Sys Rev Pharm 2020; 11(6):1487-1491
A multifaceted review journal in the field of pharmacy

Role of Paracetamol Nefopam in Immediate Postoperative Analgesia for Laparoscopic Cholecystectomy: single center

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ABSTRACT

Background: Despite the fact that it's significantly less than that for open procedure. As such pain is multimodal, so the use of drugs that act by different mechanisms is expected to be more effective. **Objectives:** We evaluated the effect of intravenous Paracetamol on postoperative pain in patients undergoing laparoscopic cholecystectomy. **Patients and Method:** This is a randomized single center study for 80 patients were selected among those presented for elective laparoscopic cholecystectomy from august 2017 to January 2018. Preoperatively, complete medical history was recorded, detailed physical examination performed and laboratory investigations assessed. The standard monitoring is non-invasive blood pressure, pulse rate, O2 saturation, ECG and capnography were applied. The patients were monitored continuously from the time just before induction of anesthesia until discharge from the post anesthetic care unit (PACU), while the study variables were recorded every 5 minute intervals. Drugs side effects are also observed. All groups received Paracetamol i.v infusion started with the induction of general anesthesia. Group A received placebo, group B received Nefopam, while group C received Tramadol by slow i.v injection. The researcher was responsible for patient allocation into the Specified groups and the preparation of the drugs under study. Neither the anesthesiologist nor the patient knew which drug was administered. **Results:** Postoperatively, the pain score was significantly lower in group B (Nefopam group) than groups A and C (P value <0.001). Similarly, the effect size for group B is significantly lower in group B (0.28) than group A (0.95) and group C (0.9) (P value 0.025). All the other variables observed were not significantly different among all of the three studied groups. No patient suffered from side effect of any of the study drugs. **Conclusion:** Intraoperative Paracetamol Nefopam combination is more effective in relieving immediate postoperative

Keywords: Single center, Nefopam, laparoscopic cholecystectomy

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Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Undergoing treatment (such as surgical procedures) may result in the occurrence of postoperative pain, and this triggers biochemical and physiological stress responses [1]. Pain is a major public health issue throughout the world and represents a major clinical, social, and economic problem [2]. Postsurgical pain is normally perceived as nociceptive pain [3]. Therefore the surgeon prefer to replace open surgical procedures with laparoscopic procedures which are minimally invasive and associated with significantly less trauma and have the potential advantage of reduced postoperative pain, shorter length of hospitalization, rapid recovery and decrease heath care costs [4]. The international Association for the Study of Pain (IASP) differentiated types of pain and noted its processing and the chemical mediators that transducer and transmit the pain through different types and sizes of neuron fibers that had led to co-administration of combinations of analgesic that have different mechanism of action through a strategy called ((multimodal)) or balanced analgesia which aims to obtain optimal level of analgesia. The basic goal of this strategy is synergistic or at least additive effect [5-6]. Postoperative pain management is one of the most important components of adequate postsurgical patient's care [7]. Pain during and after surgery can lead to sensitization and consequently oversensitivity to pain, it can also transform postoperative acute pain into chronic pain [8]. Effective postoperative pain control is important, especially with the initiation of physiotherapy and early ambulation, which hastens recovery and reduces hospital length of stay [9]. The use of opioid drugs for the pain control during and after surgery is a common procedure in anesthesia [10]. However, the use of these medications is associated with side effects such as nausea, vomiting, sedation, and respiratory depression. Prescribed method for reducing and minimizing opioid side effects is concomitant administration of a nonopioid analgesic [11].

Laparoscopic cholecystectomy: The preferred technique for gallbladder removal for treatment of symptomatic cholelithiasis, cholecysitis or gallbladder cancer, its benefits include small incision and reduced instance of post operation pain, incision hernias, wound infections, respiratory compromise and quicker discharge to home due to quicker return of ambulation in comparison with open cholecystectomy [12].

