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A Randomized Controlled Study on Effect of Intravenous Paracetamol as a Pre-Emptive Analgesic In Patients Undergoing Hysterectomy

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Abstract: ***AIM: To study the efficacy of intra-venous paracetamol as a pre-emptive analgesic for post-operative pain management. Objectives: To assess the post-operative analgesic effect of intra-venous (IV) Paracetamol, administered as pre-emptive analgesic. To assess the amount of post-operative fentanyl consumption, the pain scores, side-effects and patient satisfaction in the post-operative period. To compare the results with two group of patients; those who received intravenous paracetamol before skin closure and those patients who received intravenous saline as control. This study entitled "a randomized controlled study on effect of intravenous paracetamol as a pre-emptive analgesic in patients undergoing hysterectomy" was carried out in Department of Anaesthesiology, Krishna Institute of Medical Sciences, Karad. It was a prospective, randomized, controlled, double blind clinical study involving 60 patients undergoing hysterectomy under Spinal Anaesthesia. The patients were randomly allocated in three groups of 20 patients each.the day of the surgery a morning dose of 5mg was given orally. The pre-operative pulse rate, blood pressure (systolic, diastolic and mean) and Spo2 were recorded. All patients received tablet Diazepam 10mg orally night before the surgery for anxiolysis and on As per the groups patients were given the drugs. The drug and the control were prepared in a burette by a colleague who was blinded to the study.The anaesthesiologist performed SAB and made observations in all patients involved in study. Intra-operatively mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (Spo2) was recorded. At the end of the operation, the patients were evaluated for post-operative pain with Visual Analogue Scale (VAS). Intravenous Fentanyl was administered when the visual analogue score was equal to or more than 4. VAS scores of patient at post-operative period 0min, 15mins and 30 mins and at 1,2,4,8,12 hours was recorded. The total fentanyl consumption during the same was recorded in micrograms (mcg).Side effects were also recorded. Result: The three groups were comparable to each other with respect to all the demographic data like Age, Weight, Height, Duration of surgery,The average post-operative VAS scores in the three groups was significant,The pain scores in Group I (Pre-emptive Group) was less than Group II (Intra-operative Group) and also Group II was less than Group III (saline control Group),The average fentanyl consumption in the Pre-emptive Group was significantly less than Group II and III. However Group II patients who received paracetamol before the skin closure needed significantly less opioid than Group III patients,Incidence of nausea and vomiting was less in Pre-emptive Group compared to the Group II patients which was also lesser than Group III patients.***

Keywords: Intra-venous paracetamol, pre-emptive analgesic and post-operative pain management

1. Introduction

Effective post-operative pain control is an essential component of the care of the surgical patient. Improving post-operative pain control has become an increasingly important issue for the anaesthesiologist. Analgesia administered before the occurrence of painful stimulus may prevent or reduce the subsequent pain or the analgesic requirement. Pre-emptive analgesia is an anti-nociceptive treatment that prevents establishment of altered processing of afferent inputs which amplifies post-operative pain. This hypothesis has prompted numerous clinical studies. Prolonged pain can reduce physical activity and lead to venous stasis and increased risk of deep vein thrombosis and consequent pulmonary embolism. In addition, there can be widespread effects on gut and urinary tract motility, which may lead, in turn to postoperative ileus, nausea, vomiting and urinary retention. [1]

The choice of pain relieving techniques may be influenced by the site of surgery. Equally, it may be influenced by drug availability and familiarity with different methods of analgesia. For many years, the standard method of treating postoperative pain in the developed world has been intramuscular narcotics (usually Morphine). The effects of narcotics drugs vary greatly among patients and thus individual response cannot be predicted. Many studies have shown that under treatment of acute postoperative pain occurs because there is an overestimation of the length of action and the strength of the drugs used and fear about respiratory depression, vomiting, sedation and dependency associated with use of opioids [2-3].

The above strategy is now beginning to be recognized as constituting suboptimal management and more resources are being devoted to acute pain services, including development of continuous epidural analgesic administration and patient-controlled analgesia (PCA)[2,3].

After a patient undergoes abdominal hysterectomy and when the anaesthetic effect wears off it is observed that the patient complains of incisional pain. Post-operative pain can cause a number of sequels. Nonsteroidal anti inflammatory drugs (NSAIDS) and opioids are commonly prescribed to mitigate post-operative pain but these are burdened by side effects. Paracetamol lacks in such side-effects. Unlike other NSAIDS it does not interfere with platelet function, kidney function and unlike opioids it does not depress respiration or provoke sedation.

