Effect of Dexmedetomidine Administation on Analgesic, Respiration and Inflammatory Responses in Patients Undergoing Percutaneous Endoscopic Lumbar Discectomy: A Prospective Observational Study

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Research Article

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Abstract

Background

Local anesthesia has been recommended for percutaneous endoscopic lumbar discectomy (PELD) in recent years; however, the efficacy, including oxidative stress, inflammatory reactions and ventilation effects, when intravenous dexmedetomidine (DEX) is administered during PELD has not been thoroughly described.

Methods

Sixty patients undergoing PELD were randomly allocated to either an intravenous DEX sedation group (Group A) or a normal saline group (Group B). Respiratory data, including minute ventilation (MV), tidal volume (TV), and respiratory rate (RR), were recorded using a respiratory volume monitor (RVM), and pulse oxygen saturation (SpO_2) was measured by pulse oximetry. The visual analog score (VAS) and the plasma levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA) and glutathione peroxidase (GSH-PX) were also recorded to evaluate oxidative stress and inflammatory reactions.

Results

There were no significant differences in RR, MV, TV and SpO_2 between the two groups at any time point (p>0.05). Group B exhibited lower serum levels of GSH-PX (p<0.0001) and higher serum levels of MDA (p<0.0001) than Group A at the end of surgery. Twenty-four hours after surgery, Group B exhibited higher serum levels of IL-6 (p=0.0033), TNF-α(p=0.0002), and MDA (p<0.0001) and lower serum levels of GSH-PX (p<0.0001) than Group A. In addition, Group B exhibited lower VAS (p<0.0001) than Group A.

Conclusions

DEX administration using an RVM not only provides convenient analgesia and ventilation but also alleviates oxidative stress and inflammatory reactions in patients undergoing PELD .

Trial registration ChiCTR2100044715(http://www.chictr.org.cn/index.aspx)

Background

As a standard full-endoscopic surgical strategy for the treatment of lumbar disc herniation, percutaneous endoscopic lumbar discectomy (PELD) has become an alternative minimally invasive procedure to open lumbar microdiscectomy[1–3]. In PELD, patients are placed in the prone position, and the loose herniated nucleus pulposus is clipped out under endoscopic guidance with continuous irrigation. Local anesthetic infiltration (LAI) is recommended for PELD by most surgeons because it can detect nerve root injuries in time; however, under LAI, some patients cannot tolerate the pain caused by the instrument insertion, resulting in operative anxiety, pain-induced stress and inflammatory reactions. Then, opioids are added to prevent these conditions from occurring; this creates a challenge for anesthesiologists to assess the airway of patients in the prone position, so the implications of LAI in PELD remain contentious[4].

Dexmedetomidine (DEX), a new-generation, highly selective α_2 adrenergic receptor agonist, is widely used in spine surgery due to its effificacy to achieve equilibrium between an effective analgesia and sedation regimen, and its minimal effect on the respiratory system[5–7]. However, the efficacy of DEX administation combined with LAI during PELD has not been thoroughly described.

Oxidative stress and inflammatory reactions are two major risk factors among the serious complications impacting patient outcomes and recovery[8]. Perioperative arrangements, such as alleviating oxidative stress and inflammatory reactions, can contribute to lowering the occurrence of organ dysfunction. To better implement the concept of enhanced recovery after surgery (ERAS), it is particularly important to optimize the anesthesia method. Therefore, this study investigated the effect of respiration, oxidative stress, and inflammatory reactions to determine the superiority of intravenous DEX.

Materials And Methods

Study Design, Settings, and Patients

This prospective, randomized trial was approved by the Medical Ethics Committee of the First Affiliated Hospital of Gannan Medical University (LLSC-2020121002), and all patients provided informed consent for all treatments and trials. The study was conducted and reported in accordance with the Consolidating Standards of Reporting Trials (CONSORT) 2010 statement.

This study included adult patients with American Society of Anesthesiologists physical status (ASA) I/II who were scheduled to undergo elective PELD from June 2018 to March 2021. Patients with contraindications to LAI, allergies to any of the drugs planned to be administered, infection at the puncture site, or who had previous spine surgery, severe spinal stenosis, morbid cardiovascular impairments including preexisting heart block or compromised left ventricular function (defined as an ejection fraction <45%) were excluded from the study. Surgeons and anesthesiologists were aware of the study being conducted but were blind to participant allocation.

