Comparison of epidural morphine and epidural buprenorphine - combined with general anaesthesia for laparoscopy assisted vaginal hysterectomies: A randomized double blinded study

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Abstract

Introduction: Epidural opioid when combined with general anaesthesia (GA) for laparoscopy assisted vaginal hysterectomies (LAVH) effectively attenuates stress response caused by carbon dioxide (CO_2) pneumoperitoneum. Moreover epidural opioids provide effective pain relief in the post-operative period.

Objectives: To compare intra-operative hemodynamics and post-operative pain relief between epidural morphine and epidural buprenorphine when combined with GA for LAVH.

Methods: 40 patients posted for LAVH under American Society of Anaesthesiologists (ASA) physical classification I and II were randomly allocated into two groups. Group M received 3mg morphine and Group B received 0.15mg buprenorphine with 14ml of 0.25% bupivacaine in epidural route before GA. Blood pressure and heart rate were recorded in all the patients before epidural injection, after induction of GA, after pneumoperitoneum along with trendelenburg position, every 10minutes after pneumoperitoneum and after desufflation and straightening the table. Duration of post-operative analgesia was recorded and injection tramadol in 50mg increments was used as rescue analgesia. Total tramadol consumption was also recorded in all the patients.

Results: There was a statistically significant decrease in heart rate and blood pressure over time in both the groups ($p<0.05$). When compared between the groups there was no statistical significance ($p>0.05$). The duration of analgesia was significantly longer in Group M compared to Group B ($p<0.05$). Total tramadol consumption in Group M was significantly lesser than Group B ($p<0.05$).

Conclusion: Epidural morphine and epidural buprenorphine are equally effective in attenuating stress response in LAVH when combined with GA. Epidural morphine provides better post-operative analgesia compared to epidural buprenorphine.

Keywords: Buprenorphine; Epidural; Hysterectomy; Laparoscopy; Morphine.

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Introduction

Laparoscopic surgery though has various advantages is often challenging to anaesthesiologists owing to its unique problems associated with it. Carbon dioxide pneumoperitoneum which is an integral part of laparoscopic surgery has various cardiovascular, respiratory and neurological effects. Tachycardia and hypertension due to absorption of carbon dioxide into systemic circulation are some of the cardiovascular manifestations.[1] Raised mean and peak airway pressures, decreased lung volumes, basal atelectasis and increased intrapulmonary shunting are some of the respiratory changes. Neurological changes include increased intracranial pressure with consequent reduction in cerebral perfusion due to hypercapnia. LAVH is a common gynecological procedure which has gained popularity over traditional abdominal hysterectomy as abdominal incision and its complications are avoided. Traditionally general anaesthesia is the preferred technique for LAVH as the cardiovascular and respiratory instability can be easily controlled but has the disadvantages of delayed post-operative recovery, poor post-operative pain relief and more incidences of post-operative nausea and vomiting (PONV). Though regional anaesthesia has the advantages of awake patient, quick recovery, good post-operative analgesia, short duration of stay, and less PONV but has its own demerits like respiratory embarrassment and a high risk of aspiration.[2] Combining epidural anaesthesia with the traditional GA using epidural opioids as preemptive analgesia has a better control of pnuemoperitonium induced stress response in laparoscopic surgeries as well as provides good post-operative analgesia so that early mobilization can be achieved and complications such as deep vein thrombosis can be avoided. Hence we have aimed this study to compare the effectiveness of epidural morphine and epidural buprenorphine in LAVH surgeries when combined with general anaesthesia. Our objective is to compare the effectiveness of these two drugs in obtunding intra-operative stress response and alleviating post-operative pain in patients subjected to LAVH surgeries. We have chosen LAVH surgery

because addition of trendelenburg position has more hypertensive response when compared to other laparoscopic procedures. Post-operative pain is also significantly higher in these patients because of extensive tissue handling, peritoneal stretch and prolonged duration of lithotomy position.