Patients and method: After approval by the committee of the Scientific Council of Anesthesia and Intensive Care of the Arabic Board of Medical Specializations, this prospective double blinded

Nefopam: is a benzoxazocine (cycline analogue of Diphenhaydramine), centrally acting non–opioid analgesia agent. It inhibits reuptake of Serotonin, nor epinephrine and dopamine. Nefopam indirectly modulated the NMDA receptor and relieving alloying (perception of an ordinary non-noxious stimulus as pain) and opioid related hyper-allodia (macerate response to noxious stimulation [13].

controlled randomized clinical trial was conducted at Al-Sader Medical Teaching Complex in Najaf Governorate/Iraq. Data was collected from august 2017 to January 2018. 80 patients with ASA (American Society of Anesthesiology) class I and II were randomly selected among patients scheduled for elective laparoscopic cholecystectomy under general anesthesia and allocated into three groups (A, B and C). In this study, we aimed not only to compare analgesic effect of Nefopam plus paracetamol vs Tramadol plus paracetamol in relieving pain from laparoscopic cholecystectomy intra- and immediate post-operatively, but also to show if the paracetamol alone is as effective as analgesic agent in relieving pain resulting from laparoscopic cholecystectomy compared to the above combinations. Preoperatively, complete medical history was recorded, detailed physical examination performed and laboratory investigations assessed. An Informed consent also was obtained from every patient in accordance with local regulations. For the purpose of statistical analysis; age, sex, ASA class, pulse rate, blood pressure and fasting blood sugar were recorded for every patient. All groups received Paracetamol i.v infusion before the induction of general anesthesia. After induction of general anesthesia, group A received placebo, group B received Nefopam, while group C received Tramadol all by slow i.v injection. The researcher was responsible for patient allocation into the specified group and the preparation of the drug under study. Neither the anesthesiologist nor the patient knew which drug was administered. The standard monitoring parameters were non-invasive blood pressure, pulse rate, O2 saturation, ECG and capnography. The patients were monitored continuously from the time just before induction of anesthesia until discharge from the post anesthetic care unit (PACU), while the study variables were recorded every 5 minutes intervals. Intravenous line was inserted and paracetamol 1gm i.v infusion was given. Anesthesia was induced with Propofol (2-2.5 mg/kg) (*). Rocuronium (0.6 mg/kg) was administered (*) and tracheal intubation was performed approximately 2 min. later. Anesthesia was maintained with Isoflurane 1.2% (*). Isotonic intravenous fluid (normal saline) was used as intravenous infusion fluid. Then, the anesthesiologist introduced 10 ml of fluid by the 10 ml syringe already prepared by the researcher slowly i.v over 15 min (*), which contained either placebo (normal saline) (group A), or 20 mg Nefopam (group B) or 100 mg Tramadol (group C). The Similar trend was also observed at 0 minutes and at 5–30 minutes intervals postoperatively, P. value was significant, 0.014 and 0.001 respectively, table (2) and figure (1). The comparison of systolic blood pressure (SBP) among the studied groups revealed that the mean SBP was insignificantly different among the studied groups at baseline and intraoperative at the 5–35 minutes measurement. At immediate postoperative measurements, there was an increase in SBP in all groups, however the differences did not reach the In table (4) one can notice that O2 saturation (SpO2) was comparable in all groups and it steadily ranged between 96.1 to 99, with no significant difference anesthesiologist was responsible for recording the pulse rate, blood pressure, sweating and Lacrimation, O2 saturation and EtCO2 every 5 minutes but he did not know which of the study drugs had been administered. Upon completion of the surgery and full recovery of the patient, he/she was sent to the post anesthetic care unit (PACU) where there was another anesthesiologist available to evaluate the patient's random blood sugar immediately postoperatively and also to monitor the pulse rate, blood pressure, O2 saturation, respiratory rate, occurrence of nausea and vomiting, pain score (combined numerical and face score) and sedative score (Ramsay score) every 5 minute for 30 minutes post-operatively.

