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Original Article

Preemptive Intravenous Paracetamol with or without Tramadol for Postoperative Pain After Elective Abdominal Surgery: a retrospective study

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ABSTRACT

Introduction and aim: Prevention or reduction of postoperative (PO) pain is still a challenge, as it had different drawbacks on the healing process and patient quality of life. The current study aimed to evaluate the value of preemptive paracetamol with or without tramadol in management of postoperative pain control after abdominal surgery.

Methodology: This is a retrospective study of 90 patients who submitted to elective abdominal surgery. Patients were classified into three equal groups. The first for paracetamol, the second for paracetamol-tramadol and the third for placebo (saline). One hour before surgery a dose of paracetamol (1 gm diluted in 100 ml saline) was administered for the first two groups, in addition to 100 mg of intravenous tramadol to the second group. The primary outcome was PO pain in the first 24 hours after surgery. The secondary outcomes include time for the first analgesic request and cumulative dose of analgesia. Also, nausea and vomiting were documented.

Results: The group of paracetamol-tramadol was associated with significant lower VAS score at 4, 6, 8, 10 and 12 hours postoperatively than paracetamol alone or saline groups. Time to the first analgesic request was significantly longer in paracetamol-tramadol (138.00±24.41 minutes) than paracetamol alone (100.0±31.84 minutes) or saline group (82.33±23.73 minutes). The total cumulative analgesia in the first PO Day was significantly lower in paracetamol-tramadol (158.33±79.96 mg) than paracetamol (245.00±73.52 mg) or saline group (276.67±75.12 mg). Nausea and vomiting were reported in 9, 8 and 10 in paracetamol, paracetamol-tramadol and saline groups respectively with no significant differences.

Conclusion: The use of preemptive paracetamol alone or combined with tramadol is an effective intervention to reduce the postoperative pain after abdominal surgery. It reduces the use of postoperative analgesics with subsequent effect on the cost and healthcare system.

Keywords: Preemptive; Pain; Postoperative; Laparotomy; Analgesia.

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INTRODUCTION

Abdominal surgery is usually associated with moderate to severe pain in the postoperative period [1,2].

Adequate pain management after surgery is vital for proper healing. In addition, the poor management of postoperative pain is associated with adverse events (e.g., hypertension, respiratory impairment, poor wound healing, myocardial ischemia, arrhythmias, deep vein thrombosis (DVT) and chronic pain syndrome [3-6].

These negative effects of poorly controlled postoperative pain led to prolonged hospitalization with increase of healthcare costs and affected patient quality of life as well as financial burden [7-9].

Opioids are used for management of postoperative (PO) pain irrespective of its considerable side effects and highly addiction potential. Thus, its use is limited especially in resources-limiting sittings [10-12].

Opioid-free methods for management of postoperative pain are introduced and different regimens are in use. However, the current recommendations advocate multimodal approaches. It is usually associated with an improved recovery [13-15].

Preemptive analgesia is used to block the central nervous system (CNS) hyperexcitability, leading to reduction of postoperative pain [16,17]. However, reporting mild to moderate postoperative pain is still constant [18,19]. Thus, the management of postoperative pain is still a challenge in resources-limited countries and research for best preemptive analgesic methods is still underway.

The current work was designed to investigate retrospectively the value of preemptive paracetamol with or without tramadol in management of postoperative pain control.

PATIENTS AND METHODES

This is a retrospective study of 90 patients of three methods of preemptive analgesia before abdominal surgery. Patients were assigned for one of equal three groups. The first of paracetamol, the second for paracetamol with tramadol and the third for placebo (saline). Data was collected for patients submitted to elective abdominal surgery at Al-Azhar University hospital (Damietta), between January 2018 and January 2021.

As a retrospective study, the patient consent was not required. However, an administration consent for data collection was attained and the study protocol was approved the local research ethics committee. Data were used only for the purpose of research after coding to conceal patient identity.

