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# Intravenous dexamethasone in pain treatment after video-assisted thoracoscopic surgery

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## ABSTRACT

**INTRODUCTION.** Video-assisted thoracoscopic surgery (VATS) is a minimally invasive procedure. Despite being less invasive than thoracotomy, post-operative pain remains a significant clinical problem. The aim of this study was to investigate if perioperative intravenous (IV) dexamethasone improves pain management in VATS.

**METHODS.** Thirty-seven patients undergoing VATS with confirmed or suspected lung cancer were enrolled. The first 20 patients received standard care (Group 1) and the following 17 patients received standard care with addition of IV dexamethasone 8 mg (Group 2). The primary outcome was total opioid consumption during the first 24 hours after surgery.

**RESULTS.** The baseline characteristics between groups were comparable. After adjusting for gender and duration of surgery, the median difference of total equianalgesic dose of opioid was 23 mg (p = 0.005). Group 2 had a significantly lower median pain score at rest. The first opioid dose was administered earlier in Group 1: 1.5 hours compared with to 6.9 hours in Group 2 (p = 0.020). Time to full mobilisation was longer in Group 1, with a mean of 12 hours (p = 0.018).

**CONCLUSION**. This study suggests that addition of IV dexamethasone in VATS may reduce the need for opioids and facilitate early mobilisation.
**FUNDING.** The study was funded by the Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

**TRIAL REGISTRATION.** The study is registered with ClinicalTrials.gov (NCT04633850). The study was conducted in accordance with the Declaration of Helsinki and all participants provided written consent.

Video-assisted thoracoscopic surgery (VATS) is a minimally invasive technique, routinely performed in lung cancer surgery. A large proportion of VATS patients still experience significant acute post-operative pain [1, 2]. From open thoracotomies, it is known that post-operative thoracic pain may result in a restrictive breathing pattern leading to atelectasis, secretion stagnation, increased pulmonary shunting, hypoxaemia and post-operative pneumonia [3]. Insufficient pain management in VATS is expected to imply the same risks. Post-operative pain management practices vary widely depending on local practice [4, 5].

In other fields of surgery, especially in orthopaedic surgery, it was demonstrated that adding dexamethasone prolongs the duration of the perineural blockades [6, 7]. In VATS, methylprednisolone was shown to have a positive effect on pain [8].

Dexamethasone is frequently used as part of post-operative nausea and vomiting prophylaxis, but procedure-specific evidence regarding its place in analgesia lacks regarding VATS. In the 2021 Procedure-Specific Postoperative Pain Management (PROSPECT) guidelines for VATS, dexamethasone is not recommended [9]; and in the 2018 Enhanced Recovery After Surgery (ERAS) guidelines for VATS, it is recommended based on weak evidence [10].

The primary aim of this exploratory study was to compare post-operative opioid consumption in patients undergoing VATS with and without intravenous dexamethasone in a before-and-after setting. The hypothesis was that perioperative dexamethasone reduces opioid consumption during the first 24 hours after surgery.

## METHODS

The study was conducted in accordance with the Declaration of Helsinki. Written consent was obtained from all participants. Ethical approval was provided by the Ethics Committee of North Denmark Region (N-20200040) and the study was registered with ClinicalTrials.gov (NCT04633850).

### Study design

This prospective before-and-after cohort study was conducted from 1 September 2020 to 10 April 2021 at a single centre. Data were collected prospectively in the control group before the introduction of dexamethasone at the department and in the dexa group after the introduction of dexamethasone.

### Study population

Patients above 18 years of age, scheduled to undergo VATS due to either verified or suspected lung cancer, were recruited at the pre-operative evaluation one to three days before surgery. The exclusion criteria were: inability to understand verbal and written information, any pre-existing chronic pain condition, pre-operative daily treatment with any pain medication, previous thoracic surgery, previous chemotherapy due to thoracic malignancy and/or radiation therapy to the thorax, pregnancy, neuromuscular disease (sclerosis, peripheral neuromuscular disorders), general muscle weakness or atrophy, hypersensitivity, allergy or intolerance to bupivacaine or dexamethasone, pre-operative epidural anaesthesia and conversion to open thoracotomy.

