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ONSET AND DURATION OF ACTION OF EPIDURAL BUPIVACAINE AND DEXAMETHASONE IN PATIENTS UNDERGOING BILATERAL INGUINAL HERNIORRHAPHY

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ABSTRACT

Objective: To evaluate the onset and action of epidural bupivacaine with or without dexamethasone in patients undergoing bilateral herniorraphy. **Methods:** A prospective study of epidural bupivacaine with or without dexamethasone in patients with bilateral inguinal herniorraphy from January 2015 to December 2020 was carried out. A total of forty-eight patients were enrolled in this double-blind study. Forty-eight patients were randomized into group BD (N=24) and received 20ml of epidural bupivacaine plus 3ml (12mg) of dexamethasone or group BN (N=24) and received 20 ml of epidural bupivacaine plus 3ml of normal saline. The onset of sensory block, mean arterial blood pressure, duration of action and incidence of complications were recorded. **Results:** Effective intraoperative sensory block was achieved in all the patients in the two groups. The onset of epidural anesthesia was significantly more rapid in the epidural group with dexamethasone than in the epidural group without dexamethasone ($P < 0.001$). Duration of analgesia was markedly prolonged in the group with dexamethasone compared to control group ($P < 0.001$). One patient (4.2%) in the control group had bradycardia in the immediate post operative period ($P = 0.030$). Two patients in the dexamethasone group had bradycardia. None of the patients had vomiting in the two groups. **Conclusions:** This study showed that addition of 12mg dexamethasone to epidural bupivacaine is safe, significantly makes onset of action to be more rapid and prolongs the duration of postoperative analgesia.

KEYWORDS: Anaesthesia, analgesia, epidural, bupivacaine, dexamethasone.

INTRODUCTION

Epidural anaesthesia involves the introduction of local anaesthetic into the epidural space, usually via catheterization. The use of catheter, in situ, has helped in repeating administration seamlessly.[1] The major difference between spinal and epidural anaesthesia is that a much larger amount of anaesthetic agent is required to produce epidural block.[1,2,3] Larger volume is required because the drug must diffuse into the spinal cord, nerve roots, and cerebrospinal fluid from the epidural space, a potential space. With these processes, the onset of anaesthesia is significantly slower with epidural compared to spinal anaesthesia.[2] Average onset time of epidural analgesia, according to the work of Davis et al. was 21±4 minutes.[2]

Bupivacaine is a long-acting amide local anaesthetic, which is structurally similar to ropivacaine.[1] Its epidural onset of action ranges between 15 minutes and 30 minutes depending on the dose.[1,2,3] This longer onset of action has made the anaesthetists and surgeons to jettison the technique in the past.[3] There has lately been a dramatic revival of epidural anaesthesia, reduction of its onset of action and also increase duration of action of the local anaesthetic agents.[2,3,4] Prolonged onset time following epidural anaesthesia when local anaesthetic agents are used as sole drug of choice has been a major reason why care givers may not embrace the technique.[4] Initially, to overcome this delay in onset of action, the anaesthetists resulted to the use of high volume of local anaesthetic agents.[5] The adverse reactions, including total spinal and cardiac arrest, following the use of high concentration of bupivacaine have since discouraged the use of high concentration of the drugs.[6]

For many years, bupivacaine has been used during epidural analgesia and anaesthesia because of its long duration of action. Epidural anaesthesia has a well established role in surgery, but has the drawbacks of delayed onset of action.[3] The combined epidural

bupivacaine-dexamethasone technique may overcome these drawbacks.[3] Excellent pain relief can be given to patients undergoing surgery using many different combinations and concentrations of local anaesthetic agents, with or without adjuncts in epidural space.[7] A good management of intraoperative pain will reduce many untoward effects, and will help the surgeons to be comfortable while performing the operation.[7,8,9,10,11]