Prompted by the availability of the rectal and parenteral preparations the paracetamol treatment for post-operative pain is now being realised. In our study we will be using paracetamol for post-operative analgesia. Paracetamol is a non-opioid agent and it primarily acts upon the central nervous system by way of central cyclo-oxygenase inhibition. This drug also has a good safety profile and easily passes through the blood brain barrier which makes it an effective analgesic. The aim of this study is to examine the efficacy of intra-venous paracetamol as a pre-emptive analgesic for post-operative pain management.

Method of Data collection: This proposed study was carried out as a prospective randomized controlled study in the Department of Anaesthesiology of Krishna Hospital, Krishna Institute of Medical Sciences, Karad, Maharashtra. The patients included were posted for Abdominal Hysterectomy. This study was conducted between October 2011 to October 2013 i.e. a period of 24 months. This study was done after institution Ethical committee approval and written informed consent was obtained from all patients included in this study.

2. Study Design

Proposed work was done on patients posted for abdominal hysterectomy under spinal anaesthesia. A total of 60 patients were included. Sample size calculation was based on mean difference of 25mcg fentanyl requirement with SD of 18 mcg between the study and the control group, alpha of value of 0.05, and a power of 80% . Patients were randomly divided into three groups. The method of administration of study drug and control was as follows,

GROUP I (n=20, Pre-emptive group):
IV Paracetamol 1gm (100ml) was administered 30 minutes prior to induction, and 100ml IV normal saline was administered prior to closing of the skin incision.

GROUP II (n=20, Intra-operative group):
100ml IV normal saline was given 30 mins prior to induction and IV paracetamol 1gm (100ml) was administered prior to closing of skin incision.

GROUP III (n=20, control group):
100ml IV normal saline was given 30 mins prior to induction and prior to skin closure.
These drugs were administered in double blind manner

2.1 Inclusion Criteria

All patients routinely posted for Abdominal hysterectomy and with American Society of Anaesthesiologists ASA I and II.

2.2 Exclusion Criteria

1) ASA III and IV
2) History of allergic reactions to paracetamol or fentanyl
3) History of usage of paracetamol, opioids or NSAIDS in the 48 hours before requiring chronic analgesic treatment.
4) Chronic alcoholism, diseases of liver and kidneys
5) Cardiovascular system illness
6) Bleeding diathesis.
7) Psychiatric history or any other concomitant disease which may lead to unreliability in clinical assessments.

2.3 Pre-Anaesthetic Evaluation:

Patients included in the study underwent thorough pr-operative evaluation which included the following:

2.4 History

History of underlying medical illnesses, previous history of surgery and anaesthesia, hospitalization and hypersensitivity was noted.

2.5 Physical Examination

1. General condition of the patient
2. Vital signs
3. Height and weight
4. Examination of cardiovascular, respiratory, central nervous system and the vertebral column
5. Airway assessment

2.6 Investigations

Complete blood count, Bleeding and clotting time, renal function tests, Blood sugar levels, serum electrolytes, ECG, Chest X ray were done. Patients who satisfied the inclusion criteria were explained about the nature of the study and the anaesthetic procedure. Written and informed consent was taken from all patients included in the study.

2.7 Premedication

All patients received tablet Diazepam 10mg orally night before the surgery for anxiolysis and on the day of the surgery a morning dose of 5mg was given orally. The pre-operative pulse rate, blood pressure (systolic, diastolic and mean) and SpO2 were recorded.

3. Technique

As per the groups patients were given the drugs. The drug and the control were prepared in a burette by a colleague who was blinded to the study. In operation theatre equipment of airway management and emergency drugs were kept ready. Patient was shifted from the premedication

room to the operation theatre. The horizontal position of the operating table was checked and patient was placed on it. Non invasive blood pressure, Spo2 and ECG leads were connected to the patient. The anaesthesiologist performed SAB and made observations in all patients involved in study. Under aseptic precautions a midline lumbar puncture was performed at L3-L4 interspaces using a 25G Quincke needle in lateral recumbent position. Following free flow of clear CSF, anaesthetic solution 3.4ml was injected slowly in all the groups. Then patient was placed in supine position. Intra-operatively mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO2) was recorded. At the end of the operation, the patients were transferred to the recovery room where they were evaluated for post-operative pain with Visual Analogue Scale (VAS). Intravenous Fentanyl was administered when the visual analogue score was equal to or more than 4.(VAS 0: no pain; VAS 10: worst pain imaginable).VAS scores of patient at post-operative period 1] 0min (popain1), 2] 15mins(popain2) and 3] 30 mins(popain3) and at 4]1hour (popain4), 5]2hrs (popain5), 6]4hrs (popain6), 7]8hrs(popain7), 8]12 hrs (popain8) was recorded. The total fentanyl consumption during the same was recorded in micrograms. Side effects like nausea, vomiting, respiratory depression, itching, irritation, diarrhoea and constipation was examined and recorded. Thus the variables compared were