### Study protocol

Tumour resection was performed according to standard oncosurgical practices in lung cancer surgery. Twenty patients were included in the control group and received standard treatment. In the dexa group, standard treatment was changed to include 8 mg of intravenous (IV) dexamethasone, administered at the end of the procedure. After changing the standard treatment, inclusion of 20 patients was planned.

### Anaesthesia

Premedication: paracetamol 1 g. General anaesthesia: induced with remifentanil (0.5-1.5 mg/kg) or fentanyl (2-3 µg/kg), propofol (1-2 mg/kg) and rocuronium (0.6-1.2 µg/kg), maintained with continuous infusion of propofol (4-10 mg/kg/hr) and remifentanil (0.1-1 µg/kg/min.), supplemented by fentanyl to a total dose of 2-5 µg/kg. At the end of surgery, intercostal nerve blocks (ICBs) were internally applied by the surgeon under thoracoscopic guidance. A weight-adjusted dose of bupivacaine (< 50 kg; 2.5 mg/ml, 50-80 kg; 3.75 mg/ml, > 80 kg; 5.0 mg/ml) with a volume of 40 ml (was distributed evenly in the second to ninth intercostal spaces paravertebrally around the intercostal nerve).

### Post-operative observation and pain treatment

Standard post-operative pain management included oral paracetamol 1 g every six hours and oral ibuprofen 800

mg every 12 hours as soon as oral intake was possible. If not contraindicated, IV ketorolac 15-30 mg was administered at the end of surgery or in the PACU. Supplemental pain management was administered as IV morphine 2.5-10 mg (or equivalent doses of other opioids) pro re nata (PRN) following institution standards (reported resting numerical rating scale (NRS) ≥ 4). Prior to study commencement, we audited the ward staff to secure uniform and correct compliance with these guidelines. Patients are routinely instructed to notify the ward staff about pain.

**Outcomes**

The primary outcome measure was total opioid dose during the first post-operative day (administered from arrival at the recovery unit to 24 hours later).

The secondary outcome was number of hours between end of surgery and first post-operative administration of opioids NRS, number of hours between end of surgery and time for full mobilisation (walking with support). All patients are routinely informed about the importance of early mobilisation.

Pain intensity was measured on a NRS ranging 0-10, with 0 being 'no pain' and 10 'worst imaginable pain'. Post-operative NRS at rest, when coughing, and during mobilisation was recorded on a designated form by the nursing staff twice daily for the first two post-operative days.

**Data collection**

The patients' baseline data were collected. Normal kidney function was defined as an estimated glomerular filtration rate (eGFR) > 60 ml/min./1.73 $m^2$ and kidney failure was defined as an eGFR < 60 ml/min./1.73 $m^2$ and classified as mild (eGFR < 60 ml/min./1.73 $m^2$), severe (eGFR < 30 ml/min./1.73 $m^2$) or very severe (eGFR < 15 ml/min./1.73 $m^2$).

Perioperative data were obtained from the anaesthesia records as follows: total dose of bupivacaine used for the blockade, operation time and total dose of intraoperative fentanyl.

Post-operative administration of medication was obtained from patient records. All opioid doses were converted into equianalgesic doses of milligrams oral morphine (oral morphine μg equivalents (MME)). The drugs were converted with the following coefficients: IV fentanyl (1 μg = 0.2 MME), IV morphine (1 mg = 3 MME) and oral tramadol (1 mg = 0.2 MME) as recommended by Nielsen et al. [11].

Furthermore, time until removal of chest tube, length of hospitalisation and pain medication at discharge were recorded. Post-operative complications were registered from patient records after discharge. Data were recorded in the REDCap of the North Denmark Region.

**Sample size estimation**

Expecting that addition of adjuvants to the ICB would reduce mean ± standard deviation (SD) opioid consumption (equipotent dose) in the first post-operative day from 20 ± 10 to 10 ± 10 MME with a significance level of $\alpha = 0.05$ and a power of $\beta = 0.8$, a total of 32 test subjects equally allocated to control and intervention group needed to be included. To account for a drop-out rate of approximately 15-20%, 40 patients were planned for inclusion.

