RESEARCH

Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data

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Abstract

Objectives To evaluate the effect of postoperative use of non-steroidal anti-inflammatory drugs (NSAIDs) on anastomotic leakage requiring reoperation after colorectal resection.

Design Cohort study based on data from a prospective clinical database and electronically registered medical records.

Setting Six major colorectal centres in eastern Denmark.

Participants 2766 patients (1441 (52%) men) undergoing elective operation for colorectal cancer with colonic or rectal resection and primary anastomosis between 1 January 2006 and 31 December 2009. Median age was 70 years (interquartile range 62-77).

Intervention Postoperative use of NSAID (defined as at least two days of NSAID treatment in the first seven days after surgery).

Main outcome measures Frequency of clinical anastomotic leakage verified at reoperation; mortality at 30 days.

Results Of 2756 patients with available data and included in the final analysis, 1871 (68%) did not receive postoperative NSAID treatment (controls) and 885 (32%) did. In the NSAID group, 655 (74%) patients received ibuprofen and 226 (26%) received diclofenac. Anastomotic leakage verified at reoperation was significantly increased among patients receiving diclofenac and ibuprofen treatment, compared with controls (12.8% and 8.2% v 5.1%; $P<0.001$). After unadjusted analyses and when compared with controls, more patients had anastomotic leakage after treatment with diclofenac (7.8% (95% confidence interval 3.9% to 12.8%)) and ibuprofen (3.2% (1.0% to 5.7%)). But after multivariate logistic regression analysis, only diclofenac treatment was a risk factor for leakage (odds ratio 7.2 (95% confidence interval 3.8 to 13.4), $P<0.001$; ibuprofen 1.5 (0.8 to 2.9), $P=0.18$). Other risk factors for anastomotic leakage were male sex, rectal (v colonic) anastomosis, and blood

transfusion. 30 day mortality was comparable in the three groups (diclofenac 1.8% v ibuprofen 4.1% v controls 3.2%; $P=0.20$).

Conclusions Diclofenac treatment could result in an increased proportion of patients with anastomotic leakage after colorectal surgery. Cyclo-oxygenase-2 selective NSAIDs should be used with caution after colorectal resections with primary anastomosis. Large scale, randomised controlled trials are urgently needed.

Introduction

With leakage rates of around 3% after colonic resections and 10% after rectal resections and with mortality rates of up to 32%,^{1 2} anastomotic leakage remains a serious challenge for colorectal surgeons worldwide. In the past few years, there has been increased focus on the possible effect of non-steroidal anti-inflammatory drugs (NSAIDs) on the risk of anastomotic leakage.³⁻⁶ Retrospective studies have shown an association between anastomotic leakage and postoperative treatment with diclofenac and celecoxib, two NSAIDs that are predominantly cyclo-oxygenase-2 selective.³⁻⁵ These two drugs have a high and similar affinity for the cyclo-oxygenase-2 enzyme.⁷

Several publications focusing on adverse cardiovascular events in non-surgical patients treated with NSAIDs have shown an increased risk of cardiovascular events such as acute myocardial infarction and ischaemic stroke.⁸⁻¹¹ This effect has been shown even among young and healthy people and after short term use.^{12 13}

To investigate the possible effect of postoperative NSAID treatment on the proportion of patients with anastomotic leakage, we performed a study based on data from the Danish Colorectal Cancer Group database and electronically registered medical

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Web table 1: Risk factors for 30-day mortality after colorectal resection - univariate logistic regression analyses

Web table 2: Risk factors for 30-day mortality after colorectal resection - multivariate logistic regression analysis

records including detailed information on postoperative treatment.¹⁴

Methods

This study was based on data from the Danish Colorectal Cancer Group's national prospective database, which has a data completeness rate of over 96%,¹⁵ and electronically registered medical records with detailed information on postoperative treatment. Using these registries, we aimed to compare the risk of anastomotic leakage among patients receiving regular postoperative NSAIDs (cases) with those not receiving regular NSAID treatment (controls). In Denmark, electronic medical records were introduced to hospitals from 2003 onwards. With these new recording systems, all treatments administered at a hospital were documented. The medical staff is not allowed to administer treatment without electronic registration and, therefore, data completeness is 100%.