1. The average time at which the VAS was ≥4 from the time of skin incision to the first request of analgesic.
2. Average pain scores at different time intervals
3. Number in each group with VAS score ≥ 4 at different time intervals and required fentanyl -Frequency of fentanyl consumption.
4. Total fentanyl consumption in first 12hrs.

4. Statistical Analysis

Sample size calculation was based on mean difference of 25mcg fentanyl requirement with SD of 18 mcg between the study and the control group ,alpha of value of 0.05, and a power of 80% . The statistical analysis was done by using SPSS version 14.0 and Microsoft Excel statistics package .ANOVA Tukey and LSD multiple comparison test for Group means , Freidman test and Fishers exact test were used for analysis of parametric and non parametric data.. P value <0.05 was considered statistically significant.

5. Results

Proposed work was done in a comparative double blind controlled clinical study manner carried out on patients posted for abdominal hysterectomy under spinal anaesthesia. A total of 60 patients were taken. Sample size found with the help of ANOVA, Freidman's test.
Patients were randomly divided into three groups:

GROUP I (n=20, Study group):
IV paracetamol 1gm(100ml) was administered 30 minutes prior to induction , and 100 ml IV normal saline was administered prior to closing of the skin incision.

GROUP II (n=20, Intra-operative group):
100ml IV normal saline was given 30 mins prior to induction and IV paracetamol 1gm (100ml) was administered prior to closing of skin incision.

GROUP III (n=20, control group):
100ml IV normal saline was given 30 mins prior to induction and prior to skin closure. Observations were recorded on proforma The observation and result of the obtained data was statistically analysed and the following result was obtained and are presented as follows:

Demographic Parameters

Table 1: Age (years) wise distribution of patients

GROUP	N	AGE (MEAN± S.D)
I	20	46.15± 1.760
II	20	45.00± 1.669
III	20	44.70± 2.199

The above Table no. 1 shows the mean age in all 3 groups and

Table 2: Height (in cms) wise distribution of patient

GROUP	N	HEIGHT(MEAN±S.D)
I	20	158.55±.860
II	20	157.10±.661
III	20	157.65±.769

The above Table no.2 shows the mean height in all 3 groups. The height distribution was comparable across the three groups.

Table 3: Weight (in kilograms) wise distribution of patients

GROUPS	N	WEIGHT(IN KGS)
I	20	54.70±1.416
II	20	56.80±0.893
III	20	57.50±1.072

The above Table no.3 shows the weight wise distribution in all 3 groups. The weight distribution was comparable across the three groups.

Table 4: Demographic parameters of all 3 groups (MEAN± S.D.)

Group	Age	Height	Weight
1	46.15±1.7	158.55±.8	54.70±1.4
2	45.00±1.6	157.10±.6	56.80±.89
3	44.70±2.1	157.65±.7	57.50±1.0

Demographically all 3 groups were found to be similar and there was no significant difference between the 3 groups.

Table 5: Duration of surgery (MEAN± S.D)

Groups	*N*	*Mean*	*S.D*
I	20	150.00	16.463
II	20	157.00	9.651
III	20	152.50	10.821

Table 6: Average duration of surgery in each group compared with ANOVA

	Sum of squares	*Df*	*Mean square*	*F*	*Sig.*
Between groups	**503.333**	**2**	**251.667**	**1.569**	**.217**
Within groups	**9145.000**	**57**	**160.439**	-	-
Total	**9648.333**	**59**	-	-	-

