DANISH MEDICAL JOURNAL

Original Article

Immunological effects of post-operative epidural analgesia versus oral opioids in VATS

Jimmy Højberg Holm[1], Claus Andersen[1], Peter B. Licht[2], Palle Toft[1], Floor D. Zegers[3], Kate L. Lambertsen[4, 5, 6] & Anne C. Brøchner[7, 8]

1) Department of Anesthesiology and Intensive Care, Odense University Hospital, 2) Department of Cardiothoracic Surgery, Odense University Hospital, 3) Center for Clinical Epidemiology, Research Unit of Clinical Epidemiology, University of Southern Denmark, 4) Department of Neurobiology Research, Institute of Molecular Medicine, University of Southern Denmark, 5) Department of Neurology, Odense University Hospital, Odense, 6) Brain Research-Inter-Disciplinary Guided Excellence (BRIDGE), Department of Clinical Research, University of Southern Denmark, 7) Department of Regional Health Research, University of Southern Denmark, 8) Department of Anesthesiology and Intensive Care Medicine, Odense University Hospital – Kolding Hospital, Denmark

Dan Med J 2024;71(10):A09230582. doi: 10.61409/A09230582

ABSTRACT

INTRODUCTION. Anaesthetic choices in cancer surgery, including the use of epidural analgesia, may affect immune function during the perioperative period and might play an important role in subsequent cancer spread and recurrence.

METHODS. This was a prospective, randomised, controlled, double-blinded, single-centre study allocating patients scheduled for video-assisted thoracoscopic surgery (VATS) lobectomy to post-operative pain management using either thoracic epidural analgesia or oral morphine. We compared pre-, per-, and post-operative plasma levels of interleukin (IL)-6, IL-10, IL-12, and interferon (IFN)-γ using regression analysis, and conducted a two-year survival follow-up.

RESULTS. A total of 66 patients were randomised. Fifty-six received the allocated treatment and were analysed. None of the investigated cytokines exhibited significant between-group differences in plasma concentrations when adjusted for the chosen covariates ($p \geq 0.204$). A two-year follow-up showed no difference in survival between the two groups ($p = 0.5$).

CONCLUSION. Our study found no differences in the impact on the innate, non-specific immune system related to epidural analgesia for pain management in VATS.

FUNDING. The Danish Cancer Society (R150-A10139). Oberstinde Kirsten Jensa la Cours Mindelegat (JSP-25076). University of Southern Denmark, Region of Southern Denmark and Department of Anaesthesia and Intensive Care, Odense University Hospital.

TRIAL REGISTRATION. NCT02359175 (ClinicalTrials.gov).

Surgery remains the primary treatment for many malignant tumours. However, some primary cancer cells may persist after surgery, and tumours might dislodge and spread via the lymphovascular system. Whether these cells proliferate or lead to metastases is generally believed to depend on the balance between tumour aggressiveness and the body's capability to suppress the tumour load [1]. Surgery and trauma induce immunosuppression by an initial pro-inflammatory immune response mediated primarily by the cells of the innate immune system, followed by a compensatory anti-inflammatory reaction mainly by the adaptive immune system, restoring homeostasis [2]. Studies suggest that the anaesthetics and the adjuvants used in the

perioperative period may possibly affect cancer recurrence and survival [3]. Though some argue that it remains speculative whether any aspects of anaesthetic management influence cancer outcomes [4], a reasonable prerequisite would be that a detectable impact on the immune system is present. In the present study, we investigated the effect of epidural analgesia on the innate, non-specific immune system in patients undergoing videoscopic surgery for lung cancer by examining selected cytokines and post-operative survival, testing the hypothesis that epidural analgesia may attenuate post-operative immunosuppression.

