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Systematic review and meta-analysis of non-steroidal anti-inflammatory drugs to improve gastrointestinal recovery after colorectal surgery

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Abstract

Background: The management of delayed gastrointestinal recovery after surgery is an unmet challenge. Uncertainty over its pathophysiology has limited previous research, but recent evidence identifies intestinal inflammation and activation of mu-opioid receptors as key mechanisms. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended by enhanced recovery protocols for their opioid-sparing and anti-inflammatory properties.

Objectives: To explore the safety and efficacy of NSAIDs to improve gastrointestinal recovery and to identify opportunities for future research.

Data Sources: MEDLINE, EMBASE and the Cochrane Library were systematically searched from inception up to January 2018

Study Selection: Randomized controlled trials (RCTs) assessing the effect of NSAIDs on gastrointestinal recovery after elective colorectal surgery were eligible.

Main Outcomes: Measures of postoperative gastrointestinal recovery, including first passage of flatus, stool, and oral tolerance.

Results: Six RCTs involving 563 participants were identified. All participants received patient-controlled morphine and either NSAID (non-selective: n=4; cyclooxygenase-2-selective: n=1; either: n=1) or placebo. Patients receiving NSAID had faster return of flatus (mean difference: -17.73 hours; 95% CI: -21.26, -14.19; $P<0.001$), stool (-9.52 hours; -14.74, -4.79; $P<0.001$) and oral tolerance (-12.00 hours; -18.01, -5.99; $P<0.001$). Morphine consumption was reduced in the NSAID group of 4 RCTs (average reduction: 12.9–30.0mg). One RCT demonstrated significantly reduced measures of systemic inflammation in the NSAID group. NSAIDs were not associated with adverse events, but one study was temporarily suspended for safety.

Limitations: The data presented is relatively outdated, but represents best available evidence

Conclusion: NSAIDs may represent an effective and accessible intervention to improve gastrointestinal recovery but hesitancy over their use after colorectal surgery persists. Further

pre-clinical research to characterise their mechanisms of action, followed by well-designed clinical studies to test safety and patient-reported efficacy, should be considered.

Introduction

Ileus occurs in 10-20% of patients undergoing colorectal surgery.[1] It is characterized by a delayed return of normal bowel function, leading to abdominal distension, nausea, and delayed fecal evacuation, which may last up to 10 days.[2] Once regarded as an inevitable consequence of surgery, it is now recognized as a research priority by national organisations, such as the Association of Coloproctologists of Great Britain & Ireland.[3] Many interventions to reduce or prevent ileus have been tested, but its management remains an unmet clinical need.[4]

Uncertainty over the pathophysiology of ileus has limited previous research and this has restricted the integration of new interventions into clinical practice.[4] Recent evidence has identified intestinal inflammation and neurogenic dysfunction as key mechanisms in its development.[5] Other mechanisms such as the effects of opioid analgesia on mu-opioid receptors, and the effect of volatile anesthetic gases, are also implicated. Enhanced recovery protocols may improve ileus through fast-track care pathways which aim to maintain normal organ function and reduce the postoperative stress response.[6]

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended by enhanced recovery protocols after elective colorectal surgery.[7] They are desirable for avoiding undesirable effects of opioid analgesia, such as constipation, sedation and respiratory depression. Their anti-inflammatory properties may also be valuable for accelerating the recovery of bowel function by inhibiting the synthesis of prostaglandins and reducing neuromuscular dysfunction.[5] On the other hand, the use of NSAIDs after colorectal surgery is controversial. Their nephrotoxic properties increase the risk of acute kidney injury, which is associated with increased 1-year mortality after non-cardiac surgery.[8] They may also be associated with an increased risk of anastomotic leak according to some observational studies.[9,10]

The opioid-sparing and anti-inflammatory properties of NSAIDs are attractive in the postoperative setting. The aim of this review was to explore the safety and efficacy of NSAIDs

to improve gastrointestinal recovery after colorectal surgery from previous literature. This did not seek to determine a definitive answer, but aimed to collate the highest quality, available evidence and consider opportunities for future research in an area of considerable uncertainty.

