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Twenty-four-hour postoperative orphenadrine and ketorolac infusion efficiently precedes orphenadrine-diclofenac infusion as an opioid-sparing analgesic modality after mastectomy

Yehya Shahin Dabour, Ahmed Said Elnoury and Ahmed Abouelgheit Daoud

Department of Anesthesia & ICU, Faculty of Medicine, Benha University, Benha, Egypt

ABSTRACT

Objectives: Determination of the efficacy of postoperative (PO) infusion of orphenadrine/ketorolac (O/KT) combination for 24-h as PO analgesia and its opioid-sparing rate (OSR) compared to orphenadrine/diclofenac (O/D) and Placebo infusions for women undergoing Modified Radical Mastectomy.

Patients & Methods: A total of 129 women with operable cancer breast received the same anesthetic procedure and were randomly divided into groups I–III according to the PO infusion. Infusions were started before skin closure for 60-min and were repeated for 8-hourly for 24-h. Pain severity was assessed using the numeric rating scale (NRS) and at NRS scores >4, morphine 5 mg was given. The OSR was defined as the number of patients who required no PO morphine in the study outcome.

Results: The OSR was significantly higher with O/KT than with O/D infusion (72.1% vs. 51.2%, respectively) and the frequency of requesting multiple doses of morphine was significantly lower with O/KT than other infusions with significant difference in favor of O/D infusion than placebo. The frequency of early requests of morphine was significantly lower with O/KT having a significantly longer duration till the first request. The average pain scores were significantly lower with O/KT infusion. PO morphine-related side effects were significantly higher, while patient and surgeon's satisfaction scores were significantly lower among patients of the placebo group.

Conclusion: Cocktails of ketorolac or diclofenac with orphenadrine infusions for 24-h after mastectomy improve PO pain sensation with a reduction of opioid consumption. The O/KT infusion was superior to the O/D infusion with regard to OSR and pain scores.

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1. Introduction

Management of postoperative (PO) pain is optimal for reducing pain-induced delayed mobilization with subsequent prolonged hospital stay and consumption of resources [1]. Various regimens of opioid-sparing analgesia were tried; however, their results are discrepant and disappointing [2].

Non-steroidal anti-inflammatory drugs (NSAIDs) are indicated as PO analgesia for multiple surgical procedures; however, their use may be precluded by their side effects, especially on prolonged use [3]. The use of NSAIDs and muscle relaxants solely or in combination could successfully relieve pain due to the potentiation of pharmacological effects that allow the achievement of better treatment results [4].

Ketorolac tromethamine (KT), an NSAID that belongs to the hetero-aryl acetic acid derivatives family, is used in the management of moderate-to-severe acute pain [5], but its short half-life (~5.5 h) necessitated the use of frequent administrations in cases that require long-term analgesia [6].

Orphenadrine citrate is a centrally acting muscle relaxant with anti-muscarinic effects and was used for Parkinsonism treatment and alleviation of the antipsychotic drug-induced neuroleptic syndrome [7]. Earlier studies reported the analgesic effectiveness of the combination of orphenadrine-paracetamol in neck pain [8] and the opioid-sparing effect of the combination of orphenadrine/diclofenac (O/D combination) after unilateral total hip arthroplasty [9]. Thereafter, another study observed no improvement in pain intensity or physical functioning tests after the administration of four intravenous drugs including the O/D combination for patients with chronic low-back pain [10]. On contrary, a recent study documented the effectiveness of the infusion of an O/D combination for the relief of acute back musculoskeletal pain syndrome [4]. These discrepant results indicated the

CONTACT Yehya Shahin Dabour yehyadabour@gmail.com Department of Anesthesia & ICU, Faculty of Medicine, Benha University, Benha 13518, Egypt

effectiveness of infusion of O/D combination for the management of acute not for chronic pain, however, depending on these results other combinations may be more effective.

