to their local analgesic protocols. The number of patients that needed rescue analgesia (nalbuphine) for breakthrough pain (VAS > 5) during the first 6 h postoperative and the time that elapsed till nalbuphine was firstly requested postoperatively had been measured together with the total dose of rescue analgesia used within the first 6 h postoperatively.
B. The other criteria of recovery will be the secondary outcome which are determined by the following:

1) Extubation time (which is the time from stoppage of anaesthetic drugs till extubation).
2) PACU discharge readiness time (time to reach modified Aldrete score ≥ 9).
3) Respiratory rate and oxygen saturation were recorded immediately after extubation and every 10 min for 30 min postoperatively, and then they were recorded every hour for the next 6 h in the surgical ICU.
4) Postoperative hemodynamics including mean heart rate (bpm) and MAP (mmHg) which were recorded from the immediate post-extubation, and every hour till the next 6 h postoperatively.
5) The incidence of postoperative hypoxia (Spo_2 ≤ 90%) to which oxygen therapy was increased to 6-10 L/min via a face mask during the first 6 h postoperatively and according to response to this step, the patients were assessed clinically by (respiratory rate, Spo_2 and ABG) for the need of mechanical ventilation either non-invasive or invasive.
6) The incidence of postoperative mechanical ventilation according to ventilation guidelines during the first 6 h postoperatively.
7) Patients' satisfaction were recorded by using '4' points score (1=very good, 2=good, 3=fair, 4=poor).
8) The duration of ICU stay.

The primary endpoint to this study was the occurrence of any postoperative surgical complication needing urgent operative intervention.

Sample size

Using PASS II programme for sample size calculation and according to mulier et al. who found that the expected VAS postoperatively in study groups were 4.9 ± 0.8 and 1.7 ±0.9, a sample size of 15 patients per group can detect the difference between the two groups with power > 99% and setting alpha error at 5% (Mulier et al., 2018).

Statistical analysis

We analysed the data using the Statistical Package for Social Science (SPSS) version 22.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Non parametric data will be expressed as median and inter-quartile range (IQR). The independent samples paired *t* test of significance was used when comparing two parametric means. The Chi-square (X^2) test of significance was used to compare proportions between two qualitative parameters. Mann-Whitney *U* test was used for two-group comparisons in non-parametric data. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p* value was significant as:

- Probability (*P* value)
  - *P* value < 0.05 was significant.
  - *P* value < 0.001 was considered as highly significant.
  - *P* value > 0.05 was non-significant.

Results

A consort trial flow diagram presented in Fig. 1 illustrating that out of 40 patients approached, 4 did not meet the criteria for inclusion, 3 refused to take part in the study, 3 needed urgent postoperative explorations for acute bleeding, leaving 30 patients suitable to be enrolled in this investigation (Fig. 1).

The patients' characteristics and surgical history of the participants showed a non-significant difference amongst both groups, whilst the indications for oesophagectomy either cancerous (which was more common) or non-cancerous (Achalasia and post corrosive stricture) were statistically non-significant between both groups. Also, the duration of surgery showed a non-significant difference in both groups (6.19 ± 0.91 h and 6.87 ± 1.73 h respectively) (Table 1). The postoperative VAS was significantly lower in OFA group (A) than OBA group (B) in the measured time points (immediate postextubation, 30 min, 2 and 4 h postoperative) with *P* values 0.001, 0.001, 0.0012 and 0.0065 respectively, but at 6 h postoperative there was no statistical difference between both groups as *P* value was 0.45. Although the number of patients required rescue analgesia during the estimated time was statistically non-significant (12 (80%) vs 15 (100%) with *P* value 0.224, but the time passed till first rescue analgesia requested was significantly longer in OFA group A than OBA group B (165.8 ± 126.6 min vs 23.0 ± 12.2 min respectively) with *P* value 0.001 and the total dose of rescue analgesia given to the patients were significantly higher in group B than group A with *P* value 0.001 during the first 6 postoperative hours (Table 2).

