A Pre Induction Administration of One Gram Oral or Intravenous Acetaminophen in Control of Post-Operative Pain: A Comparative Study

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ABSTRACT

Introduction: Post operative pain after surgery is a cause of significant morbidity and patient dissatisfaction. In this study we try to compare efficacy between 1 gram acetaminophen oral dose with 1 gram acetaminophen intravenous dose in controlling post operative pain.

Material and methods: This study is a prospective, randomized and comparative study conducted at NRI institute of medical sciences, Visakhapatnam between Oct 2016 to October 2017. 90 patients belonging to ASA status I and II of both genders, age group- 18 to 60 years and undergoing surgeries under general anaesthesia lasting less than 2 hours were enrolled for the study. 2 groups out of which Group A received 1gm oral paracetamol and Group B received 1gm intravenous paracetamol. The grous were compared post operatively for pain scores at 30, 60, 90, 120, 150 minute after surgery using visual analogua scale(VAS)

Results: The mean VAS scores were 2.78, 4.07, 5.81, 6.36, 6.5 for Group A and 2.18, 3.5, 4.76, 6.04, 6.43 for Group B. Thus pain scores were consistently lesser in Group B than Group A. Pain scores were significantly lower in Group B during the time period 30 mins and 90 mins (p values 0.039 and 0.002 respectively). The time of first rescue analgesia (i.e, Fentanyl) was compared in both the groups. Mean for time of demand for analgesia was 88.67 mins and 102 mins in Group A and Group B respectively. P value was 0.05 thus a significantly earlier requirement of rescue analgesia in Group A.

Conclusion: The rescue analgesic requirement was significantly lesser in intravenous acetaminophen group. Hence 1gm intravenous paracetamol is superior to oral formulation in controlling post operative pain.

Keywords: One Gram Oral or Intravenous Acetaminophen, Post-Operative Pain

INTRODUCTION

In a vast country like India which has a major population surviving below poverty line, the cost of drugs selected plays a vital role in any doctor's practice. Acetaminophen is one of the cheapest, safest and widely used analgesics used since a long time with a proven safety profile. It has been available in many formulations including oral, rectal, suspension. The intravenous formulation was only recently approved by US FDA in the year 2010 (Ofirmev manufactured by Cadence pharmaceuticals). Adequate control of the postoperative pain plays an important role in perioperative management because, beyond the fear for the outcome of surgery, the main concern of patients is related to post-operative pain's intensity, which is often perceived as the most unpleasant event of the surgical act. Along with the thromboembolic or pulmonary complications from inadequate pain management and impaired quality of life, surgical tissue damage can cause long-term alteration of central processing of spinal nociceptive information, and this fact can cause hyperalgesia. This can induce amplification hence post-operative pain management forms an important component in an anaesthetists' routine work. Out of the different pharmacological methods for pain control, Paracetamol is one of the oldest and safest drug used. Intravenous formulation has been introduced recently and is quite costly compared to the oral formulation. Here in this study we wish to compare the efficacy in between the two in controlling post-operative pain after general anaesthesia for short duration surgeries.[1-5]

Study aimed to compare the efficacy of 1 gram acetaminophen oral dose with 1 gram acetaminophen intravenous dose, to estimate whether oral route acetaminophen is effective in controlling post operative pain and to compare the pain scores for oral and intravenous acetaminophen at each time intervals.

MATERIAL AND METHODS

Study was conducted on patients admitted to NRI Medical College Hospital, Visakhapatnam who were admitted during the period of October 2016 to October 2017, undergoing surgeries that last for less than 2 hours under general anaesthesia. This study is a prospective, randomized and comparative study. Randomization was done using '*Sealed opaque envelope system'*. Inclusion Criteria: 90 patients belonging to ASA status I and II of both genders, Age group- 18 to 60 years, Patients undergoing surgeries under general anaesthesia lasting less than 2 hours. Exclusion Criteria: Patients on chronic analgesic therapy, Pregnant or lactating patients, Patients with impaired liver function tests, Patients suffering from nausea/ vomiting, Patients with known allergy to Acetaminophen will be excluded from study. Patients were randomly allocated to 2 groups, 45 patients

