Prospective, randomized comparison of ketorolac vs. Thoracic epidural analgesia with non-muscle relaxant anaesthesia after thymectomy in myasthenic patients

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Citation

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Abstract

We test the hypothesis that ketorolac or thoracic epidural anaesthesia (TEA) without neuromuscular blockers improves pain control and pulmonary functions after thymectomy in seventy five myasthenic patients. They were randomly allocated received, either a saline placebo (n=25), ketorolac 15 mg, followed by IVI for 7.5 mg.h $^{-1}$ for 12 hours (n=25), or TEA with 10 mL of bupivacaine 0.5%, followed by 8 mL.h $^{-1}$ of bupivacaine 0.125% for 12 hours (n=25). Anaesthesia was induced with fentanyl (1.0 µg.kg $^{-1}$) and propofol and maintained with propofol and 67% N_2O. Patients receiving ketorolac and TEA had a smaller increase in HR and MAP, lower supplementary doses of fentanyl, shorter emergence and extubation times (P<0.001), and PACU stay, lower respiratory rate, better pain control, for the first 12 postoperative hours, higher PEFR values at 1 and 6 h, and no patient had to be re-intubated postoperatively. Seven patients in TEA group needed IV ephedrine. In conclusion, the use of ketorolac is safe and might be an alternative to TEA in providing excellent intra-operative anaesthesia, early extubation, and postoperative analgesia in myasthenic patients after thymectomy.

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INTRODUCTION

Extended thymectomy is an excellent operative procedure for myasthenia gravis (MG). [1] Anaesthesia for thymectomy in MG is challenging. Myasthenic patients are known to be unusually sensitive to non-depolarizing neuromuscular blockers (NMBs) agents with a higher rate of unsuccessful extubation at the end of surgery and with longer postoperative ventilatory support and hospital stay. [2] The non-muscle relaxant anaesthetic technique (NMRT) encompasses the use of general anaesthesia with the use of topical laryngo-tracheal analgesia to facilitate direct laryngoscopy and endo-tracheal intubation and to eliminate the need of NMBs. [3] In addition; depression of central respiratory drive from co-administered intra-operative opioids can further compromise respiratory functions in the immediate postoperative period. [4]The use of combined TEA and NMRT offers better intra- and postoperative pain control and on-table extubation of the trachea. [5]

Non-steroidal anti-inflammatory drugs (NSAIDs) have had the potential to replace opioids in the treatment of severe pain. Clinical evidence has shown that ketorolac and morphine are equivalent in reducing postoperative pain scores but there is a distinct benefit favouring ketorolac in terms of side effects. [6] To date, there are no reports of the peri-operative use of ketorolac in MG.

We postulated that the use of ketorolac or TEA with NMRT, for myasthenic patients undergoing trans-sternal thymectomy, might reduce the intra-operative need of supplementary analgesics, allow early extubation, and improve the postoperative analgesia and pulmonary functions. Therefore, the present study was designed to evaluate the effects of ketorolac or TEA with NMRT on the analgesic consumptions, the extubation time, and peak expiratory flow rate (PEFR) after thymectomy.

PATIENTS AND METHODS

This prospective randomized placebo-controlled study was carried out from November 2001 to October 2006 at Cardio-Thoracic Surgery Department-Mansoura University Hospitals, after approval of the Institutional Ethical

Committee. After written informed consent was obtained, we studied 75 myasthenic patients aged 18-60 years, undergoing trans-sternal thymectomy.

All patients had MG proven by electroneuro-myographic assessment and by elevated anti-acetylcholine receptor antibodies. According to the modified classification by Osserman and Genkins,[7] the clinical severity of MG was graded in five stages (I, ocular signs only; IIA, generalized mild muscle weakness; IIB, generalized moderate weakness and/or bulbar dysfunction; III, acute fulminating presentation and/or respiratory dysfunction; IV, late generalized weakness). Preoperative stabilization before thymectomy included anticholinesterase therapy, plasmapheresis, or intravenous -globulin. All patients were undergoing besides routine examinations, preoperative lung volume spirometry, and chest CT scan with contrast enhancement to look for thymoma.

