DOI: 10.7860/JCDR/2023/57000.17508

Original Article

Anaesthesia Section

Comparative Evaluation of Levobupivacaine with Fentanyl Versus Bupivacaine with Fentanyl for Postoperative Epidural Analgesia in Patients Undergoing Gynae-Oncological Surgeries: A Randomised Clinical Study

MM SHOBHA[1], BH ARATHI[2], NAMRATA RANGANATH[3], SS SRIHARI[4], VB GOWDA[5]

ABSTRACT

Introduction: Epidural analgesia is one of the preferred mode of perioperative management. Neuraxial opioids like fentanyl when used in epidural offer advantage of augmenting local anaesthetic effect and reducing the anaesthetic and analgesic requirement.

Aim: To compare the adequacy of analgesia, requirement of rescue analgesics between 0.125% bupivacaine with 2 mcg/cc fentanyl and 0.125% levobupivacaine with 2 mcg/cc fentanyl.

Materials and Methods: The randomised clinical study was carried out from September 2016 to May 2017 in 70 patients (35 in each group) of American Society of Anaesthesiologists (ASA) I and II scheduled for elective gynae-oncological surgeries. The epidural analgesia in group Bupivacaine with Fentanyl (BF) was 0.125% Bupivacaine with 2 mcg/cc Fentanyl and group Levobupivacaine with Fentanyl (LF) was 0.125% Levobupivacaine with 2 mcg/cc fentanyl. All data was statistically analysed and compared using Student t-test, Chi-square/ Fischer's-exact test.

Results: Total of 70 patients were analysed, 35 each in Group BF (mean age: 50.06±7.19 years) and Group LF (mean age: 46.43±8.41 years). Both the groups were compatible with regard to demographic data and haemodynamic variables. The mean Visual Analogue Scale (VAS) score was higher in group BF compared to group LF at 0,1,4,6,1,2 and 18 hours but the observed difference in both the groups was not statistically significant except at 2nd (p-value: 0.016) and 24th hour (p-value 0.017). Number of rescue analgesics as epidural boluses (p-value=0.001) and paracetamol (p-value=0.044) requirement were more in group BF compared to group LF, respectively.

Conclusion: On account of adequate postoperative analgesia, haemodynamic stability, levobupivacaine with fentanyl is a better option than bupivacaine with fentanyl for epidural infusion.

Keywords: Pain relief, Rescue analgesic, Visual analogue scale

INTRODUCTION

Patients undergoing gynae-oncological surgery will have surgeries with omentectomy, peritonectomy, extensive bowel handling, pelvic and para-aortic node dissection which result in extensive skin incision too. This extensive tissue injury leads to release of histamine and inflammatory mediators, which activates peripheral nociceptors and lead to severe pain. If uncontrolled, it results in wide range of detrimental effects. Control of pathophysiological process associated with acute postoperative pain has shown to attenuate the stress response, thus causing improvement in postoperative morbidity, mortality and patient related outcomes [1,2].

In multimodal approach, epidural analgesia is an integral part of analgesia. It offers a number of proven benefits as a result of pain relief and obtunding the stress response [3]. It has been shown to improve the quality of patient recovery and reduce the incidence of serious complications. Lumbar epidural has found to be effective in major abdominal surgeries [4,5]. As the spinal cord typically terminates at L1 level, lumbar epidural catheter can be safely placed [6].

Analgesia delivered through an indwelling epidural catheter is a safe and effective method for management of acute postoperative pain. Intraoperative use of the epidural catheter as part of a combined epidural-general anaesthesia technique results in less pain and faster patient recovery immediately after surgery [7]. Bupivacaine is an amino amide local anaesthetic [8]. Levobupivacaine, the pure levorotatory isomer of bupivacaine was shown to have a safer pharmacological profile with less cardiac and neurotoxic adverse effects b [9-11] Fentanyl is mainly a μ receptor agonist. Intrathecal fentanyl produces selective spinal analgesia by acting on opioid receptors in the substantia gelatinosa of the spinal cord [12].