Epidural bupivacaine anesthesia, in normal dose, is a safe and effective technique for managing both intraoperative and postoperative pain.[4] Several adjuvants have been experimented in order to reduce the onset of action of epidural bupivacaine and at the same time, prolong its duration of action.[3,12,13] Prolonging the duration of epidural anesthesia is essential because it prolongs duration of action of post operative analgesia.[3] Some adjuvants that have been tried include opioids,[14,15] dexamethasone,[3] lidocaine (20ml of 2%),[15] and ketamine.[14] The combination of epidural opioid and local anesthetic provides good pain control.[14,15] Opioids may have a synergistic effect with local anaesthetic agents in the epidural space and may improve analgesia and anaesthesia, but is associated with adverse effects such as nausea, vomiting, sedation, pruritus, urinary retention, and respiratory depression.[5,11]

In this study, we carried out a prospective, randomized comparison of onset and duration of action of epidural bupivacaine with dexamethasone and epidural bupivacaine without dexamethasone in patients undergoing bilateral inguinal herniorraphy.

METHODS

This was a prospective, randomized, placebo-controlled clinical study. The study compared onset and duration of action of epidural bupivacaine without addition of dexamethasone and epidural bupivacaine with addition of dexamethasone. Patients were recruited from those scheduled for bilateral inguinal herniorraphy. Ethical clearance and approval were obtained from institution's Ethics and Research Committee. Informed consent of all participatory patients were obtained before the commencement of the study.

Forty-eight patients scheduled for elective bilateral inguinal herniorraphy, ASA class 1 or 2 of the ASA (American Society of Anesthesiology) status, were admitted to Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria, from January 2015 to December 2020 and were recruited for this randomized, double-blind, clinical study. Exclusion criteria included patients with hypersensitivity to local anaesthetic agent and steroid. Also excluded from this study were patients with liver disease, kidney disease, diabetes mellitus, coagulopathies, and prolonged steroid therapy.

Preoperative assessment of the patients included history with detailed systemic review and examination of all systems were carried out in the ward. Routine investigation such as hemoglobin concentration, urinalysis, serum electrolytes and urea were done for each patient. Visual Analogue Scale (VAS) score for the assessment of pain, consisting of 100mm line with 0=no pain and 100mm worst pain, was explained to the patients. During the preoperative visit, they were informed that VAS between 1mm and 39mm indicated a mild pain, while between 40mm and 69mm indicated a moderate pain.

All eligible patients were randomly assigned to two groups of 24 patients each by opening unmarked envelop indicating the type of coded epidural solution package to be used. A second anaesthetist who was not involved in the study prepared the epidural solution. In group BN, each of the patients had 20 ml of isobaric 0.5% bupivacaine and 3ml of normal saline in their epidural space. Patients in group BD received 20 ml of isobaric bupivacaine 0.5% and 3ml (12 mg) dexamethasone in their epidural space. At exactly one hour after the first dose, a top up dose of 6 ml bupivacaine of epidural solution for group BN was given to each of the patients in the group, while 6 ml of the solution meant for group BD was given to each of the patients in the group. Only one top up dose was required.

In the operating room, the study protocol and the epidural procedure were explained to each patient. Each patient had multi-parameter attached for standard monitoring with pulse oximetry, electrocardiography, and noninvasive blood pressure measurement. Intravenous access was secured using 16 G needle and each patient received 15 ml/kg of intravenous normal saline within 20 minutes for preloading before induction of epidural anaesthesia.

Aseptically, epidural anaesthesia was carried out with patients in sitting position, using "loss of resistance technique" and "18 G Tuohy needle," at the L2-3 or L3-4 level, after skin infiltration with lidocaine 2%. A test dose of 3 ml lidocaine 2% and epinephrine 1 : 200000 was injected to rule out intravenous or subarachnoid injection.

Maximum sensory block height was assessed every minute for the first 15 minutes and thereafter, every five minutes following induction of epidural block, using loss of sensation to cold and gentle pin prick test. A minimum of sensory block height of T6 was the minimum allowable level for the commencement of surgery. The onset time is therefore the time taken to achieve the minimum sensory block height of T6 following injection of epidural solution.

The onset of epidural anesthesia was defined as the time interval between the end of drug injection and when the patients attained minimum sensory block of T6. The duration of epidural analgesia was defined as the time from onset of sensory block up to the time pain was

perceived at the site of surgery. All intraoperative and postoperative complications were recorded.

