Beneficial Effects of thoracic epidural anaesthesia on mortality after elective surgery for colon cancer: a survey of 215 consecutive patients

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Abstract

Background: Colorectal cancer is a major cause of death in the industrial world. The mortality and morbidity rates depend on the incidence of postoperative complications and cancer recurrence. Data from basic science support the view that regional anaesthesia reduces perioperative stress levels, potentially resulting in a lower risk of complications and cancer relapse. **Methods:** In 215 patients underwent open colon cancer surgery, carried out by the same visceral surgeon and the same oncologist we compared short and long-term outcome data for 83 patients with general anaesthesia plus thoracic epidural analgesia (EPI group) and for 132 patients with general anaesthesia alone (GA group). Oncological data from a state-wide follow-up database were included. The effects of different perioperative anaesthetic techniques on patients' short and long-term outcome (36 month) were statistically analysed (Kaplan Meyer Curve, Pearson's chi-squared test, Student's t-test, and the Wilcoxon rank sum test, as appropriate). **Results:** With the exception of a significantly higher prevalence of arterial hypertension in the EPI group in comparison with the GA group, there were no differences in demographic, tumour staging data and cancer recurrence rates between the groups. However, mortality rates were significantly different between the groups. 37 of 132 GA patients (28%) died within 36 months, in comparison with 14 of 83 EPI patients (16.9%, $P < 0.05$). Patients over the age of 70 in particular significantly benefited from perioperative epidural analgesia and had a significantly better survival compared with patients without perioperative epidural analgesia ($p < 0.05$). **Discussion:** Perioperative use of epidural analgesia reduces the 36-month postoperative mortality rate. This effect may be due to systemic effects of local anaesthetics or to a reduced stress response caused by the thoracic epidural analgesia itself. **Conclusions:** Patients with colon cancer over the age of 70 in particular significantly benefited from perioperative epidural analgesia and had a longer survival time in comparison with patients without perioperative epidural analgesia. (ISRCTN10994336, retrospective registered 07/06/2019)

Background

Cancer is a major cause of death in the industrialized world.¹ Cancer treatment is based on multimodal approaches; surgical resection is obligatory for most types of solid tumour. The survival period for the patients depends on the grade, type and stage of the lesion at the primary diagnosis, as well as on the patients' pre-existing comorbid conditions. It is known that 5% of patients who undergo surgery die during the first year afterwards, and the rate is double that for patients over the age of 65. The major causes of death are the cancer itself, followed by cardiovascular problems, kidney or liver failure, multiple organ failure and respiratory failure.² The challenge for physicians is therefore to find an optimal form of perioperative therapy capable of preventing these causes of morbidity and mortality. On the basis of results from basic science, regional anaesthesia may be a reasonable technique for reducing complications and improving the patients' long-term outcome.³

Thoracic epidural analgesia provides optimal pain therapy for many operations and may therefore be able to reduce the morbidity and mortality after major thoracic and abdominal surgery.³ In comparison with general anaesthesia, the extent to which the patient's immune system is compromised is reduced. Data

from basic science suggest that regional anaesthetic techniques may therefore reduce the risk of micrometastases. Patients undergoing cancer resection should therefore be able to benefit from epidural analgesia, as it seems plausible that it may reduce the risk of recurrent cancer and metastases after cancer surgery.⁴ It might even be possible to reduce the mortality rate in this way. It was therefore hypothesized that patients undergoing open surgery for colonic cancer who receive thoracic epidural anaesthesia should have recurrent cancer less often and should have a longer survival period in comparison with patients who only receive general anaesthesia.

Methods

Following approval for the study by the local ethics committee of the General Medical Council of the state of Lower Saxony (*Ärztchamber Niedersachsen*), prospectively collected data and medical records were routinely analysed for all patients who had undergone open colon surgery between 1999 and 2007 in St. Mary's Hospital, Vechta, Germany (*St. Marienhospital Vechta*). Hospitals can be classified into three groups in relation to colon cancer treatment, based on their annual caseload:⁵ low-volume (< 30 colon cancer operations per year), medium-volume (30–60 colon cancer operations per year) and high-volume (> 60 colon cancer operations per year).⁵ St. Mary's belongs to the high-volume group.

