Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery

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Editor’s key points
• Regular aspirin, a form of non-steroidal anti-inflammatory drug (NSAID), has been associated with reduced risk of many cancers, including colorectal cancer.
• This retrospective analysis suggests that a single intraoperative NSAID is associated with improved disease-free survival (DFS) in women undergoing conservative breast cancer surgery.
• There also appears to be an association between higher preoperative neutrophil:lymphocyte ratio and worse DFS in conservative breast cancer surgery.

Background. An association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and better outcome after mastectomy and lung surgery for cancer has been recently suggested. In a retrospective analysis, we investigated the association between intraoperative NSAIDs use in conservative breast cancer surgery and breast cancer disease-free survival (DFS). Similarly, we also evaluated the association between breast cancer DFS and preoperative neutrophil:lymphocyte ratio (NLR).

Methods. A retrospective analysis of a single-centre cohort was performed in breast cancer patients (n=720) with uni- and multivariate analyses, using a Cox regression model.

Results. In conservative breast cancer surgery, the intraoperative use of NSAIDs (ketorolac or diclofenac) was associated with an improved DFS [hazard ratio (HR)=0.57 (95% confidence interval (CI): 0.37–0.89), P=0.01] and an improved overall survival (OS) [HR=0.35 (95% CI: 0.17–0.70), P=0.03]. In these patients, an NLR >3.3 (identified by a receiver-operating characteristic curve) was associated with a shorter DFS [HR=1.99 (95% CI: 1.16–3.41), P=0.01] and OS [HR=2.35 (95% CI: 1.02–5.43), P=0.046].

Conclusions. Intraoperative NSAIDs and higher preoperative NLR are associated with improved outcome in conservative breast cancer surgery. Prospective, randomized trials to evaluate if these associations are causal are warranted.

Keywords: conservative breast cancer surgery; neutrophil:lymphocyte ratio; non-steroidal anti-inflammatory drugs

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Surgery is an important component of the treatment of solid tumours. However, surgery induces an acute inflammatory response that may exacerbate some mechanisms linked to tumour growth and dissemination.1 These mechanisms are not completely understood but could be influenced either by the tumour characteristics (e.g. size) or by the surgical technique (i.e. degree of tissue injury).1

Retrospective analyses suggest that intraoperative use of non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with a better outcome after mastectomy and lung cancer surgery.2,3 Chronic administration of low-dose aspirin has been linked to improved prevention of cancer.4–8 However, the benefit of a single low dose of NSAID remains controversial.9 Consequently, some patients receive NSAIDs during conservative cancer surgery, while others do not, regardless of their cancer staging.2,10 Considering that in animal models, a short course of NSAIDs appears to improve cancer survival,11 it is relevant to evaluate this observation in patients undergoing less invasive (i.e. conservative) surgery.

Certain markers of inflammation have been shown to be linked to tumour progression. One of these, the neutrophil:lymphocyte ratio (NLR), which is associated with low-grade systemic inflammation, was initially linked with cardiac mortality,12 and has since then been proposed as a prognostic factor for various types of cancer surgery.13–21

In this retrospective analysis, we investigated the effect of a single intraoperative dose of ketorolac or diclofenac, and the preoperative NLR, during conservative primary breast cancer surgery, on disease-free survival (DFS).
Methods

Patients and methods

Ethical approval for this study (Ethical Committee N/REF 2010/15MAR/085, No. B40320108384) was provided by the IRB (CEBH of the Université catholique de Louvain, Brussels, Belgium. Chairperson Pr J.M. Maloteaux) on March 29, 2010. We retrospectively reviewed the existing databases of breast cancer patients undergoing breast cancer surgery.

