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Research Article

EFFICACY OF DEXMEDETOMIDINE AND FENTANYL AS ADJUNCTS TO EPIDURAL ROPIVACAINE FOR ESWL

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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 ropivacaine for eswl.

Materials and Methods: Ninety ASA (American Society of Anesthesiologists) class I and II patients undergoing eswl were enrolled to receive either saline (Group RS) or fentanyl (Group RF) or dexmedetomidine (Group RD) along with epidural ropivacaine for anesthesia. All the study subjects received an epidural anesthesia with 10ml of 0.5% ropivavacaine along with either saline 2ml (Group RS) or fentanyl 1mcg/kg (Group RF) or dexmedetomidine 1.0 μg/kg (Group RD). 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 RD, together with duration of sensory and motor blockade. However incidence of sedation was more in the RD group.

Conclusion: Hence, addition of Dexmedetomidine to epidural ropivacaine 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.

INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL) is an effective, non-invasive technique for the treatment of difficult pancreatic and large bile duct calculi[1,2]. Millimetric fragmentation of pancreatic and bile duct stones by ESWL has improved the results of endoscopic therapy. The ESWL machine uses high pressure shock waves generated by an ellipsoid cup with the aid of biplanar fluoroscopy. The treatment is often painful and requires large doses of analgesics. Many different anesthetic techniques have been used for ESWL. To date general anesthesia, epidural anesthesia (EA) with local anesthetic agents or opioids, intercostal nerve blocks with local infiltration, intravenous fentanyl, combinations of intravenous analgesics and sedatives have all been used[3-12].

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[13,14].

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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[15,16]. Epidural anaesthesia and analgesia also decreases the incidence of hypercoagulability.[17]

Ropivacaine is a long-acting regional anaesthetic that is structurally related to Bupivacaine. It is a pure S(-)enantiomer, unlike Bupivacaine, which is a racemate, developed for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles[18].

Ropivacaine causes reversible inhibition of sodium ion influx, and thereby blocks impulse conduction in nerve fibres[18]. This action is potentiated by dose-dependent inhibition of potassium channels[19]. Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres; therefore, it has selective action on the pain-transmitting A δ and C nerves rather than Aβ fibres, which are involved in motor function.

Alpha 2 (α2) adrenergic agonists have been the focus of interest for their sedative, analgesic, perioperative and sympatholytic, anestheticsparing and hemodynamic stabilizing properties. Dexmedetomidine is a highly selective α2adrenergic agonist with a relatively high ratio of α2 to α1 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 ropivacaine 0.5% (10 ml) in ESWL. The variables studied include, onset of anaesthesia, duration of analgesia, alteration in vital signs (non-invasive blood pressure, heart rate, SPO2) 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 ESWL were enrolled for the study. 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 RS received Ropivacaine 0.5% (10 ml)+ saline 0.9%(2ml), Group RF received Ropivacaine 0.5% (10ml) + Fentanyl (1 mcg/kg) (2ml) and Group RD received Ropivacaine 0.5%(10 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 T_{11}-T_{12} 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 SpO2 <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.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 RS	Group RF	GroupRD
Age	45±11.34	44±10.43	45.6±12.34
Weight	65.3±6.40	64.23±7.43	66.56±6.76
Asa(I/II)	16/14	19/11	17/13
Gender(M/F)	21/9	23/7	22/8

Table 2 Comparison of baseline cardiorespiratory parameters

Parameter	Group rs	Group rf	Group rd
Heart rate	75.5±7.13	74.4±6.987	75.11±7.234
Systolic BP	123.211±9.678	124.321±10.112	123.331±9.987
Diastolic BP	76.56±5.678	77.89±6.876	78.56±6.453
MAP	93.134±6.754	93.978±6.234	93.756±6.342
SPO_2	98.124±0.78	97.985±0.65	98.345±0.86

Table 3 Comparison of initial block characteristics

Parameter	Group RS	GroupRF	Group RD
Time to max. sensory block at t6 level	18.56±1.67	12.78±1.23	9.76±0.98
Time to complete motor block	26.78±1.89	22.67±1.22	15.56±0.976