Material and Methods

This study was conducted in a 1000 bedded tertiary teaching hospital from January 2015 to December 2015, after scientific and ethical committee clearance. In our study we have used Portex®18G epidural needle with 18G epidural catheter. Injection (inj.) morphine 10mg/ml, inj. buprenorphine 0.3mg/ml and bupivacaine 0.5% were the drugs used for epidural analgesia. After getting informed consent, 40 patients of ASA physical classification I and II; who were included for the study were randomly allocated into two groups, group M (n=20) and group B (n=20). Patients who refused to participate in this study and patients of ASA physical classification III and IV were excluded from the study. The patients with intra-operative blood loss of more than 200ml were eliminated from the study. Sample size was chosen using power analysis. We have selected the sample size based on our aim to compare the hemodynamic changes from the baseline values, duration of post-operative analgesia and total consumption of analgesic supplements in 24 hours post-operative period, between group M and group B. We have used SAS version 9.0 statistical software to determine the sample size. A sample size of n=20 was arrived for a significance level of 0.05 (α=5%) and a power of 80%. Sealed envelope technique was used to prevent observer bias.

Oral premedication done with Tablet Alprazolam 0.5mg on the night before surgery. After shifting to the operating table an intravenous line using 18G cannula was placed and monitors like electrocardiogram, pulseoximeter and non-invasive blood pressure monitors were connected and the baseline heart rate, mean blood pressure and oxygen saturation were recorded. Under aseptic precaution an 18G epidural catheter through an 18G epidural needle was placed at L2-L3 (Lumbar segment) level after local infiltration with lignocaine.

The catheter was placed 5cm deep inside the epidural space. In group M patients inj. morphine 3mg added to 14ml of 0.25% bupivacaine and in group B patients inj.buprenorphine 0.15mg added to 14ml of 0.25% bupivacaine (Morphine and buprenorphine were loaded with insulin syringe for accuracy) was administered through the epidural catheter by a blinded anaesthesiologist. From then the vital parameters of the patients were monitored for every 3 minutes. All the patients had sensory block above T6 (thoracic segment) 15 minutes after epidural injection. After confirming sensory blockade, inj.fentanyl 2µg/kg, inj.midazolam 1mg, inj.ondensetron 4mg were given intravenously and patients were induced with inj.propofol 2-3mg/kg body weight titrated to loss of eyelash reflex. After induction blood pressure and heart rate were recorded. Patients were intubated with 7.5 size endotracheal tube after paralyzing with succinylcholine. General anaesthesia was maintained with fixed proportion of 50% nitrous oxide, 50% oxygen and 0.8% halothane. Ventilation was adjusted to maintain an end-tidal CO2 level of 30mmHg. Patients were placed in head down position after creating pneumoperitoneum following anaesthetic induction.

Mean blood pressure and heart rate were recorded after head down position, 10 minutes from then, till the end of the surgery and after straightening the table following release of pneumoperitoneum. Patients' heart rate and mean arterial pressure were monitored in the post-operative period for 24 hours. Post-operatively patients were monitored for adequacy of pain relief and the time of demand for first analgesia was recorded. Time from sensory blockade following epidural to demand for first analgesia was calculated as duration of analgesia. Post-operatively all patients were given rescue analgesia with inj. tramadol 50mg intravenously. The total tramadol consumption over 24 hours from end of the surgery was also noted. All the recordings were done by a blinded anaesthesiologist.

Statistical analysis: Statistical analyses were performed using SPSS version 22.0 software for windows (SPSS Inc., Chicago, USA). Heart rate and mean blood pressure changes at various points from the baseline value like, post-induction, after pnuemoperitonium and trendelenburg position, every 10 minutes after head down position and after release of CO2 pnuemoperitonium and straightening of the operating table were analyzed within each group and in between two groups using "Mauchly's test of sphericity". Parameters such as the duration of analgesia in the post-operative period and total Tramadol consumption in first 24 hours, in between two groups was analyzed using chi-square test. A 'p' value of less than or equal to 0.05 was considered significant.

Results

Table 1: Mean blood pressure changes over time in morphine (M) group

	Mean	Std. Deviation	N
Baseline MAP(0 min)	101.55	4.084	20
Post induction MAP 20 min	69.10	10.667	20
Insufflation and head low MAP 30 min	84.60	4.535	20
MAP 40 min	83.45	6.004	20
MAP 50min	83.30	3.895	20
MAP 60min	82.15	3.746	20
MAP 70 min	80.70	5.391	20
Desuflation and table straight	75.10	6.472	20

Mauchly's Test of Sphericity

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	difference	Significance
Time	.020	64.357	27	.000

(MAP-Mean Arterial Pressure)

There was statistically significant drop in blood pressure from baseline in Group M. (p value – 0.00) ($p<0.05$) [Table 1].

