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Analgesic efficacy of intravenous morphine, tramadol and ketorolac on postoperative pain in patients undergoing modified radical mastectomy

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Abstract

Background: It is the basic duty of all healthcare professionals to relieve pain, and the most important indication for treating pain after surgery is humanitarian.

Objectives: Comparing the effects of intravenous morphine, tramadol and ketorolac on post operative pain in patients undergoing modified radical mastectomy

Study design: A randomized, double blind trial.

Methods: Sixty patients randomly were assigned to receive either IV morphine 5mg (Group I, n = 20), tramadol 100 mg (Group II, n = 20), or ketorolac 60 mg (Group III, n = 20) at the end of surgery. Assessment parameters included hemodynamics, respiratory rate, oxygen saturation, sedation score, VAS score, time of first analgesic request, total amount of analgesics consumption, and side effects in the first 24 hours.

Results: The mean time to the first request for rescue analgesia was significantly prolonged in group II (11.00± 2.49 hrs ranged from 8- 15 hrs) and group III (8± 1.89 hrs ranged from 6.0 -10.0 hrs) in comparison to group I (3.75± 0.89 hrs ranged from 3 – 5 hrs) (P <0.001). Total post-operative amount of analgesics consumption over 24 hrs in the three studied groups was (7.00 ± 2.51 mg ranged from 5- 10 mg of morphine) in group I;(160.00± 68.06 mg ranged from 100-300 mg of tramadol) in group II;(80.00± 19.47 mg ranged from 60– 120 mg of ketorolac) in group III. The mean (VAS) score in studied groups, showed no significant difference between the three studied groups at all time periods(P >0.05), but there was a significant decrease in the (VAS) in each group separately over the course of 24 hrs in comparison to base line values (P <0.007). No significant differences were observed in the mean systolic and diastolic blood pressure values, respiratory rate and oxygen saturation between groups.

Conclusion: intravenous morphine, tramadol and ketorolac had similar analgesic efficacy on the post-operative pain in patients undergoing modified radical mastectomy.

Key words: Breast Cancer Surgery; Postoperative Pain; morphine, tramadol, ketorolac

Introduction

Ronald Melzack said that "By any reasonable code, freedom from pain should be a basic human right, limited only by our knowledge to achieve it" [1]. It is the basic duty of all healthcare professionals to relieve pain, and the most important indication for treating pain after surgery is humanitarian [1]. Acute pain is an important fear for most patients and influences their recovery and overall experience. Poorly treated, it could lead to undesirable effects and patient dissatisfaction. Hence, it is important to understand, assess and treat acute pain effectively [2].

Morphine remains the most widely used opioid for the management of pain and the standard against which other opioids are compared [3**]**. Tramadol is commonly referred to as an atypical centrally acting analgesic because of its combined effects as an opioid agonist and a serotonin and noradrenaline reuptake inhibitor [3].

Injectable NSAIDs (non-steroidal anti-inflammatory drugs) have potential advantages for postoperative pain management. NSAIDs attack pain by a different

mechanism than opioids. NSAIDs relieve pain without the somnolence, respiratory depression and other side effects common to opioids. Ketorolac is the first NSAID available in injectable form for use as analgesic [4, 5].

Our objective was to compare analgesic efficacy of intravenous morphine, tramadol and ketorolac on postoperative pain in patients undergoing modified radical mastectomy.

Patients and Methods

This randomized prospective clinical trial was approved by the local ethics committee of the South Egypt Cancer Institute, Assiut University, Assiut, Egypt. After written informed consent 60 patients aged (20 -60) years ,weighting (50-75 Kg), with American Society of Anesthesiologists (ASA) physical status I or II scheduled for modified radical mastectomy under general anesthesia were enrolled in this clinical trial.

Patients with a known allergy to the studied drugs, significant cardiac, respiratory, renal or hepatic disease, coagulation disorders, gastric or duodenal ulcer, psychiatric illnesses that would interfere with perception and assessment of pain were excluded from the study.

All patients were evaluated preoperatively by routine laboratory investigations and were taught how to evaluate their own pain intensity using the visual analogue scale (VAS) scored from 0 to 10 (where 0 = no pain and 10 = the worst pain imaginable) [6] .Personnel involved in data collection were kept blinded to group assignment. Analgesia was also given by a blinded anesthetist not involved in data collection. Randomization codes were not decoded till the end.

