

A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL TO ASSESS THE EFFICACY OF DEXAMETHASONE TO PROVIDE POSTOPERATIVE ANALGESIA AFTER PARAVERTEBRAL BLOCK IN PATIENTS UNDERGOING ELECTIVE THORACOTOMY

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ABSTRACT:BACKGROUND: In an attempt to improve the recovery and early rehabilitation after thoracotomy, various methods of pain-relief have been tried to prolong the duration and to improve the quality of postoperative analgesia. Paravertebral block using steroids like dexamethasone, administered as an adjuvant along with local anaesthetic agents, could be of particular interest. **METHODS:** Fifty patients undergoing elective thoracotomy were randomly assigned to one of the following groups containing twenty five patients each. Group D patients received 8 mg (2 ml) of dexamethasone added to 18 ml of 0.25% levobupivacaine as paravertebral block (total volume 20 ml). Group L patients received 18 ml of 0.25% levobupivacaine and 2 ml of isotonic saline (20 ml in total) as paravertebral block. Analgesic effect was evaluated by measuring pain intensity (VAS score) and duration of analgesia. **RESULTS:** A longer delay was observed between paravertebral block with study medication and first requirement of supplementary analgesic in group D (602.24±78.72 minutes) compared to group L (410.48±56.64 minutes). Total consumption of diclofenac sodium in first 24 hours in postoperative period was significantly less in group D. No significant side effects were noted. **CONCLUSION:** Dexamethasone, used as adjuncts to levobupivacaine for thoracic paravertebral block in patients undergoing thoracotomy, improve the quality and prolong the duration of post operative analgesia.

KEY WORDS: Dexamethasone, Levobupivacaine, Thoracotomy, Paravertebral block.

Post thoracotomy pain is particularly severe because the surgery needs muscle-dividing incision on the chest wall. Normal and deep breathing causes stretching of skin incision resulting in severe pain and reduced lung volumes and capacities. Proper control of post thoracotomy pain is essential in these patients because in addition to provide comfort to the patient, it facilitates chest physiotherapy, effective expectoration and early ambulation.

There has always been a search for a simple as well as effective method for providing postoperative analgesia in these patients. Paravertebral analgesia has been recently redefined^{1,2,3,4}. Paravertebral blocks can be performed effectively and safely and prolonged postoperative analgesia can be provided by administering local anaesthetic solutions with or without an adjuvant. An unilateral block produces predominantly unilateral sympathetic blockade, so effect on circulation and breathing is less.

Dexamethasone is potent and highly selective glucocorticoid with minimal mineralocorticoid effect. It blocks the nociceptive impulse transmission along the myelinated C fibres. So when used in association with local anaesthetics, dexamethasone prolongs the duration of local anaesthetic block^{5,6}.

This placebo controlled, double blind, prospective study is designed to assess the efficacy of dexamethasone administered as adjuvants with local anaesthetic levobupivacaine for single bolus injection of thoracic paravertebral block in patients undergoing elective thoracotomy.

METHODS: The study protocol was approved by the ethical committee of Calcutta National Medical College, Kolkata and informed consent was obtained from every patient. Fifty ASA I –II patients of either sex, aged 18-65 years, undergoing elective thoracotomy were randomly assigned to one of the two groups, containing twenty five patients each [Group size of twenty five patients was determined by power analysis study, which is mentioned as follows: the primary outcome of interest is dichotomous (success/failure, yes/no, etc). For example, 25% of the subjects on the standard therapy had a successful outcome and it is of clinical relevance only if we observe a 40% (effect size) absolute improvement for those on the study therapy (i.e. 65% of the subjects will have a successful outcome). How many subjects do we need to observe a significance difference?

