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TO EVALUATE THE EFFICACY AND SAFETY OF FLUPIRTINE AS PREEMPTIVE ANALGESIA IN PATIENTS UNDERGOING ABDOMINAL SURGERY.

Pharma

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KEYWORDS

Introduction

International Association for Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1]Pain is a parameter which is dependent on the extent of tissue damage and the site of surgery. Upper abdomen and thorax surgeries are considered to be more painful as compared to lower abdominal surgery or surgeries done on limbs.[2] There have been surveys which show that there has been unsatisfactory post-operative pain (POP) management in patients undergoing surgeries and requires an improvement. [3] Preemptive analgesia is among the new tailored techniques which have come up to decrease the pain. This technique can reduce the post-operative pain, time for requirement of rescue analgesia and cumulative post-operative analgesic requirement. A meta-analysis has suggested a possible efficacy of pre-emptive analgesia in improving post-operative acute pain management in some selected analgesic regimens.[4]

Flupirtine maleate is a drug which has been used as an analgesic and as a muscle relaxant.[5]It is a centrally acting, non-opioid and non- NSAID analgesic agent. [6] In a few studies, flupirtine maleate has been used as a preemptive analgesia. A study evaluated the efficacy of preemptive flupirtine in patients undergoing gynecological laparoscopic surgeries. They reported a statistically significant difference in the mean time to rescue analgesic use as compared to the control group which received vitamin B complex.[7]

Aims and Objectives

To evaluate the efficacy and safety of flupirtine as preemptive analgesia in patients undergoing abdominal surgery.

Material and methods

The study was conducted in the department of Pharmacology, Christian Medical College and Hospital, Ludhiana. The study subjects were taken from the patients undergoing abdominal surgeries under general anesthesia, from the Department of Surgery and Anesthesia from 15th December 2015 to 30thJune 2017. Patients undergoing any abdominal surgery who fulfilled the inclusion criteria were enrolled in the study after signing the informed consent form (Annexure I). Patient information sheet (Annexure II) was provided to the patient at the time of enrolment. Patient details were noted on patient particular sheet (Annexure III).A complete history and general physical examination was done and the details were noted in patient examination sheet (Annexure IV). Visual analogue scale (VAS) was used to evaluate post-operative pain (Annexure V).

Study design

This was a prospective, randomized, and open labelled study.

Sample size

The total sample size was 80 with 40 patients in each group.

Sample size calculation:

The sample size calculation was based on VAS score for pain assessment before the commencement of this study. To detect a difference in the postoperative VAS score among the groups with a standard deviation of 7.51 which was estimated from previous studies, with 80% power and 15% alpha error, we need to enroll 40 patients/group using the following formula:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times 2 \times S.D.}{d^2}$$

Inclusion criteria

1. Patients of both genders, aged 18- 70 years, undergoing abdominal surgery.
2. Patients who fulfill the criteria of American Society of Anesthesiologists (ASA) physical status I and II.
3. Patient who were able to comprehend the use of Visual analogue scale (VAS).

Exclusion criteria

1. Patients with known hypersensitivity to the study drug.
2. Patients who had peptic ulcer disease, hepatic or renal disease, psychiatric disease.
3. Intake of opioid medications within 28 days of scheduled surgery, and chronic painful condition requiring regular use of analgesics.
4. Pregnant and lactating females.
5. Patient with an epidural cannula for post-operative pain management.

Study Drugs

Enrolled patients were divided into two groups using computer generated random numbers. Group A patients (n=40) received tab. flupirtine 100mg and Group B patients (n=40) served as the control group.

Evaluation

Primary efficacy parameter

1. Comparison of post- operative pain in the two groups using visual analogue scale (VAS) at various time intervals over the first 24 hours post-operatively.

Secondary efficacy parameters

1. Use of first rescue analgesic in the two groups.
2. Total analgesic intake over the first 24 hours post-operative.

Safety

The safety of the study drug was measured by frequencies of adverse drug reactions yielded by check-list and spontaneous reporting.

Study procedure

Patients first underwent a clinical work up including a detailed history and general physical examination. Patients fulfilling the inclusion criteria were enrolled into the study after obtaining a written informed consent. The details of all the patients were recorded as per the protocol. Patient information sheet was provided to the patients enrolled in the study. The enrolled patients were divided into two groups by using computer generated randomization. Group A patients were administered single dose tablet flupirtine100mg and group B patients served as the control group. One day prior to the surgery, the patients were explained about the use of visual analog score for marking the intensity of pain after the surgery.

