

USES OF DEXMEDETOMIDINE AND FENTANYL AS ADJUVANTS IN EPIDURAL BLOCK WITH COMBINED ANAESTHETIC TECHNIQUE FOR GASTRECTOMY SURGERY

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ABSTRACT

Background: Opioids as epidural adjunct to local anaesthetics have been in use so long and the synergism between epidural local anaesthetic agents and opioids are well established. Dexmedetomidine (α -2 agonist) is being increasingly used for similar purpose but evidence for the combination of local anaesthetic agents with dexmedetomidine in epidural analgesia is limited. Gastric cancer is increasing day by day in our country and removal of tumor by gastrectomy surgery is choice of treatment. The present study was conducted to compare the analgesic, hemodynamic, sedative effects of epidurally administered dexmedetomidine and fentanyl when combined with bupivacaine in a patient undergoing gastrectomy surgery along with general anaesthesia.

Objective: Compare the effectiveness of epidural dexmedetomidine and fentanyl as an adjuvant to bupivacaine in gastrectomy surgery under general anaesthesia. **Materials and Methods:** This randomized controlled trial study was carried out in the Department of Anaesthesia, Analgesia and Intensive Care Medicine, BSMMU, Dhaka. The study was been conducted May 2019 to April 2020 after obtaining approval from the institutional Review Board and informed written consent from the patients. About 40 patients aged between 40 and 70 years, posted for gastrectomy surgery were included in this study. The patients were randomly allocated into two equal groups. Group A received general anaesthesia along with epidural fentanyl and bupivacaine. Group B received general anaesthesia along with epidural dexmedetomidine and bupivacaine. **Results:** Age, height, and weight were almost identical between two groups. Duration of surgery and anaesthesia were almost similar between two groups. Systolic blood pressures, diastolic blood pressure, MAP were almost similar between two groups and were statically not significant ($p > 0.05$). Mean heart rate of group B was significantly lower ($p < 0.05$) than that of group A. Post operative visual analog scale was reduced significantly ($p < 0.05$) in group B than group A. The time of first analgesic requirement was significantly higher ($p < 0.05$) in group B. The mean sedation score was also significantly higher ($p < 0.05$) in group B than group A. **Conclusions:** Dexmedetomidine seems to be a better alternative to fentanyl as an epidural adjuvant to local anaesthetics as it decreases pain intensity during post operative period, delayed time of first analgesic supplementation, provides better sedation level without harmful derangement on haemodynamics.

KEYWORDS: Dexmedetomidine, gastrectomy surgery, haemodynamic, anaesthesia.

INTRODUCTION

Gastric carcinoma is the fourth most common malignancy world wide and remains the second cause of cancer related death,^[1] the epidemiology of which has

changed within last decades. A trend of steady decline in gastric cancer incidence rate is the effect of increased standards of hygiene, nutrition and *H. pylori* eradication. The incidence shows a wide geographical variation,

more than half of the new cases occur in developing country.^[2] Incidence of gastric carcinoma is increasing day by day in Bangladesh. Surgical resection remains the gold standard in gastric cancer therapy. If a patient has a stage 0, I, II, III cancer and is healthy enough, surgery (often along with other treatment) offers the realistic chance for cure at this time. Intraoperative stable hemodynamic and optimum treatment for post operative pain has been of fundamental importance in surgical patient care.^[3] The anaesthetic technique which is conventionally used for gastric malignancy is general anaesthesia which almost always combining intravenous and inhalational agents. The downside of general anaesthesia includes inadequate pain control due to lack of analgesia and high incidence of nausea vomiting, increasing the length of hospitalization.^[4] Thoracic epidural analgesia along with general anaesthesia is an effective method for control of post operative pain and component of the enhanced recovery after gastrectomy surgery protocol because it facilitates earlier mobilization and oral food intake leading to shorter hospital stay and accelerate convalescence.^[5]

