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EFFICACY OF PREEMPTIVE AND PREVENTIVE ANALGESIA IN REDUCING POSTOPERATIVE RESCUE ANALGESIC REQUIREMENTS IN SURGICAL PATIENTS

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Abstract:
Background: To compare the efficacy of pre-emptive and preventive analgesia on postoperative requirement of rescue analgesic in surgical patients within 24 hours; along with haemodynamic changes.
Design: Prospective randomized study.
Materials and method: This study involved total of 90 patients, of either gender, aged between 18-65 years, belonging to American Society of Anesthesiology [ASA] grade I and II, who underwent surgery under general anaesthesia lasting up to 2 hours .They were randomly assigned into three groups: GROUP I-Preemptive group received1gm of IV Paracetamol(100ml) prior to skin incision and IV normal saline [NS](100 ml) prior to end of surgery; GROUP II- preventive group received IV NS(100 ml) and 1gm of IV Paracetamol(100ml) before skin incision and closure respectively ; GROUP-III control group received 100 ml of intravenous (IV) NS before skin incision and before closure.
Results: Pain scores between both Preemptive and Preventive groups observed to be non significant up to 24 hours. Between Group I vs Group III mean pain scores was observed to be higher in Control group and found to be statistically significant ($P<0.05$)up to 12 hours, whereas at 24 hours it was statistically non-significant. In comparison between the Group II vs Group III mean pain scores were statistically significant until 8 hours, whereas at 12 hours and 24 hours were found to be non-significant.
Conclusion: Surgical patients undergoing surgery under general anaesthesia preemptive analgesia may provide adequate analgesia and stable hemodynamics perioperatively and decrease postoperative analgesic consumption whereas preventive analgesia provides relief in postoperative period.

Keywords: Preemptive analgesia, Postoperative pain, Rescue analgesic, Haemodynamic.

Introduction:

Postoperative pain is a common and distressing problem that affects patient satisfaction, recovery, mobility and early discharge from the hospital. Adequate pain management is crucial for the well-being and comfort of surgical patients. Preemptive analgesia is defined as the administration of analgesic before the onset of nociceptive stimuli thus the development of peripheral sensitization and in turn central sensitisation is prevented and reduces the immediate postoperative pain thereby the development of chronic pain may be prevented. Preventive analgesia defined as a pain therapy given at any time during the perioperative period after surgical incision (incisional and inflammatory responses) which is effective enough to provide analgesia by inhibiting the development of central sensitization and hyper excitability, in a patient who has no history of preoperative pain.

The concept of preemptive analgesia is to reduce the magnitude and duration of postoperative pain which is evidence for a central component of post injury pain hypersensitivity in experimental studies [1]. Following that, an overwhelming amount of experimental data indicated that various antinociceptive treatments used prior to injury were more effective in minimizing post injury central sensitization than administration after injury [2]. Finally, the theory was clinically tested using these encouraging experimental findings. Although early studies with various clinical outcomes were mainly unfavourable, continued to believe in the benefits of preemptive analgesia [3-5].

The basic understanding of pain pathway thus central sensitization is a key notion in understanding the basis of preemptive and preventive analgesia. Acute pain (surgical stress, obnoxious stimuli), can cause long-term emotional and psychological anguish and has the potential to progress into chronic pain, which is far more difficult to tolerate and manage[6].

It has now been researched and studied to a broader concept, namely that surgical incision alone does not cause central sensitization[7-8]. Other factors, such as chronic/acute preoperative pain and additional noxious intraoperative stimuli such as retraction, manipulation of organs as well as postoperative inflammatory processes related to altered peripheral and central neuromodulation and ectopic neural activity can all cause increase in intensity of pain perception thus long-term postoperative hyperalgesia and allodynia. There are currently various multimodal techniques being studied during the perioperative period. Preemptive analgesia is observed as better since it incorporates multiple perioperative attempts to reduce postoperative pain and need of rescue analgesia which mostly opioids for early recovery and mobility as a part of ERAS in surgical patients.