We included patients from the six major centres responsible for colorectal cancer surgery in eastern Denmark (population 2.6 million, about half of the country's entire population). This area was chosen for logistical reasons, since registrations from medical records had to be performed with our physical presence in the different areas. Inclusion criteria were patients with available electronic medical records who had undergone an elective operation for colorectal cancer between 1 January 2006 and 31 December 2009 with either colonic or rectal resection, and receiving a primary anastomosis.

From the database, we retrieved information on resection type (coded as either colonic or rectal resection), demographic variables, comorbidities (pre-existing diabetes mellitus, ischaemic heart disease, chronic obstructive lung disease, or hypertension), alcohol and tobacco use, tumour T stage, intraoperative blood loss (mL) and transfusion (whether it occurred or not), open or laparoscopic procedure, and anastomotic leakage. Alcohol consumption was registered as units of alcohol per week (1 unit=12 g ethanol) in the following categories: 0 units, 1-14 units, 15-21 units, and more than 21 units. Tobacco use was registered as active smokers, previous smokers, and non-smokers. We defined anastomotic leakage, according to the definition previously proposed and used,^{16 17} as clinical leakages requiring acute surgical intervention such as re-laparoscopy or re-laparotomy. Radiological or endoscopic drainage was not considered surgical intervention.

Data for postoperative NSAID consumption from electronic medical records were registered for each patient by three observers blinded for the presence of anastomotic leakage. Furthermore, the type of NSAID (that is, the active component) was recorded. In the electronic records, this information was registered if and when a dose of a given drug was prescribed and if this dose was taken by the patient. Only doses registered as taken were included. We defined regular postoperative consumption of NSAIDs as at least two days' treatment with a relevant daily dose of an NSAID in the first seven days after surgery. This period was chosen because clinical anastomotic leakage occurs after a median of seven days postoperatively.¹⁸ We defined the relevant daily dose as at least 50 mg for diclofenac and at least 800 mg for ibuprofen. We retrieved data for 30 day postoperative mortality from the Danish Central Person Registry by looking up each patient, and related these data to the date of surgery. No information on cause of death was available; therefore, mortality was defined as all cause mortality.

Statistical analyses were performed with SPSS (version 17). We tested for distribution of variables between groups with χ^2

and two sided Fischer's exact tests for dichotomous variables and with Mann-Whitney's test for continuous variables. To identify possible risk factors for anastomotic leakage, we planned to perform univariate logistic regression analyses on all variables with less than 10% missing data. These variables included NSAID use and drug type, intraoperative transfusion, colonic or rectal resection, sex, surgical centre where surgery was performed, age at time of operation, intraoperative blood loss, American Society of Anesthesiologists' score, open or laparoscopic surgery, and tumour T stage. We included all variables with $P<0.1$ in a multivariate logistic regression analysis (method: backwards, likelihood ratio). Furthermore, we planned to test for interactions between the variables included in the multivariate analysis—we included any significant interactions in the multivariate analysis. In the multivariate analysis, we excluded patients if they had missing data for a variable included in the model. We provided the number and percentage of patients excluded from the multivariate analysis, and presented results as odds ratios or proportions with 95% confidence intervals and P values, unless stated otherwise. Differences between independent proportions were calculated as absolute risk increase with confidence intervals and calculated according to method 10 in reference 19.¹⁹

Results

Based on the inclusion criteria, we retrieved data for 2766 patients with colorectal resection and primary anastomosis, from electronic medical records. We excluded 10 patients with no information available on postoperative anastomotic leakage. Thus, 2756 patients were included in the analysis (fig 1). In this group, 1871 (68%) patients did not receive regular postoperative treatment of NSAIDs, and 885 (32%) did. Of the patients treated with NSAIDs, 655 (74%) received ibuprofen and 226 (26%) received diclofenac. Four patients received other types of NSAIDs and were not included in the univariate and multivariate analyses. In each NSAID group, 622 (95%) received at least 1200 mg ibuprofen per day and 224 (99%) received at least 100 mg diclofenac per day.

