Dexmedetomidine overrides Fentanyl and Tramadol as Epidural Adjuvant for its advantageous Anesthetic Outcomes and Immunomodulatory effects

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Abstract

Background: Surgical stress is aggravated by anesthesia especially opioid-based anesthesia. Epidural anesthesia (EA) was previously found to modulate the immune response. Bupivacaine (BUP) may suffice as anesthetic but adjuvant might increase this and possibly may modulate the stress response

Objectives: Evaluation of the effects of dexmedetomidine (DEX), fentanyl (FEN), or tramadol (TRM) as adjuvants to BUP-EA on anesthetic outcomes and serum levels of interleukin (IL)-6, IL-1β and Tumor necrosis factor-α (TNF-α) during varicose vein surgery.

Patients and methods: 120 patients received single-shoot BUP 0.5% EA alone or with 25, 50 and 100 µg of DEX, FEN and TRM, respectively. Blood samples were obtained at start (T1) and end of surgery (T2) and 24-h postoperative (PO) (T3) for ELISA estimations of cytokines' levels. Study outcomes include the effect of adjuvants on anesthetic outcome and serum cytokines.

Results: Adjuvants significantly fastened complete sensory block especially BUP/DEX and BUP/FEN with significant difference with BUP/DEX. Duration till Bromage-3 was significantly shorter and duration till Bromage-2 and 0 grades were significantly longer with DEX. Both DEX and FEN provided hemodynamic stability. Adjuvants provided significantly better PO analgesia especially DEX. Serum cytokines' levels were increased in all T2 and T3 samples than T1 levels, but levels were the lowest with DEX. Serum TNF-α and IL-6 levels were negatively affected by epidural adjuvants especially DEX.

Conclusion: EA ameliorates the surgery-induced inflammatory response and adjuvants might augment this effect. Epidural BUP/DEX anesthesia significantly suppressed, while BUP/FEN augments the serum cytokines' levels.

Keywords: Epidural anesthesia; Epidural adjuvants; Dexmedetomidine.

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Introduction

Surgical stress responses include neuroendocrine, metabolic, inflammatory and immune responses **(Dobson, 2020)** and are related to the type and invasiveness of surgery **(Hirose et al., 2022)**. The degree of stress responses proportionate with surgery invasiveness, and higher stress response is associated with postoperative (PO) complications that worsen patient outcomes and burden hospital finances **(Ludbrook et al., 2022)**.

The selection of anesthetic method and drugs is of utmost importance for patients undergoing surgical procedures for its effect on patient's immune system **(Shi and Zhang, 2019)**. Epidural use was found to prevent perioperative neuroendocrine stress responses, reduce PO pain with reduction of the use of opioids; all these variate lead to immunosuppression **(Wang et al., 2019)**.

Opioid anesthetics can modulate the surgically-induced immune stress mostly through affecting the expression and release of cytokines **(Campos-Pérez et al., 2022)**. The immunomodulatory effect of fentanyl (FEN) is probably through initiation of an anti-inflammatory effect **(Novac et al., 2021)**.

Tramadol (TRM) is safe analgesic however; its long-term use possibly induces oxidative stress secondary to mitochondrial dysfunction with subsequent inflammation **(Raj et al., 2022)**. TRM was found to have anti-tumor effects for example in breast cancer animal model TRM decreased the expression levels of estrogen and progesterone receptors with reduction of serum levels of tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 **(Kim et al., 2021)**.

Dexmedetomidine (DEX) is a selective α_2-adrenergic agonist that has unique pharmacologic profile includes sedation that parallels the natural sleep with suppressive effect on noradrenergic tone **(Persson et al., 2022)** and analgesic sparing effect with anxiolysis and sympatholysis **(Chima et al., 2022)**. Furthermore, experimentally, DEX was found to alleviate the systemic inflammatory response induced by lipopolysaccharide **(Han et al., 2022)** and suppress the inflammatory response and prolongs survival in rats with hemorrhagic shock **(Kobayashi et al., 2022)**. This study tried to evaluate the effects of dexmedetomidine (DEX), fentanyl (FEN), or tramadol (TRM) as adjuvants to bupivacaine (BUP) epidural anesthesia (EA) on anesthetic outcomes and on the systemic immune milieu in patient undergoing lower limb varicose vain surgery.