Several pre-emptive analgesic regimens have been mentioned in literature. These include

- Pharmacotherapy in the form of - intravenous doses of opioids,[9-10] non-steroidal anti-inflammatory drugs as well as NMDA receptor antagonists
- Local anaesthetic infiltration at surgical incision[11-12]
- Regional nerve blocks [13]
- Use of opioids as Epidural analgesia [14]

Multimodal analgesic regimens which consist of two or more of the above-mentioned methods[15].During recent times due to the concept of Enhanced Recovery After Surgery, there is a need for more adequate control of pain in postoperative period. However, data from several clinical studies has shown differences, and do not support this hypothesis at all times [16].

Postoperative pain relief is an essential part of patient care. The basic idea of pain prevention and possible relationship between tissue damage accompanying a surgical procedure and postoperative pain was first introduced into clinical practice by woolf [17].

Therefore, studying preemptive and preventive analgesia is important because it can lead to improved pain management strategies that minimize the use of rescue analgesics and their associated risks. This can ultimately improve patient outcomes and reduce healthcare costs.

Both preemptive and preventive analgesia aim to reduce postoperative pain and opioid consumption, but their efficacy and optimal timing of administration are still a matter of debate.

Materials and Methods:
After taking approval from Institutional Ethics Committee; informed consent was taken from all subjects who participated in the study. This was a random prospective control study, which was conducted in the Department of anaesthesia, M.M.I.M.S.R. Mullana Ambala over a period of 2 years. The study involved 90 patients of ASA grade I or II, aged 18-65 years, of either gender, who underwent surgery under general anaesthesia. The patients were divided into three equal groups, randomization was accomplished by the use of a computer-generated number and the secrecy of the randomization sequence was accomplished through the use of sequentially numbered concealed envelopes.

GROUP I- Preemptive group received 1 gm of IV Paracetamol (100ml) 30 min prior to skin incision and 100 ml Normal Saline 30min prior to closure, GROUP II the Preventive group received 100 ml IV Normal Saline 30 min prior to skin incision and 1gm IV Paracetamol (100 ml) 30 min prior to skin closure, GROUP-III received 100 ml of intravenous (IV) Normal Saline 30 min prior to skin incision and skin closure. Pre-Anaesthetic checkup was done a day before surgery. Detailed history, physical examination including HR, BP, respiratory rate and systemic examination was done. Routine investigations including hemoglobin (Hb), bleeding time (BT), clotting time (CT), liver function tests (LFT), renal function tests (RFT), complete urine examination, random blood sugar (RBS), electrocardiography (ECG) and chest x-ray was done
All patients were informed about the VAS score after surgery in order to decide the first dose of rescue analgesic at 0 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 24 hours. The time/duration of the need for recue analgesia was recorded. The total amount of rescue analgesic necessary over the course of 24 hours was noted. With a VAS value of three or above, rescue analgesia was administered. The VAS is a simple verbal scale used to assess pain based on the following scores. 0 means no discomfort, while 10 means terrible pain.

Inclusion criteria: American Society of Anaesthesiologists (ASA) Grade I and II patients of either gender aged between 18-65 years, Patients undergoing surgeries (Open cholecystectomy) under general anaesthesia and duration of surgery less than 2 hrs

Exclusion criteria: Patients belonging to American Society of Anaesthesiologists (ASA) Grade III and IV consenting patients, patients who refused for the analysis and Surgeries which take more than two hrs where excluded in the study.

Statistical analysis:
As appropriate, data were presented in terms of range, mean, standard deviation (± SD), median, frequencies (number of cases), and relative frequencies (percentages). ANOVA was used to compare quantitative factors between study groups. The Chi square ($\chi 2$) test was employed to compare categorical data, and the exact test was utilised when the anticipated frequency was less than 5. A p value of less than 0.05 was considered statistically significant. All statistical computations were performed on Microsoft Windows using the (Statistical Program for the Social Science) SPSS 21version statistical programme (SPSS Inc., Chicago, IL, USA).

