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A Comparative Study of the Diclofenac with Different Preparation of Paracetamol for Post-Operative Analgesia Following Laparoscopic Cholecystectomy

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Abstract

Pain following surgery remains a very important concern which can lead to detrimental effect over cardiovascular system, central nervous system and respiratory system. To minimise pain several analgesics are used. In that matter multimodal analgesia with diclofenac and paracetamol combination is regularly used. The paracetamol available commercially is in different formulation; Paracetamol 100 mL solution for infusion (P), containing paracetamol, cysteine hydrochloride monohydrate, disodium phosphste dihydrate, hydrocholoric acid, mannitol and sodium hydroxide and Paracetamol and lignocaine 2 mL injection (PL), containing paracetamol, lignocaine hydrochloride and benzyl alcohol. We studied comparing both the formulations of these paracetamol in combination with diclofenac in laparascopic surgeries and we did not find any significant difference between these two in terms of demography, VAS, VRS and any other side effects. However the major difference in the cost between these two formulations makes a significant impact in the economic burden.

Keywords Diclofenac; Paracetamol; Cysteine hydrochloride monohydrate; Lignocaine hydrochloride; Benzyl alcohol; Laparoscopic cholecystectomy; Postoperative pain

Introduction

Pain is one of the most common complications following surgery which primarily occurs due to handling of different organs intra-operatively leading to tissue damage. The severity of pain depends upon age, type of surgery and site of surgery, etc., [1]. So post-operative pain management plays a very important role in determining the final outcome of surgery under general anaesthesia [2]. If not managed properly it can have detrimental effect over cardiovascular system, central nervous system and respiratory system, due to over stimulation of sympathetic system. Thus multimodal analgesia came into existence for better management of post-operative pain and smooth recovery from general anaesthesia [3].

Laparoscopic cholecystectomy is the treatment of choice for cholelithiasis as it has got several advantages like smaller and more cosmetic incision, reduced blood loss, reduced post-operative stay, low post-operative complications and early mobilization. But post-operative pain is one of the major drawbacks of this procedure. Hence adequate analgesia must be given to the patient both intra and post-operatively in order to make the patient pain free. Both diclofenac and paracetamol plays very important role in pain management following laparoscopic cholecystectomy. Paracetamol is available in two forms either Paracetamol 100 mL solution for infusion (P), containing paracetamol, cysteine hydrochloride monohydrate, disodium phosphste dihydrate, hydrocholoric acid, mannitol and sodium hydroxide [PERFALGAN, marketed by Bristol-Myers Squibb India private limited] or Paracetamol and lignocaine 2 mL injection (PL), containing paracetamol, lignocaine hydrochloride and benzyl alcohol [FEVASTIN, marketed by tablets India limited]

Thus we carried out this study to evaluate the efficacy of post-operative pain control by diclofenac with Paracetamol 100 mL infusion (P) and diclofenac with Paracetamol 2 mL stat (PL).

Materials and Methods

The proposed study was carried out in the department of anaesthesiology, IMS, BHU, Varanasi from February 2015 to December 2015. After getting permission from institutional ethical committee and written informed consent from the patients, 100 patients were included in the study. They were divided into two groups with 50 patients in each group,

Group DP: Patients received Diclofenac with Paracetamol P (100 ml infusion)

Group DF: Patients received Diclofenac with Paracetamol PL (2 ml stat)

Selected patients were from either sex, age group between 20 to 50 year, average weight, belonging to ASA grade I and II posted for laparoscopic cholecystectomy. Patients with history of drug allergy, bleeding disorders [4,5], asthma, gastro intestinal system bleeding, renal insufficiency, etc were excluded from the study.

