ejpmr, 2017,4(05), 481-487

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

"EFFICACY OF DEXMEDETOMIDINE AND FENTANYL AS ADJUNCTS TO EPIDURAL BUPIVACAINE FOR LOWER ABDOMINAL SURGERIES."

Sofi Khalid*, Tantry Tariq Gani, Mir Waheed, Bhat Khairat,

Department of Anaesthesiology and Critical Care, Sher-i- Kashmir Institute of Medical Sciences, Soura, Srinagar, 190011, Kashmir, India.

***Corresponding Author: Dr. Sofi Khalid, MD**

Department of Anaesthesiology and Critical Care, Sher-i- Kashmir Institute of Medical Sciences, Soura, Srinagar, 190011, Kashmir, India.

Article Received on 01/03/2017 **Article Revised on 22/03/2017** **Article Accepted on 12/04/2017**

ABSTRACT

Background and Aims: This prospective, randomized, double blind study was undertaken to establish the effect of addition of fentanyl or dexmedetomidine, as an adjunct to epidural bupivacaine in lower abdominal surgeries. **Materials and Methods**: Ninety ASA (American Society of Anesthesiologists) class I and II patients undergoing lower abdominal surgeries were enrolled to receive either saline (Group BS) or fentanyl (Group BF) or dexmedetomidine (Group BD) along with epidural bupivacaine for surgical anesthesia. All the study subjects received an epidural anesthesia with 20 ml of 0.5% bupivacaine along with either saline 2ml (Group BS) or fentanyl 1mcg/kg (Group BF) or dexmedetomidine 1.0 µg/kg (Group BD). The onset of motor and sensory block, duration of block, hemodynamic parameters, and adverse events were monitored. **Results**: Analgesia in the postoperative period was better in Group BD, together with duration of sensory and motor blockade.However incidence of sedation was more in the BD group. **Conclusion**: Hence, addition of Dexmedetomidine to epidural bupivacaine can be advantageous with respect to early onset of both sensory and motor block and increased duration of motor and sensory blockade and arousable sedation.

KEYWORDS: Dexmedetomidine, Epidural, Fentanyl and Bupivacaine.

INTRODUCTION

Pain is a protective mechanism designed to alert the body to potentially injurious stimuli. The International Association for study of pain (IASP) has defined pain as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage". Uncontrolled postoperative pain may activate sympathetic nervous system and thereby contribute to morbidity and mortality. Sympathetic activation may increase myocardial oxygen consumption, which may lead to myocardial ischemia and infarction.[1,2] Sympathetic activation may also delay return of postoperative gastrointestinal motility, which may develop into paralytic ileus. Numerous studies have demonstrated the benefits of epidural blockade. Epidural anaesthesia or analgesia can reduce the adverse physiologic responses to surgery such as autonomic hyperactivity, cardiovascular stress, tissue break down, increased metabolic rate, pulmonary dysfunction and immune system dysfunction. Thoracic epidural analgesia has been shown to decrease the incidence of myocardial infarction and postoperative pulmonary complications.[3,4] Epidural anaesthesia and analgesia also decreases the incidence of hypercoagulability.[5] Bupivacaine is a potent long acting amide local anesthetic. It has a slow onset and long duration of action. Its longer duration of action and tendency to provide more sensory than motor blockade has made it a popular drug for prolonged analgesia. It has also been noted that there is a period of analgesia that persists even after the return of sensation. Alpha 2 (α_2) adrenergic agonists have been the focus of interest for their sedative, analgesic, perioperative and sympatholytic, anesthetic-sparing and hemodynamic stabilizing properties. Dexmedetomidine is a highly selective $\alpha_2$adrenergic agonist with a relatively high ratio of α_2 to α_1 activity (1620:1) as compared to clonidine (220:1). Lack of respiratory depression makes it a useful and safe adjunct in diverse clinical applications. Fentanyl is 75 to 125 times more potent than morphine. A single dose of fentanyl administered IV has a more rapid onset and shorter duration of action than morphine. The greater potency and more rapid onset of action reflect the greater lipid solubility of fentanyl compared with that of morphine, which facilitates its passage across the blood brain barrier. Likewise the shorter duration of action of a single dose of fentanyl reflects its redistribution to inactive tissue sites such as fat and skeletal muscles with associated decrease in its plasma concentration. The lungs also serve as a large inactive storage site with an estimated 75% of the initial fentanyl dose undergoing first pass pulmonary uptake. Addition of opioid to local anesthetics gives the opportunity to use more diluted local anesthetic solutions for better analgesia, and

reduces systemic toxicity risk and motor block incidence of local anesthetics.

