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Association between preoperative glucocorticoids and long-term survival and cancer recurrence after colectomy: follow-up analysis of a previous randomized controlled trial

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Editor's key points

- The effects of preoperative dexamethasone given as anti-emetic prophylaxis on long-term survival and recurrence after cancer surgery are unknown.
- In a subgroup analysis of a previous trial, preoperative dexamethasone was associated with increased cancer recurrence in patients undergoing colon cancer resection.
- This preliminary association suggests the need for prospective studies powered to detect effects of preoperative glucocorticoids on survival and cancer recurrence.

Background. The effect of anaesthetic drugs on long-term oncological outcomes after cancer surgery is an area of current interest. Dexamethasone is widely used in anaesthetic practice; however, its effect on long-term survival and cancer outcomes is not known. This study presents the results of a 5-yr follow-up of patients receiving dexamethasone before elective colectomy as part of a previous randomized clinical trial.

Methods. Sixty patients who underwent elective open colonic resection for any indication between June 2006 and March 2008 were randomized to receive either 8 mg i.v. dexamethasone or placebo before surgery. A 5-yr follow-up analysis was conducted to evaluate overall survival, disease-free survival and recurrence specifically for patients undergoing resection for Stage I–III colon cancer. Kaplan–Meier analysis was performed and log-rank test was used to evaluate difference in survival between groups.

Results. Forty-three of the 60 subjects had Stage I–III colon cancer and were included in the follow-up analysis. Twenty received preoperative dexamethasone and 23 received placebo. There were no significant differences between groups in baseline or disease characteristics. No differences were found between groups for overall or disease-free survival. In the dexamethasone group, there was a significantly higher rate of distant recurrence (6 compared with 1, $P=0.04$).

Conclusions. Preoperative dexamethasone was associated with a higher rate of distant recurrence in patients undergoing colectomy for colon cancer. Given the small sample size, this finding should be interpreted with caution, but warrants further investigation in a prospective study.

Keywords: colectomy; colonic neoplasms; dexamethasone; neoplasm metastasis; recurrence

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Perioperative factors including anaesthetic technique and drug choice can impact on cell-mediated immunity and potentially affect long-term oncological outcomes after cancer surgery.[1–5] Surgical resection for cancer, while aiming to remove the primary tumour, can itself promote development of metastases through several mechanisms including spillage of tumour cells into the circulation during surgical manipulation, suppression of anti-tumour immunity, release of growth factors facilitating tumour proliferation, and loss of inhibition of angiogenesis because of removal of the primary tumour.[6–9]

Dexamethasone is a glucocorticoid (GC) that is commonly used in anaesthetic practice for prophylaxis against postoperative nausea and vomiting (PONV).[10 11] When administered as a single-dose before operation, GCs attenuate the post-surgical inflammatory response and improve short-term clinical outcomes after major surgery.[12–15] However, through their anti-inflammatory and immunomodulating effects, GCs might potentially worsen perioperative immunosuppression and promote tumour proliferation and metastasis.[16–20] Despite their widespread use, there have been no clinical studies evaluating the effect of perioperative GCs on long-term oncological outcomes after cancer surgery. Although GCs have not been shown to worsen survival in patients with solid malignancy,[21–23] this has not been specifically evaluated for patients receiving a single dose before operative resection.

This study investigated the potential adverse effects of single-dose preoperative GCs on long-term survival and oncological outcomes after resection for colon cancer. A previous randomized controlled trial conducted at our institution investigated the effects of preoperative dexamethasone in patients

undergoing elective colectomy and evaluated short-term outcomes showing improvement in postoperative fatigue and a reduction in the early peritoneal inflammatory response.[24] This study presents the 5-yr follow-up analysis of this cohort to evaluate the secondary outcomes of long-term survival and cancer recurrence.

Methods

Institutional Review Board (IRB) approval was obtained and the requirement for written informed consent was waived by the IRB. The design of the double-blind randomized clinical trial, together with its short-term outcomes, has been reported previously.[24] In total, 60 subjects undergoing open elective colonic resection for any indication at our institution (Manukau Surgery Centre, Middlemore Hospital, Auckland, New Zealand) between June 2006 and March 2008 were randomized to receive 8 mg dexamethasone (Dexamethasone Sodium Phosphate Injection, 4 mg ml^{-1}; Hospira, Wellington, New Zealand) or placebo (normal saline) at least 90 min before incision. All subjects were managed within an Enhanced Recovery After Surgery programme including a standardized anaesthetic protocol as previously described.[25] The exclusion criteria included patients receiving steroids or other immunosuppressants, ASA score IV or V, requirement for a stoma, inability to speak English, or significant cognitive impairment.