Patients and methods

Design: Prospective randomized case-control comparative study

Study participants: All patients assigned for long saphenous stripping with multiple ligature procedure for widespread lower limb varicosities from June 2021 till Sep 2022 were clinically evaluated for determination of demographic data, general clinical status, ASA grade and for the presence of any of exclusion criteria.

Exclusion criteria: Patients had spinal deformities; cardiac, renal, hepatic or autoimmune disorders were excluded from the study. Also, patients had ASA grade >II, maintained on immunosuppressive drugs for any indication, the presence of uncontrolled diabetes, hypertension, coagulopathies, and endocrinopathy were excluded.

Inclusion criteria: Patients scheduled for varicose vein surgery aged, 18-60 years, of ASA grade I and II and were

free of exclusion criteria were enrolled in the study.

Setting: Department of Anesthesia, pain and ICU, Faculty of Medicine, Benha University

Ethical considerations: The study protocol was preliminarily approved by the Local Ethical Committee. The study protocol was discussed with patients and those signed the written fully informed consent were enrolled in the study. At the end of case collection, the study outcomes were approved by RC: 27.11.22.

Blindness: The labeled syringes containing the study drugs were prepared by an assistant and the authors were blinded about the contents of these syringes. Blood samples were sent to the Clinical Pathology Department in numbered innominate tubes and at the end of the case collection, the clinical and lab data were interpreted.

Randomization: The enrolled patients were randomly divided into four groups using computer system by applying the repeated 1:1 randomization method and these sequences were transformed into labels (I-IV) that were written on cards. Cards were kept in non-transparent envelops and patient was asked to choose an envelope and give it to the assistant who had to prepare the adjuvant and give it to the anesthetist.

Anesthetic protocol

Non-invasive monitoring for heart rate (HR), mean arterial pressure (MAP) and oxygen saturation were continuously applied during surgery. An 18G cannula was inserted under complete aseptic conditions for collection of blood samples for estimation of baseline levels of the studied variate (T1) and patients were preloaded by 500 ml of lactated Ringers solution, but no pre-medications were received. Patients were positions in the setting position, the back was sterilized down to the buttocks, the L4-5 interspace was identified and 1-2 ml of lignocaine were injected subcutaneously to raise a weal, an 18G Touhy needle was inserted in the pre-identified space and guided slowly to reach the epidural space depending on the loss of resistance procedure and 2 ml of 0.9% saline were injected for assurance of patency. Then, an epidural catheter was inserted in and directed upwards in the epidural space till reaching the 9-cm mark; to safeguard against failure of the single-shoot anesthesia. A test dose of 3-ml lignocaine was injected to exclude the intrathecal and intravenous catheter placement and presence of torsions in the path of the catheter. Then, the catheter was secured and bupivacaine was injected and followed by the study drug according to group. All patients received epidural injection of 15 ml of bupivacaine 0.5%; patients of groups II-IV received DEX, FEN, and TRM in dose of 25, 50 and 100 µg in 2 ml saline, respectively.

Intraoperative monitoring

1. Non-invasive monitoring of MAP and HR at time of epidural catheter insertion, immediately and 30 minute after injection and at the end of surgery.
2. Anesthetic efficacy was evaluated as follows
   a. Sensory block was evaluated using pinprick method to evaluate time lapsed to achieve complete loss of sensation.
   b. Motor block was evaluated using the 4-point Bromage scale with Bromage 3 indicates complete motor block, Bromage 2 indicates regressed block, Bromage 1 indicates motor block is fading away and Bromage 0 indicates complete motor recovery **(Bromage, 1978)**.

c. Sedation score was evaluated using modified Ramsey sedation score (mRSS) which is 7-grade scale as shown in appendix 1, with the target scores for effective sedation was determined as mRSS of 2–4. **(Ulusoy et al., 2016)**.

Postoperative monitoring

1. MAP and HR monitoring at time of arrival to PACU, and 4, 6, 8, 12 and 24 hours postoperative (PO).
2. PO sensory block data:
   - Duration of sensory block was defined as time till regaining full sensation.
   - PO pain sensation was evaluated 4-hourly for 24-h using the Numerical pain scale (NRS) which is 10-point scale with higher scores indicates more severe pain **(Williamson and Hoggart, 2005)**.
   - Duration of PO analgesia was defined as the time elapsed between complete sensory recovery and 1st time having NRS pain score of 4, which indicated the need for analgesia.
   - PO analgesia was provided as ketorolac tromethamine 15 mg/ml diluted in normal saline in 1:5 ml ratio and injected intravenously on NRS score of 4.
3. PO motor block data:
   - Duration of efficient motor block was defined as time elapsed till reaching Bromage 2 grade.
   - Duration of motor block was defined as time-lapse between Bromage 3 and 0.
4. PO sedation was assessed every 30-min till sedation mRSS-1