Statistical analysis

Data of the studied groups were entered, managed and analyzed using the statistical package for social sciences (SPSS) version 25 for windows. Descriptive statistics presented as frequencies, proportions, means and standard deviation (SD) and ranges. Statistical tests and analysis were performed according to the type of variables. Chi Square Test was used to assess the significance of association in cross-tabulation model, (categorical variables), Fisher's exact test was used as an alternative when Chi square was inapplicable (more than 20% of the cells in a table had expected values < 5). ANOVA test was used to compare means across the groups. Level of significance, (P. value) of 0.05 or less indicated significant difference, correlation or risk. Results and findings were presented in tables and figures with interpretation of the findings using the Microsoft Office Word Software version 2010.

Results

There were 90 patients enrolled in this clinical trial, patients were assigned into three groups with 30 patients in each, namely groups A, B and C. Despite that the mean fasting blood sugar (FBS) was relatively higher in group A than the other two groups, all the baseline characteristics of the patients in the three studied groups that are shown in **(Table 1.)** have no statistically significant difference in all comparisons, (P>0.05). Regarding the pulse rate, no statistically significant difference had been found at the baseline amongst the three groups. Intra-operative pulse rate was significantly increased in group A than its baseline rates, slightly increased in group B, while it reduced in group C, revealed a statistically significant difference amongst the three groups where higher rates are observed in group A than group B and C (P=0.009) statistical significance, (P>0.05). At the 5–30 minutes postoperative measurements, there was a decrease in SBP in all groups, but the differences were statistically insignificant (P>0.5), table (3), figures (3-4). The diastolic blood pressure of the studied groups was not much different in all groups and in both intraoperative and postoperative giving a non-significant differences among the groups in all measurements (P>0.05), table (3).

neither at baseline, intraoperative, nor postoperative 30 minutes observation in all comparisons, P>0.05. The mean EtCO2 at the baseline measurement was

insignificantly different among the studied groups, and it was significantly increased with time of follow up till the end point, at 35 min. intraoperative. However, these changes occurred in all groups and the comparisons among the three groups at each point of measurements were statistically insignificant in all comparisons, P>0.05, table (5), additionally, figure (7) shows intraoperative trends of changes in EtCO2 of the studied groups. anesthesia and none of the patients in the other two groups did have, at the 5th intraoperative minute, sweating and Lacrimation were reported in 23 patients (76.7%) of group A, 20 (66.7%) of group B, and 23 (76.7%) in group C. At the 10th minute only one patient in group B and one patient in group C had sweating and Lacrimation. At the subsequent time from 15 min to 25 minutes of intraoperative follow up, As it's shown in t**able (9**), the mean random blood sugar (RBS) was relatively higher in group C than group A and B. However, the difference in mean RBS was statistically insignificant amongst the three studied groups, P>0.05.

Discussion

In spite of the fact that postoperative pain after laparoscopic cholecystectomy is less than that after open cholecystectomy(29), a lot of patients still in need for strong analgesia to control the pain postoperatively and despite that the pain after laparoscopic cholecystectomy tend be mild to moderate(30), it's sometimes described as severe in many patients that require potent analgesia. Also because the type of pain that results from laparoscopic surgery is multimodal (incision somatic, referred somatic and visceral pain)(31) the requirement of multimodal analgesia is justifiable in order to minimize the undesirable effects of pain on the patient postoperatively. In this double blind controlled randomized clinical triad study we evaluated patients undergoing elective laparoscopic cholecystectomy who received the drugs of study by tracing the physiological consequence of pain on the patients who are already pain free preoperatively(10). The indirect measures of stress intraoperative, blood pressure increased O2 demand (O2 saturation), sweating and Lacrimation, EtCO2, postoperative random blood sugar (effect of increased cortical, glucagon and adrenaline). We assessed blood sugar pre- and post-operatively in all patients. Regarding the pulse rate, the study shows intraoperative significant increase in pulse rate in group A who received just paracetamol preoperatively and that might be due to milder analgesic effect of paracetamol when used alone without adjuvant agent. Also there was slight increase in pulse rate in group B who received Nefopam intraoperative and this might be attributed to anti-cholinergic effect of Nefopam (27). However, this result could not show superiority in analgesic effect of either group B or C. The blood pressure was insignificantly different among the studied groups. End tidal CO2 (EtCO2) does not differ significantly in all group but there was rising in EtCO2 with time in all groups intraoperative that can be attributed to insufflations of CO2 gas intra-abdominally which easily dissolves in the blood and then exhaled as