Exclusion criteria included contraindications to the use of NSAIDs (allergy, bleeding tendency, bronchial asthma, peptic ulcer, liver, or kidney diseases), refusal of or other contraindication to epidural anaesthesia, allergy to amide local anaesthetics, and communication barrier to pain reporting.

Before surgery, patients received instructions on how to use of a peak flowmeter, measure pain with a visual analogue scale (VAS), and to request supplementary analgesics if needed. All operations were performed by the same four surgeons. The anaesthesiologist administering the anaesthesia was not involved with subsequent postoperative patient assessment. Morning dose of pyridostigmine was continued on the day of surgery, because we are using a NMRT. No premedication was given. All patients were pre-hydrated preoperatively with Ringer's Lactate solution 7 $mL.kg^{-1}$. An arterial line (22 G) was inserted under local anaesthesia, for continuous direct arterial blood pressure recording and blood sampling for gasometry.

Patients were allocated randomly to two groups by drawing of sequentially numbered sealed opaque envelopes that each contained a computer-generated randomization code. Placebo group (n=25) received an IV bolus of 20 mL of normal saline 0.9%, 20 minutes before induction of anaesthesia, followed by a constant infusion (10 $mL.hr^{-1}$) for the first 12 postoperative hours. Ketorolac group (n=25) received an IV loading dose of 20 mL of ketorolac tromethamine [Toradol, MUP, Syntex Pharm AG] (0.75 $mg.mL^{-1}$), 20 minutes before induction of anaesthesia, followed by a constant infusion (10 $mL.hr^{-1}$) for the first 12 postoperative hours. Both placebo and the ketorolac solution looked the same. In the thoracic epidural anaesthesia (TEA) group (n=25), 20 minutes before induction of anaesthesia, patients were placed in the lateral position, and under sterile conditions, an epidural catheter was placed at the $T_{4–5}$ interspaces by using a Tuohy 18-gauge needle (Standard Epidural Catheter; Perifix ® , B. Braun, US). A 20 G multiport epidural catheter was advanced 3 cm into the epidural space. Aspiration and injection of a 3 mL test dose with 2% lidocaine excluded accidental intravascular or subarachnoid catheter position. All blocks were performed by a senior anaesthesiologist. After the placement of the epidural catheter, the patients received 2 mL increments of Bupivacaine 0.5% for a total dose of 10 mL. The adequacy of the block was tested by pinprick test to achieve a dermatomal epidural block from T_1 to L_2. Continuous infusion of bupivacaine 0.125% was started at a rate of 8 $mL.hr^{-1}$ and was continued for the first 12 hours after surgery. All the staff in the operating room was unaware of the randomization code of the patients.

All patients were monitored with five leads electrocardiography, pulse oximetry, invasive arterial blood pressure [Medexine, KONTRON instruments Ltd, Blackmore Lane, WATFORD, UK], nasopharyngeal temperature and end-tidal CO_2 ($EtCO_2$) [KONTRON KoloRMON TM 7250 plus anesthesia colour monitor] was performed.

After pre-oxygenation for three minutes, anaesthesia was induced with fentanyl (1.0 $\mu g.kg^{-1}$) followed with propofol (2-3 $mg.kg^{-1}$). Once the patient became unconscious, as judged by loss of response to command and loss of eyelash reflex, mask ventilation was initiated. Laryngoscopy was performed and the topical lidocaine 10% (Xylocaine 10% spray, Astra-Zeneca, Egypt) was sprayed on the pharynx, epiglottis, larynx, between the vocal cords, and into the upper trachea (maximum dose limited to 5 $mg.kg^{-1}$). After two minutes the trachea was intubated with a single-lumen tube. All patients received lactated Ringer's solution (7 $mL.kg^{-1}.h^{-1}$) throughout the procedure.

Anaesthesia was maintained with a continuous infusion of propofol (4-6 $mg.kg^{-1}.h^{-1}$) and nitrous oxide 67% in oxygen and supplemented by fentanyl boluses (0.5 $\mu g.kg^{-1}$) as necessary based on clinical signs (to maintain the heart rate and arterial pressure within 25% of the pre-induction

baseline values). Hypotension (blood pressure <25% from baseline measurement) was treated with incremental doses of IV ephedrine (5 mg). The lungs were ventilated with KONTRON ABT 5300 ventilator to maintain the $EtCO_2$ concentration in the range of 32 to 36 mmHg.

