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Cohort Study

Impact of enteral prophylactic antibiotics on the trends of inflammatory markers following laparoscopic colorectal cancer surgery: A retrospective and prospective Cohort Study

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ABSTRACT

Background: The study aimed to assess the effect of oral prophylactic antibiotics (OAB) with mechanical bowel preparation (MBP) on the serial measurement of postoperative inflammatory markers and clinical outcomes of the patients undergoing laparoscopic colorectal cancer resection surgery.

Methods: A retrospective and prospective data collection was carried out from January 2019 to March 2020 for the patients undergoing laparoscopic colorectal cancer resection. Daily measurements of inflammatory markers were obtained up to 7 days following surgery. The measurements of inflammatory markers were compared between patients who received a 1 week course of OAB along with MBP to those who only received MBP.

Results: There were a total of 110 patients that were divided into 2 groups: patients who received OAB and MBP (n = 44, 40%) and those who had MBP only (n = 66, 60%). There was no significant difference between the patient characteristics and preoperative staging of the cancer between the 2 groups. The overall length of stay was significantly lower in the patients who received OAB (9.09 days [SD 7.94] vs. 6.63 days [SD 4.96], P 0.02). The patients with OAB and MAP had persistently and significantly low levels of white blood cell count, CRP, and neutrophil count throughout the postoperative period as compared to those who only had MBP.

Conclusion: The study demonstrated reduction in serial measurement of inflammatory markers throughout postoperative stay for the patients receiving preoperative OAB. The use of OAB helps in physiological recovery of the patient by reducing the inflammatory process postoperatively.

1. Introduction

Elective laparoscopic colorectal cancer resectional surgery is associated with certain recognized complications including anastomotic leakage, surgical site infection, ileus and intra abdominal collection with anastomotic leakage potentially being the most catastrophic complication [1,2]. The prevalence of anastomotic leakage varies from 1% to 19%, depending upon anatomical site, pre, intra and postoperative factors [3].

The role of prophylactic antibiotics in elective colorectal cancer resection surgeries in prevention of infection, anastomotic leak and overall complication rate has been long debated. Few randomised controlled trials have been conducted to assess the use of oral prophylactic antibiotics and a recent systematic review has shown reduction in the length of stay, incidence of surgical site infection and anastomotic leak [4]. The recent guidelines from the American Society of Colon and Rectal Surgeons recommend the use of Oral prophylactic Antibiotics in elective colorectal resection to reduce peri/post operative complications [5,6]. The use of oral prophylactic preoperative antibiotics in laparoscopic colorectal cancer resectional surgery is not widespread and only few centres practise it to our knowledge from communication with colorectal centres in England through conferences.

Current evidence suggests a potentially significant role for oral prophylactic antibiotics, either in combination with mechanical bowel preparation (MBP) or alone, in the prevention of postoperative complications in elective colorectal surgery, and in reducing SSI or anastomotic leaks [7]. Oral antibiotic prophylaxis, in combination with MBP and intravenous antibiotics, was superior to MBP and intravenous

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antibiotics alone in reducing SSI after elective colorectal resections. This treatment approach was also associated with significantly lower rates of anastomotic leak, ileus, reoperation, length of stay, readmission and mortality [8]. There was no association between the combination of antibiotics and outcome, as long as an aminoglycoside was included. Aminoglycosides administered orally reach very low levels in the circulation, and toxicity is vanishingly rare [9].

In the USA, some surgeons routinely use non-absorbable oral antibiotics such as Tobramycin and Amphotericin B - also known as selective decontamination of the digestive tract (SDD) [10]. A systematic review has indicated that SDD reduces anastomotic leak rates from 7.4% to 3.3% [10]. This finding has also been replicated in a recent study of over 8000 colorectal resections, demonstrating both lower surgical site infection and anastomotic leak rates in the treatment group [11]. Despite this, SDD is not currently in widespread practice in the United Kingdom and Ireland [12]. This may be due to lack of support of its use from NICE guidelines [13], strict prevailing antibiotic stewardship nationally and lack of large multicentre clinical trials and concerns regarding Hospital Acquired Infections and incidence of *Clostridium difficile* infection [14].

