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Comparison of Preemptive Analgesic Effect of Two Preoperative Intravenous Loading Doses of Paracetamol in Total Abdominal Hysterectomy.

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Research Article

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ABSTRACT

The purpose of the study was to compare the pre-emptive analgesic effect of two preoperative intravenous doses of paracetamol in total abdominal hysterectomy and the amount of reduction in postoperative opioid consumption. A total of 51patients undergoing total abdominal hysterectomies were enrolled into the study. Patients were randomized into two groups: in Group I (25 patients) intravenous paracetamol 1 g was given 15 minutes prior to induction. In Group II (26 patients), intravenous paracetamol 2 g was given 15 minutes prior to induction. Postoperatively, all patients received morphine via patient-controlled analgesia pump. Pain scores were assessed with visual analogue scale. Total morphine consumption and side effects were recorded. Visual analogue scale pain score, in the immediate postoperative period and cumulative morphine consumption, in the first six hours were significantly reduced in group II. The total morphine consumption over 24 hours was similar in both the groups. The length of hospital stay was reduced in group II.To conclude, in total abdominal hysterectomy, compared to pre-emptive intravenous paracetamol 1 g,intravenous paracetamol 2 g provided better quality postoperative analgesia in the immediate postoperative period, early discharge rates, with no change in total 24 hour consumption of morphine.

INTRODUCTION

Investigations and results of studies show an unacceptable high rate of the observed incidence of pain after surgery [1, 2]. As many as 80% of patients report moderate to extreme pain following surgery [3]. The results of inadequate pain control after surgery are significant in terms of physical, physiological and psychological trauma and can result in immediate and long-term complications. These complications can include hypoxemia, atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, psychological trauma, and delay in improvement of bowel function, myocardial ischemia and infarction, urinary retention in the immediate and medium term postoperative period and chronic pain in the long term [4, 5]. Although opioids are still the mainstay of postoperative pain management, they are associated with many side effects [6]. It is ideal to use a multimodal approach to improve postoperative analgesia and to reduce opioid related side effects.

Preemptive analgesia is the application of an analgesic or a technique prior to the onset of a painful stimulus. This affect is achieved by suppressing, either together or independently, central or peripheral sensitization. Preemptive analgesia gives rise to a subsiding pain model, a decrease in analgesic requirements, and a decline in morbidity, promoting wellness and shortening the length of hospital stays [7, 8]. Paracetamol (acetaminophen; N-acetyl-p-aminophenol) is an acetanilide derivative with a molecular formula of C8H9NO2. It is one of the most regularly used drugs worldwide, thanks to an excellent safety profile. Paracetamol inhibits both isoforms of cyclo-oxygenase (COX); COX-1 and COX-2, also, it reinforces descending serotonergic inhibitory pain pathways [9]. Paracetamol may also involve indirect activation of cannabinoid CB1 receptors [10]. Paracetamol is very well tolerated. Two systematic reviews have found the rate of undesirable events following its administration is not significantly different to that following administration of placebo [11, 12]. A previous study has compared the effect of two doses of intravenous paracetamol for management of pain in hand surgeries [13]. They have concluded that an

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intraoperative loading dose of 2 g intravenous (iv) paracetamol improves postoperative analgesia after minor hand surgery as compared to 1 g ivparacetamol. A previous study has confirmed that in patients with no risk factors, a 2 g loading dose and a total of 5g in 24 hours gives plasma concentrations well below the toxic threshold [14]. As our literature review showed, there was no previous study to compare the preemptive analgesic effect of the two preoperative intravenous loading doses of paracetamol in total abdominal hysterectomy. Hence, we designed the present study to compare the preemptive analgesic efficacy of ivparacetamol 1g versus 2g in total abdominal hysterectomy.

MATERIALS AND METHODS

Ethical clearance was obtained by the ethical committee of the hospital. After getting written informed consent from each participant, 51women in the age group of 27–69 years, undergoing abdominal hysterectomy, were enrolled. The inclusion criteria were ASA physical status I and II, not having any contraindications to the use of the study drug. Since a more than recommended dose of paracetamol was being administered all patients were tested for liver function and any patient with abnormal LFT report was excluded from the study. Patients of age more than 70 years; having history of central nervous system disorders, impaired renal functions, impaired liver function, patients 20% more than or less than the ideal body weight, history of allergic reactions to paracetamol or morphine and patients with history of usage of chronic analgesic treatment (paracetamol, opioids, or NSAIDs) were excluded. The patients were seen one day prior to the surgery, related information and training was given about the usage of the PCA device and the VAS. Patients who were unable to understand the use of the patient-controlled analgesia (PCA) device were also excluded.