Table 2: Mean blood pressure changes over time in buprenorphine (B) group:

	Mean	Std. Deviation	N
Baseline MAP(0 min)	96.70	10.643	20
Post induction MAP 20 min	72.10	8.920	20
Insufflation and head low MAP 30 min	86.40	17.037	20
MAP 40 min	85.55	19.269	20
MAP 50min	85.75	16.986	20
MAP 60min	81.95	16.656	20
MAP 70 min	82.45	14.358	20
Desuflation and table straight	74.50	7.000	20

Mauchly's Test of Sphericity

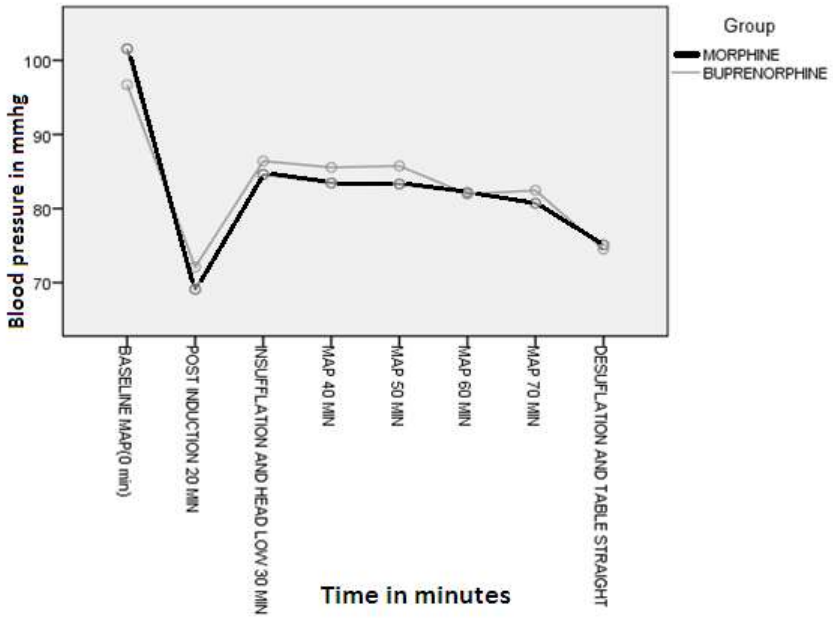
Within Subjects Effect	Mauchly's W	Approx. Chi-Square	difference	Significance
Time	.002	105.375	27	.000

There was statistically significant drop in blood pressure from baseline in Group B. (p value – 0.00) ($p<0.05$). [Table 2].

Table 3: Blood pressure change over time in between Group M and Group B pair wise comparisons

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Significance	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
Morphine	Buprenorphine	-.681	2.540	.790	-5.824	4.462
Buprenorphine	Morphine	.681	2.540	.790	-4.462	5.824

Graph 1: Change in blood pressure over time between group M and group B



There was no statistically significant change in blood pressure over time when compared between Group M and Group B. (p value – 0.79) (p>0.05). [Table 3, Graph 1]

Table 4: Mean Heart rate changes over time in morphine (M) group:

	Mean	Std. Deviation	N
Baseline HR (0 min)	87.85	11.600	20
Post induction HR 20 min	80.55	8.703	20
Insufflation and head low HR 30 min	81.10	7.826	20
HR 40min	73.35	10.168	20
HR 50min	68.85	9.965	20
HR 60min	67.15	10.282	20
HR 70min	66.55	9.736	20
HR after Desufflation	61.90	4.204	20

Manchly's Test of Sphericity

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	Difference	Significance	Epsilon		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.000	88.734	27	0.00	.279	.311	.143
HR - Heart Rate							

There was statistically significant drop in Heart rate from baseline in both Group M. (p value – 0.00) (p<0.05). [Table 4]

Table 5: Mean Heart rate changes over time in group B

Descriptive Statistics			
	Mean	Std. Deviation	N
Baseline HR (0 min)	97.15	7.293	20
Post induction HR 20 min	85.40	16.503	20
Insufflation and head low HR 30 min	79.40	15.548	20
HR 40min	75.45	12.563	20
HR 50min	72.05	12.492	20
HR 60min	70.90	12.247	20
HR 70min	69.95	12.471	20
HR after Desufflation	69.25	13.533	20