2. Objectives

This study tried to evaluate the effectiveness of PO infusion of orphenadrine/ketorolac (O/KT) combination for 24-h for PO analgesia and on the opioid consumption by patients undergoing modified Radical Mastectomy

3. Design

Prospective comparative randomized study

4. Setting

Department of Anesthesia, ICU and Pain Therapy, Faculty of Medicine, Benha University in conjunction with multiple private surgical centers.

5. Patients

All women assigned for Modified Radical Mastectomy for operable cancer breast were subjected to evaluation for inclusion and exclusion criteria.

6. Exclusion criteria

Bleeding diathesis, coagulopathies, neurological or psychological disorders, contraindication for the used drugs, maintenance on opioid or non-opioid pain therapies for any indications, distant metastasis and refusal to participate in the study are the exclusion criteria.

7. Inclusion criteria

Women who had operable cancer breast, free of exclusion criteria and accepted to participate in the study were included in the study.

8. Ethical considerations

The study was started in Jan 2020 after approval of the protocol, which was discussed with each patient before enrolment and patients who accepted to participate in the study had signed a written fully informed consent. The final approval was obtained after the completion of case collection in April 2023 by No.: RC16.4.23.

9. Blindness

The infusion bottles containing the study solutions were prepared after dose adjustment by the hospital pharmacist who numbered the bottles by I–III according to the group and was the only one to know the constituents of the infusion bottles. The anesthetists were blinded about the constituents of each bottle and were to provide the bottles assigned for each group and were responsible for the evaluation of assessment tools. At the end of the study, the pharmacist provided the anesthetists with the constituents and the results were interpreted.

10. Sample size calculation

A previous study compared the opioid-sparing effect of the combination of ketoprofen/paracetamol versus placebo for 25 patients per group and reported no obvious difference between both groups [11]. Another study used the diclofenac/gabapentin combination for 60 patients per group and reported a significant difference in requesting PO opioids [12]. Considering the rate of mastectomy in our institute, the sample size was calculated to be 43 patients per group to achieve significant differences with α value of 0.05 and β value of 20%, the study power was calculated to be 80%.

11. Randomization

Patients who signed the written consent were randomized into three groups using randomization computer software for a frequency of 1:1:1 with intersequencing dropping to allow free randomization. The obtained sequences were transformed to symbols I–III, which were written on cards enveloped in dark envelops and each patient chose one envelope and introduces it to the pharmacist who was responsible for the provision of the anesthetist by the bottles assigned for this patient.

12. Study protocol

Patients were clinically evaluated at the pre-anesthetic area for demographic data, ASA grading, presence of other medical diseases, baseline heart rate (HR) and mean arterial pressure (MAP) were determined. The study infusions were started before skin closure and continued for 60-min, and were repeated 8 h for three bottles of 500 cc of normal saline free of additives for patients of Group I, containing a combination of 150 mg diclofenac sodium (Epifenac, 25 mg/ml; 3-ml amp; Egyptian International Pharmaceutical Industries Company [EPICO], Cairo, Egypt) and 60 mg of orphenadrine citrate (Norflex, 30 mg/ml; 2-ml amp; EPICO, Cairo, Egypt) for patients of Group II or combination

of 60 mg ketorolac tromethamine (Ketolac, 15 mg/ml; 2-ml amp; Amriya Pharma, Alex, Egypt) and 60 mg of orphenadrine for patients of Group III.

13. Anesthetic procedure

Anesthesia was induced by propofol 2 mg/kg, rocuronium 0.5 mg/kg, tracheal intubation was aided by gentle tracheal pressure, and an endotracheal tube measuring 6.5 mm was inserted. After intubation of the trachea, the lungs were ventilated with 100% O_2 in the air using a semi-closed circle system. During surgery, ventilation was controlled with a tidal volume of 6–8 ml/kg, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide (Pa_{CO2}) of 32–35 mmHg. Anesthesia was maintained with sevoflurane 1.7 MAC and top-up doses of rocuronium if needed and intraoperative analgesia was provided as fentanyl, 1 µg/kg. Muscle relaxant was reversed using neostigmine 0.05 mg/kg with atropine 0.01 mg/kg.