The drug was administered to the Group A patients two hours prior to the surgery with sip of water. Other premedication drugs were omitted. General anesthesia was induced in patients of both groups, with lidocaine (1 mg/kg, intravenous [IV]), fentanyl (2 µg/kg, IV), and propofol (2 mg/kg, IV). Endotracheal intubation was facilitated with vecuronium (0.08 mg/kg, IV). Anesthesia was maintained with nitrous oxide-oxygen combination (70%:30%) and Isoflurane (1%). Injection fentanyl (1 µg/kg, IV) and vecuronium (0.02 mg/kg, IV) was repeated as and when required during surgery. Intraoperative blood pressure, pulse rate, respiratory rate, oxygen saturation and ECG was monitored. At the end of surgery, residual neuromuscular paralysis was reversed with neostigmine (0.05 mg/kg, IV) and glycopyrrolate (0.01 mg/kg, IV). After the recovery, all patients were extubated and shifted to recovery room. The procedure for anaesthesia and intra-operative fentanyl use was same for the two groups.

Acute postoperative pain was assessed using the 10-point VAS score on which 0 indicates "no pain" and 10 represents "worst imaginable pain." Intensity of post-operative pain was recorded at 0, 1, 2, 4, 6 and 24 hours, postoperatively.

Rescue medication was used if the patient complained of pain or the score on VAS was more than 3.The time to use of first rescue analgesic in the two groups was noted. The analgesic used for post-operative pain, with its dose and formulation, used in the first 24 hours post-operatively, was also recorded.

Statistical Analysis: The results were analyzed using Mann-Whitney test and Chi-square/Fisher exact test. A p value less than 0.05 was regarded as statistically significant.

Results

This study included 80 patients who were divided into two groups. Group A received capsule Flupirtine 100mg two hours prior to surgery with two sips of water. Group B served as the control group. The pre-operative and intra-operative medications remained the same for both the groups.

DEMOGRAPHIC FEATURES

A large number of participants (36 out of a total of 80, ie 45%) was in the age group of 41-60 years. There was no statistical difference in the age group of patients between the two groups.

There was a female preponderance with 60% female participants in this study. In group A, 21 were males and 19 were females. In group B, there were 11 male patients and 29 female patients. Number of female participants was significantly higher than the male participants (p value 0.011).

In this study, out of a total of 80 participants, 72 underwent laparoscopic cholecystectomy i.e. 90%. Two out of 80 i.e. 2.50% underwent mesh hernioplasty and abdominal abscess surgery each. Four out of 80 i.e. 5.00% underwent stoma reversal. In group A, 35 out of 40 ie 87.50% and in group B, 37 out of 40 i.e. 92.50% underwent laparoscopic cholecystectomy.

Visual Analogue Scale Score (VAS)

VAS was used as a primary efficacy parameter. It was used to assess the pain perceived by the study participants at various time intervals within the first 24 hours (0, 1, 2, 4, 6, 24) post-operatively.

At 24 hours, the mean VAS score of group A was 3.52 and for group B it was 3.58. VAS score at 24 hours was comparable (p value 0.668).

On analyzing the percentage change of VAS score, there was an improvement in VAS score in both the groups A and B. The difference between the two groups was not statistically significant.

The mean time for first rescue analgesia required for group A was 18.62 min and for group B it was 14.12 min. This difference between the two groups was statistically significant.

SAFETY PARAMETERS

The adverse drug reactions such as drowsiness, dizziness, nausea, vomiting, dryness of mouth, pruritus, tremors and elevated moods were monitored from the time of drug administration to till the first 24 hours post-operatively. No adverse effects were reported by the study participants post-operatively in the two groups.

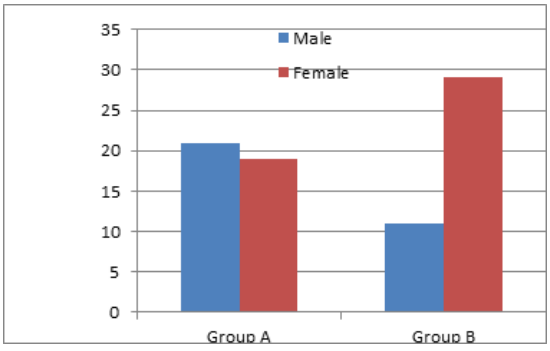

FIG-1 Gender Distribution Of Study Participants

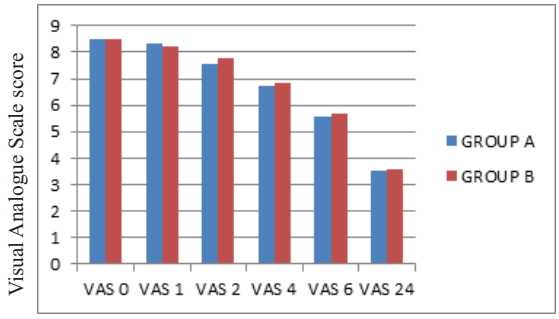

Fig-2 Comparison Of Vas Score Between The Two Groups At Various Time Intervals Between 0-24 Hours Post-operatively