For a two-sided test of 5%, a simple formula to calculate the sample size is given by
$$m \text{ (size per group)} = \frac{c \times \pi_1(1 - \pi_1) + \pi_2(1 - \pi_2)}{(\pi_1 - \pi_2)^2}$$

where $c = 7.9$ for 80% power and 10.5 for 90% power, π_1 and π_2 are the proportion estimates. Thus from the above example, $\pi_1 = 0.25$ and $\pi_2 = 0.65$. For a 80% power, we have $m \text{ (size per group)} = 7.9 \times [0.25(1 - 0.25) + 0.65(1 - 0.65)] / (0.25 - 0.65)^2 = 20.49$. Hence $21 \times 2 = 42$ subjects will be needed. Due to availability of subjects, we selected 50 patients for our study divided into two equal groups].

Patients with isolated mitral valve stenosis who were posted for closed mitral commissurotomy were selected for the study. Patients having history of cardiovascular, neurological, respiratory diseases and coagulation disorders, pregnancy, receiving chronic pain treatment, diabetes and acid peptic disease, and patients with history of anaphylaxis to local anaesthetics were excluded from the study. On preoperative round, patients were explained regarding the procedure and were also taught to interpret the visual analogue scale (VAS) (graded from 0 = no pain to 10 = maximum pain).

All patients were given tab. diazepam 10 mg and tab. ranitidine 150 mg orally on the night before surgery and tab. ranitidine was repeated on the day of surgery two hours before induction with sips of water. On the operation table, routine monitoring (ECG, pulse oximetry, NIBP) were started and baseline vital parameters like heart rate (HR), blood pressure (systolic, diastolic and mean) and arterial oxygen saturation (SpO_2) were recorded. An intravenous line was secured.

After preoxygenation for 3 minutes, induction of anaesthesia was done by fentanyl 2 $\mu\text{g}/\text{kg}$ and propofol 2 mg/kg . Inj. Lignocaine (preservative free) was given at a dose of 1.5

mg/kg 90 seconds before intubation to attenuate the pressor response. Patients were intubated with appropriate size endotracheal tube after muscle relaxation with vecuronium bromide in a dose of 0.08 mg/kg. Anaesthesia was maintained with 33% oxygen in nitrous oxide and isoflurane 0.6%. Muscle relaxation was maintained by intermittent bolus doses of vecuronium bromide. The patients were mechanically ventilated to keep EtCO₂ between 35 - 40 mm Hg. Patients received top-up of i.v. fentanyl (1µg/kg) at 1 hourly interval. Heart rate and mean arterial pressure were maintained within 20% of baseline value by giving additional bolus dose of fentanyl 25 µg and propofol 10 mg. Patients were randomly allocated using a computer generated randomization list into two groups (n=25). Sealed envelopes containing one syringe with levobupivacaine and saline or levobupivacaine and dexamethasone were prepared. The anaesthesiologist and surgeon were unaware of the nature of the drug in each syringe. At the end of the surgical procedure, ondansetron 4 mg was administered for prophylaxis against nausea and vomiting. After closure of skin, patients were put in lateral position. The back was prepared with povidine iodine and was draped with sterile towels. The paravertebral block was performed with a 18-gauge Tuohy needle using the loss-of-resistance technique and utilizing the spinous process of T₄ vertebra as a landmark before advancing the needle into the paravertebral space. In Group L, 18 ml of 0.25% levobupivacaine and 2 ml isotonic saline [total volume 20 ml] was administered into paravertebral space. Similarly Group D patients received 8mg dexamethasone (2 ml) added to 18ml 0.25% levobupivacaine [again making a volume of 20 ml].

Patients were turned supine and residual neuromuscular paralysis was reversed using intravenous glycopyrrolate and neostigmine and subsequently extubation was done. All patients were observed postoperatively by resident doctors who were unaware of the study group. Patients were transferred to postanesthesia care unit and intensity of pain and vital parameters were assessed after thirty minutes and then an hourly interval for 24 hours. Procedure was considered as unsuccessful if there was unsatisfactory postoperative analgesia with a VAS score 4 or more at the first assessment. Diclofenac sodium (75 mg) was administered i.v. as analgesic supplement if the recorded VAS pain score was 4 or more and was repeated every 8 hour, if required. Tramadol 100 mg i.v. was used as a rescue analgesic, if the patients continued to have pain even after diclofenac administration. The time to the first analgesic requirement and the total diclofenac consumption during first 24 hour after operation were also recorded.