Patient was taken into the pre-operative preparation room where intravenous (I.V) cannula was secured and 1 mg midazolam was given slow I.V. Then patient was shifted to the operation theatre and standard monitors ECG, NIBP and pulse oximeter were attached. All the patients were given injection 0.2 mg glycopyrolate I.V, 1 mg/kg body weight ondansetron I.V, 2 mg/kg fentanyl I.V as premedication. Induction was performed with 2 mcg/kg propofol I.V and after loss of consciousness 0.1 mg/kg vecuronium bromide I.V was given for muscle relaxation. Then patient was pre-oxygenated for 3 minutes and adequate size of I-gel was secured for ventilation. After confirming the

proper placement of I-gel, anaesthesia was maintained with 1 litre of oxygen and 2 litres of nitrous oxide followed by propofol infusion. Stomach was decompressed with 10 Fr size of orogastric tube via side port of I-gel. Tidal volume and respiratory rate was adjusted to maintain the $EtCO_2$ between 35-45 mm Hg. After 10 minutes of starting of surgery patients of DP group received 75 mg of diclofenac sodium aqueous I.V over a period of 10-15 minutes followed by paracetamol infusion (P) 15 mg/kg. DF group received diclofenac sodium I.V of same dose given over same period and paracetamol (PL) in same dose. After completion of surgery the muscle relaxant was reversed with injection neostigmine 0.05 mg/kg and glycopyrolate 0.01 mg/kg I.V. Once the patient gained full consciousness then shifted to post-operative care unit, where the patient was monitored for next 6 hours. The anaesthesiologist who was blinded for the study was asked to visit the patient at 30 minutes, 1 hour, 2 hour, 4 hour and 6 hour. He was also asked to keep the record of VAS score, any side effect like nausea, vomiting, headache, sedation, dizziness, rashes, neuralgia, myalgia, respiratory depression, hypotension or hypertension, bradycardia or tachycardia, shoulder pain, etc. Duration of analgesia was also recorded, starting from the time of administration of NSAIDS to perception of pain [6]. A four point verbal rating scale was used to assess the patient satisfaction following administration of analgesic drugs:

Poor control

Fair control

Good control

Excellent control

The rescue analgesia was given only on patient demand, in the form of injection pentazocine 30 mg slow I.V. over 10 minutes and the patient was monitored for the next 30 minutes for respiratory depression and sedation. Total requirement of rescue analgesia was noted in both the groups. Statistical analysis was conducted using SPSS 13 software and comparisons among the groups were analyzed by using Chi-square test. All the measurements were expressed as mean + standard deviation with P value.

Results

The demographic data showed that the mean age group was 35 years, weight was 60.10 kg, height was 160 cm and a sex ratio of female: male=55:45 in either group. The mean duration of operation was 30 ± 8 minutes and the mean duration of analgesia was 108 ± 50 minutes (Table 1). VAS taken for post-operative pain assessment was same in both the age groups over equal time interval without significant difference (Table 2). The requirements of rescue analgesia were also same in both the groups. The patient satisfaction at 6 hour was assessed by taking verbal rating scale, which was same in both the age groups (Table 3). There was no significant difference in incidence of side effect among both the groups (Table 4).

Demographic data	Group DP	Group DF	P value
Age (in years)	35.9 ± 7.3	36.1 ± 8.3	>0.05
Sex (M/F)	55 %	45 %	>0.05
Weight (kg)	60.9 ± 10	61.1 ± 3.1	>0.05
Height (cm)	160.01 ± 10	159.1 ± 3.4	>0.05
Duration of Operation (in min)	30.10 ± 30	31.2 ± 35	>0.05
Duration of Analgesia (in min)	108.8 ± 9.0	109 ± 10	>0.05

Table 1: Demographic data.

Time	Group DP	Group DF	P value
30 min	4.12 ± 1.1	4.15 ± 1.15	>0.05
1 hour	3.89 ± 1.1	3.9 ± 1.1	>0.05
2 hour	3.31 ± 1.5	3.4 ± 1.0	>0.05
4 hour	3.24 ± 1.0	3.3 ± 1.0	>0.05
6 hour	3.40 ± 1.2	3.41 ± 1.1	>0.05

Table 2: VAS pain score (n=50 in each group).

Verbal rating scale	Group DP	Group DF	P value
Poor 1	2	2	>0.05
Fair 2	9	8	>0.05

Good 3	18	19	>0.05
Excellent 4	4	4	>0.05

Table 3: Patient satisfaction at 6 hour of operation using Verbal Rating Scale.