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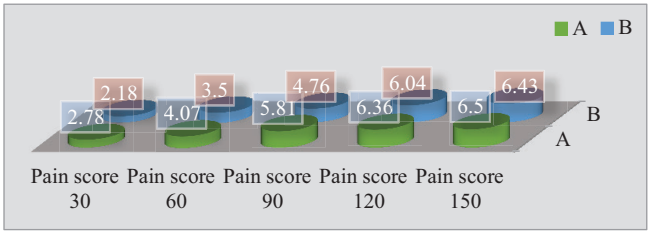
in each group using closed envelope randomization: Group A: Acetaminophen 1 gram oral. Group B: Acetaminophen 1 gram intravenous infusion. Pre-anaesthetic evaluation: A thorough evaluation was done prior to the day of surgery. Consent was taken. Patient was explained about the Visual analogue scale and its use post operatively. On the night before surgery, patient would be given: 1mg Lorazepam and 150mg Ranitidine tablet on the night before surgery. Patient was to be kept nil per orally for 8hours. On the day of surgery: Oral acetaminophen was administered 2 hours and intravenous dose was given 30 mins before induction of anaesthesia. In the operation theatre Blood Pressure (B.P.), Heart rate (HR), Oxyhaemoglobin saturation (SPO_2) monitors connected. Preoxygenation was done. Induction of anaesthesia using: Fentanyl 1mcg/kg, Propofol 2mg/kg, Vecuronium 0.1mg/kg, Controlled ventilation using N2O:O2 70:30 with Isoflurane. The following data was collected post operatively: a) The 11 point, 100 mm *Visual Analogue Scale* for pain assessment at 30, 60, 90, 120 and 150 minutes. b) The *average time of first rescue analgesic.*

STATISTICAL ANALYSIS

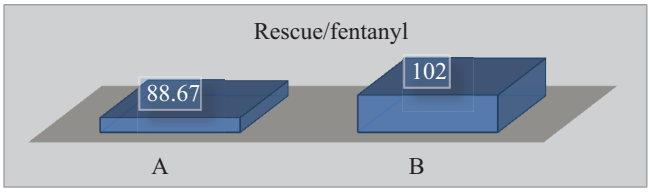
Statistical analysis was done using SPSS (Statistical Package For Social Sciences) version 19. Quantitative data was calculated using *student t test* and qualitative test was done using *Chi square test.*

RESULTS

The confounding factors like age, sex and weight were compared to rule out any significant impact on the study. The mean age in Group A was found to be 37.33 years and that of Group B was found to be 36.04 years. The *p value* was 0.471 implying no significant difference. The mean weights in the groups were found to be 60.29 kgs and 62.58 kgs in Group A and Group B respectively. The *p value* was found to be 0.277 hence the groups were comparable. Pain scores were compared for each time period and it was found that pain scores were lower at each time period in Group A compared to Group B. The mean VAS scores were 2.78, 4.07, 5.81, 6.36, 6.5 for Group A and 2.18, 3.5, 4.76, 6.04, 6.43 for Group B (graph-1). Thus pain scores were consistently lesser in Group B than Group A. Pain scores were significantly lower in Group B during the time period 30 mins and 90 mins (*p values* 0.039 and 0.002 respectively). The time of first rescue analgesia (i.e, Fentanyl) was compared in both the groups. Mean for time of demand for analgesia was *88.67 mins* and *102 mins* in Group A and Group B respectively. P value was 0.05 thus a significantly earlier requirement of rescue analgesia in Group A (graph-2).



Graph-1: Mean VAS Score



Graph-2: Rescue Analgesics (Time)