Blood sampling

Three blood samples were obtained at start (T1) and end of surgery (T2) and 24-h PO (T3). Blood sample was allowed to clot, centrifuged and serum was withdrawn and kept frozen till being ELISA assayed for estimation of serum interleukin (IL)-6 and 1β and Tumor necrosis factor-α (TNF-α) using ELISA kit (abcam Cat. No ab178013, ab46052, ab181421, respectively).

Study outcomes

1. The primary outcome is the determination of the differential effect of the used adjuvants on anesthetic outcome and serum cytokines' levels.
2. The secondary outcome is evaluation of the relation between the used epidural adjuvant and percentage of change in cytokines' levels in T2 samples in relation to levels estimated in T1 sample (T2-T1%).

Statistical analysis

The results were analyzed using paired t-test, One-way ANOVA and Chi-square test (X^2 test). Evaluations of the impact of using of EA-adjuvant on the T2-T1% of each cytokine and the cytokine that mostly affected by each adjuvant were evaluated using the Regression analysis (Stepwise method) and the Receiver Operating Characteristic (ROC) curve. Results of ROC curve analysis was expressed as area under the curve (AUC) that evaluated against the area under the reference line (AUC=0.5). The IBM® SPSS® Statistics software (Version 22, 2015; Armonk, USA) was used for statistical analyses with P value at less than 0.5 indicated significance of the difference.

Results

During the study duration 162 patients were evaluated and 42 were excluded for being of ASA grade >II (n=17), pregnant females (n=6), obese of grade II (n=5) or III (n=2), maintained on anticoagulant (n=5), and 7 patients refused to receive neuroaxial anesthesia were also excluded (**Fig. 1**).

The enrolment data of the studied patients showed non-significant differences (**Table 1**).

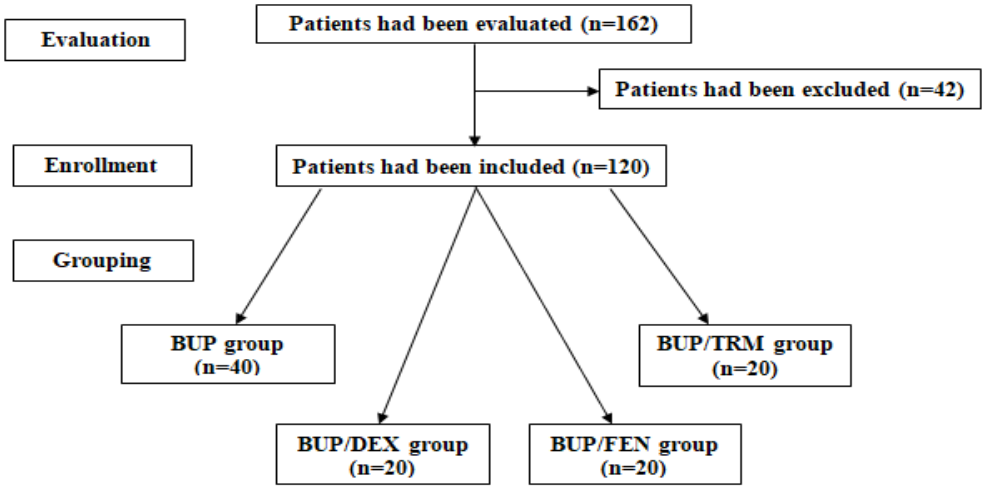

Fig. (1): Study Flowchart

Table 1. Enrolment data of the studied patients

Variate \ Group			BUP	BUP/DEX	BUP/FEN	BUP/TRM
Age (years)			34.1±5.4	34±4.4	33.4±7.8	32±5.2
Gender	**Males: Females**		11:19	14:16	13:17	15:15
Type of daily work	**Males**	**Manual: Soldiers: Officers: Nurses**	4:2:3:2	7:4:2:1	6:3:3:1	5:4:3:3
	Females	**HW: Sealers: Officers: Nurses**	7:6:2:4	5:6:1:2	7:2:1:3	8:4:2:1
Body mass index (kg/m^2)			30.6±1.5	30.4±1.5	30.2±1.7	30.3±2

