Journal of Chemical Health Risks

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JCHR (2024) 14(4), 1574-1580 | ISSN:2251-6727

A Randomised Comparative Study on the Effect of Pre-Emptive Intravenous Acetaminophen on Intraoperative Opioid Requirement in Superficial Oncological Surgeries

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(Received: 14 April 2024 Revised: 1 May 2024 Accepted: 18 June 2024)

KEYWORDS
Acetaminophen, Fentanyl, surgical pleth index (SPI), Opioid free anaesthesia (OFA), emergence, extubation.

ABSTRACT:

Background- Balanced anaesthesia for any surgery is usually achieved with the usage of Opioids peri and post-operatively for maintenance of good analgesia. Opioid-free anaesthesia (OFA) is a ground-breaking approach in the field of anaesthesia that aims to minimize or completely eliminate the use of Opioids during surgical procedures and post-operative pain management. There are limited studies related to intravenous Acetaminophen as a part of OFA. In this study, a comparison was made on the effect of pre-emptive analgesia with intravenous Acetaminophen given before the surgical stimulus versus pre-medication of intravenous Fentanyl on peri-operative and total intra-operative Fentanyl consumption in superficial oncological surgeries.

Materials and Methods- This was a randomised double-blinded study. 60 ASA physical status class I, II or III patients posted for elective thyroid and breast surgeries under general anaesthesia were recruited and randomly divided into 2 groups of 30 each with group A receiving intravenous Paracetamol 15mg/kg (1 gram/100 ml) 15 minutes before shifting to operation theatre and group B receiving 100 ml of 0.9 % normal saline with Fentanyl 1 mcg/kg. In the operating room, baseline heart rate (HR), mean arterial pressure (MAP) and surgical pleth index (SPI) were recorded. All the patients were then given standard general anaesthesia. HR, MAP and SPI was monitored until the end of surgery. Patients in both the groups received 0.5 mcg/kg bolus doses of Fentanyl if SPI value was above 50 and HR or MAP were more than 20% of baseline. A time interval of 20 minutes was maintained between the boluses and the number of doses were noted. Total amount of Fentanyl administered intra and peri-operatively, emergence time and extubation time were the parameters observed.

Results- Intra-operative requirement of Fentanyl was higher in group A, total consumption of Fentanyl was significantly higher in group B, the emergence time and extubation time were lesser in group A.

Conclusion- Intravenous Acetaminophen given to patients as pre-emptive analgesia did require intra-operative dose of intravenous Fentanyl but the total consumption of Fentanyl was

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JCHR (2024) 14(4), 1574-1580 | ISSN:2251-6727

significantly low, the patients had lesser emergence and extubation time when compared to intravenous Fentanyl as pre-medication.

Introduction

Balanced anaesthesia relies on the administration of Opioids in the perioperative period for analgesia. The clinical consequences of rampant use of intraoperative Opioids, is known to delay recovery, cause respiratory depression, urinary retention and post-operative nausea and vomiting[(1)]. Similarly, high doses of Opioids during surgery are associated with an increased perception of pain, known as hyperalgesia[(2)] and increased post-operative Opioid requirements, a phenomenon also known as the "Opioid Paradox", rendering the patient Opioid dependant for a longer period.[(1)] Therefore, Opioid-free anaesthesia (OFA)[(3,4,5,6,7)], or a combination of various Opioid-sparing techniques leading to no or reduced administration of intra-operative systemic Opioids is gaining popularity as an area of upcoming research. One key aspect of OFA involves the use of non-Opioid medications. Nonsteroidal anti-inflammatory drugs (NSAIDs) and Acetaminophen are commonly utilized to manage pain before, during and after surgery. These medications can be administered orally, intravenously, or even as part of a pre-emptive analgesic regimen. By targeting different pain pathways, these medications can help reduce the need for Opioids and provide a more comprehensive pain management approach.[(15)]

