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Efficacy of Intravenous Paracetamol for Attenuating Hemodynamic Response to Laryngoscopy and Intubation: A Prospective Randomized Study

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Abstract

Background and Aims: Laryngoscopy and endotracheal intubation violate the patients' airway reflexes and cause intense sympathetic activity. Literature suggests that this deleterious response may be blunted by drugs. Opioids are most commonly used for this purpose. However, there is no consensus regarding the best drug and best route of administration. Therefore, there has been a growing trend to find an effective substitute to lower these side effects as much as possible. Paracetamol is a non-opioid analgesic with COX-2 selective inhibiting property. The main purpose of our study was to evaluate the effect of pre-operative intravenous paracetamol on hemodynamic response to laryngoscopy and endotracheal intubation. *Methods:* After Institutional Ethical Committee clearance, 160 patients of American Society of Anesthesiologists (ASA) Physical Status I and II were enrolled in the study and divided into two groups. Group A received 1 gm paracetamol infusion (Labelled A1) in 100 ml volume whereas Group B received 0.9% normal saline infusion (B1) in 100 ml volume Intravenously (I.V.) thirty minutes prior to induction over fifteen minutes. Standard general anesthesia techniques were used for both groups. The hemodynamics were recorded at baseline, before induction, after induction, before laryngoscopy, immediately after intubation and thereafter 1, 3, 5, 7 and 10 inutes following intubation. After 10 minutes of intubation, Group A received the infusion labeled A2 (0.9% Normal saline in 100 ml volume) whereas Group B received the infusion labeled B2 (paracetamol 1 gm in 100 ml volume) over 15 minutes. *Results:* Both groups were similar in terms of age, sex, height, weight, Mallampati scores and American Society of Anesthesiologists (ASA) physical status. After 1 minute of laryngoscopy and intubation, significant increase in the heart rate was seen in both the groups. ($p \leq 0.05$) in Group A, the increase in mean heart rate produced by laryngoscopy and intubation was not statistically significant at 3 mins ($p \geq 0.05$) and remained insignificant at 5, 7 and 10 minutes after intubation. However, in Group B the increase in mean heart rate produced by laryngoscopy and intubation was significantly high at 3 min ($p \leq 0.0001$) and remained significant at 5, 7 and 10 minutes after intubation. There was significant fall in SBP, DBP and MAP ($p \leq 0.05$) from baseline after induction, laryngoscopy and after 1 minute of intubation in both Group A and Group B but inter group comparisons at these time points were statistically insignificant ($p \geq 0.05$). *Conclusion:* Administration of paracetamol (1 gram), thirty minutes prior to induction of anesthesia could not totally blunt all the cardiovascular responses to laryngoscopy and intubation, but it did show better control of heart rate after intubation.

Keywords: Anesthesia; Laryngoscopy; Intubation; Paracetamol.

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Introduction

Laryngoscopy and endotracheal intubation violate the patients' airway reflexes and cause intense sympathetic activity which lead to tachycardia, hypertension and dysrhythmias.[1] These effects have been reported since 1950, during intubation under lighter plane of anesthesia, which may be further complicated by hypoxia, hypercapnia or cough.[2,3] This response may also have deleterious effect on patients with raised intracranial and intraocular tensions.

Hemodynamic stability is an integral and essential goal of any anesthetic management plan. Increase in blood pressure and heart rate occurs most commonly from reflex sympathetic activity in response to laryngotracheal stimulation, which in turn leads to increase plasma norepinephrine concentration.[4] Literature suggests that this deleterious response may be blunted by drugs with different mechanisms of action like lignocaine, glossopharyngeal and superior laryngeal nerve blocks, calcium channel blockers, beta blockers, combined alpha-beta blockers, alpha blockers, peripheral vasodilators, narcotics, oral gabapentine and magnesium sulphate.[5]

However, there is no consensus regarding the best drug and best route of administration. Although opioids are most commonly used drugs for prevention of hemodynamic responses to intubation, these drugs are not cost effective and have unfavorable effects like nausea, vomiting, sedation and respiratory depression.[6] Therefore, there has been a growing trend to find an effective substitute to lower these side effects as much as possible.[7,8]

