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A study to compare the attenuation of haemodyanamic stress response during intubation by fentanyl, Nalbuphine and butorphanol

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Abstract
Several techniques have been tried in an effort to attenuate adverse hemodynamic stress responses to intubation. Commonly used techniques include increasing the depth of anesthesia by heavy premedication, inhalational anesthetic agents, intravenous (IV) and topical lignocaine, clonidine and dexmedotomidine, calcium channel blockers, sodium nitroprusside, beta-adrenergic blockers, and magnesium sulfate. Ninety female patients of 18-65 years of age, undergoing elective modified radical mastectomy (MRM) surgery for carcinoma breast at Kidwai Memorial Institute of Oncology, Bangalore were selected randomly. The study was conducted in the Department of Anesthesia and pain relief, Kidwai Memorial Institute of Oncology, Bangalore during the period from December 2018 to December 2019. So, in terms of Heart rate control during intubation and steady state of anaesthesia all three opioids showed efficacious control but Nalbuphine proved to be best as it prevented tachycardia during intubation.

Keywords: Fentanyl, nalbuphine and butorphanol

Introduction
Laryngoscopy and tracheal intubation after induction of anesthesia generate pressure and sympathoadrenal responses which are thought to be somatovisceral reflexes caused by the stimulation of epipharynx and laryngopharynx. These responses result in increased circulatory catecholamines, heart rate (HR), blood pressure, myocardial oxygen demand and dysrhythmias. The rise in HR and blood pressure is usually transient, variable, and unpredictable. Laryngoscopy and intubation lead to an average increase in blood pressure of 40 to 50%, and a 20% increase in heart rate. These changes are greatest one minute after intubation and last for 5 to 10 min [1].
Several techniques have been tried in an effort to attenuate adverse hemodynamic stress responses to intubation. Commonly used techniques include increasing the depth of anesthesia by heavy premedication, inhalational anesthetic agents, intravenous (IV) and topical lignocaine, clonidine and dexmedotomidine, calcium channel blockers, sodium nitroprusside, beta-adrenergic blockers, and magnesium sulfate. Newer techniques like electrical stimulation by acupuncture is applied to reduce post intubation sore throat [2]. One of the most commonly used agent for the said purpose is using opioids as Fentanyl. On the other hand, adequate post-operative analgesia leads to shortened hospital stays, reduced hospital costs, and increased patient satisfaction. The mainstay of postoperative pain therapy in many settings is still opioids. Opioids bind to receptors in the central nervous system and peripheral tissues and modulate the effect of the nociceptors [3].
Opioids can serve as a dual agent to attenuate hemodynamic stress response to laryngoscopy, intubation and as post-operative analgesia. Most commonly used agents are Fentanyl and Morphine. Fentanyl is a complete agonist opioid having side effects of respiratory depression, pruritis, nausea and vomiting and reduction in bowel motility leading to ileus and constipation [4].

Methodology
Study Design: A prospective randomized comparative study.
Ninety female patients of 18-65 years of age, undergoing elective modified radical

Mastectomy (MRM) surgery for carcinoma breast at Kidwai Memorial Institute of Oncology, Bangalore were selected randomly. The study was conducted in the Department of Anesthesia and pain relief, Kidwai Memorial Institute of Oncology, Bangalore during the period from December 2018 to December 2019. Patients were randomly divided into 3 groups. Randomization was done by simple computer generated randomization.

The study was approved by the ethics committee of Kidwai Memorial Institute of Oncology, Bangalore and all patients gave valid written informed consent.

CTRI registration taken- CTRI/2020/06/025694

Inclusion criteria

- Patients giving valid informed consent
- Patients aged between 18 – 65 years
- Patients belonging to ASA Grade l and ll.

Exclusion criteria

- Patient refusal
- Patients belonging to ASA Grade III and IV
- Patients with history of allergy to opioids group of drugs.

By power analysis and considering the P value for the ANOVA at 0.05, to achieve power of 80% and a medium effect size ($f^2 = .1089$) we got the minimum sample size at 90.We considered 30 in each arm.

After obtaining informed written consent from patients, patients were randomized and assigned to one of the three groups:

Group I: (patients=30) to receive 2 µ/kg body weight of IV Fentanyl 5 mins prior to induction of anesthesia.

Group II: (patients=30) to receive 0.2mg/kg body weight of IV Nalbuphine 5 mins prior to induction of anesthesia.

Group III: (patients=30) to receive 20µ/kg body weight of IV Butorphanol 5 mins prior to induction of anesthesia.

