Valley International Journals
Open Access Journal
New Thinking New Innovation

International Journal Of Medical Science And Clinical Inventions
Volume 3 issue 7 2016 page no. 1968-1976 e-ISSN: 2348-991X p-ISSN: 2454-9576
Available Online At: http://valleyinternational.net/index.php/our-jou/ijmsci

Randomized Comparison Of Tramadol, Nalbuphine And Fentanyl Used As Premedication In Attenuation Of Hemodynamic Response To Laryngoscopy And Postoperative Pain In Laparoscopic Cholecystecyomy

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Abstract: Background: Stress response to laryngoscopy during endotracheal intubation and pain after surgeries under General Anesthesia are one of the major concern and challenge for anesthetists. A number of methods have been used to modify the laryngoscopy and endotracheal intubation response, including different intubation devices, beta blockers, vasodilators and opioids. Opioids are good analgesics and have role in attenuation of stress response to laryngoscopy when used in premedication prior to laryngoscopy. Our aim of study is to compare the efficacy and safety of three opioids ie; Tramadol, Nalbuphine and Fentanyl as stress buster and analgesic when used in single dose as premedication in General Anaesthesia for Laparoscopic Cholecystectomy. Methods: One twenty patients of ASA grade I&II were randomly selected with forty patients in each group. Drug was given 10 min before starting the anaesthesia. Patients were assessed for change in hemodynamic parameter from baseline in Immediate post intubation (IPI), 1, 2 and 5min post intubation to note the stress response to laryngoscopy. Intra operative vitals were recorded for every 15min till end of surgery and in immediate and 5min post extubation period. VAS was recorded after awakening from anaesthesia. Any adverse reaction like nausea vomiting, respiratory depression and sedation were also recorded. Results: Nalbuphine and Fentanyl were found to be better drug compared to Tramadol for attenuation of hemodynamic response to Laryngoscopy (p<0.0001). No significant difference in hemodynamics was found intraoperatively in all the three drugs. Nalbuphine and Tramadol were having good analgesia in immediate post operative period. Mild respiratory depression and sedation was reported with Nalbuphine. Nausea vomiting was significantly high with Tramadol (p<0.001). Conclusion: Nalbuphine is one of the better choices for relieving stress to laryngoscopy and intubation, maintaining good hemodynamics intraoperatively and providing pain relief in immediate postoperative period.

Keywords: Nalbuphine, Tramadol, Fentanyl, General Anaesthesia, Laparoscopic Cholecystectomy, Laryngoscopy, Post operative pain.

I. INTRODUCTION

Stress response to laryngoscopy during endotracheal intubation and postoperative pain stress are one of the major concerns during any kind of surgery performed under general anesthesia. More common responses to endotracheal intubation are hypertension and tachycardia. A number of methods have been used to modify the laryngoscopy and endotracheal intubation response, including different intubation devices[1,2], beta blockers[3,4], vasodilators[5,6] and

DOI: 10.18535/ijmsci/v3i7.2

opioids.[4,7]

Opioid in adequate doses have been commonly used to prevent hemodynamic response at laryngoscopy and intubation.[8] Being a good analgesic opioids are commonly used in premedication to support analgesia during surgery and to provide pain relief in immediate post operative period. So in current study we chose to compare the analgesic effect and attenuation of hemodynamic response of three opioids ie; Tramadol, Nalbuphine and Fentanyl in laparoscopic cholecystectomy; which is one of the commonly performed surgeries these days and general anesthesia is the choice of anesthesia for this.

