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Comparison of Paracetamol vs. Paracetamol Nefopam Combination vs. Paracetamol Tramadol Combination Intravenous Infusion for Intraoperative and Immediate Postoperative Analgesia for Laparoscopic Cholecystectomy

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Abstract

Background: Pain during and immediately after laparoscopic cholecystectomy is still troublesome for the patients 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: to discover if Paracetamol alone, Paracetamol and Nefopam or Paracetamol and Tramadol combinations is more effective for intra and immediate post-operative pain control for laparoscopic cholecystectomy.

Patients and Methods: 90 patients were randomly selected among those presented for elective laparoscopic cholecystectomy at Al-Sader Medical Teaching Complex in Najaf Governorate/Iraq to participate in this prospective double blinded controlled randomized clinical trial from august 2017 to January 2018. Preoperatively, complete medical history was recorded, detailed physical examination performed and laboratory investigations assessed. The standard monitoring are 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 unite (PACU), while the study variables were recorded every 5 minutes 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: All the baseline characteristics of the patients in the three studied groups have no statistically significant difference in all comparisons. Intraoperatively, there was no significant difference among the three groups in all comparisons of all of the variables that are observed (P value >0.05). 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 pain for elective laparoscopic cholecystectomy than Paracetamol and Paracetamol Tramadol combination without any mentionable side effects.

Recommendations: We recommend to use Paracetamol Nefopam combination for immediate postoperative pain control for elective laparoscopic cholecystectomy in the absence of contraindications.

Keywords: Paracetamol; Nefopam; Tramadol; Laparoscopic Cholecystectomy

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Introduction

Control of postoperative pain is still a challenge and trouble to each of the surgeon, anesthetist and the patient for which it forms a deep psychological and organic effect in forms of stress, catabolism, immune dysfunction, nausea, vomiting, ileus, impaired pulmonary function, increased cardiac demand, coagulation fibrinolysis dysfunction, cerebral dysfunction, fluid homeostasis alteration, sleep disturbance and fatigue [1]. Therefor 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 [2]. The international Association for the Study of Pain (IASP) differentiated types of pain and noted its processing and the chemical mediators that transduce 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 [3-5].

These analgesics if delivered to the patient (whose is already not in pain preoperatively) at any time during the perioperative period pain will decrease, this is termed "preventive analgesia". Provided that the analgesic technique must be extensive enough to include the entire surgical field, the depth of analgesia must be adequate to block all the captive input during surgery and lastly the duration of analgesia must include both surgical and post-surgical periods [6].

Definition of Pain

The International Association of The Study of Pain has published the definition of pain as the following:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [3].

Pain Pathway

The pain processing consist of 4 steps. Functionally the interruption of any step in this pathway leads to pain free condition [7]:

- Transduction
- Transmission
- Modulation
- Perception

Classification of Pain

Pain can be classified clinically to:

Acute Pain: Pain caused by noxious stimulation from injury, disease process, or abnormal function.

Chronic Pain: Pain that persists beyond the usual course of an acute disease or after reasonable time for healing to accuse (1-6 months). May be nociceptive, neuropathic or mixed. Nociceptive pain may be further classified into 2 types:

(a) Somatic Pain: It is classified as:

- Superficial somatic pain
- Deep somatic pain

(b) Visceral pain: It is classified as 4 subtypes:

- Localized visceral pain
- Localized parietal pain
- Referred visceral pain
- Referred parietal pain [8]

Types of Pain

Depending on the mechanism by which the pain happens there are 5 types:

- Nociceptive pain
- Neuropathic pain
- Functional pain
- Inflammatory pain
- Psychogenic pain [9]

Pain Assessment

Before we begin to assess pain we must follow the consequences of poorly controlled pain to take the advantage in scaling pain which are:

- Cardiovascular system: Tachycardia, hypertension and increase in cardiac work load.
- Pulmonary: Respiratory muscle spasm (splinting) can lead to decrease in vital capacity, atelectasis and hypoxia.
- Gastrointestinal: Post-operative ileus.
- Renal: Increased risk of oliguria and urinary retention.
- Coagulation: Increased risk of thromboembolic.
- Immunologic: Impaired immune function.
- Muscular: Muscle weakness and fatigue, limited mobility with increased risk of thromboembolism.
- Psychological: Anxiety, Fear and frustration resulting in poor patient satisfaction. Routine assessment of pain is done by using a scales, these scales have many different names and application and there is no best scale exits. Some are more practical than others. The basic element to assess the pain is the history and physical examination [11].