Study Protocol

Patients were assigned randomly to receive either intravenous DEX sedation throughout the surgery (Group A) or the same volume of normal saline intravenously (Group B) using a computer-generated table of random numbers. The patient’s group allocation was concealed using a sequentially numbered, sealed opaque envelope, which was opened only by a separate investigator who prepared the anesthetic solution before the surgery. The operations were performed by a single experienced surgeon (blinded to the study protocol) using the same technique. Intravenous access was secured before the patient’s arrival in the operating room.

In the operating room, standard monitoring was applied. DEX was diluted with normal saline to obtain a concentration of 4 $\mu g \cdot mL^{-1}$, patients received 1 $\mu g \cdot kg^{-1}$ of intravenous DEX for 10 min as a loading dose, followed by continuous infusion at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ throughout the surgery (Group A), and patients in Group B received the same volume of normal saline. After the infusion of the loading dose, all patients received LAI in the surgical site using 10 ml of 1% lidocaine (Suicheng Industrial, China) and 10 ml of 0.75% ropivacaine (Qilu Industrial, China) by the same surgeon. Intravenous DEX or normal saline administration was stopped at the start of skin closure.

An administration-approved, noninvasive, bioimpedance-based respiratory volume monitor (RVM; ExSpiron, Respiratory Motion, Inc., Waltham, MA) was used to provide real-time respiratory data, including minute ventilation (MV), tidal volume (TV), and respiratory rate (RR). The predicted MV (MV_{PRED}) for nonintubated patients, representing the expected MV during quiet respiration in the awake period, was calculated based on body surface area (BSA) and patient sex. The RVM collected bioimpedance traces via an electrode padset placed in the recommended positions: at the sternal notch, xiphoid, and right midaxillary line at the level of the xiphoid. The electrode padset was applied in a fashion similar to that of standard electrocardiogram electrodes.

Intraoperative hypotension (defined as a >20% decrease in systolic pressure from baseline) was treated with 5-10 mg of intravenous ephedrine; bradycardia (defined as a heart rate <45 beats min^{-1}) was treated with 0.5 mg of intravenous atropine; and respiratory depression (an MV less than 40% of the $MV_{PRED,}$ sustained for a period of 1 minute or longer) was treated with endotracheal intubation for respiratory support.

Measurement Values

Data were recorded as the primary outcomes, including the SpO_2, MV, VT, and RR at the following time points: T_0, baseline; T_1, 10 min after the start of intravenous DEX; T_2, before the skin incision; T_3, after the skin incision; T_4, 30 min after surgery; T_5, at the end of surgery; and T_6, 24 hours after surgery. Venous blood samples were taken at T_0, T_5 and T_6 to detect serum levels of interleukin-6 (IL-6), tumor necrosis factor (TNF-α) by enzyme-linked immunosorbent assay (ELISA), and malondialdehyde (MDA) and glutathione peroxidase (GSH-PX) by colorimetric methods. The patients were asked to assess their level of pain during the procedure using a visual analog scale (VAS), which ranged from 0 (no pain) to 10 (worst possible pain), from T_2 to $T_{5.}$

Statistical Analyses

Statistical analysis was performed using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). Data are expressed as the mean ± standard deviation or the median (interquartile range). Data were analyzed using repeated-measures analysis of variance (ANOVA), and intergroup differences at the same time point were analyzed using a two-sample t test. A $p< 0.05$ was considered to indicate a statistically significant difference.

Results

Initially, a total of 65 patients were enrolled, and 5 patients were excluded after applying the exclusion criteria: 2 patients refused to provide informed consent, and 3 patients had severe hypertension or diabetes. A total of 60 subjects were divided by simple randomization to complete the study and were analyzed (Figure 1). There were no significant differences between the two groups in baseline characteristics (Table 1).

Table 1
Demographic data and surgical data

	Group A(n=30)	**Group B(n=30)**	***P* value**
Gender,M/F	24/6	20/10	0.243
Age, years	71.43±5.55	69.73±6.07	0.262
Intraoperative infusion,ml	1126.67±383.21	1150.00±289.17	0.791
Operation time, min	67.17±12.79	62.53±13.48	0.177
Data are expressed as mean±standard deviation			

Respiratory Variations

To assess the effects of procedural sedation using intravenous DEX on the patients' respiratory drive when patients were placed in the prone position, the respiratory parameters (MV, TV, RR and SpO_2) measured during PELD were analyzed. Figure 2 summarizes the recorded trends in MV, TV, RR and SpO_2, and the variables for MV, TV, RR and SpO_2 showed significant differences over time between the groups (p<0.001). There were no significant differences between the two groups in MV, TV, RR or SpO_2 at any time point (p>0.9999).

