

## The Effects of Dexmedetomidine As an Adjuvant with Levobupivacaine To Epidural Analgesia on The Outcomes of Patients Undergoing Total Abdominal Hysterectomy Surgery

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### ABSTRACT

**Background:** Total abdominal hysterectomy (TAH) characterizes as major surgery with increased risk of morbidity. It depends on adequate pain management intra- and postoperatively. Anesthesia management of TAH widely uses a regional approach with the epidural technique which administers a local anesthesia agent into the epidural space.

**Objective:** This study aims to determine the effectiveness of epidural levobupivacaine with fentanyl versus levobupivacaine with dexmedetomidine for epidural anesthesia in patients undergoing TAH.

**Methods:** This is a prospective, single-blinded trial conducted among 20 patients aged 18 to 40 years who underwent elective TAH with American Society of Anesthesiologist (ASA) class I and II status. The control group received epidural levobupivacaine 0.5% with fentanyl as an adjuvant, while the dexmedetomidine group received levobupivacaine 0.5% with dexmedetomidine as an adjuvant. We then compared the degree of pain using a numeric rating scale (NRS) 24 hours after surgery, duration of analgesia, and incidence of postoperative nausea and vomiting (PONV) in both groups.

**Result:** Duration of analgesia was  $89.60 + 7.6332$  min in group dexmedetomidine, while it was  $78.0 + 10.4562$  min in group fentanyl, respectively ( $P < 0.05$ ). The means of NRS was  $3.00 + 1.88562$  in group dexmedetomidine and  $4.80 + 1.1352$  in group fentanyl ( $p=0.019$ ). The incidence of PONV in group dexmedetomidine was three, while in group fentanyl was eight ( $p=0.025$ ).

**Conclusion:** Dexmedetomidine is preferred over fentanyl when added to levobupivacaine for epidural analgesia in TAH procedures. Dexmedetomidine offers superior quality with a prolonged duration of analgesia, lower NRS values, and a lower incidence of PONV rather than fentanyl.

**Keywords:** dexmedetomidine; epidural anesthesia; fentanyl; levobupivacaine; total abdominal hysterectomy

## INTRODUCTION

Total abdominal hysterectomy (TAH) count as a major surgical intervention which poses a substantial risk of postoperative pain and morbidity.<sup>1</sup> A wide spectrum of anesthetic methods, such as general anesthesia, epidural anesthesia, spinal anesthesia, abdominal blocks, and local infiltration have been employed for performing TAH.<sup>2</sup>

Epidural anesthesia is a regional anesthesia technique that administers a local anesthesia agent using a catheter directly into the epidural space, once or continuously. Difficult-to-access positions and vacuum effects of the epidural cavity require special catheter access techniques and local anesthesia. Several studies have reported positive effects of epidural anesthesia, such as faster recovery of bowel function and reduced pain-induced hormonal stress response.<sup>3</sup> When local anesthetics are used at therapeutic levels, concerns about side effects are brought up. As a result, several adjuvants to local anesthetics have been offered in addition to epidurals.<sup>4</sup>

Opioid use is associated with several side effects, thus, several options, including dexmedetomidine are widely studied as promising alternatives for opioid adverse effects such as respiratory depression, urinary retention, nausea, and itching.<sup>5</sup> In recent years, dexmedetomidine has been administered perineurally along with local anesthesia to block nerve conduction during spinal or epidural anesthesia.<sup>6</sup>

Dexmedetomidine, a selective  $\alpha$ -2 adrenoceptor agonist, has been used epidurally in humans without neurological deficits reports, dexmedetomidine may be added as an adjuvant either in general or regional

anesthesia and even in postoperative sedation. Dexmedetomidine produce analgesia effect by acting on  $\alpha$ -2 adrenergic receptors in the dorsal roots of the spinal cord. Due to its lipophilicity, dexmedetomidine is rapidly transported into the cerebrospinal fluid after epidural administration.<sup>6,7</sup> When compared to systemic administration, the analgesic effect of epidural administration may persist up to five times longer. Activation of  $\alpha$ -2 adrenoceptors can induce contraction of blood vessels and other smooth muscles; reduced intraocular pressure, reduced platelet aggregation, decreased shock threshold when reaching 2°C; decreased insulin release; decreased intestinal secretion and motility; inhibition of renin release; increased glomerular filtration and increased renal excretion of sodium and water.<sup>8,9</sup>