Results:
As detailed in table-1, Analysis and comparison of the study groups mean age distribution , 43.6±9.56 in group I, 42.9±9.4 in group II, and 40.0±11.0 in group III. Analysis and comparison of the study groups gender revealed that group I had 53.0% females and 47% males, group II had 67.0% females and 33% males, and group III had 70.0% females and 30% males. Analysis and comparison of the

study groups weight there was no significant difference. ASA distribution also showed no significant difference in our present study.

The table-2 below displays the post-operative mean pain scores for all three groups from 0 min to 24 hours. There was a significant difference in VAS score from 0 min to 12 hours between Group I and Group III, and a significant difference in VAS score from 0 min to 8 hours between Group II and Group III. At 24 hours, it was non significant difference between groups I and III. At 12 and 24 hours, there was non significant difference between groups II and III.

Upon examining the study groups, we deduce from table-3 that Group II had a significantly higher mean arterial pressure than Group I from the beginning of the surgery 0 to 120 minutes after it. Similarly, Group III had a significantly higher mean arterial pressure than Group I from the start of the surgery to 4 hours after it. Additionally, there was a notable difference between Group II and Group III in terms of mean arterial pressure levels at skin closure, after extubation, and at the 2 and 4 hour marks after surgery.

Table-4 indicate that when analyzing and comparing study groups, it was found that in group III, 23% of patients experienced nausea and vomiting, whereas in group II, 10% experienced vomiting. In contrast, only 3% of patients in group I experienced nausea and vomiting.

After analyzing and comparing study groups, it was observed that in table-5,only two patients in group III experienced respiratory depression in the form of tachypnea, whereas none of the patients in group I and group II had any respiratory depression. This difference was statistically non-significant.

Discussion:

Postoperatively providing efficient pain control in surgical patients is an essential part of patient care. Appropriate management of post-operative pain is one of the most important challenges recently as part of Enhanced recovery after surgery (ERAS) for better outcomes of every surgical patient. However, despite advancements in pain management techniques and medications, many patients still suffer from inadequate pain control after surgery.

Another important factor in achieving efficient pain control is the administration of appropriate interventions at the right time and in the right dose. Patients should be monitored regularly for pain intensity and side effects of medications to ensure that the treatment plan is adjusted as needed. Patient education and knowledge about options available for pain management is also essential. Our research thus, evaluates the efficacy of Preemptive and preventive analgesia on postoperative requirement of rescue analgesic in surgical patients. .

In our research, 90 patients of ASA grade I and II, between the ages of 18-65, of any gender, who underwent general anesthesia procedures lasting no longer than 2 hours were randomly assigned to one of three groups. The average age range of patients in each group was as follows: in group I it was 43.6 years with a standard deviation of 9.56, in group II it was 42.9 years with a standard deviation of 9.4, and in group III it was 40.0 years with a standard deviation of 11.0.

In the study we conducted, Group I consisted of 53.0% females and 47% males, Group II had 67.0% females and 33% males, and Group III had 70.0% females and 30% males. However, we found no significant difference when comparing the three groups.

Similarly study done by Arici et al., 2009[18] included 90 participants out of these 8 patients were excluded, the average age range of patients in each group was as follows: in group I it was 50.37 ±6.56 years, in group II it was 47.73 ±7.20 years, and in group III it was 49.0 ±6.40 years. Whereas study done by Arslan et al ., 2011[19]included 60 thyroidectomy patients (ASA class 1-2, age 18-72 years) were included in the study and randomly assigned to three groups. According to the study done by Choudhuri et al., 2011[20] 80 patients who were between the ages of 18 and 70 and undergoing laparoscopic cholecystectomy were divided into two groups: group-F with a mean age of 56 ±16.5 years, and group-P with a mean age of 54 ±19.1 years. In another study done by Koteswara et al ., 2014[21]39 patients in the age group of 16 – 69 years, undergoing FESS, were enrolled, in group I the mean age was 40.7 years ±9.24, in group II it was 43.9 ±7.58 years.