14. Intraoperative (IO) and postoperative (PO) monitoring

- Intraoperative HR and MAP were non-invasively monitored and if systolic blood pressure was decreased by >20%, rapid infusion of lactated Ringer's solution and intravenous boluses of ephedrine were given.
- Immediate PO care was provided at PACU and patients were maintained on oxygen (6 L/min) via a facemask in the PACU if oxygen saturation as judged by pulse oximetry was dropped. Patients who had a score of ≥8 on the Aldrete recovery score [13] were discharged from PACU.
- PO pain severity was assessed using an 11-point numeric rating scale (NRS) with numbers from 0 to 10 where 0 indicates no pain and 10 indicates the worst pain imaginable [14]. PO pain was assessed at the time of PACU discharge and 4-hourly for 24-hr. Patients who had NRS pain scores of >4 received PO rescue analgesia as morphine 5 mg diluted in 10-ml saline and given slowly intravenously.
- PO sedation was assessed immediately after transfer to PACU, 30-min, and 60-min PO and 8 h thereafter using the Ramsey sedation scale (RSS) [15].
- The incidence and scoring of PO nausea and vomiting (PONV) were determined at the end of 24-h PO as previously described by **Watcha & White** [16]. Ondansetron 40 mg intravenous injection was given to patients who had severe nausea or vomiting.
- Surgeons' and patients' satisfaction with PO analgesia was recorded at the end of 24-h PO using a visual analogue scale of 0–100 with a higher score and higher satisfaction [17].

15. Study outcomes

(1) The primary outcome is the opioid-sparing rate (OSR) which was defined as the number of patients who did not require PO morphine.
(2) The secondary outcomes included the effect of the PO infusions on NRS pain scores, the duration of analgesia which was defined as the duration till the 1st request of rescue analgesia and the number of requests of rescue analgesia.

16. Results

During the evaluation, 144 women were assigned to undergo surgery, 6 women were ASA grade III, 5 women were maintained on analgesia for orthopedic problems, three women had coagulopathy and one refused to participate in the study, these 15 women were excluded, and 129 women were randomly allocated into the three groups as illustrated in Figure 1 that also showed the primary outcome for each group.

The enrolment data of patients showed non-significant differences between the three groups as shown in Table 1. Also, the differences between patients of the three groups as regards operative and IO hemodynamic data and amount of blood loss were insignificant as shown in Table 2.

According to the number of requests for rescue analgesia through the 24-h PO period, the OSR of O/KT infusion was significantly ($P = 0.027$) higher than the OSR of O/D infusion (72.1% vs. 51.2%, respectively). Further, the frequency of patients who requested multiple doses of rescue analgesia was significantly higher in group I than groups II (P1 < 0.001) and III (P2 < 0.001) and in group II (P3 = 0.017) than in group III (Figure 2). The average number of requests of opioid analgesia showed significant ($P = 0.0047$) difference between the studied groups and the average dose of opioid consumed by patients who requested rescue analgesia was significantly lower in group III compared to group I (P2 = 0.0012) and group II (P3 = 0.023) with insignificantly (P1 = 0.301) lower dose requested by patients of group II than patients of group I.

The frequency of early requests of rescue analgesia was significantly lower among patients of group III than patients of group I (P2 = 0.0001) and group II (P3 = 0.036), while it was non-significantly (P1 = 0.211) lower among patients of group II than patients of group I. Also, the average duration till 1st request of rescue analgesia was significantly longer with O/KT infusion than both placeboes (P2 < 0.001) and O/D infusions (P3 = 0.0006), while it was non-significantly (P1 = 0.068) longer with O/D than placebo infusions.