Methods

Study Design

This study was registered prospectively on the PROSPERO database of systematic reviews (CRD42018087461). The results are reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.[11]

Searches

A search strategy was devised to identify randomized controlled trials (RCTs) assessing the effect of NSAIDs on gastrointestinal recovery after colorectal surgery (Supplementary File 1). The final searches were performed by two independent investigators on 3rd January 2018 using MEDLINE (via OvidSP), EMBASE (via OvidSP), and the Cochrane Database of Systematic Reviews (SJC & JG). Both investigators screened study titles for relevance prior to inspection of abstracts and full text manuscripts, and discrepancies were resolved through discussion and involvement of a third investigator (MA). Reference lists were inspected for additional eligible studies. The ClinicalTrials.gov register was queried across the same time period for ongoing or completed (but unpublished) RCTs using the search terms: ileus AND (NSAID OR non-steroidal anti-inflammatory drug OR cyclooxygenase OR COX).

Eligibility Criteria

All RCTs including adult patients (18 years and older) undergoing elective colorectal surgery were eligible for inclusion. Eligible studies had to assess the effect of NSAIDs (irrespective of cyclooxygenase (COX)-1 or COX-2 selectivity) on gastrointestinal recovery or length of hospital stay as a primary outcome. If the primary outcome was unclear, the effect of NSAIDs on gastrointestinal recovery had to be a major focus of the study, informed through inspection of clinical trial registries and correspondence with the authors if necessary. RCTs published online or in print up to 3rd January 2018 were included. All other non-randomized study designs, grey literature and manuscripts published in non-English languages were excluded.

Outcomes

The main outcome of interest was gastrointestinal recovery. Wide variation in the choice of outcome measures between studies was anticipated so these were not pre-specified.[12] Relevant outcomes included (but were not limited to) time until first flatus, stool, and tolerance to oral intake. Secondary outcomes included morphine consumption and the incidence of postoperative complications.

Definitions

NSAIDs were defined as inhibitors of COX-1 and/or COX-2 enzymes. Colorectal surgery was defined as any surgery involving the lower gastrointestinal tract (cecum to anus) with access obtained through the peritoneum. RCTs were defined as interventional studies involving random allocation of participants to at least two study arms, irrespective of phase or randomized design.

Data Extraction

Extraction of data was performed by a single investigator and checked by a second (SJC & MA). Clinical data fields included: site of surgery (colon vs. rectum vs. both), operative approach (open vs. laparoscopic vs. robotic), NSAID type/regimen and control drug type/regimen. Other descriptive data fields included: study sample size, study setting (single or multi-centre), blinding status, country of origin and year of publication. Clarification of missing or other desirable data were sought from study authors by email.

Assessment of Bias

The Cochrane Tool for Assessing Risk of Bias was used to assess eligible RCTs according to domains of selection, performance, detection, attrition and reporting bias.[13] Assessments of all domains were performed by two independent investigators (SJC & JG). An overall status of “high” or “low” risk of bias was assigned to each RCT, with “unclear” risk determined to be an indicator of bias due to inadequate reporting.