AIMS AND OBJECTIVES

The present study was done to evaluate the efficacy of dexmedetomidine 1 mcg/kg (2ml) versus fentanyl 1 mcg/kg (2ml) as adjunct to epidural bupivacaine 0.5% (20ml) in lower abdominal surgeries. The variables studied include, onset of anaesthesia, duration of analgesia, postoperative analgesic requirement for first 24 hours, alteration in vital signs (non-invasive blood pressure, heart rate, SPO_2) and adverse effects.

MATERIALS AND METHODS

This clinical study was conducted after approval by the Institutional Ethical Committee and an informed written consent was obtained from all the patients for participation in this study. A total number of 90 ASA I and II patients of either sex belonging to age group 20-60 years posted for elective lower abdominal surgery (obstetric, gynecological, lower limb, perenial and other lower abdominal surgeries) were enrolled for the surgery. Pre-anaesthetic evaluation was done for all patients. Patient refusal, raised intracranial tension, bleeding disorders or anticoagulation, infection at local site, hypersensitivity to study drugs, deformity of lumbar spine were considered as contraindications and these patients were excluded from the study. All the patients were premedicated with oral ranitidine 150mg night before surgery. On arrival to operation theatre, intravenous line was secured with 18G cannula. Standard anesthetic monitoring like electrocardiogram, noninvasive blood pressure, pulse oximetry and temperature was applied to all patients. All the baseline parameters (heart rate, blood pressure, oxygen saturation, respiratory rate) were recorded prior to epidural block. All the patients were preloaded with lactated ringers solution 20 ml/kg prior to epidural block. Patients were allocated randomly to three groups by systematic random sampling to receive one of the three solutions in epidural anesthesia. Group BS received Bupivacaine 0.5%(20 ml)+ saline 0.9%(2ml), Group BF received Bupivacaine 0.5% (20ml) + Fentanyl (1 mcg/kg) (2ml) and Group BD received Bupivacaine 0.5%(20 ml) + Dexmedetomidine (1ug/kg) (2ml) respectively. An anesthesiologist not involved in study prepared the study solutions. The procedure was carried out in lateral decubitus or sitting position using 18 gauge Tuohy epidural needle whichever was comfortable for the patient. Epidural space was identified at L3-L4 space with loss of resistance to air technique. A 20 gauge catheter was advanced for 3-5 cm into the epidural space. Correct placement of epidural catheter was verified with test dose of 3 ml lignocaine (2%) with epinephrine 1:200,000. In case of any motor block or significant rise in heart rate, patients were excluded from the study. Hypotension was defined as systolic blood pressure of < 90mmHg or drop of more than 20% from basal mean arterial blood pressure and bradycardia as heart rate less than 60 beats per minute and was treated with intravenous ephedrine 5-10 mg bolus doses and iv atropine 0.01 mg/kg bodyweight respectively. Oxygen supplementation was provided in case of respiratory depression, that is SpO_2 < 90% and respiratory rate < 10 per minute.The parameters observed after administration of epidural block were time to onset of sensory block at T6 dermatome level, time to complete motor block, first feeling of pain/ rescue analgesia, sedation score and any untoward incident or side effect. Sensory block was checked with pinprick sensation started from symphysis pubis in midline and then checked proximally. Motor blockade was assessed by Modified Bromage Scale' as: Grade 0= No Paralysis, Grade 1= unable to raise extended leg against gravity but able to flex knee, Grade 2= unable to flex knees but able to flex ankle and Grade 3= unable to flex ankle and foot. Sedation was assessed at intervals of 20 minutes intraoperative and at intervals of 2 hour postoperatively.

