Anaesthetic and Analgesic Efficacy of Dexmedetomidine versus Fentanyl as an Adjuvant to Epidural Levobupivacaine for Total Abdominal Hysterectomy: A Prospective, Randomized, Controlled Study

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ABSTRACT

BACKGROUND

After Total abdominal hysterectomy (TAH) is a major surgery and is associated with significant morbidity, if pain is not adequately controlled intra- and post-operatively. Epidural analgesia with a variety of local anaesthetics and adjuvants is widely used for TAH as it provides both intra- and post-operative analgesia. Primary objective of our study is to compare the effect of epidural levobupivacaine with fentanyl versus levobupivacaine with dexmedetomidine for analgesia and motor blockade in patients undergoing Total Abdominal Hysterectomy.

METHODS

This is a prospective, double-blinded trial conducted among 100 women aged between 35 and 65 years of age who were allocated randomly into one of the two groups for elective total abdominal hysterectomies. Group D received epidural levobupivacaine 0.5% with dexmedetomidine as adjuvant, and the other group F received epidural levobupivacaine 0.5% with fentanyl as adjuvant.

RESULTS

Time to achieve sensory level at T6 was found to be significantly lower ($p<0.001$) in Group D (9.22 + 0.86 min) as compared to Group F (11.30 + 0.99 min). The time to achieve complete motor block in Group D was 20.0 + 1.53 minutes and in Group F it was found to be 24.02 + 1.12 minutes. Complete motor block was achieved in significantly lower ($p<0.001$) time by Group D subjects as compared to Group F. Also, it was found that the duration of analgesia was significantly higher ($p<0.001$) in Group D (384.02 + 20.84 minutes) as compared to Group F (270.30 + 19.34 minutes).

CONCLUSIONS

Dexmedetomidine is a better adjuvant to levobupivacaine than fentanyl for epidural analgesia with better quality of analgesia, prolonged duration of analgesia, higher sedation scores, and no significant side effects.

KEYWORDS

Epidural Anaesthesia, Dexmedetomidine, Fentanyl, Local Anaesthetics, Levobupivacaine

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DOI: 10.18410/jebmh/2020/311

How to Cite This Article:
Pathak N, Bhavya K. Anaesthetic and analgesic efficacy of dexmedetomidine versus fentanyl as an adjuvant to epidural levobupivacaine for total abdominal hysterectomy: a prospective, randomized, controlled study. J. Evid. Based Med. Healthc. 2020; 7(30), 1474-1479. DOI: 10.18410/jebmh/2020/311

Submission 30-04-2020,
Peer Review 05-05-2020,
Acceptance 04-06-2020,
Published 27-07-2020.

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BACKGROUND

Total Abdominal Hysterectomy (TAH) is a surgical procedure which is associated with significant postoperative pain and morbidity and is considered to be a major surgery.[1] Variety of anaesthetic techniques including general anaesthesia or various modalities of regional anaesthesia like epidural, abdominal blocks, local infiltration, spinal anaesthesia etc. have been used to conduct TAH. Epidural analgesia has been widely used in patients for TAH except in those with raised intracranial tension, coagulopathy, patient refusal, local sepsis, inability to maintain stillness during needle puncture, and limited expertise.[2] Epidural analgesia is also recommended in patients who are at high risk of developing significant postoperative pain like after TAH.[3,4] In our study, we have used two different drugs - dexmedetomidine and fentanyl as adjuvants to levobupivacaine as local anaesthetic (LA) for epidural anaesthesia and compared the anesthesia and analgesia in TAH patients.

METHODS

The study was done as a prospective, randomized, controlled, double-blinded clinical trial after getting Institutional Ethical Committee approval and informed consent from the patients. Women in the age group of 35-65 years, with BMI between 20-25, of American Society of Anaesthesiologist (ASA) physical status I and II scheduled for elective total abdominal hysterectomy (TAH) were enrolled into the study after getting informed consent. Exclusion criteria included any contraindication to epidural anaesthesia, diseased or deformed spine or history of spine trauma or surgery and allergy to any of the study drugs. Preanaesthetic evaluation was done on the day prior to surgery. Randomization was done using sealed envelope technique.