Surgery was completed uneventfully regarding surgical and anesthetic complication with non-significant difference in operative time between the four groups. All adjuvants allowed more rapid complete sensory block with significant (P<0.001) difference than BUP alone. Duration till complete sensory block was significantly longer with BUP/TRM compared to BUP/DEX (P<0.001) and BUP/FEN (P=0.002) with significant (P=0.048) difference in favor of BUP/DEX. Similarly, duration till achievement of Bromage 3 was significantly (P<0.001) longer with BUP compared to other groups and was significantly (P=0.001) shorter in BUP/DEX than BUP/TRM group. Duration of sensory block was significantly (P<0.001) shorter with BUP alone than with adjuvants, but was shortest with TRM and was shorter with FEN than with DEX. Durations till regression to Bromage 2 and 0 grades were significantly (P<0.001) shorter in BUP group versus other groups, but were significantly longer with DEX than other adjuvants with non-significant (P=0.068) difference between TRM and FEN (**Table 2**).

Table 2. Estimated block data

Variate \ Group		BUP	BUP/DEX	BUP/FEN	BUP/TRM
Operative time (min)		65.5±9.6	68±11.3	66.5±10.4	65±10.4
Duration till complete block(min)		16.8±3.1	8.7±1.6*	9.9±1.4*	11.7±2.6*†‡
Duration of block (min)		148.5±19.3	379±30.9*	254±32*†	172.5±27.7*†‡
Duration (min) till Bromage grade	**3**	22.6±5.4	12.5±3.8*	14.5±4.2*	17±5.6*†
	2	112.5±13.3	185.5±24.6*	141.8±23.2*†	128.3±21.2*†
	0	132.1±16.4	300.5±36.5*	193.5±29*†	175±30.2*†

*Durations were determined since epidural injection; *: indicates significance vs. BUP group; †: indicates significance vs. BUP/DEX group; ‡: indicates significance vs. BUP/FEN group*

The frequency of patients reached the target mRSS was significantly higher at the end of surgery and at 30-min PO in favor of TRM, and at 90-min, a significantly higher number of patients had mRSS >4 with FEN. Regarding patients had mRSS score-1, the three groups showed non-significant differences till at 180-min PO whenever the frequency was significantly lower with FEN (**Table .3**).

Table 3. Postoperative (PO) sedation scores till 180-min after surgery

mRSS	Time	BUP/DEX	BUP/FEN	BUP/TRM	P-value
Target score (2-4)	End of surgery	0	0	4 (13.3%)	0.015
	30-min PO	4 (13.3%)	2 (6.7%)	9 (30%)	0.044
	60-min PO	14 (46.7%)	12 (40%)	18 (60%)	0.288
	90-min PO	28 (93.3%)	23(76.7%)	29 (96.7%)	0.030
Score-1	120-min PO	6 (20%)	4 (13.3%)	10 (33.3%)	0.165
	150-min PO	20 (66.7%)	15 (50%)	19 (63.3%)	0.378
	180-min PO	27 (90%)	24 (80%)	30 (100%)	0.035

As shown in (**Table 4**), DEX and FEN as adjuvant provided hemodynamic stability than TRM with lower HR and MAP measures than that recorded for patients of BUP and BUP/TRM groups, but such effect was more manifest with DEX.

Table 4. Intraoperative (IO) and PO hemodynamic changes

Variables		BUP	BUP/DEX	BUP/FEN	BUP/TRM
Hear rate (beats/min)					
Intraoperative data	Preoperative	78.7±4.2	78.9±4.2	80±5.7	81.7±3.9
	After epidural catheter insertion	76.5±3.1	76.4±4	77.4±5.7	77.1±3.8
	30-min after catheter insertion	81.9±3.8	73±3.6*	75.8±5*	76.3±4.5*
	At end of surgery	80.9±3.4	70.3±3.7*	71.8±4.6*	73.6±4.1*