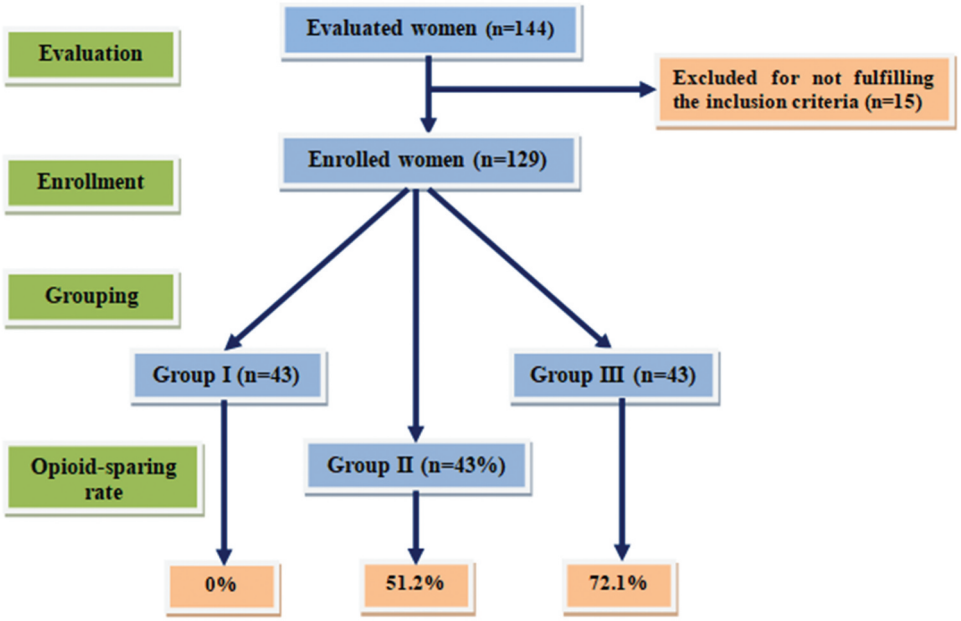

Figure 1. Study flow chart.

Table 1. Demographic and clinical data of the enrolled patients of the studied groups.

Data			Group I (Placebo)	Group II (O/D)	Group III (O/KT)	P-value
Age (years)	Average (±SD)		56±8.6	55±6.7	56±7.4	0.781
BMI (kg/m^2)	Strata	<25	1 (2.3%)	1 (2.3%)	0	0.504
		25–30	24 (55.8%)	17 (39.5%)	21 (78.8%)	
		>30–35	18 (41.9)	25 (58.2%)	22 (51.2%)	
	Average (±SD)		29.7±2.3	3.2±1.9	3.4±2.1	.283
Menopause	Pre-menopause		6 (14%)	4 (9.3%)	3 (7%)	0.549
	Post-menopause		37 (86%)	39 (9.7%)	40 (93%)	
Smoking	Smoker		2 (4.7%)	3 (7%)	1 (2.3%)	0.817
	Ex-smoker		3 (7%)	4 (9.3%)	5 (11.6%)	
	Un-smoker		38 (88.3%)	36 (83.7%)	37 (86.1%)	
Presence of other morbidities	Yes		4 (9.3%)	3 (7%)	5 (11.6%)	0.759
	No		39 (9.7%)	40 (93%)	38 (88.4%)	
ASA grade	I		36 (83.7%)	33 (76.7%)	34 (79%)	0.714
	II		7 (16.3%)	10 (23.3%)	9 (21%)	
Hemodynamic variate	Heart rate (beats/min)		8.3±2.7	81±4.8	81.3±3.5	0.414
	Mean arterial pressure (mmHg)		88±4.3	88.7±4	87.6±4.6	.510

BMI: Body mass index; P-value indicates the significance of the inter-group difference as judged by the one-way ANOVA test with Tukey HSD; *P* value at a cutoff point of ≥0.05 indicates the non-significant difference.

Table 2. Operative data of the enrolled patients of the studied groups.