**Statistical analysis**

Normality was examined by histograms and QQ plots. Normally distributed data were compared by Student's t-test and reported as mean (± SD). Non-normally distributed data were compared by the Wilcoxon rank-sum test and reported as median (interquartile range (IQR)). A p value < 0.05 was considered statistically significant.

Time to first opioid administration and time to mobilisation were analysed using log-rank test and illustrated with Kaplan-Meier failure plot.

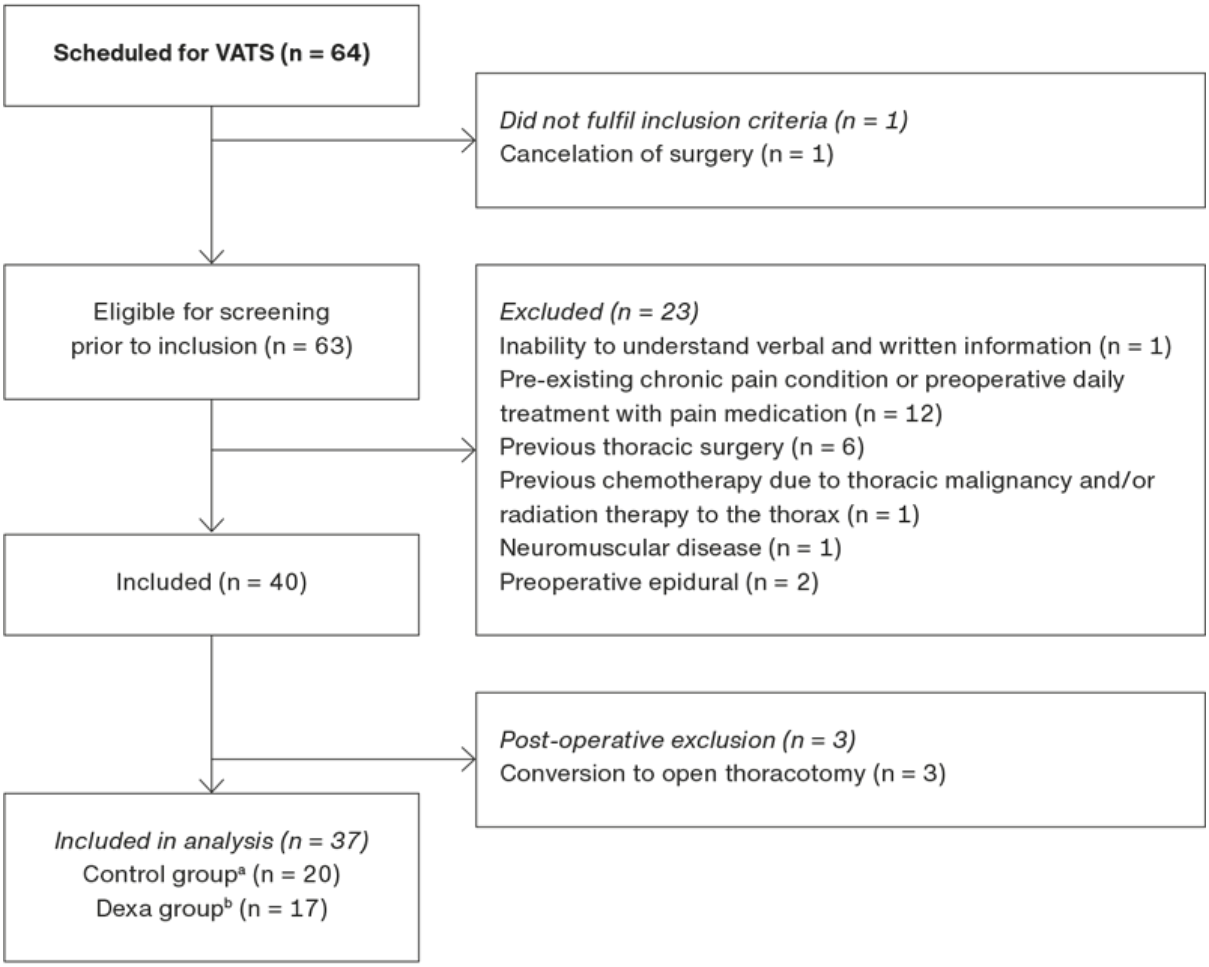
Analyses were performed with either R 4.3.1 (R core team) or Stata 16.0 (StataCorp LLC).