Twenty minutes before the end of surgery, the infusions of propofol was gradually decreased by 20% in every 5 minutes, and on completion of surgery, the infusions were discontinued. At the end of surgery, separation from mechanical ventilation was started when the patient showed the criteria for weaning from mechanical ventilation. These criteria included $PaO_2 \geq 90$ mmHg (FiO_2=0.40), $PaCO_2 \leq 50$ mmHg, pH≥7.30, and respiratory rate (R.R) ≤30 breaths.min $^{-1}$. If these criteria were not met, ventilatory support was continued postoperatively with synchronized intermittent mandatory ventilation, and the patient was weaned gradually from this support. Criteria for extubation included meeting the criteria for weaning, vital capacity (VC) ≥10 mL.Kg $^{-1}$, and inspiratory pressure better than -30 cmH_2O. Criteria for re-intubation included R.R>40 breaths.min $^{-1}$, respiratory acidosis, or VC≤8 mL.kg $^{-1}$. [8]

Heart rate (HR) and mean arterial blood pressure (MAP) were recorded immediately before [baseline] and at 30, 60, 120 minutes after intubation, and at the end of anaesthesia. The total doses of fentanyl administered throughout surgery, the time from the end of anaesthesia to eye opening and recovery of consciousness (emergence time), the duration of postoperative ventilatory support, the time from the end of anaesthesia to extubation (extubation time), the need for re-intubation, the number of patients required intra-operative ephedrine for hypotension, and length of stay in post-anaesthesia care unit (PACU) were recorded.

The postoperative R.R, arterial blood gases variables and the severity of postoperative pain were assessed on a 10-cm a VAS at rest and on cough (0 for no pain to 10 for the worst pain imaginable), at 0, 1, 2, 4, 8, 12, 16, 20, and 24 hours after surgery. After operation, tramadol (Tramal, Janssen-Cilag Pharmaceutica Ltd) 100 mg IV was prescribed when visual analogue scale scores were 5 or more at rest, and 7 or more with cough or if the patient requested additional analgesia. The time to first request for analgesia and the number of patients receiving tramadol during the first 24 postoperative hours were recorded.

We measured PEFR, with each patient in a 30° head-up position, before surgery and at 1, 6, and 12 hours after extubation. The patients exhaled forcefully three successive times into a Standard Mini Wright's peak flowmeter [Keller Medical Specialties, Antioch, IL], and the highest value was recorded.

Haematocrit values were recorded before and 48 hours post surgery. Skin Ivy bleeding time (BT) was determined preoperatively and at 1 and 24 hours postoperatively by an experienced technician.

The presence and intensity of side effects were scored as follows: sedation (four-point verbal rating scores (VRS): awake, drowsy, rousable or deep sleep); and nausea and vomiting (0 = no nausea; 1 = nausea no vomiting; 2 = nausea and vomiting) at 0, 1, 2, 4, 8, 12, 16, 20, and 24 hours after surgery. All major complications (respiratory failure, cardiovascular events, bleeding, and renal dysfunction) or other minor postoperative complications were recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistica '99 software (StatSoft, Tulsa, Okla.). Data were tested for normality using Kolmogorov-Smirnov test. One way Anova test followed by Tukey's honest significant difference Posthoc test was performed to compare the parametric values of the studied groups. Serial changes in haemodynamic and postoperative data at induction were analyzed with repeated measures analysis of variance. PEFR variables, at different times within groups were analysed with repeated measure analysis of variance (Anova test). Kruskal-Wallis-test followed by rank sum test was performed to compare the non-parametric values of the three groups. Data were expressed as mean (SD), number (%) or (median [range]). A value of $P<0.05$ was considered to represent statistical significance. Based upon our preliminary data, a prior power analysis indicated that 25 patients in each group would be a sufficiently large sample size to be adequate to detect a 20% reduction in the extubation time, with a type-I error of 0.05 and a power of approximately 90%.