Rajashree GR et al., compared the efficacy of epidural bupivacaine with fentanyl and epidural levobupivacaine with fentanyl in total abdominal hysterectomies and concluded that levobupivacaine with fentanyl offers superior analgesia than bupivacaine with fentanyl [13]. A randomised study compared patient controlled epidural analgesia using bupivacaine and fentanyl with patient controlled intravenous opioids concluded that epidural infusion offered superior analgesia compared to other study group [14]. Another clinical trial compared the efficacy of bupivacaine and levobupivacaine for supraclavicular block found similar duration of analgesia in both study groups [15].

This study was aimed to compare the adequacy of pain relief and thus patient comfort in patients undergoing gynae-oncological surgeries. Primary outcome measure was rescue analgesic requirement in first 24 hours of postoperative period whereas pain scores and changes in haemodynamic parameters were the secondary outcomes measured.

MATERIALS AND METHODS

This randomised clinical study was conducted from September 2016 to May 2017 in the Department of Anaesthesiology in Kidwai Cancer Institute, Bengaluru, Karnataka, India. Institutional Ethics Committee approval was obtained (Ref.no:KMIO/MEC/019/24. November.2016). Seventy patients posted for elective gynaeco-oncological surgeries were enrolled for the study after obtaining a written consent.

Inclusion criteria: Patient of ASA grade I and II of age group between 30-60 years with Body Mass Index (BMI) between 18-30 kg/m^2 were included in the study.

Exclusion criteria: Patients with coagulopathy, localised infection at the proposed site, inability to comprehend the scoring systems, known allergy to drugs used, opioid dependence, renal, hepatic or cardio-respiratory impairment or any neurological disorder were excluded.

Sample size calculation: The sample size was calculated keeping the power of study at 80%, confidence interval of 95% and an alpha error of 0.05. Accordingly total sample size calculated was 70, which was divided into two groups of 35 patients each.

Study Procedure

A random number for 70 patients was divided into two groups based on computer generated randomisation [Table/Fig-1]. The haemodynamic variables and Visual Analogue Scale (VAS) score were recorded in both intraoperative and postoperative period. The description of VAS score was explained to the patient prior to giving the block. The two groups were as follows:

- **Group BF:** Patients who received 0.125% bupivacaine with fentanyl 2 mcg/mL (n=35) at 5 mL/hour as epidural infusion in postoperative period.
- **Group LF:** Patients who received 0.125% levobupivacaine with 2 mcg/mL fentanyl (n=35) at 5 mL/hour as epidural infusion in postoperative period.

A detailed history, comprehensive general and systemic examination were carried out and documented. As per the institutional protocol, the patients were explained about the epidural technique, simultaneously patients were familiarised with a 10 cm VAS for pain intensity assessment and to request for rescue analgesics [16].

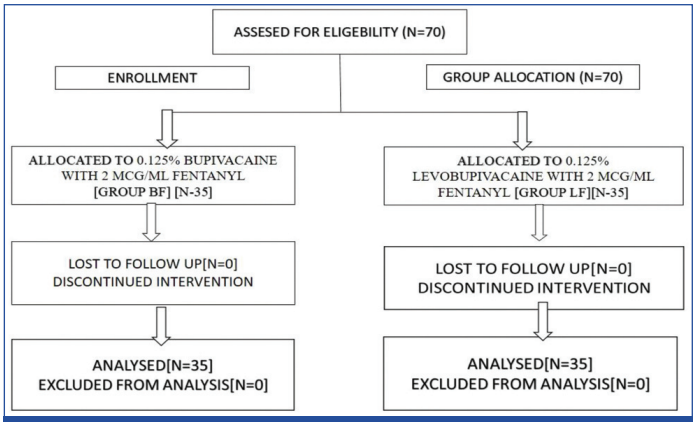
Epidural catheter was secured at L1-L2/L2-L3 prior to administration of general anaesthesia. General anaesthesia was administered as per institutional protocol. Before surgical incision, the patients were administered epidural 8 mL of either 0.125%, Bupivacaine with fentanyl 2 µg/mL or 0.125% Levobupivacaine with fentanyl 2 µg/mL according to the randomisation table. Haemodynamic parameters were noted at 0,5,10,15 and at every 30 minutes interval till the end of surgery. If the surgery lasted for more than 2 hours, patients were given additional 4 mL of the study drug epidurally. Upon arrival in Surgical Intensive Care Unit (SICU), patients were asked to rate their pain severity on the VAS for baseline VAS scores. Irrespective of the VAS score, patients were started on epidural infusion with study drug group that they belonged to at a rate of 5 mL/hr. The VAS scores and haemodynamic parameters were re-assessed at 1,2,4,6,12,18 and 24 hours of postoperative period. Patients with VAS score >4 were given 8 mL of epidural bolus as rescue analgesic. Patients with VAS score >6 were also given injection Paracetamol 1 gm i.v. along with the bolus dose. Number of rescue analgesics received was noted.