Sample Size

The primary objective of the study was to decrease the onset time of bupivacaine anaesthesia from 14.88 minutes, based on previous report,[3] while using bupivacaine alone to 8.93 minutes if bupivacaine was used alongside with dexamethasone. On the basis of this, a power analysis indicated that a minimum of 24 subjects per group would be sufficient enough to detect this 40% reduction in onset time with a study power of 80% and a =0.05. P < 0.05

Data Analysis

Statistical analyses were performed using Statistical Product and Service Solution (SPSS) for Windows version 28.0. Statistical tests such as Student's *t*-test and the chi-square test were used to assess level of significant differences between the two groups.

RESULTS

Forty-eight patients were studied in the two groups, 24 in each group. Demographic data and duration of surgery were comparable in both groups as documented in Table 1.

As shown in Table 2, using median and range, majority of the patients in group BD had attained median sensory block of T_5 and range between T_4 and T_7 in 6 minutes. Whereas patients in group BN had just attained median sensory block height of T_8 and range between T_7 and T_9. The difference is statistically significant P<0.05. However, majority of the patients in group BN had attained median sensory block of T_6 and range between T_4 and T_7 in 14 minutes.

Introperative clinical variables were shown in Table 3. Onset of epidural anaesthesia was significantly shorter (6.89 ± 3.22) in patients in the group with bupivacaine and dexamethasone than in patients in the group with bupivacaine and normal saline (14.37 ± 2.55). Duration of analgesia (528.471 ± 31.50) was significantly prolonged in patients with bupivacaine and dexamethasone epidural anaesthesia compared to patients in the group with bupivacaine and normal saline (184.59 ±92.20). The duration of surgery were comparable among the two groups.

No patients in the two groups experienced any form of pain. None of them had episodes of nausea and vomiting intraoperatively or immediate postoperative period. One patient in the group with bupivacaine dexamethasone epidural anaesthesia had hypotension. Four patients in group with placebo had hypotension, the result was not statistically significant. Two patients in the group with bupivacaine dexamethasone had bradycardia while one patient had bradycardia in the control group.

Table 1: Demographic parameters in two groups.

Characteristics	BD group (*n* = 24)	BN group (*n* = 24)	*P* value
Age (year)	35.06 ± 11.22	40.00 ± 14.41	0.63
ASA I (number)	20 (83.3%)	22 (91.7%)	0.82
ASA II (number)	4 (16.7%)	2 (8.3%)	0.59

Table 2: Sensory level attained after epidural block.

Time	BD group(n=24)	BN group(n=24	P-value
4min	$T_{10}(T_8\text{-}T_{11})$	$T_{10}(T9\text{-}T_{11})$	0.956
5min	$T_6(T_5\text{-}T_7)$	$T_9(T_8\text{-}T_{10})$	0.004
6min	$T_5(T_4\text{-}T_7)$	$T_8(T_7\text{-}T_9)$	0.008
10min	$T_4(T_2\text{-}T_5)$	$T_7(T_6\text{-}T_8)$	0.025
14min	$T_4(T_2\text{-}T_5)$	$T_6(T_4\text{-}T_7)$	0.031
15min	T4T2-T4	T6T4-T6	0.005

Table 3: Clinical variables in two groups.

Characteristics	BD group (*n* = 24)	BN group (*n* = 24)	*P* value
Sensory block T6 (minutes)	6.89 ± 3.22	14.37 ± 2.55	0.001
Duration of analgesia (minute)	528.471 ± 31.50	184.59 ± 92.20	0.001
Duration of surgery (minute	100.8 ± 18.7	100.4 ± 15.5	0.49
Nausea	0	0	1.000
Vomiting	0	0	1.000
Pain	0	0	1.000
Hypotension	1	4	0.459
Bradycardia	2	1	0.844

