

Intravenous paracetamol as an adjunctive analgesic in post-operative pain management after total abdominal hysterectomy

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Abstract : Post operative pain is one of the important factor which affects the recovery of a patient especially in major surgeries and in elderly patients. Poor pain control is associated with increased morbidity and mortality also affecting the psychological condition of the patient. Recently multimodal analgesia is advocated wherein multiple drugs acting on different receptors are used to reduce the toxicity of using a single drug and improve the quality of analgesia. In our study 54 patients undergoing total abdominal hysterectomy under GA were considered. Patients were divided into 2 groups. Towards the end of the surgery one group received 1 gm iv paracetamol and other received NS and the same repeated 6th hourly for 24 hrs. Postoperatively patient was started on PCA morphine with 1mg on demand and a lockout interval of 10 mins. Pain was assessed using visual analogue scale at frequent intervals and a rescue dose of morphine 2mg was given if VAS score was > 3. Patient was assessed with respect to pain, total dose of morphine consumed and satisfaction scores. The total dose of morphine consumed in 24 hrs was significantly more in the control group. The pain scores were comparable in both the groups. Usage of paracetamol as an adjuvant was associated with a 50% reduction in morphine consumption in the postoperative period with better satisfaction scores.

Keywords - Paracetamol, Adjuvant, Postoperative pain .

I. Introduction

The postoperative recovery of a patient depends on the adequacy of pain relief. Though opioids remain the gold standard for postoperative pain management, various other modalities for pain management are available. One of them is multi-modal analgesia where in two or more analgesics of different mechanism of action are included. This modality is associated with more effective analgesia with minimum opioid related side effects. Co-administration of nonopioid drugs, particularly nonsteroidal anti-inflammatory drugs (NSAID's), has become increasingly popular because of the belief that these drugs reduce opioid intake and therefore, the incidence of side effects, improving the quality of analgesia. Patient controlled analgesia is one of the modalities in pain management wherein the patient can administer the analgesic and titrate the dose based on the pain relief using a small microprocessor- controlled pump[1]. This method helps in maintaining a steady concentration of plasma levels minimizing side effects. The purpose of this study was to evaluate the efficacy and safety of paracetamol administration as an adjunct to PCA[Patient Controlled Analgesia] morphine in Indian population.

II. Aims And Objectives

To study the efficacy and safety of postoperative paracetamol administration as an adjunctive analgesic to IV patient controlled analgesia (PCA) morphine after total abdominal hysterectomy with respect to

1. Total dose of morphine required over 24 hours
2. Pain assessed by Visual Analogue Scale (VAS) Score at rest and on movement
3. The incidence of side-effects like post operative urinary retention, sedation, pruritus, respiratory depression or apnea
4. Overall satisfactory score with the analgesia regimen at 24 hours

III. Methodology

The study was designed to be a prospective, randomized, double blind, placebo controlled study. Approval was obtained from the departmental and institutional ethics committee .

Inclusion criteria for the study were patients undergoing total abdominal hysterectomy under general anaesthesia, adult patients aged between 25 to 70 years, ASA physical status I or II, Weighing 40-85 kgs. Patients who were excluded were those with significant hepatic or renal impairment (serum creatinine >2.0 mg/dl, serum bilirubin >2.0 mg/dl, aspartate amino-transferase or alanine amino-transferase >1.5 times the upper limit of normal), coagulopathy, uncontrolled diabetes, NYHA class 3 or 4 cardiac illness, severe respiratory insufficiency, drug or alcohol abuse, allergy to the study drugs and with BMI ≥ 35 kg.m²

Written informed consent was taken from all patients enrolled for the study. All patients were visited by anesthesiology resident the day prior to the study and were briefed and familiarised about the use of PCA pump and Visual Analogue Scale(VAS) comprising of a 100 mm straight line with zero at the left end of scale indicating no pain and 100 on the right end of scale indicating worst pain imaginable. All patients were premedicated with tab Alprazolam 0.25 mg the night prior to and the morning of surgery.