Table 1 Patients' characteristics and surgical history of the participants

	Group (A) OFA (No. 15)	Group (B) OBA (NO. 15)	Test *P* value
Age (years)			*T* = 0.644 0.525
Range	*30-60*	3-57	
Mean ± SD	*41.40 ± 7.66*	43.13 ± 7.08	
Gender			X^2 = 0.001
M/F (no.)	*10/5*	9/6	
BMI (kg/m²)			*T* = 1.48 0.151
Range	*22-32*	22-32	
Mean ± SD	*27.53 ± 3.04*	26.0 ± 2.62	
ASA status			X^2 = 0.001
ASA I-II	*11*	10	
Cause of oesophagectomy (no.)			X^2 = 0.001
• Cancer	*10*	11	
• Non-cancerous	*5*	4	
History of previous abdominal surgery			X^2 = 0.001
Yes	*8*	7	
No	*7*	8	
Duration of surgery (h)			*T* = 1.35 0.19
Mean ± SD	*6.19 ± 0.91*	6.87 ± 1.73	

BM body mass index, *ASA* American Society of Anesthesiologists, *T* student *t* test, X^2 Chi square test, *P* was significant if < 0.05

Table 2 The postoperative VAS and time needed till rescue analgesia requested and the total dose of rescue analgesia given

Postoperative VAS	Group (A) OFA	Group (B) OBA	*P* value
Immediate postoperative**			Mann-Whitney = 17.5 < 0.001*
Range	2-5	4-6	
Median (IQR)	3 (2-4)	5 (4-6)	
30 min postoperative**			Mann-Whitney = 9.5 < 0.001*
Range	2-6	5-8	
Median (IQR)	4 (3-5)	7 (6-8)	
2 h postoperative**			Mann-Whitney = 35.5 0.0012*
Range	3-6	5-8	
Median (IQR)	4 (3.25-5.75)	6 (5-7)	
4 h postoperative**			Mann-Whitney = 48 0.0065*
Range	2-6	4-6	
Median (IQR)	3 (2-5)	5 (4.25-6)	
6 h postoperative			Mann-Whitney = 95 0.45
Range	2-5	3-5	
Median (IQR)	3 (3-4)	4 (3-4)	
Number of patients needed rescue analgesia (nalbuphine)	12 (80%)	15 (100%)	$X^2 = 1.5$ 0.224
Time passed till first rescue analgesia requested (min)***			$T = 4.35$ 0.001* Mann-Whitney = 16 < 0.001
Mean ± SD Range	165.8 ± 126.6 15-360	23.0 ± 12.2 6-45	
Median (IQR)	140 (48.75-285)	20 (12.75-33.75)	
Total dose of rescue analgesia within first 6 h (mg) ***			$T = 9.69$ < 0.001*
Mean ± SD	9.0 ± 6.21	26.27 ± 3.01	

IQR inter quartile range, *T* student *t* test, *P* was significant if ≤ 0.05, *Significant

The recorded postoperative respiratory rate was significantly faster in OBA group (B) than OFA group (A) after 20, 30 min post-extubation and at the first and second hours postoperatively (25.33 ± 1.05 vs 22.27± 2.15, 28.4 ± 2.38 vs 23.20 ± 1.9, 28.47 ± 2.56 vs 22.27 ± 3.15 and 31.20 ± 2.21 vs 25.60 ± 2.23 respectively with *P* values < 0.001 for all). Also, the haemoglobin oxygen saturation (SPO_2) showed statistically significant lower values in the OBA group (B) than the OFA group (A) after 20 min, 30 min post-extubation and at the first and second hours postoperative with *P* values 0.001, 0.001, 0.001 and 0.009 respectively. However, there were non-significant differences found between both groups immediately post-extubation, 10 min post-extubation, third, fourth, fifth and sixth postoperative hours regarding the respiratory rate and SPO_2. The incidences of postoperative hypoxia and postoperative mechanical ventilation within the first 6 postoperative hours were significantly less in OFA group than in OBA group with *P* values 0.036 and 0.029 respectively (Table 3).

