



COMPARISON OF ACETAMINOPHEN AND NALBUPHINE IN ATTENUATING HEMODYNAMIC RESPONSE TO TRACHEAL INTUBATION.

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ABSTRACT: Laryngoscopy and tracheal intubation cause sympathetic overactivity in the form of increased heart rate and blood pressure, which may lead to deleterious effects. **Objectives:** The objective of this study was to compare the efficacy of acetaminophen and nalbuphine in attenuating hemodynamic response during tracheal intubation. **Study Design:** Randomized, double-blind clinical trial. **Setting:** Main operation theatre complex of Fauji Foundation Hospital Rawalpindi. **Period:** From August to December 2018. **Material & Methods:** After obtaining permission from the institutional ethical review committee of Fauji Foundation Hospital Rawalpindi. 60 Patients of ASA physical status I and II, aged 30 to 55 years, undergoing the abdominal surgical procedure of 1 to 3-hour duration were randomly divided into two groups. Patients in group N received nalbuphine hydrochloride 0.15 mg/kg body weight intravenously, 30 minutes before induction. Patients in group P received acetaminophen infusion (paracetamol) 15mg/kg body weight intravenously, 30 minutes before induction. Systolic and diastolic blood pressures were measured manually and heart rate by the pulse oximeter. Observations were made before giving analgesics, during induction, 1 minute after intubation, then at every 1- minute intervals till first 5 minutes, and thereafter at 10 minutes and at 15 minutes after intubation. The descriptive statistics of data were expressed as mean and standard deviation. Independent samples t-test was used for comparison of mean values of the variables in both groups. The value of $p < 0.05$ was considered as statistically significant. **Results:** There was a significant rise in heart rate and blood pressure after laryngoscopy and endotracheal intubation with acetaminophen (P group) as compared to the N group in which nalbuphine effectively reduced the tachycardia and hypertension. **Conclusion:** Acetaminophen has no significant effect on the prevention of hemodynamic changes due to intubation. Nalbuphine effectively reduces tachycardia and hypertension associated with laryngoscopy and endotracheal intubation.

Key words: Acetaminophen, Intubation Response, Nalbuphine, Tracheal Intubation

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INTRODUCTION

Laryngoscopy and orotracheal intubation can be associated with significant hemodynamic changes and adverse outcomes.¹ Various drugs like fentanyl, lignocaine etc. have been tried to prevent hemodynamic changes but each drug has its own limitations.^{2,3}

Opioids are important drugs in the management of attenuation of hemodynamic response during intubation. Use of opioids before induction of general anesthesia makes the intraoperative course smooth and decreases the intraoperative requirement of anesthetic agents.⁴

Nalbuphine, an ideal analgesic for use in balanced anesthesia because of its beneficial effects on cardiovascular stability and potential safety in over-dosage, which causes adverse effects like nausea, vomiting and at times respiratory depression.^{5,6}

Acetaminophen (Paracetamol) has been successfully used for management of postoperative pain in different types of operations.^{7,8}

Studies conducted in the past to assess the efficacy of acetaminophen in attenuating the

hemodynamic presser response^{9,10} found it to be efficacious. Acetaminophen has also been compared with local anesthetic agents like lidocaine.¹¹ but the literature search did not yield any comparison with the widely used opioid analgesics like nalbuphine.

Most opioid drugs like morphine, fentanyl and remifentanyl are not available in the majority of the hospitals of our country whereas nalbuphine and acetaminophen are easily available. Acetaminophen, a non-opioid analgesic, does not cause adverse effects associated with opioids such as respiratory depression, nausea and vomiting.^{7,8} Also, it has few contraindications and no significant drug interactions.¹²

Keeping in view a better profile of acetaminophen in regard to adverse effects, contraindications, and interactions with other drugs, we wanted to find out if it could be used instead of nalbuphine in attenuating the presser response during orotracheal intubation while administering general anaesthesia. This randomized clinical trial was conducted to compare both drugs with the hypothesis that acetaminophen is as effective in attenuating the hemodynamic response during tracheal intubation as nalbuphine. Variables studied in hemodynamic response were heart rate, systolic and diastolic blood pressure.