RESULTS

All 75 patients completed the study period: 25 patients in the placebo group, 25 in the ketorolac group and 25 in the TEA group. Demographic data did not significantly differ between the three groups [Table (1)]. All patients were receiving anticholinesterase therapy and no patient needed plasmapheresis or mechanical ventilation in the past.

Figure 1

Table 1: Patient data.

	Placebo group (n= 25)	*Ketorolac group (n= 25)*	*TEA group (n= 25)*
Age (Years)	(33 [19 – 60])	(23 [18 – 59])	(39 [19– 60])
Sex (Female : Male)	)٪16 : 9 (64	)٪14 : 11 (56	)٪18 : 7 (72
Weight (Kg)	70.9 (6.61)	70.1 (7.61)	76 (9.14)
Height (cm)	164 (3.92)	165 (3.55)	165 (4.21)
Surgical duration (hours)	2.2 (0.32)	2.1 (0.36)	2.2 (0.41)
Osserman's classification			
I	)٪18 (72	)٪12 (48	)٪15 (60
IIA	)٪4 (16	)٪ (287	)٪5 (20
IIB	)٪3 (12	)٪6 (24	)٪5 (20
III	)٪ 0 (0	)٪ 0 (0	)٪ 0 (0
IV	)٪ 0 (0	)٪ 0 (0	)٪ 0 (0

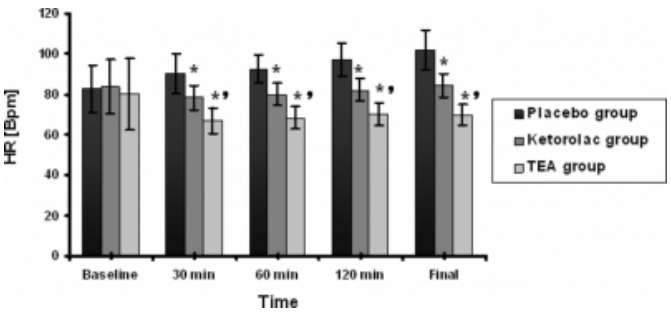
Data are expressed as (median [range]), n (%), and mean (SD).

* Significant when P < 0.05.

Baseline HR and MAP were similar between the studied groups [Figure (1), (2)].

Figure 2

Figure 1: Intra-operative heart rate (HR) [Bpm] changes.

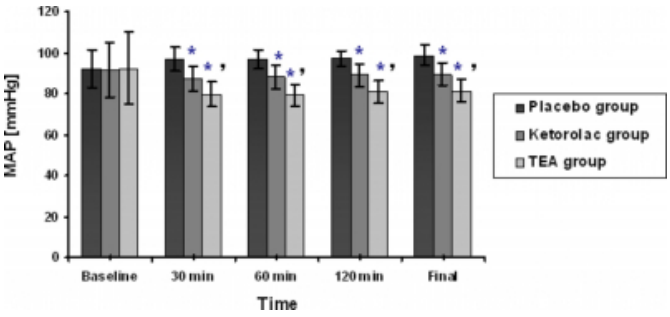


Data are expressed as mean (SD).

* P < 0.05 significant when compared with the placebo group. ˙P<0.05 significant when compared with the ketorolac group.

Figure 3

Figure 2: Intra-operative mean arterial blood pressure (MAP) [mmHg] changes.



Data are expressed as mean (SD).

* P < 0.05 significant when compared with the placebo group. ˙P<0.05 significant when compared with the ketorolac group.

The changes in HR and MAP from baseline values after induction at 30, 60, and 120 minutes, and at the end of anaesthesia were significantly greater in the placebo group than in the ketorolac and TEA groups (P<0.001). Therefore, HR and MAP were significantly lower in TEA group compared to ketorolac group at the same periods [Figure (1), (2)]. Seven patients (28%) in TEA group required rescue IV ephedrine for hypotension (P=0.02) (95% CI = 1.8 to 8). The doses of ephedrine were 15 mg (three times) in three of seven patients, 10 mg (two times) in two patients, and 5 mg (three times) in two patients.

The total doses of fentanyl administered throughout surgery were significantly lower in the ketorolac and TEA groups than in the placebo group (P<0.001) [Table (2)].

Figure 4

Table 2: The peri-operative data.