The postoperative heart rate recorded immediately post-extubation and at the first 2 h postoperatively was significantly higher in OBA group (B) than OFA group (A) with *P* values 0.001, 0.001 and 0.001 respectively, whilst the MAP showed significantly higher values in OBA group (B) than OFA group (A) immediately post-extubation and at the first 2 h postoperatively. Hemodynamic variables (heart rate and MAP) in both groups showed non-significant statistical differences at the 3rd, 4th, 5th and 6th postoperative hours (Table 4).

Regarding the extubation time was slightly longer in group (A), compared with group (B) but statistically insignificant (10.30 ± 4.84 min vs 8.24 ± 4.12 min respectively). The PACU discharge readiness time (modified Aldrete score ≥ 9) was statistically longer in OFA group (A) than OBA group (B) (20.60 ± 4.64 min vs14.42 ± 3.91min, respectively). The duration of ICU stay was significantly shorter in OFA group A than OBA group B (2.27 ± 0.59 days and 3.40 ± 1.18 days) (Table 5). The patients' satisfaction score was significantly higher in group (A) than group (B) with *P* value 0.033 (Table 6).

Discussion

Transthoracic oesophagectomy is one of the major surgical procedures that contain a lot of anaesthetic and surgical challenges with expected severe postoperative

Table 3 Postoperative patients' respiratory criteria and the incidence of early postoperative hypoxia and mechanical ventilation within first 6 h postoperatively

	Respiratory rate (RR)		*P* value	O2 saturation (SPO_2%)		*P* value
	Group (A) OFA	Group (B) OBA		Group (A) OFA	Group (B) OBA	
Immediate post-extubation Mean ± SD	23.80 ± 2.37	24.20 ± 1.90	0.614	96.80 ± 0.77	97.20 ± 0.77	0.168
10 min postoperative Mean ± SD	21.87 ± 2.64	20.67 ± 1.99	0.172	95.47 ± 1.36	95.20 ± 0.86	0.526
20 min postoperative Mean ± SD	22.27 ± 2.15	25.33 ± 1.05	< 0.001	95.40 ± 0.83	93.33 ± 1.23	< 0.001*
30 min postoperative Mean ± SD	23.20 ± 1.90	28.40 ± 2.38	< 0.001	93.73 ± 0.96	91.47 ± 1.19	< 0.001*
1 h postoperative Mean ± SD	22.27 ± 3.15	28.47 ± 2.56	< 0.001	94.27 ± 0.80	91.13 ± 1.13	< 0.001*
2 h postoperative Mean ± SD	25.60 ± 2.23	31.20 ± 2.21	< 0.001	91.60 ± 2.20	89.33 ± 2.23	0.009*
3 h postoperative Mean ± SD	24.73 ± 2.052	25.133 ± 1.457	0.544	93.467 ± 1.408	92.600 ± 1.352	0.097
4 h postoperative** Mean ± SD	24.73 ± 1.4864	25.13 ± 2.232	0.569	92.067 ± 1.438	91.33 ± 2.257	0.299
5 h postoperative Mean ± SD	24.267 ± 2.282	25.93 ± 3.453	0.132	91.67 ± 1.397	91.4 ± 2.165	.692
6 h postoperative Mean ± SD	24.13 ± 2.326	25.067 ± 2.434	0.292	92.6 ± 1.298	92.53 ± 1.246	0.887
Incidence of postoperative hypoxia ($SPO_2 \leq 90\%$)	3 (20.0%)			6 (40.0%)		0.036*
Incidence of postoperative MV	2 (13.3%)			5 (33.3%)		0.029*

T student *t* test, X^2 = Chi square test, *P* was significant if ≤ 0.05,*Significant at level 0.05

pain, and as a well-known fact that effective reduction of the perioperative pain using well-planned pain management has a beneficial influence on outcomes after major surgery (Feld et al., 2003). The impact of opioid hazards varied by the type of surgical procedure and included pulmonary complications, longer lengths of stay and greater costs (Sayal et al., 2018).