Statistical Analysis

Descriptive statistics were used to present summary data. Quantitative meta-analysis was not initially planned due to anticipated variation in outcome reporting.[12,14] When inspected, the data were determined to be of sufficient homogeneity to consider a quantitative synthesis of key outcomes. Studies were pooled together using meta-analysis models where appropriate to estimate the effects of NSAIDs on gastrointestinal recovery time. In the case of multi-arm trials, the arms receiving NSAIDs were grouped together to avoid comparisons of the same groups within the same meta-analysis. Measures of central tendency, when different from the mean, were estimated by using the median value. Standard deviations were used as a measure of central tendency. Where studies did not report standard deviation as a measure of central tendency, the standard deviation was calculated. We used previously studied methods to estimate spread of data should the standard deviation be unavailable[15]. In the case where no estimates of central tendency were reported in the main study, we imputed the average central tendency value for all studies included. In the case where sample size was below 15 patients, the standard deviations were derived from simulated distributions based on the appropriate time it would take for bowel function to be regained following a similar operation. Where time data were expressed in days, we converted to hours by multiplying by a factor of 24. Data were pooled using generalised-inverse variance models. Fixed effects models were employed if there were fewer than 25 patients per arm of the trial and random-effects models were employed where there were 4 or more trials and the presence of either statistical or clinical heterogeneity. Statistical heterogeneity was measured using the I^2 statistic and interpreted as follows; 25% or lower – low heterogeneity, 25-50% -moderate heterogeneity, greater than 50% high heterogeneity. When statistical heterogeneity was identified, studies were examined for possible sources of this. Estimates of effect size are represented as weighted mean difference per hour following operation, alongside the corresponding 95% confidence interval. Funnel plots were visually inspected to identify publication bias. Statistical significance was taken at the level of $p < 0.05$. Analyses were performed in R v3.3.2 and RevMan version 5.3.

Results

Study Characteristics

Of 179 studies initially identified, 6 RCTs involving 563 randomized participants met the criteria for inclusion (Figure 1).[16-21] Most RCTs were single centre (n=5/6; 83.3%), involving surgery of both the colon and rectum (n=5/6; 83.3%) using an open approach (n=5/6; 83.3%) (Table 1). All studies were double-blinded and five out of six were low risk of bias. The single study with high risk of bias did not meet its recruitment target due to temporary suspension over higher than expected rates of anastomotic leak. Following an interim safety analysis, the study continued but did not accrue sufficient participants.[20]

Study Interventions

Four RCTs tested non-selective NSAIDs, one tested a COX-2 selective NSAID (valdecoxib) and one tested both (Table 2). The most commonly tested NSAID was ketorolac in three RCTs.[17,20,21] NSAID regimens differed in their duration, with four studies administering the drug postoperatively for a pre-specified duration of time (6 hours to 5 days), and two discontinuing the drug according to individual analgesia requirements. In most studies (n=5/6; 83.3%), both NSAID and control drugs were administered in combination with/alongside intravenous patient-controlled morphine.

Gastrointestinal Recovery

The time to first passage of flatus was reported in five out of six included RCTs. The passage of flatus was significantly faster in patients receiving an NSAID (pooled n=277) compared to controls (pooled n=198) by a mean difference of -17.73 hours (95% CI: -21.26, -14.19) (P<0.001) (Figure 2a). The statistical heterogeneity was low (I^2=12%). The time to first passage of stool was also reported in five out of six included RCTs. The passage of stool was significantly faster in patients receiving an NSAID (pooled n=294) compared to controls (pooled n=211) by a mean difference of -9.52 hours (-14.74, -4.79) (P<0.001) (Figure 2b). The statistical heterogeneity was low (I^2=17%). Time to first oral tolerance was reported in three

out of six included RCTs. Oral intake was tolerated faster in patients receiving an NSAID (pooled n=205) compared to controls (pooled n=128) by a mean difference of -12.00 hours (-18.01, -5.99) (P<0.001) (Figure 2c). There was no statistical heterogeneity (I^2=0%). Examination of funnel plots identified no publication bias (Supplementary File 2).

Morphine Consumption

Comparisons of morphine consumption were reported in five out of six RCTs (Table 3). In four of these, morphine consumption was significantly lower in the NSAID group (reduction in total consumption: 12.9-30.0mg) and in one study, the duration of patient controlled morphine was significantly reduced (60 versus 72 hours; P<0.001). This finding was accompanied by improved gastrointestinal recovery (such as time to first flatus, stool, and oral tolerance) in all four RCTs. Conversely, one study showed no difference in morphine consumption between NSAID groups and placebo (73mg and 60.0mg versus 80mg; P=0.704), despite a quicker return of flatus and stool in patients receiving NSAIDs.[16] Another study demonstrated no significant correlation between findings of improved gastrointestinal recovery and reduced morphine consumption when modelled using simple logistical regression.[17] A single study reported significantly reduced expression of pro-inflammatory cytokines (interleukin (IL)-6 and IL-8) at multiple postoperative time points in the NSAID group (end of surgery, 6 hours and 24 hours), but did not report morphine consumption.[18]