Data			Group I (Placebo)	Group II (O/D)	Group III (O/KT)	P-value
Operative time (min)	Average (±SD)		120±12.4	122 ±12.6	124 ±12.8	0.343
Anesthesia time (min)	Average (±SD)		131±14.2	134±13.7	135±14.3	0.393
Intraoperative hemodynamics	Heart rate (beats/min)	T0	8.3±2.7	81±4.8	81.3±3.5	0.414
		T1	86±2.5*	86.7±4*	85±3.4*	.515
		T2	77±2.4*	77.6±3.9*	78±3*	.342
		T3	82.3±2*	82.9±3.5*	83.2±3.1*	.373
	Mean arterial pressure (mmHg)	T0	88±4.3	88.7±4	87.6±4.6	0.510
		T1	93.5±4.3*	94.1±3.6	93.4±4.5*	.679
		T2	79.8±5*	78.4±4.7	77.2±6.9*	.104
		T3	9.2±4.5*	9.1±4.1	89.5±4*	.709
Intraoperative blood loss (ml)			245.9±36.3	254±60	250±8.6	.830

T0: Preoperative, T1: at induction of anesthesia; T2: 1-h intraoperative; T3: at time of extubation; *: indicated significant difference versus T0 measures as determined by the paired t-test for two dependent means; P-value indicates the significance of the inter-group difference as judged by the one-way ANOVA test with Tukey HSD; *P* value at a cutoff point of ≥0.05 indicates the non-significant difference

Table 3. PO pain data of patients of the studied groups.

Data		Group I (Placebo)	Group II (D/O)	Group III (KT/O)	P-value
Number of requests for rescue analgesia	No (OSR)	0	22 (51.2%)	31 (72.1%)	P1<0.001
	Once	7 (16.3%)	5 (11.6%)	8 (18.6%)	P2<0.001
	Two	23 (53.5%)	12 (27.9%)	4 (9.3%)	P3=0.017
	Three	13 (3.2%)	4 (9.3%)	0	
	Average (±SD)	2.14±.7	1.95±.67	1.42±.51	.0047
Average of the total dose of opioid consumed by patients who requested it (mg)		1.7±3.38	9.76±3.35	7.08±2.57	P1=0.301 P2=0.0012 P3=.023 P2=0.0012 P3=0.023
Duration till 1st request of rescue analgesia (h)	2-h	8 (18.6%)	3 (7%)	0	P1=0.211
	4-h	14 (32.6%)	6 (14%)	0	P2=0.0001
	6-h	7 (16.3%)	4 (9.3%)	1 (2.3%)	P3=0.036
	8-h	8 (18.6%)	4 (9.3%)	3 (7%)	
	12-h	5 (11.6%)	0	0	
	16-h	1 (2.3%)	2 (4.7%)	1 (2.3%)	
	20-h	0	2 (4.7%)	4 (9.3%)	
	24-h	0	0	3 (7%)	
	Average (±SD)	5.9±3.4	8±5.6	16.5±8.3	P1=0.068 P2<0.001 P3=.0006 P2<0.001 P3=0.0006
Pain Numerical Rating scale score	0	1.33±1.15	.4±.88	0	<0.001
	2-h	2.14±1.45	.95±1.34	.14±.5	<.001
	4-h	2.26±1.53	1.2±1.57	.35±.8	<.001
	6-h	2.37±1.13	1.26±1.36	.7±1.1	<.001
	8-h	2.81±1.03	1.58±1.28	1.12±1.2	<.001
	12-h	2.7±1.2	1.95±1.05	1.28±.88	<.001
	16-h	2.35±1.46	2.3±.9	2.05±.87	.402
	20-h	2.37±1.46	2.5±1	2.56±.88	.735
	24-h	1.81±1.28	2.5±1.18	2.63±.85	.002
	Average (±SD)	2.26±.55	1.65±.7	1.2±.5	P1<0.001 P2<0.001 P3=.0011 P2<0.001 P3=0.0011

P1 indicates the significance of the difference between groups I & II; P2 indicates the significance of the difference between groups I & III; P3 indicates the significance between groups II and III; the significance of the difference in numerical data was estimated using the one-way ANOVA test with Tukey HSD; the significance between numbers and percentages was evaluated using Chi-square test; *P* value at a cutoff point of <0.05 indicates the significant difference.