METHODS

Study design and participants

We performed a patient- and observer-blinded, parallel-arm, randomised controlled trial at a single cardiothoracic anaesthesia and surgery department in a tertiary care hospital in Denmark, examining various aspects of using supplementary epidural analgesia in video-assisted thoracoscopic surgery (VATS) for lung cancer (ClinicalTrials NCT02359175). This trial was an adjunct trial focusing on the immunological aspects of epidural anaesthesia. Patients scheduled for elective VATS lobectomy were eligible for trial participation and screened for inclusion. If the inclusion criteria were met, we obtained written informed consent and enrolled the patient. The exclusion criteria were age < 18 years, pregnancy, contraindications to epidural catheter insertion, pre-existing other cancers or immunodeficiency, previous thoracic surgery or daily use of analgesics. We used a two-arm treatment design, with one group receiving thoracic epidural analgesia for post-operative pain management (TE Group). In contrast, the other received oral morphine (OM Group). Both groups received blinded baseline analgesics. Baseline medication, administered as premedication before surgery and at fixed predefined intervals after surgery, comprised oral acetaminophen (1 g), ibuprofen (400 mg) and placebo in the TE Group, while the OM Group received acetaminophen, ibuprofen and morphine (10 mg). Both groups received identical intraoperative pain management regimes that were replaced post-operatively with the allocated epidural infusion of either bupivacaine 1.0 mg/ml with fentanyl 2.0 µg/ml (TE Group) or saline (OM Group).

The trial study was approved by The Regional Scientific Ethical Committees for Southern Denmark, The Danish Health and Medicines Authority, and The Danish Data Protection Agency. The trial protocol and dataset are available upon request.

Randomisation and masking

According to a computer-generated randomisation list, the hospital pharmacy provided similar, consecutively numbered pre-packed boxes with the study medication. The list was generated from a validated source using block randomisation with blocks of four and a treatment-to-placebo allocation of 1:1 without stratification.

Study procedures

All participating patients were seen before surgery to assess operability and get an immunological baseline blood sample. The study procedure has been described in detail previously [5]. In short, after epidural catheter insertion and test of function, we allocated patients using a consecutive randomisation number and administered premedication. General anaesthesia was induced and maintained using propofol and remifentanil in conjunction with an epidural infusion of bupivacaine (2.5 mg/ml) containing sufentanil (1.0 µg/ml) at the anaesthetist's discretion. Surgery was performed as a strictly monitor-based, non-rib-spreading procedure. After surgery, patients went to the post-anaesthesia care unit (PACU), where the ward nurse replaced the perioperatively used standard epidural medication with a blinded project infusion comprising either active medication or saline. When fully awake, patients were transferred to the surgical ward, continuing epidural infusion and baseline analgesics until the trial concluded. Post-operative pain assessment and treatment were

ensured under the department's usual standard of care, using numeric rating scale scores with on-demand intravenous "rescue" morphine available to all patients. The trial ended after blood sampling in the morning on the first post-operative day. At that time, post-operative epidural analgesia was changed from study medication to our normally used medication and continued until the concurrent removal of the chest drain and epidural catheter as per our department's standard of care. After surgery, we performed follow-ups using the electronic patient chart, registering the cancer stage two weeks after surgery and post-operative survival two years after discharge.

Blood sampling, storage and analysis

We obtained venous blood samples at four time points. A baseline sample (T0) was obtained at least one day before surgery. A second sample was obtained when the surgeon stapled the pulmonary artery during surgery (T1). The third blood sample was drawn immediately upon arrival at the PACU (T2), and the final sample was obtained in the surgical ward on the first post-operative morning (T3). Blood sample storage, processing and cytokine measurements were done as described previously by Nielsen et al. [6] using electrochemiluminescence V-PLEX Custom Human Biomarker immunoassays (Mesoscale, Rockville, USA).

Endpoints

The primary outcome was changes in plasma levels of NK cells. The secondary outcomes were changes in NK cell activity, changes in plasma levels of interleukin (IL)-6, IL-10, IL-12, and interferon (IFN)-γ, the registered cancer stage and patient survival during the two-year follow-up period after surgery.

Statistical analyses

Studies on similar populations using comparable outcomes have found significant differences in the inflammatory parameters measured using sample sizes ranging from 20 to 57 patients [7, 8]. Using a pragmatic approach, we based our sample size on these studies and, placing ourselves in the upper range, decided on a minimum sample size of 28 patients in each group, a total of 56.