STATISTICAL ANALYSIS: The results obtained from the study are presented in the following section in a tabulated manner. The results are expressed in Mean ± SD. Comparison between groups were performed with the Kruskal-Wallis one way ANOVA by ranks or Fisher's exact test for small samples with a 5% risk. Mann-Whitney-Wilcoxon tests were performed when tests of normal distribution have failed. P value<0.05 was considered to be statistically significant [Graph Pad InStat version 3.05, Graph Pad Software, SanDiego, CA]

RESULTS:The failure rate in was 4% (1 patients) in Group D and 8%(2 patient) in Group L. These three patients were excluded from the study. Therefore data from 47 patients were available for analysis; group D (n=24) and Group L (n=23).

The two groups were comparable with regard to age, sex, body-weight, height and duration of surgery (P>0.05) (Table 1). The groups were also comparable regarding fentanyl and propofol consumption during intraoperative period (P>0.05) (Table 2). Intensity of pain

was significantly less in Group D compared to Group L at 1 hour ($P<0.01$), 2 hour ($P<0.05$) and 4 hour ($P<0.05$) following surgery. However from 6 hour, intensity of pain was comparable in both groups (Table 3).

The mean duration of analgesia (delay between the paravertebral block and the first postoperative analgesic demand) was longer in group D compared to group L (602.24 ± 78.72 minutes vs. 410.48 ± 56.64 minutes; mean \pm SD; $P<0.01$) (Table 4). Total diclofenac consumption in first 24 hours was significantly less in group D compared to group L ($P<0.01$) (Table 4). None of the patients received tramadol.

DISCUSSION: In an attempt to improve the recovery and early rehabilitation after thoracotomy, research has been directed towards developing newer techniques for postoperative analgesia. In our study, we observed the effects of dexamethasone used as adjuvant with ropivacaine administered for paravertebral block after elective thoracotomy.

The pain following thoracotomy is particularly severe and there is convincing evidence that unrelieved acute pain may result in harmful physiological and psychological effects. The site of surgery is an important factor in determining the degree of pain, its localization and duration. Pain following thoracotomy involves muscle division between the ribs and is exaggerated by movement especially deep breathing and coughing. The avoidance of deep breathing and coughing due to post thoracotomy pain may lead to a decrease in functional residual capacity, increase airway closure and hypoxaemia, segmental or lobar pulmonary collapse, retention of secretion and bronchopneumonia. Proper control of post thoracotomy pain in addition to providing comfort for the patient, facilitates chest physiotherapy, effective expectoration and early ambulation.

Thoracic paravertebral block appears promising to provide effective analgesia after thoracotomy. Paravertebral block can uniquely eliminate the cortical responses to thoracic dermatomal stimulation. It is associated with a decreased need for opioids for controlling postoperative pain⁷, decreased PONV, improved patient outcome, lowered postoperative pulmonary complications and, finally, decreased duration of post-anaesthesia care unit(PACU) stay⁸. An unilateral block may have less effect on circulation and breathing.

Dexamethasone is a potent and highly selective glucocorticoid. Because steroids block the transmission of impulse in nociceptive C fibres^{5,6}, we were interested in determining whether dexamethasone might prolong the duration of analgesia when administered for paravertebral block along with local anaesthetic agents. Local anaesthetic agents can provide analgesia for limited period of time when used as single injection. To extend the analgesia period beyond the operation rooms, various adjuvants have been tried with the aim of prolonging the duration and improving the quality of analgesia.