In our present research, we observed that 57% of patients in group I were classified as ASA grade 1, while 70% of patients in group II and 80% in group III belonged to this grade. On the other hand, 43% of patients in group I and 30% of patients in group II and 20% in group III were categorized as ASA grade 2. However, these percentages did not show a statistically significant difference.

In our present investigation, after 15 minutes, there was no significant difference in the mean pain scores between Group I and Group II, indicating that they were similar. This finding aligns with the results of previous studies [18,19],[22-24]. After 30 minutes and 1 hour, Group I had lower mean pain scores compared to Group II, but the difference was not statistically significant. This finding is consistent with the results of previous studies. [18],[22-24] However, the studies by Arslan et al ., 2011[19], Koteswara et al ., 2014[21] showed that Group I had significantly lower mean pain scores compared to Group II, which is not in agreement with our study.

Koteswara et al ., 2014[21] found that after 6 hours, Group II had higher mean pain scores compared to Group I with significant results, which is not consistent with our study. They noted that the Preemptive group experienced effective pain relief when the study drug was administered 15 minutes before skin incision. Arora et al., 2021[24] also observed similar results between both groups, which were not significant, just like our study.

From 4 hours to 24 hours, Group II had lower mean pain scores compared to Group I, and the difference was not statistically significant, which was in concordance with previous study [19].

In our study, we found that Group III had significantly higher pain scores compared to Group I from 0 minutes to 12 hours, but the difference was not statistically significant at 24 hours, and the pain scores were similar between the two groups. Arici et al., 2009 [18] conducted a study and found that the VAS score in Group I was significantly lower than Group III during rest and movement from 1 hour to 12 hours, but not significantly different at 24 hours, which is consistent with the results of our study.

Our study found that Group III received their first rescue analgesia medication earlier than Group I and Group II, with a time of 18.63±14.05 minutes compared to 48.50±56.81 minutes and 36.97±32.21 minutes, respectively. We observed statistically significant differences between the Preemptive and Control group as well as the Preventive and Control group. When comparing Group I and Group II, we found that the time of analgesia needed was similar and not statistically significant. This contradicts the findings of studies by Arslan et al ., 2011, [19] Koteswara et al ., [21], 2014, Hassan et al ., 2014[23] which reported significant results. When comparing Group I and Group III, we found significant results as the time of rescue analgesia needed was longer in Group I. This aligns with the findings of studies by Arslan et al ., 2011, [19] Choudhuri et al., 2011 [20] When comparing Group II and Group III, we found significant results as the time of rescue analgesia needed was longer in Group II compared to Group III. This is consistent with the previous study [19].

According to our current study, Group I required a lower total amount of rescue analgesic than Group II and Group III, with a cumulative dose of 65.8±67.60 mcg compared to 87.8±69.80 mcg and 124.3±83.89 mcg, respectively. We observed significant differences between Group I and Group III as well as Group II and Group III, but no significant differences between Group I and Group II in accordance with study by Arslan et al ., 2011[19] they proved that the consumption of IV Tramadol for 24 hours was lower in Group I compared to other study groups, indicating that preemptive analgesia was effective in providing adequate pain relief.

Choudhuri et al., 2011[20] found that the group receiving preemptive analgesia had a statistically significant reduction in the need for rescue analgesics compared to the placebo group, which is consistent with the findings of our study.

In our current study, we analyzed and compared the study groups and found significant differences in heart rate between Group I and Group II from 0 minutes to 120 minutes, between Group I and Group III from 0 minutes to 4 hours, and between Group II and Group III at skin closure and up to 4 hours after surgery.

The study carried out by Hassan et al ., (2014)[23] found that the Preemptive group had significantly higher heart rate, systolic blood pressure, and diastolic blood pressure than Group II immediately

after the surgery, which is not consistent with our findings. This suggests that intravenous paracetamol may not be effective in controlling hemodynamics in some cases.

In our current analysis of the study groups, we found a significant and higher difference in systolic blood pressure between Group II and Group I from 0 minutes to 120 minutes, as well as a significant and higher difference in Group III compared to Group I from 0 minutes to 4 hours. We also observed a significant difference between Group II and Group III at skin closure and up to 4 hours after surgery.