Patients were treated and data collected according to the most recent guidelines.\(^2\)\(^2\)\(^-\)\(^2\)\(^7\) For data collection, we used the same methodology as previously described.\(^2\) \(^2\) One thousand seven hundred and two patients were screened (Fig. 1). Seven hundred and twenty-six patients met the following inclusion criteria: tumorectomy, with or without axillary clearance between February 2003 and December 2008. Exclusion criteria were: cancer in the past 5 yr (excluding cutaneous basocellular and in situ uterine cervix carcinomas), previous ipsilateral, and/or non-curative surgery. Six additional patients were excluded because of incomplete medical charts. Four hundred and fifty-one patients had a preoperative leucocyte count assessed in our clinical laboratory in the 6 weeks preceding surgery and were included in the analysis. Indications for surgery were defined according to international recommendations and guidelines.\(^2\)\(^2\)\(^-\)\(^2\)\(^7\) These indications were discussed weekly by the multidisciplinary board of our breast clinic and regularly updated and adjusted with new international recommendations and data of the literature. All surgeries were performed by the same surgeon (M.B.) and followed-up jointly with an oncologist (J.-P.M.). Chemotherapy, radiotherapy, and hormone therapy were performed according to the international expert consensus (9th and 10th St-Gallen consensus).\(^2\)\(^2\)\(^-\)\(^2\)\(^7\)

After surgery, patients were followed-up trimonthly for 2 yr, then twice a year for 3 yr, and annually thereafter. The following data were obtained from the medical records: preoperative (patient characteristic) characteristics, tumour size, histological grade and type, oestrogen and progesterone receptor status, HER-2 expression, extent of axillary nodal disease, administration of adjuvant chemotherapy, radiotherapy, or endocrine therapy. The Nottingham prognostic index was calculated based on the histological findings.\(^2\)\(^2\)\(^-\)\(^2\)\(^7\) These data were compared between patients receiving or not intraoperative NSAIDs (Table 1). Except for age, all patient and tumour characteristics were similar between the two groups.

Leucocyte count

Leucocyte count was typically included in the routine preoperative evaluation and prospectively registered in a computed database. The latest preoperative value was recorded. All venous blood samples were processed in a blood analyzer (Sysmex; TOA Medical Electronics, Kobe, Japan) for the determination of the complete blood cell counts and differential counts of leucocytes. We recorded the neutrophil and the lymphocyte counts, and calculated the NLR.

Table 1 Characteristics of 720 patients undergoing conservative breast cancer surgery after the intraoperative use of the NSAIDs ketorolac or diclofenac. Data are presented as mean (SD) (range) or as number (%). \(^*\)\(P=0.007\) compared with no NSAID (Student’s t-test). NLR, preoperative neutrophil:lymphocyte ratio. Before 2009, histological grade was not determined for invasive lobular carcinoma. Lymph node invasion was analysed only if excised

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NSAIDs use (n = 510)</th>
<th>No NSAID use (n = 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (range)</td>
<td>56 (25-88)</td>
<td>60 (27-89)*</td>
</tr>
<tr>
<td>Tumour size (mm)</td>
<td>16 (12)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>99 (19%)</td>
<td>43 (20%)</td>
</tr>
<tr>
<td>2</td>
<td>182 (36%)</td>
<td>67 (32%)</td>
</tr>
<tr>
<td>3</td>
<td>179 (35%)</td>
<td>76 (36%)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>50 (10%)</td>
<td>24 (11%)</td>
</tr>
<tr>
<td>Lymph node invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>287 (66%)</td>
<td>140 (76%)</td>
</tr>
<tr>
<td>1-3 positive lymph nodes</td>
<td>121 (28%)</td>
<td>35 (19%)</td>
</tr>
<tr>
<td>&gt;3 positive lymph nodes</td>
<td>28 (6%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Nottingham prognostic index</td>
<td>6.8 (4.1)</td>
<td>6.8 (2.5)</td>
</tr>
<tr>
<td>Hormonal receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestrogen positive</td>
<td>434 (85%)</td>
<td>167 (80%)</td>
</tr>
<tr>
<td>Progesterone positive</td>
<td>411 (81%)</td>
<td>162 (77%)</td>
</tr>
<tr>
<td>HER-2 expression</td>
<td>50 (10%)</td>
<td>17 (8%)</td>
</tr>
<tr>
<td>NLR</td>
<td>2.71 (1.56)</td>
<td>2.98 (1.79)</td>
</tr>
<tr>
<td>Ketorolac use</td>
<td>363 (71%)</td>
<td>—</td>
</tr>
<tr>
<td>Diclofenac use</td>
<td>147 (29%)</td>
<td>—</td>
</tr>
</tbody>
</table>
NSAIDs administration

Intraoperative use (always preincisional) of ketorolac (typically 20 mg in patients under 60 kg, and 30 mg in patients more than 60 kg) or diclofenac (75 mg) was recorded. The NSAIDs choice was at the anaesthesiologist’s discretion according to contraindications (renal, gastrointestinal). All surgeries were performed under general anaesthesia.