Major abdominal surgery is associated with extensive tissue destruction and postoperative pain. Epidural analgesia is the most preferred technique among the various existing analgesic methods. It provides early mobilization, accelerates recovery of gastro-intestinal function and reduction of pulmonary and cardiovascular morbidity in early postoperative period after abdominal surgery.^[6] Epidural analgesia decreases sympathetic outflow, preventing ileus and incidence of post operative myocardial infarction by providing favorable redistribution of coronary blood flow, attenuating the stress response and hypercoagulability.^[7] Administration of local anaesthetics at effective doses raise the concern about adverse events such as hypotension, bradycardia and motor weakness. So several adjuvants such as morphine^[8] fentanyl,^[9] clonidine,^[10] ketamine^[11] neostigmine,^[12] magnesium^[13] dexamethasone^[14] have been introduced for epidural usages with varying degree of efficacy. Opioids are considered the reference standards among those adjuvants. Unfortunately opioids carry risk for respiratory depression, delayed intestinal recovery, pruritus, nausea vomiting. Dexmedetomidine is α_2 agonist used for intravenous sedation in intensive care setting.^[15] The unique analgesic properties of dexmedetomidine have encouraged the anaesthesiologists to use it.^[16]

The dexmedetomidine is a potent and highly selective α_2 adrenoreceptor agonist with sedative, analgesic, anxiolytic, sympatholytic, amnesic properties.^[17] Dexmedetomidine exerts analgesic effect on spinal and supraspinal level. Suggested mechanism is activation of α_2 receptors causing decrease in nor-epinephrine release from pre-synaptic neurons with inhibition of postsynaptic activation in the brain stem.^[18]

The dexmedetomidine has the ability to potentiate the effect of all intra operative anaesthetics^[19] demonstrated that intraoperative administration of dexmedetomidine maintained haemodynamic stability by attenuating the stress-induced sympatho-adrenal responses for intubation, surgery and also emergence from anaesthesia. Most of the previous studies are related to the intraoperative administration of dexmedetomidine to relieve the surgery-induced acute pain relief. However, more studies are required to support its potential effect for postoperative pain relief and maintaining haemodynamic stability by using in epidural route.

Dexmedetomidine provides numerous beneficial effects when it is used through epidural route^[20] It acts on both pre and post synaptic sympathetic nerve terminal and central nervous system thereby decreasing the sympathetic outflow and nor-epinephrine release causing sedative, anti-anxiety, analgesic, sympatholytic and haemodynamic effects.^[21] Dexmedetomidine causes manageable hypotension and bradycardia but the striking feature of this drug is the lack of opioid related side effects like respiratory depression, pruritis, nausea, and vomiting^[22]

Bupivacaine is a long acting and potent amide local anaesthetic agent. It binds and inhibits voltage-gated sodium channel and thus prevents membrane depolarization of neurons. It produces its action within 10 to 20 minutes after infiltration having a biological half-life of about 3.5 hours in adults (relative duration of action is about 2-8 hours).^[23]

Fentanyl has been used traditionally as an adjunct for epidural administration in combination with a lower dose of local anaesthetic to achieve the desired anaesthetic effect.^[9] The addition of opioid provides a dose sparing effect of local anaesthetic and superior analgesia but there is always a possibility of an increased incidence of pruritis, urinary retention, nausea, vomiting and respiratory depression.^[24]

Although adjuvants like fentanyl have a dose-sparing effect and provide superior analgesia after major upper abdominal surgeries,^[5] there is always the possibility of an increased incidence of pruritus, urinary retention, postoperative nausea and vomiting and respiratory depression.^[24] Recently, it is found that use of fentanyl could result in post operative hyperalgesia with a paradoxical increase in the intensity of pain and subsequent fentanyl consumption due to opioid induced hyperalgesia.^[16]

Dexmedetomidine seems to be better alternative to fentanyl as an epidural adjuvant. It does not decrease gut motility, facilitates early enteral feeding, maintain ciliary function and blood flow of gut. It reduces time to anastomosis of gut, increases surgical compliance and reduces time of hospital stay. It does not cause post operative pruritus, nausea, vomiting.

METHODS

After approval from ethical committee of BSMMU, this prospective randomized study was conducted in the department of Anaesthesia Analgesia and Intensive Care Medicine Unit on Total 40 patients were included in this study who were scheduled for gastrectomy surgery, age 40-70 years old of either sex and physical status ASA I, II. Informed written consent with full explanation of the procedure was obtained from the patient before starting.

On arrival to the operation room, a 18-G intravenous cannula was secured and standard electrocardiograph, non invasive blood pressure and pulse oximetry monitoring were well established. Baseline heart rate, systolic, diastolic, mean arterial pressure were obtained. A preload with Ringer's lactate solution was done to every patient according to body weight before start of operation.

