The effect of epidural dexmedetomidine on oxygenation and shunt fraction in patients undergoing thoracotomy and one lung ventilation: A randomized controlled study

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Abstract

Background and Aims: Role of epidural dexmedetomidine in providing analgesia is well documented, but its effect on oxygenation and shunt fraction is not well established. We studied the hypothesis that epidural dexmedetomidine may improve oxygenation and shunt fraction during one-lung ventilation (OLV).

Material and Methods: After taking Institutional Ethics Committee approval, sixty patients undergoing thoracotomy and OLV were randomized to receive epidural ropivacaine with saline (RS group) or epidural ropivacaine with dexmedetomidine (RD group). Group RS received 7 ml of ropivacaine 0.5% with 1.5 ml normal saline (NS) bolus while RD group received 7 ml of 0.5% ropivacaine with 1 mcg/kg dexmedetomidine reconstituted in 1.5 ml NS. This was followed by infusion of 5 ml/h of 0.5% ropivacaine in RS group and 5 ml/h of 0.5% ropivacaine containing 0.2 mcg/kg of dexmedetomidine in RD group. Arterial and central venous blood gas parameters were obtained 15 minutes after intubation during two lung ventilation (TLV15), 15 and 45 min after OLV (OLV15, OLV45) and 15 minutes after reinstitution of two lung ventilation (ReTLV).

Results: RD group had better oxygenation (254.2 ± 72.3 mmHg, 240.60 ± 59.26 mmHg) as compared to RS group (215.2 ± 64.3 mmHg, 190.7 ± 61.48 mmHg) at OLV15 (P = 0.04) and OLV45 (P = 0.004) respectively. Shunt fraction in RD group was (30.31 ± 7.89%, 33.76 ± 8.89%) and (35.14 ± 7.58%, 39.57 ± 13.03%) in RS group at OLV15 and OLV45, respectively. The increase in the shunt fraction from TLV15 was significantly greater in RS group than RD group both at OLV15 (P = 0.03) and OLV45 (P = 0.03). The sevoflurane and fentanyl requirement was lower in RD group.

Conclusion: Epidural dexmedetomidine improves oxygenation and reduces shunt fraction during OLV in patients undergoing thoracotomy. It also reduces intraoperative anesthetic and analgesic requirement.

Key words: Dexmedetomidine, one lung ventilation, oxygenation, shunt fraction, thoracotomy

Introduction

Thoracic epidural anesthesia (TEA) is the most commonly used technique for intraoperative and postoperative analgesia in patients undergoing lung surgeries. However, sympathetic blockade caused by local anesthetics given epidurally may cause attenuation of hypoxic pulmonary vasoconstriction (HPV) leading to increase of shunt fraction and impairment of oxygenation. Further, various adjuvants added to epidural local anesthetic for improving analgesia may also influence the HPV. Dexmedetomidine; an alpha-2 agonist, may have possible favorable effects on HPV leading to better oxygenation. Studies have shown that intravenous dexmedetomidine results in a reduction of shunt fraction. However, the hemodynamic effects of intravenous dexmedetomidine may be bothersome. Further, although this is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

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epidural dexmedetomidine has been shown to be a useful adjunct in epidural analgesia with minimal systemic effects, its effect on oxygenation and pulmonary shunt fraction has not been evaluated. We hypothesized that dexmedetomidine as an adjuvant to epidural analgesia for thoracic surgeries would favorably influence the shunt fraction during one-lung ventilation (OLV) and provide better oxygenation. The primary objective of this study was to evaluate the effect of epidural dexmedetomidine on oxygenation and shunt fraction, and secondary objective was to determine the effect of epidural dexmedetomidine on the general anesthetic requirement.