Table 1 presents demographic variables and patient characteristics. The median age of the entire study population was 70 years (interquartile range 62-77), of whom 1441 (52%) were men. We found 996 (36%) laparoscopic procedures and 768 (28%) rectal anastomoses. Overall, 179 (6.5%) patients had anastomotic leakage confirmed at reoperation, and 91 (3.3%) died within 30 days after surgery. Among patients with anastomotic leakage the rate of all cause mortality at 30 days was 9.5% (17/179). All patients were subjected to 30 day follow-up, but we could not retrieve information on 30 day mortality in four patients (0.1%).

Table 2 presents patient characteristics in the three study populations, based on presence and type of NSAID use. Compared with controls, the proportion of patients with anastomotic leakage confirmed at reoperation was significantly higher in the NSAID groups than in the control group. Anastomotic leakage occurred in 29 (12.8%) patients treated with diclofenac, in 54 (8.2%) treated with ibuprofen, and in 95 (5.1%) controls ($P<0.001$ for diclofenac v controls; $P=0.004$ for ibuprofen v controls). In effect, after unadjusted analyses and when compared with controls, the increase in absolute risk of anastomotic leakage was 7.8% (95% confidence interval 3.9% to 12.8%) after diclofenac treatment, and 3.2% (1.0% to 5.7%) after ibuprofen treatment.

We saw no significant differences in 30 day postoperative mortality between the three groups. We found four (1.8%) deaths

in the diclofenac group, 27 (4.1%) in the ibuprofen group, and 59 (3.2%) in the control group within 30 days after operation ($P=0.31$ for diclofenac *v* controls; $P=0.26$ for ibuprofen *v* controls; unadjusted data; table 2). Thus, compared with controls, there was a reduction in absolute risk of -1.4% (95% confidence interval -2.8% to 1.4%) after diclofenac treatment, and an increase in absolute risk of 1.0% (-0.6% to 2.9%) after ibuprofen treatment. Furthermore, mortality after anastomotic leakage did not differ between groups. Eight of 54 patients died in the ibuprofen group (14.8% (5.3% to 24.3%)), none of 29 died in the diclofenac group (0% (0% to 9.5%)), and eight of 95 died in the control group (8.4% (2.8% to 14.0%); $P=0.082$; unadjusted data).

In the control group ($n=1871$), 231 (12.3%) patients received fewer than two days of regular postoperative treatment with, or a single dose of, an NSAID. This subgroup of the control group did not differ from the remaining part of the control group with regard to the proportion of patients with anastomotic leakage ($12/231$ (5.2%) *v* $83/1640$ (5.1%), difference in absolute risk 0.1% (-2.4% to 3.9%); $P=1.0$; unadjusted data). There were more laparoscopic procedures among controls than among patients receiving NSAID treatment. We also saw more non-smokers among the patients receiving diclofenac, and alcohol was ingested in larger quantities among those receiving ibuprofen. Body mass index was higher among patients treated with diclofenac. The volume of intraoperative blood loss was higher among patients treated with NSAIDs, and transfusion was also given more often in patients receiving NSAIDs (table 2).

To identify individual risk factors for anastomotic leakage, based on less than 10% missing data, we did univariate logistic regression analyses (table 3). Based on the $P<0.1$ limit, we included NSAID treatment and drug type, sex, intraoperative transfusion, hospital where surgery was performed, and colonic or rectal resection in the multivariate analysis.