Mauchly's Test of Sphericity

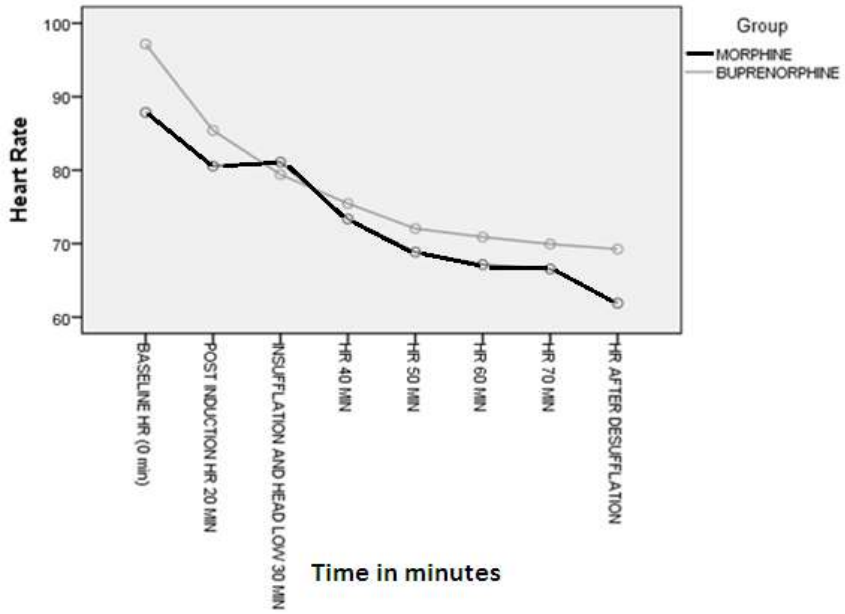
Within Subjects Effect	Mauchly's W	Approx. Chi-Square	Difference	Significant	Epsilon		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.000	226.625	27	.000	.330	.379	.143

There was statistically significant drop in Heart rate from baseline in Group B. (p value – 0.00) (p<0.05) (Table 5).

Table 6: Heart rate change over time in between Group M and Group B

Pairwise Comparisons						
(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Significance	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
Morphine	Buprenorphine	-4.031	3.324	.233	-10.760	2.697
Buprenorphine	Morphine	4.031	3.324	.233	-2.697	10.760

Graph 2: Change in heart rate over time between group M and group B

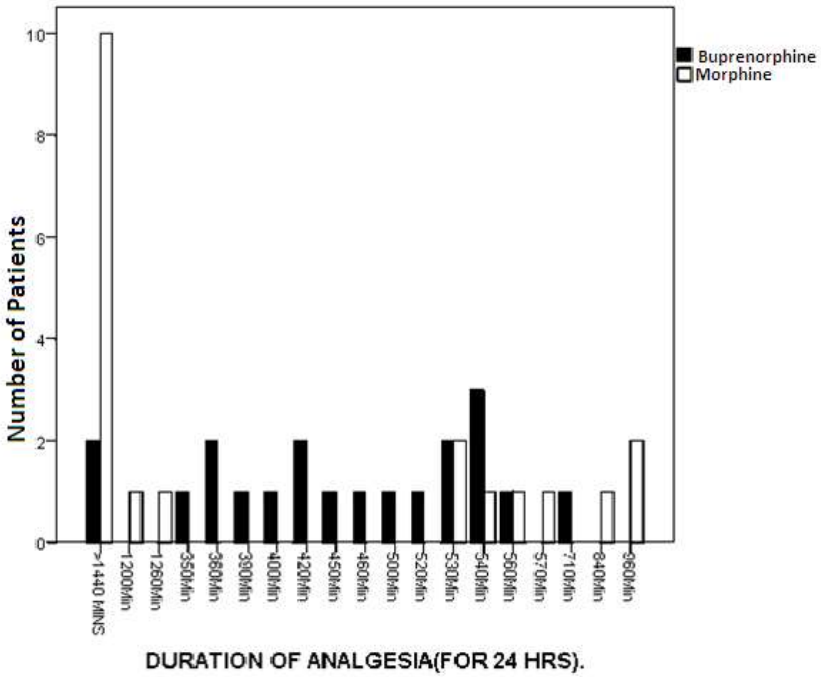


There was no statistically significant change in Heart rate over time from baseline when compared between Group M and Group B. (p value-0.233) (p>0.05).[Table 6, Graph 2]

Table 7: Comparison of duration of pain relief between Group M and Group B

Chi-Square Tests				
	Value	Difference	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	24.333[a]	18	.144	.035
Likelihood Ratio	31.822	18	.023	.058
Fisher's Exact Test	22.707			.025
N of Valid Cases	40			

Graph 3: Comparison of duration of analgesia over 24 hours between group M and group B

