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Comparative Efficacy and Safety Study of Analgesic Effect of Fentanyl I.V. and Paracetamol I.V. in Postoperative Patients in Multidisciplinary Hospital.

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ABSTRACT

The aim of this study was to evaluate the analgesic efficacy and safety of a single dose of intravenous acetaminophen in comparison with intravenous fentanyl in patients experiencing pain after surgery. 75 patients were chosen in each group for comparison and a randomized parallel group study was initiated bearing in mind the inclusion and exclusion criteria. Two analgesic drugs, an opioid and a nonopioid were selected for the study with the idea that a non opioid drug if proved to be therapeutically more effective in relieving pain would be useful clinical indicator. Statistically it was observed that acetaminophen 1 gm intravenous dose was not as efficacious as fentanyl 100 mcg (2 ml)dose administered post operatively on a pain scale measured 4 hours after the procedure and 3 days post-surgery.

Keywords: Comparative efficacy, Randomized, Analgesic, Opioid, QoR-Quality of Recovery, Confidence interval Fentanyl, Paracetamol

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INTRODUCTION

Effective Pain management is an important component of Post surgical care. The Taxonomy Committee of International Association for the study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]**.** Postoperative pain is considered a form of acute pain due to surgical trauma with inflammatory reaction and initiation of an afferent neuronal barrage. Pain being a subjective phenomenon is perceived only by the sufferer. The adequacy of postoperative pain control is one of the most important factors in determining when a patient can be safely discharged from the outpatient facility. Because inadequately treated pain is a major cause of prolonged stays or unanticipated hospital admissions after surgery, thus introduction of multimodal analgesia including opioids and non-opioids, either alone or in combination with other drugs have greatly improved the efficacy of pain control. Woman requires less analgesia than men [2] probably due to difference in neuro-endocrine mechanism of pain relief. Smokers metabolize analgesics considerably faster than non-smokers [3] and need more as a result.

Opioids remain the agents of choice for severe pain; however, this class of analgesics is associated with dose dependent side effects and negative postoperative outcomes [4,5]**.**

Non-opioid analgesics are commonly used alone or as adjuncts to opioid-based analgesia to treat moderate to severe pain. The oral route for administration of drugs may be denied because of the nature of the surgery and drugs may have to be given by injection. Normally, postoperative pain should decrease with time and the need for drugs to be given by injection should cease. Strong opioids may no longer be required and adequate analgesia can be obtained by using non-opioids alone or in combination with weak opioids. Whilst opioids are the mainstay for relief of severe pain, they are far from perfect analgesics as they have many significant side effects.

Acetaminophen has a well established safety and analgesic profile. Until recently, there has not been an intravenous acetaminophen solution available because it is poorly soluble in water and not stable in solution. A ready-to-use formulation of intravenous acetaminophen has recently been developed that does not require reconstitution and is not associated with contact dermatitis or pain at injection site. The availability of intravenous acetaminophen preparation may aid accurate administration of drug to patients at higher risk of dose related hepatic toxicity, including neonates.

MATERIALS AND METHODS

Study Design

This study was randomized, two-parallel group study comparing 1g intravenous acetaminophen with 100 mcg intravenous fentanyl and was conducted in multi-disciplinary hospital of South Mumbai. Patients were studied over the first 4 hr after surgery and consecutively for 3 days post-surgery wherein paracetamol IV was given 3 to 4 time a day and fentanyl was administered 3 times a day.

Patients aged at least 18 years who were recovering from surgery performed were eligible for study. Exclusion criteria included patients aged above 70 years. Patients were also excluded if combination of analgesics were given postoperatively. Patients in the I.C.U. who were kept in sedation state due to intolerance and uncomfortable feeling after surgery were excluded.

The study was conducted in accordance with good clinical practice and was approved by institutional review board.

Intravenous acetaminophen was chosen as a comparator because it is widely prescribed in hospital and is a recently marketed form for management of acute pain after surgery. Since it is available as 1g solution, dose chosen was 1 g for intravenous acetaminophen and 100 mcg for intravenous fentanyl.