The participants' baseline demographics and trial data are presented as frequencies and percentages or as means and standard deviations (SDs). The cytokine level measurements were analysed using linear mixed models with and without the duration of the surgical procedure and the cancer stage as covariates, both including and excluding interaction effects between treatment groups and time. We evaluated the normality assumptions visually using the models' residuals. We used a log-rank test to examine whether a significant survival difference existed between the two treatment groups. All statistical analyses were done without imputation using Stata/BE 17.0 (StataCorp LLC, College Station, Texas, USA) software, and two-sided p-values below 0.05 were considered statistically significant.

Trial registration: NCT02359175 (ClinicalTrials.gov).

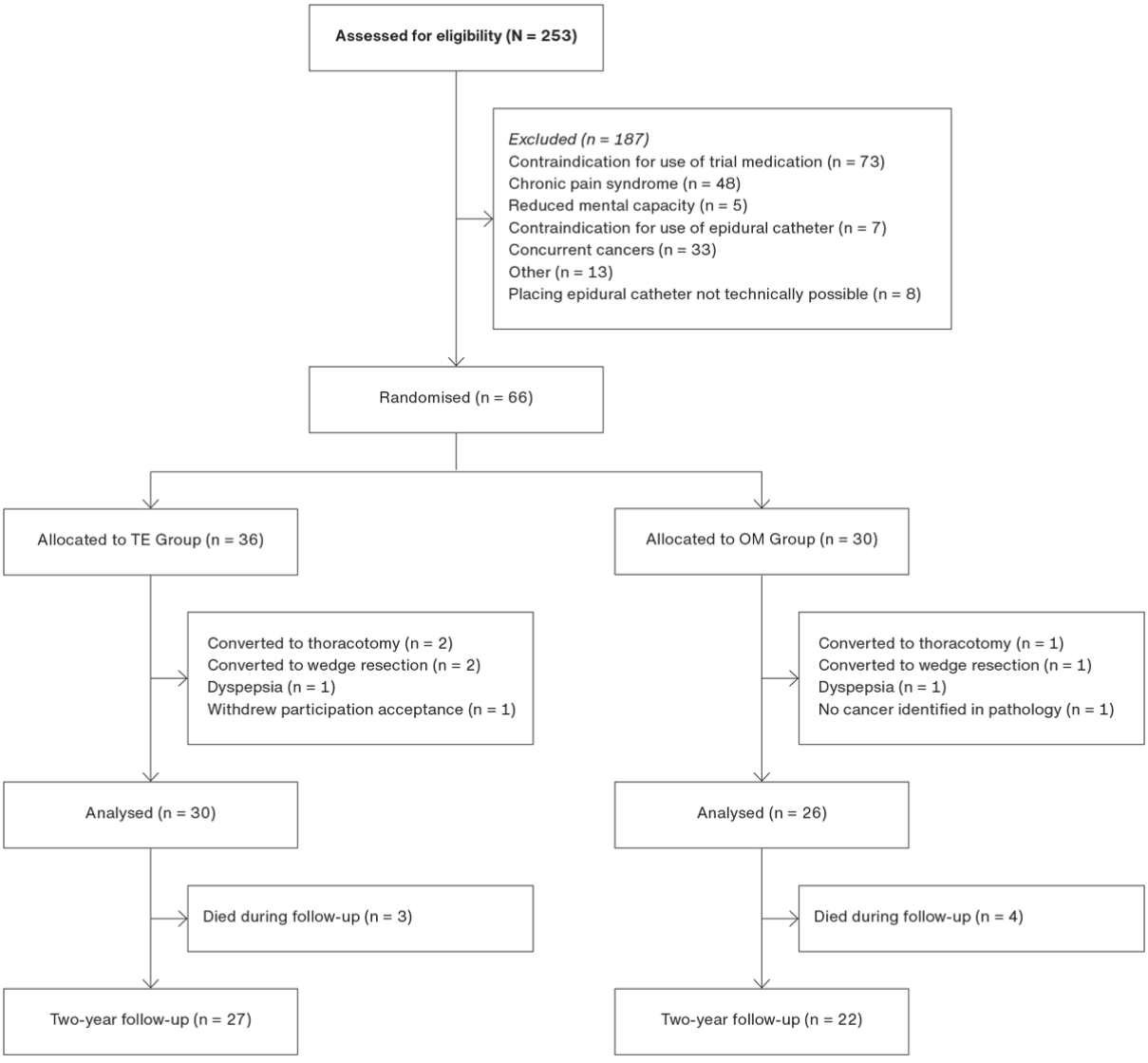
RESULTS

Patient flow

Patients were consecutively included from 17 January 2017 to 11 January 2019. The last patient was discharged from the hospital on 24 January 2019, thus concluding the two-year follow-up on 24 January 2021. As shown in **Figure 1**, we screened 253 scheduled VATS lobectomy patients and excluded 187 patients following the predefined criteria, leaving 66 for trial randomisation. Ten patients were excluded after inclusion, leaving 56 patients for the final analyses. Among these, 49 were alive at the two-year follow-up. The baseline patient characteristics and trial data are shown in **Table 1**. The patients' demographics and baseline data were

comparable in the randomised groups, except for the American Society of Anesthesiologists (ASA) classifications and the Lung Cancer Stage Grouping, which were somewhat skewed. We examined experienced pain in the two treatment groups using the same definitions as in a previous publication. We found no statistically significant difference in experienced pain, either at rest ($p > 0.05$) or during activity ($p > 0.06$) [5]. The measured plasma levels of IL-6, IL-10, IL-12 and IFN-γ are aggregated in **Figure 2**. Summary statistics and levels of missing values are shown in the Supplementary File. The regression analyses of plasma cytokine levels are presented in **Table 2**. None of the examined cytokines exhibited significant differences in plasma concentrations between the two treatment groups when adjusted for time of blood sampling, $p \geq 0.204$. However, cytokine levels varied significantly over time for all the examined interleukins. Three patients in the TE Group and four in the OM Group died during the two-year follow-up after surgery. The log-rank test showed no significant difference in survival between the two treatment groups ($p = 0.5$). The trial concluded with no patients experiencing serious adverse events or reactions.

FIGURE 1 Participant flow.