However, until this date, we only found two studies who evaluate the use of adjuvant and spinal anesthesia in gynecological procedure such as TAH. Chiruvella et al in 2018 evaluated postoperative analgesia with epidural dexmedetomidine compared with clonidine following TAH which showed dexmedetomidine as a better neuraxial adjuvant for providing early onset and prolonged postoperative analgesia and stable cardiorespiratory parameters.<sup>10</sup> Pathak et al in 2020 evaluated dexmedetomidine versus fentanyl as an adjuvant to epidural levobupivacaine for TAH which showed 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.<sup>11</sup>

Nevertheless, dexmedetomidine have showed superiority as adjuvant to epidural anesthesia in orthopedic procedure with faster onset ( $7.67 \pm 1.37$  minutes), good quality (higher patient satisfaction;  $5.07 \pm 0.37$  and lower score visual analog score (VAS)  $0.37 \pm 0.49$ ), and prolonged duration ( $462.20 \pm 9.72$  minutes) with no relevant adverse effects.<sup>12</sup>

On the other side, hysterectomy considered as the second most performed gynecological procedure after C-Section. The incidence rates of hysterectomy vary significantly across regions, with the United States exhibiting a high rate (510 per 100,000 in 2004). Additionally, total abdominal hysterectomy being more prevalent in low income countries (175 of 193 (90.6%)) compared to middle-income (752 of 1.463 (51.4%))<sup>13,14</sup>

Considering these advantages and the urgency of such procedure, thus, we evaluate the effects of dexmedetomidine as an adjuvant to epidural analgesia with levobupivacaine versus fentanyl in patients undergoing TAH. The aim of this study was to compare the analgesia duration, the degree of postoperative pain, and the frequency of postoperative nausea and vomiting (PONV) in both groups.

## METHOD

### Study Design

The design of this study is a prospective, randomized, comparative clinical study using single-blind control. Before initiate the study procedure, the participant will be explained regarding the description of the procedure and completed a written informed consent form if agreed.

### Study Population

The inclusion criteria for research participants were patients aged 18 to 40 years who underwent elective TAH with ASA physical status I – II; body mass index (BMI)  $\leq 35$ . The exclusion criteria were patient who declined to participate, had allergies to any of the study drugs, or were contraindicated for epidural anaesthesia, suffered spine abnormalities, experienced or history of systemic illness, neurological or psychiatric disorders. We performed total random sampling from population target in the specified timeframe.

### Study Procedure

Preoperative clinical examinations and appropriate tests were performed on each participant. Additionally, we provided all subjects with knowledge regarding the numeric rating scale (NRS) to quantify discomfort and pain intensity. All patients received a premedication of 0.25 mg of oral alprazolam and 150 mg of oral ranitidine both the night prior to and the morning of the procedure. They were also instructed to fast appropriately according to ASA guidelines.

The patients were in sitting position under routine monitoring and vital signs recording. L1-L2 level was identified with landmark technique. Low-frequency curved-array ultrasound probe was used to identify the lumbar interspaces until the correct interlaminar space was located and marked. The entrance site was anesthetized with 1% lidocaine. The epidural catheter was inserted and secured with the tip at the T10 level. This procedure was performed under thorough sterilization using an 18 gauge Tuohy needle. A test dosage was administered using 3 milliliters of Lidocaine hydrochloride 2% solution with 1:200,000 adrenaline. If the rapid onset of neuroaxial block or tachycardia

develop, the catheter was withdrawn and repositioned in different interspace. In the epidural space, 12 mL of 0.5% Levobupivacaine with 50 mcg Fentanyl (1 mL) was administered to Group C, and 12 mL of 0.5% Levobupivacaine with 50 mcg Dexmedetomidine (1 mL) was administered to Group D. After administering the epidural medication, the sensory level was evaluated using a pin prick test. The targeted sensory level was T6. Surgical incision was performed 15 minutes following the introduction of epidural medication.