*Trial registration:* The study is registered with ClinicalTrials.gov (NCT04633850). The study was conducted in accordance with the Declaration of Helsinki and written consent from all participants was obtained.

## RESULTS

A total of 64 patients eligible for inclusion were identified during the study period. Forty patients were included. Exclusions and loss to follow-up are presented in **Figure 1**. Three patients were excluded after surgery due to conversion to open thoracotomy. These patients were not replaced by new inclusions. Therefore, the total number of patients in the study was 37.

**FIGURE 1** Study flow chart.




VATS = video-assisted thoracoscopic surgery.
a) Standard care.
b) Standard and dexamethasone treatment.

Baseline characteristics including anaesthesia and surgical data are listed in **Table 1.**

**TABLE 1** Baseline data for video-assisted thoracoscopic surgery patients (N = 37).

| | Control group[a] ($n_c$ = 20) | Dexa group[b] ($n_d$ = 17) |
|---|---|---|
| Age, mean (± SD), yrs | 71.5 (± 8.0) | 65. 1 (± 17.8) |
| Gender: male/female, n (%) | 9 (45)/11 (55) | 5 (29.4)/12 (70.6) |
| BMI, mean (± SD), kg/m² | 26.2 (± 4.8) | 29.2 (± 5.9) |
| ASA score: 2/3/4, n (%) | 10 (50)/9 (45)/1 (5) | 5 (29.4)/12 (70.6)/0 |
| Duration of surgery, mean (± SD), min. | 137 (± 41.6) | 100.6 (± 52.0) |
| *Laterality, n (%)* | | |
| Left | 9 (45) | 10 (58.8) |
| Right | 11 (55) | 7 (41.2) |
| *Type of resection, n (%)* | | |
| Lobectomy | 8 (40) | 7 (41.2) |
| Segmental resection | 2 (10) | 0 |
| Wedge resection | 10 (50) | 10 (58.8) |
| Bilobectomy | 0 | 0 |
| Diabetes: yes/no, n (%) | 1 (5) | 2 (11.8) |
| Affected liver function: yes/no, n (%) | 0 (0)/20 (100) | 0 (0)/17 (100) |
| *Kidney failure[c], n (%)* | | |
| Normal function | 16 (80) | 13 (76.5) |
| Mild failure | 4 (20) | 3 (17.7) |
| Moderate failure | 0 | 1 (5.9) |
| Severe failure | 0 | 0 |
| Perioperative fentanyl, mean (± SD), µg | 335 (± 111.3) | 300 (± 96.8) |
| Perioperative ketorolac: yes/no, n (%) | 9 (45)/11 (55) | 11 (64.7)/6 (35.3) |
| Time to drain removal, median (IQR), hrs | 23.8 (21.8-48.1) | 46.5 (22.3-70.9) |
| Patients with ≥ 1 complications, n (%) | 6 (30) | 2 (11.85.9) |
| Bupivacaine dose, median (IQR), mg | 145 (130-160) | 150 (134-166) |

ASA = American Society of Anesthesiologists; eGFR = estimated glomerular filtration rate; IQR = interquartile range; SD = standard deviation.
a) Standard care.
b) Standard and dexamethasone treatment.
c) Assessed by eGFR.

The median opioid dose was 30 (IQR: 22-48.1) MME in the control group receiving standard treatment before transition to adjuvant dexamethasone and 10 (IQR: 5-35) MME in the dexa group receiving adjuvant dexamethasone (p = 0.039) (**Table 2**). After adjusting for gender and duration of surgery, the total median opioid dose was 23 MME higher in the control group (95% confidence interval (CI): 4-42; p = 0.017).