According to randomization code, each patient of group A was received a bolus dose of 6 ml of 0.1% bupivacaine and 1µg/ml fentanyl via epidural catheter before skin incision, followed by a continuous epidural infusion of 6ml/h of 0.1% bupivacaine and 1µg/ml fentanyl through syringe pump for 24 hours. Each patient of group B was received a bolus dose of 6 ml of 0.1% bupivacaine and 0.5µg/ml dexmedetomidine via epidural catheter before skin incision, followed by a continuous epidural infusion of 6ml/h of 0.1% bupivacaine and dexmedetomidine 0.5µg/ml dexmedetomidine through syringe pump for 24 hours.

For group A, the epidural administered medication was prepared as, 10ml 0.5% bupivacaine+1ml(50µg) fentanyl+39ml normal saline to obtain bupivacaine concentration of 0.1% and fentanyl 1µg/ml.

Hemodynamic variables such as systolic, diastolic, mean arterial pressure and heart rate were monitored before

administering anaesthesia and throughout intraoperative period. Hemodynamic variables were recorded at baseline, immediate after induction, every 15 minute thereafter till 30 minute and then 30 min there after till 120 min and till end of surgery. After completed surgery, patient were shifted to post operative ward, pain was assessed using 10 point visual analog scale (VAS) in which score 0 indicated no pain and score 10 indicated worst pain. Duration analgesia was recorded when VAS score was more than 4 in post operative period and rescue analgesic was given to patient.

Statistical analysis

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. Chi-Square test with Yates correction was used to analyze the categorical variables like sex, ASA status and surgical compliance which were shown with cross tabulation. Student t-test was used for continuous variables like systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) at different interval.

RESULT

This study was conducted in department of Anaesthesia, Analgesia, and Intensive Care Medicine of Bangabandhu Sheikh Mujib Medical University. The study duration was one year from May 2019 to April 2020. The sample size was 40 and they were selected as simple random sampling technique. The following parameters of my study were statically analyzed. Forty-Eight patients scheduled for gastrectomy surgery were assessed for the study eligibility and 42 patients were eligible and involved in the study. Two patients were excluded from the study (due to failure of localization of epidural space). Forty patients (20 patients in each group) remained for analysis.

Demographic data of my study patients are as follows:

Table I: Comparison of two groups by demographic variable (n=40).

Demographic variable	Group-A (n=20)	Group-B (n=20)	P value
Age (in years)	54.3±9.4	52.2±8.9	0.472
Height (cm)	157.9±5.2	156.6± 6.9	0.505
Weight (kg)	58.8±9.8	56.5±7.1	0.401
Sex			
Male	12(60.0%)	14(70.0%)	0.507
Female	8(40.0%)	6(30.0%)	
ASA physical status			
Grade I	15 (75.0%)	17(85.0%)	0.429
Grade II	5(25.0%)	3(15.0%)	

Values are expressed as percentage (%) and mean±SD, Data are analyzed by student's t test in age, height, weight and chi square test in sex, ASA physical status. p value <0.05 considered as significant. n = number of study population.

Table I shows demographic variable of the study patients. It was observed that mean age was found 54.3±9.4 years in group A and 52.2±8.9 in group B. Male were predominate in this study patients in both groups, which was 12(60.0%) in group A and 14(70.0%)

in group B. Most of the patients 15(75.0%) in group A and 17(85.0%) in group B in ASA physical status I. The

difference was statistically not significant ($p>0.05$) between two groups.

Table II: Comparison of two groups in term of duration of anaesthesia and surgery.(n=40)

Duration of anaesthesia and surgery	Group-A (n=20)	Group-B (n=20)	P value
Duration of anaesthesia (mins)	149.8±12.5	142.2 ±10.8	0.137
Range (min, max)	120-160	100-160	
Duration of surgery (mins)	107.4±10.3	101.6±10.7	0.088
Range (min, max)	90-130	70-140	

Values are expressed as mean±SD, Data are analyzed by student 't' test. p value <0.05 considered as significant. n = number of study population.

difference was statically not significant($p>0.05$) between two groups.

Table II shows mean duration of anaesthesia and surgery of the study patients, it was observed that the mean duration of anaesthesia was found 149.8±12.5 mins in group A and 142.2 ±10.8 mins in group B. The

Mean duration of surgery was found 107.4±10.3 mins in group A and 101.6±10.7 mins in group B. The difference was statistically not significant ($p>0.05$) between two groups.