Postoperative data	At PACU admission	79.5±2.7	73.5±3.5*	75.4±4.2*	75.1±3.2*
	4-h	82.5±3.3	74±4.2*	74.7±3.9*	77.6±3.5*
	8-h	82.4±3.2	73.1±3.3*	74.3±3.4*	79.4±4*
	12-h	81.9±4.7	75±3.4*	76.7±3.1*	79.9±4.3†‡
	24-h	78.3±4.9	75.4±3*	77.3±3.3	80.9±3.5*†‡
Mean arterial pressure (mmHg)					
Intraoperative data	Preoperative	89.3±5.6	89.7±6.3	90.2±6.3	88.4±4.3
	After epidural catheter insertion	85.5±4.2	86.2±4.7	85.8±5.7	85.2±4.1
	30-min after catheter insertion	81.9±3.8	80.7±5	81±5.4	80.4±3.5
	At end of surgery	80.9±3.4	76±4.6*	77.7±5.2*	76.1±3.3*
Postoperative data	At PACU admission	79.5±2.7	75.4±3*	74.5±5*	77.1±3.7*‡
	4-h	82.5±3.3	72.3±2.7*	76.7±3*†	81.8±3.1†‡
	8-h	82.4±3.2	73.5±4.2*	77.7±4.5*†	84.7±2.7†‡
	12-h	81.9±4.7	76.5±3.8*	81.8±4.6†	85.9±3.3*†‡
	24-h	78.3±4.9	80.5±3.6	86±4.9*†	86±4.2*†‡

**: significant difference versus BUP group I, †significant difference versus BUP/DEX group, ‡: significant difference versus BUP/FEN group;*

The used adjuvants significantly prolonged the duration till the 1st request of PO analgesia in comparison to BUP alone with significantly longer duration with DEX and FEN than with TRM. The average NRS pain score during the 24-h was significantly lower with DEX and FEN, but was non-significantly lower with TRM compared to BUP. Ten patients did not request PO analgesia; 8 with DEX and 2 with FEN with significant (P=0.038) difference in favor of DEX. Twenty-three patients required PO analgesia for two times; 14 and 9 with BUP and TRM, respectively with non-significant difference in favor of TRM (**Table 5**).

Table 5. PO pain data

Variate \ Group		**BUP**	**BUP/DEX**	**BUP/FEN**	**BUP/TRM**
Duration of PO analgesia (h)		4.9±2.3	13.9±4.5*	13.7±7.3*	9.3±4.1*†‡
Collective NRS		2±1.5	1.7±1.5*	1.7±1.5*	1.8±1.5
Times of requesting PO analgesia	**0**	0	8 (26.7%)	2 (6.7%)	0
	1	16 (53.3%)	22 (73.3%)	28 (93.3%)	21 (70%)
	2	14 (47.7%)	0	0	9 (30%)

*: significant difference versus BUP group I, †significant difference versus BUP/DEX group, ‡: significant difference versus BUP/FEN group

As shown in (**Table.6**), serum cytokines' levels in T1 samples were non-significantly different between all samples of the studied groups, but were increased progressively in T2 and T3 samples of all patients in relation to T1 levels. The increases were significant with serum levels of TNF-α and IL-1β, while were insignificant in case of IL-6. Despite of the increased

levels in T2 and T3 samples, estimated levels were the lowest in samples of patients who received DEX and were the highest in samples of BUP group. Moreover, the differences in serum levels of TNF-α and IL-6 in samples of patients received DEX group were significant than in samples of patients received FEN or TRM.

Table 6. Estimated serum cytokines' levels

Lap variate	Samples	BUP	BUP/DEX	BUP/FEN	BUP/TRM
TNF-α (ng/ml)	**T1 sample**	3.91±0.33	4.05±0.68	4.1±0.5	3.92±0.48
	T2 sample	6.26±1.3⁑	4.88±0.77*⁑	6.1±1.3†⁑	5.6±0.9⁑
	T3 sample	6.98±1.23⁑∫	5.31±0.77*⁑	6.68±1.33†⁑	6.14±0.85*†⁑∫
IL-6 (ng/ml)	**T1 sample**	9.73±2.67	9.53±3.59	9.37±3.08	9.82±3.49
	T2 sample	15.72±2.2	11.73±3.44*‡	13.85±3.62	12.21±2.82†
	T3 sample	17.65±2.2	13.53±2.1*	17.3±4.54†	16.32±3.45*
IL-1β (pg/ml)	**T1 sample**	3573±1208	3237±1503	3438±1123	3389±1373
	T2 sample	5610±1639⁑	4156±1535*	5171±1330⁑	4981±1582⁑
	T3 sample	6198±1595⁑	4827±1558*⁑	5578±1277⁑	5347±1632⁑

**: indicates significance vs. group I; †: indicates significance vs. group II; ‡: indicates significance vs. group III; ⁑: indicates significance vs. T1; ∫: indicates significance vs. T2*

