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Comparative evaluation of dexmedetomidine and clonidine in epidural anesthesia in females in PMCH

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Abstract
Nowadays, Thoracic epidural anaesthesia is one of the most common anaesthesia technique used to conduct elective open cholecystectomy among all methods. As regional anaesthetic technique provides intraoperative anaesthesia as well as excellent post-operative analgesia without systemic side effects. But only limiting factor is duration of block. Several combinations of LAs and adjuvants such as tramadol, sufentanyl, clonidine, and fentanyl have been employed in the search for near ideal agent, which remains elusive. Alpha 2 – adrenoceptor agonists prolong the duration of sensory and motor block with local anaesthetics. Most of clinical studies about the intrathecal Alpha-2 adrenoceptor agonists are related to Clonidine. Dexmedetomidine is eight times more selective Alpha-2 adrenoceptor agonist emerging as a valuable adjunct to regional anaesthesia and analgesic. Hence from the present finding the present study was planned for Comparative Evaluation of Dexmedetomidine and Clonidine in epidural Anesthesia in Females Admitted to PMCH.
The present study was planned in Department of Anesthesia, Patna Medical College and Hospital, Patna, Bihar. The study was conducted from July 2017 to June 2018. The 30 females undergoing the vaginal hysterectomies were enrolled in the present study. The 15 cases were enrolled in the Group A administered with the Ropivacaine & Dexmedetomidine for epidural anesthesia. The another 15 females were administered with the Ropivacaine & Clonidine.
The data generated from the present study concludes that dexmedetomidine is a better adjuvant than clonidine in epidural anaesthesia as far as patient comfort, stable cardio-respiratory parameters, intraoperative and post-operative analgesia is concerned. Overall the experience with dexmedetomidine was quite satisfactory as compared to clonidine because of its superior sedative and anxiolytic properties during the surgical procedure under regional anaesthesia.

Keywords: clonidine, dexmedetomidine, epidural anaesthesia, ropivacaine, vaginal hysterectomy, etc

Introduction
Epidural anesthesia is a central neuraxial block technique which involves use of local anesthetics injected into the epidural space to produce a reversible loss of sensation and motor function and is one of the most common regional technique used for lower abdominal and lower limb surgeries. Epidural anesthesia provides excellent operating conditions for surgical procedures below the umbilicus. Advantages of epidural anesthesia over spinal anesthesia is that it is able to provide anesthesia for prolonged surgeries with better hemodynamic stability. Advantages of epidural anesthesia over general anesthesia is that the intubation and extubation responses are avoided and there will be a choice to provide postoperative analgesia. Epidural anesthesia can reduce the adverse physiologic responses to surgery too. Different local anesthetics are used for epidural anesthesia, most popular being lignocaine and bupivacaine. The drawback of lignocaine is its intermediate duration of action and drawback of bupivacaine, though long acting is increased incidence of cardiac toxicity.
Epidural nerve block has become a significant advance in neuraxial anesthesia and analgesia. Dr. James Leonard Corning described the procedure in 1885 [1] and Cuban anesthesiologist Manual Martinez Curbelo, in 1947, first used an epidural catheter [2]. The procedure is commonly performed as a sole anesthetic or in combination with spinal or general anesthetic. The duration of anesthesia or analgesia is prolonged when epidural catheters are used. Patients are able to control their pain with patient-controlled epidural analgesia (PCEA) in a manner similar manner to that of intravenous patient-controlled analgesia (IV PCA). Local anesthetic epidural blockade may be useful in conjunction with aggressive physical therapy or manipulation of a painful limb associated with joint stiffness or limited range of motion. Lumbar sympathetic blocks are more appropriate for evaluating and treating complex regional pain syndromes, as they provide a more selective evaluation by providing a discrete sympathetic block.
In comparison to epidural blocks, epidural injections of local anesthetic, steroids, or both are considered for the treatment of radicular pain symptoms secondary to disk herniation or postsurgical radicular pain. Epidural injections do not alter the course of the underlying process but may offer effective pain relief in selected patients. Epidural injections may be performed in the spinal region, including the cervical, thoracic, lumbar, and sacral regions. Fluoroscopic guidance may be necessary in patients with congenitally, surgically, or pathologically altered anatomy. The injections should be delivered into the area of the known pathology using midline, paravertebral, or transforaminal approaches. Caudal steroid injections should only be used for patients with leg pain of sacral origin or in

whom direct access to the lumbar region is impossible.