STATISTICAL ANALYSIS

Descriptive and Inferential statistical analysis has been carried out in the present study. Significance is assessed at 5% level of significance. Student t-test (two-tailed, independent), Leven's test, Chi-square/Fischer's-exact test, Non parametric tests were used according to the group variables. The p-value <0.05 was considered to be significant. The Statistical software Statistical Package for the Social Sciences (SPSS) version 18.0 and R environment version 3.2.2 were used for the data analysis.

RESULTS

The study population comprised of 70 patients posted for elective gynae-oncological surgeries and were allocated into two groups of 35 patients each as shown in [Table/Fig-1].



[Table/Fig-1]: CONSORT flowchart.

The two groups were similar with regard to demographic characteristics of age, BMI, and ASA physical grade [Table/Fig-2].

The mean VAS scores were higher in group BF compared to group LF at 0,1,2,4,6,12,18 and 24 hours but the observed difference in both the groups was not statistically significant (p>0.05) except at 2 and 24 hours [Table/Fig-3].

Characteristics	Group BF	Group LF	p-value
Age (Years) (Mean±SD)	50.06±7.19	46.43±8.41	0.100
BMI (kg/m^2) (Mean±SD)	21.61±1.37	21.39±1.62	0.552
ASA (I:II)	17:18	17:18	1.0

[Table/Fig-2]: Demographic characteristics.
BMI: Body mass index; SD: Standard deviation; p<0.05 significant, ASA: American society of anaesthesiologists

VAS score	Group BF	Group LF	p-value
0 hrs	5.94±2.34	5.71±2.86	0.715
1 hrs	3.97±2.15	3.06±1.89	0.063+
2 hrs	3.51±1.44	2.80±0.93	**0.016***
4 hrs	3.77±1.44	3.20±1.43	0.100
6 hrs	4.11±1.53	3.77±1.50	0.347
12 hrs	3.60±1.96	3.26±1.34	0.395
18 hrs	4.34±1.97	3.94±1.81	0.380
24 hrs	3.46±0.85	2.94±0.91	**0.017***

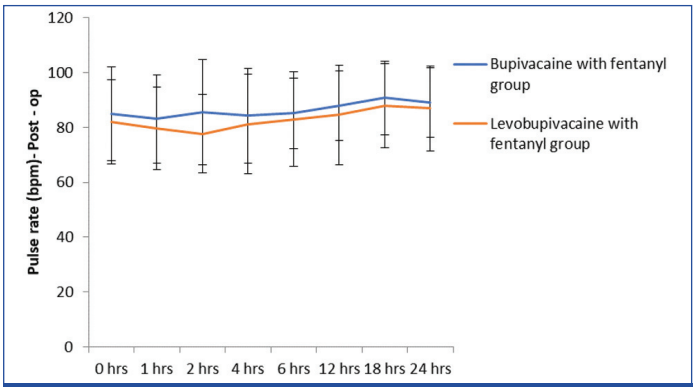
[Table/Fig-3]: VAS score comparison.
#-Student t-test (two tailed, independent); Bold p-values are significant

All patients in group BF and LF required epidural boluses as rescue analgesics in the study period. The difference between Group BF and Group LF in requirement of epidural boluses as rescue analgesic was statistically significant. In Group BF, 8.6% and in group LF 25.7% of patients did not require Inj. Paracetamol as additional rescue analgesics. The number of patients requiring epidural boluses and additional Inj. Paracetamol as rescue analgesics were significantly higher in group BF compared to group LF [Table/Fig-4].