Patients who underwent elective open colon cancer resection and were over the age of 18 were included in the analysis. Patients who underwent emergency operations were excluded. An electronic database was used to determine the baseline demographic variables, the type of anaesthesia administered, and the date of surgery. All of the oncological data and oncological follow-up data were prospectively stored in an official electronic database (the Epidemiological Cancer Registry for Lower Saxony, *Epidemiologisches Krebsregister Niedersachsen*). All clinically relevant and potential interacting factors associated with tumour outcome and progression were recorded in a clinical database.

Anaesthesia

The patients underwent elective colonic surgery for tumour resection either under general anaesthesia combined with thoracic epidural analgesia (EPI group) or with general anaesthesia alone (GA group). In both groups, anaesthesia was induced with propofol 2–3 mg/kg bodyweight, rocuronium 0.6 mg/kg bodyweight for muscle relaxation, and fentanyl (GA group) or sufentanil (EPI group) for pain control during intubation. Inhaled anaesthetics were used in both groups to maintain anaesthesia.

The decision on whether epidural analgesia should be used was taken by the patient in consultation with the attending anaesthesiologist. In the EPI group, the thoracic epidural catheter was inserted preoperatively. Before surgical incision, 10 ml bupivacaine 0.25% was injected. The epidural analgesia was maintained for 96 hours postoperatively using a patient-controlled epidural analgesia (PCEA) technique with bupivacaine 0.125% plus 0.5 µg/ml sufentanil (rate 5–7 ml/hour, 2 ml bolus on demand, lockout time after bolus 20 min). The patients were visited once per day, or more often if needed, by the hospital's acute pain service to ensure adequate postoperative analgesia.

Statistical analysis

Table 1 shows the demographic data for the patients in the two groups, allowing comparison of pre-existing medical conditions. The groups were also compared using Lee's Revised Cardiac Risk Index (Table 2).⁶ The data for the patients in the two study groups were compared in relation to all potential confounding factors using Pearson's chi-squared test, Student's *t*-test, and the Wilcoxon rank sum test, as appropriate. A Cox regression model was used to investigate effects on mortality for all of the patients as the primary end point. Statistical analysis was carried out using the IBM PASW statistics program, version 18 (*t*-test, chi-squared test, Cox regression).

Results

A total of 215 patients underwent open colorectal surgery between 1999 and 2007. Eighty-three patients underwent surgery under general anaesthesia combined with thoracic epidural analgesia (EPI group) and 132 patients received surgery with general anaesthesia alone (GA group). The patients' demographic data are shown in Table 2. The anaesthesia periods were significantly longer in the EPI group than in the GA group, but the patients in the EPI group were discharged from the intensive-care unit (ICU) and from the hospital significantly more quickly than the patients in the GA group (Table 3). The tumour stages in the two study groups were comparable (Fig. 1) ($P = 0.10$). The rates of regional lymph-node metastasis were N0 55.4%, N1 13.3% and N2 31.3% in the EPI group and N0 55.7%, N1 18.3% and N2 26.0% in the GA group ($P = 0.44$). The rates of distant metastasis were M0 89.2%, M1 10.8% in the EPI group and M0 87.9%, M1 12.1% in the GA group ($P = 0.72$).

With regard to the pre-existing conditions, only the rate of hypertension was significantly higher in the EPI group in comparison with the GA group ($P = 0.002$) (Table 1). With regard to the Lee index (Table 2), 73.5% of the EPI group and 70.5% of the GA group had one factor; 20.5% of the EPI group and 18.9% of the GA group had two factors; 6.0% of the EPI group and 9.8% of the GA group had three factors; and only 0.8% of the GA group had four factors. The Lee index scores were therefore comparable in the two groups ($P = 0.65$). No significant differences between the two study groups were noted in relation to the incidence of postoperative surgical or general complications. 6% of the patients in the EPI group and 8.4% of those in the GA group developed pneumonia; cerebral strokes occurred in 2.3% of the GA group, and pulmonary embolisms in 1.2% of the EPI group ($P = 0.45$). Postoperative surgical complications were diagnosed in 8.4% of the EPI group (three anastomotic leakages, two wound dehiscences, one later resection and one other complication) and 6.8% of the GA group (four anastomotic leaks, three wound dehiscences, one case of postoperative peritonitis, and one other complication) ($P = 0.66$).