Conclusion

none of the patients had sweating and Lacrimation, while at the next 5 minutes sweating and Lacrimation reported in 3, 4 and 3 patients in group A, B and C respectively. At the end point of follow up, the 35th minute, the number of patients who developed sweating and Lacrimation increased to 10 (33.3%) in group A, 7 (23.3%) in group B and 5 (16.7%) in group C. However, no statistically significant differences had been found among the three studied groups regarding the incidence of sweating and Lacrimation along the whole time of follow up in all comparisons (P> 0.05). Ramsay score tends to be reduced than its levels at immediate checkup postoperatively, then reduced and almost fixed in all studied groups at all evaluations postoperatively with no statistically significant difference among the studied groups (P> 0.05)

EtCO2(32) . About the sweating and Lacrimation there were no statistical differences among the three studied groups along the whole time of follow up in all comparisons. It had been observed that (76.7%) of group A, (66.7%) of group B and 76.7% in group C patients developed sweating and Lacrimation at the 5th intraoperative min. that might be due to lightened level of anesthesia of i.v induction agent before adequate level is reached by inhalational agent. Similarly, the re-occurrence of sweating and Lacrimation towards the end point of follow up (the last 5 min.) can be related to lightened anesthetic level as the anesthesiologist started to recover the patient from anesthesia (33.3% in group A, 23.3% in group B and 16.7% in group C)(33). There was no statistically significant difference amongst any of the three studied groups in random blood sugar post operatively and that is not in favor of any group. The pulse rate was declining in all groups post operatively after 5 min. that might be due to analgesic effect of the studied drugs and relieving the stress of emergence from anesthesia. However, the lesser reduction in pulse rate that is noted in group A than groups B and C might reflect more potent analgesic effects of Nefopam and Tramadol. There was an increase in the systolic blood pressure immediately post-operatively perhaps because of emergence from anesthesia. Later on, there was a decrease in systolic blood pressure in all groups after 5 min. postoperatively as it happened with pulse rate. Regarding the O2 saturation (SpO2), respiratory rate and sedation score (Ramsay score) the study shows that the comparisons and trends of changing in these parameters at different check points at postoperative follow up were not significantly different neither among groups nor within each group. The pain score assessment showed that pain score of group B (Nefopam group) was significantly lower than that in each of the two other groups and not only that, but the effect size of Nefopam group was significantly larger than the other two groups. The pain score in group C (Tramadol group) was also lower than group A (placebo group) which indicated apparent decrease in pain score when using Tramadol plus paracetamol than using paracetamol alone, however the difference in mean pain score didn't reach the statistical significance and this might be attributed to the small sample size.

The use of paracetamol plus Nefopam combination during induction of anesthesia is more effective for intra and immediate post-operative pain control for elective laparoscopic cholecystectomy than paracetamol alone or paracetamol plus Tramadol combination.

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Table (1): Baseline characteristics of the studied groups

		A (n = 30)		B (n= 30)		C (n= 30)		P
		No.	%	No.	%	No.	%	
Age (year)	≤ 20	1	3.3	2	6.7	3	10.0	
	21 - 30	2	6.7	3	10.0	2	6.7	
	31 - 40	7	23.3	8	26.7	9	30.0	
	41 - 50	10	33.3	13	43.3	11	36.7	0.77
	51 - 60	5	16.7	2	6.7	4	13.3	
	> 60	5	16.7	2	6.7	1	3.3	
Sex	Male	6	20.0	5	16.7	7	23.3	
	Female	24	80.0	25	83.3	23	76.7	0.75
ASA	I	22	73.3	21	70.0	23	76.7	
	II	8	26.7	9	30.0	7	23.3	0.84
FBS preoperative	Mean	101.6		94.4		92.7		0.11
	SD	12.4		16.2		15.7		-