No premedication were given and basic monitoring probes included ECG (electrocardiogram), non invasive blood pressure, end-tidal carbon dioxide, pulse oximetry and temperature were applied. General anesthesia was induced with I.V. fentanyl 2 µg/kg, propofol 1- 2 mg/kg, and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by cis-atracurium 0.15 mg/kg, and was maintained with isoflurane 1.5–1.7 MAC, cis-atracurium 0.03 mg/kg and controlled ventilation in ventilation parameters that maintain normocapnia (35- 45 mmHg). Neuromuscular block was antagonized by neostigmine 50µg/kg and atropine 20µg/kg. Base line VAS, sedation score, systolic and diastolic blood pressure, heart rate, respiratory rate and oxygen saturation were assessed immediately after the end of surgery.

Using an online research randomizer (http://www.randomizer.org), Patients were allocated into one of three groups of 20 patients each to receive:

- ***Group I***: (n=20) received IV 5mg morphine sulphate (morphine SO4®, Misr CO Pharma).
- ***Group II***: (n=20) received IV 100 mg tramadol Hcl (tramadol®, October Pharma S.A.E).
- ***Group III***: (n=20) received IV 60 mg ketorolac tromethamine (ketolac®, Amriya Pharma).

Patients were transferred to the post anesthesia care unit (PACU) and kept there for 24 hours. During this period of observation heart rate, systolic and, diastolic blood pressure, respiratory rate and oxygen saturation were recorded at 2, 4, 6, 8, 12, 18 and 24hrs postoperatively. The severity of postoperative pain was measured by using VAS score at the above mentioned time points and patients who had pain scores ≥ 3 received an additional dose of analgesia for each respective group (3 mg morphine for group I,100 mg tramadol for group II and 30mg ketorlac for group III). The time to first request for analgesia and the total consumption of studied drugs for each group for first 24hrs were recorded.

In addition, side effects such as nausea, vomiting, respiratory depression and sedation (using sedation score from 0 to 4, where 0= awake, 1= easily aroused, 2= awaken after verbal stimulation, 3=awaken after tactile stimulation and 4= not arousable) were recorded and treated. Analgesic medications in each group were repeated according to the patients' needs in order to keep VAS ≤ 3 for 24hours postoperatively.

Statistical analysis:

Our power analysis was based on estimating an effect size of 0.5 of difference between means of three independent groups. A calculated sample size of 20 for each group would have an 80% power of detecting a difference at a 0.05 level of significance using a confidence interval of 95%.

Data entry and analysis were done using SPSS version 19 (Statistical Package for Social Science). Data were presented as number, percentage, mean and standard deviation. Chi-square test was used to compare qualitative variable among studied groups. Quantitative data were analyzed by analysis of variance (ANOVA) between groups. Independent samples t- test was used to compare quantitative variables between each two of the studied groups. Paired samples t-test was used to compare between pre and post follow-up in each group. Differences were considered to be significant at P <0.05.

Results

Sixty Patients with breast cancer subjected for modified radical mastectomy were included in this study with no patient drop out. No significant difference was found among the groups as regard to demographic data, ASA score, site and duration of surgery (P >0.05) (tables 1 & 2).

As regard to the postoperative hemodynamic variables (mean heart rate, mean systolic and diastolic blood pressure), respiratory rate and oxygen saturation. There was no significant difference between the three groups or within the same group comparing each time point with base line (P >0.05) (figure 1, 2, 3).

No significant difference in the mean (VAS) score between each two of three studied groups at all time periods (P >0.05), but there was a significant decrease in the (VAS) in each group separately over the course of 24 hrs in comparison to base line values (P <0.007) (figure 4).

Table (1): Demographic data and clinical data of studied groups

	Group I (n= 20)		Group II (n= 20)		Group III (n= 20)		P-value
	No.	%	No.	%	No.	%	
Age: (years)							
< 50	7	35.0	11	55.0	6	30.0	0.233
≥ 50	13	65.0	9	45.0	14	70.0	
Mean ± SD	50.90 ± 12.32		45.25 ± 13.95		46.25 ± 10.42		0.309
Weight: (Kg)							
Mean ± SD	62.20 ± 4.61		64.10 ± 4.22		65.10 ± 6.03		0.113
Range	50 – 70		55 – 72		58 – 75		
ASA score:							
ASA I	8	40.0	13	65.0	11	55.0	0.280
ASA II	12	60.0	7	35.0	9	45.0	