The objective of this study was to compare the efficacy of acetaminophen and nalbuphine in attenuating hemodynamic response during tracheal intubation.

MATERIAL AND METHODS

This was a randomized, double-blind, clinical trial carried out in Fauji Foundation Hospital Rawalpindi over a period of four months from August to November 2018. Permission from the institutional ethical review committee was obtained.

A detailed history was elicited and physical examination performed during pre-anesthesia assessment. Complete blood count, liver function tests, renal function tests, bleeding time, and clotting time were carried out before enrolling each

patient as a study subject. Patients in American Society of Anesthesiologists (ASA) physical Status I and II, 30 to 55 years of age, of either sex, with weight 40 to 75 kg, undergoing abdominal surgical procedures, with the expected surgical duration of 1 to 3 hours, were included in this study. Patients who were unwilling to participate in the study, patients with difficult intubation, or those with systemic diseases such as severe hypertension, ischemic heart disease, hepatic or renal disorder, patients on tricyclic inhibitors, pregnant and lactating females, those in obese range and those with chronic opioid therapy, and addiction to any drug or alcohol were excluded from the study.

Informed consent was obtained in writing on a structured proforma. Two groups namely Nalbuphine (N) group and Paracetamol (P) group were formed. Sample size calculated by WHO sample size calculator was 30 subjects in each group. Randomization was done by preparing 60 envelopes containing plan of the drug to be used for attenuation of hemodynamic response.

Half of them (n=30) were allocated nalbuphine and the other half (n=30) were allocated Paracetamol (acetaminophen) as the drug to be used. The envelopes were not labeled and one of the envelopes was selected randomly by the anaesthesiologist of the case. The drug was administered by the anaesthesiologist.

Hemodynamic parameters during and after tracheal intubation were recorded by an observer who was blinded to the preparation and administration of the study drug. Patients who received nalbuphine were included in Group N whereas those who received acetaminophen were included in Group P.

Independent variable in this study was the drug – nalbuphine or acetaminophen – used for attenuation of hemodynamic response during tracheal intubation. Dependent variables that were studied in both groups included heart rate, systolic blood pressure and diastolic blood pressure. Demographic variables were also recorded and compared for both groups. These

included age, gender, weight, ASA grade and duration of surgery in each patient.

After confirming adequate starvation period, all routine monitors including noninvasive blood pressure, pulseoximeter and ECG were attached to the patient. An 18 G intravenous catheter was secured in all patients.

No premedication was given and then according to the randomization, each patient was administered either nalbuphine hydrochloride 0.15 mg/kg or acetaminophen infusion 15mg/kg intravenously 30 minutes before induction. Systolic and diastolic blood pressure and heart rate were noted.

Patients were pre-oxygenated for 5 minutes. Systolic and diastolic blood pressure was noted manually and heart rate by pulse oximeter before giving analgesics. Thirty minutes after administration of analgesic drug, anesthesia was induced with propofol 2 mg/kg injection in titrated doses. Muscle relaxation was achieved with injection atracurium 0.5 mg/kg and all patients were manually ventilated with O₂:N₂O (50:50) for 3 minutes. Tracheal intubation was done under direct laryngoscopy by anesthesiologist. Systolic and diastolic blood pressure and heart rate were again noted at the time of induction, then at every 1-minute interval after intubation till first 5 minutes, and thereafter at 10 minutes and 15 minutes after intubation.

Anesthesia was maintained with O₂ and N₂O, isoflurane, atracurium and intermittent injection propofol so that blood pressure and heart rate should remain within 20% of baseline value. Injection ketorolac 30 mg was added to enhance the analgesia.

At the end of the surgery, isoflurane was tapered off gradually and after completion of the procedure and resumption of spontaneous respiration, anesthesia was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.008 mg/kg.

All patients were extubated after they resumed good muscle tone and respiration, their vital

parameters noted and then shifted to the postoperative care unit.

The descriptive statistics of data were expressed as mean and standard deviation. Independent samples t-test was used for comparison of mean values of the variables in both groups. The value of $p < 0.05$ was considered as statistically significant.

RESULTS

Groups N and P were comparable with respect to age, weight, gender ratio and ASA classification. They were also similar with respect to the type and duration of operative procedures Table-I.