Variables	Group BF	Group LF	p-value
No. of epidural bolus			
1	3 (8.6%)	8 (22.9%)	**0.001****
2	17 (48.6%)	25 (71.4%)	
3	15 (42.9%)	2 (5.7%)	
No. of PCT+epidural bolus			
0	3 (8.6%)	9 (25.7%)	**0.044***
1	23 (65.7%)	24 (68.6%)	
2	8 (22.9%)	2 (5.7%)	
3	1 (2.9%)	0 (0%)	

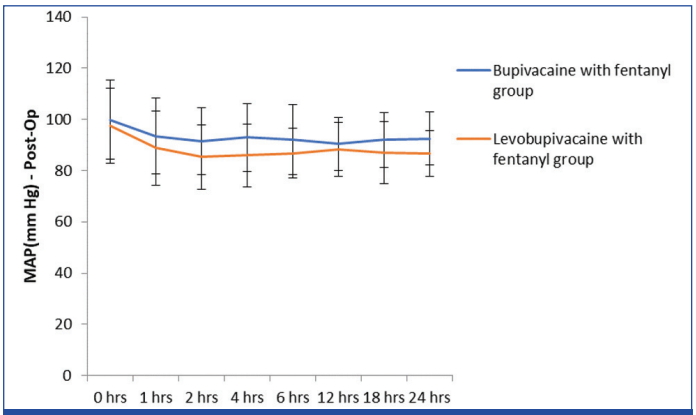
[Table/Fig-4]: Comparison of rescue analgesics.
Fischer's-exact test used; PCT: Paracetamol

Haemodynamic parameters such as Pulse Rate (PR), Mean Arterial Pressure (MAP) and Oxygen Saturation (SpO_2) postoperatively were comparable among the two groups at 0,1,2,4,6,12,18 and 24 hours of postoperative period. [Table/Fig-5] shows the comparison of PR (beats/minute) among the groups at 0,1,2,4,6,12, 18 and 24 hours of postoperative period. The analysis of variance showed that there was no significant (p-value >0.05) difference in HR among the groups at all the time periods.



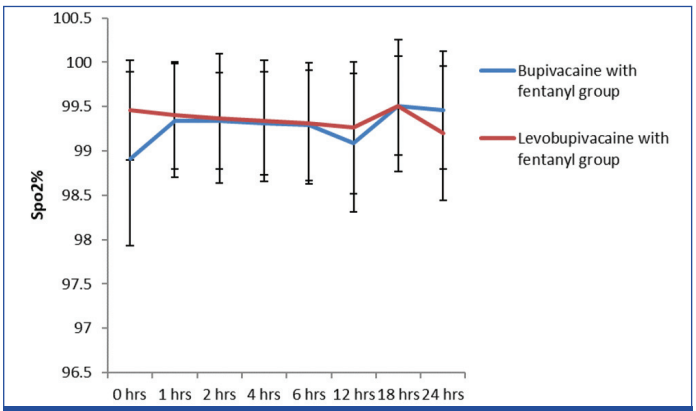
[Table/Fig-5]: Comparison of Pulse Rate (PR) (beats/minute).
Postop: Postoperative; ANOVA test used

The analysis of variance showed that the MAP in group BF at 2nd, 4th and 24th hour was more postoperatively in comparison to MAP of group LF with significant p-value (p<0.05) as shown in [Table/Fig-6]. However, the above finding was clinically insignificant.



[Table/Fig-6]: Mean Arterial Pressure (MAP) (mmHg)-Comparison in two groups.
ANOVA test used

The baseline SpO_2 between the groups BF and LF was similar (p>0.05). The analysis of variance showed that there was no significant (p>0.05) difference in SpO_2 among the groups at all the time periods [Table/Fig-7].