II. MATERIAL AND METHOD

This comparative study was conducted in Pacific Medical College and hospital with the permission of ethical committee of the hospital. Study was conducted over the period of 1yr. After written informed consent of 120 adult patients aged 30-60yrs of both sex and ASA grade I and II undergoing laparoscopic cholecystectomy. Patients with diabetes, hypertension, bleeding disorders, heart diseases, chronic lung disease, anemia and having history of any substance abuse were excluded from the study. All patients were examined preoperatively and history noted. Patients having easy intubation (MPG grades I and II with adequate mouth opening) were included in the study to avoid extra stress and time of difficult intubation. All the patients were investigated for Hb, CBC, BT, CT, RFT, LFT, ECG and Chest X-Ray. One hundred and twenty patients were randomly allocated in 3 groups, 40 patients in each Group. They were named:

Group Nalbuphine (N)

Group Tramadol (T)

Group Fentanyl (F)

They were instructed to the concept of VAS to record pain. After receiving the patient in preoperative ward baseline vitals ie; SBP, DBP and PR were recorded. Patients were given premedication 10 mins before induction in combination of glycopyrollate 0.04mg/kg, ondasetron0.1mg/kg, and midazolam.02mg/kg and opioid according to the group assigned. Opioids used in the doses of: Tramadol 2mg/kg, Nalbuphine 0.3mg/kg and Fentanyl 2µg/kg. All patients received Xylocard 1.5mg/kg IV prior to induction. Patients were induced with propofol 2mg/kg, after checking adequacy of ventilation IV succcynylcholine 2mg/kg was given. After ventilating for 3mins Direct Laryngoscopy was done using appropriate size Mac Intosh blade Laryngoscope. Trachea was intubated with appropriate size PVC cuffed endotracheal tube .Ventilation was maintained by closed circuit anesthesia workstation ventilator. Maintenance of anesthesia was done by O_2, N_2O and Sevoflurane. Relaxation was maintained by vecuronium0.1mg/kg followed by intermittent bolus 0.02mg/kg every 30 min. All patients were monitored for continuous lead II Electrocardiogram, heart rate (HR), non invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse oximetry and end tidal CO2. Hemodynamic parameters were recorded prior and subsequent to intubation followed by 3 and 5min post intubation. Intraoperatively hemodynamic parameters were recorded every 15min till completion of surgery. Subsequently any variation in hemodynamic during intraoperative period was managed by adjusting flow of Sevoflurane.. At the time of reversal IV Xylocard1.5mg/kg was given prior to oropharyngeal suction. Reversal was done by Myopyrollate (Neostigmine2. 5mg +glycopyrollate0.4mg). Hemodynamic parameters were recorded in immediate post extubation period and 5min after extubation. Patients were observed for any sign of nausea and vomiting, delayed awakening and respiratory depression.

DOI: 10.18535/ijmsci/v3i7.2

Delayed awakening was assessed by using University of Michigan Sedation Scale[9]

Score:0: Awake and alert

1: Minimally sedated/ sleepy, appropriate response to conversation/or sound

2: Moderately sedated, somnolent/sleepy, easily aroused with tactile Stimulation/or simple verbal command

3: Deeply sedated, deep sleep, arousable only with significant stimulation

4: Unarousable

Respiratory depression was assessed by any fall in respiratory rate 12/min from higher baseline and fall in SPo_2 <95%.

Postoperatively pain score was assessed using Visual Analogue Scale (VAS)[10]

VAS Score: 0: No pain

1-4: Mild pain

5-7: Moderate Pain

8-10: Sever pain

After recording VAS, pain was treated with same opioid assigned to that group.

All the data were calculated as mean and standard deviation. Data were compared between groups using t/X^2 test and a p-value≤0.05 was considered statistically significant.