Statistical analyses defined serum TNF-α and IL-6 levels as the most negatively affected by the presence of an epidural adjuvant (**Fig. 2a**) and by using DEX as an epidural adjuvant (**Fig. 2b**). On contrary, FEN as adjuvant was found to positively affects the change in serum levels of TNF-α and IL-6 (**Fig. 2c**). Both DEX and FEN non-significantly affected the change in serum levels of IL-1β. Interestingly, TRM showed bidirectional effect where it significantly affected the change in serum IL-1β in positive direction and IL-6 in negative direction, but positively despite being non-significantly affected the change in serum TNF-α and IL-6 (**Table 7, Fig. 2d**).

Table 7. Statistical analyses of the effect of the presence of an epidural adjuvant on the change of serum cytokines' levels at the end in relation to at the start of surgery

Variate	T2-T1% of the studied cytokines	ROC curve analysis			Regression analysis	
		AUC (SE)	P-value	95% CI	β	P-value
Presence of adjuvant	**TNF-α**	0.696 (0.056)	0.001	0.585-0.807	-0.263	0.002
	IL-6	0.777 (0.044)	<0.001	0.691-0.864	-0.347	<0.001

	IL-1β	0.580 (0.054)	0.192	0.474-0.686	0.031	0.710
DEX as adjuvant	**TNF-α**	0.822 (0.044)	<0.001	0.735-0.909	-0.386	<0.001
	IL-6	0.771 (0.053)	<0.001	0.666-0.875	0.329	0.001
	IL-1β	0.641 (0.061)	0.030	0.522-0.760	-0.150	0.103
FEN as adjuvant	**TNF-α**	0.322 (0.058)	0.006	0.207-0.436	0.275	0.004
	IL-6	0.282 (0.059)	0.001	0.167-0.397	0.378	<0.001
	IL-1β	0.481 (0.065)	0.765	0.353-0.608	0.112	0.252
TRM as adjuvant	**TNF-α**	0.357 (0.063)	0.027	0.233-0.481	0.093	0.339
	IL-6	0.577 (0.063)	0.238	0.453-0.700	-0.248	0.013
	IL-1β	0.249 (0.053)	<0.001	0.146-0.352	0.426	<0.001

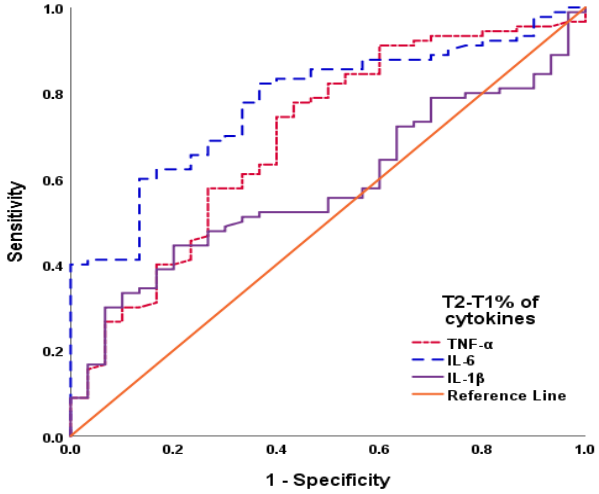

Fig.2a. ROC curve analysis for the cytokine most probably affected by the epidural adjuvants

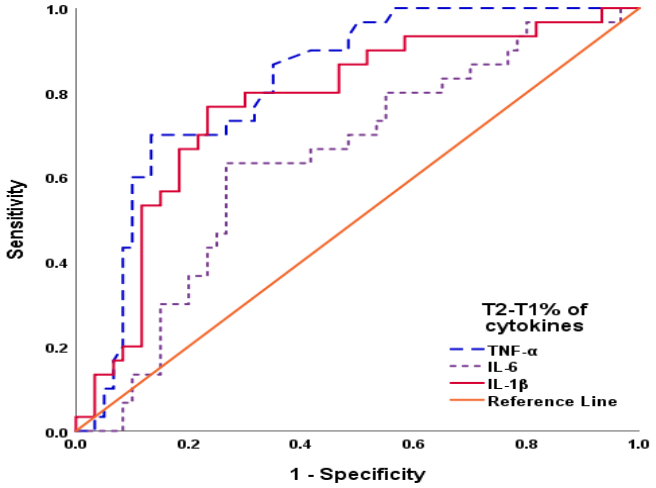

Fig. 2b. ROC curve analysis for the cytokine most probably affected by the epidural DEX as adjuvant