DISCUSSION

Epidural anaesthesia is an excellent choice for surgical anaesthesia when an indwelling functioning epidural catheter is in place.[1,2,5,7] Unlike spinal anaesthesia, Epidural anaesthesia provides unrestricted ability to titrate the desired level of analgesia or anaesthesia.[3] The

volume and concentration of local anaesthetic agents used for surgical anaesthesia are higher than those used for analgesia.[4] In recent years, regional anaesthesia techniques for surgery, obstetrics and post operative pain management have been performed on patients with increasing frequency.[6] Bupivacaine is a long-acting amide local anaesthetic, which is structurally similar to ropivacaine.[1] in the past, its epidural onset of action ranges between 15 minutes and 30 minutes depending on the dose.[2,3] This longer onset of action has discouraged the care giver from popularizing the technique.[3] There has lately been a dramatic interest in reducing the onset of action and also increase duration of action of epidural bupivacaine.[2] Prolonged onset time following epidural bupivacaine has been a major burden, especially when it is used as sole drug of choice. This is a major reason why both surgeons and anaesthetists are not usually embracing the technique.[4]

Initially, to overcome this delay in onset of action, the anaesthetists resulted to the use of high volume of local anaesthetic agents.[5] It was discovered that the higher the dose of bupivacaine, the faster is the onset time. The onset time of a low dose could range between 15 to 30 minutes. Whereas, onset time of a high dose of epidural bupivacaine could be as low as 15 or less. The adverse reactions following the use of high concentration of bupivacaine have made the anaesthetist to exercise a little modicum of caution while administering high concentration of the drug.[6] choice of dose and duration of action of anaesthetic drugs depends on the type of surgery. For epidural anaesthesia, the choice of drug and its dose is essentially a question of how long is the desired duration of anaesthesia.[4,5,8] Bupivacaine 0.5% is the drug of choice for in-patient surgery because of its longer duration of action. The time to obtaining surgical anaesthesia and motor block is somewhat longerthan the less concentrated solutions.[8,9]

In study of Song et al.[12] the author felt the need to increase the dosage of local anaesthetic mixture to 26ml during anaesthesia for ceasarean section. Their study was to measure plasma concentration of lidocaine and observe the possible systemic toxicity of local anaesthetics with the total dosage beyond the recommended value. Epidural local anaesthetics were administered as follows: Group 1, received 20ml of 0.5% bupivacaine (100 mg) plus 2% lidocaine 80 mg plus fentanyl 100 µg. Group 2 received 26ml of 2% lidocaine 520 mg without fentanyl. Group 3 received 24ml of 2% lidocaine 480 mg plus fentanyl 100 µg. They found that sensory blockade up to T4 level could be accomplished within 10 minutes in group 1. The onset is more rapid in group 2 and 3, the group with lidocaine. They found that addition of lidocaine to bupivacaine further reduce the onset time without significant side effects. According to their study, they found that lidocaine onset time is significantly lower than bupivacaine onset time.[12] They recommended that epidural anesthesia for cesarean section required sensory block up to T4 level would require 18 to 20 ml of 0.5% bupivacaine or 2% lidocaine. This is in keeping with the dose of bupivacaine administered to the patients in our study.

In our study, it is discovered that addition of dexamethasone to epidural bupivacaine significantly reduce onset time of analgesia action to as low as six minutes compared to epidural bupivacaine alone which is as high as 20 minutes. Apart from making the onset time more rapid, epidural dexamethasone also prolongs the duration of postoperative analgesia in our study population. Our observations are in keeping with the work of Razavizadeh et al.

Razavizadeh et al.[3] evaluated the effect of adding dexamethasone to epidural bupivacaine on postoperative analgesia in unilateral inguinal herniorrhaphy. Forty-four patients were enrolled in the double-blind, study. Patients were randomly allocated into dexamethasone or control group. In the dexamethasone group, patients received 18 ml of bupivacaine 0.5% and 2 ml (8 mg) of dexamethasone; in the control group, patients received 18 ml of bupivacaine 0.5% and 2 ml of normal saline. They found that the onset of epidural anesthesia was significantly more rapid in the dexamethasone group than in the control group. Duration of analgesia was markedly prolonged in the dexamethasone group than in the control group. They concluded that adding dexamethasone to bupivacaine significantly reduce onset time and prolongs the duration of postoperative analgesia.[3] The findings of Razavizadeh et al corroborated our study. According to our study, the onset time is shorter among the patients in our study than the onset time in the patients in Razavivadeh et al.[3] The shorter onset time is probably due to the higher doses of bupivacaine and dexamethasone administered into our patients.