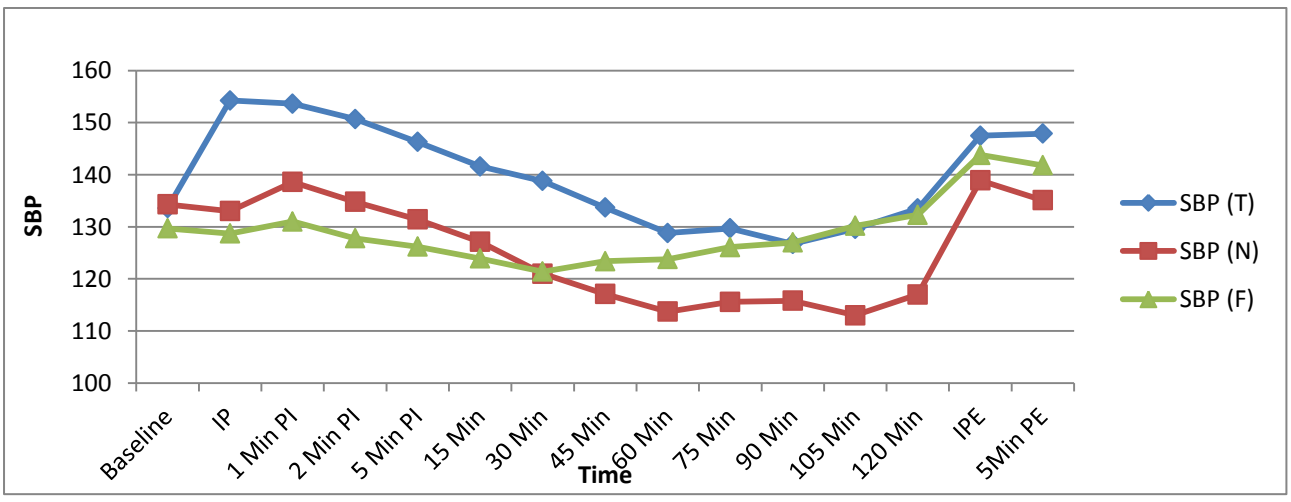
III.RESULTS

Table-1: Demographic data:

	Group(T) *N=40*	*Group(N)* *N=40*	*Group(F)* *N=40*
AGE	44±7.3	44±7.4	44±7.2
SEX (M:F)	19:21	17:23	18:22
WEIGHT(Kg)	63.7±6.57	64.58±5.16	63.44±4.12
DURATION OF ANESTHESIA (Min)	83.41±15	85.5±26	86.25±26

Three groups were found to be comparable with regard to age, weight, sex and duration of anaesthesia.

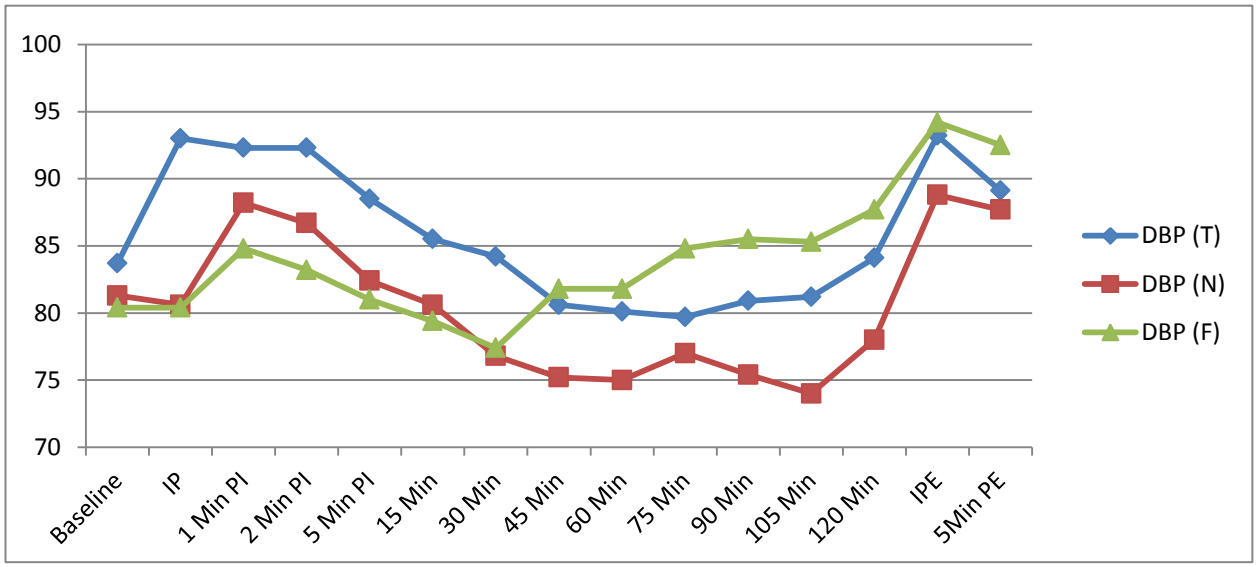
Figure-1: Change in SBP (mmHg) in three groups:



DOI: 10.18535/ijmsci/v3i7.2

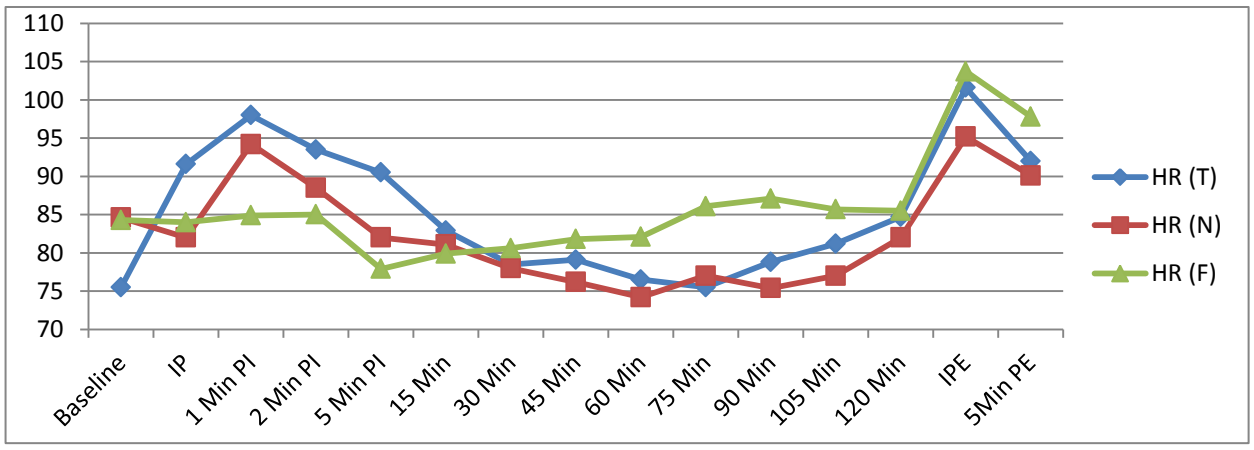
Significant rise in SBP from baseline was found in IPI period in Group T ($p<0.0001$). Group N and F showed some fall in SBP in IPI period but the difference was not significant. All the three Groups showed rise of SBP at 1mins post intubation but the rise was significant only in Tramadol group ($p<0.0001$). SBP came back near to baseline in Group F and N early (1min in Group F and 5min in Group N). Group T showed persistent rise till 15 mins which was gradually managed by adjusting the flow of Sevoflurane. All the three Groups showed rise of SBP in immediate post extubation period. Rise was significant in Group F and T (0.0001). Group N showed early return of SBP towards baseline.

Figure-2: Change in DBP (mmHg) in three groups:



Rise in DBP in IPI period and at 1min PI was seen in all the three groups but this was significant in Group T ($p<0.0001$). DBP touched the baseline early in Group F followed by Group N. Group T showed persistent rise in DBP above baseline till 15mins of intubation which was managed by adjusting flow of Sevoflurane. All the three Groups showed rise in DBP in immediate post extubation period which was significant in Group F and T ($P<0.0001$). DBP remained high in all the three groups till 5mins post extubation.

Figure-3: Change in HR (beats/min):



DOI: 10.18535/ijmsci/v3i7.2

Significant rise in HR was noted in Group T in IPI period 1, 2 and 5 min PI (p<0.0001). Group N and F reported fall in HR from baseline in IPI but it was insignificant. In both the groups HR increased at 1min but the difference was not significant when compared to baseline. HR touched baseline early in Group F followed by Group N and T. All the groups reported increase in HR immediately after extubation which was significant in Group F and T (P<0.0001).