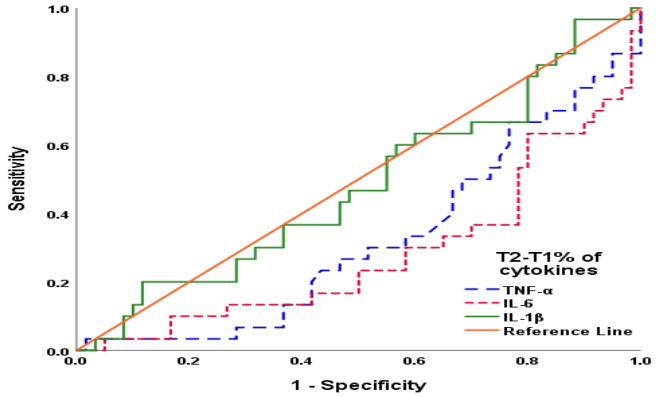

Fig. 2c. ROC curve analysis for the cytokine most probably affected by the epidural FEN as adjuvant

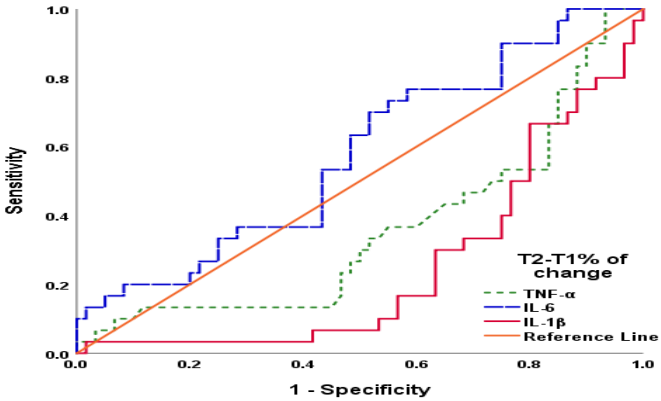

Fig. 2d. ROC curve analysis for the cytokine most probably affected by the epidural TRM as adjuvant

Discussion

The current study evaluated the outcomes of single-shot epidural bupivacaine anesthesia with or without an adjuvant and no continuous infusion was provided. In line with the efficacy of single-shot epidural anesthesia, a previous study documented the efficacy of the PO single-shot bolus of epidural BUP/FEN in providing pain relief after lumbar decompression surgery **(Alicaan et al., 2020)**. Thereafter, the efficacy of ultrasound-guided single-shot epidural anesthesia as an alternative strategy for subumbilical laparoscopic procedures in infants was assured **(Opfermann et al., 2021; 2022)**.

The use of epidural adjuvant significantly improved outcomes of epidural anesthesia in the form of shorter duration of onset and longer duration of action. These data are in hand with multiple previous studies evaluated each adjuvant alone wherein, an earlier study found epidural TRM is safe and effective as a standalone PO analgesic for open spinal-fusion surgery and assured its cost effectiveness **(Ilangovan et al., 2017)**. A comparative study found epidural levobupivacaine with TRM or morphine as analgesia after major abdominal surgeries was effective than local anesthetic alone but the frequency of PO nausea and vomiting was higher with morphine **(Türkoğlu et al., 2019)**. Another comparative study documented the efficacy of BUP/DEX over BUP/morphine for geriatric epidural anesthesia in terms of significantly shorter time to reach the sensory and motor block with longer duration of block, lower pain scores and longer time till the first request of PO analgesia **(Gousheh et al., 2019)**. Further, BUP/DEX pediatric caudal anesthesia was found to provide better and prolonged PO analgesia with significantly lower HR, MAP, pain score and consumption of analgesia in comparison to placebo **(Imani et al., 2021)** or morphine **(Ismail et al., 2021)** as adjuvant. Two recent prospective comparative studies assured the efficacy of epidural FEN but detected non-significant difference in pain scores between low and high concentrations of epidural FEN during ambulation after cesarean section **(Oshima and Aoyama, 2022)** or in antral cross-sectional area at 2h after epidural placement in non-fasted laboring women **(Fiszer et al., 2022)**; both studies recommended the use of the lower dose of FEN to guard against the potential adverse events.