Paracetamol is a non-opioid analgesic and is in clinical use for last hundred years.[9] Paracetamol is, on average, a weaker analgesic than NSAIDs or COX-2 selective inhibitors but is often preferred because of its better tolerance.[10] Intravenous paracetamol has an onset and peak effect of *15 minutes* or less and a duration of analgesic effect between *4* and *6 hours*.[11,12] Recently the prodrug of paracetamol has been shown to have blunting effect on hemodynamic response to laryngoscopy and intubation.[13]

However, there is limited data about the effects of I.V. paracetamol on hemodynamics.Therefore, the main purpose of our study was to evaluate the effect of pre-operative intravenous paracetamol on hemodynamic response to laryngoscopy and endotracheal intubation.

Materials and Methods

This study was conducted in our hospital after approval from institutional ethics committee and informed consent. We included 160 patients between *18 and 60 years* of age belonging to American Society of Anesthesiologists class I and II having Mallampati grade of either I or II who underwent elective non-cardiac surgeries requiring general anesthesia with endotracheal intubation. Patients with known hypertension, autonomic neuropathy, diabetes mellitus or other endocrinopthy, patients taking cardioactive drugs, antiepileptic drugs or antipsychotic drugs and patients with anticipated difficult mask ventilation or laryngoscopy and all emergency surgical cases were excluded from the study.

All patients were provided with patient information sheet and written informed consent was obtained. Pre-anesthetic check up and investigations were done. The patients were kept fasting overnight after *10:00 pm* and received tablet ranitidine *150 mg* orally and tablet alprazolam *0.25 mg* orally as premedication the night before surgery. All patients were monitored using standard American Society of Anesthesiologists (ASA) monitors like non-invasive blood pressure (NIBP), pulse oximetry, and electrocardiography (ECG). Intravenous access was secured using an 18 G cannula in the forearm of the non-dominant hand.

Patients were randomized into two groups, either Group A or Group B, consisting of 80 patients each using computer generated random number table. Double blind technique was used in which both the anesthesiologist administering the drug as well as the patients were unaware as to which group the patient belonged to. One anesthesiologist labeled the intravenous (I.V.) infusions which were then administered to the patients by another anesthesiologist who did not know the contents of the infusion. The parameters were recorded by the second anesthesiologist.

Group A received *1 gm* paracetamol infusion (Labeled A1) in *100 ml* volume whereas Group B received 0.9% normal saline infusion (B1) in *100 ml* volume intravenously (I.V.) thirty minutes prior to induction over fifteen minutes. After pre-oxygenation with 100% O_2 for three minutes and premedication with injection Fentanyl *1 mcg/kg* intravenously (I.V.), the patients were induced with injection Propofol *2 mg/kg* I.V. and intubated with appropriate sized cuffed endotracheal tube with injection Vecuronium *0.1 mg/kg* I.V. after establishment of neuromuscular blockade confirmed with disappearance of single

twitch response with a nerve stimulator. The hemodynamics were recorded at baseline, before induction, after induction, before laryngoscopy, immediately after intubation and thereafter, *1, 3, 5, 7 and 10 minutes* following intubation. After *10 minutes* of intubation, Group A received the infusion labeled A2 (0.9% Normal saline in *100 ml* volume) whereas Group B received the infusion labeled B2 (paracetamol *1 gm* in 100 ml volume) over *15 minutes*.

Anesthesia was maintained with isoflurane (0.6 to 1%) in a mixture of O_2 and N^2O (1:2) and injection vecuronium bromide. Total intubation time (in seconds) was defined as the time from insertion of the tip of the endotracheal tube into the trachea, up to the time of tube confirmation.

Statistical Analysis

All statistical analysis was performed using Statistical Packages for Social Science version 19 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean (standard deviation) for quantitative variables like age, weight, SBP, DBP, HR. Independent sample *t*-test and Mann-Whitney tests were applied to compare the mean/median difference between groups for age, weight. The paired *t*-test was used to compare within-subject effect for HR and BP. $p < 0.05$ was considered as significant.