Pre-emptive intravenous Paracetamol or Acetaminophen has been used before in some studies and has been shown to reduce post-operative rescue analgesic requirement[(8,9,10)]. However, its use in reducing intraoperative requirement of Opioids has not been studied much, but still there are studies showing that it helps in decreasing the peri-operative opioid requirements too[(11,12)]. Similar findings have been reported in studies involving patients undergoing abdominal surgery[(13)], gynaecological procedures[(14)], and cardiac surgery . One of the main advantage of it is its safety profile and it being generally well tolerated by all.[(15)] One should be very careful about the contraindication for Acetaminophen administration like hepatic failure.[(16)]

In the present study, pre-emptive intravenous Acetaminophen was compared to intravenous Fentanyl as pre-medication in intraoperative Opioid requirement by analysing the effectiveness of intravenous Paracetamol (Acetaminophen) given before surgical incision in reducing SPI[(17)],HR and BP guided by intraoperative Fentanyl requirement, total Fentanyl used peri-operatively and on the time required for emergence and extubation (recovery profile).

Materials and Methods

This was a prospective double-blinded randomized controlled study.

Inclusion Criteria

Patients belonging to

- ASA grades 1 to 3
- Aged between 18 to 60 years
- Belonging to both the genders
- Undergoing elective thyroid and breast surgeries

Exclusion Criteria

Patients with

- ASA grade 4 or above
- Blood Urea Nitrogen (BUN) > 40mg/dl, or Serum Creatinine > 2.0 mg/dl
- Patient with known coagulopathy or nephropathy
- History of allergy to Paracetamol or Opioids
- Patient with uncontrolled hypertension, Diabetes mellitus or cardiac disorders
- Patient on regular use of sedatives, abuse substances, alcohol addiction or antipsychotics
- Patients on Opioids of any kind for pain relief

Post Inclusion Exclusion Criteria

- Intraoperative haemodynamic event

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- Intraoperative decision to electively ventilate the patient
- Duration of surgery more than four hours

Sample Size

The parameter, mean postoperative opioid consumption, in a similar study, carried out by Ozmete et al in 2016, in 60 patients posted for Caesarean section[9] was used for sample size calculation. The statistical software G*Power 3.1.9.2 (Universistat , Dusseldorf, Germany) was used for the same. ANOVA test was used for repeated measures within the factors. For effect size of 0.2, α-error probability of 0.05, and power (1-β error) of 0.95, a total of 60 patients were recruited as Sample size for the study.

Study Groups

- Group A (n=30) : patients received 15 mg/kg Paracetamol IV bolus (1 gram/100 ml) 15 minutes before surgical incision in the pre-operative holding area.
- Group B (n=30) : patients received 1mcg/kg Fentanyl in 100ml 0.9% normal saline in the preoperative holding area.

Methodology

After Institutional Ethical Committee approval, 60 ASA physical status class I to III patients posted for elective thyroid and breast surgeries under general anaesthesia were recruited for the study. After routine pre-anaesthetic check-up and implementation of exclusion and inclusion criteria, patients' willingness to participate in the study was taken in the form of a written informed consent. The patients were explained in detail about the study procedure in their own language. In the pre-operative holding area, the fasting status and informed consent were confirmed. As per randomization, group A patients received intravenous Paracetamol 15mg/kg (1 gram/100 ml) 15 minutes before shifting to the operation theatre and group B received 100 ml of 0.9% normal saline with Fentanyl 1mcg/kg in a double blinded manner. In the operating room, the patients were connected to the monitors and baseline heart rate (HR), mean arterial blood pressure (MAP) and surgical pleth index (SPI) were recorded. The patients were pre-oxygenated with 100% Oxygen for 3 minutes. They were induced with Injection Propofol 1-2mg/kg until loss of verbal response followed by Injection Atracurium 0.5mg/kg. They were intubated at the end of 3 minutes, anaesthesia was maintained with Sevoflurane 2 MAC with fresh gas flow of 4 litres per minute (Oxygen and air) and intermittent boluses of Injection Atracurium. Patients in both the groups received 0.5mcg/kg bolus doses of Fentanyl if SPI value was above 50 and either HR or MAP was more than 20 % of baseline. A time interval of 20 minutes was maintained between the boluses and number of such boluses was noted. When the skin closure was completed, Sevoflurane was stopped and gas flows were increased to 8 litres and the time was noted. Patients were reversed with Injection Neostigmine and Injection Glycopyrrolate and thereafter extubated when response to verbal commands was satisfactory with regular respiration generating adequate tidal volume was noticed ensuring complete reversal of neuromuscular blockade. The parameters observed were:

- Total amount of Fentanyl administered intra-operatively and peri-operatively.
- Time taken from stoppage of Sevoflurane to eye opening on verbal command in minutes in each case as emergence time.
- Time taken from stoppage of Sevoflurane to extubation in minutes in each case as extubation time.

Statistical Analysis

The collected numerical data was entered in to excel worksheet and was analysed using SPSS software version 20.0. The statistical test employed was the Student's t-test between the two groups, the p-value was obtained and was made into double plotted graphs. A p value of less than 0.05 was considered significant. Categorical data was analysed with chi-square test for statistical significance.

Observations

Table 1: Demographic Variables

PARAMETERS	Group A (n=30)	Group B (n=30)	p value
AGE (yrs)	43.97±13.03	46.2±11.6	0.53
SEX (M/F)	7M/23F	6M/24f	0.75

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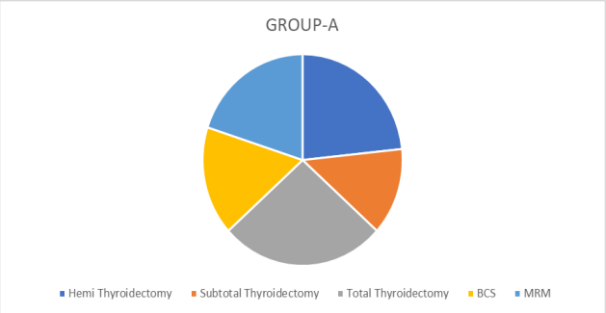
HEIGHT (cm)	161±5.41	163.37±5.41	0.73
WEIGHT (kg)	62.3±9.4	61.0±6.7	0.60

Age, sex, height and weight were indicated as Mean ± SD (Standard deviation)

All the participants were comparable on the ground of age, sex, height, weight.



BCS-Breast conversation surgery, MRM-Modified Radical Mastectomy

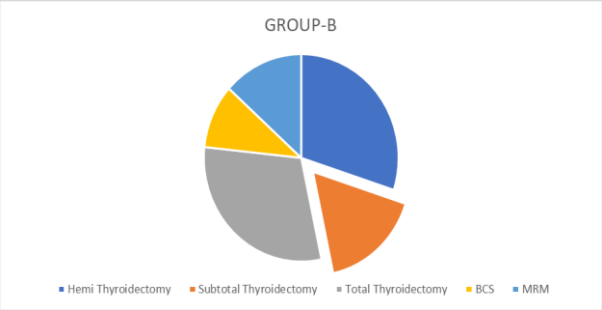


Figure 1 showing pie-chart distribution of surgeries in both groups

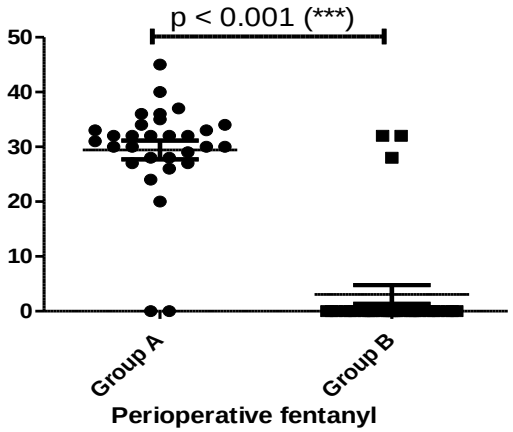
Both groups had comparable number of different types of surgeries.