Table 4 Comparison of intraoperative and postoperative block characteristics

Parameter	Group RS	Group RF	Group RD
Duration of motor blockade (regression to bromage 0)	102.34±10.456	140.43±15.432	190.12±13.568
Time to first feeling of pain	130.76±14.89	160.23±12.43	250.65±15.98
Total no of topup doses	4.52±0.67	2.97±0.56	0.43±0.12

The duration of motor block/motor regression to Bromage scale 0 in Group RS ranged from 90 to 114 minutes with a mean of 102.34±10.456 minutes, in Group RF from 100 to 180minutes with a mean of 140.43±15.432 minutes and in Group RD from 150 to 230 minutes with a mean of 190.12±13.568 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 250.65±15.98mins in Group BD followed by Group BF 160.23±12.43mins and 130.76±14.89 mins 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 Incidence of side effects in patients of all the three groups

Parameter	Rs	Rf	Rd
Nasuea	3	5	4
Vomiting	2	4	4
Hypotension	7	9	11
Bradycardia	7	6	13
Resp.depression	0	1	0
Headache	3	4	3
Dry mouth	2	3	4
Shuvering	5	4	3
Dizziness	2	5	4
Urinary retention	2	5	4

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 6 Sedation Score

Parameter	Group RS		Group RF		Group RD	
	Number	Percent	Number	Percent	Number	Percent
Sedation score 0	30	100	03	10	00	00
Sedation score 1	00	00	23	77	05	17
Sedation score 2	00	00	03	10	11	37
Sedation score 3	00	00	01	03	14	47
Sedation score 4	00	00	00	00	00	00
Sedation score 5	00	00	00	00	00	00

In our study no patient in control group had sedation. Sedation score 1 was found in 23(77%) patients in group RF and 5 (17%) patients of group RD. Sedation score 2 was found in 3(10%) in group RF, 11(37%) in group BD. Sedation score 3 was found in 1(3%) in group RF, 14(47%) in group RD. Sedation score 4 and 5 was not found in any patient. Statistically the relation between groups is significant (p <0.01) (Table 6).

DISCUSSION

Selection of exclusive epidural route during this study was done to avoid general anesthesia, invasive dural penetration technique with spinal needle as well as to provide postoperative pain relief. Epidural analgesia offers superior pain relief and early mobilization especially when local anesthetic dose is combined with an adjuvant as compared to LA alone[20].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[21,22].The use of neuraxial opioids is associated with quite a few side effects, so various options including α2 agonists are being extensively evaluated as an alternative with emphasis on opioid-related side effects such as respiratory depression, nausea, urinary retention and pruritus[23,24,25]. The pharmacologic properties of α2 agonists have been extensively studied and have been employed clinically to achieve the desired effects in regional anaesthesia[26,27,28,29]. Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis[30,31]. 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[32]. Moreover, Maroof *et al*. used epidural dexmedetomidine, approximately 1.5 mcg/kg to decrease the incidence ofpostoperative shivering, without any reports of neurological deficits[33].

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≤0.0001) between Group RS and Group RD.Our findings are consistant with Park SJ *et al*[34].

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.Kiran s. *et al* [35] showed that The mean time for onset of sensory block, in minutes, was 18.6 ± 4.4 in R Group, 12.8 ± 1.8 in RF Group and 10.8 ± 2.7 in RD Group (P < 0.001). There was a statistically significant difference with regard to degree of motor block, with RD Group faring better than RF Group and R Group 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[36]. 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 dosedependent 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.[37-41]

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 also consistent with the study done by Bajwa S J S *et al*[42].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.

Narcotic analgesics are well-known for the potential side effects such as pruritus, nausea, vomiting, urinary retention and respiratory depression[43]. 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 [44].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[45].The patients were continuously observed for respiratory depression with SpO2 (< 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).

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 perioperative period. Dexmedetomidine acts on pre and postsynaptic 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.

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.

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