In subsequent repeated multivariate logistic regression analyses, we tested for any possible interactions between drug specific NSAID treatment and the other variables (table 4). We found only one significant interaction (between NSAID and intraoperative transfusion; $P=0.032$). Accordingly, this interaction was included in the final analysis with multivariate logistic regression. The final analysis included 2743 patients, because nine (0.3%) had missing data, and four (1%) received NSAIDs other than ibuprofen and diclofenac. The analysis showed a significantly increased risk of anastomotic leakage among patients receiving postoperative diclofenac (odds ratio 7.2 (95% confidence interval 3.8 to 13.4); $P<0.001$). With regard to postoperative ibuprofen treatment, no increased risk was found (1.5 (0.8 to 2.9); $P=0.18$). Mean daily doses of NSAIDs were 120 mg (standard deviation 29) for diclofenac and 1430 mg (326) for ibuprofen. No patients received two or more types of NSAIDs. Male sex, intraoperative transfusion, the hospital where the surgery was performed, and rectal anastomosis (*v* colonic) were also associated with an increased risk of anastomotic leakage (table 5, fig 2).

Using the same methods as described above, we also performed univariate and multivariate analyses with 30 day mortality as the dependent variable, to identify risk factors for mortality within 30 days of surgery (web tables 1-2). In short, these risk factors included anastomotic leakage verified at reoperation, intraoperative transfusion, increasing age, and an American Society of Anesthesiologists' score of III or IV. Postoperative treatment with diclofenac or ibuprofen did not influence 30 day mortality.

Discussion

Principal findings

In this study, based on prospective data from a nationwide clinical database and electronic medical records including information on postoperative treatment, we have shown an increased risk of anastomotic leakage requiring reoperation with postoperative diclofenac treatment after colorectal resections for cancer. Postoperative treatment with ibuprofen, another NSAID, did not increase the risk of anastomotic leakage after multivariate analysis. We obtained data from national databases where data registration is mandatory, and thus data were valid and not biased.

NSAIDs are often used in postoperative analgesic regimens, especially in fast track settings, and are currently a part of the recommended analgesic treatment after colorectal resections.^{20 21} Our results could therefore have an important effect on daily clinical practice. Future studies should investigate whether NSAIDs influence healing in anastomoses in the upper gastrointestinal tract as well as in other surgical areas where early tissue healing is crucial.

Strengths and weaknesses of the study

The primary strengths of this study lie in the strict design and the validity and accuracy of the data. Data from the Danish Colorectal Cancer Group database, including those for anastomotic leakage, are controlled consecutively and have been validated previously. Data completeness is above 96%.^{14 15 22} Anastomotic leakage was defined as clinically significant leakages requiring surgical intervention. Thus, all leakages were verified at reoperation. Moreover, registrations on postoperative NSAID use were not only based on the departments' standard analgesic regimens, but also performed as individual patient-by-patient registrations by observers blinded for the presence of anastomotic leakage. Furthermore, only NSAID doses registered as taken by the patients were included by the observers. All analyses, including subgroup analyses of different NSAIDs, were preplanned and performed according to the protocol approved by the Danish Colorectal Cancer Group. We also defined the drug specific use of NSAIDs in the protocol (at least two days of treatment), distinguished from the non-use of NSAIDs.

The optimal study design would have been a randomised controlled trial. To identify a decrease in risk of 30 % in anastomotic leakage, the trial would require 2100 patients in each group (based on $\alpha=0.05$ and $\beta=0.20$). Until such a study is performed, recommendations can be based on large samples with valid data, such as those obtained from large prospective clinical databases. In database studies such as the present study, the risk of confounding by indication is often mentioned, and this risk could be a potential limitation in our study. Although confounding can never be ruled out, several points suggest that our results are not subject to confounding by indication to a degree that would change our conclusions.