The Pain Scales

- **Visual analog scale (VAS):** It is a continuous scale represented by (100 mm) line with no pain at one end and pain as bad as it could be on the other end. Patients are asked to draw a line through where their pain is on that scale.
- **Numeric rating scale (NRS):** It is from 1-10 line intensity of pain [0=no pain], [10=worst pain imaginable]. It's widely used in practice because it's reliable. Valid reliability means it measures pain intensity from one time to the next and validity means that it accurately measures pain intensity in addition it's easy and quickly understood by people that are poorly educated and easily scored and record. Inexpensive and readily available and suitable for people of different cultures.
- **Face pain scale:** It works on the Wong-baker face was developed for use with children but it is appropriate for adult (especially poorly communicated people). It's gain preference due to the cartoon like features. For this reason, the combination of the face scale with the (NRS) is preferred to give the adult a choice in pain rating scale. This combination is currently the most wildly use in both children and adults in the United States. the face pain scale do not describe age, gender or culture and has been translated to many language to become universal[14].

- **Multidimensional pain scale:** It assesses the effect of pain on mood by MC Gill pain questionnaire (MPQ). It's reliable and valid in older adult such as patient with cancer pain, 6 month after cardiac surgery, painful diabetic peripheral neuropathy and traumatic stress [12].

- **Opioid consumption scale:** 24 hrs. consumption of opioid is often used as a measure of pain control (*).

Laparoscopic Cholecystectomy

Is 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 [13].

Drugs

Acetaminophen (Paracetamol): It should be regarded as first line analgesia for mild-moderate pain and as a component of multimodal analgesia in the treatment of moderate to severe pain. It's widely used as an analgesic and antipyretic [14-16]. Paracetamol acts both centrally and peripherally. It reduces prostaglandin synthesis from arachidonic acid. It acts on the central serotonergic (5-HT) pathways. It plays a role in the inhibition of nitric oxide synthetase. Its antipyretic effect results from inhibition of prostaglandin system in the hypothalamus.

Tramadol: Synthetic phenylpiperidine opioid analogue of codeine. It's a pure agonist at Mu opioid receptors and enhance (5-HT) release and also delta and kappa receptor agonist and inhibits noradrenalin uptake. It's also a non-competitive NMDA (N-methyl-D-aspartic acid) receptor antagonist that is contributing to its central mechanism. It may have peripheral local anesthetic effect for minor surgical procedures. It's effective in the treatment of moderate postoperative pain with acetaminophen that may decrease its side effects.

Nefopam: It is Benzoxazocine (cyclized analogue of Diphenhaydramine). Centrally acting non-opioid analgesia agent. It inhibits reuptake of Serotonin, norepinephrine and dopamine. Nefopam indirectly modulated the NMDA receptor and relieving allodynia (perception of an ordinary non-noxious stimulus as pain) and opioid related hyper-allodia (macerate response to noxious stimulation).

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 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. 90 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, O_2 saturation, ECG and capnography. The patients were monitored continuously from the time just before induction of anesthesia until discharge from the post anesthetic care unite (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 anesthesiologist was responsible for recording the pulse rate, blood pressure, sweating and lacrimation, O_2 saturation and $EtCO_2$ every 5 minutes but he did not know which of the study drugs had been administered. Upon completion of the surgery and full recoveryy of the patient, he/she was sent to the post anesthetic care unite (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, O_2 saturation, respiratory rate, occurrence of nausea and vomiting, pain score (combined numerical and face score) and sedative score (Ramsay score) every 5 min for 30 min 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).

Similar trend was also observed at 0 minutes and at 5-30 min intervals postoperatively, P. value was significant, 0.014 and 0.001 respectively (Table 2) (Figures 1 and 2).

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 intraoperatively at the 5-35 min measurement. At immediate postoperative measurements, there was an increase in SBP in all groups, however the differences did not reach the statistical significance, (P>0.05). At the 5-30 min postoperative measurements, there was a decrease in SBP in all groups, but the differences were statistically insignificant (P>0.5) (Table 3) (Figures0 3 and 4).

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	0.77
	41-50	10	33.3	13	43.3	11	36.7	
	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	0.75
	Female	24	80.0	25	83.3	23	76.7	
ASA	I	22	73.3	21	70.0	23	76.7	0.84
	II	8	26.7	9	30.0	7	23.3	
FBS	Mean	101.6			94.4	92.7		0.11
preoperative	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-operative 5-35 min	96	13	91	11	88	11	0.009
Post-operative 0 min	101	9	99	9	86	9	0.014
Post-operative 5-30 min	89	8	80	4.6	79	6	0.001

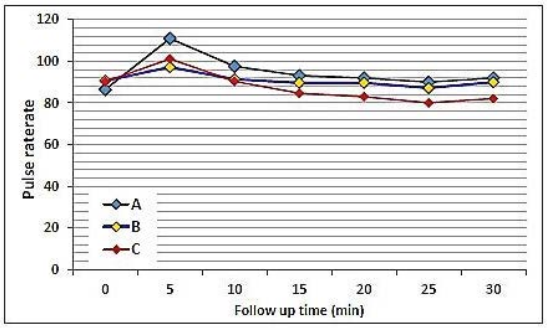

Figure 1: Intraoperative trends and changes in pulse rate of the studied group.