When considering epidural nerve block, clinicians should follow a stepwise approach. First, an accurate diagnosis must be made by obtaining a pertinent neurological history and examination and performing the appropriate diagnostic confirmatory tests. In the ever-expanding field of interventional pain management, epidural injections of pain medications like steroids play an important role in chronic pain management. Long-term indwelling epidural catheters are helpful in managing severe pain in cancer and noncancer chronic pain conditions. Certain conditions with sympathetic mediated or maintained pain are treated with the epidural local anesthetic since it provides sympathetic blockade.

The cephalad part of the spinal epidural space begins at the level of foramen magnum, where the periosteal and spinal layers of dura fuse together. The caudal part extends to the sacrococcygeal membrane. The anterior portion of the epidural space is formed by the posterior longitudinal ligament, which covers the posterior part of the vertebral body and the intravertebral disk. Posteriorly, the epidural space is formed by the anterior lateral surface of the vertebral lamina and the ligamentum flavum. Laterally, the epidural space is formed by the pedicles of the vertebrae and the intravertebral foramen. The ligamentum flavum is used as the key landmark for identification of the epidural space. It is thinnest in the cervical region. Also note that the epidural space is narrowest in the cervical region, with an anterior/posterior diameter of 2-3 mm. The images below show the interlaminar epidural space.

An understanding of the basic anatomy of the epidural space also requires recognition of the following key anatomic features of the spine. The spine is composed of cervical, thoracic, lumbar, sacral, and coccygeal vertebrae. The cervical spine is much more mobile than the thoracic or lumbar regions of the spine. Unlike the other regions of the spine, the cervical spine has foramina in each vertebra for the arteries supplying blood to the brain. The vertebrae support most of the weight to the spine. A bony projection on either side of the vertebral body called the pedicle supports the arch that protects the spinal canal. The laminae are the parts of the vertebrae that form the back of the bony arch that surrounds and covers the spinal canal. A transverse process is on either side of the arch, where some of the muscles of the spinal column attach to the vertebrae. The spinous process is the bony portion of the vertebral body that can be felt as a series of nodules in the center of an individual's spine.

Between each vertebra in the spine are disks that act as shock absorbers and also permit some movement between the vertebral bodies. They are made up of a strong outer ring of fibers called the annulus fibrosus and a soft center called the nucleus pulposus. The annulus helps keep the disk's inner layer intact. In addition to the invertebral discs, facet joints between each of the vertebral bodies allow the individual bones of the spine to move and rotate with respect to each other. Several muscle groups that move the trunk and the limbs also attach to the spinal column. The neural foramen is the opening where the nerve roots exit the spine and travel to the rest of the body. Between each pair of vertebrae are 2 neural foramina (1 on each side). Finally, the spinal cord extends from the base of the brain and ends at the lower level of the first lumbar vertebra and the top of the second lumbar vertebra. The group of nerves at the end of the spinal cord is called the cauda equina. The dura mater forms a protective watertight sac around the spinal cord and nerves. The spinal cord is surrounded by spinal fluid inside this sac.

Epidural and spinal anesthesia are used extensively, consistently, and securely in modern practice. Although the technique appears relatively straightforward in experienced hands, it is not free of potential complications. Awareness of complications is required for a safe practice of these techniques [3].