Firstly, for elective colorectal resections, surgical centres use standard analgesic regimens that are prescribed before the operation. Thus, a surgeon admitting a patient to hospital would have already determined whether the postoperative analgesic treatment will include NSAIDs. The only reason for not including NSAIDs, if these drugs were part of the department's standards, was a history of peptic ulceration. Secondly, NSAID treatment was defined in the protocol as two or more days of regular treatment, thereby ruling out patients receiving a single dose administered in the acute setting owing to increased

abdominal pain or other reasons for pain such as musculoskeletal pain. Thirdly, we have performed multivariate logistic regression and adjusted for interactions between variables, as is recommended to reduce confounding. Finally, for breakthrough pain, strong opioids are normally used in Denmark,²³⁻²⁵ as recommended.²¹

Another limitation lies in the poor registration of comorbidities such as ischaemic heart disease and diabetes in the database (about 50% of missing data). Thus, no conclusions with regard to the effect of these factors on anastomotic leakage rates can be made on the basis of this study. Also, as shown in table 2, the groups were not comparable with regard to all preoperative factors registered. However, most differences were small and not of clinical significance. Furthermore, among the unevenly distributed factors, only intraoperative transfusion (fewer transfusions among patients treated with diclofenac) was associated with an increased risk of anastomotic leakage verified at reoperation. Intraoperative transfusion is already known to increase the risk of anastomotic leakage,²⁶⁻²⁸ which only strengthens our result of increased risk among patients treated with diclofenac. Finally, some might argue that instead of using univariate and multivariate logistic regression analyses, we should have analysed the data by propensity scores and propensity score matching. Propensity scores can balance covariates observed at baseline, but can not balance unmeasured covariates (possible confounders).²⁹ Consequently, confounding is reduced similarly with multivariate analysis and propensity score and therefore, we decided to perform a classical multivariate analysis.

Comparison with other studies

In the multivariate analysis, in addition to diclofenac treatment, we identified risk factors for anastomotic leakage. These findings correspond well with the literature and thus confirm the validity of our data. Male sex,^{14 17} blood transfusion,²⁶⁻²⁸ and rectal resections have been suggested to increase the risk of anastomotic leakage.^{17 30} In our study, intraoperative transfusion was associated with a high odds ratio of 7.00 for anastomotic leakage (table 5). This result can be expected, since intraoperative transfusion will impair immune function³¹ and is a surrogate marker for a difficult procedure, perhaps an insufficient anastomotic perfusion caused by anaemia or hypotension, or a suboptimal surgical technique.

Previously, Schlacta and colleagues performed a randomised controlled trial evaluating the possible opioid saving effect of postoperative ketorolac treatment.⁶ Ketorolac is an NSAID with primarily cyclo-oxygenase-1 specificity.³² The authors reported an increased risk of anastomotic leakage among the patients receiving regular ketorolac in the postoperative period. However, with the small sample size, statistical significance was not achieved. Moreover, retrospective studies have shown significantly increased risk of anastomotic leakage with treatment using NSAIDs that are cyclo-oxygenase-2 selective. Holte and colleagues showed an increased number of leakages in a period when celecoxib was used as regular analgesic treatment in a fast track setting.³ We have also previously shown a significantly increased risk of anastomotic leakage when diclofenac was used for postoperative analgesia after laparoscopic colorectal resections.⁴ Celecoxib and diclofenac have a high and similar affinity to cyclo-oxygenase-2.⁷

Recently, Gorissen and colleagues found an increased risk of anastomotic leakage after non-selective NSAID treatment but not after treatment with compounds that were more cyclo-oxygenase-2 selective (although their study had a limited

sample size).⁵ The authors stated that diclofenac was the most commonly prescribed non-selective compound. However, they did not provide the precise number of patients treated with diclofenac. The study did show a dose-response association, with increased risk after three to five days of exposure.⁵ In the three previous studies on this subject, NSAID use was registered on the basis of department standards³ and postoperative prescriptions,^{4 5} whereas the present study included only NSAIDs recorded electronically as administered to the patient, which improved data accuracy.