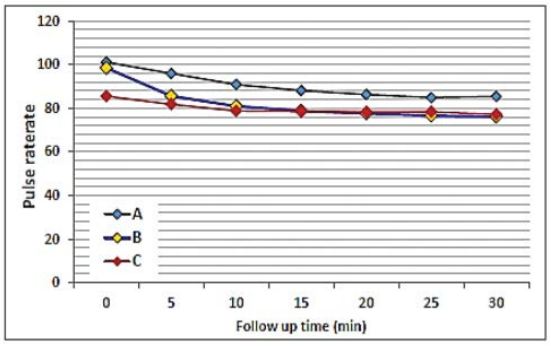

Figure 2: Postoperative trends and changes in pulse rate of the studied groups.\

Table 3: Comparison of systolic and diastolic blood pressure of the studied groups.

Blood Pressure (BP)	A (n = 30)		B (n= 30)		C (n= 30)		*P*
	Mean	SD	Mean	SD	Mean	SD	
SBP baseline	130.3	12.9	131.8	12.0	127.3	13.49	0.39
SBP Intra-op. 5-35 min.	130.7	25.3	132.6	15.6	125.5	8.78	0.30
SBP Post-op. 0 min.	138.9	18.5	136.8	14.0	134.7	24.1	0.41
SBP Post-op. 5-30 min.	129.1	9.1	122.4	8.7	127.1	12.0	0.29
DBP baseline	86.2	13.4	86.9	6.5	81.1	11.05	0.18
DBP Intra-op. 5-35 min.	80.7	6.8	84.1	7.8	80.7	7.09	0.14
DBP Post-op. 0 min.	88.0	15.5	85.8	10.3	85.3	10.6	0.66
DBP Post-op. 5-30 min.	80.0	13.5	78.0	6.8	80.2	9.0	0.24

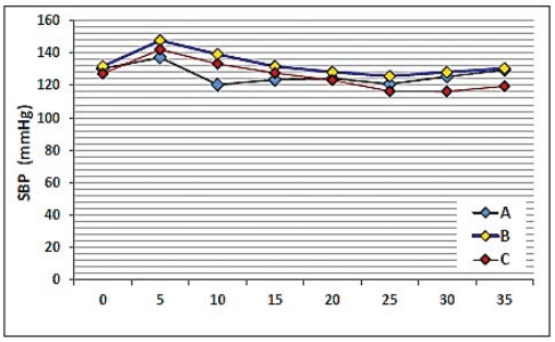

Figure 3: Intraoperative trends and changes in SBP of the studied groups.

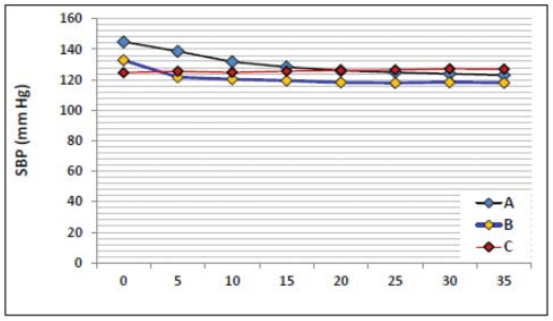

Figure 4: Postoperative trends and changes in SBP of the studied groups.

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) (Figures 5 and 6).

In table 4 one can notice that O_2 saturation (SpO_2) was comparable in all groups and it steadily ranged between 96.1 to 99, with no significant

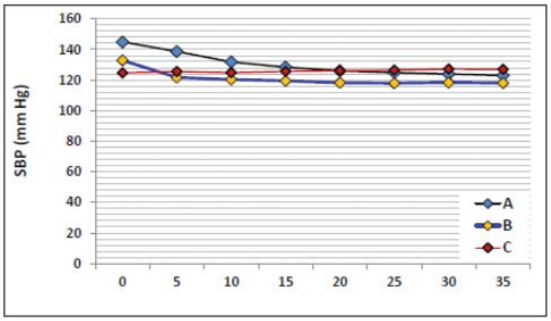

Figure 5: Intraoperative trends and changes in DBP of the studied groups.