Sedation was assessed by Subjective Sedation Scale as Grade 0 =Awake conscious no sedation to slightly restless, Grade 1= Calm and compose, Grade 2 = Awake on verbal command, Grade 3= Awake on gentle tactile stimulation, Grade 4= Awake on vigorous shaking and Grade 5= Unarousable.

Any untoward incident or side effect like nausea, vomiting, hypotension, respiratory depression, drowsiness, headache, dizziness, and urinary retention was recorded. Patients were evaluated for 24 hours regarding total duration of analgesia, and postoperative analgesic requirements. Pre and postoperative pain was recorded by using Visual Analogue Scale (VAS) between 0 and 10 (0 = no pain, 10 = most severe pain). Rescue analgesia was given on VAS score of more than 4. For rescue analgesia, 6ml of 0.25% bupivacaine was administered through epidural catheter. Descriptive statistical analysis was carried out. Analysis of variance (ANOVA) was used to find the significance of study parameters on continuous scale. Chi-square/Fisher Exact test were used to find the significance of study parameters on categorical scale. P value ≤ 0.05 was considered statistically significant. The statistical software namely SPSS 17.0, was used for analysis.

RESULTS

The three groups were comparable with respect to age, weight, sex, and ASA Status (Table 1).Baseline cardiorespiratory parameters were comparable between the groups (Table 2).

Table 1: Comparison of demographic profile parameters of the BS, BF and BD groups

Parameters	Group BS	Group BF	Group BD
Age (years)	46±11.24	44.5±12.24	46.76±11.732
Weight (kg)	66.4±7.758	64.9±7.989	63.666±7.359
ASA (I/II)	18/12	17/13	18/12
Gender M/F	23/07	15/15	18/12
P>0.05			

Table 2: Comparison of baseline cardiorespiratory parameters

Parameters	Group BS	Group BF	Group BD
Preop HR	73.7±7.19	72.1±6.728	73.5±7.099
Preop SBP	124.433±9.583	125.533±8.740	124.366±8.787
Preop DBP	78.96±6.21	78.4±6.991	78.00±7.235
PreopRR	16.3±1.41	16.266±1.741	16.466±2.013
Preop MAP	94.1222± 6.43892	94.1111± 7.3267	93.4556 ± 6.959
Preop SpO_2	98.07±0.583	97.7±0.952	97.87±0.86
P>0.05			

Table: 3 Comparison of initial block characteristics

Parameters	Group BS	Group BF	Group BD
Time to maximum sensory blockade at T6 level	18.23 ± 0.97	13.73± 1.08	10.07± 0.94
Time to complete motor block (minutes)	27.8 ±1.42	23.17+0.87	18.03+1.56
P<0.01			

Onset of sensory block at T6 level and time to complete motor block was significantly lower in Group BD as compared to other groups with p value of <0.01 (Table 3).

Table: 4 Comparison of intraoperative and postoperative block characteristics

Parameters	Group BS	Group BF	Group BD
Duration of motor blockade (regression to Bromage 0)	129.13 ± 12.36	255.03 ± 16.03	451.3 ± 22.41
Time to first feeling of pain (minutes)	171.1±11.37	381.46±15.28	621.83±22.91
Total no of top up doses	6.4±0.81	4.53±0.68	2.96±0.81