Table III: Comparison of two groups by the time of first rescue analgesic requirement in post operative period. (n=40)

Analgesic requirement	Group-A (n=20)	Group-B (n=20)	P value
Time of first rescue analgesic requirement (minutes)	168.6±38.9	258.6±32.8	0.001

Values are expressed as mean±SD, Data are analyzed by student 't' test. p value <0.05 considered as significant. n = number of study population.

patients; it was observed that mean time of first analgesic requirement was found 168.6±38.9 minutes in group A and 258.6±32.8 minutes in group B. The difference was statistically significant ($p<0.05$) between two groups.

Table III shows that time of first rescue analgesic requirement in post operative period of the study

Table IV: Comparison of two groups in term of heart rate.(n=40)

Heart rate (bpm)	Group-A (n=20)	Group-B (n=20)	P value
Baseline	82.86±4.75	80.60±4.45	0.128
During induction	92.80±4.46	93.20±4.47	0.779
At 15 minute	76.60±4.95	76.90±4.83	0.847
At 30 minutes	74.20±5.00	69.75±9.28	0.001
At 60 minutes	72.85±4.64	68.30±2.83	0.001
At 90 minutes	78.75±7.62	73.60±5.62	0.019
At 120 minutes	80.95±5.45	75.45±6.89	0.001

Values are expressed as mean±SD, Data are analyzed by student 't' test. p value <0.05 considered as significant. n = number of study population.

heart rate at baseline, during induction, 15 minutes were not statically significant between two groups ($p>0.05$). But at 30, 60, 90, 120 minutes the differences were statically significant ($p<0.05$) between two groups.

Table IV shows heart rate in different follow up of the study patients. It was observed that the difference of

Table V: Comparison of two groups in term of systolic blood pressure. (n=40)

Systolic blood pressure (mmHg)	Group-A (n=20)	Group-B (n=20)	P value
Baseline	130.65±12.40	125.45±14.70	0.334
During induction	135.70±16.80	131.10±12.50	0.332
At 15 minutes	122.90±16.10	115.70±14.80	0.068
At 30 minutes	123.80±12.70	119.30±14.80	0.335
At 60 minutes	124.90±12.30	121.10±12.40	0.334
At 90 minutes	125.40±14.40	119.10±12.30	0.145
At 120 minutes	117.90±12.90	117.10±14.40	0.273

Values are expressed as mean \pm SD, Data are analyzed by student 't' test. p value <0.05 considered as significant. n = number of study population.

Table V shows systolic blood pressure at baseline, 15, 30, 60, 90, 120 minutes between two groups. The differences of mean systolic blood pressure between two groups were statistically not significant ($p>0.05$).

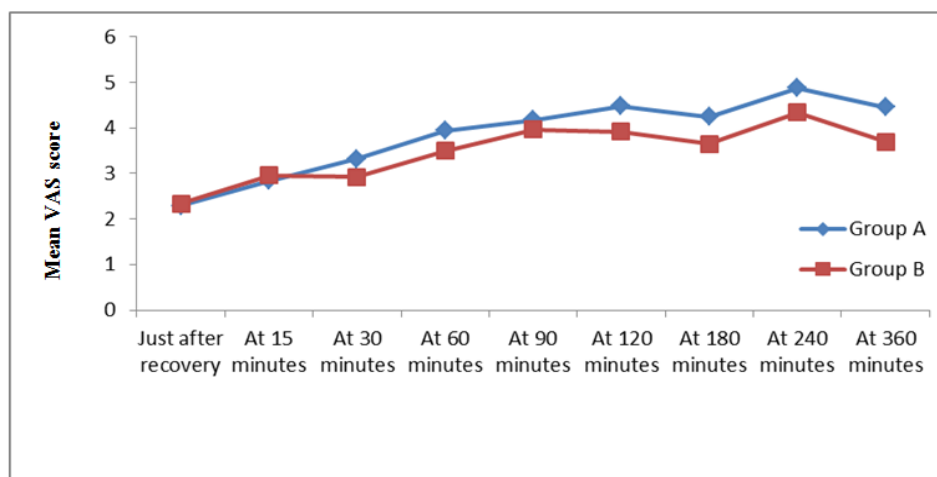


Figure I: Line diagram shows mean VAS score.