Detailed endpoints definitions

Survival time was measured from the date of surgery to the date of death. Patients were censored at the date of last follow-up if alive at the end of follow-up. Since cancer recurrence could not be excluded in many cases (no autopsy), overall survival (OS), often proposed as the gold standard endpoint was considered. DFS was measured from the date of surgery to the date of first recurrence or death from any cause (whichever comes first); patients were censored at the date of last follow-up if recurrence-free and alive at the end of follow-up. New primary breast cancer was not considered as a recurrence in the present analyses.

Objectives

Our primary objectives were to investigate the effect on outcome (DFS and OS) of intraoperative NSAIDs (ketorolac or diclofenac) and the prognostic significance of preoperative NLR value. Consequently, our primary endpoints were OS time and length of DFS.

Statistical analysis

Before the start of the study, a power analysis was performed based on previously published data. Using a log-rank test, we found that 325 patients per group would be needed to confirm a difference based on recurrence rate of 11% in the control group and 5% in the NSAIDs group. Therefore, as we were able to include more than 700 patients, we conducted the analyses. Patients’ baseline characteristics are presented as mean (sd) or number (%). Categorical variables between patients receiving or not intraoperative NSAIDs were compared with the χ² test, and continuous ones with the Student t-test. The univariate Cox model and log-rank test were used to assess the potential impact of these baseline characteristics and to investigate the prognostic value of NLR on outcome. The Kaplan–Meier analyses were used to estimate DFS and OS probabilities. Assuming the possibility of a non-linear impact of the NLR value on outcome, violating the Cox model’s assumption, we introduce it as a binary variable (NLR >3.3 or ≤3.3) after identifying the optimal cut-off with a receiver-operating curve (data not shown). After univariate analysis, the Cox regression model was used for multivariate analysis while adjusting for any baseline factors and intraoperative or oncological factors related to the outcome in the univariate analysis (P ≤0.05). We used stepwise manual backward regression and all factors significant at P-value of ≤0.05 were retained in the final model. STATISTICA (data analysis software system) version 7 (Statsoft Inc., 2004, Tulsa, OK, USA) was used for all analyses.

Results

Patients and tumour characteristics

The data from 720 patients meeting the inclusion criteria were reviewed. Ketorolac was the most frequently used NSAID (n=363/510, 71%). Because few patients received diclofenac (n=147/510, 29%), the data for ketorolac and diclofenac were pooled for subsequent analyses. Patient characteristic data, tumours characteristics, and oncological prognostic factors are shown in Table 1. Apart from age, all characteristics of the patients receiving intraoperative NSAIDs, compared with those without NSAID, were comparable. The median follow-up time was 69.8 months (inter-quartile range 25–75, 53.5–89.9). Cancer relapse was observed in 72 patients (36 locoregional recurrences, in the same breast or in the related lymph nodes, and 36 distant metastases occurrences). Death occurred in 37 patients.

Effect of NSAIDs and NLR on DFS and OS in uni- and multivariate analyses

Univariate analysis showed that greater tumour size, negative hormonal receptor status, NLR >3.3, and no intraoperative NSAID were significantly associated with shorter DFS (Table 2). Tumour size, NLR >3.3, and no NSAID were also prognostic factors for OS (Table 2). This was confirmed by the analyses of the Kaplan–Meier curves of DFS and OS (Figs 2–5). For DFS and OS, we performed two multivariate Cox’s regression model (including age, tumour size, histological grade, lymph node invasion, hormonal receptor status, HER-2 expression, NLR >3.3, and NSAIDs use) with stepwise manual backward selection. Tumour size, NLR >3.3, and NSAIDs use were the only independent risk factors retained in our two models (Table 3).