This randomised prospective comparative study highlighted the role of OFA as an effective substitute for OBA with significantly lower VAS in the OFA group (A)

Table 4 Postoperative hemodynamics including heart rate (bpm) and mean arterial blood pressure (mmHg) during the first 6 h postoperatively

	Heart rate (bpm)		*P* value	MAP (mmHg)		*P* value
	Group (A) OFA	Group (B) OBA		Group (A) OFA	Group (B) OBA	
Immediate post-extubation Mean ± SD	88.33 ± 4.51	109.80 ± 6.53	< 0.001	91.00 ± 6.16	102.73 ± 4.80	< 0.001
1 h postoperative Mean ± SD	99.60 ± 6.48	108.80 ± 6.72	< 0.001	79.67 ± 5.77	92.67 ± 7.94	< 0.001
2 h postoperative Mean ± SD	93.60 ± 6.74	103.20 ± 4.51	< 0.001	86.20 ± 8.36	98.73 ± 4.11	< 0.001
3 h postoperative Mean ± SD	86.133 ± 3.248	87.000 ± 4.209	0.533	90.13 ± 4.26	92.13 ± 6.128	0.309
4 h postoperative Mean ± SD	85.267 ± 7.4973	88.4 ± 4.9541	0.189	94.133 ± 5.8416	96.8 ± 5.9064	0.224
5 h postoperative Mean ± SD	86.933 ± 5.0915	88.933 ± 3.9725	0.241	90.933 ± 8.3876	92.600 ± 6.9980	0.559
6 h postoperative Mean ± SD	89.467 ± 7.2197	92.600 ± 4.8226	0.175	93.2 ± 8.2997	95.200 ± 6.1899	0.461

Bpm beat per minute, *MAP* mean arterial pressure, *P* was significant if ≤ 0.05,*Significant at level 0.05

Table 5 Comparing the average extubation time, PACU discharge readiness time and duration of ICU stay (days)

	Group A OFA	Group B OBA	*t* test *P* value
Extubation time (min)	10.30 ± 4.84	8.24 ± 4.12	1.255 0.22
PACU discharge readiness time (min)	20.60 ± 4.64	14.42 ± 3.91	3.945 < 0.001*
Duration of ICU stay (days)			
Mean ± SD	2.27 ± 0.59	3.40 ± 1.18	0.003*

T student *t* test, *P* was significant if ≤ 0.05,*Significant at level 0.05

than OBA group (B) during the first 4 postoperative hours with longer times needed till rescue analgesia was requested for breakthrough pain and smaller total doses of such rescue analgesia in spite of statistically non-significant number of patients required rescue analgesia. Also, other recovery criteria including PACU discharge readiness time (modified Aldrete score ≥ 9) was statistically longer in OFA group (A) than OBA group (B) together with respiratory rate, SPO_2, heart rate and MAP which showed significant outcomes in favour of OFA. The duration of ICU stay was significantly shorter and the patient satisfaction score was significantly better in the OFA group (A). The extubation time, the incidences of postoperative hypoxia and mechanical ventilation showed clinically significant differences between both groups, but statistically were insignificant.