Table 7: Multiple comparison of average duration of surgery in all 3 groups

Multiple comparison

	(I)Group	(J) Group	Mean Difference (I-J)	Std Error	Sig	95% Confidence Interval	
						Lower Bound	Upper Bound
Tukey HSD	Group 1	Group 2	-7.000	4.005	-197	-16.64	2.64
		Group 3	-2.500	4.005	-808	-12.14	7.14
	Group2	Group1	7.000	4.005	-197	-2.64	16.64
		Group3	4.500	4.005	504	-5.14	14.14
	Group3	Group1	2.500	4.005	808	-7.14	12.14
		Group2	-4.500	1.005	504	-14.14	5.14
Dunnett t-(2-	Group1	Group3	-2.500	4.005	758	-11.56	5.58
	Group2	Group3	4.500	4.005	429	-4.58	13.58

a. Dunnett t-tests treat one group as a compare all other group against it

The average duration of surgery was compared by ANOVA test. P value is 0.217. It shows there is no significant difference in the mean duration of surgery between the three groups.

Observations Made In The Post-Operative Period:

Table 8: shows the means of the pain scores at different post operative period:

		Group			
		Group 1	*Group 2*	*Group 3*	*Total*
Mean	Popain 0	.10	.50	1.40	1.40
	Popain 0.25	3.30	3.45	3.90	3.90
	Popain 0.5	2.20	3.55	3.55	3.55
	Popain 1	3.00	3.55	4.40	4.40
	Popain 2	3.05	3.35	4.10	4.10
	Popain 4	3.10	3.60	4.15	4.15
	Popain 8	3.15	3.35	3.85	3.85
	Popain 12	3.00	3.50	3.95	3.95
Std. Deviation	Popain 0	.308	.513	.883	.883
	Popain 0.25	.979	.945	1.119	1.119
	Popain 0.5	1.436	1.905	1.877	1.877
	Popain 1	.973	.605	1.188	1.188
	Popain 2	1.119	1.040	1.021	1.021
	Popain 4	.759	.681	1.309	1.309
	Popain 8	.587	.587	.988	.988
	Popain 12	.562	.761	.887	.887
N	Popain 0	20	20	20	20
	Popain 0.25	20	20	20	20
	Popain 0.5	20	20	20	20
	Popain 1	20	20	20	20
	Popain 2	20	20	20	20
	Popain 4	20	20	20	20
	Popain 8	20	20	20	20
	Popain 12	20	20	20	20

Table 9: shows the LSD and Tukey HSD multiple comparison test for Group means for post operative period pain scores multiple comparisons

Measure: MEASUIRE -1

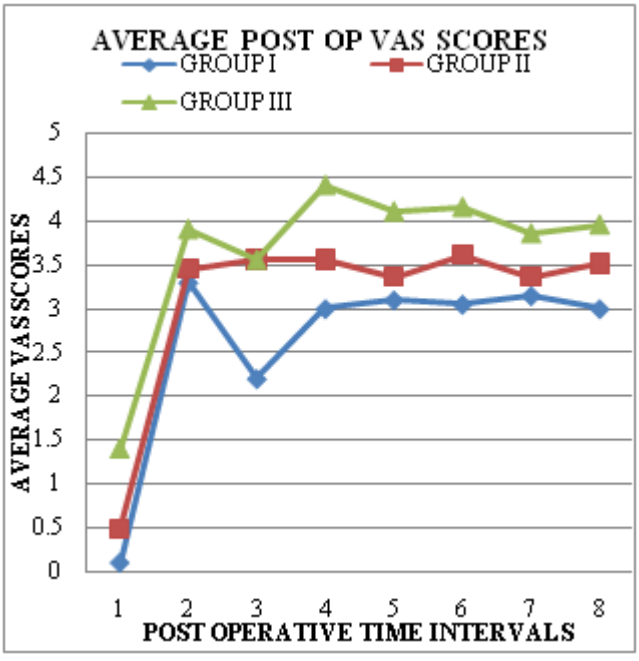
	(I) Group	(J) Group	Mean Difference (I-J)	Std Error	Sig	95% Confidence Interval	
						Lower Bound	Upper Bound
Tukey HSD	Group 1	Group 2	-.49*	.101	.000	-.74	-.25
		Group 3	-1.05*	.101	.000	-1.29	-.81
	Group 2	Group1	.49*	.101	.000	.25	.74
		Group3	-56*	.101	.000	-.80	-.31
	Group 3	Group1	1.05*	.101	.000	.81	1.29
		Group2	.56*	.101	.000	.31	.80
LSD	Group 1	Group 2	-.49*	.101	.000	-.70	-.29
		Group 3	-1.05*	.101	.000	-1.25	-.85
	Group 2	Group1	.49*	.101	.000	.29	.70
		Group3	-.56*	.101	.000	-.76	-.35
	Group3	Group1	1.05*	.101	.000	.85	1.25
		Group2	.56*	.101	.000	.35	-76

Based on observed means

***. The Mean difference is significant at the 0.05 level.**

The average post-operative pain score in the pre-emptive Group-I and intra-operative Group- II were significantly lower than in Group- III. (P<0.05).The pain scores in group I was less than group II also group II demonstrated significantly less pain scores than group III (p<0.05).Repeated measure analysis of variance and Tukeys HSD and LSD multiple comparison tests of group means was used for analysis .