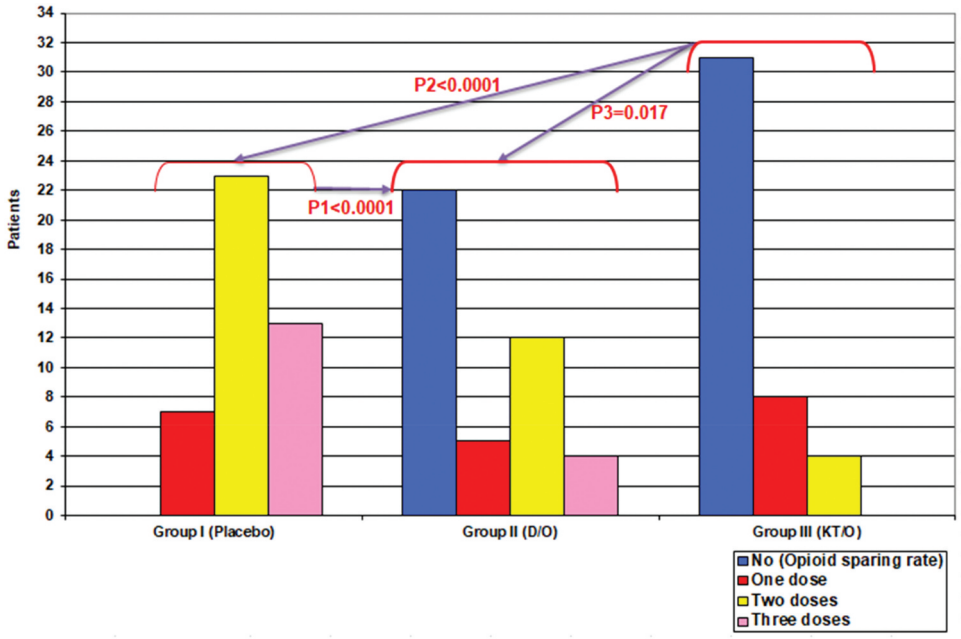

Figure 2. Patients' distribution according to the received doses of PO opioids.

Pain NRS scores showed inter-group significant differences till 12-h PO and were non-significant at 16-h and 20-h, while it was significantly lower among patients of group I than patients of groups II and III at 24-h. The average value of NRS score was significantly (P1 & P2 < 0.001) lower among patients of groups II and III, respectively, than patients of group I with significantly (P3 = 0.0011) lower average score for patients of group III than patients of group II (Table 3).

Till 60-min PO, patients' distribution according to RSS showed a non-significant difference between the three groups, while thereafter the frequency of patients who had high RSS was significantly higher among patients of group I. Similarly, the frequency of patients who had high PONV scores was significantly higher with a significantly higher number of patients who required anti-emetic therapy among patients of group I. The amount of wound drainage at the end of 24-h was non-significantly higher among patients of groups II and III in comparison to patients of group I. Patients' satisfaction scores by the outcome of PO analgesia were significantly higher with KT/O infusion than with placebo (P2 < 0.001) and D/O infusion (P3 < 0.001) with significant (P1 = 0.005) difference in favor of O/D than placebo infusion. Moreover, surgeons' satisfaction scores were significantly higher with the outcomes of KT/O infusion than placebo (P2 < 0.001) and D/O (P3 = 0.01) infusions and by the outcome of D/O infusion (P1 = 0.003) than by placebo infusion (Table 4).

17. Discussion

At the end of the 24-h follow-up after surgery, 53 patients of groups II and III did not request opioids for OSR of the used PO infusion of 61.6%. The OSR with the use of O/KT infusion was significantly higher than the OSR after the O/D infusion (72.1% vs. 51.2%). Further, the frequency of patients who frequently requested opioid analgesia was significantly higher in groups I and II versus group III with significantly higher consumption by patients of group I. By this, the total dose of opioids consumed and pain scores were significantly lower in groups II and III than in group I with a significant difference in favor of group III.