**Study Outcomes**

After completion of surgery, we proceeded to assess the analgesia duration (the interval between the first epidural infusion and the first request for further painkillers), degree of pain using NRS 24 hours after surgery, and the occurrence of PONV in both groups.

**Statistical analysis**

All the recorded data were analysed utilizing Statistical Package for Social Science (SPSS) version 22.0. The unpaired t test was employed to assess the disparity in means among several

subgroups of variables. The Chi-square (X<sup>2</sup>) test was employed to evaluate the significance of the differences in proportions between qualitative parameters, with the P value reported at the 95% confidence interval. P <0.05 was considered statistically significant.

**RESULTS**

A total 20 patient were recruited during mentioned period with demographic characteristics varied within age (years) 30.70, BMI (22.737 – 23.149), NRS (3.00 – 4.80) and duration of analgesia (min) (78.0 – 89.60).

Age and BMI data were analysed using an unpaired t test, and revealed no significant difference (p-value >0.05) between the study groups (Table 1).

The statistical analysis showed that there was significant difference (p-value <0.05) in all variables. Compared to Fentanyl, Dexmedetomidine provides longer analgesia duration (p=0.011; Table 2), lower NRS values (p=0.019; Table 2), and less PONV incidence (p=0.025; Table 3).

**Table 1.** Demographic profile

Demographic Characteristics	Group Fentanyl (n=10)	Group Dexmedetomidine (n=10)	P-value
Age (years)	30.70 ± 4.8773	30.70 ± 6.9129	1.00
BMI <sup>a</sup>	23.149 ± 4.1936	22.737 ± 4.0169	0.825
NRS <sup>b</sup>	4.80 ± 1.1352	3.00 ± 1.88562	0.019
Duration of Analgesia (min)	78.0 ± 10.4562	89.60 ± 7.6332	0.011

<sup>a</sup>Body Mass Index

<sup>b</sup>Numeric Rating Scale

**Table 2.** Comparison of analgesia duration and NRS values.

Variable	Group C (n=10)	Group D (n=10)	P-value
Duration of Analgesia (min)	78.0 ± 10.4562	89.60 ± 7.6332	0.011
NRS <sup>a</sup>	4.80 ± 1.1352	3.00 ± 1.88562	0.019

<sup>a</sup>Numeric Rating Scale

**Table 3.** Chi Square of PONV in both groups.

Variable		Group C (n=10)	Group D (n=10)	P-value
PONV <sup>a</sup>	Yes	8	3	0.025
	No	3	7	

<sup>a</sup>Post Operative Nausea and Vomiting

**DISCUSSION**

Epidural analgesia is a conventional method for providing pain relief during and after surgery. The efficacy of epidural block is solely constrained by the duration of the local anesthetic's impact when given as a one-time injection without catheter implantation. Consequently, various adjuvants have been employed to extend the duration of the local anesthetic's effects.<sup>15</sup>

The most utilized local anesthetic is bupivacaine; however, due to its potential adverse effects on the cardiovascular system and central nervous system, researchers are actively seeking safer alternatives. From there, other alternative local anaesthetics, levobupivacaine, were started to be widely sought after for research. This agent affects the sodium channels which resulting in blocking generation and propagation of nerve action potential. The motor blockage induced by levobupivacaine is less dense, but its onset is delayed while its duration remains unchanged. An escalation in the concentration of levobupivacaine leads to a proportional rise in the duration of both motor and sensory blocks. Prior research has demonstrated that levobupivacaine has reduced cardiotoxicity by inducing less pronounced suppression of cardiac contractility in comparison to bupivacaine.<sup>16</sup>