It was observed that VAS score just after recovery, at 15 minutes in post operative period no statically significant difference between two groups ($p>0.05$). But at 30, 60,

90, 120, 180, 240, 360 minutes in post operative period the differences were statically significant ($p<0.05$) in term of VAS score between two groups.

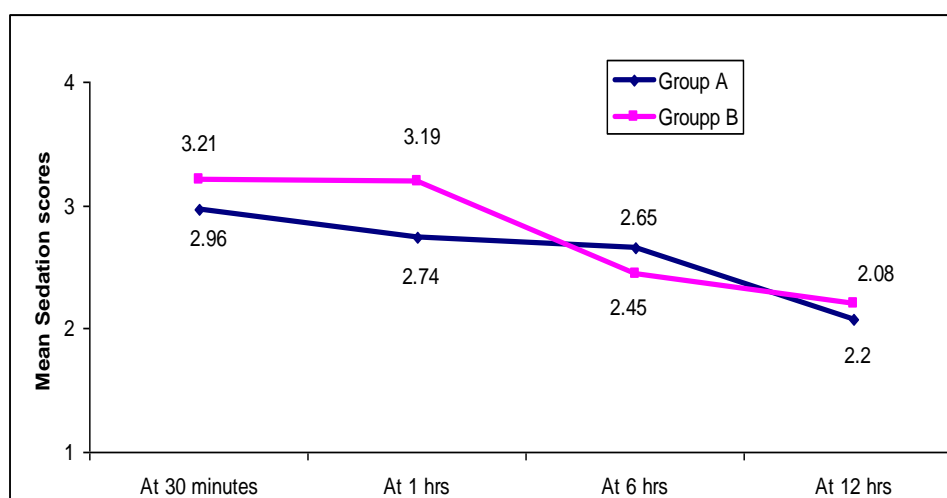


Figure II: Line diagram shows mean sedation scores. (Ramsay sedation score)

It was observed that Ramsay sedation score at 30 mins, 1 hour, 6 hours, 12 hours in post operative period between two groups. The differences were statically significant (p

<0.05) between two groups. Data were analysis using chi square test.

Table VI: Surgeons' satisfaction during operation between two groups. (n=40)

Surgeons' satisfaction (Numerical rating scale)	Group-A (n=20)		Group-B (n=20)		P value
1 (Very dissatisfied)	0	0.0	0	0.0	
2 (Dissatisfied)	0	0.0	0	0.0	
3 (Neutral)	1	5.0	0	0.0	0.539
4 (Satisfied)	8	40.0	7	35.0	
5 (Very satisfied)	11	55.0	13	65.0	

Values are expressed as percentage (%), Data are analyzed by chi square test. p value <0.05 considered as significant. n = number of study population.

Table VI showed that majority (55.0%) surgeon very satisfied in group A and (65.0%) in group B. The difference was statistically not significant ($p>0.05$) between two groups.

DISCUSSION

Gastrectomy surgery is conventionally done under general anaesthesia. General anaesthesia has some drawbacks such as intra and post-operative hypertension, increasing blood loss, which may in turn lead to a prolonged surgical time, an increased need for blood transfusion and delayed wound healing^[26] General anaesthesia along with epidural is an alternative which carries more advantages. Epidural analgesia offers superior pain relief and early mobilization especially when local anaesthetic dose is combined with an adjuvant as compared to LA used alone.^[27] The administration of epidural opioids under general anesthesia was examined by Bourke *et al.* for laminectomy operation and they found that it provided better pain control with fewer doses required for analgesia. Opioids are usually associated with an increased incidence of, shivering, and pruritus. Recently, it was found that opioids could result in post operative hyperalgesia with a paradoxical increase in the intensity of pain and subsequent opioid consumption.^[16] Dexmedetomidine causes a manageable hypotension and bradycardia, but the striking feature of this drug is the lack of opioid related side effects such as respiratory depression, pruritus, nausea, and vomiting.^[22]

In this study it was observed that mean age group of group A was 54 ± 9.4 and group B was 52.2 ± 8.9 . It was also observed that majority of the patients (60%) belonged to age > 50 years and the difference in the mean age between two groups was not statically significant ($p>0.05$).

Cho *Js et al.* 2017³⁰ showed that mean age of group A was 51.7 ± 10.7 and group B was 54 ± 10.7 . In their study the mean age between two groups had no significant difference ($p>0.05$). In that study they compared the effect of patient controlled epidural and intravenous analgesia on post operative bowel function after laparoscopic gastrectomy surgery. They used ropivacaine and fentanyl as adjuvant in patient-controlled analgesia and ramifentanyl as intravenous analgesia. They measured the post operative pain score, post operative bowel function and duration of hospital stay.