Mean baseline heart rate measured after injecting analgesic drugs was less in N group as compared to the P group (Table-II).

There was an increase of heart rate after intubation initially in both groups as compared to heart rate taken at time of induction.

However, this was significantly higher ($p = .000$) with acetaminophen (P group) and remained significantly high for another 15 minutes as compared to those who received nalbuphine (N group) where heart rate remained near baseline.

Table-III shows systolic blood pressure at time of induction and changes after intubation.

There was an increase of systolic blood pressure after intubation initially in both groups, however, this was significantly higher in the group that received acetaminophen and remained significantly high for further 15 minutes as compared to nalbuphine group where systolic blood pressure remained near baseline.

Diastolic blood pressure after intubation showed no rise in N group but was raised in P group (Table-IV). The difference in means of both groups remained significant over the next 15 minutes ($p \leq .007$).

Variables	Group N Nalbuphine	Group P Acetaminophen	P-Value
Age in years (Mean \pm SD)	43.87 \pm 7.9	42.17 \pm 7.1	.385
Gender (Male/Female)	11 / 19	12 / 18	.791
Weight in kg (Mean \pm SD)	61.83 \pm 4.6	60.70 \pm 4.5	.341
ASA Grade (I/II)	23 / 7	25 / 7	.374
Duration of surgery (<90 mins / >90 mins)	16 / 14	18 / 12	.397

Table-I. Comparison of basic parameters in each group.

Time Interval	Mean Heart Rate \pm SD(bpm)		P-Value
	Group N (n=30)	Group P(n=30)	
Before analgesics	81.27 \pm 7.343	79.07 \pm 13.375	.433
During induction(30 min after analgesics)	72.13 \pm 4.812	87.87 \pm 12.159	.000
1 min after intubation	75.67 \pm 8.327	93.90 \pm 9.484	.000
2 min after intubation	76.40 \pm 7.677	98.47 \pm 9.794	.000
3 min after intubation	73.47 \pm 5.507	102.13 \pm 9.497	.000
4 min after intubation	70.77 \pm 5.624	101.20 \pm 11.112	.000
5 min after intubation	70.63 \pm 5.768	102.87 \pm 8.299	.000
10 min after intubation	69.57 \pm 5.661	105.40 \pm 8.224	.000
15 min after intubation	69.70 \pm 5.167	107.00 \pm 6.983	.000

*beats per minute

Table-II. Comparison of mean heart rate in both groups.

Time Interval	Mean Systolic BP \pm SD(mmHg)		P-Value
	Group N (n=30)	Group P(n=30)	
Before analgesics	129.17 \pm 9.105	124.83 \pm 15.227	.186
During induction (30 min after analgesics)	119.73 \pm 9.063	127.63 \pm 12.802	.008
1 min after intubation	122.83 \pm 10.642	131.83 \pm 12.831	.004
2 min after intubation	124.23 \pm 9.100	136.33 \pm 12.383	.000
3 min after intubation	119.93 \pm 8.038	132.43 \pm 15.167	.000
4 min after intubation	119.40 \pm 6.896	132.50 \pm 13.630	.000
5 min after intubation	119.00 \pm 7.240	131.17 \pm 14.062	.000
10 min after intubation	118.40 \pm 6.468	133.67 \pm 13.892	.000
15 min after intubation	116.50 \pm 5.894	136.17 \pm 13.814	.000

Table-III: Comparison of means of systolic BP in both groups.

Time Interval	Mean Diastolic BP \pm SD(mmHg)		P-Value
	Group N (n=30)	Group P(n=30)	
Before analgesics	78.43 \pm 5.823	76.97 \pm 10.005	.490
During induction (30 min after analgesics)	71.03 \pm 5.524	80.87 \pm 8.792	.000
1 min after intubation	76.20 \pm 8.075	85.53 \pm 10.494	.000
2 min after intubation	77.50 \pm 8.460	84.17 \pm 9.914	.007
3 min after intubation	73.13 \pm 6.976	84.63 \pm 10.391	.000
4 min after intubation	73.10 \pm 6.381	85.73 \pm 10.174	.000
5 min after intubation	68.93 \pm 6.767	86.57 \pm 11.038	.000
10 min after intubation	69.40 \pm 5.525	87.13 \pm 9.540	.000
15 min after intubation	69.03 \pm 4.529	89.50 \pm 7.847	.000

Table-IV. Comparison of means of diastolic BP in both groups.