Average Vas Score in Post Operative Period in All 3 Groups



The above graphs show an average VAS scores in all 3 groups at different time interval and there was a significant difference among all 3 groups (p<0.05)

Table 10: Total fentanyl doses required in the post-op period in each group

	N	MEAN	Std. Deviation	Std. error	95confidence lower	Interval Upper	Min	Max
GROUP I	20	46.25	16.771	3.750	38.40	54.10	25	100
GROUP II	20	77.50	11.180	2.500	72.27	82.73	50	100
GROUP III	20	108.75	23.333	5.217	97.83	119.67	50	100

The above table shows that the mean of total fentanyl dose required in group 1 is 46.25±16.77mcg that in group 2 is 77.50±11.18 and highest being in group 3 that is 108.75±23.33.

Table 11: Comparison of total fentanyl required between and within the groups by ANOVA

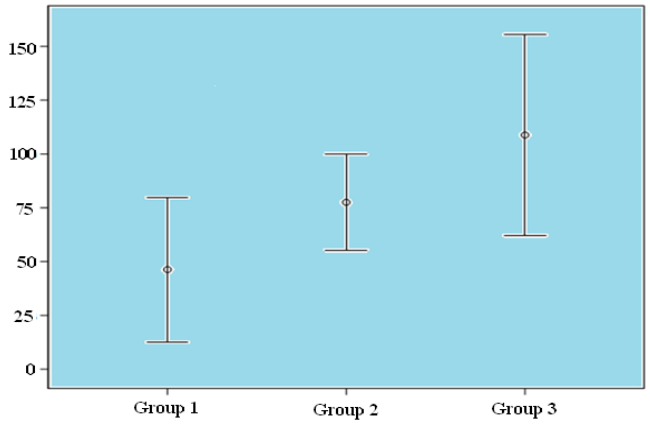
	Sum of Squares	*df*	*Mean Square*	*F*	*Sig*
Between Group	39062.500	2	19531.250	61.635	.000
Within Group	18062.500	57	316.886		
Total	57125.000	59			

Table 12: Comparison of total fentanyl required between and within the groups by POST HOC LSD multiple comparison test for group means

	(I)Group	(J) Group	Mean Difference (I-J)	Std Error	Sig	95% Confidence Interval	
						Lower Bound	Upper Bound
LSD	Group 1	Group 2	-31.250*	5.629	.000	-42.52	-19.98
		Group 3	-62.500*	5.629	.000	-73.77	-51.23
	Group2	Group1	31.250*	5.629	.000	19.98	42.52
		Group3	-31.250*	5.629	.000	-42.52	-19.98
	Group3	Group1	62.500*	5.629	.000	51.52	73.77
		Group2	31.250*	5.629	.000	19.98	42.52

***. The Mean difference is significant at the .05 level.**

As seen in table no.11 and 12 the average fentanyl consumptions in the pre-emptive Group-I was less than group II and III ($p<0.05$) .However Group-II patients who received paracetamol before the skin closure needed significantly less opioid than group III patients.($p<0.05$).ANOVA and Tukeys multiple comparison test for group means were used for multiple comparison



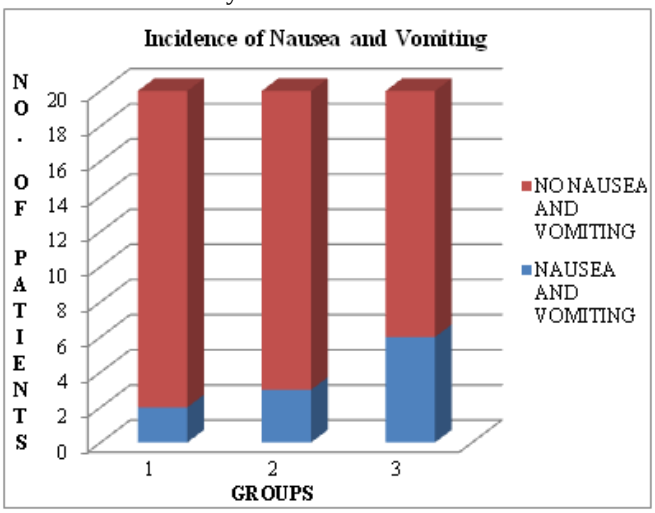
Graph: showing mean of fentanyl dose required in all 3 Groups

The above graph shows the average fentanyl consumption (mean± S.D.) in all the 3 groups.