We only included adult patients (18 years or older) who were ASA physical status I or II. On the other hand, patients with concomitant chronic medical or psychiatric diseases were excluded. In addition, patients with history of drug abuse or who used non-steroidal anti-inflammatory drugs or paracetamol within 24 hours before surgery and patients with known allergy to paracetamol or tramadol were excluded.

The day before surgery, a complete medical evaluation was performed by a physician who taught patients to use the visual analogue scale for self-reporting of their pain score.

At the night of the surgery, a paracetamol (1g) diluted in 100 ml of saline was intravenously administered to patients of groups 1 and 2. One hour before surgery a second dose of paracetamol (as previous) was administered for the two groups. The second group (tramadol) received 100 mg of intravenous tramadol. The third (placebo) group received saline 100 ml one hour before surgery.

The premedication was achieved by intravenous administration of dexamethasone (8 mg), diazepam (5 mg) and cimetidine (400mg). The baseline data were recorded and pain severity was assessed by the VAS.

All patients were submitted to general anesthesia (the same protocol) and standard monitoring was applied. It included pulse oximetry, non-invasive blood pressure monitoring, and electrocardiography. A propofol 2.5mg/kg, fentanyl (50 µg) with ketamine 0.3 mg/kg were used for induction of anesthesia and tracheal intubation was performed after injection of succinylcholine (2mg/kg) after 5 minutes of preoxygenation. Anesthesia was maintained by isoflurane with oxygen mixture at a gas flow 2-3 L /minute according to the clinical situation and required depth of anesthesia. The neuromuscular block was maintained by Vecuronium and parameters of mechanical ventilation were adjusted according to patients' age and weight.

At the end of the surgery, the residual neuromuscular blockage was antagonized by atropine 0.2 mg/kg and neostigmine 0.05 mg/kg. Then, patients were transferred to recovery room.

The outcome data collection started in the post-anesthesia care unit. All patients were asked to determine their pain intensity on the visual analogue scale from 0 (absent pain) to 10

(the most severe pain). Values from 0 to 3 indicate mild pain and there was no need for additional analgesia. Values >3 to 7 indicate moderate pain and analgesia was administered on the patient request. The values above 7 indicate severe pain which usually need additional analgesia. However, additional analgesia confined for patient request. Pain was assessed on regular intervals (each 2 hours till the end of the 12 hours postoperatively, then each 4 hours till the end of the first postoperative 24 hours). The postoperative pain was considered as the primary outcome in the current work. On the other hand, 24-hours postoperative total analgesic consumption (all analgesia administered in the first 24 hours), time to the first analgesic request and incidence of nausea and/or vomiting were document and represented the secondary outcome. The first 24-h postoperative analgesia was achieved by an intravenous injection of tramadol (50 mg). After the first postoperative day, analgesia continued by oral NSAIDs according to our institution protocol. When nausea and/or vomiting was recorded, IV metoclopramide 10 mg and dexamethasone 4 mg were administered.

Statistical analysis of data: The collected data were coded and entered to an excel sheet. Then, transferred to the statistical package for social science (SPSS) for windows, version 20 (IBM®SPSS®, Armonk, NY, USA). The quantitative data were expressed by their means and standard deviations and sometimes their minimum (Min.) and Maximum (Max.) while categorical data were presented by their relative frequencies and percentages. Groups were compared by one way analysis of variance (ANOVA) for quantitative data and if ANOVA is significant, the post-hoc least significant differences were calculated to measure the difference between each two groups. Qualitative data were analyzed by the Chi square test. A P-value ≤ 0.05 was considered significant.

RESULTS

The current work included 30 patients in each group. Their age ranged 20 and 54 years with increased incidence of female percentages in all three groups. They were mainly of ASA- class I. Their weight is mainly normal with some overweight patients. The operative time ranged between 95 and 144 minutes while anesthesia duration ranged between 113 and 162 minutes. There were no significant differences between studied groups (Table 1).