All the patients were premedicated with oral alprazolam 0.25 mg and oral ranitidine 150 mg the night before surgery and on the morning of surgery and were advised adequate fasting as per ASA guidelines. After shifting into the operating room, preinduction monitors were connected, which included pulse oximetry, electrocardiogram, and noninvasive blood pressure monitoring. The baseline values were recorded and documented. While maintaining all aseptic precautions, in sitting position, L1-L2 level was identified with landmark technique, local application of 2% lignocaine as subcutaneous wheal was done. 18G Tuohy epidural needle was introduced and epidural space was identified with loss of resistance to air technique and skin to space depth was noted. Epidural catheter was then inserted and fixed with the aim of the tip being at T10 level. After making the patient supine, a test dose of 3 mL 2% lignocaine with 5mcg/mL adrenaline was given to rule out intrathecal and intravascular placement of the catheter. Sensory level we aimed to achieve was T6. Adults in group D received 12 mL of 0.5% levobupivacaine with 50 mcg dexmedetomidine (1 mL) in the epidural space, while those in Group F received 12 mL of 0.5% levobupivacaine with 50 mcg fentanyl (1 mL) in the epidural space. The drugs for administration in the epidural block were prepared by an anaesthesiologist not participating in the study. The epidural anaesthesia was performed in the sitting position by another anaesthesiologist who was blinded to the drug that was injected. After epidural drug administration, sensory level achieved was assessed by pin prick, time to achieve the sensory level at T_6 was noted and time taken for complete motor blockade (Modified Bromage scale level 3) was noted. Surgical incision was given after 15 minutes of epidural drug administration. The patients with complaint of pain, observation for any limb movement, increase in heart rate or mean arterial pressure by 20% more than the baseline values, were noted and presence of any of these parameters was considered a failed epidural block. These patients were excluded from the study. Intraoperative monitoring included heart rate, noninvasive blood pressure measurement, pulse oximetry, and end-tidal capnography. The recorded parameters were documented every 5 min intraoperatively till completion of surgery.

After completion of surgery, time was recorded from time of epidural block till the patient first feels pain (VAS of ≥4). Side effects such as hypotension, bradycardia, nausea and vomiting, respiratory depression, sedation (Ramsay Sedation score), urinary retention were noted and adequately treated. Respiratory depression was defined as an oxygen saturation of <94% on the pulse oximeter or respiratory rate <10 per minute requiring oxygen supplementation and assisted ventilation. Bradycardia was defined as heart rate <60 per minute or 20% below the baseline value, whichever was lower and was treated with atropine 20 mcg/Kg intravenously. Hypotension was defined as systolic blood pressure 20% less than the baseline value that was treated with injection mephentermine in fractionated doses.

Post operatively once the patient complained of pain (VAS of ≥ 4), infusion of local anaesthetic drug was given through the epidural catheter as per department protocol. Catheter was removed 48 hours after insertion.

The sample size was calculated as 50 subjects per group, to detect a difference in the duration of analgesia with an alpha error of 0.05 and beta error of 0.09. Allowing exclusion due to failed epidural, 120 women in the age group of 35-65 years coming for elective TAH surgeries were enrolled in the study. Analysis was done using the Statistical Package for the Social Sciences (SPSS) version 15.0 software. The observed variables are expressed as mean and standard deviation or numbers and percentage. Continuous covariates were compared using analysis of variance. The comparison was studied using the Chi-square test or Fisher's exact test or independent t-test as appropriate, with the P value reported at the 95% confidence interval. P <0.05 was considered statistically significant.

RESULTS

We had enrolled 120 subjects, but due to change of anaesthesia plan (6), epidural failure (4), failure to give consent (10) in 20 patients, we studied 50 patients in each group. Demographic variables like weight (p=0.979) and age wise distribution (p=0.216) of subjects of both the groups were statistically similar and were statistically insignificant as shown in Table 1. Baseline hemodynamic variables of both the groups were also statistically similar and statistically insignificant.

Parameter	Group F	Group D	Statistical Significance
Mean Age	47.28+10.06	49.18+11.41	$\chi 2$=4.459; p=0.216
Mean weight (Kg)	59.00	58.98	'ŧ' = 0.026; p=0.979

Table 1. Distribution of Study Population

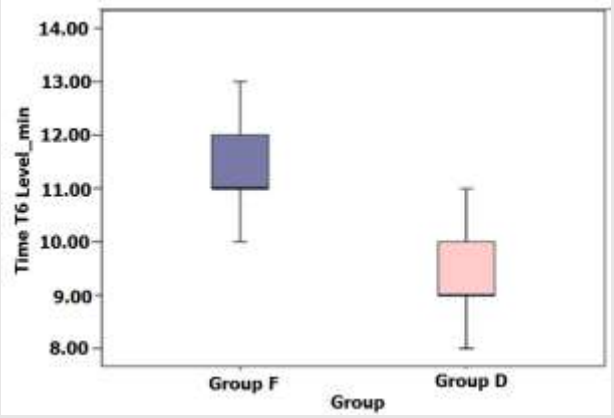

Figure 1. Time to Achieve Sensory Level at T6

Time to achieve sensory level at T6 was assessed by pin prick after giving epidural bolus of the LA with respective adjuvant was noted. Time to achieve sensory level at T6 was found to be significantly lower (p<0.001) in Group D (9.22 ± 0.86 min) as compared to Group F (11.30 ± 0.99 min) as shown in Figure 1.