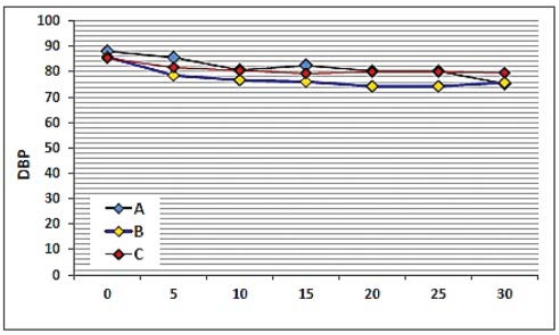

Figure 6: Postoperative trends and changes in DBP of the studied groups.

Table 4: Comparison of O_2 saturation of the studied groups.

SpO_2	A (n = 30)		B (n= 30)		C (n= 30)		*P*
	Mean	SD	Mean	SD	Mean	SD	
SpO_2 Baseline	97.5	1.5	98.0	1.7	98.4	1.0	0.33
SpO_2 Intra-op. 5-35 min	99.0	0.3	99.0	0.3	99.0	0.3	1.0
SpO_2 Post-op. 0 min	96.8	3.1	97.5	1.8	97.2	1.9	0.30
SpO_2 Post-op. 5-35 min	97.4	1.2	97.6	1.4	97.2	1.6	0.92

difference neither at baseline, intraoperative, nor postoperative 30 min observation in all comparisons, P>0.05.

The mean $EtCO_2$ 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 intraoperatively. 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, the figure shows intraoperative trends of changes in $EtCO_2$ of the studied groups.

Table 6 summarizes the incidence of sweating and lacrimation among patients in the three studied groups. It had been observed that only one patient in group B had sweating and lacrimation before induction of 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, 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

Table 5: Comparison of $EtCO_2$ of the studied groups.

$EtCO_2$	A (n = 30)		B (n= 30)		C (n= 30)		*P*
	Mean	SD	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 6: Incidence of Sweating and Lacrimation among patients in the three studied groups along the follow up period.

Sweating and Lacrimation	A (n = 30)		B (n= 30)		C (n= 30)		P. value
	No.		No.		No.		
0 min	0	0.0	1	3.3	0	0.0	0.36
5 min	23	76.7	20	66.7	23	76.7	0.51
10 min	0	0.0	1	3.3	1	3.3	0.60
15 min	0	0.0	0	0.0	0	0.0	-
20 min	0	0.0	0	0.0	0	0.0	-
25 min	0	0.0	0	0.0	0	0.0	-
30 min	3	10.0	4	13.3	3	10.0	0.89
35 min	10	33.3	7	23.3	5	16.7	0.25

Table 7: Comparison of pain scores of the studied groups.

Pain Score	A (n = 30)		B (n= 30)		C (n= 30)		*P*
	Mean	SD	Mean	SD	Mean	SD	
0	5.3	1.8	2.6	1.1	4.2	0.7	<0.001
5	5.0	1.4	2.6	1.2	4.5	0.9	<0.001
10	5.5	1.0	2.1	1.0	5.1	1.0	<0.001
15	5.9	0.5	1.9	0.6	5.6	0.8	<0.001
20	5.9	0.4	1.9	0.7	5.6	0.8	<0.001
25	6.3	1.1	1.9	0.7	5.8	1.1	<0.001
30	6.3	1.2	1.9	0.7	5.9	1.2	<0.001

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).

The pain score assessment revealed that the mean score was significantly lower in group B (mean=2.6) at immediate postoperative checkup (0 time), and it's still significantly lower at each subsequent 5 min. interval checkups till the last measurement at 30 min. postoperatively. The pain score tends to increase in the other two groups, in all comparisons, P<0.05, (Table 7 and Figure 7). Further comparison was performed to compare the mean pain scores during the whole postoperative period of follow up (0-30 min) and revealed that the mean pain score of group B was significantly lower than that in each of the two other groups (A and C) and the effect size was large (0.95 and 0.91) respectively (P<0.001). On the other hand the mean pain score was significantly lower in group C than that in group A, with a small effect size of (0.28), (P=0.025) (Figure 8).

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) (Table 8 and Figure 9).