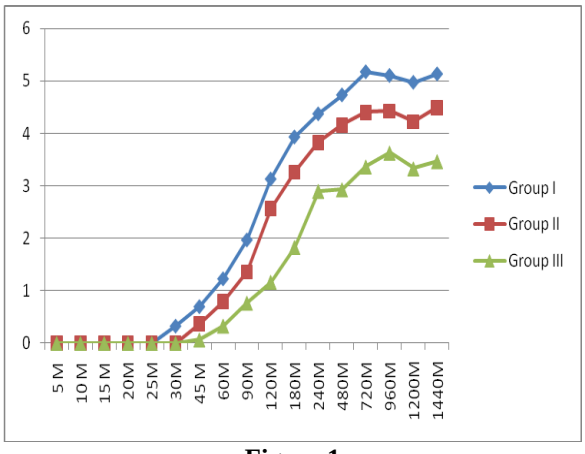

Figure 1

The duration of motor block/motor regression to Bromage scale 0 in Group BS ranged from 110 to 155 minutes with a mean of 129.13 ± 12.36 minutes, in Group BF from 238 to 295 minutes with a mean of 255.03 ± 16.03 minutes and in Group BD from 408 to 491 minutes with a mean of 451.3 ± 22.41 minutes. The difference was statistically significant between the groups with p value of < 0.01(Table 4). Although wide variations were seen in intra and postoperative pain score, however, dexmedetomidine group had lowest VAS score compared to control and fentanyl group. VAS at different time intervals was significant between three groups (P <0.01) (Figure 1). The time gap between initial epidural medication and the time to 1st epidural top-up was highest 621.83±11.37 mins in Group BD followed by Group BF 381.46± 15.28 mins and 171.1±22.91mins in Group BS of patients. The difference among groups was statistically significant (p=<0.01). The number of top-ups was also reduced in Group BD as compared to Group BF and Group BS (p=<0.01) (Table 3).

Table 5: Comparison of intraoperative and postoperative cardiorespiratory parameters

Parameters	Group BS	Group BF	Group BD
Intraop and postop HR	84.159±3.08	82.04±2.81	74.18±3.02
Intraop and post-op SBP	119.548±2.732	118.198±2.597	117.435±2.4
Intraop and postop DBP	77.66±1.627	77.99±2.040	77.09±2.480
Intraop and postop RR	17.37±0.31	17.53±0.38	17.32±0.23
Intraop and postop MAP	84.21±8.78	83.08±7.96	84.56±8.24
Intraop and postop SpO_2	98.52±0.21	98.56±0.21	98.52±0.19

There was a non-significant change in SBP, DBP, MAP, RR and SPO_2 during intra-operative and postoperative period. A significant difference in mean pulse rate ($p \leq 0.0001$) between Group BS and Group BD and non-significant difference ($p > 0.05$) between Group BS and Group BF was found (Table 5).

Table: 6 Incidence of side effects in patients of all the three groups

Parameters	Group BS	Group BF	Group BD
Nausea	3	6	5
Vomiting	3	5	4
Hypotension	8	10	13
Bradycardia	8	6	12
Respiratory depression	0	0	0
Headache	2	3	3
Dry mouth	1	2	5
Shivering	4	3	9
Dizziness	2	2	3
Urinary retention	2	4	3

There was no significant difference between the three groups regarding nausea, vomiting, urinary retention, dizziness, dry mouth, shivering, headache, hypotension and bradycardia. ($P > 0.05$).

Table: 7 Sedation Score

Characteristics	Group BS(n = 30)		Group BF (n = 30)		Group BD(n = 30)	
	Number	Percent	Number	Percent	Number	Percent
Sedation score 0	30	100	2	07	00	00
Sedation score 1	00	00	21	70	06	20
Sedation score 2	00	00	06	20	09	30
Sedation score 3	00	00	01	03	15	50
Sedation score 4	00	00	00	00	00	00
Sedation score 5	00	00	00	00	00	00

N = Number of patients in each study group

In our study no patient in control group had sedation. Sedation score 1 was found in 21(70%) patients in group BF and 6 (20%) patients of group BD. Sedation score 2 was found in 6(20%) in group BF, 9(30%) in group BD. Sedation score 3 was found in 1(3%) in group BF, 15(50%) in group BD. Sedation score 4 and 5 was not found in any patient. Statistically the relation between groups is significant ($p < 0.01$) (Table 7).