A routine pre-anaesthetic examination was conducted on the evening before surgery, assessing history, general condition of the patient, height, weight, comorbidities, history of chemotherapy/radiation. Airway assessment by Mallampati grading. A detailed examination of the cardiovascular system, respiratory system and central nervous system was done.

The following investigations were done in all patients.

- Complete blood count
- Random blood sugar
- Blood urea and Serum creatinine
- Liver function test
- Standard 12-lead electrocardiogram and Echocardiography.
- Chest radiograph

The patients were premedicated with tablet alprazolam 0.5 mg and tablet pantoprazole 40 mg orally at bed time on the previous night before surgery. They were kept nil orally for 8 hours prior to procedure. On the day of surgery PAC reviewed.

Results

The study was conducted on (N=90) female patients with carcinoma breast, 30 patients in three groups each. Mean age of the patients was 48.79 years with SD ±9.209.The mean height of the patients was 9.209 cm (SD ±6.277) while the mean weight of the patient was 57.13 Kg (SD ±10.751) (Table 1).

Table 1: Age, height, and weight distribution in 3 groups of the sample

Group	Age (Mean)	SD	Mean height (cm)	SD	Mean weight (Kg)	SD
Fentanyl	48.77	9.246	158.53	5.438	58.30	10.574
Nalbuphine	46.63	8.512	155.47	5.923	57.20	11.517
Butorphanol	50.97	9.622	155.67	7.082	55.90	10.357
Total (N=90)	48.79	9.209	156.56	6.277	57.13	10.751

Table 2: Description of baseline hemodynamic parameters at different time points

Time Point	Medications	Heart Rate (beats/min)		SBP (mm of Hg)		DBP (mm of Hg)		MAP (mm of Hg)		SpO2 (%)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	Fentanyl	91.4	13.1	147.8	16.0	93.0	10.5	111.2	11.8	98.8	.39
	Nalbuphine	88.6	12.6	147.3	13.9	90.6	10.4	109.5	10.4	100.0	.00
	Butorphanol	90.7	11.9	146.8	15.9	88.2	9.4	107.7	10.8	100.0	.00
	Total	90.2	12.4	147.3	15.1	90.6	10.2	109.5	11.0	100.0	.00
@3 min post-Opioid	Fentanyl	87.1	14.0	139.7	16.8	87.8	10.5	105.1	11.8	100.0	.00
	Nalbuphine	82.1	12.7	134.9	14.4	82.5	9.8	100.0	10.5	100.0	.00
	Butorphanol	86.4	10.2	141.9	18.2	86.4	8.6	104.9	11.3	100.0	.00
	Total	85.2	12.4	138.8	16.6	85.6	9.8	103.3	11.4	100.0	.00
@Intubation	Fentanyl	87.9	13.3	139.8	21.9	89.0	14.6	105.9	16.5	100.0	.00
	Nalbuphine	87.5	11.8	144.7	20.2	88.7	14.2	107.4	15.6	100.0	.18
	Butorphanol	95.2	15.0	150.0	20.3	95.1	14.0	113.5	15.1	100.0	.00
	Total	90.2	13.7	144.8	21.0	90.9	14.4	108.9	15.9	100.0	.00
@1 min after Intubation	Fentanyl	84.3	13.3	130.3	18.7	81.3	10.8	97.7	12.8	100.0	.11
	Nalbuphine	83.1	12.4	125.6	18.9	80.1	12.4	95.2	13.7	100.0	.00
	Butorphanol	89.1	12.8	133.5	21.9	86.2	13.3	102.0	15.5	100.0	.00
	Total	85.5	13.0	129.8	19.9	82.6	12.3	98.3	14.2	100.0	.00
@3 min after Intubation	Fentanyl	82.1	12.5	122.0	20.6	75.7	13.0	91.2	15.1	100.0	.00
	Nalbuphine	81.2	11.6	118.3	18.0	73.8	12.5	88.8	13.4	100.0	.00
	Butorphanol	83.1	12.6	124.1	17.3	80.6	11.9	95.1	13.1	99.8	.38
	Total	82.1	12.1	121.5	18.6	76.7	12.7	91.7	14.0	100.0	.18