Severe complications of regional anesthesia are far less commonly disclosed. According to a 2003 survey of 79 regional anesthesiologists and regional anesthesia fellows, the complication rates provided to patients may not match those cited in the literature [4]. The risks of regional anesthesia that are most commonly disclosed to patients by academic regional anesthesiologists occur frequently and are benign in nature.

Severe complications (eg, spinal epidural hematoma) leading to temporary or permanent disability have been attributed to central neuraxial blocks. Infections like meningitis and abscesses, or cerebral ischemia or hemorrhage have also been linked directly or indirectly to spinal or epidural anesthesia. On rare occasion, central nerve blocks have caused permanent damage to the spinal cord or nerve roots [5]. The etiology of this damage in many cases remains unclear.

Perhaps the clearest picture of the numbers and types of injuries from regional anesthesia is provided by the American Society of Anesthesiologists (ASA) Closed Claims Project database [6]. The report clearly noted twice the complications with general anesthesia than with regional anesthesia. The primary reason for death remains cardiac arrest associated with neuraxial blockade. This complication now represents only 30% of deaths (vs 61% in the 1970s and 40% in the 1980s) [7].

A database on early and delayed complications was collected in a prospective study of 6 weeks' duration [8]. Two hundred and fifteen patients who underwent 790 consecutive cervical epidural nerve blocks were observed. Unintentional dural puncture and superficial infection at the injection site were reported. This study concluded that cervical epidural nerve block has been reported as a safe modality in the treatment of various painful conditions.

A report reviewed 32 studies published between January 1, 1995, and December 31, 2005 [9]. The main objective was to investigate neurological complications of regional anesthesia. The review suggested that the rate of neurological complications after central nerve blockade is less than 0.04% and that the rate of neuropathy after peripheral nerve blockade is less than 3%.

An epidural block interrupts both somatic and sympathetic nerve conduction; thus, cardiovascular changes, including hypotension and tachycardia, may occur. These cardiovascular changes can produce overwhelming complications if not promptly identified and treated. Respiratory compromise or failure can occur if the phrenic nerve or respiratory centers of the brain stem are inadvertently blocked. For this reason, epidural nerve blocks should be performed only by clinicians trained in airway management and resuscitation. Appropriate monitoring of vital signs is imperative, and resuscitation equipment must be readily available during the procedure.

Minor adverse effects and complications of epidural nerve

block include pain at the injection site, unintentional dural puncture [10], and vasovagal syncope. Major complications include damage to neural structures, epidural hematoma, and epidural abscess. These major complications are rare but can be life-threatening when they occur. Coexisting Harlequin and Horner syndromes after high thoracic paravertebral block have also been reported [11].

With the exception of the decreased incidence of inadvertent dural puncture, the complications of the caudal approach to the epidural space mirror those of the lumbar approach. Because of the proximity of the rectum, conscientious attention to sterile technique must be observed to avoid infection, which can easily spread to the epidural space via the Batson plexus. Because of the vascular nature of the caudal epidural space, the potential for local anesthetic toxicity remains ever present.

During the postoperative period, patients should be observed closely to detect potentially treatable sources of neurologic injury, including expanding spinal hematoma or epidural abscess on neurologically vulnerable sites. New neurologic deficits should be evaluated promptly by a neurologist to formally document the patient's evolving neurologic status [12]. If necessary, the neurologist can arrange further testing or intervention and provide long-term follow-up and prognosis.

Cauda equina is formed by nerve roots caudal to the level of spinal cord termination. Cauda equina syndrome has been defined as low back pain, unilateral or usually bilateral symptoms in the distribution of sciatic nerve, saddle sensory disturbances, bladder and bowel dysfunction, and variable lower extremity motor and sensory loss. This may occur with neurotoxicity from local anesthesia. In the past, continuous spinal catheters with local anesthetics were associated with this syndrome. Those types of catheters and infusions are no longer in use.

Neurotoxicity associated with lower back pain that radiates to the buttocks and posterior thighs is likely due to transient lumbosacral nerve root irritation.