Material and Methods

After obtaining Institutional Ethics Committee approval and clinical trial registration (CTRI Number — CTRI/2014/11/005182) 60 patients were recruited for the trial. American Society of Anesthesiologists I-II patients of either gender, with age of 18-60 years, weighing 40-70 kg undergoing thoracotomy and OLV for lung surgery were included in the study. Patients with a contraindication to epidural anesthesia, known allergy to the study drugs, severe cardiovascular disease, history of myocardial infarction, arrhythmias, hypotensive patients on treatment with alpha-2 agonists, severe neuropsychiatric disease, renal dysfunction (serum creatinine more than 1.5 mg/dl), hepatic dysfunction, long-term alcohol, or other drug addiction were excluded from the study. Written informed consent was taken from all recruited patients.

All patients were randomly divided into two groups, epidural ropivacaine with saline (RS group) and epidural ropivacaine with dexmedetomidine (RD group) using computer generated randomization chart. The serially labeled opaque envelopes containing the group allocation were opened immediately before study and study drugs were prepared by an anesthesia operation theater technician who did not participate in the process of anesthesia and subsequent analysis. The bolus drug syringe contained 7 ml of 0.5% ropivacaine with 1.5 ml normal saline (NS) in RS group and 7 ml of 0.5% ropivacaine with 1 mcg/kg of dexmedetomidine (reconstituted to 1.5 ml with NS) in RD group. For infusion a 50 ml syringe containing 45 ml 0.5% ropivacaine and 5 ml of study drug were prepared. In group RD, dexmedetomidine 2 mcg/kg reconstituted to 5 ml with NS was the study drug, while 5 ml of NS was added in group RS. All preoperative and intraoperative management were performed by the same anesthesiologist who was blinded to study drug, and intraoperative data were noted by an investigator who was blinded to the patient group allocation.

Intravenous glycopyrolate 0.2 mg was given as premedication on arrival to operating room (OR). Arterial line was secured, and central venous catheter was placed into the right atrium through right internal jugular vein. Heart rate (HR), electrocardiography, pulse oximetry, end-tidal carbon dioxide (EtCO$_2$), end-tidal sevoflurane (EtSev), peak airway pressure (Paw), mean arterial pressure (MAP), central venous pressure (CVP), urine output and temperature were monitored. Depth of anesthesia was measured by Entropy (GE Healthcare Finland Oy, Helsinki, Finland). Baseline Arterial blood gas on room air was taken, and hemodynamics at baseline and preinduction were noted. Crystalloid was administered so as to achieve a baseline CVP of 5-8 mmHg.

Epidural catheter was placed in T3-T4/T4-T5 space. A test dose of 2 ml of 2% lidocaine was injected through the catheter to exclude intrathecal placement. Then the bolus drug as stated earlier was administered over 10 min as per the group allocation. The infusion was started after confirming the sensory blockade. In RS group, the patients received ropivacaine 0.5% and RD group received dexmedetomidine 0.2 mcg/kg/h along with ropivacaine 0.5% at 5 ml/h. Patients were induced 20 min after administration of bolus drug.

All patients were preoxygenated for 3 min. After administering fentanyl 2 mcg/kg and injection midazolam 0.04 mg/kg, induction was achieved with propofol titrated to get entropy values of 40-60. Propofol dose required for loss of vocal response was also noted. No inhalational agent was used during induction and intubation. Tracheal intubation was facilitated with rocuronium 1 mg/kg. Hemodynamic response at 1 and 5 min after intubation was recorded. No intervention like catheterization, positioning which can affect the hemodynamic values was allowed during this period.