@5 min after Intubation	Fentanyl	82.1	14.2	123.0	17.2	79.2	13.0	93.7	13.6	99.9	.25
	Nalbuphine	77.2	11.1	114.4	18.4	73.0	12.6	86.9	13.7	99.7	.45
	Butorphanol	81.0	11.2	117.1	14.8	75.6	11.1	89.4	11.6	99.7	.47
	Total	80.1	12.3	118.2	17.0	76.0	12.4	90.0	13.1	99.7	.48
@30 min after Intubation	Fentanyl	81.1	14.5	129.0	19.2	82.8	9.8	98.3	12.4	99.7	.46
	Nalbuphine	73.2	10.6	119.0	14.8	76.7	10.2	90.8	10.8	98.8	.39
	Butorphanol	78.1	11.1	117.2	9.7	76.1	9.8	89.8	9.2	100.0	.00
	Total	77.5	12.5	121.7	15.8	78.5	10.3	93.0	11.4	100.0	.00
@60 min after Intubation	Fentanyl	77.7	12.0	122.3	11.8	79.0	9.1	92.9	9.1	100.0	.00
	Nalbuphine	73.6	9.4	122.3	10.1	77.6	9.9	92.7	9.1	100.0	.00
	Butorphanol	76.6	9.3	118.5	8.8	74.4	8.9	95.1	12.7	100.0	.00
	Total	76.0	10.3	121.0	10.4	77.0	9.4	93.6	10.4	100.0	.00

On post-hoc pairwise comparison using the Bonferroni correction, compared to baseline (time 1) significant drop of heart rate in all time points except time 3(intubation) was observed. Heart rate changes were not significant between time points 5, 6, and 7. So, HR somewhat stabilized after 5 min after intubation.

On post hoc pairwise comparison using the Bonferroni correction, compared to baseline (time 1) significant drop of SBP in all time points except time 3(intubation) was observed. SBP changes were not significant between time points 5, 6, 7, 8. So, SBP stabilized after 5 min after intubation. In between subject effects, we did not find significant effect of any medication group on Systolic BP, F (2, 87) = 0.698, p= 0.5.

We observed that compared to baseline (time 1) significant drop of DBP in all time points except time 3(intubation). DBP changes were not significant between time points 5, 6, 7, 8. So, DBP stabilized after 5 min after intubation (time 4). In between subject effects, we did not find significant effect of any medication group on Diastolic BP, F (2, 87) = 1.356, p= 0.263.

Discussion

As we can see from the result, there was mean drop of HR after 3 min of medication compared to baseline in all treatment arms. Highest Mean drop was noted in Nalbuphine group (7.24%), followed by Fentanyl (4.61%) and Butorphanol (4.3%) group. In one-way ANOVA statistics, these differences were not found to be statistically significant (p= 0.213). This finding is similar to the study conducted by Teong *et al*. [5] where the decrease of HR was maximum when Fentanyl was given 2 minutes prior to intubation and decrease was 3.42%. Ahire *et al*. [6] found Butorphanol reduced HR from baseline of 88.53±9.82 beats per minute to 80.93± 9.75 which is similar to our findings.

During intubation HR reduced highest in Fentanyl group by 3.72 beats per minute from baseline followed by Nalbuphine group by 0.1 beats by minutes whereas increased in Butorphanol group by 5 beats per minutes. Nalbuphine and Fentanyl group showed increase in heart rate of 3.81% and 6.03% respectively by the study conducted by Madhu S *et al*. [7] which differed in our study.

On post-hoc analysis of time effect showed that compared to baseline (T1) significant drop of heart rate in all time points except T 3(intubation) was observed. Heart rate changes were not significant post intubation. So, HR stabilized after 5 min after intubation and maintained in steady state of anaesthesia. The above finding is similar to studies we reviewed where HR stabilized post intubation like Chawda *et al*. [8], and B. LefÃ¨vre *et al*. [9].

So, in terms of Heart rate control during intubation and steady state of anaesthesia all three opioids showed efficacious control but Nalbuphine proved to be best as it prevented tachycardia during intubation.

On post hoc pairwise comparison using the Bonferroni correction, compared to baseline (T1) significant drop of SBP at all-time points except T 3(intubation) was observed. SBP changes were not significant post intubation time points. So, SBP stabilized after 5 min after intubation and maintained intraoperatively. This finding is seen in multiple studies like B. LefÃ¨vre *et al*., Weiss BM, Schmid ER, Gattiker RI, Khan FA *et al*. [10-12].

Conclusion

We can conclude from our study that Nalbuphine is best amongst the three to control haemodynamic stress response during intubation and steady state of anaesthesia. Both Nalbuphine and Butorphanol give excellent post-operative analgesia and lesser side effect profile, although Butorphanol has best profile amongst the two.

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