In our study group analysis, we found a significant and higher difference in diastolic blood pressure between Group II and Group I from 0 minutes to 120 minutes, as well as a significant and higher difference in Group III compared to Group I from 0 minutes to 4 hours. We also observed a significant difference between Group II and Group III at skin closure, after extubation, and 2 and 4 hours after surgery.

Hassan et al ., (2014)[23] showed that Preemptive analgesia group had significant control of hemodynamic changes before delivery of the baby on comparison with the preventive group which is similar to our study. Whereas results in Preemptive group showed higher HR, SBP, and DBP than Group II immediately postoperative with extreme statistically significant difference ($P < 0.001$) not in accordance with our study implying the decreased efficacy of IV PCM in control of hemodynamics Arici et al., (2009),[18] reported a reduction in the average values of heart rate, systolic blood pressure, and diastolic blood pressure during surgery after preemptive administration of paracetamol, which is consistent with the results of our study.

In our current study, we observed a significant and higher difference in mean arterial pressure between Group II and Group I from 0 minutes to 120 minutes, as well as a significant and higher difference in Group III compared to Group I from 0 minutes to 4 hours. We also found a significant difference between Group II and Group III at skin closure, after extubation, and 2 and 4 hours after surgery

Our study did not find any significant differences in SpO2 between the groups at all time points. However, in contrast to the study by Hassan et al, in which Group II showed lower SpO2 than Group I immediately postoperative with high significance .There were no significant differences in SpO2 during the preoperative, intraoperative, and 1 h and 2 h postoperative , which is consistent with the study by Arici et al., (2009)[18].

In our current analysis and comparison of study groups, There were 23% patients who experienced nausea and vomiting in Group III and 10% experienced vomiting in Group II while only 3 % of patients who experienced nausea and vomiting in Group I. There were 7 % of patients in group III experienced respiratory depression while none of the patients in group I and Group II. It is observed that higher requirement of opioid in few patients caused it's related the side effects. Compared to study by Arici et al., (2009),[18] the incidence of side effects such as postoperative nausea, vomiting, itching and respiratory depression were found to be statistically significant and higher in control group not similar to our study as PCA morphine was used which causes more side effects compared to our rescue analgesic. Arslan et al ., (2011)[19] study, showed that incidence of side effects were higher in group II and III compared to group I which was not in accordance with our study. The study conducted by Koteswara et al., (2014)[21] found that patients in the control group had a higher incidence of nausea and vomiting, which is similar to our study. However, no other adverse effects such as respiratory depression due to opioids were observed. Choudhuri et al., 2011 [20], Arora et al., 2021[24] conducted studies that found no significant occurrences of nausea, vomiting, or respiratory depression, which is consistent with our own study.

Limitations:

In providing efficient pain control in surgical patients is an essential part of patient care.as multiple factors are responsible for initiation and memory of pain through the pain pathway It requires a collaborative effort between the surgical team, anesthesiologists and the patient to ensure a multimodal approach to prevent morbidity and mortality with enhanced recovery post operatively. By addressing pain management as a priority, healthcare providers can improve patient outcomes, reduce complications, and increase patient satisfaction.

Conclusion:

Administering IV Paracetamol preemptively in surgical patients resulted in better management of intraoperative hemodynamic parameters and longer duration before requiring the first rescue analgesia, indicating effective post-operative pain control. The total cumulative dose of opioid rescue analgesia required in 24 hours was comparatively less in the postoperative period. These outcomes contribute to a better recovery process as seen in the Enhanced Recovery after Surgery (ERAS) approach, which can reduce hospital stay and minimize the incidence of side-effects while improving patient satisfaction.