Using a regional electronic patient information database (Concerto 6.3, Orion Health, Auckland, New Zealand), a follow-up analysis was conducted in January 2013 to evaluate mortality and recurrence specifically for patients undergoing curative resection for colonic malignancy. Patients with benign disease, non-malignant polyps, or metastatic (Stage IV) disease at the time of operation were excluded from the analysis. All-cause mortality was defined as death from any cause, while cancer-specific mortality was defined as death due to metastatic progression of disease. Overall survival was calculated from the date of operation to the date of death from any cause. Disease-free survival was calculated from the date of operation to the date of recurrence or death (from any cause). Recurrence was categorized as distant or locoregional, and time to recurrence was calculated from the date of operation to the date of recurrence. Patients without evidence of recurrence at death were censored at the date of death, while patients alive at the time of follow-up were censored at the date of follow-up analysis.

Baseline characteristics including age, gender, body mass index, ASA score, Colorectal Physiological and Operative Severity score for the enUmeration of Mortality and morbidity (Cr-POSSUM),[26] epidural use, operation type, cancer stage, tumour pathology, and adjuvant chemotherapy treatment were compared between groups. Postoperative complications up to 30 days after surgery were prospectively recorded using predefined criteria[25] and graded using the Clavien-Dindo classification system.[27] In subjects with multiple complications, the complication with the highest grade is reported.

Statistical analysis

Data were analysed using SPSS for Windows version 19.0 (SPSS, Inc., Chicago, IL, USA). Parametric and non-parametric tests were used for statistical comparison as appropriate. Groups were compared using Fisher's exact test for categorical variables or Mann–Whitney *U*-test for ordinal data and data without normal distribution. Differences in survival between groups were compared using Kaplan–Meier curves and tested using the log-rank (Mantel–Cox) test. Statistical significance was defined a priori as $P<0.05$.

Results

Forty-three of the 60 subjects included in the randomized clinical trial were included in the follow-up analysis. Of the 17 subjects excluded from the analysis, 8 subjects underwent surgery for benign disease, 4 subjects had non-malignant polyps on operative histology, 3 subjects had metastatic disease at the time of operation, 1 subject underwent colonic resection for metastatic melanoma, and 1 subject was lost to the long-term follow-up. Twenty subjects received preoperative dexamethasone while 23 subjects received placebo. There were no differences in baseline characteristics between groups (Table 1). The majority of subjects underwent right-sided colectomy and had Stage II or III disease. There were no differences in grade or type of postoperative complications between groups (Table 2).

At the time of analysis, the median duration of the follow-up for all patients was 5.8 yr (range 4.8–6.5 yr). There was no significant difference in all-cause mortality or overall survival between groups (Table 3, Fig. 1). There was a non-significant trend towards higher cancer-specific mortality in the dexamethasone group (5 compared with 1, $P=0.08$). Overall recurrence and time to recurrence were not significantly different between groups. However, the number of subjects who developed distant recurrence was significantly higher in the dexamethasone group (6 compared with 1, $P=0.04$). Of the four subjects who had an anastomotic leak after operation, two developed distant recurrence and were both in the dexamethasone group. The 5-yr disease-free survival rate for subjects receiving dexamethasone and placebo was 60 and 74%, respectively, with no significant difference between groups (Fig. 2).

Discussion

This study reports the 5-yr follow-up of subjects receiving preoperative dexamethasone or placebo before elective colectomy for colon cancer. There was no difference in overall or disease-free survival. However, subjects receiving dexamethasone had a significantly higher rate of distant recurrence and a non-significant trend towards higher cancer-specific mortality.

Long-term outcomes related to anaesthetic management and other perioperative factors is an area of increasing interest, particularly with regard to cancer recurrence and metastasis.[1 2] A useful analogy for the impact of perioperative factors on the development of postoperative metastases has been made with the development of surgical wound infections since