DISCUSSION

Epidural analgesia offers superior pain relief and early mobilization especially when local anesthetic dose is combined with an adjuvant as compared to LA alone.[6] Selection of exclusive epidural route during this study was done to avoid invasive dural penetration technique with spinal needle as well as to provide postoperative pain relief. The synergism between epidural local anesthetics and opioids is well established but evidence regarding combination of LA with dexmedetomidine through epidural route is scarce in literature.[7,8] The use of neuraxial opioids is associated with quite a few side effects, so various options including α_2 agonists are being extensively evaluated as an alternative with emphasis on opioid-related side effects such as respiratory depression, nausea, urinary retention and pruritus.[9-11] The pharmacologic properties of α_2 agonists have been extensively studied and have been employed clinically to achieve the desired effects in regional anaesthesia.[12-15] Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis.[16,17] In humans, the dose of epidural dexmedetomidine reported is in the range of 1.5-2 mcg/kg. Fukushima *et al.* administered 2 mcg/kg epidural dexmedetomidine for postoperative analgesia in humans without any reports of neurological deficits.[18] Moreover, Maroof *et al.* used epidural dexmedetomidine, approximately 1.5 mcg/kg to decrease the incidence of

postoperative shivering, without any reports of neurological deficits.[19]

In the present study, the three groups were comparable having no statistical significance with regard to age, weight, sex, baseline cardiorespiratory parameters like heart rate, SBP, DBP, MAP, respiratory rate and oxygen saturation.

With regard to intraoperative and postoperative cardiorespiratory parameters, there was statistically significant change in heart rate between three study groups. There was a significant difference in mean pulse rate ($p \leq 0.0001$) between Group BS and Group BD. Our results are consistent with the study conducted by Shahi V et al.[20] They also found statistically significant value ($p = <0.01$) for mean pulse rate between the groups receiving bupivacaine with saline and bupivacaine with dexmedetomidine. The decrease in heart rate caused by α-2 agonist can be explained on the basis of their central action by decreasing sympathetic outflow and norepinephrine release.[21-23]

Onset of sensory block at T6 level and time to complete motor block was statistically significant between the three study groups with p value of <0.01. Shahi V et al. showed that the time to onset of sensory block at T10 was 19.7 ± 2.1 mins in group of patients receiving total of 14ml plain 0.5% bupivacaine and 14.6 ± 1.9 mins in patients receiving a total of 14ml plain 0.5% bupivacaine plus dexmedetomidine 0.5 mcg/kg (1ml) in lower limb surgeries. Our study showed that the time to onset of sensory block was 18.23 min to T6 level in Group BS receiving 20ml of 0.5% bupivacaine and 10.07±0.94 min in Group BD receiving 20ml plain 0.5% bupivacaine with dexmedetomidine 1 mcg/kg (2ml). Earlier onset of sensory block in our study is attributed to increased volume and dose of drug. GuptaK et al. studied epidural 0.5% levobupivacaine with dexmedetomidine and fentanyl for vaginal hysterectomy. The onset of sensory analgesia at T10 (7.25 ± 2.3 versus 9.27 ± 2.79 min) and time to achieve complete motor blockade (19.27 ± 4.7 versus 22.78±5.57 min) was significantly earlier in patients of LD Group. In our study, the addition of dexmedetomidine with bupivacaine shortens the onset of sensory and motor block as compared to fentanyl with bupivacaine or bupivacaine with saline. Thus our results are consistent with the results of Gupta K et al.[24]

The duration of motor block/motor regression to Bromage scale 0 was statistically significant between the groups with p value of < 0.01. The mechanisms by which α-2 adrenoceptor agonists prolong the motor and sensory block of local anesthetics is not well understood. It is not a result of altered systemic absorption, as the plasma level of bupivacaine was not altered after the addition of intrathecal clonidine to bupivacaine spinal injection.[25] It may be an additive or synergistic effect secondary to the different mechanisms of action of the local anesthetic and the α-2 adrenoceptor agonist. The local anesthetic acts by blocking sodium channels, whereas the α-2 adrenoceptor agonist acts by binding to presynaptic C fibers and postsynaptic dorsal horn neurons. The α-2 adrenoceptor agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons. This antinociceptive effect may explain the prolongation of the sensory block when added to spinal or epidural anesthetics. On the other hand, Yakshhas shown that intrathecal α-2 adrenoceptor agonists can cause a dose-dependent decrease in motor strength in animals. The prolongation of the motor block of spinal anesthetics may result from the binding of α-2 adrenoceptor agonists to motor neurons in the dorsal horn. Although the prolonged duration of sensory blockade with dexmedetomidine can improve postoperative pain management, the delayed recovery of motor function may have its disadvantages and may be inappropriate in day care surgeries.[26-30]

Although wide variations were seen in intra and postoperative pain score, however, dexmedetomidine group had lowest VAS score compared to control and fentanyl group. VAS at different time intervals was significant between three groups ($P < 0.01$).