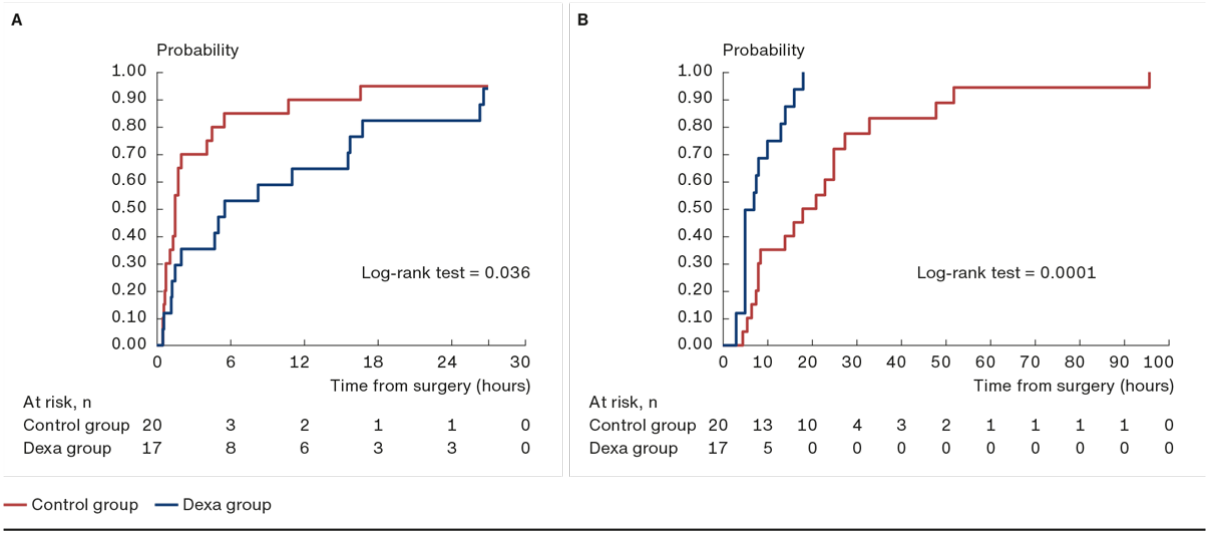
**TABLE 2** Results for video-assisted thoracoscopic surgery patients (N = 37).

| | Control group[a] ($n_c$ = 20) | Dexa group[b] ($n_d$ = 17) | p value |
|---|---|---|---|
| Opioid use 1st post-operative day, median (IQR), MME | 30 (21-48.1) | 10 (5-35) | 0.039 |
| *Pain intensity, NRS [0-10]* | | | |
| 1st post-operative day, evening: | | | |
| At rest, median (IQR) | 3 (0-5.25) | 0 (0-2) | 0.014 |
| During coughing, median (IQR) | 3.5 (2.25-5.5) | 2 (1.5-3) | 0.103 |
| During mobilization, mean (± SD) | 3.5 (± 2.1) | 2.7 (± 3.1) | 0.600 |
| 2nd post-operative day, morning: | | | |
| At rest, median (IQR) | 2.5 (1-4.25) | 2 (0.5-3.5) | 0.727 |
| During coughing, median (IQR) | 5.9 (3.1) | 4.5 (2.8) | 0.260 |
| During mobilization, mean (± SD) | 3.9 (± 2.7) | 3.5 (± 3.2) | 0.751 |
| Time to 1st opioid administration, median (IQR), hrs | 1.5 (0.8-4.2) | 5.5 (1.5-15.7) | 0.41 |
| Time for full mobilization, median (IQR), hrs | 19.5 (8-25.6) | 5 (5-10) | < 0.001 |
| Length of stay, median (IQR), days | 2 (1-4.2) | 2 (2-4) | 0.706 |

MME = morphine µg equivalents; NRS = numerical rate scale; SD = standard deviation.
a) Standard care.
b) Standard and dexamethasone treatment.