A left sided double lumen tube (size 37/35 for males and 35/32 for females) was inserted and the position was confirmed by auscultation and fibreoptic bronchoscopy before and after patient positioning to lateral decubitus position. The patient’s lung was ventilated with intermittent positive pressure ventilation with tidal volume (Vt) of 8-10 ml/kg, FiO$_2$ of 1 and inspiratory to expiratory ratio of 1:2. The respiratory rate (RR) was adjusted to get an EtCO$_2$ between 30 and 35 mmHg. During OLV, Vt was decreased to 4-6 ml/kg and RR was adjusted to maintain the EtCO$_2$ of 30-35 mmHg. No positive end-expiratory pressure (PEEP) was used however PEEP to the dependent lung was applied in patients who failed to maintain an adequate oxygenation (SpO$_2$ >92%) with the above ventilator settings. Patients requiring PEEP or other recruitment maneuvers for oxygenation were excluded from final analysis. Intraoperatively atracurium infusion (0.5 mg/kg/h) was used to maintain muscle relaxation. Sevoflurane concentration...
was increased or decreased to keep the entropy values within 40-60. Intraoperative hypotension (defined as decrease of MAP more than 20% from baseline) was treated with a fluid bolus of 200 ml NS. If the MAP did not return to baseline even after two boluses, injection mephenetermine 3 mg was administered. In case of significant blood loss (more than 20% of estimated blood volume), blood was transfused. Patients who had persistent hypotension despite the above measures and required continuous infusion of vasoactive drugs were excluded from the study. Bradycardia (defined as HR <50) was treated with injection atropine 0.6 mg. Tachycardia and/or hypertension (defined as 20% increase from baseline) were managed with increasing concentration of sevoflurane if entropy was more than 60. If entropy was within normal range, then inadequate analgesia was considered and fentanyl bolus 20 mcg was given till HR/MAP reached within 20% of baseline. If the gradient between response entropy (RE) and state entropy (SE) was >5, additional 5 mg atracurium was administered. The total amount of crystalloid, mephentermine, and fentanyl administered was noted. Forced air warming device (3M™ Bair Hugger™ warming unit, model no 750 by Arizant Healthcare Inc., USA) was used in all patients to keep the nasopharyngeal temperature between 35°C and 36.5°C.

Arterial and central venous samples were obtained for blood gas analysis, 15 min after intubation during two-lung ventilation (TLV15), 15 and 45 min after institution of OLV (OLV15, OLV45) and 15 min after reinstitution of TLV (ReTLV). The corresponding entropy values and EtSev concentrations were also noted. HR and MAP were recorded at baseline, preinduction, 1 and 5 min after intubation and also at TLV15, OLV15, OLV45, and ReTLV. Pulmonary shunt fraction (Q/Qs) was calculated using the following formula.

$$Q/Q_s = (CcO_2 - CaO_2)/(CcO_2 - CvO_2).$$

Whereby CaO_2 (oxygen content of arterial blood) = (PaO_2 × 0.0031) + (Hb × 1.34 × SaO_2).

CvO_2 (oxygen content of venous blood) = (PvO_2 × 0.0031) + (Hb × 1.34 × SvO_2).

CcO_2 = ([FiO_2 × (PB − pH_2O) − (PaCO_2/RQ)] × 0.0031) + (Hb × 1.34).

PB – Barometric pressure (760 mmHg), pH_2O – 47 mmHg, Hb – Hemoglobin, RQ – Respiratory quotient (0.8).

The study concluded 15 min after ReTLV.

Patients were excluded after initial inclusion if there was a failure to achieve epidural anesthesia, lung isolation was improper, the requirement of PEEP for maintaining oxygenation, significant bleed (Hb <8 despite transfusion), that required use of vasoactive drug or if OLV time was <45 min.

Patients were extubated on the table when the criterion for extubation was met. Postoperative management was at the discretion of the intensivist in the Intensive Care Unit.

**Statistical analysis**

Data were analyzed using SPSS version 20 (2011, IBM, Armonk, NY, United States of America). The sample size was determined based on our pilot study of 10 patients, where PO_2 at OLV15 was 214 ± 42 mmHg and 252 ± 50 mmHg in RS and RD group, respectively. With an alpha error of 5% and power of 80%, a sample size of 25 in each group was required to detect a PaO_2 difference of 38 mmHg between the two groups at OLV15. Hence, thirty patients in each group were recruited to account for possible exclusions. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequency of occurrence and percentage. Parametric data were compared with independent sample t-test. The categorical data (gender, side, and type of surgery) were compared by Chi-square test. Comparison of within the group data (OLV15, OLV45 with baseline/TLV) was done for parameters such as pH, PaCO_2, PaO_2, and Q/Q_s using ANOVA for repeated measures with post hoc analysis using Dunnet test. P < 0.05 was considered significant for all the tests.

