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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
This study involved 60 Hysterectomic patients treated with spinal anaesthesia with potential, randomly assigned, regulated dual Blind Clinical administrations. The medications were prescribed according to the divisions of patients. A colleague who has been oblivious to the research arranged the medication to regulated means in a lab. There were recorded intra-operational average blood pressure, heartbeat rate, saturation of peripheral oxygen ($Sp.O_2$). Patients with Visual Analogue Scale (VAS) were tested at the conclusion of the procedure for the postoperative discomfort. Intra-venous fentanyl was given if the visual analog scores were >= 4. Patient AS scores were registered at the 0-minute, 15-minute and 30-minute postoperative intervals and 1, 2,4,8,12 hours. In microgram (mcg) the total utilization of fentanyl in the same duration was traced as well.

Keywords: surgical anaesthesia, Paracetamol, Pre-operative process, Post-operative process, Pre-emptive analgesia, opioids

1. Introduction
An integral part of surgical patient treatment is an efficient postoperative pain management. An exceedingly significant problem for the anaesthesiologist has been the enhancement of the postoperative pain management. Before unpleasant stimuli may arise, analgesia may avoid or reduce future discomfort or analgesic demand. Pre-emptive analgesia is an antinociceptive therapy that helps to prevent the processing of afferent inputs that intensifies after the operation. Various research trials have been driven by this theory [1]. Long pain may lead to physical exercise and venous stasis as well as to an elevated risk of profound as well as pulmonary thrombosis of the vein 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. [2].

The choice of strategies for alleviating pain can be greatly affected by the wounded area. The quality and effectiveness of medicines with multiple analgesic approaches can often be affected. Over several years, intra-muscular opioids (usually morphine) have become the main procedure over managing post-operative discomfort in the developing world. The results of drugs differ considerably between individuals, which makes it difficult to anticipate individual reactions. Several experiments have found that there is an over estimation of the length of operation and intensity and anxiety for respiratory distress, vomiting in severe post-operative pain regardless of medication, sedation and dependency associated with the use of opioids [3, 4].

The paracetamol treatment for post-operative pain is now being carried out in response to the availability of rectal and parenteral preparations. For post-operative analgesia we will use paracetamol in our study. Paracetamol is a non-opioid drug that is mainly used to suppress cyclo-oxygenase in the central nervous system [5]. This treatment has also a strong protection profile and moves quickly via the blood brain barrier (bbb), rendering it a powerful analgesic.

1.1 Aims and Objectives
The aim of this study is to examine the efficacy of intra-venous paracetamol as a pre-emptive analgesic for post-operative pain management. This also aims to:

1. To assess the amount of post-operative fentanyl consumption, the pain scores, side-effects and patient satisfaction in the post-operative period.
2. 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.

2. Literature Review
Pain is currently characterized as a significant psychological distress experience correlated with tissue harm or possible damage by the International Association for the Analysis of Pain (IASP). Various approaches have been used for this like use of opioid, NSAIDS, incision site infiltration of local anaesthetic agent, regional anaesthesia technique [6,7]. Moreover, narcotics though provide good results, has elicited unwanted side effects like respiratory depression, nausea, vomiting, drowsiness and interference with neurological examination.

Pain is currently characterized as a significant psychological distress experience correlated with tissue harm or possible damage by the International Association for the Analysis of Pain (IASP). paracetamol 1 g every 6 hours and IV meperidine (n = 20, group MP) into a peripheral vein for 24 hours [8].

Memis *et al* [9] in 2010 Paracetamol reduced the use of

opioids, extubation time, and opioid related adverse effects after major surgery in intensive care unit. Patients were randomized posto-peratively into 2 groups in ICU. Patients received either 100 mL of serum saline intravenous (IV) every 6 hours and IV meperidine (n=20 group M) or IV paracetamol 1g every 6 hours and IV meperidine (n=20, group MP) into a peripheral vein for 24hrs. Behavioral Pain Scale and VAS scores were significantly lower in group paracetamol-meperidine at 24hrs (P<0.05). In group MP, postoperative meperidine consumption (76.75±18.2mg vs. 198±66.4mg) and extubation time (64.3±40.6 min vs. 204.5±112.7 min) were lower than in group M (P<0.01). Postoperative nausea-vomiting and sedation scores were significantly lower in group MP when compared with group M (P<0.05). These data suggest that intravenous paracetamol is a useful component of the multi-modal analgesia model, especially after major surgery.