Results

A total of 160 patients were included in the study with 80 patients each in Group A (Paracetamol group) and Group B (Normal saline). However, four patients from Group A and five patients from Group B were excluded from the study as they needed more than one attempt for intubation. There was no statistical difference between the two groups in terms of age, sex, height, weight, Mallampati scores and American Society of Anesthesiologists (ASA) physical status shows in (**Table 1**).

Table 1: Baseline characteristics between the groups (mean ± SD)

Characteristics	Group A (n = 76)	Group B (n = 75)	p - value
Age (In years)	35.98 ± 0.22	35.50 ± 10.39	0.95
Sex (M/F)	33/43	31/44	0.87
Weight (Kg)	55.06 ± 8.61	54.4 ± 9.28	0.32
Height (In cms)	157.76 ± 9.62	158.4 ± 1.56	0.35
MPS (I/II)	19/57	17/58	0.85
ASA (1/2)	54/22	50/25	0.56

SD = Standard deviation; n = number of patients; ASA = American Society of Anesthesiologists; MPS = Mallampati score.

The baseline heart rates (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressures (MAP) were comparable in both the groups. The decrease in the mean heart rates after induction was also statistically insignificant in both the groups. ($p \geq 0.001$) after *1 minute* of laryngoscopy and intubation, significant increase in the heart rate was seen in both the groups. ($p \leq 0.05$) In Group A, the increase in mean heart rate produced by laryngoscopy and intubation was not statistically significant at *3 mins* ($p \geq 0.05$) and remained insignificant at 5, 7 and *10 minutes* after intubation.

However, in Group B the increase in mean heart rate produced by laryngoscopy and intubation was significantly high at *3 min* ($p \leq 0.0001$) and remained significantat *5, 7 and 10 minutes* after intubation. Shows (**Table 2**) the mean baseline values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were similar and statistically insignificant ($p > 0.05$) between Group A and Group B. There

Table 2: Mean Heart Rate at different pre-defined points of time

Heart Rate (beats per minute)			Intra Group (compared to the baseline)		Inter Group (compared between similar points of time)
	Group A Mean ± SD	Group B Mean ± SD	Group A p - Value	Group B p - Value	p - Value
Baseline	78.44 ± 13.39	80.24 ± 11.97			0.19
Before induction	78.34 ± 13.59	80.36 ± 11.60	0.48	0.47	0.16
After induction	77.32 ± 11.61	79.90 ± 12.28	0.29	0.43	0.20
Before laryngoscopy	78.22 ± 11.78	79.22 ± 12.46	0.45	0.30	0.31
1 min after intubation	84.28 ± 11.50	98.44 ± 12.74	0.04	< 0.0001	< 0.0001
3 min after intubation	84.05 ± 11.15	94.16 ± 13.56	0.07	< 0.0001	< 0.0001
5 min after intubation	81.60 ± 10.30	87.33 ± 12.22	0.06	0.0002	0.0013
7 min after intubation	80.46 ± 8.25	86.91 ± 11.64	0.052	0.0003	0.0003
10 min after intubation	78.57 ± 10.85	82.88 ± 11.75	0.69	0.007	0.012

SD = Standard deviation.

was significant fall in SBP, DBP and MAP ($p \leq 0.05$) from baseline after induction, laryngoscopy and after *1 minute* of intubation in both Group A and Group B but inter group comparisons at these time points were statistically insignificant ($p \geq 0.05$). The mean SBP, DBP and MAP at *3, 5, 7* and *10 minutes* showed no difference between Group A and Group B ($p \geq 0.05$) shows in (**Tables 3,4,5**), along with displays (**Graphs 1–3**).