Across all 60 patients, we noted a significant decrease in RR from 18.81±1.79 breaths per minute to 16.43±1.069 breaths per minute in Group A compared with 18.81±1.69 breaths per minute to 16.49±4.13 breaths per minute in Group B (p<0.05), and the RR reached the minimum at T_3. Similarly, we measured a significant decrease in TV (from 444.00±39.7 to 417.47±28.38 compared with 447.97±56.7 to 414.97±42.79 ml) and MV (from 8.83±1.45 to 6.70±0.95 compared with 8.84±1.61 to 6.68±0.86 L/min) in Group A and Group B, respectively (p<0.05).

Interestingly, the decrease in MV, TV, and RR was accompanied by a significant compensatory increase in SpO_2 from 97.33±1.09% to 99.30±0.95% in Group A (p<0.05) and 97.27±1.14% to 99.20±0.92% in Group B (p<0.05).

Comparison of VAS

There was no significant difference in the VAS at T_0 between the 2 groups (p>0.05); however, compared with Group B, there were significantly lower VAS from T2-T5 in Group A (p<0.0001) (Table 2).

Table2 **Comparision of VASs**

	Group A(n=30)	Group B(n=30)	*P* value
T_2	2.57±0.86	3.93±0.83**	<0.01
T_3	2.57±0.86	4.50±0.62**	<0.01
T_4	2.43±0.56	5.73±0.87**	<0.01
T_5	3.00±0.83	5.03±0.81**	<0.01

Data are expressed as mean±standard deviation.

*P< 0.05 compared with group A. **P< 0.01 compared with group A.

Serum concentrations of GSH-PX, MDA, IL-6 and TNF-α

There was no significant difference in T_0 (the baseline inflammatory reactions and oxidative stress) between the 2 groups (p > 0.05). Compared with T_0, the levels of GSH-PX, MDA, IL-6 and TNF-α in both groups increased at T_5 and T_6 (p<0.05). Compared with Group B, the levels of GSH-PX in Group A were significantly higher at T_5 and T_6 (p < 0.001) and serum levels of MDA were lower at T_5 and T_6 (p < 0.001). In addition, Group A exhibited lower serum levels of IL-6 (p=0.0033) and TNF-α(p=0.0002) at T_6 than Group B (Figure 3).

No patients required endotracheal intubation for respiratory support, and no cases of MV less than 40% of the MV_{PRED} that were sustained for a period of 1 minute or longer. No patients required atropine for bradycardia or ephedrine for hypotension. No patients suffered cerebrospinal fluid leakage, nerve root injury, intraspinal hematoma, postoperative neuritis or other related complications.

Discussion

This study demonstrated that the effect of DEX administation in non-intubated, spontaneously breathing patients undergoing PELD was safe and effective, although the patients were prone-positioned. Meanwhile, intravenous DEX could alleviate oxidative stress response and inflammatory reactions,which is of great significance for the concept of ERAS.

A novel RVM has been developed to continuously measure and display the MV, TV, and RR to monitor ventilation clinically, and a previous study demonstrated the accuracy of the RVM when compared with ventilators, as well as the accuracy of the RVM when compared to spirometry measurements[9]. DEX is excellent at preserving airway patency and preventing respiratory compromise, but the result was based on SpO_2 instead of MV, emphasizing the need for continuous ventilation monitoring in nonintubated patients[10]. Respiratory parameters were quantified during the administration of midazolam and propofol and the postoperative administration of opioids, but there was a lack of data during the administration of intravenous DEX[11–13]. In our study, we found that compared with T_0, the MV, TV, and RR values of the two groups largerly declined from T_1 to T_4, which may be related to the prone position resulting in chest and abdominal organ compression, impaired diaphragmatic activity and reduced ventilation. Ventilation parameters, including the MV, TV and RR, presented a downward trend but were accompanied by a normal range of $SpO_{2,}$ and we noted that the remarkable improvement in SpO_2 lacked clinical significance.

Respiratory depression was defined as an MV below 40% of the MV_{PRED} for 1 minute or more, the criteria for a low MV (below 40% of the MV_{PRED}) were originally based on the Acute Respiratory Distress Syndrome Network protocol[14], and previous studies have demonstrated that real-time MV measurements can be used to risk-stratify patients in the post-anesthesia care unit (PACU), where patients with an MV less than 80% of their predicted MV prior to opioid administration had reductions to a critical level of less than 40% of the predicted MV after opioid administration[12, 15]. Similarly, we propose that it is feasible to identify the risk, and there were no patients with an MV less than 40% of their MV_{PRED} that was sustained for a period of 1 minute or longer in this study, which reveals that intravenous DEX is less likely to result in respiratory depression when patients are in the prone position.