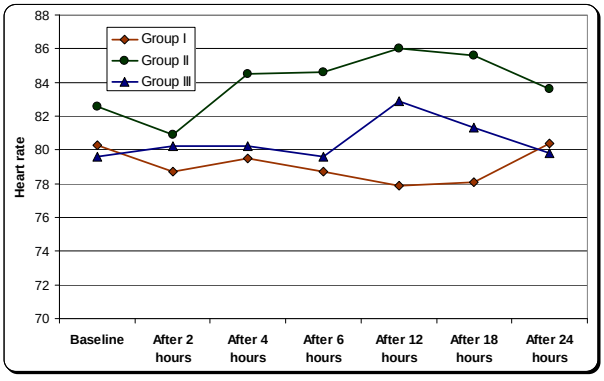
Group I: Morphine **ASA**: American society of anesthesiologists
Group II: Tramal **Data** expressed as (Mean ± SD) and number (%)
Group III: Ketorolac

Table (2): Operative data of studied groups

	Group I (n= 20)		Group II (n= 20)		Group III (n= 20)		P-value
Duration of surgery: (mins)							
Mean ± SD	113.00 ± 15.08		121.00 ± 25.73		115.00 ± 27.53		0.281
Range	90 – 130		80 – 130		80 – 130		
Site of surgery: No. (%)							
Right modified radical mastectomy	9	45.0	7	35.0	8	40.0	0.812
Left modified radical mastectomy	11	55.0	13	65.0	12	60.0	

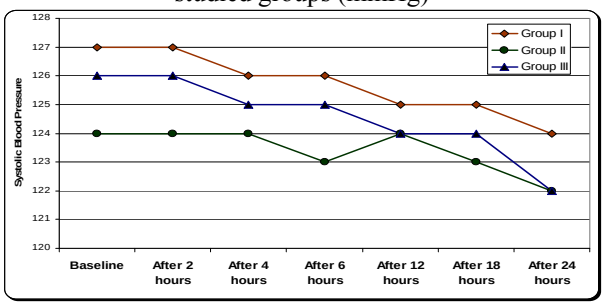
Group I: Morphine **Group II:** Tramal **Group III:** Ketorolac
Data expressed as (Mean ± SD) and number and %

Figure (1) Changes in post-operative heart rate in the three studied groups (beat/ min)



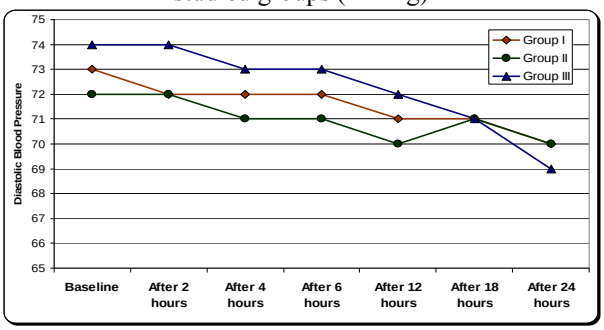
Group I: Morphine Group II: Tramal Group III: Ketorolac
Baseline (immediately post-operative preanalgesic),
After 2,4,6,12,18,24 hrs (postoperative post analgesic

Figure (2): Systolic Blood Pressure changes in three studied groups (mmHg)



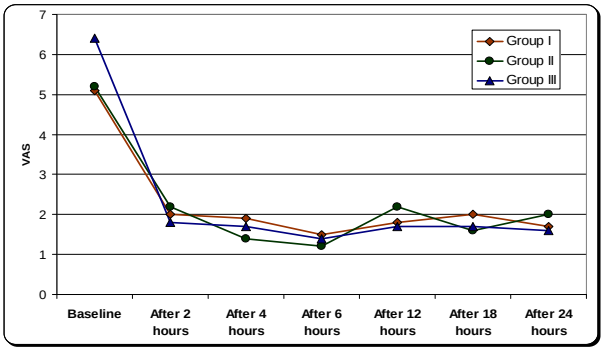
Group I: Morphine Group II: Tramal Group III: Ketorolac
Baseline (immediately post-operative preanalgesic),
After 2,4,6,12,18,24 hrs (postoperative post analgesic)

Figure (3) Diastolic Blood Pressure changes in three studied groups (mmHg)



Group I: Morphine Group II: Tramal Group III: Ketorolac
Baseline (immediately post-operative preanalgesic),
After 2, 4, 6,12,18,24 hrs (postoperative post analgesic)

Figure (4): Visual analogue scale (VAS) changes in three studied groups



Group I: Morphine Group II: Tramal Group III: Ketorolac
Baseline (immediately post-operative preanalgesic),
After 2,4,6,12,18,24 hrs (postoperative post analgesic)

Total amount of post-operative analgesics consumption over 24 hrs in the three studied groups was (7.00 ± 2.51 mg ranged of 5- 10 mg of morphine) in group I;(160.00± 68.06 mg ranged of 100-300 mg of tramal) in group II;(80.00± 19.47 mg ranged of 60– 120 mg of ketorolac) in group III were shown (table 3).