Possible explanations

NSAIDs regulate prostanoid production via inhibition of the cyclo-oxygenase-1 and cyclo-oxygenase-2 enzymes.³³ It remains unclear by which mechanism (or mechanisms) NSAIDs exert their effect on colorectal anastomoses. Effects on collagen production and cross-linking have been proposed in experimental studies.³⁴⁻³⁶

Furthermore, in patients at risk of cardiovascular disease, studies have shown an increased risk of adverse cardiovascular events with NSAID treatment, especially with NSAIDs that are more selective to cyclo-oxygenase-2 and after therapy of short duration.⁸⁻¹³ In all of these studies, similar to those studies indicating a link between anastomotic leakage and NSAIDs,³⁻⁵ diclofenac and other drugs with a high level of cyclo-oxygenase-2 selectivity were among the NSAIDs with the highest hazard ratios. Moreover, in a randomised clinical trial comparing valdecoxib (a cyclo-oxygenase-2 selective NSAID) with placebo for postoperative analgesia after coronary artery bypass grafting, the incidence of postoperative thrombotic cardiovascular events increased greatly with valdecoxib treatment.³⁷ Thromboses occurred during NSAID treatment within the first 10 postoperative days.

Thus, microthromboses or microemboli, and therefore limitation of blood supply to the fragile anastomosis, is possibly an important mechanism behind the adverse effect of NSAIDs that are cyclo-oxygenase-2 selective NSAIDs. Also, the lower risk of thromboembolic events with ibuprofen and other non-selective or cyclo-oxygenase-1 selective drugs⁸⁻¹³ could therefore explain why only diclofenac and not ibuprofen increased the risk of anastomotic leakage in this study.

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Contributors: MK was responsible for the study conception and design; acquisition, analysis and interpretation of data; manuscript drafting and revision; and is the study guarantor. IG and JR were responsible for the study conception and design, critical manuscript revision and approval, supervision, and administrative support. All authors have had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any

What is already known on this topic

- NSAIDs are recommended as part of a balanced multimodal analgesic regimen after colorectal resection
- Retrospective studies have suggested an increased rate of anastomotic leakage when using cyclo-oxygenase-2 (COX-2) selective NSAIDs after surgery
- However, these studies had limited sample sizes, and NSAID consumption was not registered prospectively

What this paper adds

- Risk of anastomotic leakage increased with postoperative use of diclofenac, a COX-2 selective NSAID; use of the COX-1-selective NSAID ibuprofen did not increase risk
- COX-2 selective NSAIDs should be used with caution after colorectal resection and primary anastomosis
- Large scale randomised controlled trials should be conducted to determine whether use of these types of NSAIDs should be abandoned after colorectal resection

organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the Scientific Council of the Danish Colorectal Cancer Group and by the Danish Data Protection Agency before initiation (J 2008-41-2484). According to Danish law, because of the study design with no patient contact and not involving biological material, ethical committee approval should not be obtained for this type of study.

Data sharing: Dataset and multivariate analyses examining risk factors for all cause mortality at 30 days are available from the corresponding author at madsklein1@gmail.com.