Side effects	Group DP	Group DF	P value
Nausea and Vomiting	3	3	>0.05
Sedation	0	0	>0.05
Headache	3	2	>0.05
Restlessness	1	0	>0.05
Dizziness	1	1	>0.05
Rashes	0	0	>0.05

Table 4: Incidence of side effects (n=50 in each group).

Discussion

Post-operative pain is the most common contributing factor for fear and anxiety associated with surgery. If not managed properly, post-operative pain can not only cause physical suffering but also delays recovery from surgery leading to increase hospital stay and morbidity [7]. The analgesics used for post-operative pain control are either opioids or NSAIDS or both. Diclofenac sodium is the most extensively used NSAID for this purpose. It has got analgesic, anti-inflammatory and antipyretic effect. It inhibits prostaglandin synthesis and somewhat COX-2 selective. Paracetamol is N-acetyl-Para amino-phenol diethyl amino acetic ester. It has got a good antipyretic effect and weak anti-inflammatory action. Paracetamol is available in two forms in market, as described in the introduction.

Beck et al. carried out a study among patients undergoing gynecological surgery involving vaginal and abdominal hysterectomies, in which they used paracetamol 20 mg/kg, 40 mg/kg alone and paracetamol 20 mg/kg single rectal dose in combination with diclofenac sodium 100 mg with a observational period of 24 hour after surgery, the result showed that combination of drugs had better pain management than paracetamol alone [8]. Breivik et al. carried out study in patients undergoing dental surgery with impacted IIIrd molar tooth, he used diclofenac 100 mg, paracetamol 1000 mg alone and diclofenac 100 mg with paracetamol 1000 mg single rectal dose with 8 hours of observational period [9]. He observed that combination therapy has better pain control with 13-20% and 25-30% incidence of nausea and vomiting respectively. Matthews et al. used diclofenac 50 mg alone, diclofenac 50 mg with paracetamol 500 mg and used paracetamol 500 mg single oral dose before dental surgery for impacted IIIrd molar tooth with 12 hours observational period and found that pain intensity negative and no adverse effect [10]. Montgomery et al used paracetamol 1500 mg alone, diclofenac 100 mg alone and paracetamol 1500 mg in addition to diclofenac 100 mg single rectal dose given before surgery with 24 hours of observation following elective gynecological surgery. He found pain intensity to be positive and higher percentage of nausea and vomiting, which could be due to morphine used in higher doses [11]. Munishankar et al also found same result as Montgomery et al [12]. Riad et al carried out a study in children undergoing inguinal hernia surgery and they used diclofenac 1 mg/kg, paracetamol 40 mg/kg and a combination of diclofenac 1 mg/kg with paracetamol 40 mg/kg, in which all drugs were given rectally 1 hour before surgery. They found pain intensity to be lesser in combination of drug [13]. Siddik et al used placebo, diclofenac 100 mg rectally, paracetamol 2 gm I.V. and combination of paracetamol 3 gm I.V. 6 hourly with diclofenac 100 mg rectally 8 hourly for 24 hours following caesarean section operation. They found that pain was significantly lower in combination group and no difference in incidence of nausea and vomiting [14]. Hyllested et al. documented the analgesic efficacy was better in combination than paracetamol alone in regards to pain score, rescue analgesia and pain relief [15]. Other side effects like dizziness, sedation was either not recordable or was significantly low.

Conclusion

In our study we found out that both the group of patients have almost equal analgesic effect and patient satisfaction, when drugs were given as combination therapy in same dose. But if we compare their market price then we can see huge difference, Inj Paracetamol P (paracetamol 100 mL bottle) is more costly as compared to Inj Paracetamol PL (paracetamol 2 mL ampoule) in same dose. Both of these products have lots of thing in common like $t_{1/2}$ (2-3 hours) and duration of analgesia. But there is huge difference in their cost; Inj Paracetamol P costs around 30 times more than Inj Paracetamol PL. This cost factor plays a very important role in developing and resource poor country like India.

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