Variable		Group I	Group II	Group III	P value
Age (in years)		43.63±9.56	42.93±9.45	40.07±11.04	0.350
I VS II					0.788
I VS III					0.173
II VS III					0.272
Sex (F:M)		16:14	20:10	21:9	0.366
Weight in Kgs		64.57±7.43	64.00±8.27	61.87±8.36	0.393
ASA grade Status	1	17	21	24	0.147
	2	13	9	6	

Table1: Demographic profile of groups

Table 2: Post-operative VAS scores

VAS /Time in Min	Group-I	Group-II	Group-III	p-Value	I VS II	I VS III	II VS III
					p-value	p-value	p-value
T0_ 0min	0.50±0.51	0.60± 0.50	2.37± 0.72	0.000	0.509	0.000	0.000
T1_15 min	1.40± 0.97	1.57± 1.07	3.20 ±0.85	0.000	0.506	0.000	0.000
T2_30min	1.90± 0.76	1.90± 1.32	3.53± 1.14	0.000	1.000	0.000	0.000
T3_1hr	2.43± 1.45	2.73± 1.74	3.37 ±0.72	0.031	0.400	0.010	0.048
T4_2hr	1.90 ±0.92	2.20± 1.21	3.00 ±0.83	0.000	0.250	0.000	0.003
T5_4hr	1.87± 0.90	1.97± 0.72	2.37 ±0.61	0.029	0.609	0.012	0.043
T6_8hr	1.13± 0.78	1.17± 0.75	1.93± 0.69	0.000	0.862	0.000	0.000
T7_12hr	0.67± 0.61	0.87± 0.57	1.03± 0.67	0.076	0.213	0.024	0.298
T8_24hr	0.10± 0.31	0.27± 0.45	0.17± 0.38	0.242	0.095	0.502	0.314

Table 3: Mean Arterial Pressure at different time interval

	Group I	Group II	Group III	p-value	I VS II	I VS III	II VS III
					p-value	p-value	p-value
MAP (baseline)	88.96 ±7.24	89.16 ±7.11	88.31± 7.71	0.898	0.916	0.735	0.658
T0_ 0min	93.01 ±8.14	100.36± 7.19	99.73± 7.89	0.001	0.000	0.001	0.757
T1_10 min	89.74± 10.06	97.99 ±7.41	98.50± 7.99	0.000	0.000	0.000	0.818
T2_20min	89.90± 6.89	99.19± 7.85	98.13 ±6.58	0.000	0.000	0.000	0.568
T3_30min	88.32 ±7.41	100.19 ±7.96	97.84± 4.85	0.000	0.000	0.000	0.190
T4_60min	87.66± 5.00	99.49 ±7.31	97.63± 3.81	0.000	0.000	0.000	0.200
T5_90min	88.54 ±5.94	99.22 ±7.74	97.63± 5.65	0.000	0.000	0.000	0.347
T6_120min	86.67± 5.14	97.91 ±7.56	96.47± 5.45	0.000	0.000	0.000	0.365
T7_(skin closure)	91.09± 6.34	91.62± 7.10	98.49± 6.09	0.000	0.752	0.000	0.000
T8_(After extubation)	90.64± 6.12	88.31± 6.81	100.04± 5.87	0.000	0.154	0.000	0.000
T9_2hrs(Post Op)	86.60± 4.40	87.62 ±6.51	96.89±5.58	0.000	0.479	0.000	0.000
T10_4hrs(Post Op)	86.76 4.63	88.49 6.09	97.20±5.70	0.000	0.226	0.000	0.000

Table 4: Comparison of the adverse effects of rescue analgesia (nausea and vomiting)

		Group I		Group II		Group III		Total	P-value
		No. of case	%	No. of case	%	No. of case	%		
NAUSIA AND VOMITI NG	No	29	97	27	90	23	77	79	0.055
	Yes	1	3	3	10	7	23	11	
Total		30		30		30		90	

		Group I		Group II		Group III		Total	Chi Square Value	p-Value
		No.of case	%	No. of case	%	No. of case	%			
Respiratory Depression	No	30	100%	30	100%	28	93	88	4.091	0.129
	Yes	0	0	0	0	2	7	2		
Total		30	100%	30	100%	30	100%	90		

Table 5: Side effects of rescue analgesia (respiratory depression)

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