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Tables

Table 1 | Population characteristics and data completeness

Variable	Total study population (n=2756)	Missing data (%)
Age (years)*	70 (62-77)	0
Sex		
Male	1441 (52)	0
Female	1315 (48)	
Body mass index*	24.8 (22.4-27.8)	23
ASA score		
I	637 (23)	1
II	1639 (60)	
III	428 (16)	
IV	20 (1)	
Tobacco use		
Active smoker	441 (20)	18
Previous smoker	950 (42)	
Non-smoker	854 (38)	
Alcohol consumption (units/week)		
0	621 (28)	19
1-14	1152 (52)	
15-21	183 (8)	
>21	271 (12)	
Ischaemic heart disease		
Yes	341 (26)	52
No	974 (74)	
Hypertension		
Yes	834 (64)	52
No	478 (36)	
Lung disease		
Yes	196 (15)	54
No	1084 (85)	
Diabetes mellitus		
Yes	259 (20)	52
No	1060 (80)	
Tumour T stage		
1	161 (6)	1
2	330 (12)	
3	1720 (63)	
4	516 (19)	
Procedure		
Open	1760 (64)	0
Laparoscopic	996 (36)	
Resection		
Colonic	1988 (72)	0
Rectal	768 (28)	
Intraoperative blood loss (mL)*	210 (100-500)	0
Intraoperative transfusion		
Yes	573 (21)	0
No	2178 (79)	

Table 1 (continued)

Variable	Total study population (n=2756)	Missing data (%)
Anastomotic leakage	179 (6)	0
Death within 30 days of surgery	91 (3)	0

Data are number (%) of patients unless stated otherwise. Totals of patients in each category do not add necessarily add up to 2756, owing to missing data.

ASA=American Society of Anesthesiologists.

*Median (interquartile range).

Table 2| Population characteristics according to type of NSAID use

Variable	Ibuprofen users (n=655)	Diclofenac users (n=226)	Controls (n=1871)	P
Age (years)*	70 (62 to 77)	69 (60 to 76)	70 (62 to 77)	0.19
Sex				
Male	349 (53)	130 (58)	960 (51)	0.18
Female	306 (47)	96 (43)	911 (49)	
Body mass index*	24.7 (22.2 to 27.6)	25.6 (23.0 to 29.1)	24.8 (22.4 to 27.8)	0.030
ASA score				
I	176 (27)	48 (21)	412 (22)	0.086
II	373 (58)	146 (65)	1118 (60)	
III	94 (15)	30 (13)	303 (16)	
IV	4 (1)	0	16 (1)	
Tobacco use				
Active smoker	72 (16)	36 (19)	333 (21)	<0.001
Previous smoker	219 (49)	33 (18)	696 (43)	
Non-smoker	158 (35)	117 (63)	578 (36)	
Alcohol consumption (units/week)				
0	95 (21)	62 (33)	462 (29)	0.009
1-14	237 (53)	92 (49)	822 (52)	
15-21	45 (10)	16 (9)	122 (8)	
>21	66 (15)	16 (9)	189 (12)	
Ischaemic heart disease				
Yes	77 (28)	24 (34)	240 (25)	0.21
No	203 (73)	47 (66)	722 (75)	
Hypertension				
Yes	167 (60)	44 (63)	621 (65)	0.35
No	112 (40)	26 (37)	340 (35)	
Lung disease				
Yes	41 (15)	9 (13)	146 (16)	0.80
No	230 (85)	62 (87)	790 (84)	
Diabetes mellitus				
Yes	56 (20)	15 (20)	188 (19)	0.93
No	224 (80)	56 (80)	778 (81)	
Tumour T stage				
1	46 (7)	10 (4)	105 (6)	0.20
2	70 (11)	25 (11)	235 (13)	
3	393 (61)	149 (67)	1175 (63)	
4	140 (22)	39 (17)	336 (18)	
Procedure				
Open	442 (67)	162 (72)	1153 (62)	0.001
Laparoscopic	213 (33)	64 (28)	718 (38)	
Resection				
Colonic	470 (72)	169 (75)	1346 (72)	0.65
Rectal	185 (28)	57 (25)	525 (28)	
Intraoperative blood loss (mL)*	250 (100 to 595)	265 (100 to 515)	200 (75 to 500)	0.010
Intraoperative transfusion				
Yes	185 (28)	32 (14)	355 (19)	<0.001
No	470 (72)	193 (85)	1512 (81)	
Anastomotic leakage	54 (8)	29 (13)	95 (5)	<0.001
30 day mortality	27 (4)	4 (2)	59 (3)	0.20

Table 2 (continued)

Variable	Ibuprofen users (n=655)	Diclofenac users (n=226)	Controls (n=1871)	P
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Data are number (%) of patients unless stated otherwise. Totals of patients in each category do not add necessarily add up to 655 (for ibuprofen users), 226 (for diclofenac users), and 1871 (for controls), owing to missing data. ASA=American Society of Anesthesiologists.