There was no significant variation in hemodynamic parameters intraoperatively in all the three groups. Insignificant variation in BP was managed by adjusting the flow of Sevoflurane. None of the patients in any group reported bradycardia and hypotension.

Table-2: Incidence of adverse drug reactions:

	Groups(T) N=40	*Groups(N) N=40*	*Group(F) N=40*
DELAYED AWAKENING	2(5%)	12(30%)	Nil
NAUSEA AND VOMITING	17(42.5%)	5(12.5%)	2(5%)
RESPIRATORY DEPRESSION	3(7.5%)	5(12.5%)	1(2.5%)

Delayed awakening was assessed by using Michigan sedation scale. Sedation score of ≥2 was considered delay in awakening. Delayed awakening was found in 2 (5%) patients in Group-T, 12 (30%) in Group-N and none in Group-F. This difference was found to be significant (p<0.0002).

Significant difference in the incidence of Nausea and vomiting was reported between the groups ie; 17 (42.5%) of the patients in Group-T, 5 (12.5%) in Group- N and 2 (5%) in Group-F (p<0.0002).

Mild respiratory depression was found in all the groups 12.5% in Group N followed by Group- T (7.5%) and Group-F (2.5%). But the difference was not significant. Respiratory depression was managed by supplementing oxygen for 5mins. None of the patients required endotracheal intubation or other laryngeal device to maintain airway and respiration.

Table-3: Postoperative pain (VAS)

VAS	*Group-T N=40*	*Group-N N=40*	*Group-F N=40*	
0-3	13(32.5%)	25(62.5%)	2(5%)	<0.001
3-7	24(60%)	13(32.5%)	5(12.5%)	
7-10	3(7.5%)	2(5%)	33(82.5%)	

X^2 = 75.6, DF (Degree of freedom) = 4, P<0.001

Significant difference in pain was reported among the groups (p<0.001). Most of the patients in Group N reported mild pain (62.5%) to moderate pain (32.5%). Only 5% of the patients in Group N

DOI: 10.18535/ijmsci/v3i7.2

were having sever pain. Compared to this more patients in Group F reported sever pain (82.5%). Most of the patients in Group T reported moderate pain (60%).

IV.DISSCUSSION

Manipulation of airway particularly laryngoscopy and endotracheal intubation is associated with increase in HR and BP resulting from sympathetic nervous system stimulation and catecholamine's release. Effective management of stress response to laryngoscopy and post operative pain are major concern for anesthetist during surgeries under GA. Opioids in adequate doses have been commonly used to prevent hemodynamic response to laryngoscopy and intubation. Good analgesic efficacy and sedative property makes opioids a better choice to be used as a part of premedication in GA. Opioids maintains hemodynamics at the time of laryngoscopy by suppressing release of sympathomimetic agents and provides analgesia by their action on pain receptors. Nalbuphine Tramadol and Fentanyl are commonly used opioids now a day. Nalbuphine is a semi synthetic opioid of phenenthrene series which is structurally related to agonist oxymorphone and the antagonist naloxone[11]. It has similar potency that of Morphine and results in respiratory depression at equipotent doses. However it demonstrates ceiling effect for respiratory depression with increasing doses. Maximum respiratory depression occurs at 30mg dose in average adults. Usual dose of Nalbuphine is 10-20mg every 4-6hrs. Onset of analgesia 2-3mins and duration of action is around 3-6hrs[11]. It has lesser tendencies for nausea and vomiting but causes more sedation. Tramadol is atypical weak synthetic opioid. It has low μ receptor affinity but also exerts GABAnergic, Noradrenergic and Serotonergic effects[12]. Potency is 10% that of Morphine. It causes no clinically significant respiratory depression at usual doses. Onset of analgesia 10min and duration of action is 2-3hrs. It is associated with higher incidences of nausea and vomiting[12]. Fentanyl is highly lipid soluble, highly protein bound synthetic opioid with analgesic potency 100 times that of Morphine. It is rapid in onset (3-4mins) and is having short duration (45mins -1hr.