Patients were randomly allocated into one of 2 groups by the draw of lots: Group P and Group S. Patients in both the groups received the study drug half an hour prior to skin closure and 6th hourly for a period of 24 hrs.

Group P: Received intravenous paracetamol 1 gm in 100 ml (perfalgan® Bristol-Myers Squibb Pharmaceuticals, Italy)

Group S: Received Saline 100 ml.

Observer 1: Anaesthesiology postgraduate who did the pre-operative and post-operative assessment of the patient, explained about VAS scale and PCA pump and commences the PCA pump

Observer 2: Anaesthesiology team in charge of the case who administered the study drug intra-operatively and suggested to the postoperative nurse to administer the study drug.

Once the patient was in the operating room, routine physiological monitoring devices such as 5-electrode electrocardiogram, NIBP and pulse oximeter were connected.

After adequate preoxygenation, anaesthesia was induced with IV fentanyl 2 µg.kg⁻¹ and IV propofol 2.5 mg/kg body weight (to loss of verbal response). Ability to mask ventilation was confirmed and muscle paralysis was obtained with IV vecuronium bromide 0.1 mg.kg⁻¹. Following three minutes of ventilation with 1-2% isoflurane in 100% oxygen, trachea was intubated. Anaesthesia was maintained with O₂ (40%) and N₂O (60%) with isoflurane 1-1.5% aiming to achieve a MAC of 1.3. Fentanyl was repeated at 1 µg.kg⁻¹.hr⁻¹ from the second hr of surgery. Half an hour prior to skin closure, all the patients received the study drug wrapped in a brown paper as an IV infusion and anti-emetic prophylaxis of IV ondansetron 0.15mg.kg⁻¹.

At the end of surgery, isoflurane and nitrous oxide were tapered. With resumption of spontaneous breathing efforts, neuromuscular blockade was reversed with IV 0.01 mg.kg⁻¹ glycopyrrolate and 0.05 mg.kg⁻¹ neostigmine. Trachea was extubated after confirming signs of neuromuscular blockade reversal and patient awake.

In the post-operative ICU, pain was assessed by VAS score on arrival and a VAS score of more than 3 was treated by IV morphine boluses of 2 mg at 10 min intervals till the VAS score is less than 3. All the study patients received IV morphine by PCA pump (Graseby 3300 PCA pump, Graceby Medical Ltd. UK). The patient had an option to use boluses of 1 mg morphine, through the pump, with a lock-out period of 10 min with no basal infusion. Patients were assessed at intervals of 1st, 2nd, 6th, 12th and 24th hrs following surgery. Resting pain and pain on movement (deep breathing/cough) were assessed by the blinded observer using VAS. A rescue analgesic of 2 mg IV morphine was administered if VAS score at rest is greater than 3.

The total doses of fentanyl used intraoperatively in both the groups were recorded along with total morphine consumption over a period of 24 hrs. The occurrence of nausea and vomiting was scored as follows

- 0- No nausea or vomiting
- 1- Nausea present but no vomiting
- 2- Both nausea and vomiting present.

Presence of nausea and or vomiting was treated with additional doses of IV ondansetron 0.15 mg.kg⁻¹. Other endpoints such as postoperative urinary retention, sedation, pruritus, apnea or respiratory depression and overall patient satisfaction with the analgesia regimen (11 point scale; 0= completely dissatisfied to 10= completely satisfied) was collected. The study ends at 24 hrs after surgery and further analgesic management was left to the discretion of pain clinic consultant/ concerned surgeon.

IV. Statistical Analysis

Sample size estimation: A pilot study was conducted with 4 patients in each group. Based on the data obtained analysis was done. With 10 mg morphine as significant difference between the two groups with 5% alpha error and a power of 90 the sample size was determined to be 27 in each group. Statistical analysis was done using SPSS version 16 for windows.