Table (2): Comparison of pre and post-operative pulse rate of the studied groups

Pulse Rate	A (n = 30)		B (n= 30)		C (n= 30)		P
	Mean	SD	Mean	SD	Mean	SD	
Baseline	87	14	91	8	90	12	0.34
Intra-	96	13	91	11	88	11	0.009
Post-	101	9	99	9	86	9	0.014
Post-	89	8	80	4.6	79	6	0.001

Table (3): Comparison of EtCO2 of the studied groups

EtCO2	B (n= 30)		C (n= 30)		P
	Mean	SD	Mean	SD	
Baseline	35.5	4.1	38.9	5.0	39.4	2.2	0.13
5 min.	38.6	4.2	39.6	4.0	40.1	2.9	0.28
10 min.	38.5	4.2	40.7	2.2	40.5	3.6	0.21
15 min.	39.5	4.2	41.2	1.9	40.0	3.4	0.29
20 min.	39.7	3.7	42.0	2.1	40.9	4.0	0.34
25 min.	41.0	3.4	42.3	2.2	41.1	4.1	0.27
30 min.	41.7	3.0	43.1	2.3	40.6	4.9	0.34
35 min.	43.0	3.0	42.9	2.4	41.7	4.6	0.17

Table (4): Comparison of Ramsay scores of the studied groups

Ramsay Score	A (n = 30)		B (n= 30)		C (n= 30)		
	Mean	SD	Mean	SD	Mean	SD	
Ramsay 0	3.3	1.3	3.4	0.6	3.5	0.6	0.69
Ramsay 5	2.6	0.9	2.8	0.6	2.6	0.5	0.62
Ramsay 10	2.1	0.5	2.1	0.3	2.1	0.3	0.94
Ramsay 15	1.9	0.4	2.0	0.2	2.0	0.2	0.12
Ramsay 20	1.9	0.3	2.0	0.0	2.0	0.1	0.86
Ramsay 25	1.9	0.3	2.0	0.0	2.0	0.1	0.86
Ramsay 30	1.9	0.3	2.0	0.0	2.0	0.2	0.86

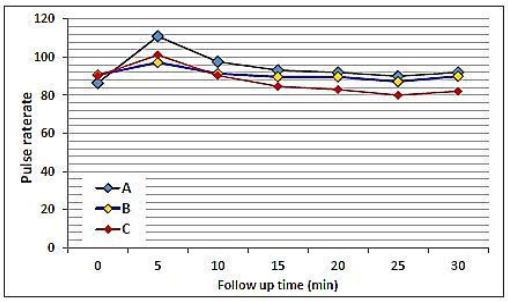
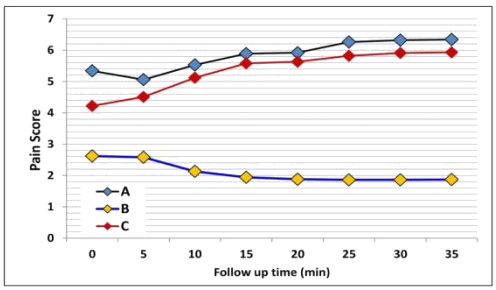


Figure 1. Intraoperative trends and changes in pulse rate of the studied groups



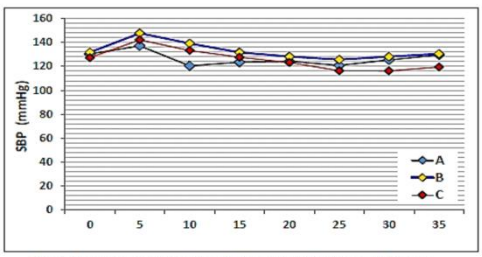


Figure 3. Intraoperative trends and changes in SBP of the studied groups

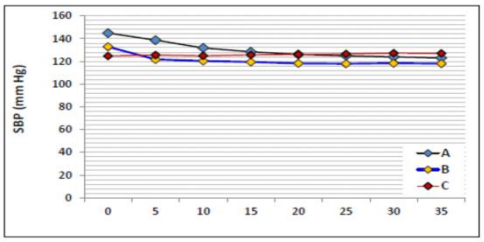


Figure 4. Postoperative trends and changes in SBP of the studied groups