Most of the previous studies compared morphine and pethidine with Tramadol, Nalbuphine, Fentanyl and its derivatives (Remifentanyl and Sufentanyl), in terms of analgesia[1,15,18,22,24,25,26,27,28,29,30] (intraoperative as well as postoperative), side effect profile[21,31,32], and attenuation of laryngoscopic response[11,13,20]. Morphine and pethidine are rare in use now a days due to their side effects like nausea and vomiting, delayed awakening and prolong respiratory depression. Tramadol, Nalbuphine and Fentanyl have replaced older opioids owing to their lesser side effects.

In our study we tried to compare relative efficacy and side effect profile of these three opioids: Tramadol, Nalbuphine and Fentanyl when used as premedication in General Anesthesia to attenuate stress response to laryngoscopy and postoperative pain relief.

We found Nalbuphine and Fentanyl to be superior to Tramadol when used in premedication in relieving stress response to laryngoscopy as SBP, DBP and HR did not rise significantly in immediate post intubation (IPI) period and returned to baseline early with Nalbuphine and Fentanyl. Fentanyl showed some decrease in HR in IPI owing to its vagomimetic effect. Study by Van den Berg et al[13] support this as they did not found Tramadol to attenuate the cardiovascular

DOI: 10.18535/ijmsci/v3i7.2

responses either chronotropic or inotropic to laryngoscopy and tracheal intubation when compared to Nalbuphine and Pethidine. Pang et al[14] found Tramadol to be less effective agent then Fentanyl in attenuating stress response to laryngoscopy, as when Tramadol was administered right before thiopental induction, the increase in heart rate lasted longer than Fentanyl. Muhammad Qamar et al[15] compared the hemodynamic response of equipotent analgesic doses of Morphine and Tramadol to laryngoscopy and endotracheal intubation and found Morphine is a better drug as compared to Tramadol for attenuation of laryngoscopy and endotracheal intubation response.

In our study postoperative pain was better managed with Nalbuphine and Tramadol as compared to Fentanyl. Van den Berg AA et al[16] also found Nalbuphine and pethidine superior to other opioid and nonopioid analgesic in ENT surgery. In our study most of the patients were having mild pain with Nalbuphine when compared to Tramadol where moderate pain was reported by majority though the difference was not found to be significant. This result was supported by the study of Van den berg et al[13] who found Nalbuphine better than Tramadol when given in premedication to provide postoperative analgesia in patients undergoing adenotonsillectomy. They found Tramadol and Nalbuphine to be equally effective in maintaining intraoperative vitals as in our study. Recovery in postoperative period was delayed with pethidine in their study which shows increase safety profile of Tramadol and Nalbuphine. Similarly in our study all the three drugs showed no significant respiratory depression and delay in recovery. Bone ME et al[17] also found lower pain scores with Nalbuphine when compared to Fentanyl in day care surgery. Shiv Akshat et al[18] found that Nalbuphine provides less effective intraoperative analgesia when compared to morphine in patients undergoing open gynecological surgery under general anesthesia. But Nalbuphine was found to be similar to morphine in providing postoperative analgesia and had similar hemodynamic and side effect profile. Delayed awakening or increase sedation score was found more associated with Nalbuphine than Tramadol and Fentanyl in our study but it was not significant. This is supported by the study done by Solanki et al[12] who also found more sedation scores in patients who received Nalbuphine as compared to Tramadol. Though, none of their patients had significant sedation as in our study. This was in contrary to study by Mostafa Galal et al[19] who found more sedation score with Tramadol as compared to Nalbuphine when given intrathecally along with 0.5%Bupivacaine for bladder surgery. Khalid Mahmood Siddique[20] also found Tramadol to be more sedative than Nalbuphine. Study by Crul J et al[21] who found fewer incidences of respiratory depression and nausea vomiting with Nalbuphine when compared to Fentanyl. Minai et al[22] also reported less nausea vomiting in Nalbuphine group compared to Morphine.

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