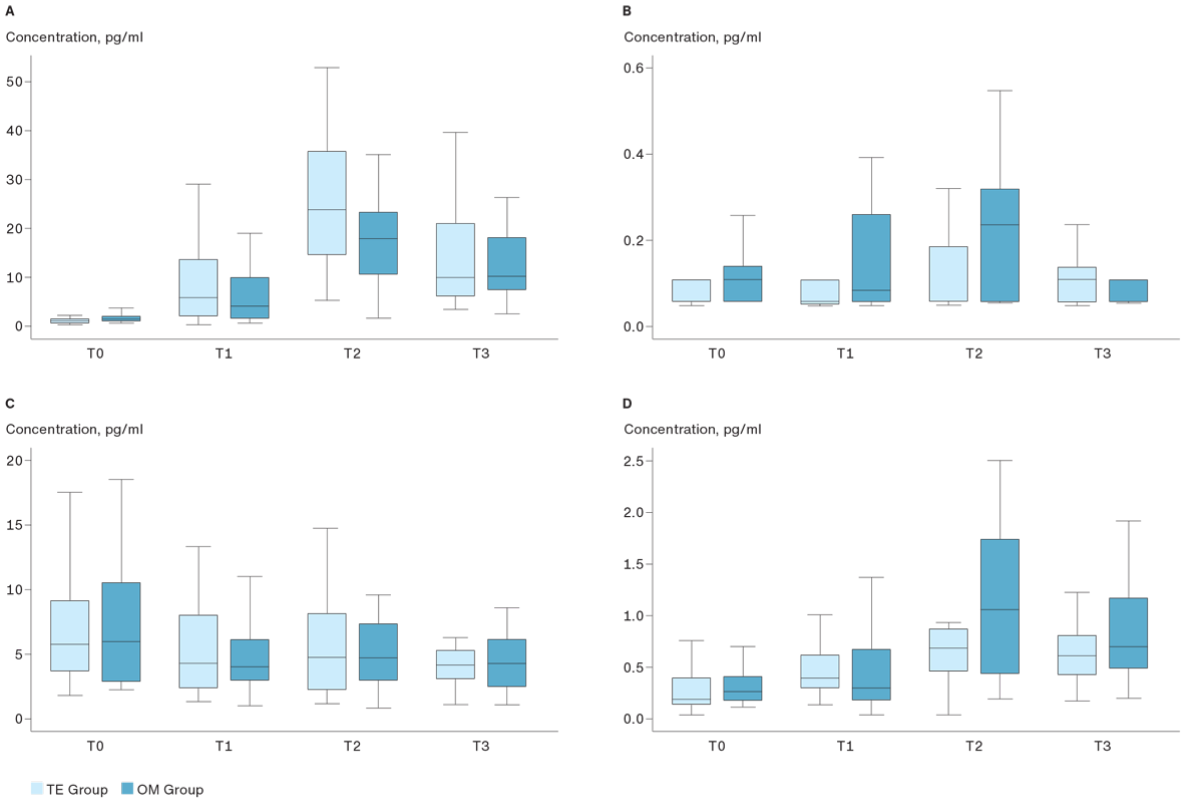
OM = oral morphine; TE = thoracic epidural.

TABLE 1 Baseline characteristics and trial data. Patient demographics and data of the trial patients, by randomisation group.

	TE Group (N_{TE} = 30)	OM Group (N_{OM} = 26)
Baseline demographics[a]		
Males, n (%)	14 (47)	13 (50)
Age, mean (± SD), yrs	68.3 (± 8.1)	70.3 (± 8.3)
Height, mean (± SD), cm	172 (± 9)	170 (± 10)
Weight, mean (± SD), kg	76.3 (± 16.0)	78.1 (± 11.7)
Smoking, n (%):		
History of	28 (97)	21 (95)
Active	8 (28)	9 (43)
ASA classification, n (%):		
ASA I	0	13 (50)
ASA II	20 (67)	5 (19)
ASA III	10 (33)	8 (31)
Anaesthetics and opioids, mean (± SD)		
Perioperative consumption:		
Propofol, mg	1,108 (± 535)	1,267 (± 701)
Remifentanil, µg	2,108 (± 973)	2,302 (± 733)
Fentanyl, µg	41 (± 72)	79 (± 78)
Epidural sufentanil, µg	16 (± 8)	15 (± 3)
Rescue morphine consumption, IV, mg	6 (± 9)	10 (± 16)
Fentanyl consumption, epidural, µg	284 (± 35)	0
Morphine consumption, enteral, mg	0	35 (± 6)
Surgical data		
Duration of surgery, mean (± SD), min.	96 (± 30)	102 (± 28)
Surgical ports, n (%)[b]:		
1	1 (4)	1 (4)
2	4 (14)	5 (19)
3	24 (83)	20 (77)
Perioperative data, n (%)		
Lung cancer stage grouping[c]:		
I	19 (63)	11 (42)
II	6 (20)	14 (54)
III	4 (13)	1 (4)
IV	1 (3)	0
Blood transfusion	0	1 (4)
Died during the 2-year follow-up	3 (10)	4 (15)
Laboratory data, mean time (± SD), min.		
Between samples: OP → PACU	97 (± 28)	106 (± 32)
Between samples: PACU → surgical ward	1,377 (± 99)	1,350 (± 104)

ASA = American Society of Anesthesiologists; IV = intravenously; OM = oral morphine; OP = operation; PACU = post-anaesthesia care unit; SD = standard deviation; TE = thoracic epidural.
a) Homogeneity testing of baseline values has been omitted, as recommended in the CONSORT 2010 Statement.
b) 1 patient in the TE Group had no registration of the number of surgical ports.
c) Cancer stage grouping is according to the 8th ed. of the TNM Classification for Lung Cancer.