The physiological mechanisms for the effects of dexamethazone in the epidural space is related to steroid effects which is attributed to its anti-inflammatory action, edema reduction, or shrinkage of connective tissue.[10] It has been observed that local steroid application was found to suppress transmission in thin unmyelinated C-fibers but not in myelinated A-beta fibers.[15] It has also been observed that steroids may bind directly to the intracellular glucocorticoid receptor, and their effects are predominantly mediated through altered protein synthesis through gene transcription.[3,11,16]

It has been discovered that epidural dexamethasone is having effect on intraspinal prostaglandin formation. Stimulation of peripheral tissues during acute noxious surgical stimulation leads to activation of phospholipase A2 and up-regulation of the expression of cyclo-oxygenase-2 in the spinal cord. This leads to synthesis of prostaglandin and a resultant hyperalgesic state.[17,18,19] Surgical incision causes inflammatory, metabolic, hormonal and immune responses. These responses can be attenuated by pre-operative administration of steroids.

These responses are reduced as a result of steroid anti-inflammatory and immunosuppressive effects. these inhibit both phospholipase A2 and cyclo-oxygenase-2 enzymes. This was evidence with the reduction of C-reactive protein levels, pain and fatigue scores in patients who received pre-operative dexamethasone. Different doses of pre-operative epidural dexamethasone have been used in different clinical trials.[13,17,18,19]

Ahadian et al.[13] investigated the efficacy, dose-response profile, and safety of three doses of epidural dexamethasone. Subjects were randomized to receive epidural dexamethasone 4mg, 8mg or 12mg. they found that the three doses were safe in the patients. Hence, the need to use 12mg epidural dexamethasone in our study.

Hefni et al.[11] studied different doses of epidural dexamethasone. They evaluated the effectivenss and safety of different doses of epidural dexamethasone for postoperative analgesia. Patients received 10 ml epidural plain bupivacaine 0.25% in the control group with 4 mg, 6 mg, and 8 mg dexamethasone in the other groups. After surgery, the time to first analgesic requirement was significantly prolonged in the dexamethasone groups compared with the control group. There was a significant reduction in postoperative meperidine consumption during the first 24 h in the dexamethasone groups in comparison with the control group. The visual analogue scale (VAS) scores were significantly lower and the patient satisfaction score was significantly higher in the dexamethasone groups compared with the control group. Similar to our study, this finding showed that epidural dexamethasone reduces postoperative pain following surgery. They discovered that epidural dexamethasone in a dose of 8 mg was more effective for post-operative analgesia in patients undergoing TAH than lower doses. There were no side-effects of dexamethasone usage such as increase of blood glucose, delayed wound healing and wound infection. In our study, 12mg epidural dexamethasone was used. This was based on the early findings by other authors that the higher the dose, the higher the concentration of the drug in the epidural space and the faster the onset time and the better the effectiveness of post operative analgesia.[5,8,14,20]

The study of Naghipour et al.[8] confirms our findings. In 2013, they observed that the addition of dexamethasone (8 mg and 4 mg in lumbar and thoracic epidural catheterization, resp.) to bupivacaine and fentanyl for postoperative epidural analgesia results in an increased duration of analgesia (372 ± 58.1 versus 234.6 ± 24.3 min). The pain score and pentazocine use in the dexamethasone group were less than those in the control group (37.1 ± 19.7 mg versus 73.1 ± 17.6 mg, resp.; P = 0.001). Although the study used bupivacaine and dexamethasone only for postoperative analgesia, the result corroborates the results of our study.

CONCLUSION

Patients in this present study had epidural bupivacaine with or without dexamethasone. This is discovered to be safe and effective. Addition of dexamethasone also enhances shorter onset of action of anaesthesia and prolonged duration of action of epidural anaesthesia. Whenever shorter onset is desired, dexamethasone can be added to epidural bupivacaine because it significantly makes onset of action to be more rapid and prolongs the duration of postoperative analgesia.

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