As part of our local Enhanced recovery programme in 2019 all patients received mechanical Bowel preparation and all of them only had stat dose of IV antibiotics prophylaxis just prior to the incision. However, later in the year, it was agreed to start all the patients on a 7 day prophylactic oral Neomycin regime prior to surgery for elective laparoscopic colorectal cancer resection. The policy was based on the presumed benefit of prophylactic oral antibiotics in reducing the risk of postoperative infections.

There is little evidence on how the oral prophylactic antibiotic course interacts with patients physiology to reduce the risk of infection and enhance early recovery. We hypothesize that the oral antibiotics suppress the surge of inflammation due to dissection and gut microbes which aids in early recovery of the patient and reduces the risk of infection. The aim of the study is to assess the effect of enteral prophylactic antibiotics on the inflammatory markers, length of stay and postoperative complications following elective laparoscopic resections for colorectal cancers.

2. Method

It was a retrospective cohort study. Before initiating the study, permission from the ethics, research and clinical governance department was obtained as study was designed to involve human subjects. The data was collected from January 1, 2019 to March 1, 2020 using Social Science Statistics online Software, version 2021 and Microsoft Office. The study was conducted in the department of colorectal surgery, Southend University Hospital, Essex, UK. The inclusion criteria of the study was as follows: any adult patient over the age of 16 undergoing laparoscopic curative resection for colorectal cancer. Up to August 2019, the departmental policy for pre-operative preparation for elective laparoscopic resection of colorectal cancer was for the patients to have mechanical bowel preparation a day before the operation and a stat dose of intravenous antibiotics just prior to skin incision. The departmental policy changed from August 2019 for preparation of colorectal cancer operation. The new policy consisted that all patients should receive a 7 day pre-operative oral Neomycin regime along with mechanical bowel preparation a day before the operation and intravenous antibiotic just prior to skin incision perioperatively. Hence, the study compared the patients who received oral prophylactic antibiotic courses to those who did not have it.

The data was collected retrospectively by accessing the electronic medical records of the patients involved and retrospectively tracking the blood results of the patients up to 7 days postoperatively. All of the patients had blood tests including full blood count and CRP done preoperatively as well as daily post-operatively as per the department's policy which helped in the data collection. For each patient, the inflammatory markers were recorded in the data collection. These included haemoglobin count, white blood cell count, lymphocyte count, neutrophil count, monocytes count, and CRP. The clinical outcomes were also noted for each patient that included length of stay, individual post-operative complications, overall complication rate, and any readmission to the hospital for postoperative complication 7 days after being discharged from the hospital.

The population distribution for each outcome was assessed for skewness and kurtosis. It was found to be non-parametric. Hence, Chi-square test was used to compare categorical variables and Mann Whitney *U* test was used to compare continuous variables. Some patients in the follow up period recovered early and their inflammatory markers settled before 7 days. They were discharged before 7 days. For data analysis and comparison of the average levels of inflammatory markers, it was assumed that their inflammatory markers were within the normal range for the missing values that corresponded to them being discharged earlier than 7 days. We also checked that these patients were not readmitted to the hospital for any infection in the following 7 days after being discharged from the hospital to reassure the assumption made for the data analysis.

The research was retrospectively registered with the research registry, the unique identification number is "researchregistry693'' www.researchregistry.com.

The work has been reported in line with the STROCSS criteria: Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C and Mathew G, for the STROCSS Group. The STROCSS 2019 Guideline: Strengthening the Reporting of Cohort Studies in Surgery. International Journal of Surgery 2019; 72:156–165 [16].