Additional adjuvants are added into epidural anaesthesia to provide supplementary advantages such as

sedation, extended postoperative pain relief, and enhanced hemodynamics. The addition of adjuvants to levobupivacaine for epidural blocking can enhance the quality and duration of analgesia, while also reducing toxicity. Our study utilised opioid (fentanyl) and  $\alpha 2$  adrenergic agonist (dexmedetomidine), both of which possess analgesic and sedative effects, as adjuvant to epidural analgesia.<sup>16</sup>

Opioids and  $\alpha 2$  agonists used as adjuvants in regional anesthesia yield strong analgesic effects. Fentanyl exerts its effects either by directly impacting the spinal nerve or by crossing the dura mater to act on the dorsal roots that contain places where opioid-binding sites located.<sup>17</sup> Dexmedetomidine exerts its effects on the central nervous system's pre and postsynaptic nerve terminals, resulting in a reduction of sympathetic outflow and norepinephrine release. It may produce hypotension and bradycardia. Nevertheless, it lacks the adverse effects commonly observed with opioids, such as respiratory depression, pruritus, and PONV. The motor block can arise from the binding of  $\alpha 2$  agonists to the motor neurons located in the dorsal horn.<sup>18</sup>

Our study demonstrated a statistically significant difference between the two groups, with longer analgesia duration (p=0.011), lower NRS values (p=0.019) and smaller cases of PNOV (p=0.025) being noted in dexmedetomidine group.

Align with our result, a prospective, randomized, controlled study regarding the adjuvant to epidural analgesia with levobupivacaine in TAH by Pathak et al. discovered similar findings. They found that dexmedetomidine works superior compared to fentanyl. The analgesia duration for dexmedetomidine ( $384.02 \pm 20.84$  min) was longer than fentanyl ( $270.30 \pm 19.34$  min) with a  $p$ -value  $< 0.001$ . Regarding the PONV, fentanyl was observed to cause more PONV although this difference was not statistically significant.<sup>11</sup>

Moreover, our study aligns with Chiruvella et al who stated the addition of dexmedetomidine to levobupivacaine as an adjuvant resulted in an earlier onset ( $7.26 \pm 0.96$  min), prolonged duration of analgesia ( $405.6 \pm 20.32$  min), only 42.5% patient required rescue analgesic (injection diclofenac sodium) and decreased mean VAS score. The incidence of other side effects such as nausea, vomiting, and shivering were comparable in both groups and found to be statistically nonsignificant ( $P > 0.05$ ). None of the patient showed hypotension, bradycardia, dizziness, and respiratory depression in either group.<sup>12</sup>

Other than gynecological procedures, our result was also supported by Shukla et al. which compared the efficacy of three adjuvant agent, namely fentanyl, tramadol, and dexmedetomidine to epidural analgesia with levobupivacaine in lower limb orthopedic surgeries. In their report, dexmedetomidine group exhibited lower VAS scores and longer analgesia duration. Furthermore, they draw the conclusion that dexmedetomidine is superior to other agent due to various properties, including faster onset, higher quality (lowest Bromage score 2), longer duration, and produce no apparent

adverse effects.<sup>12</sup> We conducted our study only on patients undergoing whole abdominal hysterectomies to ensure consistency in the severity and nature of post-operative pain across all participants. Due to the convenience of the lumbar epidural approach, we opted for lower abdominal procedures.

The limitations of our study include a limited sample size and a focus exclusively on the female population, preventing us from evaluating the impact of medications on the male population.

## CONCLUSION

Finally, we concluded that dexmedetomidine showed better performance over fentanyl when added to levobupivacaine for epidural analgesia in TAH procedures. Dexmedetomidine offers superior quality with a prolonged analgesia duration lower NRS values, and a lower incidence of PONV rather than Fentanyl.

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