Table 13: Shows The Frequency of Opioid Demand in the Post Operative Period :

Frequency of Opioid Demand	≥1 and< 2	≥2 and < 3	≥3
Group I	5	14	1
Group II	0	1	19
Group III	0	1	19

There was significant difference in frequency of fentanyl administration between the groups ($p<0.05$). Fisher's exact test was used for analysis.



Graph: shows incidence of nausea and vomiting in post-operative period

Graph shows the incidence of nausea and vomiting in all 3 groups. 2 patients complained of nausea and vomiting in the pre-emptive group compared to the intra-operative group where 3 patients complained of nausea and vomiting whereas it was highest in saline control group with 6 patients complaining. With the help of Chi square tests of goodness of fit and independence p value was 0.235 which was not significant. Hence there was no significant difference among the group with respect to incidence of nausea and vomiting.

6. Discussion

In the present study, we used IV paracetamol 1 g, use of which as a pre-emptive analgesic in hysterectomy cases has recently begun. We assessed its effects on intra-operative hemodynamics, postoperative analgesia effectiveness, fentanyl consumption, frequency of side effects, and determined that administration of paracetamol 1 g 30 min before skin incision resulted in decreased postoperative VAS values and total fentanyl consumption over 24 h. Furthermore, we observed fewer side effects.

Relieving pain is one of the fundamental responsibilities of medical practitioners and is frequently a primary goal of patients seeking care. The pain that accompanies surgical procedures remains prevalent and is an aspect of the perioperative experience that generates the greatest concern for patients about to undergo surgery. The goal for postoperative pain management is to reduce or eliminate pain and discomfort with minimum side effects, in a very cost effective manner. Insufficient postoperative pain control leads to complications. Among these complications, atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, psychological trauma, elongated intestinal distension, urine retention, myocardial ischemia, and infarction may be considered. [38] Due to the negative effects and complications, postoperative pain has to be treated in a fast and effective manner.

Pain management should be started prior to pain initiation. The choice of pain relieving techniques may be influenced by the site of surgery. Equally, it may be influenced by drug availability and familiarity with different methods of analgesia. Due to effective post-operative pain control the patients have lesser anxiety, side-effects, complications and lesser hospital stay. Hence our study mainly revolves around the post-operative pain management to avoid these complications.

The aim of pre-emptive analgesia, which has been investigated in recent years, is to provide analgesia prior to a painful stimulus and to prevent central sensitization caused by the painful stimulus and, consequently, to decrease the need for postoperative analgesia. [39] Pain signals from damaged tissue are not transmitted to the central nervous system (CNS) through 'hard-wired' pathways. In contrast, nociceptive signals, once initiated, will launch a cascade of alterations in the somato-sensory system, including an increase in the responsiveness of both peripheral and central neurons.

These alterations will increase the response to subsequent stimuli and thus amplify pain [40]. Pre-emptive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by the procedure. Owing to this 'protective' effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented [3].

Methods and agents for which pre-emptive analgesic effectiveness has been researched are mostly NSAIDs, opioids, ketamine, peripheral local anaesthetics and epidural analgesia. [3] In our study we have used intravenous paracetamol. Nonsteroidal Anti inflammatory drugs and acetaminophen (paracetamol) are commonly used in the management of moderate to severe pain alone or in combination with opioids [41]. Conventional Nonsteroidal anti inflammatory drugs may be associated with serious unwanted effects (such as bleeding or renal impairment) when used peri-operatively. Short-term use of acetaminophen at adequate dosages has a well-established safety profile [42]. IV administration is the route of choice when oral administration is not possible or when rapid analgesia is needed after surgery.