Table – 2: Comparing Intra-Operative Fentanyl Consumption In Both Groups (In Mcg)

Group A	Group B	p-value
33.63 ± 15.3	3 ± 9.168	<0.001

There was a significant difference in perioperative consumption of Fentanyl which was more in group A compared to group B.

GRAPH - 1



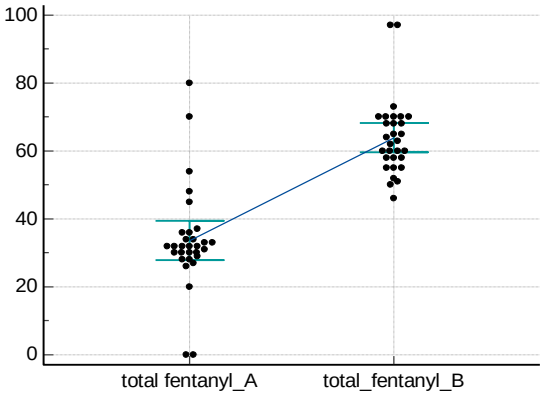
The above graph is a Dot-Plot graph showing group A had to be given perioperative Fentanyl doses in most of the cases when compared to group B, hence comparison was statistically significant.

Table – 3: Comparing Total Peri-Operative Fentanyl Consumption In Both Groups (In Mcg)

Group A	Group B	p value
33.63 ± 15.3	63.33 ± 11.35	<0.001

There was more total peri-operative Fentanyl consumption in group B than in group A. The patients in group A received 0.5 mcg/kg of Fentanyl boluses in the intraoperative period whereas the group B received 1 mcg/kg of dose prior to induction along with bolus requirements.

GRAPH – 2



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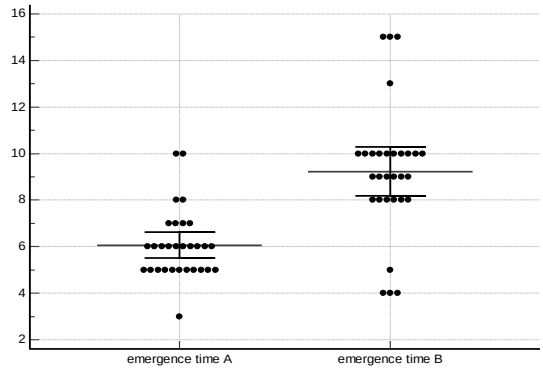
The above graph is a Dot-Plot graph showing group B had consumed more Fentanyl in comparison with group A. The p- value obtained was less than 0.001, hence significant.

Table – 4: Comparison Of Emergence Time In Both Groups (In Minutes)

Group A	Group B	p value
6.07 ± 1.48	9.23±2.81	<0.001

There was a significant delayed emergence in group B. Since the total Fentanyl consumption (Table – 3) was higher in group B when compared to group A, this might be the reason for delayed emergence.

GRAPH - 3



The above graph is a Dot-plot graph comparing the emergence time in both group A and B, showing group B had delayed emergence time.

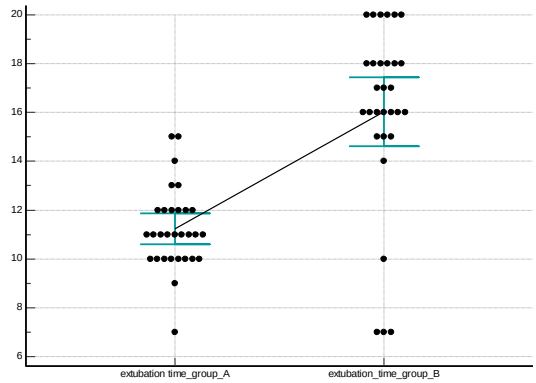
The p value came out to be below 0.001 and hence the comparison was significant.