3. Results

There were a total of 110 patients included in the study. It was divided into 2 groups: patients who received prophylactic enteral antibiotics (n = 44, 40%) and those who did not (n = 66, 60%). The average age of the patients was 69.6 years and 53.9% (n = 60) of them were males. The pathological staging of the study population was as follows: Stage 1 (n = 24, 21.4%), Stage 2 (n = 33, 29.4%) and Stage 3 (n = 45, 40.2%). The types of laparoscopic surgeries were as following: anterior resection (n = 55, 50.0%), right hemi-colectomy (n = 35, 31.8%), abdominoperineal resection (n = 9, 8.2%), left hemi-colectomy (n = 8, 7.3%), and subtotal colectomy (n = 2, 1.8%). The common comorbidities associated with the patient population were ischaemic heart disease (n = 15, 13.6%), diabetes (n = 11, 10.0%), Chronic obstructive lung disease (COPD/asthma) (n = 12, 10.9%), obesity (n = 39, 35.4%), and mean ASA grade (2.3 SD 0.63). The average length of stay was 8.12 days (SD 7.61). The overall complication rate was 19.1% (n = 21).

The study population was divided into 2 groups, those who did not receive preoperative enteral antibiotics (n = 66, 60%) and those who received them (n = 44, 40%). The descriptive statistics of the 2 groups in the patient population are shown in Table 1. There was no significant difference between the characteristics of the 2 groups, however, the proportion of obese patients was significantly higher in patients who received preoperative enteral antibiotics (21 [47.7% vs. 18 [27.3%], P 0.03).

As shown in Table 2, the overall length of stay was significantly lower in the patients who received preoperative enteral antibiotics (9.09 days [SD 7.94] vs. 6.63 days [SD 4.96], P 0.02). There was no significant difference in other post-operative outcomes.

The serial measurement and comparison of the white blood cell count, CRP and neutrophil count showed that the patients with enteral preoperative antibiotics had persistently and significantly low inflammation markers throughout the post-operative period as compared to those patients who did not receive antibiotics *(Fig. 1)*. The average baseline preoperative counts were not significantly different in the 2 groups for white blood cell count (6.89 vs. 6.86, P 0.46), CRP (3.52 vs. 5.55, P 0.45) and neutrophil count (5.35 vs. 5.47, P 0.82) (see Table 3).

Table 1
Patient characteristics of the 2 comparative groups.

Characteristics	Patients without pre-op enteral antibiotics (n, %)	Patients who received pre-op enteral antibiotics (n, %)	P value
Male sex	32 (48.4%)	28 (63.6%)	0.12
Type of operation			
Anterior resection	35 (53.0%)	20 (45.4%)	0.44
Right hemi-colectomy	21 (3.8%)	16 (36.3%)	0.34
Left hemi-colectomy	3 (4.5%)	5 (11.4%)	0.18
Abdominoperineal resection	7 (10.6%)	2 (4.5%)	0.25
Cancer Staging			
Stage 1	14 (21.2%)	15 (34.1%)	0.13
Stage 2	24 (36.4%)	11 (25.0%)	0.06
Stage 3	28 (42.4%)	18 (40.9%)	0.87
Ischaemic heart disease	9 (13.6%)	6 (13.6%)	0.99
Diabetes	6 (9.1%)	5 (11.4%)	0.69
COPD/Asthma	9 (13.6%)	3 (6.8%)	0.25
Obesity	18 (27.3%)	21 (47.7%)	**0.03**
Autoimmune condition	11 (16.6%)	8 (18,2%)	0.84
Current smoker	17 (25.7%)	9 (20.4%)	0.52
Average ASA grade (SD)	2.28 (0.64)	2.32 (0.63)	0.89

Table 2
Comparison of postoperative clinical outcomes between the 2 groups.

Post-operative outcome	Patients without pre-op enteral antibiotics (n, %)	Patients who received pre-op enteral antibiotics (n, %)	P value
Length of stay (days) (mean [SD])	9.09 (7.94)	6.63 (4.96)	**0.02**
Overall complication rate (mean [SD])	0.34 (0.66)	0.22 (0.40)	0.49
Wound infection/ dehiscence	4 (6.1%)	2 (4.5%)	0.73
Anastomotic leak/ intra-abdominal collection	2 (3.0%)	0 (0%)	0.81
Bowel obstruction	2 (3.0%)	1 (2.3%)	0.81
Ileus	3 (4.5%)	1 (2.3%)	0.53
Intra-abdominal bleeding	2 (3.0%)	0 (0%)	0.81
Re-laparotomy	4 (6.1%)	0 (0%)	0.35
Cardio-pulmonary complication	1 (1.5%)	3 (6.8%)	0.14