Ropivacaine is replacing bupivacaine as drug of choice in epidural anesthesia. Ropivacaine is a long-acting amino amide local anesthetic structurally related to bupivacaine. Ropivacaine has been shown to have an increased therapeutic index in human volunteer studies [13]. In several studies it was concluded that ropivacaine was less cardiac depressant, less arrhythmogenic and less neurotoxic than bupivacaine [14]. However it has some limitations. The onset of sensory and motor blockade may be delayed. The duration of analgesia provided by a dose of epidural ropivacaine is only 4-6 hours, thereby requiring frequent administration of the drug for post op analgesia. There is also no intra operative sedation leading to inadvertent use of sedatives. Therefore a number of drugs have been tried as adjuvants to epidural ropivacaine to overcome these limitations. Alpha-2 adrenergic agonists have both analgesic and sedative properties when used as an adjuvant in regional anaesthesia.

Dexmedetomidine is a relatively selective alpha2-adrenergic agonist, not only decrease sympathetic tone and attenuate the stress response to anesthesia and surgery, but also cause sedation and analgesia. The majority of patient receiving were effectively sedated yet were easily arousable, a unique feature not observed with other sedatives [15]. Dexmedetomidine suppresses the activity in the descending noradrenergic pathway, which modulates nociceptive neurotransmission, terminates propagation of pain signals leading to analgesia. The hypnotic and supraspinal analgesic effects are mediated by the hyperpolarization of noradrenergic neurons, which suppresses neuronal firing in the locus ceruleus along with inhibition of norepinephrine release and activity in the descending medullospinal noradrenergic pathway, secondary to activation of central alpha-2 adrenergic receptors. This suppression of inhibitory control triggers neurotransmitters that decrease histamine secretion producing hypnosis similar to normal sleep, without ventilatory depression, making dexmedetomidine a near ideal sedative [16].

Clonidine is an established alpha 2 adrenoceptor agonist with antihypertensive properties, when administered epidurally has an analgesic action that is largely mediated by alpha 2 adrenoceptors in dorsal horn of spinal cord clonidine is useful adjuvant to opioid and LA agent for postop analgesia after major abdominal surgeries and orthopedic surgery [17]. Clonidine enhances both sensory and motor blockade from epidural injection of local anesthetics.

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Methodology

The present study was planned in Department of Anesthesia, Patna Medical College and Hospital, Patna, Bihar. The study was conducted from July 2017 to June 2018. The 30 females undergoing the vaginal hysterectomies were enrolled in the present study. The 15 cases were enrolled in the Group A administered with the Ropivacaine & Dexmedetomidine for epidural anesthesia. The another 15 females were administered with the Ropivacaine & Clonidine.

Patients were administered epidural block with 18 gauge Touhy needle and catheter was secured 3−4 cm into epidural space and a test dose of 3 ml of 2% lignocaine hydrochloride solution containing adrenaline 1:200,000 was injected. After 4−6 minutes of administering the test dose, patients in group A received 17 ml of 0.75% ropivacaine and 2 µg/kg of clonidine. Patients in group B were administered 17 ml solution of 0.75% ropivacaine and 1.5 µg/kg of dexmedetomidine.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the

present study.

Inclusion Criteria: female patients of ASA (American Society of Anaesthesiologists) grade I and II between the ages of 44 and 65 years.

Exclusion Criteria: Females with female patients of ASA (American Society of Anaesthesiologists) grade I and II between the ages of 44 and 65 years.

All patients will undergo pre anaesthetic evaluation on the previous day of surgery. Basic lab investigations like CBC, FBS or RBS, blood urea, serum creatinine chest X-ray and ECG will be carried out. The entire procedure will be explained to the patient. All the patients were visited in the previous night of proposed surgery day and tab alprazolam 0.5mg given at bed time and tab ranitidine 150mg given at bed time and also on the day of surgery with sip of water 2 hours before anesthetic procedure. Patient is shifted to procedure room on the day of surgery. Drug and equipments necessary for resuscitation and general anesthesia are kept ready. An IV line is secured using 18G cannula and 500ml of RL infusion started which is given for all patients half an hour before anesthetic procedure as pre loading. Base line blood pressure, heart rate and respiratory rate will be noted.