The mean time to first request for rescue analgesia was significantly prolonged in group II (11.00± 2.49 hrs ranged from 8- 15 hrs) and group III (8± 1.89 hrs ranged from 6.0 -10.0 hrs) in comparison to group I (3.75± 0.89 hrs ranged from 3 – 5 hrs) (P <0.001) (table 3).

No significant differences were observed between the three studied groups as regard to incidence of nausea and vomiting. No other complication as respiratory depression, urinary retention, drowsiness and itching were observed in the studied groups (P >0.05) (figure 5).

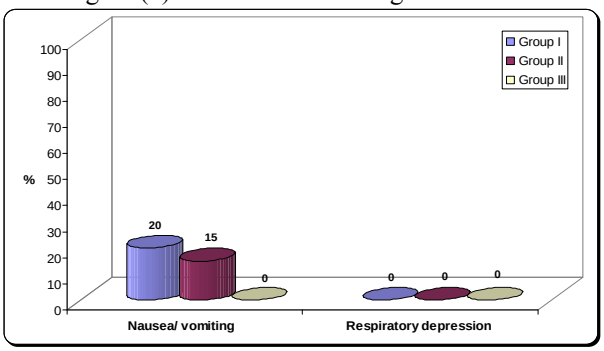
There was no significant difference in post analgesics sedation score between the three studied groups (P >0.05), but there was a significant decrease in sedation score in each group separately over the course of 24 hrs compared to base line values (P <0.05) (figure 6).

Table (3): Amount of Post-operative analgesia consumption and first request

	Group I (n= 20)	**Group II (n= 20)**	**Group III (n= 20)**	**P-value**
Total amount: (mg) of analgesic				
Mean ± SD	7.00 ± 2.51	160.00± 68.06*	80.00 ± 19.47	0.000*
Range	5 – 10	100 – 300	60 – 120	
First request of analgesia: (hrs)				
Mean ± SD	3.75 ± 0.89	11.00 ± 2.49*	8.00 ± 1.89	0.001*
Range	3.0 – 5.0	8.0 – 15.0	6.0 – 10.0	

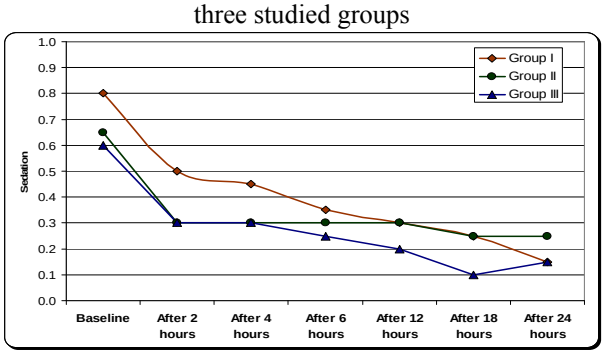
Group I: Morphine **Group II:** Tramal **Group III:** Ketorolac **Data** expressed as (Mean ± SD)
* Significant p value compared to group I

Figure (5): Side effects of analgesics studied



Group I: Morphine Group II: Tramal Group III: Ketorolac

Figure (6): Changes in post analgesic Sedation score of three studied groups



Group I: Morphine Group II: Tramal Group III: Ketorolac

Discussion

Optimal pain management may decrease the stress response to surgery, reduce complications, improve recovery time, and result in improved economic and quality-of-life outcomes [7].

The present study showed that there were no significant changes in postoperative hemodynamic variables, VAS and sedation scores in the three studied groups, but the first request for analgesia was prolonged in tramadol and ketorolac groups in comparison to morphine group.

In the present study postoperative hemodynamic variables showed no significant differences among the three studied groups all over the 24 hours of postoperative observation; this is in agreement with Karaman et al., [8] who studied the effect of intravenous morphine during the postoperative period in patient undergoing total abdominal hysterectomy, and they found no significant changes in hemodynamic variables. Also Shankariah et al., [9] coinciding with our finding as they compared intramuscular 30 mg ketorolac versus IM 100mg tramadol in patients undergoing maxillofacial surgery and they didn't find significant change in hemodynamic variables in the two groups.

Also Naguib et al., [10] who conducted a study to compare the efficacy of IV 100mg tramadol versus IV 10 mg morphine followed by PCA for analgesia in patients undergoing laparoscopic cholecystectomy and they found no significant changes postoperatively in the hemodynamic variables in both groups.