Time to first PRN opioid administration was significantly longer in the dexa group (1.5 (IQR: 0.8-4.1) hours) than in the control group (6.9 (IQR: 1.6-16.2) hours); p = 0.020. One patient in each group did not receive post-operative opioids during their hospitalisation. The time to first administration of opioid is illustrated in **Figure 2** A.

**FIGURE 2** The control group received standard care and the dexa group received standard care with dexamethasone treatment. **A**. Kaplan-Meier failure plot representing time to first opioid administration (hours). One patient in each group did not receive post-operative opioids during hospitalisation. **B**. Kaplan-Meier failure plot representing time to mobilisation (hours).



Adjusted for gender and duration of surgery, time to full mobilisation was ten hours longer in the control than in the dexa group (95% CI: 1.7-17.4 hours; p = 0.019). The Kaplan-Meier failure analysis of the time to mobilisation is shown in Figure 2 B. The only significant difference in NRS was at rest on the first post-operative evening (Table 2).

Six patients in the control group experienced post-operative complications, of whom one experienced more than one of following complications: post-operative bleeding (n = 1), pneumothorax after chest tube removal (n = 2), atelectasis (n = 1), subcutaneous emphysema (n = 1), reoperation (n = 1), air leakage (n = 2) or hypotension (n = 1). One patient in the dexa group experienced air leakage and one patient experienced air leakage, reoperation, and empyema as post-operative complications.

## DISCUSSION

The findings of this study suggest that adding IV dexamethasone intraoperatively may reduce opioid requirements on the first post-operative day and prolong the time to first opioid administration in lung cancer patients undergoing VATS. Furthermore, time to full mobilisation was reduced in patients receiving dexamethasone. NRS pain intensity did not differ significantly between the groups.

Optimal post-operative pain management encompasses multiple advantages as the risk of post-operative complications is decreased [3]. The reduction of total opioid dose and the postponement of supplemental opioid administration potentially provide multiple benefits to patients by reducing opioid-related adverse effects. Early mobilisation, maybe as a result of dexamethasone alone, may be owed to fewer opioid-related effects and may also decrease postsurgical complications [12, 13]. This exploratory study was not powered to investigate differences in the incidence of post-operative complications but demonstrated that patients who received dexamethasone received less opioids and were mobilised earlier with no increase in post-operative pain intensity. This indicates that both groups were sufficiently treated, when in pain, and that delayed mobilisation was not caused by pain itself in the control group [14].

The 8 mg dexamethasone dose was chosen since this dose is used as the standard protocol in other patient groups in our centre. Furthermore, literature on mixed nonthoracic surgical fields suggested that doses from 0.1 mg/kg are more efficient in reducing pain scores and opioid use than lower doses [15, 16]. Higher doses may improve pain control even more but should be tested in a randomised controlled study.

We chose to administer dexamethasone intravenously since the product lacks approval for perineural use. Maher et al. [17] showed that a combination of perineural and systemic steroids increased the duration of ICB analgesia and decreased post-operative opioid consumption after VATS; and also suggested that increasing the dose of dexamethasone by the same administration route failed to improve the analgesic effect [18].

We found a shorter time to mobilisation after administering dexamethasone. This corresponds well with previous studies, demonstrating that dexamethasone may in general decrease not only pain but also nausea and fatigue, and possibly also reduce sedation and sleep disturbances [8].

This study did not detect any adverse effects to dexamethasone.

### Study limitations

This was a small single-centre before-and-after study, and the treatment was neither randomised nor blinded. With the unblinded nature of the study, the number of complications, probably unrelated to the pain management, was higher in the control group. This skew may potentially bias the results, leading to a longer time to mobilisation in the control group.

The study examined the combined effect of IV dexamethasone and ICB in a VATS population. The design did not distinguish if dexamethasone affects the intercostal blockade itself but only in combination with ICB. Studies in orthopaedic surgery have established that dexamethasone has a direct effect on the blockade itself [6, 18].