In a cumulative analgesic diet following a gynaecological surgery, Soltani and collegues [10]. evaluated the roughly comparable morphine intake of 4 doses of 2g or ketorolac 30mg in propacetamol. Total morphine, pain threshold as well as widespread efficiency were evaluated for patients. Maximum needs of morphine between the propacetaminol (10.6±4.8 mg) and ketorolac (10.2±4.4 mg) category were found not to be substantially different. The expression of pain tolerance in both groups revealed identical trends. The VAS levels were calculated at rest or in motion. Khan *et al*. in an another report [11]. Of 60 patients who received PRC, 1,000 mg of oral paracetamol were given as a preventative analgesic as well as the findings were contrasted with a placebo sample. And they observed that in the prevention community, post-operative pain ratings dropped in 24 hours.

Materials and Methods

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.

3.1 Mehtod

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 18mcg between the study and the control group, alpha of value of 0.05, and a power of 80 percent. The patients were randomly divided into three groups.

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.

Pre-operative Examinations

Pre-operative evaluations were performed on the patients prior to the anaesthetic studies.

3.2 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.

Intravenous Fentanyl was administered when the visual analogue score (VAS) was equal to or more than 4 (VAS 0: no pain; VAS 10: worst pain imaginable). Figure 1 shows the scheme of visual analogue scale. VAS scores of patient at post-operative periods were taken at:

a. 0 min (popain-1),
b. 15 mins(popain-2)
c. 30 mins(popain-3)
d. 1 hour (popain-4),
e. 2 hrs (popain-5),
f. 4 hrs (popain-6),
g. 8 hrs(popain-7),
h. 12 hrs (popain-8) was recorded.

The total fentanyl consumption during the same was recorded in micrograms.

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.

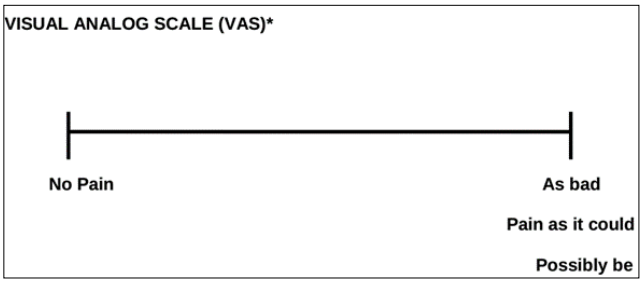

Fig 1: Visual analogue scale [12].

3.3 Statistical Analysis

The calculation for sample size was based on mean differences of 25mcg fentanyl requirement with SD of 18 mcg among the study and the control group, alpha of value of 0.05, as well as with 80% power.

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.

The value of P < 0.05 was found to be statistically acceptable.

Observations and 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.

The observation and result of the obtained data was statistically analysed and the following result was obtained and are presented as follows:

Table 1 below shows the mean age in all 3 groups whereas, Figure 1 shows the age wise distribution in all 3 groups. The age distribution was comparable across the three groups.

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

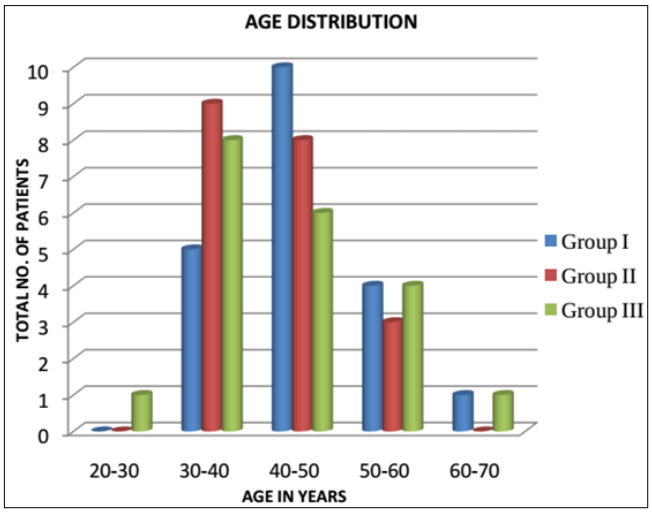

Fig 2: Age (years) wise distribution of patients

The average duration of surgery was compared by ANOVA test. P value is 0.217. It shows the mean surgery period for the 3 patient groups is not significantly different (Table 2 and Table 3).

Table 2: average duration of surgery in each group compared with ANOVA

	Sum of squares	Df	Mean^2	F	P
Among groups	503.333	2	251.667	1.569	0.217
In groups	9145.000	57	160.439	-	-
Total	9648.333	59	-	-	-

Table 3: Time taken for the surgery (Mean± S.D)

Groups	N	Mean	Std. Dev.
I	20	150.00	16.463
II	20	157.00	9.651
III	20	152.50	10.821

Post-operative observations

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.