Postoperative Complications

There were no significant differences in the incidence of postoperative complications between NSAID and control groups in any of the studies (Table 4). The impact of NSAIDs on renal function was reported in only one RCT[16]. No differences in creatinine clearance were noted between NSAID and control groups on days 1, 3 and 5 after surgery. The incidence of anastomotic leak was similar between groups in most studies, however one RCT was temporarily suspended due to concerns over a disproportionate number of anastomotic leaks

in the NSAID (ketorolac) group (final incidence: n=4/22; 18% versus n=1/22; 4.5%).[20] With no previous precedent for this, it was determined to represent an anomalous observation.

Registered Studies

Of 19 study records identified on the ClinicalTrials.gov register, two eligible RCTs comprising a total planned recruitment of 180 participants were identified (Table 5). One of these (NCT02790203) will test the COX-2 inhibitor celecoxib using simple measures of gastrointestinal recovery (return of flatus and stool). The other (NCT02958566) will test ketorolac (non-specific COX inhibitor) within a multi-modal opioid-sparing strategy using measures of bowel function and economic costs.

Discussion

This review demonstrated an improvement in gastrointestinal recovery in patients receiving NSAIDs after colorectal surgery. This was in the absence of increased complications, but low event rates in each of the included studies limited this interpretation. Whilst an opioid-sparing effect of NSAIDs was clearly apparent, a concurrent, therapeutic, anti-inflammatory mechanism could not be discounted. The mechanism of improved gastrointestinal recovery conferred by NSAIDs therefore remains unclear. Interestingly, all included studies were published between 2005 and 2009 and only a handful of future trials are planned.

The pathophysiology of ileus is uncertain. Previous evidence describes two distinct phases in its development, including a short-acting neurogenic phase and a longer acting inflammatory phase.[5] The use of opioid analgesia augments these mechanisms by activating peripheral mu-opioid receptors. The current review demonstrated convincing evidence that NSAIDs enhance gastrointestinal recovery by reducing opioid requirements in the postoperative setting. Evidence of an anti-inflammatory effect was also demonstrated, but the relative contribution of this to gastrointestinal recovery was unclear. NSAIDs exert their anti-inflammatory effects through inhibition of COX-1 and COX-2, subsequently leading to inhibition of prostanglandins. This is relevant in the days following surgery, where the effects of ileus are probably mediated by a cascade of mast cells, macrophages, and inflammatory cytokines involving the bowel muscularis.[5] Previous research has shown that this inflammatory response is safely mitigated using pharmacological and non-pharmacological interventions, and in doing so, the return of gastrointestinal function can be accelerated.[4] On this notion, NSAIDs may represent a cost-effective and accessible intervention to improve gastrointestinal recovery, whilst also providing effective postoperative analgesia.

Although these properties are attractive, there is reluctance in prescribing NSAIDs after colorectal surgery.[2] Some have called for NSAIDs to be avoided until further research can better characterise their risk profile.[22] These concerns are likely influenced by two factors. The first is the risk of acute kidney injury, especially in high risk patients undergoing invasive

resectional surgery. Although the majority of acute kidney injury in this setting is mild, recent evidence has identified an increased risk of mortality one year after surgery.[8] The second is an apparent link between NSAIDs and anastomotic leak, demonstrated by several interventional and observational studies, and quantified recently in a pooled meta-analysis[23]. In one prospective cohort of elective colorectal surgery, diclofenac was associated with increased risk of leak on multivariate analysis (Odds Ratio: 7.16; [95% Confidence Interval: 3.82-13.4]; *P*<0.001), but not with ibuprofen (1.54 [0.82-2.86]; *P*=0.18).[9] In another retrospective cohort, NSAIDs were associated with increased risk of leak (1.24 [1.01-1.56]; *P*=0.04), but when sub-analyzed, this was isolated to emergency surgery only (1.70 [1.11-2.68]; *P*=0.01).[10] With a high risk of bias expected in both studies, and with uncertain pathophysiology, these findings remain contentious but noteworthy.