Despite a wide use of acetaminophen, no injectable form has been available because of instability in aqueous solution [43, 44]. Recently, an aqueous solution of acetaminophen has been developed by controlling hydrolysis through adding a pH buffer to maintain a stable pH and oxidation through the addition of a powerful antioxidant and through an oxygen-free manufacturing process. These processes result in an infusible formulation of acetaminophen that does not need reconstitution and that overcomes the disadvantages of the former available prodrug, propacetamol (i.e., injection site pain, the risk of making errors during the reconstitution procedures, and risk of contact dermatitis for the nursing staff) [45]. Hence we gave injectable paracetamol as a pre-emptive analgesic in our study because the use of this drug in post-operative analgesia has not been extensively studied. And it was also seen with our results the pre-emptive group had lesser VAS scores than the intra-operative post-incisional group thus making pre-emptive analgesia a better choice of management than plain post-operative pain management.

It was demonstrated that paracetamol rapidly passes the blood-brain barrier, reaches a high concentration in the cerebrospinal fluid and has an anti-nociceptive effect mediated by the central nervous system. [46,47] This central effect has been regarded primarily as an indirect and reciprocal influence through cyclooxygenase enzyme inhibition, and probably through the serotoninergic system as well. Besides this central effect, it is accepted that paracetamol has a peripheral anti-inflammatory influence, although this effect is somewhat limited. [48] Jarde O, Boccard E et al Showed that IV paracetamol had a better faster and effective analgesia compared to equivalent oral dose of paracetamol [49] Clinical studies have found that 1 g iv paracetamol employed alone is just as effective as 30 mg ketorolac, 75 mg diclofenac or 10 mg morphine.[50,51] Studies have also shown that iv paracetamol has an opioid-sparing effect and enhances patient satisfaction by reducing the opioid requirement.[36,52-53] Paracetamol is a viable alternative to NSAIDS especially because of the lower incidence of adverse effects and should be preferred choice in high risk patients.[34]

Descriptive statistics were used to summarize the demographic characteristic of patients. The demographic data (age, height and weight) was compared between three groups. The age group (table no.1) was ranging from 30 to

70 yrs with a mean of 46.15± 1.760 in group I. In group II the mean was 45±1.669 and that in group III was 44.70±2.199. The mean of height (table no.2) in group I was 158.55 ±0.860 in group II was 157.10± 0 .661 and in Group III was 157.65±0. 869. The mean of weight (table no.3) in group I was 54.70 ±1.416 , in Group II it was 56.80 ±0.893 and that in group III was 57.50± 1.072 . Demographically all the three groups were similar. The duration of surgery (table no.5) was also measured . There was no significant difference in the mean duration of surgery between the three groups.

Varrasi and colleagues[32] assessed the relative morphine consumption in a combined analgesic regimen after gynaecologic surgery with iv doses of propacetamol 2 g or ketorolac 30 mg. Patients were assessed regarding total dose of morphine, pain intensity and global efficacy. They established that total morphine requirements were not significantly different between the propacetamol (10.6±4.8 mg) and ketorolac (10.2±4.4 mg) groups. The evolution of pain intensity also showed similar patterns in the two groups. The VAS scores at rest and in motion were determined. In another study by Vaideanu et al.[54] on 60 patients who had a pan-retinal photocoagulation operation, they administered 1,000 mg oral paracetamol as a pre-emptive analgesic and compared the results with a placebo group. Subsequently, they found that postoperative pain scores subsided in the preemptive group in 24 h.

In another study of [55] patients undergoing breast biopsy, it was determined that parenteral administration of 20 mg tenoxicam both pre-emptively and postoperatively increased the first analgesia demand time and lowered the VAS scores in the preemptive group. Consequently, it was deduced that tenoxicam has pre-emptive analgesic effectiveness in breast surgery. Reuben et al [56] in their study comprising 60 patients who underwent arthroscopic knee surgery under spinal anaesthesia, employed 50 mg rofecoxib as a preoperative analgesic and administered it before incision and at the end of the operation. They found that when compared with the placebo group, the first analgesia demand time was longer and total 24 h morphine consumption and pain scores were lower in the pre-emptive group relative to the other two groups.

In our study it was found that Group III had more patients with VAS score of ≥4 compared to other groups I and II as shown in graph 4. The low values of the pain scores in the groups under medication may be explained by decreases in excitability in the central nervous system through blockade of nociceptive stimuli before damaging tissue. As was seen in graph no.7 the VAS scores of group I and II were comparable and significant difference was found implicating that VAS scores of Group II (intra-operative group) was higher than Group I (pre-emptive group). In our study, as shown table no. 8,9 and 10 the total fentanyl consumptions in the pre-emptive Group I and intra-operative Group II were lower than in Group III. Where total fentanyl required in Group I was mean of 46.25±16.77mcg that in group 2 is 77.50±11.18 and highest being in group 3 that is 108.75±23.33. There was a significant difference found in the 3 groups.