Regarding postoperative pain, there was no significant differences between groups at postoperative 2, 12, 16, 20 and 24 hours. However, there was significant differences at 4, 6, 8 and 12 hours. The paracetamol alone as a preemptive analgesic was associated with significant reduction of postoperative pain from 2 to 12 hours postoperatively. Adding tramadol to paracetamol yields more reduction of postoperative pain at the same time window (2 to 12 hours) (Table 2).

Regarding secondary outcome, the time to first analgesia request was significantly shorter in saline (control) than paracetamol or paracetamol-tramadol groups (82.33±23.73 vs 100.0±31.84 and 138.00±24.41 minutes, respectively), and in paracetamol than paracetamol-tramadol group. Subsequently the paracetamol-tramadol group consumed significantly lower quantities of postoperative analgesics than paracetamol and saline groups. In addition, there was significant reduction of cumulative analgesia in paracetamol than saline (paracetamol) group (Table 3).

Table (1): Comparison between study groups regarding patient characteristics, operative time and anesthesia duration

Variables	Measures	Paracetamol	Paracetamol plus tramadol	Saline	Test	P
Age (year)	Mean±SD	38.37±10.95	39.50±9.03	39.00±9.89	0.10	0.91
	Min.-Max.	20-54	22-54	22-54		
Sex (n,%)	Male	12(40.0%)	13(43.3%)	10(33.3%)	0.65	0.72
	Female	18(60.0%)	17(56.7%)	20(66.7%)		
ASA (n,%)	I	25(83.3%)	26(86.7%)	27(90.0%)	0.58	0.75
	II	5 (16.7%)	4(13.3%)	3 (10.0%)		
Weight (kg)	Mean±SD	68.23±7.09	69.43±5.85	68.53±5.67	0.30	0.74
	Min.-Max.	56-80	58-80	57-81		
BMI (kg/m²)	Mean±SD	24.93±0.78	25.02±0.84	24.94±0.39	0.16	0.85
	Min.-Max.	23.05-26.64	22.66-26.73	24.03-25.56		
Operative time (min)	Mean±SD	117.23±13.57	116.17±13.70	118.80±12.89	0.29	0.75
	Min.-Max.	95-144	101-142	100-143		
Anesthesia duration (min)	Mean±SD	134.57±13.04	134.40±13.43	136.93±12.83	0.35	0.71
	Min.-Max.	113-162	119-160	118-162		

Table (2): Comparison between study groups regarding postoperative pain (VAS)

Variables	Paracetamol	Paracetamol plus tramadol	Saline	Test	P
VAS_2	1.80±0.61	1.73±0.45	1.50±0.51	2.68	0.074
VAS_4	2.70±0.79#	2.43±0.50#$	3.27±0.78	***10.86***	***<0.001****
VAS_6	4.27±0.69#	2.53±0.68#$	4.50±0.68	***73.79***	***<0.001****
VAS_8	4.43±0.68#	2.70±0.65#$	5.17±0.95	***80.79***	***<0.001****
VAS_10	3.23±0.68#	2.97±0.56#$	3.63±1.16	***4.79***	***0.011****
VAS_12	2.80±0.61	2.87±0.73	2.70±0.65	0.48	0.62
VAS_16	2.47±0.57	2.40±0.62	2.43±0.57	0.10	0.91
VAS_20	2.07±0.74	2.03±0.76	2.17±0.79	0.25	0.78
VAS_24	1.63±0.72	1.67±0.76	1.70±0.75	0.06	0.94

# indicates significant reduction when compared to saline (control) group. $ indicates significant reduction of VAS when compared to paracetamol group. * Indicates significant variances between the three groups.