The results identify a number of opportunities for further research, including essential steps to justify a definitive, phase-3 RCT of NSAIDs to reduce ileus. Firstly, although NSAIDs accelerate gastrointestinal recovery when measured using conventional outcomes of bowel function, the relevance of these to patients and their expectations is unclear. Contrasting results for commonly reported outcome measures (such as “time to first flatus” and “oral tolerance”) make for difficult interpretation, and other complementary measures (such as length of hospital stay) are flawed by organizational confounders.[24] The absence of meaningful, standardised, patient-focussed outcomes is an ongoing challenge, but is being addressed elsewhere.[14] Secondly, the interpretation of safety in this review is limited by small study populations and low event rates. Future RCTs will offer high quality evidence for efficacy and effectiveness but the feasibility of capturing sufficient events (such as acute kidney injury and anastomotic leak) to determine safety is limited. Instead, large, well-conducted, observational studies will provide valuable information, and are currently ongoing.[25] As long as NSAIDs remain recommended by enhanced recovery guidelines, their use as postoperative analgesia after colorectal surgery in low risk patients is justified. However, further investigation into their effects on gastrointestinal recovery, including pre-clinical work to elucidate the therapeutic mechanisms is warranted.[7] Thirdly, the state of clinician and

patient equipoise must be explored prior to considering an RCT with the expectation of definitive and generalizable results. Whilst it is arguable that patients remain in satisfactory equipoise, pre-existing biases held by the colorectal and perioperative community around complications (anastomotic leak and acute kidney injury) are an important barrier to recruitment. This should be addressed via a scoping exercise to determine how split equipoise can be addressed within the design of a phase-3 RCT. Finally, in considering future RCTs, the financial impact of delayed gastrointestinal recovery on health services should be explored. If shown to be effective and safe, NSAIDs may represent a cost-effective and clinically-accessible intervention in most healthcare systems. This is in contrast to other interventions, such as mu-receptor antagonists, which appear effective in clinical studies, but have not entered clinical practice outside of the United States due to issues of licensing and cost.[4]

Strengths and limitations of this review are recognized. The main strength is the inclusion of RCTs with low risk of bias, which permitted a meaningful synthesis of data. Consideration to the following limitations must also be balanced. Firstly, all of the included RCTs were published between 2005 and 2009 and have not yet been replicated, possibly due to hesitancy over the perceived risks of NSAIDs. In the meantime, an NSAID tested in one of the included studies (valdecoxib) has since been removed from international markets due to safety concerns relating to cardiovascular adverse events.[19] Also, most of the included RCTs included open surgical technique, but minimally invasive techniques are increasingly favoured. The data is therefore relatively outdated, but represents the best available evidence with important implications for current practice. Secondly, meta-analysis of pooled data was not prospectively planned due to wide variation expected in outcome reporting, however upon inspection, a quantitative synthesis was determined to be feasible and informative.[12,14] Whilst the methods utilised are justified, this should be interpreted with an element of caution as a deviation from protocol. Finally, the review is unable to offer a definitive answer on the role of NSAIDs in gastrointestinal recovery, but this was not its aim. Endorsement by enhanced recovery guidelines, at the same time as safety concerns expressed by observational studies, has

produced considerable uncertainty on the use of NSAIDs after colorectal surgery. This review sets out a proposed direction based on a balanced assessment of the literature to explore this further.

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Figure 1: PRISMA flow diagram of included studies

Figure 2: (a) Forrest plot showing meta-analysis of first passage of flatus; (b) Forrest plot showing meta-analysis of first passage of stool; (c) Forrest plot showing meta-analysis of first oral tolerance