	Placebo group (n= 25)	*Ketorolac group (n= 25)*	*TEA group (n= 25)*
Intra-operative fentanyl consumption (μg.kg^{-1})	(1.5 [1.5 – 2.5])	(1.5 [1 – 1.5]) *	(1.25 [1 –1.5])*
Emergence time (minutes)	18.7 (9.64)	5.8 (1.52) *	7.5 (2.31) *
Postoperative ventilatory support (minutes)	22.9 (12.23)	3.3 (1.51) *	8.9 (2.31) *
Extubation time (minutes)	31.5 (13.20)	9.1 (1.91) *	11.5 (2.42) *
Length of stay in PACU (hours)	3.7 (0.71)	1.3 (0.34) *	1.5 (0.52) *
Respiratory rate (breath.min^{-1})			
0 hour	(23 [17 – 26])	(20 [15 – 23]) *	(19 [15 – 21]) *
1 hour	(22 [19 – 27])	(19 [17 – 21]) *	(19 [18 – 23]) *
2 hours	(20 [19 – 23])	(18 [17 – 20]) *	(19 [17 – 20]) *
4 hours	(19 [17 – 21])	(16 [15 – 18]) *	(17 [16 – 21]) *
8 hours	(18 [15 – 21])	(14 [14 – 17]) *	(16 [14 – 20]) *
12 hours	(19 [14 – 22])	(14 [13 – 16]) *	(14 [13 – 16]) *
16 hours	(18 [16 – 22])	(15 [14 – 18]) *›	(17 [13 – 19])
20 hours	(18 [17 – 21])	(19 [16 – 23])	(19 [16 – 23])
24 hours	(18 [15 – 21])	(18 [14 – 21])	(18 [16 – 21])
Haematocrit (%): Pre-operative	40.8 (3.45)	39.7 (2.37)	42.1 (2.83)
48 h postoperative	37.2 (3.73)	36.8 (2.08)	39.0 (3.13)

Data are expressed as mean (SD), n (%), and (median [range]).

* P < 0.05 significant when compared with the placebo group.

› P<0.05 significant when compared with the TEA group.

In the ketorolac and TEA groups, all patients were extubated in the operating room. The emergence time, the duration of postoperative ventilatory support, the time to extubation, and length of stay in PACU were significantly shorter in the ketorolac and TEA groups than in the placebo group [Table (2)].

The patients in the TEA and ketorolac groups experienced lower increases in the mean R.R, with no significant changes in blood gases variables, and significantly lower pain scores [VAS] at rest and on cough, than in the placebo group, for the first 12 and 16 postoperative hours, respectively, (P<0.01) [Table (2), (3)].

The time to first tramadol request in the ketorolac group [3.7 (1.76) hours] and in the TEA group [4.3 (1.41) hours] was significantly longer than in the placebo group [1.9 (1.31) hours] (P=0.003) [Table (2)]. Additionally, the number of patients receiving tramadol was significantly higher in the placebo group than in the TEA and ketorolac groups for the first 12 and 16 postoperative hours, respectively (P<0.04) [Table (4)]. VRS scores for sedation were similar in the three groups.

Figure 5

Table 3: Visual analogue scale (VAS) assessment of postoperative pain, at rest and on cough, in the studied group.