4. Conclusion

Previous studies have demonstrated that following colorectal resection surgeries CRP progressively increases till 3rd postoperative day and then steadily declines, and that a continuous rising CRP after 3rd day of surgery warrants further investigations and assessment to ascertain any complications including infection, anastomotic leakage and intra-abdominal collection [15]. To our knowledge, a serial measurement of inflammatory markers has not been performed previously to assess the impact of oral prophylactic antibiotics on post operative physiological response in elective colorectal surgery. These tests are routinely done in surgical wards and understanding their trends may help predict post-operative complications and infection.

Our study shows that use of oral prophylactic antibiotics induces a significant reduction in inflammatory markers, including CRP, WCC and neutrophils, evident on postoperative daily serial measurement of these markers. It is hypothesized that use of oral antibiotics reduces the load of gut microbes as well as stops the translocation of these microbes into systemic circulation causing secondary infection leading to reduction in body inflammation following colorectal surgery. However, this has to be further evaluated.

A recent meta-analysis to assess clinical impact of prophylactic antibiotics in colorectal surgery showed promising results including a reduced rate of surgical site infection, reduced number of anastomotic leakage, post-op ileus and overall morbidity [5]. This validates use of oral prophylactic antibiotics in colorectal cancer resections and their role in improving the surgical outcome. Our study showed that patients who had preoperative oral antibiotics had reduced length of hospital stay, however it did not directly show a reduction in postoperative complications such as anastomotic leakage, surgical site infection and intra abdominal collection. It may be due to the small number of patients in the study compared to the compiled data from meta-analysis.

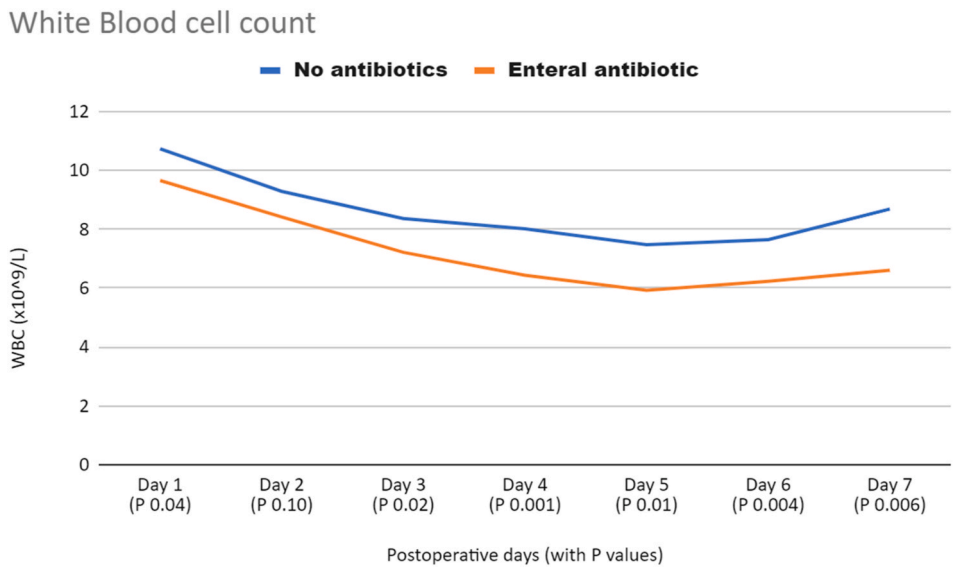
Various NHS trusts across the UK have different pre-operative regimes for colorectal cancer surgery, and mechanical bowel preparation is a widely practised constant and part of almost all of these regimes in the UK. Currently routine use of oral antibiotics is not in clinical practice in the UK owing to lack of National and regional studies. We currently advocate the usage of routine preoperative oral antibiotics along with mechanical bowel preparation owing to its desirable impact. In our study oral neomycin was given for 7 days prophylactically along with mechanical bowel preparation, which is part of the current pre-operative regime in our centre, and their concomitant use showed benefits but it is not clear whether the oral antibiotics are working in synergy with mechanical bowel preparation or have a similar effect on their own without it [5]. This is an area for potential research in further studies to provide high quality evidence.