No significant differences between the GA and EPI groups were noted with regard to cancer survival: 21 of the 132 patients in the GA group (15.9%) and eight of the 83 patients in the EPI group (9.6%) died due to recurrences or metastases of colon cancer ($P < 0.19$).

Thirty-seven of the 132 patients in the GA group (28%) died within 36 months, in comparison with 14 of the 83 patients in the EPI group (16.9%, $P < 0.05$). Figure 2 shows the Cox regression analysis and *P* value.

Cox regression analysis in patients who were over the age of 70 at the time of surgery (Fig. 3) showed that epidural analgesia significantly reduced the mortality ($P = 0.02$).

Discussion

A recent meta-analysis has suggested that epidural anaesthesia may have a beneficial effect on the overall survival after cancer surgery, particularly in patients with colorectal cancer. However, the use of epidural analgesia did not further reduce the numbers of recurrent cancers. The meta-analysis suggests that epidural anaesthesia and/or analgesia may be associated with improved overall survival in patients with operable cancer (especially colorectal cancer) who undergo surgery.⁷

The results of the present study show that administration of thoracic epidural analgesia for perioperative analgesia during and after colon cancer resection was associated with a reduced 36-month mortality rate. These results support the findings of the earlier meta-analysis.⁷ Patients over the age of 70 at the time of surgery benefit more from epidural analgesia and survive significantly longer than patients in whom only a balanced anaesthetic technique is used. However, no reduction in the incidence of recurrent cancer was noted after adjustment for confounding variables.

Colon cancer is a systemic disease. Despite curative tumour resection, it is important to note that as many as 25–40% of patients who undergo curative tumour resection nevertheless subsequently develop metastatic disease, suggesting that there may be undetected micrometastases that play a pivotal role in relapses. One of the major causes of relapse is the presence of disseminated tumour cells shed from the primary carcinoma into the circulation before, during, or after surgery.⁸ Due to profound perioperative immunosuppression, the perioperative period appears to be a vulnerable time for potential metastasis in patients with malignancies. This vulnerability is mainly attributed to the suppression of cell-mediated immunity – the first-line defence mechanism against cancer. The depression of the immune system occurs within hours of surgery, lasts for several days, and is proportional to the extent of surgical trauma.⁴ With colorectal surgery, the perioperative and postoperative period is characterized by surgical stress and pharmacological influences, which affect cell-mediated immunity during this vulnerable phase for tumour cell dissemination. In particular, natural killer cells and cytotoxic T cells are suppressed by high levels of stress biomarkers such as epinephrine and norepinephrine.^{9,10} Thoracic epidural analgesia blunts the neural transmission of the stress response and avoids negative effects of hypothalamic–pituitary–adrenal activation such as immune suppression.⁴ In addition, thoracic epidural analgesia reduces the amount of anaesthetics and analgesics required. These facts appear to be important, as some of these types of drug can promote immune suppression.⁴ Using carefully considered anaesthetic techniques might therefore be able to reduce the inhibition of hormonal and cellular immune function and may even reduce the pro-angiogenic effect on tumour growth, resulting in fewer tumour recurrences in these oncological patients.⁴