Eskandar A M et al.[31] studied effects of epidural dexmedetomidine and low-volume bupivacaine on postoperative analgesia after total knee replacement. The demographic data were comparable in both groups. Visual analogue scale of pain showed a significant reduction between the two groups at both rest and movement, and the total dose of nalbuphine consumption during the study period was significantly reduced ($P < 0.002$) in group receiving dexmedetomidine (5 ± 5.15) than in group receiving bupivacaine (11 ± 7.63). Thus our results are also consistent with Eskandar A M et al.

Fentanyl acts primarily as agonist at μ-opioid receptors to enhance the analgesia. The dorsal roots contain opioid-binding sites and fentanyl either acts directly on the spinal nerve or by penetrating the duramater to act at the spinal roots. Casimiro *et al.* compared levobupivacaine with fentanyl and bupivacaine with fentanyl and concluded that both groups showed similar anesthetic effects but higher proportion of patients receiving levobupivacaine lacked dense motor block.[32]

Motor and sensory blockade effects of local anesthetics are enhanced by dexmedetomidine. We found in our study that the time gap between initial epidural medication and the time to 1st epidural top-up was highest 621.83±11.37 mins in Group BD followed by Group BF 381.46±15.28 mins and 171.1±22.91mins in Group BS. The difference among groups was statistically significant ($p = <0.01$). The number of top-ups was also reduced in Group BD as compared to Group BF and Group BS ($p = <0.01$).Our results are consistent with the study done by Shahi V et al. They observed that the mean time of Ist top up was 587.8±64.3 minutes in

dexmedetomidine group and 157.3±23.80 minutes in bupivacaine group. The difference in time is attributed to lesser drug volume and dose used in their study. Our results are also consistent with the study done by Bajwa S J S et al.[33] They observed the mean time of 1st top-up was prolonged in patients receiving dexmedetomidine with ropivacaine as compared to patients receiving fentanyl with ropivacaine undergoing lower limb and orthopedic surgeries.

Sedation is a side effect frequently associated with use of dexmedetomidine in postoperative analgesia often in conjunction with opioids. In our study there was a significant relation between the groups ($p < 0.01$) regarding sedation. The sedative properties of dexmedetomidine are far superior to fentanyl, as no patient required any other sedative during the peri-operative period. Dexmedetomidine acts on pre and post-synaptic sympathetic nerve terminal and central nervous system thereby decreasing the sympathetic outflow and norepinephrine release to cause sedation, analgesia and hemodynamic effects. It acts peripherally by blocking conduction through Aα and C fibers to enhance the effects of local anesthetics without increasing the incidence of side effects.

Narcotic analgesics are well-known for the potential side effects such as pruritus, nausea, vomiting, urinary retention and respiratory depression.[34] Delayed respiratory depression is the most troublesome of these side effects and appears to be largely responsible for the reluctance of anesthesiologists to use intrathecal or epidural narcotics. This phenomenon is thought to be due to transport of drug in cerebrospinal fluid from the lumbar region to the fourth ventricle, with consequent depression of the medullary respiratory centers. The incidence of delayed respiratory depression appears to be greatest with poorly lipid-soluble narcotic drugs, like morphine.[35] Bromage suggested that lipid-soluble, highly protein bound narcotic analgesics might be less likely to exhibit this phenomenon and this appears to be true for both butorphanol and fentanyl.[36] The patients were continuously observed for respiratory depression with SpO_2 (< 90%) and RR (< 10). No case of respiratory depression was observed in any group, consistent with other studies.