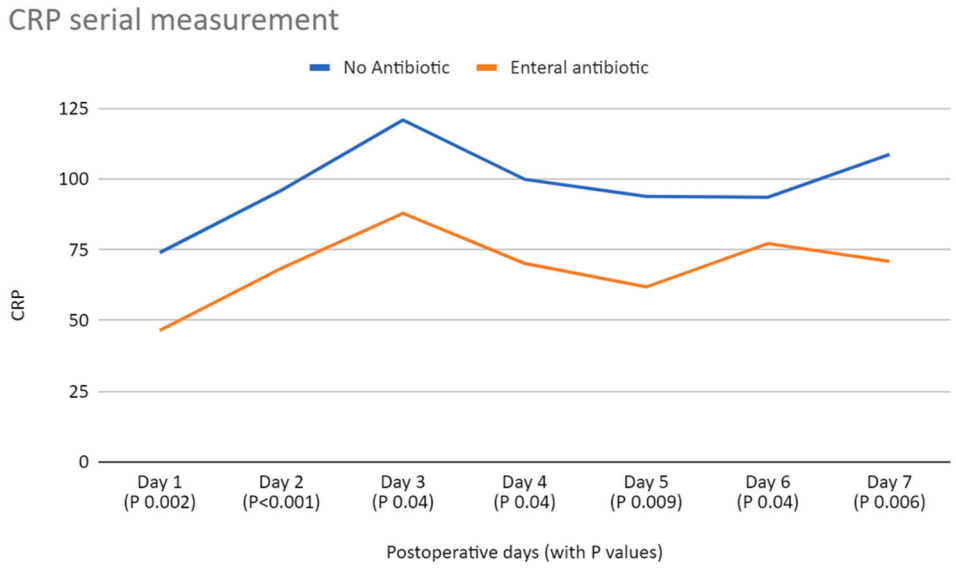
The study had certain limitations to be considered. The study was carried out in patients undergoing elective laparoscopic colorectal cancer surgery only which makes it prone to selection bias. However, this was done to make the comparative groups similar so that the effects of oral antibiotics is demonstrable without any confounding factors that impact the inflammatory process postoperatively. In our data, the 2 comparative groups had similar patient demographics, type of surgeries conducted and the staging of bowel cancer. Any elected laparoscopic colorectal cancer cases that had to be converted to open surgery were excluded from the study as open surgery can be a confounding factor towards postoperative complications including wound infection, intra-abdominal collection, prolonged recovery and increased hospital stay. Patients undergoing elective colorectal surgery for inflammatory bowel disease were also not included in the study as they do have significant underlying inflammation and assessment of the role of antibiotics on the systematic response to surgery would have been difficult to interpret. It will be interesting to perform another study to evaluate the impact of prophylactic antibiotics on the patients undergoing open colorectal surgery and surgery for inflammatory bowel disease. There were some patients in the study that were discharged earlier than 7 days because they recovered well. These patients were followed up and none of them had unplanned readmission in the next 7 days. For the analysis of the study, their inflammatory markers were assumed to be normal as they all had trending down from inflammatory to normal when they were discharged home.

The study showed substantial evidence in favour of preoperative prophylactic OAB along with MBP, this is owed to the fact that significant reduction in postoperative WCC, neutrophils and CRP was seen in the group taking OAB. When these results are analyzed in the light of recent meta-analysis [5], there is enough evidence of a significant role of preoperative oral antibiotic in elective laparoscopic colorectal cancer resection surgery and they should be made a part or preoperative regime across the UK.

Ethical approval

He study was conducted as a part of audit in our surgical department. We performed annual evaluation of our cancer operations. The audit approval was obtained from surgical audit department at Southend University hospital.