Our findings regarding the higher analgesic effectiveness of OFA with longer periods of pain-free intervals till rescue analgesia requested with lesser doses of rescue analgesia go in agreement with Elsaye et al. who compared between the impact of opioid-free anaesthesia (OFA) and opioid-based anaesthesia (OBA) on postoperative analgesia in morbidly obese patients underwent laparoscopic cholecystectomy as a primary outcome and the hemodynamic stability, the total amount of pethidine consumption postoperatively and postoperative complications in PACU, and they found OFA provides postoperative pain relief and intraoperative hemodynamic stability without significant associated adverse effects compared with OBA (Elsaye et al., 2019). Also, Xu et al. have shown significantly more improved postoperative pain and enhanced recovery of bowel functions in patients undergoing abdominal hysterectomy with intravenous infusion of lidocaine combined with dexmedetomidine than patients received intravenous infusion of each agent solely or placebo (Xu et al., 2017). Toleska and Dimitrovski stated that the postoperative needed opioids were significantly lesser in the OFA group at rest and coughing, compared to the opioid group (Toleska & Dimitrovski, 2019). Choi et al. compared continuous intraoperative infusion of fentanyl, remifentanil and dexmedetomidine on postoperative analgesia, perioperative hemodynamics, and sedation quality in laparoscopic total hysterectomy and proved that the postoperative VAS was not significantly different amongst dexmedetomidine, fentanyl and remifentanil groups. They attributed those results to the stronger analgesic effects of fentanyl and remifentanil than dexmedetomidine when used solely to achieve an OFA technique (Choi et al., 2016).

Table 6 Patients' satisfaction score

Patients satisfaction score	Group A OFA	Group B OBA	X^2 *P* value
Very good	12 (80 %)	5 (33.33%)	6.816 0.033*
Good	2 (13.33%)	8 (53.33%)	
Fair	1 (6.67%)	2 (13.33%)	
Poor	0 (0.0%)	0 (0.0%)	

X^2 Chi-square test, *p* value > 0.05 NS; **p* value < 0.05 S

These better outcomes in postoperative VAS, pain-free interval and rescue analgesia consumption could be explained by the assumed synergistic analgesic effect of the infused lidocaine, ketamine and dexmedetomidine as a part of the multimodal analgesic protocol used. Opioid-induced hyperalgesia seems to be another more reasonable cause for this finding. We used intravenous ketamine in a sub-anaesthetic dose, as this offers powerful analgesia with clinical safety equivalent to that of intravenous morphine (Motov et al., 2015). Ketamine acts as a non-competitive antagonist at the NMDA receptor with resultant analgesic, anti-tolerance, anti-hyperalgesic and anti-allodynia properties together with the opioid-sparing effects in sub-anaesthetic doses, increasing respiratory and hemodynamic stability (Cromhout, 2003; Guinot et al., 2019). Lidocaine intravenous infusion showed significant analgesic effects which have been repeatedly prolonged beyond its half-life which is approximately 1.5 h even if administration of lidocaine was ceased at the end of the operative procedure after bolus or infusion extending up to 12 h (Vadivelu et al., 2016; Farag et al., 2013; Groudine et al., 1998). Intravenous lidocaine analgesic action explained by having a modulatory effect on the initiation of the surgically induced inflammatory response primarily. The lidocaine prolonged

analgesic influence, which extends well beyond the infusion time, might be ultimately justified by sustained concentrations of lidocaine in the cerebrospinal fluid (Herroeder et al., 2007). Besides, lidocaine metabolites have analgesic effects by inhibiting the glycine transporter1, which was proven not only to reduce pain but also to improve cognitive function in an animal model of chronic pain (Tsai et al., 1998). Dexmedetomidine with its alpha-2 adrenergic receptor agonist action results in sedation, analgesia, anxiolysis, perioperative sympatholytic, cardiovascular stabilising effects, reduced anaesthetic requirements and preservation of respiratory function (Tanabe et al., 2008).