Steroids have block prolonging effect according to their anti-inflammatory potency. Dexamethasone is a powerful and predominantly anti-inflammatory steroid. So it prolongs the action of local anaesthetics when used together⁹. The pharmacodynamics and pharmacokinetics of the drugs when administered in regional nerve block is difficult to explain. There are some proposed mechanisms of actions of glucocorticoids when used with bupivacaine micro-spheres to extend the block effect¹⁰. Kopacz DJ and colleagues¹¹ explored the effects of dexamethasone in bupivacaine micro-capsule for intercostals blockade in healthy human volunteers and concluded that dexamethasone micro-capsules are well tolerated and inclusion of dexamethasone had increased the duration of intercostals block to at least 96 hours. The author assumed the similar probable mechanisms when dexamethasone was mixed with levobupivacaine solution. The

dense and prolonged block in the dexamethasone group is due to the synergistic action with local anaesthetic levobupivacaine on blockade of nerve fibres⁹. The block prolonging effect of dexamethasone is due to its local action, not a systemic one^{12, 13}. It has been found that this effect of steroid is mediated via steroid receptors¹⁴.

In our study, the means of assessing postoperative analgesia was the time to first analgesic administration, the total amount of analgesic consumed in the first 24 hour period after surgery and the VAS scores at different time in first 24 hour. The delay between paravertebral block with levobupivacaine and dexamethasone and supplementary analgesic administration in the form of i.v. diclofenac was 602.24±78.72 minutes in our study compared to paravertebral block using levobupivacaine alone (410.48±56.64 minutes) and the difference was statistically significant. Mean requirement of diclofenac sodium in the first 24 hour was also lesser in group D as compared to group L. In a similar study using paravertebral block for postoperative analgesia after thoracotomy, Santosh Kumar and colleagues¹⁵ found that time period for first analgesic request after administering bupivacaine for paravertebral block was 427.83±60.15 minutes and this finding was comparable to our study.

In our study, we applied thoracic paravertebral block using single-level injection. Whether a multilevel injection of paravertebral block (T₃-T₆) is superior to a single-injection technique has not been evaluated and published reports on analgesia are quite similar. Although the incidences of pneumothorax and intravascular injection in paravertebral blocks are small, we find it logical to perceive that the risk of complications per patient increases when multiple injections are performed.

In conclusion, dexamethasone administered as adjuvant to local anaesthetic levobupivacaine for thoracic paravertebral block improves the quality and duration of postoperative analgesia and reduces the consumption of diclofenac sodium in patients undergoing elective thoracotomy.

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Table 1
Patients Characteristics

Variables/Groups	Group L (n=23)	Group D (n=24)	P value
Age (Year)	44.6 ±9.6	43.6 ±10.8	0.49
Sex (M/F)	9/14	10/14	
Weight (kg)	48.3 ± 9.4	50.4±10.48	0.56
Height(cm)	153.72±5.3	154.36±4.6	0.34
Duration of surgery (minutes)	78.62.±22.8	80.8 ± 22.6	0.62

Table 2
Fentanyl and propofol consumption in the intraoperative period (Mean± SD)

Parameters	Group L(n=23)	Group D(n=24)	P value
Fentanyl consumption(µg)	112.76 ±12.64	115.62 ±12.86	0.57
Propofol consumption(mg)	138.34 ± 14.4	135.42±13.28	0.59

Table 3

Intensity of Pain in Postoperative Period
Intensity of Pain(VAS)

Postoperative Period	Group L(n=23) (Mean±SD)	Group D (n=24) (Mean±SD)
1 hour	2.82±0.58	1.94±0.54**
2 hour	3.02±0.62	2.2±0.63*
4 hour	4.02±1.02	3.16±0.72*
6 hour	3.67±0.9	3.62±1.02
10 hour	3.73±1.08	3.64±1.08
14 hour	3.52±0.9	3.42±1.02
18 hour	3.64±1.04	3.56±1.05
24 hour	3.67±1.1	3.63±1.06

* = P< 0.05; ** = P< 0.01

Table 4

Duration of analgesia and diclofenac consumption in the postoperative period (Mean± SD). [P value was determined by comparing group L and group D]

	Group L(n=23)	Group D(n=24)
Duration of Analgesia (minutes)	602.24±78.72	410.48± 56.64 **
Diclofenac consumption in 24 hours (mg)	157.4±28.4	108.6±24.4**

* = P< 0.05 ; ** = P< 0.01