Each group had a satisfactory analgesia without significant difference in VAS between the three studied groups all over the study period. However, time to the first request for rescue analgesia was significantly prolonged in tramadol (11.00± 2.49 hrs) and ketorolac groups (8± 1.89 hrs) in comparison to morphine group (3.75± 0.89 hrs). This is in accordance with Wang et al., [11] who reported similar satisfactory analgesics efficacy in patients undergoing gastric cancer surgery, was observed by using either patient controlled intravenous analgesia (PCIA) with lornoxicam plus tramadol, PCIA morphine alone and PCIA tramadol alone in the postoperative period.

Our study was also in agreement with Sacerdote et al., [12] who concluded that the postoperative analgesic effects of 100mg tramadol and 10 mg morphine were similar and the VAS values after the administration at the end of abdominal surgery for uterine carcinoma were not significantly different.

Also in coincidence with our results Gopalraju et al., [13] who concluded that the use of pre-operative IV ketorolac 30 mg in the patients who underwent routine third molar extraction, delayed the onset of postoperative pain and increasing the pain threshold compared to IV tramadol 50 mg, there was a remarkable reduction in the amount of analgesics required postoperatively in ketorolac group. This did not only reduce the cost to patients but also lessened the burden of adverse reactions.

Contrary to our findings, Shankariah et al., [9] who concluded that intramuscular 100 mg tramadol and 30 mg ketorolac resulted in significant decrease in pain intensity from the 2nd to 24th post-operative hour in patient underwent maxillofacial surgery. However, tramadol always resulted in better pain control than Ketorolac at all postoperative hours and intramuscular Tramadol seemed useful in controlling pain following surgery, with better levels of tolerance than intramuscular Ketorolac. This is most probably explained by a different dose of ketorolac (60 mg) and different route of administration of both drugs in our study.

Moreover, Lehmann, [14] had reported that intramuscular Tramadol 100 mg given postoperatively for management of acute pain (trauma pain) was less potent than 10 mg of morphine.

Brown et al., [15] had shown that a 30 mg IM ketorolac can provide analgesia equivalent to 12 mg IM morphine after major abdominal surgeries (abdominal hysterectomy, Myomectomy and Laparotomy ovarian tumor) .Objecting to this is a research by Power et al., [16] who had shown that a dose of 30 mg IM ketorolac did not provide a comparable analgesic efficacy to even a dose of 10 mg IM morphine after cholecystectomy.

Anthony and Jasinski,[17] compared morphine versus ketorolac in the postoperative period and summarized that morphine remains the number one drug for pain relief and ketorolac is an effective analgesic agent for mild to moderate postoperative pain in adult population without inducing respiratory depression. However, in cases of severe pain ketorolac does not achieve comparable analgesia to morphine and must be supplemented with morphine.

Disagreeing to our results, Cepeda, et al., [18] conducted a study to compare analgesic efficacy of IV 10 mg morphine versus IV 60 mg ketorolac followed by PCA after elective intra-abdominal operations. Twenty-two of the 26 patients in the ketorolac group required doses of morphine for breakthrough pain. This is most probably explained by the different nature of surgery in our study

The most common side effects associated with morphine and tramadol were nausea and vomiting. Only four patients (20%) in morphine group had an episode of nausea and/or vomiting while three patients only (15%) developed it in tramadol group during initial postoperative hours. These patients were given a single dose of intravenous metoclopramide following which no further episodes of vomiting were reported. Nausea and vomiting are induced by morphine's activation of the μ receptors in the chemoreceptor trigger zone (CTZ) in the area postrema of the medulla; the CTZ is one of many sensory inputs that stimulate the vomiting center **[19]**. Tramadol has a dual mechanism of action that involves weak affinity for opioid (μ) receptors and also inhibition of reuptake of serotonin and norepinephrine which may account for the increased incidence of nausea/vomiting [20]. In accordance with Shankariah et al., [9] who concluded that tramadol and ketorolac produced mild side effects (nausea and vomiting) and this did not appear to influence the outcome. Also Wang et al.,[11] who compared (PCIA) using lornoxicam with tramadol, PCIA morphine, and PCIA tramadol in patients undergoing gastric cancer surgery and they found no one have nausea and vomiting in

lornoxicam with tramadol, four patients with morphine and one patient with tramadol.

The small number of patients studied in a single institution, limiting the generalizability of the conclusions.

In conclusion, intravenous morphine, tramadol and ketorolac produced similar analgesic efficacy on the post-operative pain in patients undergoing modified radical mastectomy.

Abbreviations

NSAIDs: non-steroidal anti-inflammatory drugs
VAS: visual analogue scale
ECG: electrocardiogram
PACU: post anesthesia care unit
PCIA: patient controlled intravenous analgesia
IV: intravenous.

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