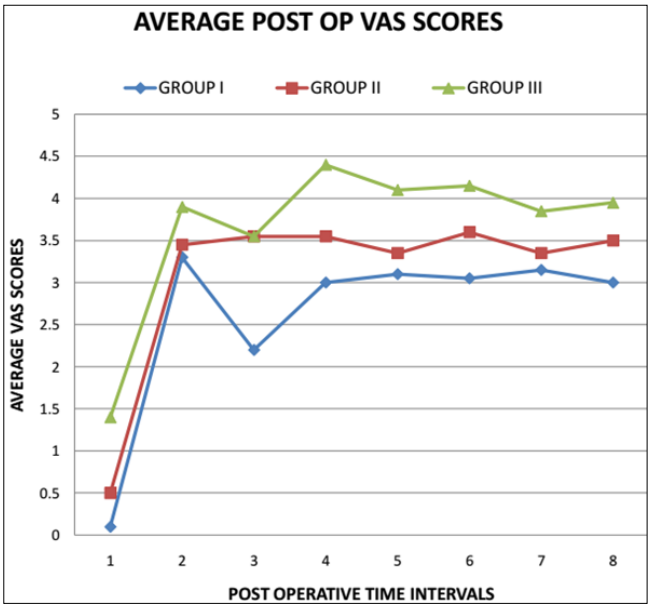

Fig 3: Average VAS score in post-operative period in all 3 groups

Figure 3 show an average VAS scores in all 3 groups at different time interval and a significant difference between all the three groups (p<0.05) was observed.

Table 4: Total fentanyl doses required in the post-op period in each group

	N	Mean	S.D.	S.E.	95% confidence	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 5: Comparison of total fentanyl required between and within the groups by ANOVA

	Sum of Squares	Df	Mean^2	F	P
Among Group	39062.500	2	19531.250	61.635	0.000
In Group	18062.500	57125.000	57		
Total	59	316.886			

As seen in Table 5 the average fentanyl consumptions in the pre-emptive Group-1 was less than group-2 and group-3 (p<0.05). However, Group-2 patients who received paracetamol before the skin closure needed significantly less opioid than group-3 patients (p<0.05) (Table 6). ANOVA and Tukeys multiple comparison test for group means were used

For multiple comparison.

Table 6: Frequency of opioid demand in the post-operative period

Frequency of opioid demand	≥1 and< 2	≥2 and < 3	≥3
Group-1	5	13	2
Group-2	0	2	18
Group-3	1	1	18

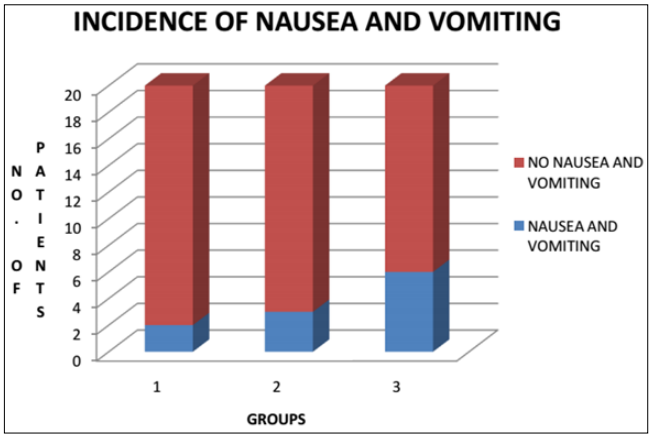

Fig 4: post-operative incidences of vomiting and nausea

Figure 4 represents the incidence of nausea and vomiting in all the 3 groups. 2 patients complained of vomiting and nausea 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 this p was not a large p value of 0.235. Hence the occurrence of vomiting and nausea was not considerable in the cohort study.

Conclusion

In this analysis we used IV paracetamol 1 g which has recently started to use it as a preemptive analgesic in instances of hysterectomy. We evaluated the impact of paracetamol 1 g 30 minutes before surgical procedure, reduced post-operative VAS values as well as overall fentanyl utilization, ascertained that the use of paracetamaol in intraoperatively was reduced by 24 hours. In addition, less side effects were observed. Pain management is one of the professional professionals' fundamental duties and sometimes the primary priority for those needing medical attention. The pain involved with surgery is usual which is a part of the peri-operative process that brings patients a high levels of discomfort for operation. Intravenous paracetamol when administered as pre-emptive or intra-operative analgesic reduces post-operative 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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