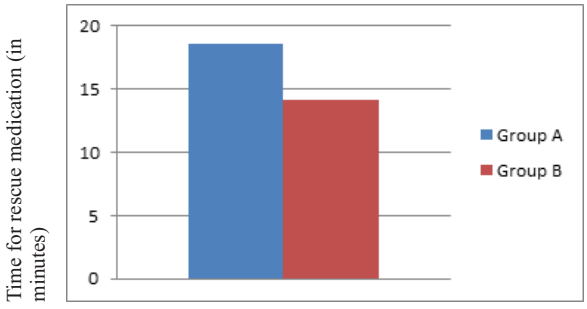

FIG 3- Comparison Of Time For First Rescue Analgesic Between Group A And Group B

Discussion

This study was done to evaluate the efficacy of flupirtine as a preemptive analgesic in patients undergoing elective abdominal surgeries under general anesthesia. The concept of preemptive analgesia was introduced for optimal management of post-operative pain, reduce the requirement of analgesics and improve patient satisfaction.

The parameters used to assess the efficacy of flupirtine as a pre-emptive analgesic were evaluation of post-operative pain at various time intervals, time for rescue analgesia and analgesic requirements over the first 24hours. These are the parameters that have been used for studies for assessing efficacy of preemptive analgesics: some studies use all the three, while the others have used a combination of any two of these parameters.[8,4]

Flupirtine was introduced so as an alternative to NSAIDs and opioid analgesics. Although efficacious, in varied painful conditions, they are also associated with serious adverse effects. In clinical studies, flupirtine has been shown to be beneficial in the short-term treatment of acute pain such as dysmenorrhea, backache and postoperative pain.

Among our study participants, 90% of them underwent laparoscopic surgery. Of the total number of study participants, 60% were females and 40% were males this showed a female preponderance. As majority of the participants in this study underwent a laparoscopic cholecystectomy, and it is known there is a higher incidence of females in their forties, this may account for the higher number of female patients in this study. Unisa et al did a study on the prevalence of cholelithiasis and its associated risk factors in north India. They concluded that females had 5.59% higher prevalence of cholelithiasis than the males.[9]

Many pain scales like Visual analogue scale, Numeric rate scale, Verbal categorical rating scale are some of the commonly used pain scales which have been used for the measurement of post-operative pain. Visual analogue scale has been used extensively in studies conducted for various pain-related studies and is considered to be the gold standard for the same. VAS is commonly used because of its reproducibility, practicality and sensitivity to effect of analgesic drug given and easy assessment of the pain score.[10,11] In this study, VAS was used to assess the post-operative pain by the participants as a primary efficacy parameter. It was assessed at various time intervals (0, 1hr, 2hr, 4hr, 6hr and 24hr). The mean standard deviation was comparable in both the groups and the P value for the groups at different time

intervals was statistically not significant. In an another study where flupirtine was used as a preemptive analgesic in patients undergoing surgery, it was reported that patients in the flupirtine group had lower VAS scores in the first and second post-operative hour, but there was no difference thereafter until 24 hours.[12] Yadav et al. found that there was an improvement in the VAS score in the flupirtine group in the first four hours in patients undergoing laparoscopic cholecystectomy as compared to the control group which received capsule B-complex. There was no difference between the groups after four hours up to twenty four hours. [13]

It is possible that these studies demonstrated a pre-emptive effect of flupirtine used at a higher dose of 200mg while a dose of 100 mg was used in this study.

Time for first rescue analgesic and total analgesic intake by patient in first 24 hours was noted as a secondary parameter for this study. The mean standard deviation was 18.62 ± 6.3 minutes for group A and was 14.12 ± 6.29 minutes for group B and the p-value was 0.002 which was statistically significant. Other studies using pre-emptive analgesics have also reported an increase in time for first analgesic intake. The use of intravenous tramadol as a pre-emptive analgesic in patients undergoing abdominal hysterectomy reported a higher time to rescue analgesic requirement as compared to the control group which received saline, and the difference was statistically significant.(p 0.019).[14]

The total analgesic requirement over the first 24 hours post-operatively has also been used as a parameter to assess the efficacy of pre-emptive analgesia. In our study, about 44% of the patients received morphine and 34% patients received paracetamol for rescue analgesia, the rest of the patients were given either tramadol or diclofenac.

In this study, the patients were monitored for adverse effects but these were not reported. In one study, nausea was reported in one patient when flupirtine was compared to diclofenac for post-operative pain management. [14]A few other studies have reported sedation among the patients.[7,13] Although the adverse effects have been reported in other studies, it is possible that no adverse drug reactions were reported in the study as only a single dose of the drug was used.

Conclusion

To conclude, there was no difference between the flupirtine maleate and control group on the post-operative pain, as reflected by the VAS score or the total consumption of rescue analgesics in the study group but there was a significant difference in the time for rescue analgesic between the two groups.

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