Furthermore, suspected adverse events and change of protocol led to a two-month interval between the control and dexa group, which may reflect a slight change in routines. Though no formal change was made to routines in the study period, efforts towards mobilisation at the stationary ward could have changed during the study period without our knowledge. Naturally, as this was a before-and-after study, we were unable to control for this.

## CONCLUSION

This study suggests that addition of IV dexamethasone in VATS with ICB may reduce the need for opioids, prolong the time to first opioid request and facilitate early mobilisation. Improving these outcomes carries the potential to improve patient satisfaction and post-operative pain management. Future larger scale trials are necessary to determine the possible beneficial effects of dexamethasone on perioperative pain management and impact on post-operative complications after VATS.

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**Conflicts of interest** none. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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**References** can be found with the article at ugeskriftet.dk/dmj

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## REFERENCES

1. Sun K, Liu D, Chen J et al. Moderate-severe postoperative pain in patients undergoing video-assisted thoracoscopic surgery: a retrospective study. Sci Rep. 2020;10(1):795.
2. McKenna RJ, Houck W, Fuller CB. Video-assisted thoracic surgery lobectomy: experience with 1,100 cases. Ann Thorac Surg. 2006;81(2):421-5, discussion 425-6.
3. Wenk M, Schug SA. Perioperative pain management after thoracotomy. Curr Opin Anaesthesiol. 2011;24(1):8-12.
4. Piccioni F, Segat M, Falini S et al. Enhanced recovery pathways in thoracic surgery from Italian VATS group: perioperative analgesia protocols. J Thorac Dis. 2018;10(suppl 4):S555-S563.
5. Steinthorsdottir KJ, Wildgaard L, Hansen HJ et al. Regional analgesia for video-assisted thoracic surgery: a systematic review. Eur J Cardiothorac Surg. 2014;45(6):959-66.
6. De Oliveira GS, Alves LJC, Nader A et al. Perineural dexamethasone to improve postoperative analgesia with peripheral nerve blocks: a meta-analysis of randomized controlled trials. Pain Res Treat. 2014;179029.
7. Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. Anaesthesia. 2015;70(1):71-83.
8. Bjerregaard LS, Jensen PF, Bigler DR et al. High-dose methylprednisolone in video-assisted thoracoscopic surgery lobectomy:

a randomized controlled trial. Eur J Cardiothorac Surg. 2018;53(1):209-15.

9. Feray S, Lubach J, Joshi GP et al. PROSPECT guidelines for video-assisted thoracoscopic surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 2021;77(3):311-25. doi: 10.1111/anae.15609.
10. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery after Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019;55(1):91-115.
11. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf. 2016;25(6):733-7. doi: 10.1002/pds.3945.
12. Das-Neves-Pereira JC, Bagan P, Coimbra-Israel AP et al. Fast-track rehabilitation for lung cancer lobectomy: a five-year experience. Eur J Cardiothorac Surg. 2009;36(2):383-91, discussion 391-2.
13. Kalisch BJ, Lee S, Dabney BW. Outcomes of inpatient mobilization: a literature review. J Clin Nurs. 2014;23(11-12):1486-501.
14. Fang J, Shi Y, Du F et al. The effect of perineural dexamethasone on rebound pain after ropivacaine single-injection nerve block: a randomized controlled trial. BMC Anesthesiol. 2021;21(1):47.
15. De Oliveira GS, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115(3):575-88.
16. Moore SG. Intravenous dexamethasone as an analgesic: a literature review. AANA J. 2018;86(6):488-93.
17. Hersini KJ, Andreasen JJ, Gazerani P et al. Prevalence, characteristics and impact of the post-thoracotomy pain syndrome on quality of life: a cross-sectional study. J Pain Relief. 2015;4(5):1000201.
18. Maher DP, Serna-Gallegos D, Mardirosian R et al. The combination of IV and perineural dexamethasone prolongs the analgesic duration of intercostal nerve blocks compared with IV dexamethasone alone. Pain Med. 2017;18(6):1152-60.

 