A total of 54 patients were enrolled in the study. Patient characteristics, ASA-Physical status and duration of surgery were comparable in both the groups. There was no significant statistical difference in the pain scores on rest and on movement between the two groups at all time points except at 2nd hour where the patients in Group S had higher VAS Scores than group P. Even this difference in the pain scores between the 2 groups was clinically insignificant (TABLE 1, 2). The morphine demand was more in the Group S when compared to the Group P at all time points.(TABLE 3). The total morphine intake in Group P is less than Group

S at all time points over 24 hrs. Over a period of time there is a progressive increase in the consumption of morphine in the group S when compared to the group P. The total morphine consumption in 24 hrs was significantly more in group S than group P (TABLE 4). The patients of group S consumed more morphine (PCA and boluses) than patients in group P over a period of 24 hrs which is clinically and statistically significant (TABLE 5). The side effects of both the groups were comparable. The patients in both groups were equally satisfied with the analgesia regime with respect to analgesia and comfort.

V. Figures And Tables

Table 1: VAS scores at rest

TIME Hrs	GROUP P G.Mean(SD)	GROUP S G.Mean(SD)	p value*
0	36.71 (3.76)	58.84(2.42)	0.12
1	38.03 (1.49)	47.81(1.58)	0.061
2	26.50 (2.18)	43.52(1.48)	0.001
6	22.15 (1.30)	30.99(1.540)	0.062
12	15.40 (1.50)	20.76(2.06)	0.628
24	12.37 (1.46)	15.81(2.38)	0.791

Table 2: VAS scores at movement

Time Hrs	Group P in mg G.Mean(SD)	Group S in mg G.Mean(SD)	p value*
0	59.42(2.37)	69.06(2.42)	0.095
1	59.30(1.29)	63.70(1.42)	0.408
2	51.50(1.34)	62.94(1.34)	0.016
6	46.73(1.30)	51.16(1.35)	0.254
12	39.70(1.5)	38.13(1.49)	0.723
24	34.34(1.46)	34.44(1.47)	0.979

G. Mean-Geometric mean *Independent t test

Table 3: Morphine demand in 24 hours

Time Hrs	Group P in mg Median (IQR)	Group S in mg Median (IQR)
1	4(2-18)	7(4-8)
2	11(4-20)	12(9-33)
6	23(10-39)	30(21-57)
12	29(17-51)	48(30-90)
24	44(26-75)	68(53-146)

IQR- Interquartile range

Table 4: Morphine delivery in 24 hours

Time in hrs	Group P in mg Median (IQR)	Group S in mg Median (IQR)
1	3(1-5)	4(3-6)
2	5(3-8)	7(6-10)
6	10(7-16)	14(13-20)
12	15(11-20)	23(17-30)
24	25(18-32)	38(33-42)

Table 5: Total morphine intake in 24 hrs

	Group P Mean(SD)	Group S Mean(SD)	p Value*
Total morphine delivered by PCA in 24 hrs in mg	25.59(9.90)	38.48(8.19)	<0.05
Total morphine bolus in mg	5.33(2.48)	7.22(2.91)	0.014
Total morphine in mg	30.93(10.31)	45.70(8.76)	0.0001

*Independent t test

VI. Discussion

Post operative pain if not adequately treated is associated with short term and long term complications. Good post operative pain relief is associated with reduced pulmonary and cardiovascular complications, anxiety, morbidity, cost and length of stay in the hospital. Exacerbations of acute pain can lead to neural sensitization and release of mediators both peripherally and centrally. This leads to N-Methyl D-Aspartate (NMDA) activation, central sensitization, long-term potentiation of pain (LTP), and transcription-dependent sensitization.

Advances in the knowledge of molecular mechanisms have led to the development of multimodal analgesia in the management of post operative pain.

Morphine is a gold standard drug for the management of post operative pain, but is associated with side effects. The use of PCA helps to titrate the requirement of opioids. Simultaneous use of adjuvant analgesics like paracetamol or NSAIDs may reduce the morphine requirement.