FIGURE 2 Calculated plasma concentrations of the cytokines IL-6 (**A**), IL-12 (**B**), IFN-γ (**C**), and IL-10 (**D**). Box-and-whisker plots showing the calculated concentrations (pg/ml) of plasma cytokines pre-, per-, and post-operatively in the two treatment groups. The boxes are medians and 25th/75th percentiles. Whiskers represent 2.5th/97.5th percentiles. Outliers have been omitted in the plot for clarity.



IFN = interferon; IL = interleukin; OM = oral morphine; T0 = preoperatively; T1 = perioperatively; T2 = post-anaesthesia care unit; T3 = surgical ward; TE = thoracic epidural.

TABLE 2 Regression analyses of cytokine levels.

Cytokine	Coefficient[a] (95% CI)	SE	p value
IL-6			
OM Group	−3.85 (−9.80-2.09)	± 3.03	0.204
Time:			
T1	6.73 (0.88-12.59)	± 2.99	0.024
T2	22.45 (16.64-28.72)	± 2.97	< 0.001
T3	15.63 (9.81-21.45)	± 2.97	< 0.001
IL-12			
OM Group	0.02 (−0.05-0.10)	± 0.04	0.520
Time:			
T1	0.02 (−0.04-0.08)	± 0.03	0.524
T2	0.07 (0.01-0.13)	± 0.03	0.034
T3	0.05 (−0.01-0.11)	± 0.03	0.078
IFN-γ			
OM Group	−0.31 (−3.83-3.22)	± 1.80	0.865
Time:			
T1	−2.15 (−3.99-−0.30)	± 0.94	0.023
T2	−2.70 (−4.54-−0.86)	± 0.94	0.004
T3	−3.09 (−4.94-−1.24)	± 0.94	0.001
IL-10			
OM Group	0.31 (−0.52-1.15)	± 0.43	0.465
Time:			
T1	0.28 (−0.62-1.18)	± 0.46	0.544
T2	1.65 (0.76-2.53)	± 0.45	< 0.001
T3	0.50 (−0.39-1.38)	± 0.45	0.528

CI = confidence interval; IFN = interferon; IL = interleukin; OM = oral morphine; SE = standard error; T0 = preoperatively; T1 = perioperatively; T2 = post-anaesthesia care unit; T3 = surgical ward.
a) Time: T0 is baseline.

DISCUSSION

This study found no difference in post-operative immunological markers or mortality in patients having VATS, regardless of whether the post-operative analgesic regimen comprised central neural blockade or oral morphine. IL-6 and IL-10 followed the expected course with a significant rise during and immediately after surgery. This was followed by a reduction towards the preoperative levels of the pro-inflammatory IL-6 and a post-operative increase in the anti-inflammatory IL-10 [9]. Plasma levels of IL-12 increased after surgery, reaching statistically significant elevations at T2. These findings run contrary to most previous results showing

IL-12 depression after major vascular surgery [10], cardiac surgery [11] and orthopaedic surgery [10]. The post-operative reduction in the pro-inflammatory IFN-γ observed in our study aligns with what has been reported in other studies [12], including thoracic surgery [11].