These findings illustrated the opioid-sparing effect of the used combination and supported the results of recent work that evaluated similar cocktails for cases of

Table 4. PO side effects and satisfaction scores by the use of PO infusions.

Data			Group I (Placebo)	Group II (D/O)	Group III (KT/O)	P-value
Ramsey Sedation score	Immediate PO	2	31 (72.1%)	28 (65.1%)	33 (76.7%)	0.487
		3	12 (27.9%)	15 (34.9%)	10 (23.3%)	
	30-min PO	1	6 (14%)	2 (4.6%)	0	0.079
		2	29 (67.4%)	31 (72.1%)	36 (83.7%)	
		3	8 (18.6%)	10 (23.3%)	7 (16.3%)	
	60-min PO	1	10 (23.3%)	6 (14%)	3 (7%)	0.305
		2	28 (65.1%)	30 (69.7%)	34 (79%)	
		3	5 (11.6%)	7 (16.3%)	6 (14%)	
	8-h PO	2	17 (39.5%)	29 (67.4%)	23 (53.5%)	0.031
		3	19 (44.2%)	13 (3.3%)	18 (41.9%)	
		4	7 (16.3%)	1 (2.3%)	2 (4.6%)	
	16-h PO	2	9 (2.9%)	22 (51.1%)	16 (37.2%)	0.022
		3	23 (53.5%)	18 (41.9%)	22 (51.2%)	
		4	11 (25.6%)	3 (7%)	5 (11.6%)	
	24-h PO	2	8 (18.6%)	23 (53.5%)	25 (58.2%)	0.0004
		3	29 (67.4%)	20 (46.5%)	16 (37.2%)	
		4	6 (14%)	0	2 (4.6%)	
Postoperative nausea & vomiting	Nausea score	1	20 (46.5%)	32 (74.5%)	39 (90.7%)	0.0002
		2	13 (3.2%)	9 (2.9%)	4 (9.3%)	
		3	6 (14%)	2 (4.6%)	0	
		4	4 (9.3%)	0	0	
	Vomiting score	0	30 (69.8%)	37 (86%)	41 (95.4%)	0.016
		1	11 (25.6%)	6 (14%)	2 (4.6%)	
		2	2 (4.6%)	0	0	
		3	0	0	0	
Need for antiemetic injection		Yes	8 (18.6%)	2 (4.6%)	0	0.0036
		No	35 (81.4%)	41 (95.4%)	43 (100%)	
24-h amount of wound drainage (ml)			195±54.4	215±82.7	234±88.2	.065
Satisfaction' scorings (Average ±SD)	Patient's satisfaction score		70±13	78±12.9	90±7.2	P1=0.005 P2<0.001 P3<0.001
	Surgeons' satisfaction score		76±1.6	83±1.6	88±6.7	P1=0.003 P2<0.001 P3=.010 P2<0.001 P3=0.010

P1 indicates the significance of the difference between groups I & II; P2 indicates the significance of the difference between groups I & III; P3 indicates the significance between groups II and III; the significance of the difference in numerical data was estimated using the one-way ANOVA test with Tukey HSD; the significance between numbers and percentages was evaluated using Chi-square test; *P* value at a cutoff point of <0.05 indicates significant difference

acute non-operative pain syndromes [4,18]. Further, the obtained results go in hand with **George et al**. [19] who found diclofenac infusion significantly decreased 24-h pain intensity and opioid consumption with a significantly shorter length of hospital stay after total knee arthroplasty compared to the standard perioperative analgesic regimen. Also, the results of the current study are in line with **Sorokina et al**. [20] and **Eremenko et al**. [21] who documented the safety, high analgesic efficacy and significant opioid-sparing effect of O/D infusion after cardiac surgery.