Bajwa *et al.*^[20] showed that mean age of compared groups were lower than my study. In this study compared cardio respiratory parameter, sedation score, time to onset of analgesia, maximum sensory analgesic level and time to first analgesic requirement in two groups who were getting epidural dexmedetomidine and fentanyl for

lower orthopedic surgeries. Orthopedic surgeries may occur any age group but gastric cancer surgeries usually occur in specific age group. So age group was smaller than my study.

Sarkar *et al.*^[28] compared between epidural dexmedetomidine and epidural fentanyl in post operative pain control in lower limb surgery. In this study age of patient range from 20-50. Maximum number of patients presented in 20-30(41.7%). The result was conflicting with my study.

In this study it was found that most of the patients of both groups belonged to ASA I. In group A 75% patients were ASA I and In group B 85% were ASA I. The difference of ASA physical status between two group statically not significant. ($p>0.05$)

In this study systolic, diastolic and mean arterial pressures were lower in group B then group A at different times but it was not statically significant ($P>0.05$).

Sarkar *et al.*^[29] showed conflicting result with my study. In this study mean systolic pressure was lower in fentanyl group than dexmedetomidine group which was statically significant ($p<0.05$). For the diastolic pressure difference between two groups was not statically significant($p>0.05$).

In this study showed that mean heart rate is lower in group B than group A. In this study heart rate is significantly lower in group B in different times such as 30, 60, 90, 120 minutes ($p<0.05$) and other point of times statically not significant ($p>0.05$).

Bajwa *et al.*^[20] observed a more prominent reduction in heart rate in patients receiving epidural dexmedetomidine as compared with fentanyl. Dexmedetomidine leads to reductions in heart rate by increasing vagal tone and reducing sympathetic drive.

In this study first rescue analgesic time is more in group B than group A. The result is statically significant. ($P<0.05$).

Bajwa *et al.*^[20] showed in study time to first rescue analgesic is more dexmedetomidine and fentanyl group.

In this study showed VAS score is lower in dexmedetomidine group than fentanyl group. The mean VAS score in post operative period was similar to group A and group B. The difference was not statically significant ($p>0.05$). Then VAS score reduced more in group B than group A and the differences were statically significant in 30, 60, 90, 120, 180, 240, 360minutes ($p<0.05$).

Bajwa *et al.*^[20] showed similar findings of my study. In this study it was observed that in dexmedetomidine

group 38% and 42% of patient exhibited grade II and grade III sedation as compared to 16% and 2% in fentanyl group. So sedation was significantly more in dexmedetomidine group than fentanyl group. ($p < 0.001$).

Muhamad et al.^[6] showed OAAS sedation score is less in dexmedetomidine group than fentanyl group which was not statically significant. ($p > 0.05$). So dexmedetomidine provided better sedation level, than fentanyl. In this study dexmedetomidine and fentanyl epidural infusion along with bupivacaine was used in thoracic epidural for gastrectomy surgery. The result was similar to my study.

In this study showed that most of the surgeons are very satisfied it was 55% in group A and 65% in group B. The satisfaction level is better in dexmedetomidine group due over all well maintained hemodynamics and less complication with better surgical compliance. But difference was not statically significant ($P > 0.05$).

Despite the clinically safe result observed in my study with regards to possible adverse events of dexmedetomidine, there were not able to find any significant difference in respiratory depression, bradycardia, hypotension, shivering along with fentanyl group. In my study in group A 10% patients had vomiting, 5% patient had bradycardia, hypotension, shivering. In group B 10% patients suffering from bradycardia and hypotension. It was showed that vomiting is more in fentanyl group and hypotension, bradycardia was higher in dexmedetomidine group as intra and post operative complication.

Bajwa et al.^[20] showed nausea, vomiting occurred in 26% and 14% of the patients in fentanyl group as compared 14% and 4% in dexmedetomidine group. This study showed similar findings of my study.

CONCLUSION

Epidural analgesia with dexmedetomidine and bupivacaine is effective and safe, reduces post operative pain, produce better sedation and keeps the hemodynamic status more stable than epidural fentanyl and bupivacaine during intraoperative period in patient undergoing gastrectomy surgery.

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