Table 3: Mean SBP at different pre-defined points of time

SBP			Within Group		Inter Group
	Group A	Group B	Group A	Group B	
	Mean ± SD	Mean ± SD	*p* - V alue	*p* - Value	*p* - Value
Baseline	122.57 ± 11.82	124.49 ± 11.96			0.11
Before induction	122.76 ± 11.99	123.88 ± 10.91	1.0	1.0	0.59
After induction	115.97± 11.03	116.25 ± 11.66	0.012	0.001	0.25
Before laryngoscopy	113.73 ±10.38	116.56 ± 11.63	0.001	0.002	0.85
1 min after intubation	131.54 ± 13.23	134.96 ±15.22	0.001	< 0.0001	0.32
3 min after intubation	126.16 ± 11.86	126.83 ± 12.13	0.59	0.96	0.49
5 min after intubation	120.45 ± 12.07	119.47 ± 12.66	0.97	0.22	0.72
7 min after intubation	119.78 ± 9.99	121.61 ± 12.81	0.86	0.16	0.51
After intubation	119.72 ± 10.33	119.45 ± 11.66	0.84	0.21	0.40

Table 4: Mean DBP at different pre-defined points of time

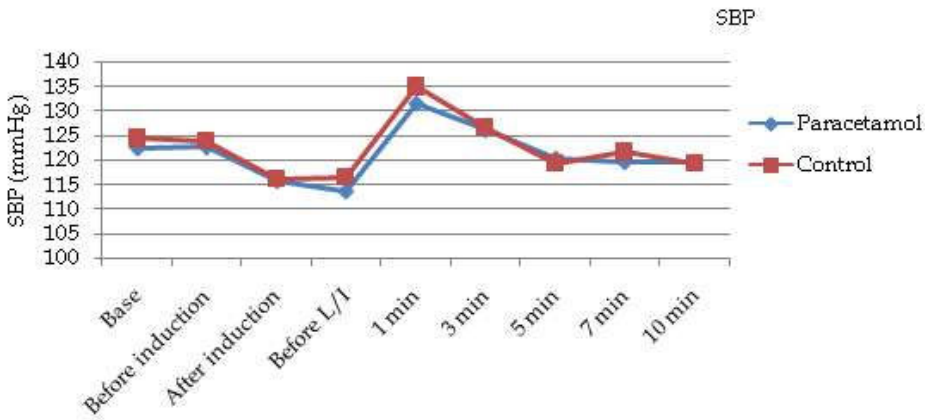
DBP			Within Group		Inter Group
	Group A	Group B	Group A	Group B	
	Mean ± SD	Mean ± SD	*p* - Value	*p* - Value	*p* - Value
Baseline	76.01 ± 9.82	76.97 ± 11.12			0.13
Before induction	76.34 ± 11.41	77.85 ± 10.02	1.0	1.0	0.14
After induction	71.57 ± 9.32	73.21 ± 8.89	0.003	0.001	0.38
Before laryngoscopy	72.00 ± 10.84	72.92 ± 9.53	0.02	0.005	0.41
1 min after intubation	82.39 ± 10.95	86.27 ± 15.06	0.005	< 0.0001	0.38
3 min after intubation	77.74 ± 10.98	79.68 ± 12.72	0.98	0.86	0.42
5 min after intubation	74.47 ± 10.29	74.97 ± 9.83	0.99	0.97	0.10
7 min after intubation	74.37 ± 9.74	77.13 ± 10.87	0.99	1.0	0.13
10 min after intubation	73.26 ± 10.31	75.08 ± 10.38	0.79	0.98	0.24

DBP = Diastolic Blood Pressure; SD = Standard deviation.