Further, the current study detected more superior anesthetic outcomes with the BUP/DEX than with BUP/FEN or BUP/TRM especially in regard to the hemodynamic stability. In line with these findings, a comparative study found epidural DEX was superior to FEN for providing faster onset of anesthesia, better PO analgesia and reduced amount of PO ropivacaine with minimizing the opioid-related side effects **(Pang et al., 2022)**.

Serum cytokines' levels estimated in at end of surgery (T2) and at 24-h PO (T3) samples were significantly higher than preoperative levels, irrespective of the use of adjuvant or its type. This indicated the surgically-induced upregulation of the expression levels of inflammatory cytokines. Similarly, a recent study detected significantly higher levels of TNF-α and IL-6 in the lung epithelial lining fluid of patients undergoing lung surgery at 30-min after the end than at the start of one-lung ventilation **(Okuda et al., 2022)**. Another recent study found open splenectomy decreased, whereas minimally invasive splenectomy significantly increased the normalized ΔTNF-α releasing capacity **(Dragomir et al., 2022)**.

The estimated serum cytokines' levels were significantly lower in T2 than T3 samples of all patients, this finding spots light on the ameliorative effect of epidural anesthesia per se on the inflammatory cytokines and after complete resolution of the block, cytokines' levels had flared up. In line with these findings, a recent study found thoracic epidural anesthesia significantly reduced IL-6 concentration in the lung epithelial lining fluid than general anesthesia **(Okuda et al., 2022)**. Another study detected differential effect of different types of anesthesia on cellular immunity variables and serum levels of inflammatory cytokines but the difference was in favor of epidural anesthesia **(Hu et al., 2022)**.

Interestingly, DEX significantly reduced the estimated serum cytokines' levels in T2 and T3 samples in comparison to FEN and TRM as adjuvants. These findings indicated the efficacy of DEX as a regulator for the release of inflammatory cytokines. Further, statistical analyses showed that the percentage of change in serum levels of TNF-α and IL-6 in T2 sample in relation to T1 sample are the mostly affected by neuroaxial adjuvant especially for IL-6, and DEX is the best adjuvant to control inflammatory cytokines release because of its inhibitory effect included the three cytokines.

In support of these assumption, a previous study found DEX paravertebral block during general anesthesia decreased lung inflammation, with higher CD4+/CD8+ cells at the end thoracic surgery in comparison to general anesthesia alone or with paravertebral block without DEX **(Zhang et al., 2020)**. Recently, significantly lower intraoperative levels of cortisol, and TNF-α were obtained with perioperative DEX during gastrointestinal tumor surgery **(Guo et al., 2022)**. Further, the use of DEX for patients undergoing transplantation surgery significantly reduced myocardial injury secondary to inflammation by decreasing the release of inflammatory factors during perioperative reperfusion **(Dong et al., 2022)**. In a similar comparative study of intrathecal morphine, DEX or both, it was found that cellular immunity was significantly reduced in all groups during 24-h PO with significant effect of morphine, while IL-6 was significantly reduced by DEX than morphine, which significantly reduced both inflammatory and anti-inflammatory cytokines **(Kamal et al., 2022)**.

Epidural FEN was found to positively affect the immune response in the inflammatory direction, while TRM inhibit IL-6 but augments IL-1β. These data illustrate the effect of opioids on immune response and supported the previously reported that opioids had an inflammatory effect that was ameliorated by the use of adjuvant blocks **(Relland et al., 2020; Matas et al., 2021)** or opioid-free anesthesia to reduce opioid concentration and PO inflammatory response by limiting concentrations of pro-inflammatory cytokines **(Titon et al., 2021)**. Further, a recent study found FEN upregulat the levels of inflammatory cytokines/chemokines, elevate the proportions of Th1 cells and macrophages in the colonic mucosa of experimental animal model of colitis **(Wang et al., 2022)**.

Conclusion

Epidural anesthesia could ameliorate the surgery-induced inflammatory response. Epidural adjuvant might augment the ameliorative effect of epidural anesthesia on inflammatory cytokines.

Epidural BUP/DEX anesthesia significantly suppressed the surgery-induced immune stress response, while BUP/FEN augments this response.

Study's limitations

The short duration of surgery, surgery was not dealing with an inflammatory indication, also the missed estimation of serum levels of anti-inflammatory cytokines are the shortage of the study.

Recommendation

Wider scale multicenter studies for evaluation of the effects of neuroaxial adjuvants during major surgeries especially for inflammatory indications are mandatory.

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