We observed no between-group differences in any of the measured cytokines, showing no or only a minimal effect of epidural analgesia on post-operative cytokine levels in our setup. Previous studies have indicated an attenuating effect on post-operative immunosuppression when using epidural analgesia in both open and videoscopic surgery [13-15]. A 2017 trial on VATS lobectomies found an attenuating effect on the post-operative levels of IL-6 and INF-γ [16]. More recently, a study by Okuda and colleagues showed a significant between-group difference in IL-6 and IL-10 levels in the lung epithelial lining fluid but no differences in plasma levels [17]. We were unable to reproduce these findings in our study. However, most surgical procedures investigated in the studies were considerably more extensive than the thoracoscopic approach used in our trial, and the extent of surgery has been shown to influence the release of both pro-and anti-inflammatory cytokines [18, 19]. This may indicate that the extent of immune system activation in minimally invasive surgery is insufficient for epidural analgesia to exert any statistically significant effects on plasma cytokine levels. However, previous studies have examined the effects of epidural analgesia versus no epidural analgesia perioperatively, whereas our study used similar epidural analgesia in both groups perioperatively, changing to two different regimes post-operatively. Our setup might not allow epidural analgesia enough time to exert any attenuating effect on the immune response. Studies using a setup with a different perioperative epidural analgesia are needed to comprehensively examine any attenuating immune response attributable to epidural analgesia in VATS.

We found no difference in survival between the two groups using the log-rank test ($p = 0.5$). Evidence preceding our study has indicated a potential positive effect of epidural analgesia on post-operative mortality (odds ratio = 0.60) [3]. No studies on VATS existed at the time. Subsequently, a 2021 RCT on 400 VATS procedures in lung cancer patients showed no difference in post-operative survival using epidural analgesia compared with general anaesthesia alone [20]. Our study aligns with these results but is potentially underpowered to determine this with only seven events recorded during the two-year follow-up.

Our study has limitations that need to be addressed. First, our planned primary outcome measure was changes in plasma levels of NK cells after surgery. Because of technical difficulties in the laboratory, NK cell count and activity analyses were not performed. This might leave the study underpowered to detect differences in cytokine levels and post-operative survival. Second, the observed skewness in the baseline cancer stage and ASA classification might impact results. We speculate that a "healthier" OM Group, as indicated by the ASA classification, might reduce any ameliorating effect of epidural analgesia on post-operative immune suppression after cancer surgery. Conversely, the higher cancer staging in this group may suggest a more severe immunosuppression, which could potentially lead to an additional beneficial effect in this group due to baseline skewness. This, however, remains pure speculation. In the regression analysis, the duration of the surgical procedure and the patient's cancer stage did not add significantly to the regression model and were omitted from the final analysis. Likewise, the interaction effect between the treatment group and time was insignificant for all cytokines and was therefore omitted.

CONCLUSION

No significant differences were seen in the plasma cytokine levels or the two-year post-operative survival in VATS lobectomy when comparing epidural analgesia to enteral opioids as post-operative analgesics.

Correspondence *Jimmy Højberg Holm.* E-mail: jimmy.hoejberg.holm@rsyd.dk

Accepted 9 June 2024

Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

Acknowledgements We thank the patients for participating in the trial. We thank the nurses and staff of the Department of Cardiothoracic Surgery and the Department of Anesthesia and Intensive Care of Odense University Hospital for their assistance with data collection. We take this opportunity to express our indebtedness to Study Nurse *Susanne Petersen* for all her hard work in all aspects of the trial.

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

Cite this as Dan Med J 2024;71(10):A09230582

doi 10.61409/A09230582

https://content.ugeskriftet.dk/sites/default/files/2024-06/a09230582-supplementary.pdf