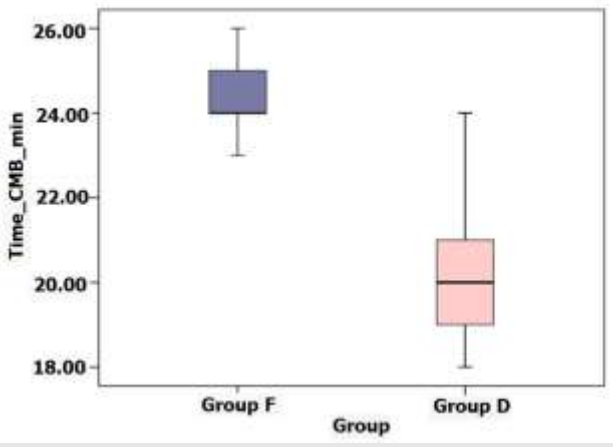

Figure 2. Time to Achieve Complete Motor Block

The time to achieve complete motor block (CMB) in Group D was 20.0 ± 1.53 minutes and in Group F it was found to be 24.02 ± 1.12 minutes. Complete motor block was achieved in significantly lower (p<0.001) time by Group D subjects as compared to Group F subjects as shown in Figure 2.

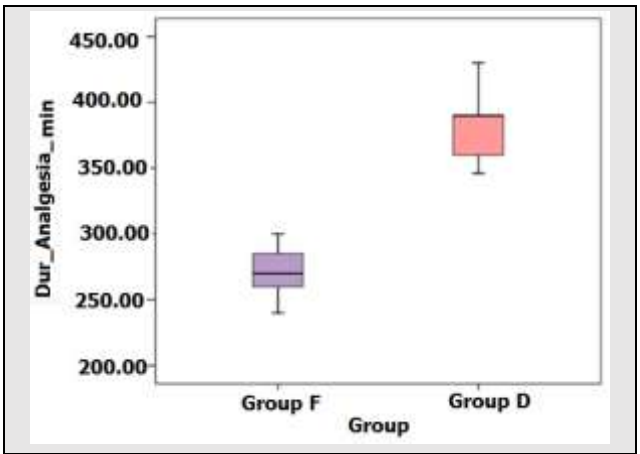

Figure 3. Duration of Analgesia

The duration of analgesia was significantly higher (p<0.001) in Group D (384.02 ± 20.84 minutes) as compared to Group F (270.30 ± 19.34 minutes) as shown in Figure 3.

Side Effects	Group F		Group D		Statistical Significance	
	No.	%	No.	%	$\chi 2$	'P' Value
Nausea/vomiting	17	34.00	11	22.00	1.786	0.181
Respiratory distress	0	0	0	0	–	–
Hypotension	3	6.0	4	8.0	0.154	0.695
Bradycardia	2	4.0	3	6.0	0.211	0.646
Urinary Retention	5	10.0	9	18.0	1.329	0.249
Ramsay Sedation Score	2.12 (mean)		3.32 (mean)		p<0.001 (significant)	

Table 2. Side Effects in Study Population

Though nausea and vomiting were found to be in a higher proportion of subjects from Group F as compared to Group D but this difference was statistically not significant (p=0.181). Lesser sedation (Ramsay Sedation point 2- Ramsay sedation score) was found in significantly higher proportion of subjects from Group F (82%) as compared to Group D (12%). None of the subjects from Group F reported Ramsay Sedation point 4 and 5.

There was no statistically significant difference in the hemodynamic parameters between the two groups.

DISCUSSION

Epidural blockade is often used either as a sole anaesthetic technique or as an adjuvant technique as it reduces the surgical stress response and postoperative pain. We used an exclusive epidural route in our study so that postoperative analgesia can be provided and also invasive dural penetration was avoided. The patients remained conscious thus retaining their spontaneous reflexes and cognitive responsiveness leading to early mobilization.[5] Other advantages of Epidural anaesthesia are that it reduces the blood loss, decreases incidence of deep vein thrombosis and also improves respiratory and bowel function. Hemodynamic fluctuations may occur if large volumes of local anaesthetic drugs are used.[6,7] Thus incremental doses are generally used with close monitoring of vitals. In our study, we gave a single

shot bolus dose for intraoperative anaesthesia, and placed a catheter for postoperative analgesia.