Table (3): Comparison between study groups regarding secondary outcome measures

Variables	Measures	Paracetamol	Paracetamol plus tramadol	Saline	Test	P
Time to first analgesic request (min)	Mean ± SD	100.0±31.84#	138.00±24.41	82.33±23.73#$	33.51	<0.001*
	Min.- Max.	60-180	90-180	60-120		
Total (cumulative) analgesia (mg/24 h)	Mean ± SD	245.00±73.52@	158.33±79.96	276.67±75.12@&	19.36	<0.001*
	Min.- Max.	100-400	50-350	150-400		
Nausea and/or vomiting	N, %	9(30.0%)	8 (26.7%)	10(33.3%)	0.32	0.85

# indicates significant shortening of time when compared to paracetamol-tramadol group. $ indicates significant shortening of time when compared to paracetamol group. @ indicates significant increase of total cumulative analgesia when compared to paracetamol-tramadol group. & indicates significant increase of total cumulative analgesia when compared to paracetamol group. * Indicate significant variances between the three groups.

DISCUSSION

The current work showed that the use of tramadol with paracetamol as preemptive analgesics leads to significant reduction of postoperative pain than paracetamol alone and in paracetamol than saline (control), especially from the second to the 12th hour postoperatively. In addition, it was associated longer duration for the first analgesic request and significant reduction of cumulative postoperative analgesia during the first postoperative day.

Using a combination of two analgesic drugs into a single regimen was recognized as multimodal analgesia. It might have a great promise for limiting the sensitization of nervous system to different noxious stimuli [20].

In addition, different preemptive analgesics modalities are associated with a multi-level interruption of nociceptive stimuli before tissue damage, increase the threshold of pain and reduced the activation of nociceptors [21,22].

Our results are in agreement with **Aweke *et al.*** [4] who reported significant increase of total postoperative analgesia in paracetamol-tramadol than paracetamol alone group (154.76 ± 70.54 vs 250 ± 79.06 mg, respectively). Also, they reported longer time of first analgesic request in paracetamol-tramadol than paracetamol alone (144.05 ± 14.72 vs 87.62 ± 20.95, respectively, $p < 0.05$). However, they do not have a control group. In addition, they use the numerical rating scale for pain assessment. But they also had significant differences of pain score after the second to the 12 hours postoperatively.

In addition, these results are in line with **Solmaz and Kovalak** [23] who reported a significantly lower postoperative pain (VAS) in paracetamol-tramadol combination compared to paracetamol alone when used with ambulatory arthroscopic meniscectomy. Their patients did not need any analgesia after the first day of surgery. Interestingly, the significant differences

between groups regarding postoperative pain was confined to the first 2 hours after operation. Then, the difference was not significant. This could explain the absent need for additional analgesia after the first 24 hours. Another note is the short duration of operative and anesthetic times in their study than the current one (Their operative time around 30 minutes and their anesthetic time is about 37 minutes).

Reviewing literature about different preemptive analgesic modalities we found a diversity in protocols and used drugs. It extended from single drug [24] to three-drugs combination [25] or the use of single drug with different concentrations [26].

Also, few studies have a control group. But others compare drugs directly. This reflecting one strength point of the current work (the presence of control group), which confirms the action of preemptive analgesia either by single or two-drugs. The use of paracetamol related to its availability and safety profile. In addition, tramadol is a weak opioid than morphine [4]. However, the retrospective nature of the study is a weak point, where bias cannot be avoided.

In an interesting systematic review, **Steinberg *et al.*** [17] included 69 studies to evaluate the value of preemptive analgesia before abdominal hysterectomy. Their results showed that, from non-narcotic drugs, paracetamol, gabapentin and rofecoxib combined with gabapentin showed significant improvement in pain control than placebo. The patient satisfaction was higher with the combined use of paracetamol and gabapentin than gabapentin alone. They added, using preemptive paracetamol, gabapentin, bupivacaine, and phenothiazine were associated with a significantly lower narcotic usage than placebo. In addition, all narcotic drugs (e.g., ketamine, morphine, fentanyl) are associated with significant improvement in pain control than placebo. Narcotics are associated with a significant reduction in pain scores than nonnarcotics, and their use led to lower total narcotic usage.

In conclusion: the use of preemptive paracetamol alone or combined with tramadol is an effective intervention to reduce the postoperative pain after abdominal surgery. It reduces the use of postoperative analgesics with subsequent effect on the cost and healthcare system.

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