	Placebo group (n= 25)		*Ketorolac group (n= 25)*		*TEA group (n= 25)*	
	At rest	On cough	At rest	On cough	At rest	On cough
0 hour	(5 [0 – 8])	(7 [2 – 10])	(2 [0 – 4]) *	(4 [2 – 6]) *	(1 [0 – 3]) *	(3 [2 – 6]) *
1 hour	(4 [1 – 9])	(6 [3 – 10])	(3 [1 – 4]) *	(5 [3 – 6]) *	(2 [1 – 5]) *	(4 [2 – 5]) *
2 hours	(4 [3 – 10])	(6 [4 – 10])	(2 [1 – 6]) *	(4 [3 – 8]) *	(2 [1 – 5]) *	(5 [3 – 7]) *
4 hours	(4 [3 – 7])	(6 [5 – 9])	(3 [0 – 4]) *	(5 [2 – 6]) *	(2 [0 – 4]) *	(5 [2 – 7]) *
8 hours	(5 [1 – 9])	(7 [3 – 10])	(3 [1 – 5]) *	(5 [3 – 7]) *	(2 [1 – 6]) *	(5 [3 – 7]) *
12 hours	(4 [0 – 7])	(6 [2 – 9])	(2 [0 – 4]) *	(4 [2 – 6]) *	(2 [0 – 3]) *	(4 [2 – 6]) *
16 hours	(5 [1 – 9])	(7 [3 – 10])	(3 [2 – 5]) *	(5 [5 – 7]) *	(4 [3 – 8])	(6 [5 – 10])
20 hours	(3 [0 – 7])	(4 [2 – 9])	(2 [0 – 9])	(4 [2 – 10])	(4 [1 – 9])	(6 [2 – 10])
24 hours	(3 [0 – 6])	(5 [2 – 8])	(2 [0 – 8])	(4 [2 – 10])	(4 [0 – 8])	(4 [2 – 9])

Data are expressed as (median [range]).

* P < 0.05 significant when compared with the placebo group.

Figure 6

Table 4: The postoperative analgesia.

	Placebo group (n= 25)	*Ketorolac group (n= 25)*	*TEA group (n= 25)*
Time to first request for analgesia (hours)	1.9 (1.31)	3.7 (1.76) *	4.3 (1.41) *
	Number receiving tramadol		
0 – 4 hours	20 (80%)	7 (28%) *	8 (32%) *
4 – 8 hours	18 (72%)	6 (24%) *	6 (24%) *
8 – 12 hours	17 (68%)	5 (20%) *	8 (32%) *
12 – 16 hours	18 (72%)	11 (44%) *›	19 (76%)
16 – 20 hours	15 (60%)	18 (72%)	20 (80%)
20 – 24 hours	13 (52%)	14 (56%)	16 (64%)

Data are expressed as mean (SD), and n (%).

* P < 0.05 significant when compared with the placebo group.

› P<0.05 significant when compared with the TEA group.

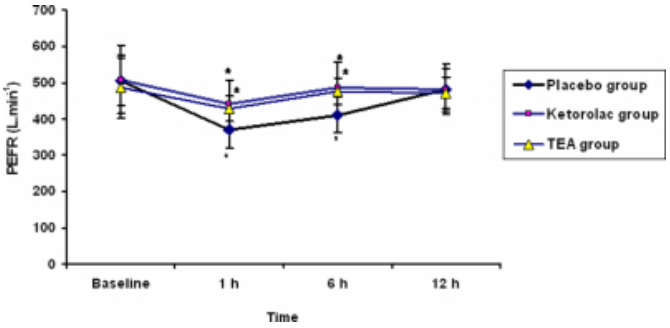
Six patients in the placebo group and no patient in the ketorolac and TEA groups required subsequent re-intubation for respiratory support (P=0.004) (95% CI = 1.2 to 7).

There was no significant difference in the pre-operative PEFR values between the studied groups [Figure (3)]. The patients in the ketorolac and TEA group showed significantly higher values of mean PEFR compared to the patients in the placebo group, at 1 and 6 hours after extubation [441 (65.91) and 428 (33.91), respectively vs. 371 (50.35) L.min $^{-1}$, at 1h] (P<0.001) and [485 (71.51) and 475 (37.01), respectively vs. 410 (48.81) L.min $^{-1}$, at 6h] (P<0.01) [Figure (3)]. Compared to the baseline and at 12 hours after extubation values, PEFR values decreased significantly in the placebo group at 1 and 6 hours after

extubation (P< 0.01) [Figure (3)].

Figure 7

Figure 3: Peri-operative peak expiratory flow rate (PEFR) [L.min] changes.



Data are expressed as mean (SD).

* P < 0.05 significant when compared with the placebo group. ˙P<0.05 within group significant changes compared to the baseline and at 12 h values.

The pre-operative and 48-hours postoperative haematocrit values were similar in the three groups and no patient required blood transfusion [Table (2)]. Preoperative and postoperative bleeding times did not change significantly.

We found no differences between the three groups in the incidence of postoperative major or minor side effects, which included respiratory failure, cardiovascular events, bleeding, renal dysfunction, nausea, vomiting, and pruritus.