Discussion

In this retrospective analysis of patients undergoing conservative breast cancer surgery, we observed an association between the use of NSAIDs (ketorolac or diclofenac), and a high preoperative NLR, and reduced DFS.

The association between the intraoperative administration of NSAIDs (ketorolac or diclofenac) with a longer DFS and OS in breast cancer patients after conservative surgery is consistent with our previous data. It suggests that, even in patients with small tumours, undergoing conservative breast cancer surgery, NSAIDs may improve breast cancer outcome. In contrast, in patients with prostate cancer, there did not seem to have been an association between intraoperative administration of ketorolac during prostatectomy and improved DFS. It is possible that any putative effect of NSAIDs might be tumour-specific. The host’s immune response to different tumours may also perhaps be affected differently by NSAIDs, since NSAIDs have been reported to reduce tumour/host interactions, such as tumour cell adhesion to endothelial cells or tumour cell invasion.

The other finding of this study is the potential prognostic value of high NLR for breast cancer recurrence and
postoperative mortality. In a previous study, NLR correlated with tumour size and patient age. Our present results suggest that the prognostic value of NLR for DFS is independent of tumour size and patient's age. There are several possible explanations for this discrepancy. Patients' differing immune responses to cancer include activation of tumour-associated neutrophils, which are implicated in the production of reactive oxygen species, basic fibroblast growth factor, prostaglandin E2 (PGE2), and vascular endothelial growth factor. PGE2 decreases the number and activity of natural killer cells and increases the proportions of tumour-associated immunosuppressive cells.

Table 2 Univariate analyses of possible prognostic factors associated with DFS and OS in 720 patients operated for conservative breast cancer surgery, with a median follow-up of 69.8 months (inter-quartile range 25–75, 53.5–89.9). Data are presented as factor effect (β) estimated from the univariate Cox regression model, HR, and associated 95% CI and P-value.

<table>
<thead>
<tr>
<th></th>
<th>Disease-free survival</th>
<th>Overall survival</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n = 720</td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>−0.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Tumour size</td>
<td>0.025</td>
<td>1.02</td>
</tr>
<tr>
<td>Histological grade</td>
<td>−0.006</td>
<td>0.99</td>
</tr>
<tr>
<td>Lymph node invasion</td>
<td>0.41</td>
<td>1.50</td>
</tr>
<tr>
<td>Hormonal receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestrogen positive</td>
<td>0.011</td>
<td>1.01</td>
</tr>
<tr>
<td>Progesterone positive</td>
<td>0.010</td>
<td>1.01</td>
</tr>
<tr>
<td>HER-2 expression</td>
<td>−0.001</td>
<td>0.998</td>
</tr>
<tr>
<td>NLR &gt; 3.3</td>
<td>0.79</td>
<td>2.20</td>
</tr>
<tr>
<td>Ketorolac or diclofenac use</td>
<td>−0.58</td>
<td>0.56</td>
</tr>
</tbody>
</table>

This study has many methodological limitations, especially its retrospective design, with its inherent selection bias. Concerning the statistics, a false-positive error remains possible. Uncontrolled and unrecognized biases are possible, even though we used prospectively listed patients and high-quality databases. NSAIDs were administered depending on the preference of the anaesthesiologist in charge of the patient. In summary, our results suggest that intraoperative administration of NSAIDs may be associated with prolonged DFS after conservative breast cancer surgery. Moreover, preoperative high NLR might be a marker for adverse outcome in breast cancer patients undergoing conservative surgery.
prospective, randomized trial to investigate if these associations are truly causal (NCT01806259) is underway.

Authors’ contributions

P.F., C.B., J.-P.M., and M.B. contributed to the design, the data collection, and the redaction of the manuscript. P.G.C. and M.D.K. contributed to the design and the redaction of the manuscript.

Declaration of interest

None declared.

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References

8 American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in


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