As it's shown in the table 9, the mean random blood sugar (RBS) was relatively higher in group C than group A and B. However, the

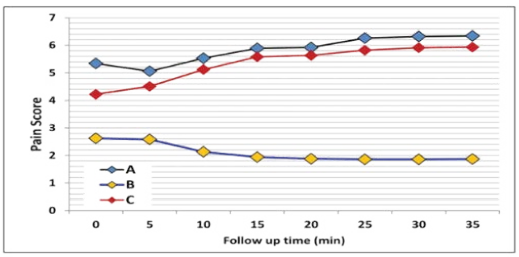

Figure 7: Postoperative trends and changes in pain scores of the studied groups.

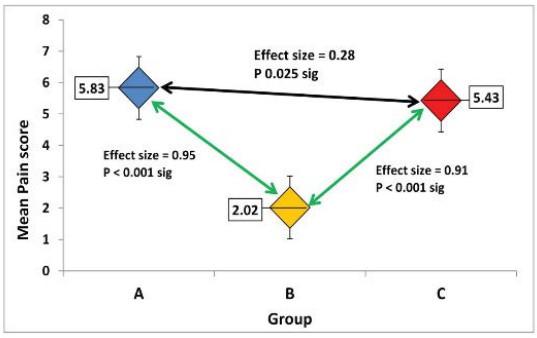

Figure 8: Comparison of mean pain scores recorded at 5-30 min. postoperatively.

Table 8: Comparison of Ramsay scores of the studied groups.

Ramsay Score	A (n = 30)		B (n= 30)		C (n= 30)		*P*
	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

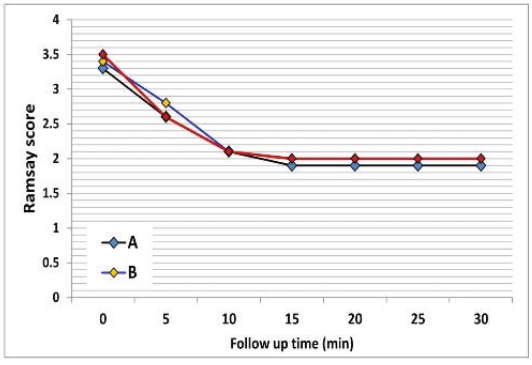

Figure 9: Postoperative trends and changes in Ramsay score of the studied groups.

Table 9: Comparison of postoperative random blood sugars of the studied groups.

		A (n = 30)	B (n= 30)	C (n= 30)	P
RBS	Mean	158.4	159.0	162.2	0.81
Postoperative	SD	28.9	24.8	17.1	-

difference in mean RBS was statistically insignificant amongst the three studied groups, P>0.05.

Table 10 shows the comparison and trend of changes in respiratory rate at different check points at postoperative follow up where no significant difference had been observed neither among nor within groups (P>0.05).

Table 10: Comparison of respiratory rate of the studied groups.

Respiratory Rate	A (n = 30)		B (n= 30)		C (n= 30)		P. value
	No.		No.		No.		
0 min	18.6	1.6	17.5	0.9	18.5	2.0	0.65
5 min	18.6	2.1	17.9	1.3	18.8	1.7	0.78
10 min	19.0	1.5	17.7	1.1	18.8	1.7	0.22
15 min	18.5	1.6	17.9	1.2	18.2	1.3	0.28
20 min	18.3	1.2	17.8	1.0	18.6	1.4	0.21
25 min	18.4	1.3	18.1	1.3	18.7	1.8	0.33
30 min	18.2	1.3	20.2	11.7	18.6	1.5	0.51
35 min	10	33.3	7	23.3	5	16.7	0.25

Discussion

In spite of the fact that postoperative pain after laparoscopic cholecystectomy is less than that after open cholecystectomy, 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, it's sometimes described as severe in many patients that require potent analgesia [17-20]. Also because the type of pain that results from laparoscopic surgery is multimodal (incisional somatic, referred somatic and visceral pain) 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. The indirect measures of stress intraoperatively, blood pressure, increased O_2 demand (O_2 saturation), sweeting and lacrimation, $EtCO_2$, postoperative random blood sugar (effect of increased cortisol, 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 intraoperatively and this might be attributed to anti-cholinergic effect of nefopam. 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 CO_2 ($EtCO_2$) does not differ significantly in all group but there was rising in $EtCO_2$ with time in all groups intraoperatively that can be attributed to insufflation of CO_2 gas intra-abdominally which easily dissolves in the blood and then exhaled as $EtCO_2$. About the sweating and lacrimation there was 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 [21,22]. 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). 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 a 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 [23-25]. 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 O_2 saturation (SpO_2), 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 [26-28].

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.

Conclusion

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.

Recommendation

We recommend to use Paracetamol and Nefopam combination during induction of anesthesia for control of intra and immediate post-operative pain for elective laparoscopic cholecystectomy in the absence of any contraindication to use any of these drugs.

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