*Median (interquartile range).

Table 3| Risk of anastomotic leakage confirmed at reoperation based on univariate logistic regression analyses

Variable	P	Odds ratio (95% CI)
NSAID use and drug type	<0.001	—
None	—	1
Ibuprofen	0.003	1.68 (1.19 to 2.38)
Diclofenac	<0.001	2.75 (1.77 to 4.28)
Intraoperative transfusion	<0.001	5.14 (3.77 to 7.02)
Rectal v colonic resection	<0.001	1.87 (1.37 to 2.54)
Male sex	0.001	1.74 (1.27 to 2.39)
Surgical centre*	0.002	—
1	—	1
2	0.03	0.11 (0.02 to 0.82)
3	0.05	0.56 (0.32 to 1.00)
4	0.12	1.39 (0.92 to 2.11)
5	0.76	1.08 (0.66 to 1.76)
6	0.07	1.51 (0.98 to 2.35)
Age	0.14	0.90 (0.79 to 1.03)†
Intraoperative blood loss	0.17	1.02 (0.99 to 1.04)‡
ASA score	0.23	—
I	—	1
II	0.90	1.02 (0.70 to 1.51)
III	0.10	1.75 (0.93 to 2.39)
Laparoscopic v open surgery	0.24	0.83 (0.61 to 1.13)
Tumour T stage	0.90	—
4	—	1
3	1.00	1.00 (0.48 to 2.09)
2	0.79	0.92 (0.52 to 1.66)
1	0.66	1.09 (0.73 to 1.64)

ASA=American Society of Anesthesiologists.

*Centres numbered from 1 to 6.

†For each increment of 10 years.

‡For each increment of 100 mL.

Table 4| Interactions between NSAID use and selected variables

Variable	P*
NSAID use and drug type, and intraoperative transfusion	0.032†
NSAID use and drug type, and sex	0.053
NSAID use and drug type, and rectal/colonic resection	0.21
NSAID use and drug type, with surgical centre	0.80

*P value of interaction when included in multivariate logistic regression analysis, using the variables in table 3 that had P<0.1.

†Based on P<0.05, this interaction was included in the final multivariate logistic regression analysis.

Table 5| Risk of anastomotic leakage confirmed at reoperation based on multivariate logistic regression analysis

Variable	P	Odds ratio (95% CI)
NSAID use and type	<0.001	—
None	—	1
Ibuprofen	0.18	1.54 (0.82 to 2.86)
Diclofenac	<0.001	7.16 (3.82 to 13.4)
Intraoperative transfusion	<0.001	7.00 (4.51 to 10.9)
Rectal v colonic resection	<0.001	2.26 (1.62 to 3.15)
Male sex	0.003	1.65 (1.18 to 2.30)
Surgical centre*	0.003	—
1	—	1
2	0.021	0.09 (0.01 to 0.69)
3	0.98	0.99 (0.51 to 1.91)
4	0.77	1.09 (0.62 to 1.91)
5	0.21	1.50 (0.80 to 2.77)
6	0.007	2.10 (1.23 to 3.58)

Model included the variables from univariate analyses (table 3) with $P < 0.1$; and the significant interaction between NSAID use and drug type, and intraoperative transfusion (table 4).

*Centres numbered from 1 to 6.

Figures

Fig 1 Flowchart of patients included in study

Fig 2 Risk factors for anastomotic leakage after multivariate analysis