There was no significant difference between the three groups regarding nausea, vomiting, urinary retention, pruritus, dizziness, dry mouth, shivering, headache, hypotension and bradycardia($p>0.05$). Pruritus was found in 12(40%) patients receiving bupivacaine with fentanyl. Naulty JS et al.[37] found the incidence of pruritus in caesarean delivery with epidural fentanyl to be 41%. Incidence of pruritus following epidural opioid administration was 47% in a study by Ackerman et al (1989).[38] Shivering was seen in all the three groups, but was more common in Group BD (30%). The probable mechanism could be due to hypothermia caused by local epidural anesthetic injection and partially resulting from thermal redistribution from the central to the peripheral region.[39]

CONCLUSION

Fentanyl and dexmedetomidine are safe adjuncts to epidural anesthesia.Dexmedetomidine produces rapid onset of anesthesia, prolongs the duration of analgesia and produces significant sedation. Quality of analgesia is excellent in dexmedetomidine group as compared to fentanyl group as adjunct to bupivacaine in epidural anesthesia.

BIBLIOGRAPHY

1. Liu S, Carpenter RL, Neel JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anaesthesiology, 1995; 82: 1474-506.
2. Wu CL, Fleisher LA. Outcomes research in regional anaesthesia and analgesia, 2000; 91: 1232-42.
3. Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: A meta-analysis. Anesth Analg, 2001; 93: 853-8.
4. Ballantyne JC, Carr DB, DeFerranti S. The comparative effects of postoperative analgesic therapies on pulmonary outcome: Cumulative meta-analysis of randomized, controlled trials. Anesth Analg 1998; 86: 598-612.
5. Tuman K, McCarthy R, March RJ. Effects of epidural anaesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 1991; 73: 696-704.
6. Kehlet H. Acute pain control and accelerated postoperative surgical recovery. Surg Clin North Am 1999; 79:431‑43.
7. Soto RG, Fu ES. Acute pain management for patients undergoing thoracotomy. Ann Thorac Surg, 2003; 75: 1349‑57.
8. Burmeister MA, Gottschalk A, Wilhelm S, Schroeder F, Becker C, Standl T. Ropivacaine 0.2% versus bupivacaine 0.125% plus sufentanil for continuous peridural analgesia following extended abdominal operations. AnasthesiolIntensivmed Notfallmed Schmerzther, 2001; 36: 219‑23.
9. Filos KS, Goudas LC, Patroni O, Polizou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A doseresponse study. Anesthesiology, 1994; 81: 591-601.
10. Chiary A, Lorber C, Eisnach JC, Wildling E, Krenn C, Zavrsky A, et al. Analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of labor. Anesthesiology, 1999; 91: 388-96.
11. Arian SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg, 2004; 98: 153-8.
12. Kamibayashi T, Maze M. Clinical uses of alpha-2 adrenergic agonists. Anaesthesiology, 2000; 93: 1345-9.
13. Scafati A. Analgesia and alpha agonists 2. Medens Rev., 2004; 4-7.

14. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusions in humans. Br J Anaesth, 2001; 86: 5-11.
15. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnesic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg, 2000; 90: 699-705.
16. Mauro VA, Brandão ST. Clonidine and dexmedetomidine through epidural route for post-operative analgesia and sedation in a cholecystectomy. Rev Bras Anestesiol, 2004; 4: 1-10.
17. Gabriel JS, Gordin V. Alpha 2 agonists in regional anaesthesia and analgesia. Curr Opin Anaesthesiol, 2001; 14: 751-3.
18. Fukushima K, Nishimi Y, Mori K, Takeda J. Effect of epidurally administered dexmedetomidine on sympathetic activity and postoperative pain in man. Anesth Analg, 1996; 82: S121.
19. Maroof M, Khan SA, Jain D, Khan RM, Maroof SM. Evaluation of effect of dexmedetomidine in reducing shivering following epidural anesthesia. Anesthesiology, 004; 101: A495.
20. Shahi V, Verma AK, Agarwal A, Singh CS. A comparative study of magnesium sulfate vs dexmedetomidine as an adjunct to epidural bupivacaine: Journal of Anaesthesiology Clinical Pharmacology, Oct, 2014; 30(4): 538-42.
21. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs, 2000; 59: 263-70.
22. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine: A novel alpha2‑adrenoceptor agonist in healthy volunteers. Pain, 1991; 46: 281-5.
23. Talke P, Richardson CA, Scheinin M, Fisher DM. Postoperative pharmacokinetics and sympatholytic effects ofdexmedetomidine. Anesth Analg, 1997; 85: 1136-42.
24. Gupta K, Rastogi B, Gupta P K, Jain M, Gupta S, Mangla D. Epidural 0.5% levobupivacaine with dexmedetomidine versus fentanyl for vaginal hysterectomy: A prospective study. Indian Journal of Pain, Sept, 2014; 28(3): 149-154.
25. Boico O, Bonnet F, Mazoit JX. Effects of epinephrine and clonidine on plasma concentrations of spinal bupivacaine. Acta Anaesthesiol Scand, 1992; 36: 684-8.
26. Eisenach JC, De Kock M, Klimscha W. Alpha (2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology, 1996; 85: 655-74.
27. Lawhead RG, Blaxall HS, Bylund DB. Alpha-2A is the predominant a-2 adrenergic receptor subtype in human spinal cord. Anesthesiology, 1992; 77: 983-91.
28. Smith MS, Schumbra UB, Wilson KH, Page SO, Hulette C, Light AR, *et al*. Alpha 2-Adrenergic receptor in human spinal cord: Specific localized expression of mRNA encoding alpha-2 adrenergic receptor subtypes at four distinct levels. Brain Res Mol Brain Res., 1995; 34: 109-17.
29. Yaksh TL, Jage J, Takano Y. Pharmacokinetics and pharmacodynamics of medullar agents. The spinal actions of a-2 adrenergic agonists as analgesics. In: Atikenhead AR, Benad G, Brown BR, *et al*. Baillieres Clinical Anaesthesiology, London: Bailliere Tindall, 1993; 7: 597-614.
30. Fairbanks CA, Wilcox GL. Spinal antinociceptive synergism between morphine and clonidine persists in mice made acutely or chronically tolerant to morphine. J Pharmacol Exp Ther, 1999; 288: 1107-16.
31. Eskandar AM, Ebeidb AM. Effects of epidural dexmedetomidine and low-volume bupivacaine on postoperative analgesia after total knee replacement: Ain-Shams Journal of Anesthesiology, 2014; 07: 193–197.
32. Casimiro C, Rodrigo J, Mendiola MA, Rey F, Barrios A, Glisanz F. Levobupivacaine plus fentanyl versus racemic bupivacaine plus fentanyl in epidural anesthesia for lower limb surgery. Minerva Anestesiologica, 2008; 74: 381-91.
33. Bajwa SJS, AroraV, Kaur J, Singh A, Parmar SS. Comparative evaluation of Dexmedetomidineand fentanyl for epidural analgesia in lower limb orthopedic surgeries: Saudi Journal of Anaesthesia, Oct, 2011; 5(4): 365-70.
34. Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of extradural and intrathecal opiates: Report of a nationwide survey in Sweden. Br J Anaesth, 1982; 54: 479-86.
35. Camporesi EM, Nielsen CH, Bromage PR, Durant PA. Ventilatory CO_2 sensitivity after intravenous and epidural morphine in volunteers. Anesth Analg, 1983; 62: 633-40.
36. Bromage PR. The price of intraspinal narcotic analgesics: Basic constraints(editorial). Anaesth Analg, 1989; 68: 323-7.
37. Naulty JS, Johnson M, Burger GA, Datta S, Weiss JR, Morrison J, *et al*. Epidural fentanyl for post cesarean delivery pain management. Anesthesiol, 1983; 59: 415.
38. Ackerman WE, Juneja MM, Kaczorowski DM and Colclough GW. A comparison of theincidence of pruritus following epidural opioid administration in the parturient: Can JAnaesth, 1989; 36(4): 388-91.
39. Sessler DI, Ponte J. Shivering during epidural anesthesia. Anesthesiology, 1990; 72: 816-21.