Table – 5: Comparison of Extubation Time In Both Groups (In Minutes)

Group A	Group B	p value
11.23 ± 1.67 min	16.03 ± 3.75 min	<0.001

The extubation time was delayed in group B. The total Fentanyl consumption (Table - 3) was higher in group B than group A which could have prolonged the extubation time.

GRAPH - 4



The above graph is a Dot-plot graph comparing the extubation time in groups A and B, with most of the patients in group A having lesser extubation time. Statistical analysis obtained a p value of less than 0.001 which was hence significant.

Discussion

The study was performed primarily on superficial oncological procedures like breast tumours and thyroid swelling removals, etc. Participants in both the groups were comparable for age, sex, height and weight. OFA [3,4,5,6,7] is indeed an innovative approach aimed at reducing the use of Opioids during surgery and post-operative management. This innovative approach has gained momentum in recent years, driven concerns surrounding the Opioid epidemic and the desire to reduce the associated risks and complications of Opioid use, [1] including addiction, respiratory depression, and overdose. By relying on alternative pain management techniques and medications, OFA offers a safer and more effective way to control pain management techniques and medications. OFA offers a safer and more effective way to control pain while minimizing the potential for Opioid-related harm. [1,2]

The utilization of pre-emptive intravenous Acetaminophen as an analgesic adjunct in surgical settings has garnered significant attention in recent literature. Numerous studies have investigated the impact of pre-emptive intravenous Acetaminophen on intra-operative Opioid consumption, like the study by Chengluan et al in 2021[18] and the study by Dilek Memis et al in 2010[11]. This reduction in Opioid requirements aligns with the broader efforts to minimize Opioid exposure and its associated risks. The usual traditional

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balanced general anaesthesia involves the use of Opioid as a pre-medication as well as intra-operative Opioid boluses or as a maintenance infusion.

The current study findings of total consumption of Fentanyl were in line with the findings of Chengluan et al in 2021[18] which concluded that pre-emptive Acetaminophen administration significantly reduced the Opioid consumption within the initial 24 hours following general anaesthesia which was a meta-analysis of multiple RCT's.

The findings of emergence time and extubation time of the current study were similar to the findings of Dilek Memis et al in 2010[6] which concluded that pre-emptive intravenous Acetaminophen reduced extubation time and Opioid related adverse effects.

The findings of this study were also similar to the findings of Semihi Arici et al in 2009[19] which concluded that pre-emptive 1 gram of intravenous Acetaminophen was an effective post-operative analgesia in total abdominal hysterectomy and also reduced post-operative Morphine consumption.

The findings of this study were also in line with the findings of Mustafa Arslan et al in 2013[12] which concluded that the use of pre-emptive intravenous Acetaminophen reduced Opioid requirements, prolonged the duration to first need of analgesia and provided significant reduction in post-operative pain scores in cholecystectomy.

In one study by Christina Massoth et al in 2021[20] which was a randomized control trial on laparoscopic gynaecological surgeries, the results were contradicting to the current study, the study concluding that multimodal analgesia with Dexmedetomidine and Ketamine as a part of OFA did not reduce the post-operative requirement of analgesia and Morphine requirements. This could be probably attributed to short duration of action of Dexmedetomidine and Ketamine and probably the current study not involving laparoscopic surgeries to justify.

The current study population underwent thyroid and breast surgeries, but the results were in line with the results of most of the authors whose studies included different types of surgeries.

Results

- Intraoperative requirement of Fentanyl was higher in group A than group B.
- Total consumption of Fentanyl was significantly higher in group B compared to group A.
- The emergence time and extubation time were significantly lesser in group A compared to group B.

Conclusion

- Intravenous Acetaminophen given as pre-emptive analgesia does require intra-operative dose of intravenous Fentanyl but its total consumption of was significantly lower when compared to intravenous Fentanyl as pre-medication.
- Intravenous Acetaminophen given as pre-emptive analgesic has lesser emergence and extubation time when compared to intravenous Fentanyl as pre-medication.

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