The incidence of postoperative hypoxia and mechanical ventilation were significantly lower in the OFA group, where only 3 participants (all were males and heavy smokers) suffered from postoperative hypoxia, only 2 participants needed mechanical ventilation which may be explained by the underlying lung pathology together with the postoperative reduction in work of breathing. Meanwhile, 6 participants of the OBA group developed postoperative hypoxia, only 5 of them needed mechanical ventilation. These findings can be explained by the highly efficient analgesic effect of the used combination in addition to avoidance of the serious postoperative sedative and respiratory depressant effects of the opioids (Lee et al., 2015). The postoperative respiratory rate was significantly higher in the OBA group (B) immediately post-extubation, 10 min, 20 min, 30 min, 1st hour and 2nd hour postoperative, whilst the SPO_2 was significantly higher in OFA group (B) immediately post-extubation, 10 min, 20 min, 30 min, 1st hour and 2nd hour postoperative and both variables were statistically indifferent later in between both groups. The current study findings are concordant with Bhardwaj et al. who compared outcomes between OFA (with dexmedetomidine, lignocaine, ketamine) and OBA in obese patients undergoing urological procedures and stated that OFA provided better postoperative pain control and the hemodynamic parameters like heart rate, mean arterial pressure and respiratory rate were significantly lower (more stable) in OFA group compared to OBA group whereas saturation remained comparable in both the group (Kemp et al., 2008). This reflects better respiratory pattern, which is explained by the OFA superiority of analgesia and sedation without respiratory depression over the OBA, especially during the first 4 h. Also, the indifference after the 2nd postoperative hour might be explained by the wearing off the infused agents' effects. The extubation time showed statistically non-significant despite clinically noticeable results which cannot be explained except by the small sample size and the need for a larger sample to detect a significant difference if ever existed.

The postoperative hemodynamics represented by the postoperative heart rate and MAP showed statistically significant differences between both groups as described earlier which goes with many studies supporting the better postoperative hemodynamics. These findings could be explained by the analgesic, sedative and sympatholytic action of dexmedetomidine with an elimination half-life of 2.1–3.1 h is reported in healthy volunteers (Yoo et al., 2015). Patient satisfaction scores were also significantly better in the OFA group (A) than the OBA group (B).

In our study, we can strongly recommend the use of opioid-free anaesthetic techniques which is globally recognised as 'state-of-the-art anaesthesia technique' by comparison with the current standard of care such as 'opioid-based anaesthesia' or 'balanced anaesthesia' with a significantly safe and better quality of patient recovery and overall experience after transthoracic oesophagectomy surgeries. However, our observations require more analytical reviews of the implications of OFA over a larger number of patients and the creation of large multicenter databases.

Conclusion

We emphasise the perioperative safety and efficacy of the opioid-free anaesthesia techniques provided for transthoracic oesophagectomy with better postoperative analgesia and other postrecovery criteria.

Abbreviations

OFA: Opioid-free anaesthesia; OBA: Opioid-based anaesthesia; NMDA: N-Methyl-D-Aspartate; FVC: Forced vital capacity; FEV1: Forced expiratory volume 1; CPAP: Continuous positive airway pressure; VAS: Visual pain analogue scale; MAP: Mean arterial pressure; CVP: Central venous pressure; BIS: Bispectral index; IV: Intravenous; HR: Heart rate; NIBP: Non-invasive blood pressure; PACU: Post-anaesthesia care unit; ICU: Intensive care unit; SPO_2: Haemoglobin oxygen saturation; ABG: Arterial blood gases

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Authors' contributions

TNA contributed to the conception and design of the study, organised the data collection, reviewed and greatly contributed to the interpretation of results, checked the statistical analysis and revised the manuscript critically for important intellectual content. WSG performed data collection and organised data preparation. All authors actively discussed the manuscript, critically reviewed its comprehensive content and finally approved the version to be submitted for publication.

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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. The email address of the corresponding author is tamernabil610@gmail.com

Declarations

Ethics approval and consent to participate

Ethics Committee's approval of General Surgery Research Ethics Committee of Ain Shams University approved this study. This study was registered in the Pan African Clinical Trials Registry (https://pactr.samrc.ac.za/) in 2nd July, 2020, with the following ID (PACTR202010907549506).
Informed written consent to participate in the study was provided by all participants according to our local and international research ethical guidelines.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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