Results & Discussion

Use of neuraxial adjuvants have an advantage of reduced requirement of dose and rapid onset of action of local anaesthetics, quicker onset of both sensory and motor blockade, long duration of analgesia which extends into the post-operative period and stable hemodynamic parameters. Patient compliance can be improved by reducing the adverse effects associated with high dose of a single local anaesthetic agent. These properties had made them as effective adjuvants in regional anaesthesia [18]. They include sodium bicarbonate, vasoconstrictors, opioids, α2 agonists, N-methyl- D- aspartate (NMDA) antagonists, cholinergic agonists and γ- amino butyric acid (GABA) receptor agonists. Opioids when used as adjuvants cause few side-effects such as respiratory depression, urinary retention and pruritis, hence evaluation is under process to replace them with α-2 agonists. α-2 agonists act by altering transmembrane potential and ion conductance, thus cause hyperpolarisation of nerves in the brainstem (Locus coeruleus) [19, 20]. Epidural administration of these drugs is associated with analgesia, anxiolysis, sedation and hypnosis. Among the α2 agonists, Clonidine is being widely used since past 10 years and the advent of dexmedetomidine may offer more advantage as adjuvant in regional anaesthesia

Table 1: Basic Details

Parameters	Group A	Group B
Anesthesia by	**Ropivacaine & Dexmedetomidine**	**Ropivacaine & Clonidine**
No. of Cases	**15**	**15**
Age	42 – 58 years	46 – 59 years
Weight	45.4 – 66.1 kg	52.4 – 65.3
ASA		
Class I	11	10
Class II	4	5
Surgery Duration	81 – 110	87 – 114

Table 2: Basic Details

Parameters	Group A	Group B
Anesthesia by	**Ropivacaine Dexmedetomidine**	**Ropivacaine & Clonidine**
No. of Cases	**15**	**15**
Onset time of sensory block at T10 (in minutes)	6.3 – 10.8	6.1 – 13.2
Maximum sensory block Level	T5-6	T6-7
Time to maximum sensory block level (in minutes)	9.4 – 17.3	10.2 – 21.3
Time in minutes for complete motor block	12.2 – 22.3	15.3 – 23.7
Mean total dose of Mephenteramine requirement (mg)	10.6	8.4

Table 3: Sedation Score & Side Effects

Parameters	Group A	Group B
Anesthesia by	**Ropivacaine & Dexmedetomidine**	**Ropivacaine & Clonidine**
No. of Cases	**15**	**15**
Sedation scores during surgery		
1	2	4
2	8	9
3	5	2
4	0	0
5	0	0
Side Effects		
Nausea	3	2
Vomiting	1	1
Shivering	1	1
Headache	1	1
Dizziness	1	1
Dry mouth	2	1
Respiratory depression	4	3

Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S. *et al* conducted a prospective randomized study which included 50 adult female patients between the ages of 44 and 65 years of ASAI/II grade who underwent vaginal hysterectomies with epidural block with ropivacaine and dexmedtomidine (group RD) and ropivacaine and clonidine (group RC). It is concluded that Dexmedetomidine is a better neuraxial adjuvant compared to clonidine for providing early onset of sensory analgesia, adequate sedation and a prolonged post-operative analgesia [21].

Bajwa SJ, Bajwa SK, Kaur J conducted a randomized double blind study among 51 healthy parturients, scheduled for elective cesarean section by epidural block with ropivacaine (group R) and ropivacaine with clonidine (group RC).It is concluded that addition of clonidine to isobaric epidural ropivacaine results in longer, complete and effective analgesia with similar block properties and helped to reduce the effective dose of ropivacaine when compared with plain ropivacaine for cesarean delivary [22].