To the best of our knowledge, this is the first ventilation monitoring study using an RVM to assess the respiratory status of patients receiving intravenous DEX. The advantage of using an RVM is that respiratory data can be monitored stably and reliably without patient discomfort, regardless of their body movements or position.

DEX has been recently used for procedural sedation, and the benefits and risks during PELD remain undetermined. Epidural anesthesia (a low concentration of ropivacaine) and LAI, instead of general anesthesia, were recommended by most surgeons for PELD because the surgeon can still obtain feedback from the patient to avoid nerve injury[16]. Our study demonstrated that no significant difference was found in neurological complications between the two groups, which confirms the safety of DEX. DEX exerts its hypnotic action through the selective activation of central pre- and postsynaptic alpha-2 adrenergic receptors in the locus coeruleus. Akeju et al. assumed that the altered arousal states induced with the administration of DEX neurophysiologically approximate natural sleep, and he termed this “biomimetic sleep”[17]. The pharmacological effect that produces biomimetic sleep makes it suitable for surgeons to obtain feedback from the patient to avoid nerve injury. As the result shown above, the administation of DEX did not increase the risk of cerebrospinal fluid leakage, nerve root injury, intraspinal hematoma, postoperative neuritis or other related complications.

In addition, stress, such as from surgical procedures and intraoperative pain, can cause the release of a large number of inflammatory factors, such as TNF-α and IL-6, further activating neutrophils and monocytes, which can indirectly lead to neurological dysfunction[8]. The level of inflammatory factors in the internal environment can directly reflect the stress state of the organism. When the level of oxidative stress in the body is significantly increased, the body will release a large amount of antioxidant enzymes such as MDA, GSH-PX and catalase. These antioxidant enzymes can resist oxidative stress and prevent the body from being damaged by oxidative stress. This study shows that DEX can markedly attenuated the increases in IL-6, TNF-α and MDA, meanwhile, DEX signifcantly increase the production of GSH-PX. The significant reduction in the VAS in Group A reveals that DEX could provide ideal analgesia during PELD so as to attenuate inflammatory response and pain-induced oxidative stress. DEX can activate the alpha-2 adrenergic receptor and consequently activate cholinergic transmitters to alleviate the inflammatory response; moreover, DEX can reduce the levels of inflammatory factors by inhibiting the activation of the NF-κB/Toll-like receptor signaling pathway, and perioperative dexmedetomidine administration attenuates neurological injury after brain I/R injury, possibly through up-regulation of astrocyte Cx43. [18, 19]

Conclusion

DEX administration prevented the incidence of respiratory depression in the patients who underwent PELD, without serious side effects. It also providse ideal analgesia so as to alleviate oxidative stress and inflammatory reactions. Therefore, we recommend the use DEX in patients undergoing PELD.

Declarations

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Author contributions Reai Shan designed the study and acquired the funding. Xiaoli Zhang and Luying Lai wrote the main manuscript text and Lifang Zhan prepared figures and tables. Wenping Zhao and Cong Sun completed the procedure and Chunlin Xiao completed the surgery. Zhihua Huang detected serum levels of IL-6, TNF-α, MDA and GSH-PX.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This prospective, randomized trial was approved by the Medical Ethics Committee of the First Affiliated Hospital of Gannan Medical University (LLSC-2020121002). Written informed consents were obtained either from the patients or legal representatives.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Initially, a total of 65 patients were enrolled, and 5 patients were excluded after applying the exclusion criteria: 2 patients refused to provide informed consent, and 3 patients had severe hypertension or diabetes. A total of 60 subjects were divided by simple randomization to complete the study and were analyzed

Figure 2

summarizes the recorded trends in MV, TV, RR and SpO_2, and the variables for MV, TV, RR and SpO_2 showed significant differences over time between the groups (p<0.001). There were no significant differences between the two groups in MV, TV, RR or SpO_2 at any time point (p>0.9999).

Figure 3

There was no significant difference in T_0 (the baseline inflammatory reactions and oxidative stress) between the 2 groups ($p > 0.05$). Compared with T_0, the levels of GSH-PX, MDA, IL-6 and TNF-α in both groups increased at T_5 and T_6 (p<0.05). Compared with Group B, the levels of GSH-PX in Group A were significantly higher at T_5 and T_6 ($p < 0.001$) and serum levels of MDA were lower at T_5 and T_6 ($p < 0.001$). In addition, Group A exhibited lower serum levels of IL-6 (p=0.0033) and TNF-α(p=0.0002) at T_6 than Group B