[Table/Fig-7]: Comparison of SpO_2.
ANOVA test used

DISCUSSION

The principle site of action for neuraxial blockade is believed to be the nerve root. Local anaesthetic is injected into the epidural space containing nerve root. Larger volumes and quantities of local anaesthetic molecules are needed for epidural block [17]. Blockade of neural transmission in the posterior nerve root fibres interrupts somatic and visceral sensation, whereas blockade of anterior nerve root fibers prevents efferent motor and autonomic outflow [5].

The main finding of this study was that patients in Group BF had higher VAS scores compared to patients in Group LF. Patients in group BF required more number of rescue analgesics in the form of epidural boluses and Inj. Paracetamol in comparison with group LF which was statistically significant (p<0.05). In this study, group BF and group LF were comparable with respect to PR, MAP and SpO_2. Similar findings were observed in the study conducted by Ilham C et al., [15].

Parate LH et al., compared the effect of addition of low dose fentanyl to epidural 0.5% bupivacaine in 70 patients undergoing elective caesarean. The pain assessment was done using VAS and it was found that addition of fentanyl to epidural bupivacaine significantly reduces the VAS scores and prolongs the duration of postoperative analgesia [18]. In this study, 2 mcg/mL Fentanyl was added to local anaesthetic for the epidural infusion.

Neera Sah et al., conducted study to compare analgesic efficacy and intensity of motor block with continuous infusions of ropivacaine, bupivacaine, and levobupivacaine in combination with fentanyl for labour epidural analgesia. They concluded that there were no significant differences in pain VAS and Bromage scores between 0.1% ropivacaine, 0.125% bupivacaine, and 0.1% levobupivacaine given for labor epidural analgesia [19].

Cenk Ilham et al., in a randomised double-blind comparative study, compared efficiency of levobupivacaine and bupivacaine for supraclavicular block in adult population. They concluded that both 0.5% bupivacaine and 0.5% levobupivacaine are similar in block characteristics and duration of analgesia [15]. However the requirement of rescue analgesics were not assessed in their study. In this study, in addition to VAS analysis for pain the requirement of rescue analgesics were compared between the study groups.

Pasquale De Negri et al., compared the epidural infusion of 0.125% bupivacaine, levobupivacaine, and ropivacaine on postoperative analgesia and motor blockade in children after hypospadias repair. They concluded that, no difference with regard to postoperative analgesia could be detected among the three different local anaesthetics studied and significantly less unwanted motor blockade was associated with postoperative epidural infusions of 0.125% levobupivacaine or ropivacaine as compared with a similar infusion of bupivacaine [20].

The dose of bupivacaine and levobupivacaine for postoperative analgesia was selected according to potency ratio and the recommendation in the literature which was 0.125% bupivacaine and levobupivacaine [21]. It was observed that the addition of fentanyl had a stronger effect than the local anaesthetic alone. The benefit and sparing effect of local anaesthetic by the use of fentanyl is well known [22,23]. In this study,on account of adequate postoperative analgesia, haemodynamic stability, 0.125% levobupivacaine with 2 mcg/mL fentanyl is a better option than 0.125% bupivacaine with 2 mcg/mL fentanyl for epidural infusion for patients undergoing elective gynae-oncological surgeries.

Limitation(s)

This study was not double-blinded and was not designed for cost analysis. It was limited only to ASA I and ASA II grade.

CONCLUSION(S)

The present study concludes that when bupivacaine with fentanyl and levobupivacaine with fentanyl are administered in equal volumes epidurally for patients undergoing gynae-oncological surgeries, Levobupivacaine with Fentanyl has good postoperative

analgesia and less requirement of rescue analgesics compared to Bupivacaine with Fentanyl.

REFERENCES

[1] International association for study of pain, subcommittee on taxonomy. Pain Terms: A list with definitions and notes on usage. Pain. 1979;6:249-52.

[2] Kawase S, Horiuchi T, Nagahata T. 0.125% 8 mL/h v.s. 0.25% 8 mL/h of levobupivacaine in continuous paravertebral block for postoperative analgesia in video-assisted thoracoscopic surgery: A randomized, controlled, double-blind study. J Anesth. 2022. Doi: 10.1007/s00540-022-03114-y. Epub ahead of print. PMID: 36255525.