DISCUSSION

This study evaluated the comparative efficacy between a one gram oral acetaminophen dose to a one gram intravenous acetaminophen before induction of general anaesthesia in patients undergoing surgeries lasting less than 2 hours. We evaluated results from 90 patients with 45 patients in each group. Both the groups were comparable in terms of age, sex, weight distribution. Comparison of time of injection of Fentanyl post operatively: The time of first rescue analgesia was compared in both the groups. Mean for time of demand for analgesia was 88.67 mins and 102 mins in Group A and Group B respectively. P value was 0.05 thus a significantly earlier requirement of rescue analgesia in Group A. Comparison of pain scores at each time period: Pain scores were lower in each time period for intravenous acetaminophen group compared to the oral group. Pain score was significantly lower at 30 min and 90 min with p values 0.039 and 0.002 respectively. At 150 min the difference was minimal. This finding also correlates with another study where they found that the difference between intravenous and oral groups was less marked after 150 minutes but the intravenous preparation gave higher plasma concentrations throughout the study period.[1] Various other studies have evaluated the efficacy of acetaminophen in various types of surgeries. In a study comparing intravenous acetaminophen as a method of intrapartum analgesia and they observed that acetaminophen is a safe and effective drug that can also be used in intrapartum period.[2] Majumdar S et al[3] in 2014 conducted a prospective, double-blinded, and randomized-controlled study to compare the efficacy of preoperative 1g intravenous acetaminophen with placebo in providing postoperative analgesia in head-neck cancer surgery. They also observed that patients getting acetaminophen 1g had a shorter stay in SICU and hospital stay. In patients undergoing lumbar discectomy post-operative pain was adequately controlled by starting intravenous acetaminophen 20 minutes before start of surgery.[4] In patients undergoing total abdominal hysterectomy it was concluded that a pre-emptive intravenous dose of 1 gm provides good quality of post-operative analgesia and results in a decreased consumption of morphine.[5] In This study also we found that intravenous formulation was better overall in post-operative pain scores. This result may be because of a lower loading dose taken for oral paracetamol. It has been suggested that a 2 gm loading dose of oral paracetamol gives comparable plasma concentrations to 1 gm intravenous formulation.[6] Holmer Pettersson PH, Owall A, Jakobsson J in 2004 compared the plasma concentration of three acetaminophen drug dosages.[7]

They compared plasma concentrations after 1 gm oral, 2 gm oral and 1 gm intravenous acetaminophen. They found that within 40 minutes intravenous group gave a mean plasma concentration of 85 µmol/l. After oral administration, there were huge inter-individual differences at all time points studied. At 80 min after oral acetaminophen the median plasma concentrations were 36 and 129 µmol/l for the 1- and 2-g groups, respectively. But in another study conducted by Silvanto M et al found that 3 gm iv paracetamol loading dose has significant side effects and is not advisable as a routine recommendation. So 2 gm oral paracetamol can be considered as the higher limit of a safe dose.