**Results**

The study cohort included thirty patients each in RS and RD group. Out of these, three patients in RS group and four in RD group were excluded. The patient characteristics and other demographic data were comparable in both groups [Table 1]. The propofol dose required for loss of verbal commands and induction were 67.78 mg and 82.59 mg respectively in RS group as compared to 51.92 mg and 70.77 mg in RD group. The patients in RD group required significantly lesser propofol than the patients in RS group (P = 0.006 and 0.048). EtSev concentration required to maintain entropy within 40-60 was much lower in RD group at all 4 time points [Figure 1].

The hemodynamic data of both groups are presented in Table 2. The baseline hemodynamic data were comparable in both groups. The intubation response at 1 and 5 min was significantly lower in RD group. Both HR and MAP were significantly lower in RD group at all-time points, but the need for interventions for significant changes were comparable between the groups. The requirement of additional fentanyl for
Our study suggests that epidural dexmedetomidine improves oxygenation and reduces shunt fraction. It also reduces inhalational anesthetic and analgesic requirement.

\[ Q/Q_r \text{ of 1-3\% is normal, which is attributable to pleural, thebesian, and bronchial vessels. It rises to 10\% after induction of general anesthesia and can rise up to 40-50\% after institution of OLV.}\]

However, the natural compensatory phenomenon, HPV decreases the blood flow to the nonventilated lung by almost 50\%. The major stimulus for HPV is \( \text{PaO}_2 \), which stimulates the precapillary vasoconstriction, via inhibition of nitric oxide and cyclooxygenase pathway.\[7\]

HPV has a biphasic response, first response starts immediately and reaches a plateau in 20-30 min. The second starts after 40 min and plateaus after 2 h.\[8\] Hence, we assessed the shunt and oxygenation as a surrogate measure for HPV at 15 and 45 min.

Anesthetic drugs and techniques can influence the shunt by altering cardiac output, the pulmonary vascular tone, and modification of HPV.\[9\] As PEEP or recruitment maneuvers can affect the pulmonary vascular tone and thus HPV, patients requiring these were excluded from the study. Further, the hemodynamic parameters and anesthetic requirement which may have an influence on the shunt were also measured as secondary outcomes.

Intravenous anesthetic regimen has been shown to minimally affect HPV.\[10\] However, all inhalational agents have been shown to inhibit HPV at least in \emph{in vitro} models.\[11-13\] A study by Kellow \emph{et al.} comparing isoflurane and propofol showed a significant increase in shunt with isoflurane anesthesia.\[10\] Wang \emph{et al.} also found that sevoflurane inhibits HPV equivalent to that of isoflurane.\[14\] Since inhalational drugs have a potential to inhibit HPV, it is probable that drugs reducing inhalational anesthetic requirement will minimize attenuation of HPV and will have a favorable effect in terms of improved oxygenation. In our study, reduced sevoflurane requirement in RD group might have led to better oxygenation and reduced shunt fraction.

Studies investigating the effect of TEA on HPV have been inconclusive.\[1-3,15-17\] However, a study by Ozcan \emph{et al.} has well established that epidural has little or no effect on the HPV.\[18\] The effect of several adjuvants added to epidural anesthesia on HPV and thereby shunt fraction and oxygenation has been investigated by many authors.\[12,4\] The choice of drugs during anesthesia for thoracotomy requiring OLV is often influenced by their effect on HPV. The role of dexmedetomidine as an adjuvant to epidural anesthesia is well established but its effect on HPV has also not been evaluated earlier.\[19-22\] In this study, we have studied this effect of the drug.
The effect of dexmedetomidine on hemodynamics is mainly through alpha receptors. Dexmedetomidine is an alpha-2 agonist with alpha-2:alpha-1 affinity ratio of 1600:1.[21] A biphasic response with dexmedetomidine has been elicited in healthy volunteers. This includes initial increase in systolic blood pressure due to action on alpha-2b receptors causing vasoconstriction and later a fall in both systolic blood pressure and HR to below baseline which is mediated by an alpha-2a mediated sympatholysis.[24] Talke et al. in their studies well demonstrated the sympatholytic effect of dexmedetomidine.[25,26] They found that on intraoperative administration of dexmedetomidine both HR and systolic blood pressure showed a decrease along with plasma epinephrine and norepinephrine. However, an animal study has shown a rise in pulmonary artery pressure and pulmonary vascular resistance owing to its direct effect on vascular smooth muscles through alpha receptors.[27] Even healthy human volunteers had similar changes when dexmedetomidine infusion was used to achieve a plasma concentration of 1.9 ng/ml. Because of the conflicting effects on pulmonary vasculature, the effect of dexmedetomidine on HPV is difficult to predict.