Epidural analgesia is the traditional technique of provision of intra and postoperative analgesia. The effectiveness of epidural block is only limited by the duration of action of the local anaesthetic, when administered as a single-shot injection without placement of catheter. This has led to the use of several adjuvants to prolong the duration of action of the local anaesthetic.

Local anaesthetics like levobupivacaine act on sodium channels by blocking generation and propagation of nerve action potential. Bupivacaine is one of the most widely used local anaesthetic used, but because of the associated cardiovascular (CVS) and central nervous system (CNS) effects safer alternatives are being searched for. Its commercial preparation is a racemic mixture of two enantiomers, levobupivacaine, S (-) and dextro bupivacaine, R (+) isomer. It is found that most CVS and CNS adverse reactions are due to R (+) isomer and the levo (S-)isomer has a safer profile.[8,9] The decreased CNS and CVS adverse effects of levobupivacaine are said to be due to its faster protein binding rate.[10] The onset of sensory block (8–30 min), maximum upper spread (T7 - T8 after L2 - L3 or L3 - L4 lumbar injection) and duration (4-6 hours) are similar after equal doses of levobupivacaine and bupivacaine (15 mL 0.5%).[11,12] The motor blockade with levobupivacaine is less dense but onset is delayed with comparable duration.[13,14] The duration of motor and sensory block increases with an increase in concentration of levobupivacaine. Studies have shown that Levobupivacaine has less cardiotoxic effects as it causes less direct depression of myocardial contractility as compared to bupivacaine.[15,16]

Various adjuvants are added to epidural anaesthesia for added benefits like sedation, prolonged postoperative analgesia and improved hemodynamics. Adjuvants when added to levobupivacaine for epidural blockade may increase the quality and duration of analgesia and may further decrease toxicity. Opioid adjuvants like fentanyl improves analgesia and decreases the risk of local anaesthetic (LA) toxicity.[17,18] In our study we have used opioid (fentanyl) and α2 adrenergic agonist (dexmedetomidine) both of which have analgesic and sedative properties when used as an adjuvant in epidural.[19]

Fentanyl, a widely used analgesic adjuvant is an agonist at μ-opioid receptors. Its main site of action is the substantia gelatinosa on the dorsal horn of spinal cord. It blocks fibers carrying nociceptive impulses both pre and post synaptically[20.] The dorsal roots have opioid-binding sites on which fentanyl either acts directly on the spinal nerve or by penetrating the dura mater to act at the spinal roots.[21,22]

In recent years, the perioperative use of dexmedetomidine has increased, including its use in central and peripheral nerve block and intravenously during surgery. Several studies have shown a definite improvement in the duration of analgesia when dexmedetomidine is used along with local anaesthetics. Epidural administration of α2 agonist drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis[23,24] α-2 adrenoreceptor agonists have analgesic action by depressing release of C - Fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons.[25,26,27] Addition of 1 μg/Kg dexmedetomidine leads to early onset of analgesia with prolonged duration, faster achievement of maximum level of blockade, both motor and sensory, good sedation without much hemodynamic effects.[28,29,30,31]

We conducted our study in one surgery that is total abdominal hysterectomies so as to maintain uniformity in intensity and quality of post-operative pain in all the patients. Since we have used lumbar epidural because of ease of the technique we had to use lower abdominal surgeries.

The limitations of our study are small sample size and that it was limited to the female population only and we could not assess the effect of drugs on male population.

On analysis of the demographic profile the age and weight were comparable in both the groups.

Mean time for sensory level at T6 was found to be significantly lower with dexmedetomidine which shows that the onset of sensory block was faster in dexmedetomidine than fentanyl.

Mean time for complete motor block achieved in significantly lower ($p<0.001$) time by dexmedetomidine subjects as compared to fentanyl which tells that the onset of motor block was faster in dexmedetomidine than fentanyl. Duration of analgesia was significantly higher in Group D (384.02 + 20.84 minutes) as compared to Group F (270.30 + 19.34 minutes). It means that Dexmedetomidine provided longer duration of analgesia than Fentanyl.

Sedation was more in the dexmedetomidine group than fentanyl group. Nausea and vomiting was found to be in higher proportion in fentanyl as compared to dexmedetomidine but this difference was statistically not significant.

Patients were hemodynamically stable throughout the perioperative period in both the groups. Though, a slight decrease in heart rate and mean arterial pressure was observed in both the groups but it never fell down to more than 20% of the baseline values.

CONCLUSIONS

We conclude that dexmedetomidine is a better adjuvant to levobupivacaine than fentanyl for epidural analgesia with better quality of analgesia, prolonged duration of analgesia, higher sedation scores, and no significant side effects.

Financial or Other Competing Interests: None.

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