The study was single centre, randomized, double-blind, and 2-parallel group study. The computer-generated block randomization schedule was prepared using random number generator to create a list of random numbers by a statistician. A total of two anaesthetists were involved in the study. No person was aware of group assignment until all the 51 patients were included and the assessments were completed. Ultimately, there were 51 sequentially numbered opaque envelopes containing a code specifying the dose of paracetamol to be administered.

Group I patients (n=25) received ivparacetamol 1g, 15 minutes prior to induction. In Group II (n=26), ivparacetamol 2 g was given 15 minutes prior to induction. In the operating room, electrocardiogram (ECG), non-invasive blood pressure (NIBP), heart rate (HR), and peripheral oxygen saturation (SpO2) were monitored. Anaesthetic technique was standardized using propofol (2 mg/kg), fentanyl (2 µg/kg), and vecuronium bromide (0.8 mg/kg) and maintained using N2O in oxygen and sevoflurane. Patients were extubated when fully awake. All the patients were transferred to post anaesthesia care unit (PACU). Intravenous PCA with morphine was given postoperatively to all patients (1 mg/ml morphine and a PCA device programmed for a 2 mg bolus with a 10-min lockout period and a 0.4 mg/ kg 4-h limit). For postoperative pain assessment, Visual analogue scale (VAS) was used (VAS: 0-10; 0: no pain, 10: worst pain imaginable). An anaesthesiologist, not a part of anaesthesia team, assessed various parameters like VAS for pain scores at 0, 1st, 2nd, 6th , 12th and 24th hour and the cumulative morphine consumption during the periods 1st, 2nd, 6th , 12th and 24th hour was recorded in mg. Also the side effects like nausea, vomiting, hypotension and respiratory depression were recorded over 24 hours. The LFT was repeated after 24 hours of surgery and any altered LFTs were recorded. Statistical analysis was performed using Medcalc 12.6.1.0 for windows. P values <0.05 were considered significant.

OBSERVATIONS AND RESULTS

Table 1: Demographic and intraoperative characteristics

Group	Age (years)	Weight (kgs)	Duration of surgery (minutes)
Group I	46 (10)	64 (11)	115 (19)
Group II	50 (12)	58 (14)	118 (18)

Table 1: VAS (mm)

Group	0 hour	1st hour	2nd hour	6th hour	12th hour	24th hour
Group I	4.4 (1.8)	4.0 (1.1)	3.7 (1.4)	2.2 (1.4)	1.8 (0.8)	1.2 (1.0)
Group II	2.4 (0.8)	2.2 (1.0)	2.6 (1.1)	2.5 (1.0)	1.6 (1.1)	1.1 (0.7)
P value	P < 0.0001	P < 0.0001	P = 0.0030	P = 0.3814	P = 0.4628	P = 0.6799

Data expressed as mean (SD). Statistical significance when P<0.05

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Table 3: Cumulative postoperative morphine consumption.

Group	1st hour	2nd hour	6th hour	12th hour	24th hour	Length of hospital stay
Group I	8.9 (0.6)	13.4 (1.4)	18 (2.4)	28.5 (2.2)	44 (4.7)	5.16 (0.5)
Group II	6.0 (1.1)	12.6 (2.0)	16.9(1.8)	24.3 (2.9)	42 (2.8)	4.79 (0.64)
P value	P < 0.0001	P = 0.1056	P = 0.0082	P = 0.0694	P = 0.0697	P = 0.0261

Data expressed as mean (SD). Statistical significance when P<0.05.

Table 4: Side effects observed in the two groups

Groups	Nausea	Vomiting	Respiratory depression	Altered LFT	itching
Group I	2	2	-	-	1
Group II	2	1	-	-	1