Analgesic drugs have different sites of action in the nervous system, which may result in a better pain relief. Paracetamol is an analgesic in the management of moderate pain and is associated with minimum side effects. Its site of action is mainly central, although there are different hypotheses concerning the precise mechanism involved: Inhibition of prostaglandins and activation of descending serotonergic inhibitory pathways. A few studies have suggested a peripheral anti-inflammatory action of paracetamol. However, opioids produce analgesia as a result of their agonist effect on opioid receptors in the central nervous system. Therefore, these two drugs have complementary analgesic actions—peripheral and central nervous system levels making this combination an important component of multimodal pain therapy. One study using lornoxicam and ketorolac as preemptive analgesics showed decrease in the VAS scores and the need for opioids with lornoxicam compared to ketorolac in abdominal surgeries[2]. Earlier studies have used paracetamol orally and as rectal suppositories. Bioavailability of these preparations are less compared to IV paracetamol. Paracetamol now available as an IV preparation and is associated with better bioavailability, rapid and steady and predictable plasma concentration

The significant finding of our study was that the use of 1 gram IV paracetamol 6th hourly for 24 hours as an adjunct to postoperative PCA morphine administration following total abdominal hysterectomy produced a significant opioid-sparing effect. There was a 50% reduction in opioid consumption in the paracetamol group when compared to the control group. This is consistent with the findings in various studies where opioid-sparing effects of NSAIDs, COX-2 inhibitors, and paracetamol have been found to be in the range of 20-40%. [3,4,5]

Cobby and colleagues observed a morphine sparing effect of 36% when paracetamol 1.3g was administered rectally at the end of hysterectomy[6]. This hypothesis is strengthened by the results of another trial showing that after rectal administration of a high dose of paracetamol (40 and 60mg kg⁻¹) pain score and analgesic demand were significantly reduced in the early postoperative period. Palazon JH et al conducted a study in patients who underwent spinal fusion surgery where 2 gms propacetamol was administered every 6 hrs along with PCA morphine for 72 hrs. Their study demonstrated a 46% reduction in morphine consumption in the propacetamol group. The pain scores were also significantly less than the placebo group, but there was no significant difference in the side effects between the 2 groups[7]

Peduto et al conducted a similar study in orthopedic surgeries which showed that paracetamol has a significant morphine sparing effect of 46% but had better pain scores. With respect to the hourly morphine consumption there was significant difference in both groups beyond 6 hours[4]. A study was conducted by Arici S et al to evaluate the preemptive analgesic effects of paracetamol wherein one group received 1 gm IV paracetamol 30 min prior to induction and the other group received 1 gm IV paracetamol at skin closure in total abdominal hysterectomy. PCA morphine was given for both groups. It was found that there was a significant reduction in morphine consumption in both the groups.[7]

In our study there was no difference in the adequacy of analgesia as assessed by the visual analogue score between both the groups though the values were lower in the paracetamol group at all time points. This is consistent with the principle of PCA in which patient has the ability to provide satisfactory analgesia by increasing the cumulative dose of morphine. This finding is in contrast to another study conducted on neurosurgery patients by Cakan .T. et al which showed an improvement in the quality of post operative analgesia but did not reduce the narcotic requirement[8]. In our study pain scores at rest and at movement were significantly lower in the paracetamol group at 12th, 18th and 24th hrs with a p value < 0.001. There was no significant difference in morphine consumption between the two groups. Patients in the paracetamol group rated their pain management as excellent.

Our study did not show any decrease in the incidence of morphine related side effects during the first 24 hours after surgery. This finding has been observed by F.Aubrun et al in his study. Paracetamol was well tolerated with very few side effects. The side effects in this group were probably linked to morphine usage[9]

Both groups were equally satisfied with respect to the overall analgesia over 24 hours. This finding is consistent with the study conducted by Tasmacioğlu et al on cancer pain where the VAS score, side effects and satisfaction scores were comparable in both the groups[10].

Our study demonstrates a possible additive effect of combining paracetamol with systemic morphine on postoperative analgesia, resulting in a decreased opioid requirement and slightly improved or similar pain relief. Paracetamol presents a viable alternative to NSAID's and should be used in combination of opioids whenever possible.

VII. Conclusion

Use of intravenous paracetamol combined with PCA morphine for postoperative pain management in total abdominal hysterectomy showed a significant degree of morphine sparing effect with comparable incidence of opioid related side effects and patient satisfaction scores.

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