DISCUSSION

Direct laryngoscopy involves stretching the oropharyngeal tissues in an attempt to straighten the angle between the mouth and the glottic opening, and this stretch can cause pain and trigger stress response.¹³ The plasma levels of sympathetic hormones like dopamine, adrenaline and noradrenaline could rise during laryngoscopy and endotracheal intubation. This results in a hemodynamic response that causes complications in high risk patients, leading to increased morbidity and mortality.¹⁴

In order to blunt the responses to endotracheal intubation, various drugs have been used such as lignocaine and opioids and non-narcotic analgesics.^{2,3} An ideal drug should be easily administered, have a rapid onset of action, relatively short duration of action, and be safe. Ideal drugs include fentanyl and alfentanil but unfortunately these drugs are unavailable in most hospitals in Pakistan. Nalbuphine, on the other hand, is easily available. It acts as an antagonist on μ receptors and an agonist on κ receptors. Its onset of action is between 2 to 3 minutes and the duration of action is 3 to 6 hours. There are minimal side effects in the dose of 0.2-0.4mg/kg and no deleterious effects on cardiovascular stability.^{4,6}

Another analgesic drug which is easily available is acetaminophen (paracetamol). Paracetamol has a well-established safety and analgesic profile.¹⁵ Its main mechanism of action is inhibition of cyclooxygenase enzyme which is responsible for the production of prostaglandins, an important mediator of inflammation, pain and fever. Its maximum recommended dose in adults is 4000 mg/day. Onset of action is within 5 to 10 minutes of administration and the duration of action is 4 to 6 hours.¹⁵

In this study we used paracetamol 15 mg/kg body weight in comparison with nalbuphine 0.15 mg/kg body weight to observe blunting of the hemodynamic response brought on by intubation. This results of this study show that acetaminophen is significantly less effective in blunting the hemodynamic response as

compared to nalbuphine. The hypothesis of this study therefore stands rejected. These findings are contrary to a double-blind, randomized study by Ayatollahi V et al that showed intravenous acetaminophen to be efficacious in blunting hemodynamic responses to tracheal intubation in comparison to placebo.⁹

KordValeshabad et al¹¹ in a study proved that paracetamol one hour prior to intubation attenuates heart rate response after laryngoscopy but is not effective to prevent acute alterations in blood pressure after intubation. Results of our study are not in conformity with their findings as we found acetaminophen to be ineffective in controlling hemodynamic response.

Opioid administration is not recommended in parturient patients undergoing cesarean section because of its depressant effects on the newborn. A placebo controlled trial conducted by Soltani G et al on these patients showed that acetaminophen reduced tachycardia in response to endotracheal intubation when used before induction but has no effect on rise in blood pressure.¹⁰ Our trial partially agrees with this study as it shows no significant blunting in rise of heart rate as well as blood pressure.

Kashif et al, in a study to evaluate the efficacy of intravenous paracetamol in the prevention of hemodynamic changes during intubation, reported that paracetamol probably has no role in preventing hemodynamic alterations due to intubation.¹⁶ These results compare favorably to those of our study in which administration of intravenous acetaminophen 30 minutes before surgical procedure has no significant effect on preventing hemodynamic changes at the time of endotracheal intubation.

The strength of our study is that it is the first randomized clinical trial to compare acetaminophen with nalbuphine, as an alternate pharmacologic agent to be used for blunting hemodynamic response to endotracheal intubation. We conclusively established that it does not compare in efficacy to nalbuphine for this purpose. The sample size (n=60) is relatively

small but is sufficient in evaluation of the research question and is comparable with previous studies on the subject. Further studies are recommended to compare other pharmacologic agents with opioids in order to find an effective alternate to opioids for attenuation of pressor response.

CONCLUSION

Acetaminophen has no significant effect on the prevention of hemodynamic changes due to intubation, as compared to nalbuphine which effectively reduces tachycardia and hypertension.



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AUTHORSHIP AND CONTRIBUTION DECLARATION

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3	Imran Haider	Helping in research work & collection of data.	
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