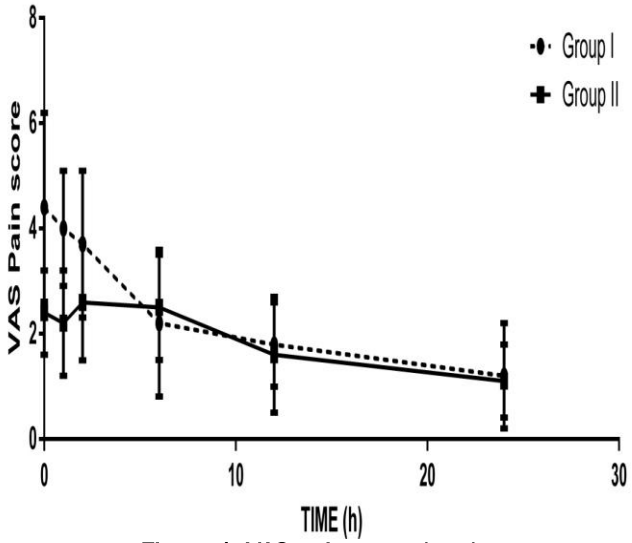

Figure 1: VAS pain score (mm)

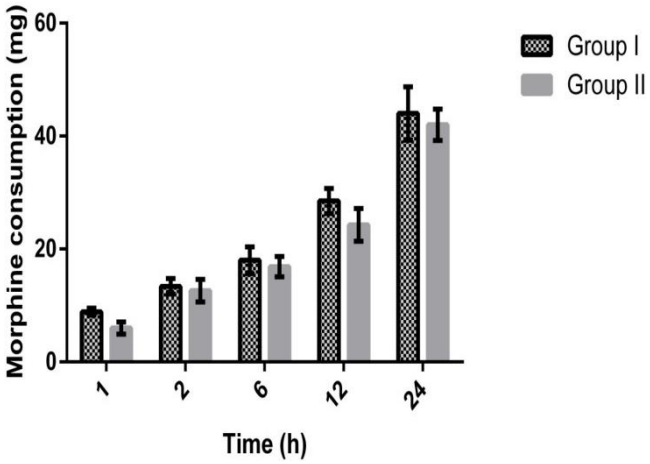

Figure 2: Cumulative postoperative morphine consumption.

A total of 64 patients were screened for the study, out of which, 51 were enrolled and randomized as the rest did not meet the inclusion criteria. The groups were comparable with respect to demographic and intraoperative characteristics Table 1. Table 2 shows VAS for pain scores at 0, 1st, 2nd, 6th, 12th and 24th hour. The difference in VAS pain score was statistically significant between group 1 and group 2 in the 0, 1st and 2nd hour. Table 3 shows cumulative postoperative morphine consumption at 1st, 2nd, 6th, 12th and 24th hour. The morphine consumption of the cases in group II was found to be significantly reduced in the first six hours. When the total morphine consumption amounts for 24 h were compared, there was no significant difference between the two groups. The incidence of side effects such as postoperative nausea, vomiting, respiratory depression and itching is shown in Table 4 according to patient groups. No difference in incidence of side effects in either group was observed. The length of hospital stay in group II was significantly reduced.

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DISCUSSION

In the present study, we have compared two doses of ivparacetamoli.e. 1g versus 2g, as a pre-emptive analgesic in 51 patients who underwent total abdominal hysterectomy. We assessed the effects of the two different doses on postoperative analgesia, 24 hour morphine consumption, frequency of side effects, and total hospital stay length. We determined that in comparison with administration of paracetamol 1g 15 min before induction, paracetamol 2g resulted in decreased immediate postoperative pain and decreased morphine consumption in the first 6 hours, but had no effect on total morphine consumption over 24 hours. We observed no difference in the incidence of side effects. However the length of hospital stay was found to be significantly reduced in patients who received paracetamol 2g. To conclude, immediate postoperative analgesia was better with paracetamol 2g given intravenously 15 minutes prior to induction compared to paracetamol 1g along with reduced length of hospital stay.

Inadequate pain control after surgery results in physical, physiological and psychological trauma and can lead to immediate and long-term complications. These complications can include hypoxemia, atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, psychological trauma, delay in resuming bowel function, myocardial ischemia and infarction, urinary retention in the immediate and medium term postoperative period and chronic pain in the long term [4, 5]. In fact, chronic pain is reported by 5–32% of women after hysterectomy[15].Pre-emptive analgesia is the application of an analgesic or a technique prior to the onset of a painful stimulus. Due to the negative effects and complications it causes in the patient, postoperative pain has to be treated in a fast and effective manner. Pain management should be started prior to pain initiation [16]. The methods and agents for which pre-emptive analgesic effectiveness has been researched are mostly NSAIDs, opioids, ketamine, peripheral local anaesthetics and epidural analgesia [17].