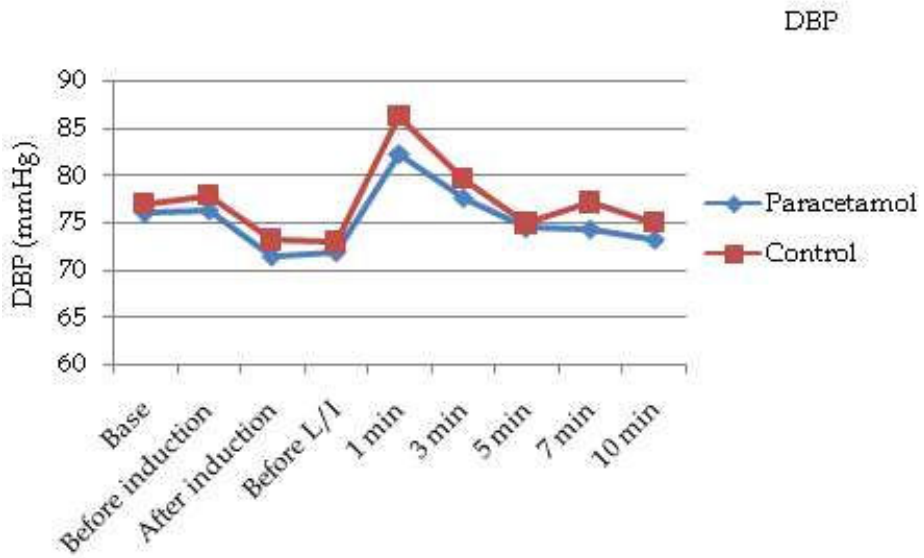
Table 5: Mean of MAP at different pre-defined points of time

MAP			Within Group		Inter Group
	Group A	Group B	Group A	Group B	
	Mean ± SD	Mean ± SD	*p* - Value	*p* - Value	*p* - Value
Baseline	91.29 ± 11.03	92.77 ± 11.24			0.06
Before induction	91.49 ± 11.99	94.07 ± 10.65	1.0	0.9	0.11
After induction	86.24 ± 9.10	87.37 ± 8.53	0.002	0.001	0.37
Before laryngoscopy	86.01 ± 10.33	87.49 ± 9.35	0.002	0.007	0.19
1 min after intubation	99.26 ± 11.94	103.43 ± 15.53	< 0.0001	< 0.0001	0.55
3 min after Intubation	95.07 ± 11.31	96.57 ± 11.86	0.39	0.47	0.06
5 min after intubation	90.47 ± 10.24	90.85 ± 10.08	1.0	0.98	0.63
7 min after intubation	90.54 ± 8.25	91.76 ± 10.52	1.0	1.0	0.23
10 min after intubation	89.43 ± 9.49	91.05 ± 10.60	0.98	0.99	0.54

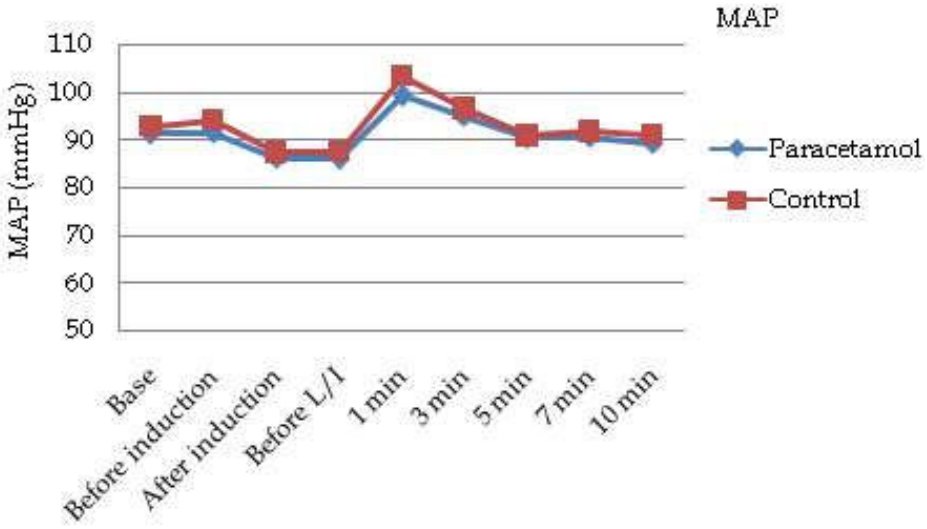
MAP = Mean Arterial Pressure; SD = Standard deviation.