Fentanyl citrate is a narcotic analgesic. The principal actions of therapeutic value are analgesia and sedation. . Fentanyl appears to have less emetic activity than either morphine or meperidine. The onset of action of fentanyl is almost immediate when the drug is given intravenously. Strong opioids are a fundamental component of acute and cancer pain management. Other studies have confirmed the need for opioid analgesia in the early postoperative period [57-59]. Because of its ability to titrate to individual needs, IV patient controlled analgesia (PCA) is considered as the "gold standard" for delivery of IV opioids for the management of postoperative pain [60]. It is used not only in major surgery, but also in minor surgery for providing postoperative analgesia [61, 62].

Opioids, however, have a range of side effects such as nausea and vomiting as well as dizziness and respiratory depression. Therefore, because of their synergistic action, a combination of opioid and non opioid analgesics are often used to enhance analgesic efficacy and reduce side-effects of opioids caused by intravenous patient-controlled analgesia (PCA) [59,63]. Fentanyl thus being a shorter acting, having lesser ventilatory depression comparatively was used in our study. We gave all our patients Inj Fentanyl 25mcg IV whenever the VAS score was equal to or more than 4 in the post –operative period as an acute pain relief. If required the dose was repeated after 5 mins. However all our patients had achieved pain relief by this bolus dose and did not require a repeat after 5 mins.

The pain scores over time were significantly different between the groups (table no.8 and 9).The VAS scores of the patients in Group II at different time intervals were significantly higher as compared to Group I. The greater analgesic requirement observed in Group II as compared to Group I can be explained by the gradual reduction in effect of the paracetamol administered postoperatively . Since the pre-emptively delivered paracetamol prevents central sensitization, its analgesic effect continues longer than its effect period.

It was also seen (Table no 14 and Graph no.8) that the incidence of side –effects like nausea and vomiting was more commonly seen in group III (6 patients) compared to group II (3 patients) than group I (2 patients). There was no significant difference among the group with respect to incidence of vomiting. Several recent articles have, at least in general, evaluated whether opiate sparing reduces the incidence or severity of opiate side effects or what the authors have termed "clinically meaningful events" (CMEs)[64,65]. This work resulted from the development of cyclooxygenase (COX)-2 analgesics for peri-operative pain. In the control group, the incidence of a CME and the number of CMEs was related to the dose of opiate analgesic administered.

Interestingly, the authors also found that below a morphine equivalent threshold of approximately 10 mg, opiate-related symptoms did not occur. In another study, Gan et al. [64] found after a cholecystectomy and using the same symptom distress questionnaire that the opiate sparing produced by the co-administration of a COX-2 similarly reduced the incidence of CMEs proportional to the reduction in opiate

administration. Hence we also conclude that higher incidence of nausea and vomiting in control group in our study was because of more opioid consumption. But however there was no significant difference seen in between the groups. This could be because of the smaller sample size which was taken depending on the fentanyl consumption.

Roberts et al.[66] have confirmed, in a prospective study, that the incidence of nausea and vomiting are both increased in a dose-dependent manner by the amount of opiate administered. This study included epidural, IV, and oral opiate administration for patients after either orthopaedic or abdominal surgery, thereby covering a wide spectrum of opiate requirements. They found an exponential relationship between opiate dose and nausea, with each halving of the opiate dose reducing the incidence of vomiting by 6% (and a little more for nausea).

One caveat of the Roberts et al. study is that pain itself may induce nausea and vomiting [67]. This makes it difficult to determine if pain or the opiate is causing nausea and vomiting. In our study we found similar finding of increased nausea and vomiting in Group III and hence there were two contributing factors mainly one due to increased VAS scores in these patients and secondly increased fentanyl consumption.

7. Conclusion

Intravenous paracetamol when administered as pre-emptive or intra-operative analgesic reduces postoperative pain score and opioid consumption.The efficacy of intravenous paracetamol is better when administered as a pre-emptive analgesic as compared to its intra operative administration.Since it reduces postoperative pain and thereby opioid requirement, it is associated with less opioid related side effects.

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