All patients were closely monitored and patient's pain intensity was recorded. Patients reporting none to extreme pain intensity on a five-point verbal pain intensity categorical scale. (0= none, 1=slight, 2= moderate, 3= severe, 4= extreme).

The aim of this study was to judge good analgesic after surgery which depends upon type of surgery performed and recovery process. Patients reported quality of recovery score (QoR) on three point scale. (0= not at all, 1= some of the time, 2= most of the time). Both pain intensity and Quality of Recovery was measured after 4 hour of surgery.

Efficacy measurement

Post operative pain relief was the major concern of this study. Intravenous Fentanyl and Intravenous acetaminophen is having similar half-life which is around 4 hour. Hence pain intensity was measured after 4 hour of surgery in which either of the drugs was prescribed postoperatively. Pain was measured on four-point categorical scale. (0= none, 1= slight, 2= moderate, 3= severe, 4=extreme). When the patient was asleep no attempt was made at arousal.

Safety Assessments

Side-effects or adverse events were monitored throughout the study period. The following side effects were reported during study: Nausea, Vomiting, and Dry Mouth.

Statistical Analysis

Sample Size: Analysis on sample size of 75 patients per group was performed in the intention-to-treat patients. Data are expressed as mean and 95% confidence interval. Student's *t-test* was used to compare means. All comparisons were two-tailed and ***P*** value of less than 0.05 was required to rule out the null hypothesis.

RESULTS

A total of 150 patients were included in study as per criteria and were considered for analysis, 75 in fentanyl group and 75 in acetaminophen group. Both the groups were comparable with respect to demographics and surgical procedures.

Patient Characteristic Data

Characteristics	Fentanyl group (n=75)	Acetaminophen group (n=75)
Age (yr)	46.78 (+/-) 16.17	49.08 (+/-) 15.86
Men	34	33
Women	41	42
Pain score	1.625 (+/-) 1.13	2.410 (+/-) 1.30
QoR Score	15.78 (+/-) 1.68	15.21 (+/-) 1.82
Nausea	19 (25.33%)	17 (22.66%)
Vomiting	0	4 (5.35)
Dry mouth	33 (44%)	18 (24%)

Efficacy Measures

Pain Intensity Score (Single Dose)

The primary efficacy criterion was pain relief. For both active groups, Pain Scores of intravenous acetaminophen were higher than those of fentanyl group with significant difference between the two active groups ($P< 0.05$).

The pain score in acetaminophen group was 2.410 (+/-) 1.30 as compared to fentanyl group which was 1.625 (+/-) 1.13 which was much lower as compared to previous group. In general, response was better in fentanyl group than acetaminophen group which was statistically significant. Moreover the fentanyl group responded to pain relief faster and for a prolonged period than the paracetamol IV group. Post operatively, three days observation showed that the pain was almost minimal in the opiod group . Paracetamol IV patients complained of lingering pain despite the continuous IV infusion of the medicine.

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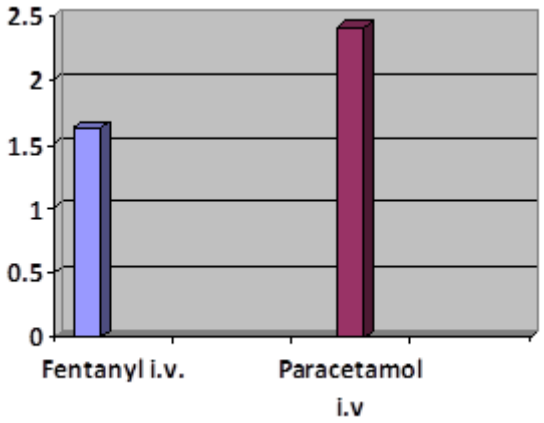

Figure 1: Average pain score of both active groups after single dose administration and 4 hour.

Quality of Recovery Score (QoR Score)

Second end point of study was quality of recovery after surgery. The aim of the analgesic technique should be not only to lower pain scores, but more importantly to facilitate earlier mobilization and rehabilitation by reducing complications after discharge. The QoR score was 15.78 (+/-) 1.68 in fentanyl group which was higher as compared to 15.21 (+/-) 1.82 in Paracetamol group. In general there was difference in quality of recovery after surgery but it was not statistically significant.