[3] Hu C, Zhang S, Chen Q, Wang R. Effects of different anesthetic and analgesic methods on cellular immune function and stress hormone levels in patients undergoing esophageal cancer surgery. J Healthc Eng. 2022;2022:4752609. Doi: 10.1155/2022/4752609. PMID: 35313517; PMCID: PMC8934230.

[4] Chung JNC, Kamarajah SK, Phillips AW. Author response to: Multimodal analgesia with thoracic epidural after transthoracic oesophagectomy: Do we need more evidence? Br J Surg. 2021;108(11):e388. Doi: 10.1093/bjs/znab271. PMID: 34297810.

[5] Seif NE, ELbadawy AM. Comparative study of mid-thoracic spinal versus epidural anaesthesia for open nephrectomy in patients with obstructive/restrictive lung disease: A randomized controlled study. Saudi J Anaesth. 2019;13(1):52-59. Doi: 10.4103/sja.SJA_415_18. Retraction in: Saudi J Anaesth. 2019 Oct-Dec;13(4):402. PMID: 30692889; PMCID: PMC6329241.

[6] Wang J, Yin Y, Zhu Y, Xu P, Sun Z, Miao C, et al. Thoracic epidural anaesthesia and analgesia ameliorates surgery-induced stress response and postoperative pain in patients undergoing radical oesophagectomy. J Int Med Res. 2019;47(12):6160-70. Doi: 10.1177/0300060519866943. Epub 2019 Aug 19. PMID: 31426685; PMCID: PMC7045687.

[7] Miller RD, Eriksson I, Fleisher A, Wiener-Kronish JP, Young WI. Millers anaesthesia. 8th ed. United States of America. Natasha Andjelkovic. 2015.

[8] Campos JH, Seering M. Does the amount of opioid consumption really matter in video-assisted thoracoscopic lobectomy-thoracic epidural analgesia versus liposomal bupivacaine. J Cardiothorac Vasc Anesth. 2019;33(3):699-01. Doi: 10.1053/j.jvca.2018.07.027. Epub 2018 Jul 23. PMID: 30143358.

[9] Heppolette CAA, Brunnen D, Bampoe S, Odor PM. Clinical pharmacokinetics and pharmacodynamics of levobupivacaine. Clin Pharmacokinet. 2020;59(6):715-45. Doi: 10.1007/s40262-020-00868-0. PMID: 32034727.

[10] Mitra S. Editorial commentary on: Using dexamethasone as an adjuvant to levobupivacaine in epidural anaesthesia to change the pain intensity and duration in painless labor. Saudi J Anaesth. 2018;12(2):346-47. Doi: 10.4103/sja.SJA_508_17. PMID: 29628855; PMCID: PMC5875233.

[11] Mostafa MF, Herdan R, Elshazly M. Comparative study of levobupivacaine and bupivacaine for bilateral maxillary nerve block during pediatric primary cleft palate surgery: A randomized double-blind controlled study. Korean J Anaesthesiol. 2018;71(2):135-40. Doi: 10.4097/kjae.2018.71.2.135. Epub 2018 Apr 2. PMID: 29619786; PMCID: PMC5903109.

[12] Comer SD, Cahill CM. Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. Neurosci Biobehav Rev. 2019;106:49-57. Doi: 10.1016/j.neubiorev.2018.12.005. Epub 2018 Dec 5. PMID: 30528374; PMCID: PMC7233332.

[13] Rajashree GR, Dinesh S, Anandan H. Randomized clinical comparison of epidural bupivacaine with fentanyl and epidural levobupivacaine with fentanyl in patients undergoing total abdominal hysterectomy. Int J Sci Stud. 2016;4(8):203-07.

[14] Moslemi F, Rasooli S, Baybordi A, Golzari SEJ. A comparison of patient controlled epidural analgesia with intravenous patient controlled analgesia for postoperative pain management after major gynecologic oncologic surgeries: A randomized controlled clinical trial. Anesth Pain Med. 2015;5(5):e29540.