REFERENCES

1. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer. 2003;3(6):453-8. https://doi.org/10.1038/nrc1098
2. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth. 2010;105(2):106-15. https://doi.org/10.1093/bja/aeq164
3. Pöpping DM, Elia N, Van Aken HK, et al. Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials. Ann Surg. 2014;259(6):1056-67. https://doi.org/10.1097/sla.0000000000000237
4. Buggy DJ, Riedel B, Sessler DI. Can anaesthetic technique influence cancer outcome? The next steps …. Br J Anaesth. 2021;127(1):5-7. https://doi.org/10.1016/j.bja.2021.04.005
5. Holm JH, Andersen C, Toft P. Epidural analgesia versus oral morphine for postoperative pain management following video-assisted thoracic surgery: a randomised, controlled, double-blind trial. Eur J Anaesthesiol. 2024;41(1):61-9. https://doi.org/10.1097/eja.0000000000001921
6. Nielsen HH, Soares CB, Høgedal SS, et al. Acute neurofilament light chain plasma levels correlate with stroke severity and clinical outcome in ischemic stroke patients. Front Neurol. 2020;11:448. https://doi.org/10.3389/fneur.2020.00448
7. Brøchner AC, Mikkelsen S, Hegelund I, et al. The immune response is affected for at least three weeks after extensive surgery for ovarian cancer. Dan Med J. 2016;63(6):A5243
8. Pan Y, Wu Y, Ji J, et al. Effect of cytokine-induced killer cells on immune function in patients with lung cancer. Oncol Lett. 2016;11(4):2827-34. https://doi.org/10.3892/ol.2016.4284
9. O'Bryan LJ, Atkins KJ, Lipszyc A, et al. Inflammatory biomarker levels after propofol or sevoflurane anesthesia: a meta-analysis. Anesth Analg. 2022;134(1):69-81. https://doi.org/10.1213/ane.0000000000005671
10. Jedynak M, Mroczko B, Siemiatkowski A, et al. Decreased serum level of IL-12 in the course of ischemia and reperfusion during abdominal aortic surgery. Folia Histochem Cytobiol. 2011;49(3):465-71. https://doi.org/10.5603/fhc.2011.0066
11. Franke A, Lante W, Kurig E et al. Is interferon gamma suppression after cardiac surgery caused by a decreased interleukin-12 synthesis? Ann Thorac Surg. 2006;82(1):103-9. https://doi.org/10.1016/j.athoracsur.2006.02.042
12. D&;browska AM, S&;otwi&;ski R. The immune response to surgery and infection. Cent Eur J Immunol. 2014;39(4):532-7. https://doi.org/10.5114/ceji.2014.47741
13. Fares KM, Mohamed SA, Hamza HM, et al. Effect of thoracic epidural analgesia on pro-inflammatory cytokines in patients subjected to protective lung ventilation during Ivor Lewis esophagectomy. Pain Phys. 2014;17(4):305-15.
14. Wang L, Liang S, Chen H et al. The effects of epidural anaesthesia and analgesia on T lymphocytes differentiation markers and cytokines in patients after gastric cancer resection. BMC Anesthesiol. 2019;19(1):102. https://doi.org/10.1186/s12871-

019-0778-7

15. Dong H, Zhang Y, Xi H. The effects of epidural anaesthesia and analgesia on natural killer cell cytotoxicity and cytokine response in patients with epithelial ovarian cancer undergoing radical resection. J Int Med Res. 2012;40(5):1822-9. https://doi.org/10.1177/030006051204000520
16. Xu Q, Shi NJ, Zhang H, Zhu YM. Effects of combined general-epidural anesthesia and total intravenous anesthesia on cellular immunity and prognosis in patients with non&;small cell lung cancer: a comparative study. Mol Med Rep. 2017;16(4):4445-54. https://doi.org/10.3892/mmr.2017.7144
17. Okuda J, Suzuki T, Wakaizumi K, et al. Effects of thoracic epidural anesthesia on systemic and local inflammatory responses in patients undergoing lung cancer surgery: a randomized controlled trial. J Cardiothorac Vasc Anesth. 2021;36(5):1380-86. https://doi.org/10.1053/j.jvca.2021.08.026
18. Kuda T, Kamada Y, Nagamine N et al. Evaluation of inflammatory-response-induced thoracoscopic surgical stress. J Thorac Cardiovasc Surg. 2002;50(5):206-9. https://doi.org/10.1007/bf03032287
19. Yim AP, Wan S, Lee TW, Arifi AA. VATS lobectomy reduces cytokine responses compared with conventional surgery. Ann Thorac Surg. 2000;70(1):243-7. https://doi.org/10.1016/s0003-4975(00)01258-3
20. Xu ZZ, Li HJ, Li MH et al. Epidural anesthesia-analgesia and recurrence-free survival after lung cancer surgery: a randomized trial. Anesthesiology. 2021;135(3):419-32. https://doi.org/10.1097/aln.0000000000003873