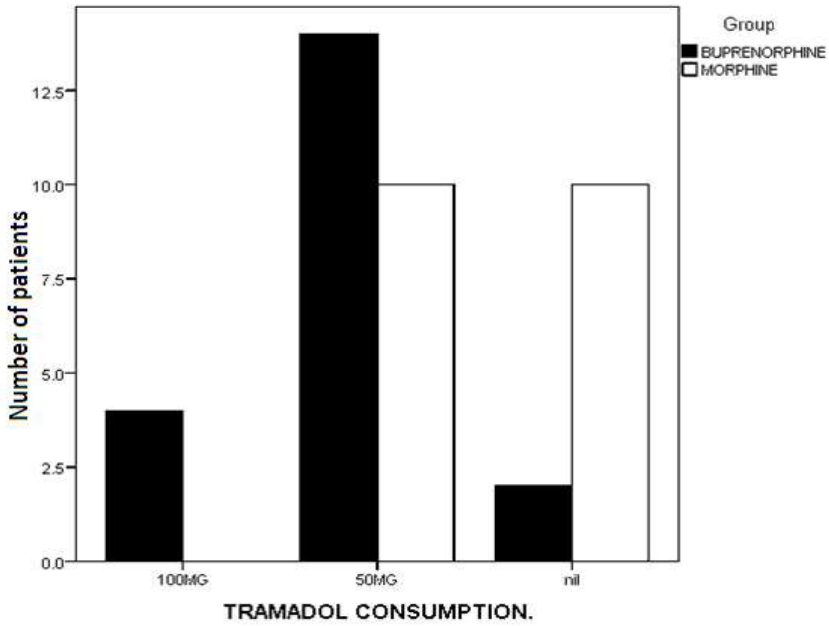


In Group M there was statistically significant increase in duration of analgesia compared to Group B. (p value – 0.025) ($p<0.05$) [Table 7, Graph 3]

Table 8: Comparison of total Tramadol consumption between Group M and Group B

Chi-Square Tests				
	Value	**Difference**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**
Pearson Chi-Square	10.000[a]	2	.007	.006
Likelihood Ratio	12.037	2	.002	.004
Fisher's Exact Test	9.678			.006
N of Valid Cases	40			

Graph 4: Comparison of total tramadol consumption in 24 hours between group M and group B



In Group M there was statistically significant decrease in Tramadol consumption compared to Group B. (p value – 0.025) ($p<0.05$). [Table 8, Graph 4]

Discussion

Compared to open surgeries, laparoscopic procedures are minimally invasive and offer advantages like small surgical scar, less post-operative pain, early ambulation, less morbidity and decreased duration of hospital stay. Co_2 which is used to create pneumoperitoneum in laparoscopic surgeries gets absorbed into the systemic circulation and causes hypercapnia which in turn stimulates the chemoreceptors of carotid sinus and aortic body leading to surge in plasma levels of catecholamines. Further co_2 pneumoperitoneum can cause pain due to stretch of diaphragm, peritoneum, and abdominal muscles. Both hypercapnia and stretch pain together can cause sympathetic stimulation which thereby results in tachycardia and hypertension.[1] Various modifications in surgical techniques have been done to alter the stress response in laparoscopic surgeries. Using low pressure pneumoperitoneum instead of the routine pressure pneumoperitoneum but found no significant alteration in systemic stress response.[3] Using nitroglycerin infusion to attenuate stress response, decreased the mean arterial pressure effectively but there was significant increase in heart rate which was not desirable.[4]

Clonidine, an α_2 adrenergic agonist is used successfully in many centres over years for attenuation of stress response in laparoscopic surgeries as it decreases both heart rate and mean arterial pressure.[5] Studies which compared the effects of oral, intramuscular and intravenous clonidine for decreasing the sympathetic stimulus in laparoscopic surgeries found significant decrease in heart rate and mean arterial pressure when given in intravenous route rather than intramuscular route.[6,7] Dexmedetomidine, another α_2 adrenergic agonist, not only decreases heart rate and mean arterial pressure in laparoscopic surgeries but also decreases analgesic consumption in the intra-operative and post-operative period.[7] One study which compared clonidine and dexmedetomidine for attenuation of stress response and analgesic consumption in laparoscopic gastric sleeve surgery concluded that both yielded similar outcome.[9] Another study which compared clonidine and fentanyl for attenuation of hemodynamic changes in laparoscopic surgeries, found both were equally effective.[10] Though clonidine and dexmedetomidine are very effective in attenuation of hemodynamic changes, both can cause bradycardia and hypotension in immediate post-operative period. Esmolol, and remifentanil had also been tried in laparoscopic surgeries for attenuation of stress response.[11, 12] The cost of esmolol and availability of remifentanil limits its use.