Contrary to the reported opioid-sparing effect of O/D combination versus placebo, **Zeiner et al**. [22] documented the failure of this combination to reduce the dose of opioid used in comparison to diclofenac alone or to placebo. However, this may be attributed to the small sample size; 23 patients per group that might prevent significant differences to be evident, also the use of patient-controlled analgesia devices may allow the patient to receive opioids on a pain score of <4 and the use of only two 8-hourly infusions and recording the opioid consumption during 72-h PO despite the previously documented decrease of plasma diclofenac concentration down to 39% at 8-h after administration and if augmented by a second dose the plasma concentration decreases to zero at 16-h after the initial dose [23], so the current study supplemented patients by a third dose to cover 24-h and no later on evaluation, while **Zeiner et al**. [22] continued to evaluate the effect after fading away of the drug. Furthermore, **de Paiva Carvalho et al**. [24] experimentally found t½ plasma level after diclofenac topical application in injured animals was 30-min, while it was 4-h in non-injured animals, thus indicating rapid consumption in surgical patients.

Considering orphenadrine as a fixed partner for both combinations, the reported difference between Groups II and III indicates the superiority of ketorolac over diclofenac as an analgesic and opioid-sparing drug. In line with this finding, a review of studies evaluating the opioid-sparing effect of NSAIDs detected a reduction of opioid use by 17–50% and 9–66% with diclofenac and ketorolac, respectively [25]. Also, in a systemic review, **McNicol et al**. [26] documented the efficacy of intravenous ketorolac for PO analgesia with a longer time to request rescue analgesia and a slightly higher rate of adverse events than placebo.

In support of the efficacy of ketorolac as an opioid-sparing drug, **Lombana et al**. [27] found adding ketorolac to liposomal bupivacaine for transversus abdominis plane blocks improved pain control and decreased opioid use. Further, **Wu et al**. [28] found prophylactic administration of ketorolac alone or in combination with dezocine significantly reduced IO opioid consumption, allowed IO stable hemodynamics and increased PO analgesia in comparison to placebo. Also, **Zhang et al**. [29] and **Shim et al**. [30] reported less IO and PO opioid consumption with better PO pain scores in patients who received IO intravenous dexmedetomidine and ketorolac during robot-assisted laparoscopic radical prostatectomy with rectus sheath blocks.

The amount of blood in wound drain and hematoma formation during 24-h PO showed a non-significant difference between the study groups and this points to the safety of the used combination and supported the results of the recent systemic review that included 12 studies, which documented the safety of NSAIDs during breast surgery [31].

The reported analgesic effect of diclofenac or ketorolac may be attributed not only to their inhibition of both cyclooxygenase isoenzymes with subsequent reduction of prostaglandin (PG) production peripherally and centrally [32] but also to the downregulation of the expression of nociceptive cytokines especially interleukins (IL)-6 in response to surgical trauma [33]. Regarding ketorolac, experimental studies observed the ability of ketorolac to inhibit caspase catalysis through a COX-independent pathway with subsequent prevention of cell death and reduction of the generation of pro-inflammatory cytokines [34]. Another study reported that ketorolac increased the thresholds for pain sensation with a significant reduction of the levels of tumor necrosis factor-α (TNF-α), IL-6, and IL-1β [28]. Recently, an animal-model study showed that ketorolac eye drops suppress PGE_2, TNFα and IL-6 levels in plasma and aqueous humor more than animals of no treatment group [35]. Clinically, ketorolac eye drops significantly reduced IL-8 and PGE_2, in aqueous humor than other medications [36,37].

18. Conclusion

Using a cocktail of ketorolac or diclofenac with orphenadrine infusions for 24-h after mastectomy improves PO pain sensation with subsequent reduction of opioid consumption. The O/KT infusion did well than the O/D infusion with regard to opioid-sparing rate and pain scores. The used cocktails also allowed early patients' ambulation secondary to the decreased pain, and decrease of opioid-induced side effects and provided high patient and surgeon satisfaction.

19. Limitation

Estimation of serum levels of nociceptive cytokines and comparison of the effects versus an opioid analgesic was required before the establishment of these results.

20. Recommendation

Wider-scale multicenter comparative studies including patients with varied surgical procedures are required to fulfil these outcomes.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Yehya Shahin Dabour http://orcid.org/0000-0002-2559-7232

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