Accumulated evidence indicates that inflammation may play a critical role in the initiation, development, growth, and metastasis of cancer.¹¹ Regional anaesthesia may therefore have a potential anti-

inflammatory effect, attenuating an excessive immune reaction induced by surgical trauma, and it appears to have a beneficial effect on the outcome for the patients.⁵ Bupivacaine inhibits prostaglandin E₂ (PGE₂) E-prostanoid 1 (EP1) receptor signalling at clinically relevant concentrations and affects physiological responses such as fever, inflammation, and hyperalgesia during the perioperative period.¹² Local anaesthetics have a time-dependent inhibitory effect on G protein-coupled receptor signalling.¹³ They are known to be effective in suppressing neutrophil priming, a process that is responsible in part for the hyperactive neutrophil response.¹⁴ Local anaesthetics can even inhibit thromboxane A2 signalling, a mediator of perioperative myocardial ischaemia, vasoconstriction, and thrombosis.^{15,16} They also inhibit the activation of human *N*-methyl-d-aspartate (NMDA) receptors. This effect reduces the hyperalgesia and opiate tolerance that is observed after systemic administration of local anaesthetics.¹⁷ Results published by Piegeler *et al.* indicate that amide local anaesthetics may have antimetastatic effects. The mechanism behind this interesting pharmacological finding is inhibition of tumour necrosis factor- α -induced Src activation and intracellular adhesion molecule-1 phosphorylation.¹⁸ This molecular mechanism with amide-type local anaesthetics is again independent of the sodium channel blockade. It would be of major interest to determine whether some of the effects of epidural analgesia may be due to the systemic effects of local anaesthetics.

Despite these promising results from basic science and theoretical models, however, the results of the present study do not support the view that perioperative administration of thoracic epidural analgesia leads to less recurrent cancer. This may be due to the familiar problems of retrospective analysis, such as unrecorded confounding factors and changes in the patients' medical care. This potential deficiency was reduced in the present study, as the surgeon and oncologist were the same throughout the recorded study period. However, it is not known how often the patients may have required additional surgery for other medical conditions, with the same level of surgical stress and the same immunosuppressive effects. Nor is it known whether the patients were receiving medication with statins, beta-blockers, or cyclooxygenase (COX) inhibitors perioperatively, which also appear to have antimetastatic properties.⁴ Along with the rapid advances being made in oncological treatment, it will therefore be very difficult to prove whether a specific anaesthetic technique is really able to reduce the risk of recurrent cancer.

However, thoracic epidural analgesia is an important component of fast-track rehabilitation in colon surgery. In addition to faster recovery, some authors have also described a reduction in general morbidity,^{19,20} with fewer cardiovascular adverse events due to epidural anaesthesia and perioperative stress protection, analgesia, and sympathicolysis. The incidence of thrombosis and embolism is reduced. Epidural analgesia reduces the use of systemic opioids, and in combination with splanchnic sympathicolysis, prevents intestinal hypomotility and accelerates convalescence and a return to oral nutrition for the patients. It has also been reported that pain-induced pulmonary atelectasis and pneumonia can be prevented.^{3,21} In a population-based study, Cummings *et al.*²² compared epidural analgesia and traditional forms of pain management in relation to their effects on survival and recurrent cancer after colectomy. In this large observational study, including 42,151 patients, the 5-year survival rate

was 61% in the epidural group and 55% in the non-epidural group.²² The difference was analysed using adjusted Cox regression and strongly supports the data obtained in the present study.

This study has certain limitations, the most important of which is that it is a small, single-centre retrospective study. For conclusive findings on whether regional anaesthesia is capable of reducing the risk of tumour relapse, a large, multicentre study with a prospective and randomized design would be needed. In a trial of that type, patients would need to be included within a very short study period in order to reduce the possibility of changes in oncological regimens that would make it difficult to compare the study groups. Prospective trials are currently in progress, but no data from them have so far been published. The present study excludes the possibility of variations resulting from different surgeons and oncologists participating, and it may therefore be of special interest.

Conclusions

The data presented here support the theory that epidural analgesia appears to be beneficial for colon cancer patients in reducing the overall mortality rate. The effect is age-dependent; the mortality was reduced particularly in elderly patients (>70 years) .

Abbreviations

EPI	= epidural anaesthesia
EPI group	= group of patients with epidural and general anaesthesia
GA	= general anaesthesia
GA group	= group of patients with general anaesthesia alone
ICU	= intensive care unit
kg	= kilogram
N	= N in TNM refers to the involvement of lymph nodes in the cancer.
M	= The M refers to whether the cancer has metastasized.
mg	= milligram
min	= minute
µg	= microgram
P	= p – value: All hypothesis tests ultimately use a p-value to weigh

the strength of the evidence (what the data are telling you about

the population). The p-value is a number between 0 and 1.