Sole regional techniques like spinal anaesthesia, epidural anaesthesia and combined spinal-epidural anaesthesia has been tried in laparoscopic surgeries. These techniques attenuate sympathetic response, prevents airway manipulation, provides awake patient and effective post-operative analgesia.[2] Requirement of high level of dermatomal blockade, severe hypotension, shoulder discomfort due to diaphragmatic irritation, respiratory embarrassment because of pneumoperitoneum as reported in studies, limits its use.[13]

LAVH is the preferred surgical technique compared to open hysterectomy because it is minimally invasive and abdominal incision is avoided. Compared to routine laparoscopic surgeries LAVH has got other considerations which are described below. Head down tilt done in all LAVH surgeries for better visualization of the uterus, can cause further increase in mean arterial pressure. Surgical dissection, trendelenburg position, and muscle stretch due to pneumoperitoneum can cause severe pain in the post-operative period.

Epidural analgesia offers better pain relief compared to intravenous opioids and non-steroidal anti-inflammatory drugs (NSAIDS) in these patients.[14] By suppressing intra-operative sympathetic stimulus and providing post-operative pain relief, epidural anaesthesia attenuates surgical stress, enhances early recovery and minimizes hospital stay.[15] When epidural anaestheisa was combined with general anaesthesia, serum epinephrine, insulin, and interleukin-6 levels were found to be significantly low in epidural group compared to control group which received only general anaesthesia.[16] This technique also decreases requirement of inhalational anaesthetics, intravenous opioids, and muscle relaxants thereby enhances recovery from general anaesthesia.[17,18] Further it partially compensates for the decrease in femoral blood flow due to venous stasis caused by pneumoperitoneum which creates pressure over inferior vena cava.[19]

Various opioids had been tried in epidural analgesia including morphine, buprenorphine, fentanyl, sufentanil and oxymorphone, among which morphine was found to provide prolonged pain relief.[20] Common disadvantages of epidural opioids are urinary retention and pruritus, since bladder was catheterized in all the LAVH patients one could not assess the incidence of urinary retention and the incidence of pruritus was less if used at lesser dose.[21]

LAVH is associated with hypertensive response because of CO_2 pneumoperitoneum and trendelenburg position. Intravenous opioids and NSAIDS were not effective in management of post-operative pain in these patients. Considering these two factors and based on evidences from previous studies we have designed this study to compare the efficacy of epidural morphine and epidural buprenorphine in attenuation of intra-operative sympathetic response and post-operative pain relief in

LAVH surgeries. We have chosen LAVH surgeries, as these surgeries are associated with exaggerated hypertension because of deep trendelenburg in addition to pneumoperitoneum. We have compared the efficacy of morphine 3mg and buprenorphine 0.15mg in epidural route when given along with general anaesthesia. The epidural dose of morphine and buprenorphine was adopted from previous studies.[20,22] The general anaesthesia technique used was also standardized.

There was a significant (but within safe limits) decrease in heart rate and mean arterial pressure in both groups following epidural injection and induction of general anaesthesia. After pneumoperitoneum and trendelenburg position the mean arterial pressure increased from post-induction levels, but not exceeding the baseline values. This effect was desired for LAVH surgery. There was no statistical difference in change in heart rate and mean arterial pressure when compared between two groups. Hence both epidural morphine and epidural buprenorphine were equally effective in attenuation of sympathetic stimulation following pneumoperitoneum. Serum markers of sympathetic stimulation like serum catecholamines and cortisol level estimation were not done; this might be the limitation of our study. The duration of analgesia was significantly prolonged in group M compared to group B. The total tramadol consumption was significantly less in group M compared to group B. This shows that epidural morphine provides better post-operative analgesia compared to epidural buprenorphine. Various options like continuous epidural technique for preemptive and post-operative analgesia and usage of additives like clonidine, dexmedetomidine, butarphanol etc. are available for future researches based upon our study.

Conclusion

Pre-emptive epidural analgesia with both morphine and buprenorphine attenuates sympathetic stimulation following pneumoperitoneum in LAVH surgeries. Epidural morphine provides better post-operative analgesia compared to epidural buprenorphine in LAVH surgeries.

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