Graph 1: Mean SBP of both the groups at different times



Graph 2: Graph showing the mean DBP of both the groups at different times



Graph 3: Showing intergroup MAP at different times

Discussion

Laryngoscopy and endotracheal intubation are the basis of protecting the airway in patients receiving general anesthesia. In addition to securing the airway, preventing aspiration and aiding delivery of anesthetic gases, they are also responsible for various stress responses such as tachycardia, hypertension, laryngospasm, bronchospasm, raised intracranial pressure and intraocular pressure.[1] Several drugs have been used previously to attenuate these stress responses to the manipulation and stimulation of the airway during laryngoscopy and intubation. Fentanyl, beta-adrenergic receptors blockers, and lignocaine have all been used previously with varying results.[14]

In our study, we compared the efficacy of preoperative administration of intravenous paracetamol *1 gram* in *100 ml* volume on attenuation of hemodynamic responses after laryngoscopy and tracheal intubation. Patients of both the groups were premedicated with I.V. Fentanyl *1 mcg/kg*, as other no pharmacological agent was used to prevent hemodynamic response in any single patient undergoing laryngoscopy and intubation. The study was designed to evaluate the efficacy of paracetamol to attenuate the hemodynamic responses caused by the pain of laryngoscopy and endotracheal intubation.

Paracetamol has a well-established safety and analgesic profile. The main mechanism of action is inhibition of the enzyme cyclo-oxygenase, which is responsible for the production of prostaglandins, an important mediator of inflammation and pain.[15] The exact mechanism of paracetamol on hemodynamic responses is unclear but may be attributable to its analgesic effect mediated by its anti prostaglandin action.[16]

Although the peri-operative analgesic effects of intravenous paracetamol are well-known, literature documenting the attenuation of hemodynamic responses to laryngoscopy and intubation are very rare. Ali Kord Valeshabad *et al.* compared the prodrug of paracetamoli in 2 gram intravenous propacetamol with intravenouslidocaine *1.5 mg/kg* and found that propacetamol attenuated the heart rate responses to laryngoscopy but not the blood pressure responses to intubation.[13] Propacetamol [4-(acetamido) phenyl N, N-diethylglycinate] is a prodrug, which is quickly hydrolyzed by plasma esterase to vigorous paracetamol; *1 gr* propacetamol metabolized to *500 mg* paracetamol.[17] These findings were quite similar to our study. Our findings showed that preoperative administration of paracetamol did help attenuate the heart rate response to laryngoscopy and endotracheal intubation as compared to normal saline. However, paracetamol did not have any beneficial effect on attenuation of blood pressure responses to laryngoscopy and intubation. Acute increase in heart rate in their study was better attenuated than ours, which could be attributed to a higher dose of fentanyl (*2 mcg/kg*) used by them.

Ayatollahi V *et al.*, studied the effect of pre-operative administration of intravenous paracetamol during cesarean section on hemodynamic variables relative to intubation in 60 patients and observed that paracetamol prevented significant increase in SBP, DBP, MAP and HR at all times after laryngoscopy and intubation.[18] Hossam *et al.*, too evaluated the effect of *1 gram* of pre-operative intravenous paracetamol on hemodynamic variables after intubation in 60 obstetric patients planned for cesarean section and concluded that preoperative administration of intravenous paracetamol was effective in preventing hemodynamic responses to intubation.[19] In both the studies by Ayatollahi V *et al.* and Hossam *et al.*, opioids were not used before intubation as the patients were all obstetric cases. So, in the absence of opioids, probably the antinociceptive activities of paracetamol might have been augmented. However, another study by Ozmete *et al.* on the effect of pre-operative paracetamol on hemodynamic responses after intubation and its role on post cesarean delivery pain did not find any favorable effect on the hemodynamic variables following laryngoscopy and intubation.[20]

Thus, different studies have different opinions on the role of pre-operative paracetamol on attenuation of hemodynamic response to intubation. However, the context of these studies were not similar; in some studies opioids were used as premedication and in some they were not used. Hence, it may be recommended that further studies with similar context and larger sample sizes are carried out to find out the exact role of paracetamol among the pharmacological armamentarium available for blunting of hemodynamic responses.

Conclusion

Administration of paracetamol (*1 gram*), thirty minutes prior to induction of anesthesia could not totally blunt all the cardiovascular responses to laryngoscopy and intubation, but it did show better control of heart rate after intubation.

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