It has been 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[18,19]. 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[20]. Clinical studies have found that 1g ivparacetamol employed alone is just as effective as 30 mg ketorolac, 75 mg diclofenac or 10 mg morphine[21, 22].

The role of paracetamol as a drug that can provide pre-emptiveanalgesia has already been studied[8, 16, 23]. In their study (23) Vaideanu and colleagues studied 60 patients who had a pan-retinal photocoagulation operation. They administered 1,000 mg oral paracetamol as a pre-emptiveanalgesic and compared the results with a placebo group. Subsequently, similar to our study, they found that postoperative pain scores subsided in the pre-emptivegroup in 24 h. In our study we have used intravenous paracetamol instead of oral paracetamol.

In a previous study [16]Arici and colleagues have concluded that, pre-emptively administered iv paracetamol 1 g, in patients undergoing a total abdominal hysterectomy operation, has no negative effects on intraoperative or postoperative hemodynamic parameters, ensures an effective analgesia during the postoperative period, increases patient satisfaction by reducing postoperative morphine consumption and side effects, and thereby shortens the length of hospital stay. In their study, they have compared paracetamol 1g injected intravenously 30 mins prior to induction (Group I) and in another group paracetamol 1g (group II) was injected prior to closure. The third group received normal saline only and served as placebo group. When the VAS scores of the patients in Group III were compared with Groups I and II, they were found to be significantly higher at all-time points ($p<0.05$). The VAS values of the cases in Group III were also found to be significantly higher ($p<0.05$) than the values of Groups I and II. Unlike their study, in our study we have compared two groups, in which paracetamol has been given preoperatively only.

In their review article [9], C. D. Oscier and Q. J. W. Milner have concluded that use of a 2 g loading dose is likely to be a safe way to achieve meaningful early plasma concentrations, especially after oral administration. The recommended dose of paracetamol is 4 g in 24 hours and a previous study has confirmed that in patients with no risk factors, a 2 g loading dose and a total of 5g in 24 hours gives plasma concentrations well below the toxic threshold [14]. Hence we sought to see the pre-emptiveeffect of 2 g paracetamol on postoperative analgesia.

G. Juhl and E. Boccard, in their study [24], evaluated the analgesic efficacy in the immediate postoperative setting of 2 g of i.v.paracetamol compared to the recommended 1 g dose. They found that pain relief and pain intensity difference scores of 2 g were significantly superior to 1 g from. The difference was significant in the first 6 hrs, similar to the observation we have made in the present study.

Cornesse D and colleagues compared the analgesic efficacy between two intraoperative intravenous loading doses (2g versus 1g) of paracetamol on pain after minor hand surgery. Similar to our study, it was a 2 group randomized controlled study. They found that verbal numeric pain scores during the first 24 hours after surgery were significantly lower in the 2 g paracetamol group as compared to the 1 g paracetamol group. No differences

were found between the two groups with regard to rescue analgesic consumption, sleep quality and patient's satisfaction.

Depending on the dosage of opioids, complications such as respiration depression, nausea, vomiting, urine retention, and itching may develop. In our study, we found that incidence of complications were similar. Respiratory depression was not noticed in any case. Only one patient in each group had itching, which subside without any intervention. Two patients in each group had nausea which subside with a dose or rescue anti-emetic. Two patients in group 1 had vomiting whereas in group 2 only patient had vomiting, which subsided with rescue antiemetic. Since we were using a higher than recommended dose of paracetamol, all patients were tested for any alteration of LFTs after 24 hours after the surgery. None of the patients were found to have altered LFTs.

Even though, 24 hour consumption of morphine was similar in both groups, the length of hospital stay was significantly shorter in Groups 2 as compared to Group 1. This was possibly due to the better pre-emptive analgesic effect of 2g paracetamol, resulting in greater degree of analgesia in the immediate post-operative period as reflected by the VAS scores and time specific morphine consumption rates in the group. This emphasizes the importance of good quality analgesia in the intraoperative and immediate postoperative stage. In our study we attribute it to the better pre-emptive effect delivered by intravenous paracetamol 2g given 15 mins before the induction.

CONCLUSION

This study demonstrated that when given pre-emptively, compared to intravenous paracetamol 1g, paracetamol 2g provides better early postoperative analgesic effect and due to this effect, can reduce the length of hospital stay in patients undergoing total abdominal hysterectomy. Since single dose of intravenous paracetamol 2g, has no effect on liver function, it can be safely used as a pre-emptive analgesic for postoperative pain management.

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