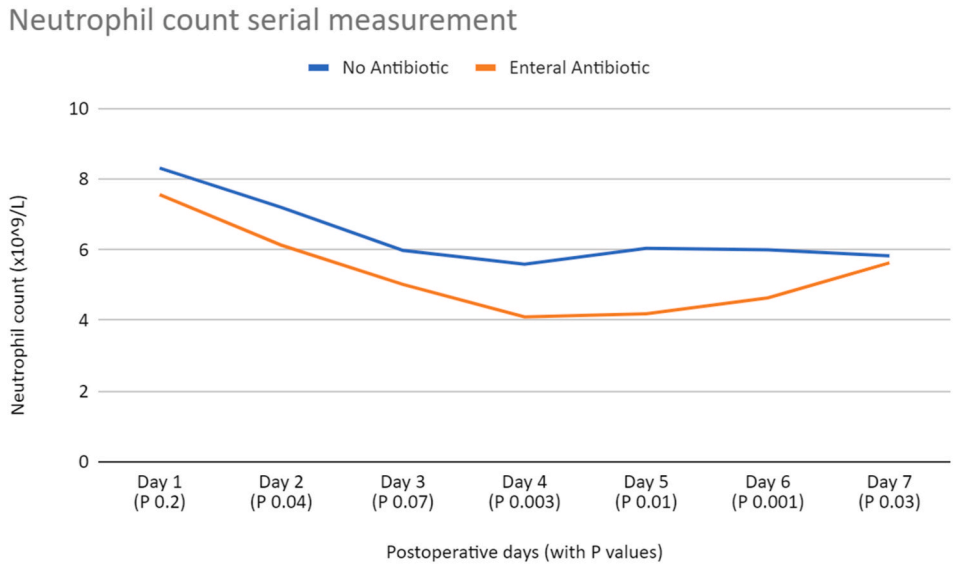


Fig. 1. a and b. Postoperative serial measurement of white blood cell count and CRP.
Figure 1c. Postoperative serial measurement of neutrophil count.

Table 3
Serial measurement and comparison of haemoglobin and lymphocyte count.

Blood test	Pre-operative	Post-op Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Haemoglobin (g/L) mean [SD]								
No Antibiotic	125.67 (25.55)	114.62 (24.63)	116.20 (20.44)	118.09 (21.57)	119.25 (19.89)	119.26 (20.11)	121.67 (22.23)	118.36 (21.45)
Pre Op oral antibiotic	128.86 (18.86)	114.67 (24.29)	117.77 (15.86)	116.67 (25.38)	117.19 (15.11)	117.14 (17.57)	117.24 (21.34)	115.00 (24.57)
P value	0.53	0.86	0.51	0.86	0.79	0.69	0.64	0.76
Lymphocyte count ($x10^9$/L) mean [SD]								
No Antibiotic	2.58 (2.26)	1.00 (0.48)	1.09 (0.54)	1.04 (0.62)	0.95 (0.51)	1.15 (1.42)	0.91 (0.49)	0.98 (0.41)
Pre Op oral antibiotic	2.83 (1.93)	0.96 (0.39)	1.10 (.58)	1.31 (1.78)	0.97 (0.53)	0.86 (0.37)	0.82 (0.41)	0.8 (0.25)
P value	0.19	0.96	0.92	0.58	0.6	0.92	0.72	0.79

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Author contribution

Dr Amal Najdawi: Data collection, study analysis and writing the paper. Mr Ahsan Rao: Study analysis and interpretation. Dr Humayun Razzaq: Data Collection and writing the paper. Mr Michael Dworkin: Study concept and design.

Registration of research studies

1. Name of the registry: the Research Registry.
2. Unique Identifying number or registration ID: researchregistry6931
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Provenance and peer review

Not commissioned, externally peer reviewed.

Consent

This study did not require consent as this is a cohort study compliant with the STROCSS criteria.

Guarantor

Mr Michael Dworkin- Colorectal and General Surgeon Consultant.

Declaration of competing interest

There is no conflict of interests to declare for any of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102752.

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