Vieira AM, Schnaider TB, Brandao AC, Pereira FA, Costa ED, Fonseca CE. *et al* conducted a randomized double-blind study among 40 patients, aged 18 to 50 years, weighing 50 to 100 kg, physical status ASA I or II, submitted to subcostal cholecystectomy with epidural clonidine and ropivacaine and with dexmedetomidine with ropivacaine. It is concluded that there is an association of clonidine or dexmedetomidine to 0.75% ropivacaine in inducing

analgesia and sedation in 2 and 6 hours after anesthetic recovery in patients submitted to subcostal cholecystectomy and that clonidine promotes more prolonged analgesia [23].

Salgad PF, Sabbag AT, Silva PC, Brienze SL, Dalto HP, Modolo NS. *et al* conducted a double-blinded study with 40 patients, ASA physical status 1 and 2, scheduled for hernia repair surgery or varicose vein surgery, who were operated under epidural anesthesia with ropivacaine plus saline and ropivacaine plus dexmedetomidine. It is concluded that there is a clear synergism between epidural dexmedetomidine and ropivacaine. Dexmedetomidine increases sensory and motor block duration during epidural anesthesia with ropivacaine, prolongs postoperative analgesia and does not cause hemodynamic instability. Sedation and no respiratory depression is an advantage of the association between ropivacaine and dexmedetomidine. [24].

Gupta S, Raval D, Patel M, Patel N, Shah N conducted a randomized double blind study with 60 adult patients of ASA grade 1 and 2 scheduled for post op pain relief in total knee replacement surgeries by epidural clonidine with bupivacaine and with bupivacaine alone. It concluded that addition of clonidine to bupivacaine epiduraly prolongs motor and sensory block and analgesia, without an increased incidence of side effects [25].

Bajwa SJ, Arora V, Kaur J, Singh A, Parmar SS conducted a study on 100 patients aged 21-56 years of ASA 1 and 2 who underwent lower limb orthopedic surgery with epidural ropivacaine plus dexmedetomidine and ropivacaine plus fentanyl. It seems that dexmedetomidine to be better alternative to fentanyl as an epidural adjuvant as it provides comparable stable hemodynamic, early onset, and establishment of sensory anesthesia, prolonged post op analgesia, lower consumption of post op LA for epidural analgesia, and much better sedation levels [26].

Rockemann MG, Seeling W, Brinkmann A, Goertz AW, Hauber N, Junge J. *et al* conducted a study on 45 patients scheduled for pancreatectomy in combined general/epidural anesthesia. This study characterizes analgesia and hemodynamics after epidural clonidine 8microg/kg or clonidine 4microg/kg plus morphine 2mg in comparison to epidural morphine 50microg/kg. it concluded that hemodynamic alteration after epidural clonidine under conditions of stable filling pressures is caused mainly by a decrease in HR. It is not an effect of analgesia but of the intrinsic anti-hypertensive action of clonidine [27].

One of the most important limitations of our study was that BIS (Bispectral Index) was not monitored in any case. We could not measure the plasma concentration of dexmedetomidine or clonidine. If measured, it might have corrected the possibility of inter-individual variability, so also help to comment on optimum sedative as well as analgesic plasma concentration of dexmedetomidine and clonidine. We could not document any synergism or antagonism of the study drugs by isobologram. Pain being a subjective phenomenon, measurement of pain should be individualised. We have also not studied electromyography (EMG) study or nerve conduction velocity study after offset of motor or sensory block. If studied, it might be possible to detect the actual duration of sensory and motor block.

Conclusion

The data generated from the present study concludes that dexmedetomidine is a better adjuvant than clonidine in epidural anaesthesia as far as patient comfort, stable cardio-respiratory parameters, intraoperative and post-operative analgesia is concerned. Overall the experience with dexmedetomidine was quite satisfactory as compared to clonidine because of its superior sedative and anxiolytic properties during the surgical procedure under regional anaesthesia.

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