Acetaminophen exhibits some special differentiating features from both NSAIDS and Opioids. Unlike NSAIDS it is ineffective in inflammatory and intense pain and doesn't produce any cardio-renal or gastrointestinal side effects and compared to opioids it is ineffective in pain arising from smooth muscle spasm or hollow viscus, it doesn't have any depressant action on respiration. Acetaminophen exhibits antipyretic action as well and is widely used for this property. Acetaminophen is able to inhibit Cyclooxygenase (COX) but only if peroxide concentration is low which is the reason why acetaminophen is inactive in inflammatory conditions where peroxide concentrations are high but remains active in brain owing to low levels of peroxides.[8] Acetaminophen is a weak inhibitor of Prostaglandin synthetase in brain which plays a major role in its antipyretic action. Studies have suggested that Acetaminophen is an inhibitor of COX-3 which is a splice variant of COX-1. This may be the mechanism by which it causes analgesia and hypothermia.[9] But recent data shows that COX-3 is more active in canines than humans thus a definitive correlation is still lacking. Acetaminophen also acts by activation of spinal serotoninergic descending projections, involved in the analgesic effect of acetaminophen.[10] Spinal and supraspinal analgesia induced by high doses of acetaminophen involves brain opioid systems.[11] Acetaminophen-induced analgesia in rats is associated with a decrease of dynorphin A levels in the frontal cortex, and is prevented by blockade of k-opioid receptors. Other suggested mechanisms of action of acetaminophen have included inhibition of nitric oxide generation[11] and of hyperalgesia induced by either N-methyl-D-aspartate or substance P.[12] Acetaminophen bears a striking resemblance to the fatty acid amide N-arachidonoylphenolamine (AM404). AM404 is a potent activator of vanilloid subtype 1 receptors (TRPV1)[13], and an inhibitor of the anandamide uptake into cells (anandamide membrane transporter, AMT), which leads to increased levels of endogenous cannabinoids. It was shown that Acetaminophen on deacetylation forms p-aminophenol which on conjugation with Arachidonic acid in brain and spinal cord forms AM404. The enzyme involved is Fatty acid amide hydrolase. Thus, increased cannabinoids decrease the body temperature as well as analgesia. It was shown that a CB1 receptor antagonist, at a dose level that completely prevents the analgesic activity of a selective CB1 receptor agonist also completely prevents the analgesic activity of acetaminophen. The adult oral doses of acetaminophen for the treatment of pain or fever are 650-1000 mg every 4 hours, up to a recommended maximum daily dose of 4 g. The pediatric oral doses are 10-15 mg/kg/dose every 4-6 h, up to a maximum of 5doses/day. The time to peak concentration is approximately 45-60 min after oral administration.[14] Liquid acetaminophen (drops, syrup) has a time to peak of about 30 min.[14] Peak concentrations of acetaminophen after recommended oral doses range from 8 to 32 µg/mL. Food reduced the maximum concentration of oral acetaminophen by 49% hence acetaminophen should not be taken with food or after a meal, especially if high in carbohydrates.[15] Acetaminophen is subjected to a first-pass metabolism, with hepatic extraction ratio of 0.11-0.37 in adults, thus the oral bioavailability is 60-89% and the absorption half-life is 4.5 min with no lag time Intravenous: The time course of action is quick with iv Acetaminophen as it reaches peak concentration as soon as infusion is complete (about 15 minutes).[16] The analgesic effect starts within 5 minutes, peaks at 1 hour and lasts 4 to 6 hours. This is consistent with a plasma half-life of 2.7 hours - i.e. about two half-lives. The antipyrexial activity lasts 6 hours. Rectal: The absorption from the rectal route of administration is erratic and unpredictable[17], with reported values of bioavailability ranging from 24 to 98% 36 the mean absorption half-life is 35 min with 40 min lag time. The time to peak plasma concentration ranges from 107 to 288 min after rectal administration. A rectal dose of 45 mg/kg has been reported to produce in children a mean peak plasma concentration of 13 µg/mL[18] which is comparable with that obtained with an oral dose of 10-15mg/kg.[19] At plasma concentrations of less than 60 µg/mL, acetaminophen does not apparently bind to plasma proteins; at 90 µg/mL protein binding is less than 5%; after toxic doses, with plasma concentrations of up to 250 µg/mL, protein binding varies from 8 to 43% with no correlation between binding and plasma acetaminophen concentration.[20] The volume of distribution is 1 to 2 L/kg in adults and 0.7 to 1 L/kg in children.[21] Acetaminophen is uniformly distributed throughout most body fluids, freely crosses the placenta and penetrates the blood-brain barrier. In adults, the majority (approximately 90%) of acetaminophen is conjugated with glucuronide (40-67%) and, to a lesser extent (20-46%), with sulphate or cysteine (3%)[22] to form inactive and harmless metabolites. In premature infants, newborns, and young infants, the majority of acetaminophen is conjugated with sulphate. A fraction usually ranging from 5 to 15% is oxidized by CYP2E1, CYP1A2, CYP3A4, and CYP2A6 subfamilies of the P450 mixed-function oxidase system, resulting in the formation of the highly reactive N-acetyl-p-benzoquinoneimine (NAPQI)41. Glutathione quickly combines with this intermediate, and the resulting complex is then converted to non-toxic cysteine or mercaptate conjugates, which are eliminated in urine. In the overdose situation, when the sulphate and glucuronide stores are saturated, a large percent of the dose is oxidized to cysteine and mercapturic acid conjugates. Only 1 to 4% of acetaminophen is excreted unchanged in the urine. The metabolic products are excreted mainly by the kidney. The

urinary clearance of acetaminophen Is 13.5 L/h. Formation of oxidative metabolites and renal excretion follow first-order kinetics (i.e., elimination rate is concentration-dependent); the conjugation of sulphate and glucuronide metabolites follows Michaelis-Menten kinetics (combined zero- and first-order). Elimination occurs almost entirely through the kidneys. As a moderately lipid soluble weak organic acid, acetaminophen undergoes glomerular filtration with subsequent extensive tubular reabsorption, whereas the highly polar glucuronide and sulphate conjugates are actively secreted by the tubules.

CONCLUSION

1. There was statistical difference in mean VAS scores at 30 and 90 minutes interval with p values 0.039 and 0.002. So intravenous acetaminophen being more efficacious than oral acetaminophen.
2. The rescue analgesic requirement was significantly lesser in intravenous acetaminophen group.
3. The oral group patients demanded for rescue analgesic by 88.67 minutes whereas the intravenous group demanded at 102 minutes.
4. Efficacy of intravenous paracetamol was insignificant at 150 minutes hence both oral and intravenous groups were comparable at 150 minutes.
5. Thus the average duration of analgesia was 89 -102 minutes for acetaminophen in the post-operative period for oral and intravenous groups respectively.

We conclude that a 1gram oral paracetamol is inferior to 1gram IV paracetamol in controlling post operative pain. As a further continuation to this study we propose a study to evaluate the efficacy of 2gm oral paracetamol compared to the 1gram IV paracetamol.

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