DISCUSSION

Transsternal thymectomy is an established surgery for MG and several anaesthetic techniques have been described for its management. The present study demonstrated that NMRT with propofol-fentanyl, combined with ketorolac or TEA, allow early extubation in the immediate postoperative period, and achieve effective pain relief with improvement in the respiratory functions in myasthenic patients undergoing thymectomy.

We avoided muscle relaxants and inhalational anaesthetics in myasthenic patients because; their use has been associated with a higher rate of unsuccessful extubation at the end of surgery with longer postoperative mechanical ventilation and hospital stay. [9,10,11,12]

We recorded lower increase in intra-operative HR and MAP, lower supplementary doses of fentanyl, and shorter emergence and extubation times in our ketorolac and TEA groups. Ketorolac proved to have morphine sparing effect, improve analgesia, reduce opioid requirements, attenuate the stress response, and to reduce the incidence of adverse effects and respiratory depression commonly associated with opioids. [5, 13,14] Similarly, the combined use of propofol and TEA bupivacaine 0.125% infusion 4–6 mL.hr $^{-1}$ for thymectomy in MG eliminates the need of NMBs and offers better peri-operative pain control in addition to on-table extubation of the trachea. [15] However, in the current study, the patients in the TEA group showed significant haemodynamic instability.

Not surprisingly, rapid emergence from anaesthesia, shorter duration of ventilatory support, and shorter time to extubation in the ketorolac and TAE group was facilitated by providing maximal analgesia and by minimizing the side effects of opioids. Moreover, our results are in accordance with another study, which reported successful early tracheal extubation, after thymectomy in myasthenic patients, managed with propofol combined with epidural administration of bupivacaine and sufentanil (n=12), and delayed extubation for 3-4 hours, in those managed with balanced anaesthetic technique included various inhalational agents with small doses of opiates (n=24) (odds ratio=4.2 (1.1–9.7), P=0.03). [11]

The present study showed improved analgesia and decreased tramadol consumption for the first 12 and 16 postoperative hours with using of TEA and ketorolac, respectively, which may coincide with the duration of action of the drugs infusions. This was similar to those reported in previous studies, that general anaesthesia combined with ketorolac or TEA improved postoperative analgesia.[15,16] O'Hara and others' (1987) compared single IM doses of either ketorolac or morphine for relief of moderate to severe postoperative pain in 155 patients. This study showed that ketorolac, 30 and 90 mg to be a safe and effective analgesic for relief of postoperative pain, similarly to morphine, 12 mg, for the first 3 hours after IM injection, with no reported serious side effects. [17]

Impaired pulmonary function due to MG is further compromised by thymectomy. PEFR measurement is a useful postoperative screening test for restrictive pulmonary disorders included MG.[18,19] PEFR values in the present study were significantly higher in the ketorolac and TEA groups, at 1, and 6 hours after extubation. Therefore, we reported lower increase in the mean R.R without a difference in $PaCO_2$ in the TEA and ketorolac groups for the first 12 and 16 postoperative hours, respectively. Pain relief is,

therefore, essential to facilitate coughing and deep breathing and to promote postoperative pulmonary functions. [20] Similarly, Kirsch and co-workers' (1991) reported better analgesic quality and lower R.R for the first 12 postoperative hours after epidural morphine (7 mg) in myasthenic patients (n=10) after thymectomy. [21]

Platelet inhibition with altered haemostasis is among the list of adverse effects associated with the administration of ketorolac. The overall risk of operative site bleeding related to ketorolac therapy is only slightly higher than with opioids. However, this risk increases with high doses or prolonged therapy (>5 days). [22] In the present study, we found no evidence of increased peri-operative blood loss in those receiving ketorolac. This may be attributed to the relatively small doses of ketorolac and the limited periods of continuous IV infusion.

In conclusion, in this study intravenous ketorolac with NMRT is safe and might be an alternative to TEA in providing excellent intra-operative anaesthesia, postoperative analgesia, and allowed early extubation after thymectomy, in myasthenic patients, with no reported adverse effects. Therefore, TEA is associated with potential complications and success rate greatly depends on experience.

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