[15] Ilham C, Bombaci E, Yurtlu S, Çolakŏglu S. Efficiency of levobupivacaine and bupivacaine for supraclavicular block: A randomized double-blind comparative study. Rev Bras Anestesiol. 2014;64(3):177-82.

[16] Barash, Cullen PG, Stoelting BF, Cahalan RK, Stock MK, Christine M, et al. Clinical anaesthesia. 7th ed. United States of America. Lippincott Williams & Wilkins; 2013.

[17] Simpson D, Curran MP, Oldfield V. Ropivacaine: A review of its use in regional anaesthesia and acute pain management. Drugs. 2005;65(18):2675-17.

[18] Parate LH, Manjrekar SP, Anandaswamy TC, Manjunath B. The effect of addition of low dose fentanyl to epidural bupivacaine (0.5%) in patients undergoing elective caesarean section: A randomized, parallel group, double blind, placebo controlled study. J Postgrad Med. 2015;61(1):27-31.

[19] Sah N, Vallejo M, Phelps A, Finegold H, Mandell G, Ramanathan S, et al. Efficacy of ropivacaine, bupivacaine, and levobupivacaine for labor epidural analgesia. J Clin Anesth. 2007;19(3):214-17. Doi: 10.1016/j.jclinane.2006.11.003. PMID: 17531731.

[20] De Negri P, Ivani G, Tirri T, Modano P, Reato C, Eksborg S, et al. A comparison of epidural bupivacaine, levobupivacaine, and ropivacaine on postoperative analgesia and motor blockade. Anesth Analg. 2004;99(1):45-48. Doi: 10.1213/01.ane.0000120162.42025.d0. PMID: 15281501.

[21] Baliuliene V, Macas A, Rimaitis K. The optimal concentration of bupivacaine and levobupivacaine for labor pain management using patient-controlled epidural analgesia: A double-blind, randomized controlled trial. Int J Obstet Anesth. 2018;35:17-25. Doi: 10.1016/j.ijoa.2018.05.002. Epub 2018 May 18. PMID: 29914785.

[22] Ahuja V, Luthra A, Chauhan R, Meena SC, Parmar K. Intermittent peri-tubal instillation of dexamethasone and ropivacaine on postoperative analgesia after percutaneous nephrolithotomy: A prospective randomized controlled trial. Int J Urol. 2022;29(8):876-83. Doi: 10.1111/iju.14929. Epub 2022 May 21. PMID: 35598084.

[23] Srihari S, Henjarappa K, Arathi B, Rashmi N, Gowda V, Ranganath N, et al. Evaluation of ropivacaine versus ropivacaine with fentanyl for postoperative epidural analgesia in patients undergoing elective lower abdominal oncosurgeries-A randomised clinical study. J Clin Diagn Res. 2021;15(6):UC01-UC04. Doi: 10.7860/JCDR/2021/48890.14927.

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Anaesthesiology, Subbaiah Institute of Medical Sciences, Shivamogga, Karnataka, India.
2. Associate Professor, Department of Anaesthesiology and Pain Medicine, Kidwai Cancer Institute, Bengaluru, Karnataka, India.
3. Professor, Department of Anaesthesiology and Pain Medicine, Kidwai Cancer Institute, Bengaluru, Karnataka, India.
4. Assistant Professor, Department of Anaesthesiology, Subbaiah Institute of Medical Sciences, Shivamogga, Karnataka, India.
5. Professor and Head, Department of Anaesthesiology and Pain Medicine, Kidwai Cancer Institute, Bengaluru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
SS Srihari,
Assistant Professor, Department of Anaesthesiology, Subbaiah Institute of Medical Sciences, NH-3, Purle, Shivamogga-577202, Karnataka, India.
E-mail: itsmedrshree@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Aug 30, 2022
- Manual Googling: Dec 17, 2022
- iThenticate Software: Jan 05, 2022 (20%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 29, 2022**
Date of Peer Review: **Oct 28, 2022**
Date of Acceptance: **Dec 20, 2022**
Date of Publishing: **Feb 01, 2023**