PCEA = patient controlled epidural analgesia

% = percent

SRC = Proto-oncogene tyrosine-protein kinase Src, also known as proto-oncogene c-Src or simply c-Src, is a non-receptor tyrosine kinase protein that in humans is encoded by the SRC gene. This protein phosphorylates specific tyrosine residues in other tyrosine kinases.

TNM = The TNM Classification of Malignant Tumors (TNM) is a globally recognised standard for classifying the extent of spread of cancer.

Declarations

Ethics approval:

The study was approved by the ethical committee of the General Medical Council of the state of Lower Saxony (letter from Mr. Kay Bogs, Geschäftsführer der Ethikkommission der Ärztekammer Niedersachsen).

Consent to participate:

Not applicable.

Consent for publication

All authors revised the final manuscript critically. All authors read and approved the final manuscript.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author.

Competing interests

None.

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Authors' contributions

All authors took part in the work and agree with the contents of the manuscript. CH, KH and HVA provided concepts. EW, SM, CH, MRL conducted the data acquisition and data analysis. MRL, DD, OH, AG and CH did the literature review. SM and MRL drafted the initial manuscript equally (first authorship), AG critically revised and CH submitted the final manuscript (corresponding author).

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Tables

Table 1 Demographic data and prevalence of pre-existing conditions in the group with general anaesthesia plus thoracic epidural anaesthesia (EPI group) and the group with general anaesthesia alone (GA group)

	EPI group (n = 83)	GA group (n = 132)	<i>P</i> value
Male vs. female (n)	48 vs. 35	66 vs. 66	0.326
Age (years)	67.5 ± 10.75	67.3 ± 10.66	0.884
Height (cm)	171 ± 7.6	169 ± 17.4	0.273
Weight (kg)	79.6 ± 14.6	76.4 ± 16.5	0.136
Body mass index (kg/m ²)	26.9 ± 3.75	26.3 ± 5.16	0.373
Diabetes mellitus (%)	18.1	16.7	0.79
Hypertension (%)	67.5	46.2	0.002
Coronary artery disease (%)	16.9	16.7	0.969
History of myocardial infarction (%)	2.4	3.0	0.79
Chronic obstructive pulmonary disease (%)	10.8	9.1	0.67
Peripheral arterial occlusive disease (%)	6.0	9.8	0.32
Renal insufficiency (%)	9.6	7.6	0.59
Serum creatinine > 2 mg/dl (%)	1.2	0	0.21

Table 2 Lee's revised cardiac risk index.⁶ Each risk factor is assigned one point

1	High-risk surgical procedures
2	Ischaemic heart disease
3	History of congestive heart failure
4	History of cerebrovascular disease
5	Insulin therapy for diabetes
6	Preoperative serum creatinine > 2.0 mg/dL

Table 3 The patients’ intraoperative and postoperative characteristics

	EPI group (n = 83)	GA group (n = 132)	<i>P</i> value
Duration of anaesthesia (min)	177 ± 48.3	144 ± 47.7	0.001
Length of stay on ICU postoperatively (hours)	43 ± 23.4	65 ± 40.2	0.001
Length of hospital stay (days)	18.7 ± 5.67	21.6 ± 9.53	0.006
Transfusion of packed red blood cells (units)	0.9 ± 1.56	1.3 ± 1.93	0.153

Figures

1a

1b

1c

Figure 1

1a: Distribution of tumour stages in the two study groups. Numbers are shown in percentages, tumor stage. 1b: Distribution of tumour stages in the two study groups. Numbers are shown in percentages, Nodal status. 1c: Distribution of tumour stages in the two study groups. Numbers are shown in percentages, metastatic stage.

Figure 2

Cox regression survival mode for EPI vs. GA ($n = 215$).

Figure 3

Cox regression survival mode for EPI vs. GA; age > 70 years ($n = 100$).