The effect of intravenous dexmedetomidine on oxygenation and shunt fraction has been studied by several authors[6,28] However, lower doses of the bolus and infusion (0.3 mcg/kg bolus followed by 0.3 mcg/kg/h) was used by Kernan et al. due to fear of hypotension and bradycardia.[28] They did not find any improvement in oxygenation with the above doses.[28] Elhakim et al. used epidural dexmedetomidine in a dose of 1 mcg/kg followed by 0.2 mcg/kg/h infusion. Though the primary objective of the study was to determine its effect on awareness in patients undergoing OLV they also showed a reduced shunt fraction and improved oxygenation.[15] They also found reduced bispectral index values, lesser intraoperative awareness, and lesser analgesic requirements in patients who received epidural dexmedetomidine. Consistent with these results our patients in the dexmedetomidine group required lesser dose of propofol for induction and lesser sevoflurane for maintenance of anesthesia. The additional fentanyl requirement was also lower in these patients. These effects may be explained by the sedative and analgesic-sparing effects of dexmedetomidine, respectively. Dexmedetomidine produces sedative effect due to central action mediated via locus coeruleus, whereas analgesic effect is due to action on dorsal horn of spinal cord.[29,30] The neuroaxial effects of epidural dexmedetomidine contribute to the analgesic effects. The preinduction HR, MAP and also their response to intubation were lower in the RD group suggestive of systemic effects of dexmedetomidine. Sedation, reduced anesthetic requirements may also have resulted from systemic

| Parameters | RS group (n = 27) | RD group (n = 26) | Significance (P) |
|------------|------------------|------------------|------------------|
| Age (years) | 36.8 (11.8) | 36.1 (9.5) | 0.81 |
| Sex (Male/ Female) | 17/10 | 19/7 | 0.13 |
| Height (cm) | 161.3 (8.7) | 163.9 (10) | 0.29 |
| Weight (kg) | 54.3 (11.4) | 55.3 (12.6) | 0.77 |
| FEV₁ (%) | 72.2 (13.6) | 66.9 (18.5) | 0.24 |
| FVC (%) | 78.6 (15.5) | 72 (15.2) | 0.13 |
| FEV₁/FVC | 90 (9.4) | 92.5 (12) | 0.40 |
| Duration of anesthesia (minutes) | 206.4 (60.1) | 197.8 (53.2) | 0.58 |
| Duration of OLV (minutes) | 265.1 (53.8) | 242.3 (47.5) | 0.11 |
| Duration of OLV15 (minutes) | 101.4 (44.6) | 106.8 (49.7) | 0.678 |
| Crystalloid (ml) | 1514.8 (466) | 1480.8 (407.9) | 0.78 |
| Urine Output (ml) | 3713.1 (176.3) | 362.3 (227.1) | 0.87 |
| Side of surgery (Right/Left) | 15/12 | 15/11 | 0.55 |

### Table 1: Demographic and perioperative data

| Nature of surgery | Decortication | Upper lobectomy | Middle lobectomy | Lower lobectomy | BPF repair | Pneumonectomy |
|-------------------|---------------|----------------|------------------|----------------|-------------|---------------|
|                  | 6 | 8 | 1 | 10 | 0 | 2 |