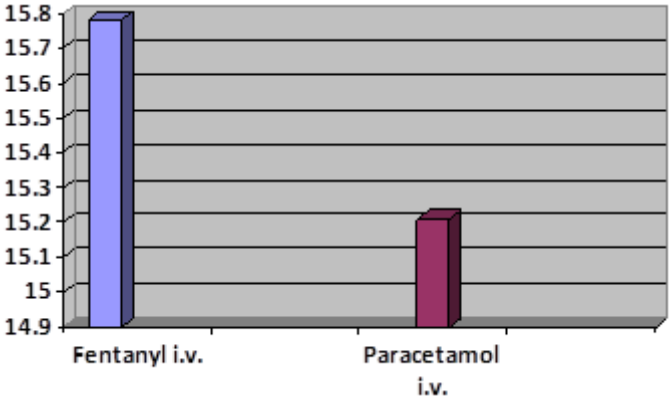

Figure 2: Average QoR score of both active groups after single dose administration and 4 hour.

At different age, pharmacokinetics and pharmacodynamics of drugs changes and hence efficacy of drug also changes. Below table shows the age wise classification of average pain score of drugs in both the active groups.

Age	Fentanyl group (n=75)	Acetaminophen group (n=75)
18-30	1.16	2.33
31-45	1.85	2.35
46-60	1.56	2.06
61-75	1.85	2.86

Safety Assessments

Age	Fentanyl group (n=75)	Acetaminophen group (n=75)
18-30	1.2	2.0
31-45	1.66	2.09
46-60	1.77	2.05
61-75	1.65	2.15

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Continuous monitoring on Day1, Day 2 Day 3/Day 4 based on pain scores

Side-effects were closely monitored during study and nausea, vomiting and dry mouth were reported. 19 patients (25.33%) reported Nausea in Fentanyl group as compared to 17 patients (22.66%) in Acetaminophen group.

4 patients (5.33%) reported vomiting in Acetaminophen group and no Vomiting reported in fentanyl group.

Dry mouth was the major concern in this study and it was frequently reported. 33 patients (44.0%) reported dry mouth in Fentanyl group whereas 18 patients (24.00%) reported dry mouth in Paracetamol group.

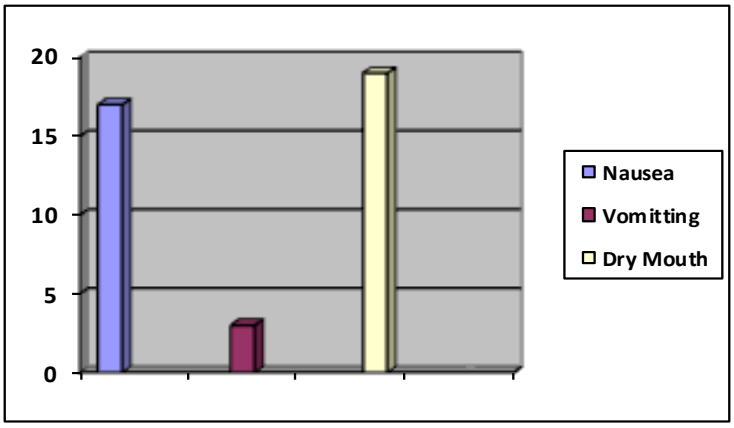

Figure 3

CONCLUSIONS

It was observed that the use of paracetamol intravenous as an analgesic was effectively better but not as good as Fentanyl. It can be preemptively suggested that post operatively Fentanyl can be given to alleviate pain for a short period of 2 days and the patient can then be weaned to paracetamol IV. This can reduce the sedatory effects and drowsiness observed due to the Opiod analgesic Fenatnyl. Otherwise the pain coefficient score was better on fentanyl usage compared to a 1 gm IV of Paracetamol 3 times a day. Both the medicines can be effectively used in combination.

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