Data expressed as mean (SD) or number of patients, SD = Standard deviation, RS group = Ropivacaine with saline group, RD group = Ropivacaine with dexmedetomidine group, FEV₁ = Forced expiratory volume in 1 s, FVC = Forced vital capacity, OLV = One lung ventilation, BPF = Broncho pleural fistula

| Parameter | Group | HR | MAP |
|-----------|-------|----|-----|
| Baseline  | RS    | 85.5 (14.3) | 85.9 (8.2) |
|           | RD    | 87.3 (14.9) | 87.03 (8.1) |
| Preinduction | RS | 85.7 (11.8) | 85.3 (11.6) |
|           | RD    | 76.4 (10.3) | 79.8 (6.9) |
| 1 min after intubation | RS | 95.9 (13.8) | 92.7 (15.5) |
|           | RD    | 84.3 (14.7) | 82 (9.8) |
| 5 min after intubation | RS | 95.7 (12.2) | 93.6 (13.5) |
|           | RD    | 84.5 (10.1) | 83.3 (12.3) |
| TLV15     | RS    | 87.7 (10.9) | 84.3 (10.1) |
|           | RD    | 72.6 (6.3) | 78.6 (7.3) |
| OLV15     | RS    | 81.1 (13) | 82.7 (10.9) |
|           | RD    | 72.3 (4.9) | 77.1 (7.1) |
| OLV45     | RS    | 80.6 (11.3) | 81.8 (6.7) |
|           | RD    | 71.5 (7.6) | 77.2 (7.5) |
| ReTLV     | RS    | 80.6 (12.7) | 83.4 (8.4) |
|           | RD    | 71.5 (9.3) | 79.3 (6.1) |

*P < 0.05 between the groups, †P < 0.05 within the group from baseline, Data presented as mean (SD), SD = Standard deviation, RS = Ropivacaine with saline group, RD = Ropivacaine with dexmedetomidine group, TLV15 = 15 min after institution of two lung ventilation, OLV15 = 15 min and OLV45 = 45 min after institution of one lung ventilation, ReTLV = 15 min after re institution of two lung ventilation, HR = Heart rate, MAP = Mean arterial pressure

### Table 2: Hemodynamic parameters in the two groups
absorption from the epidural space. The systemic effects were not significant to result in serious bradycardia or hypotension. There are however no studies on pharmacokinetics of epidural dexmedetomidine.

In our study, both the RS and RD group showed a fall in oxygenation following institution of OLV, but the fall was less severe in RD group and plateaued between the 2 time points. Q/Qs was also lower in the RD group.

The better oxygenation and improved shunt fraction can have two possible explanations. First, due to dexmedetomidine-induced central sympathetic and vasodilation, blood flow divers to the dependent, ventilated lung leading to better ventilation-perfusion match. Second, reduction in requirement of sevoflurane, which has been shown to attenuate HPV, might have led to better oxygenation. Further, in a study by Yang et al. dexmedetomidine was found to have lung protective effect in rats with ventilator-associated lung injury. This effect was due to inhibition of interleukin-6 and endothelin-induced inflammatory reaction. Although this lung protective mechanism has not been studied in humans and in patients on short-term ventilation, this could be a possible explanation for the improved oxygenation.

Our study had some limitations. First we did not use cardiac output monitoring. This would have given a better insight into the actual hemodynamic perturbations caused by epidural dexmedetomidine. Second we used central venous sample instead of mixed venous sample as pulmonary catheter placement is not routine in thoracotomy cases at our institute. However, this technique has been validated and used in many earlier studies. Both left and right thoracotomies and multiple lung pathologies were included in the study. Designing a study in patients with similar pathologies and a single sided thoracotomy may bring out more accurate results.

### Conclusion

The addition of dexmedetomidine as an adjuvant to ropivacaine for TEA improved oxygenation and shunt fraction. It reduced general anesthetic requirement. It also attenuated hemodynamic response to intubation and did not cause any adverse hemodynamic changes. Thus, dexmedetomidine can be used as a safe adjunct to epidural ropivacaine during OLV for lung surgeries.

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Conflicts of interest
There are no conflicts of interest.

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