Post-Operative Ileus After Digestive Surgery: Network Meta-Analysis of Pharmacological Intervention.

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Abstract

Background: Several medicinal treatments for avoiding post-operative ileus (POI) after abdominal surgery have been evaluated in randomised controlled trials. This network meta-analysis aimed to explore the relative effectiveness of these different treatments on ileus outcome measures. Methods: A systematic literature review was performed to identify randomised controlled trials (RCTs) comparing treatments for post-operative ileus following abdominal surgery. A Bayesian network meta-analysis was performed. Direct and indirect comparisons of all regimens were simultaneously compared using random-effects network meta-analysis. Results: A total of 38 randomised controlled trials were included in this network meta-analysis reporting on 6371 patients. Our network meta-analysis shows that prokinetics significantly reduce the duration of first gas (Mean difference (MD) (hours) – 16; credible interval - 30, - 3.1; surface under the cumulative ranking curve (SUCRA) 0.418), duration of first bowel movements (Mean difference (MD) (hours) -25; credible interval - 39, - 11; SUCRA 0.25) and duration of post-operative hospitalisation (Mean difference (MD) (hours) – 1.9; credible interval – 3.8, - 0.040; SUCRA 0.34). Opioid antagonists are the only treatment that significantly improve the duration of food recovery (Mean difference (MD) (hours) - 19; credible interval - 26, - 14; SUCRA 0.163). Conclusion: Based on our meta-analysis, the two most consistent pharmacological treatments able to effectively reduce POI after abdominal surgery are prokinetics and opioid antagonists. The absence of clear superiority of one treatment over another highlights the limits of the pharmacological principles available.

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Key Words: post-operative ileus; abdominal surgery; digestive surgery; post-operative complication; network meta-analysis; ileus; pharmacology.

ABSTRACT

Background : Several medicinal treatments for avoiding post-operative ileus (POI) after abdominal surgery have been evaluated in randomised controlled trials. This network meta-analysis aimed to explore the relative effectiveness of these different treatments on ileus outcome measures.

Methods:

A systematic literature review was performed to identify randomised controlled trials (RCTs) comparing treatments for post-operative ileus following abdominal surgery. A Bayesian network meta-analysis was performed. Direct and indirect comparisons of all regimens were simultaneously compared using random-effects network meta-analysis.

Results:

A total of 38 randomised controlled trials were included in this network meta-analysis reporting on 6371 patients. Our network meta-analysis shows that prokinetics significantly reduce the duration of first gas (Mean difference (MD) (hours) – 16; credible interval - 30, - 3.1; surface under the cumulative ranking curve (SUCRA) 0.418), duration of first bowel movements (Mean difference (MD) (hours) -25; credible interval - 39, - 11; SUCRA 0.25) and duration of post-operative hospitalisation (Mean difference (MD) (hours) – 1.9; credible interval – 3.8, - 0.040; SUCRA 0.34). Opioid antagonists are the only treatment that significantly improve the duration of food recovery (Mean difference (MD) (hours) - 19; credible interval - 26, - 14; SUCRA 0.163).

Conclusion:

Based on our meta-analysis, the two most consistent pharmacological treatments able to effectively reduce POI after abdominal surgery are prokinetics and opioid antagonists. The absence of clear superiority of one treatment over another highlights the limits of the pharmacological principles available.

INTRODUCTION

Post-operative ileus is a common condition occurring after abdominal surgery and reflects a slowing or complete cessation of bowel motility[1]. This complication is common and variable among series, affecting between 10 and 25% of patients after abdominal surgery[2]. The costs associated with post-operative ileus are considerable. In the United States, the total annual cost of care for all hospitalisations related to paralytic ileus increased from $7.1 billion in 2001 to $12.3 billion in 2011[3]. Post-operative ileus (POI) induces its own morbidity and prolongs hospital length of stay. Pathophysiologic studies have identified at least two phases in post-operative ileus, an early phase involving neural pathways known as the "neurogenic phase" and a later phase which is characterised by inflammatory features[4]. Since the end of the 1970s, numerous clinical trials have been set up to evaluate the efficacy of different pharmacological treatments targeting inflammation, gastric movement or microbiota. Based on the variety of treatments and definitions of ileus in current clinical practice, it seemed necessary to compare the various pharmacological approaches used in the treatment of ileus[5]. A network approach using hierarchical Bayesian models allows indirect comparisons

of pharmacological therapies for ileus after abdominal surgery and produces previously unexplored relative effectiveness. We conducted a systematic review identifying all randomised controlled trials evaluating pharmacological interventions to treat post-operative ileus after abdominal surgery[5]. After identifying the studies, we performed a networked meta-analysis of all available high-quality trials to provide new evidence in favour of pharmacological treatments to reduce ileus.

METHODS

The study protocol was prospectively registered on PROSPERO (registration number: CRD42021284953) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[6] checklist.

Search strategy and data collection

All studies reporting on pharmacological intervention for POI treatment and prevention were considered eligible for analysis. The literature was systematically reviewed by searching in the PubMed, EMBASE and Cochrane Libraries with no restrictions concerning the publication period. The search period ended on 1st July 2022. The medical subject headings (MESH) used are summarised in Supplemental Table 1. The full search strategies are listed in Supplement Table 1. They are adapted from previous systematic reviews including ones from our team's work[5] and used with bibliographic databases in combination with database-specific filters for controlled trials where available. Trials investigating pharmacological treatments for post-operative ileus after abdominal surgery were searched by adding boundaries for randomised controlled trials (with the exploded terms "random" "trial" or "RCT").

Inclusion and exclusion criteria

The studies included were randomised controlled trials comparing at least two different therapies for the treatment and prevention of POI. The treatments studied were medicinal treatments. We excluded all non-medicinal interventions. Studies focusing on peri-operative protocol management were excluded (e.g. early rehabilitation measures on post-operative course, enhanced recovery pathways, surgical techniques). Also excluded were paediatric surgical studies (patients under 18 years of age), observational studies, reviews, congress abstracts, letters to the Editor and articles not written in English. The Cochrane Collaboration tool for assessing risk of bias in randomised controlled trials was utilised to assess quality of studies[7]. Studies with a high risk of bias in one domain (randomisation, deviations from intended intervention, missing outcome data, measurement of outcome, selection of the reported results) and in the overall bias were excluded.

Outcome parameters

To date, there is no consensus in the measurement of POI. Thus, the measurement of POI is currently the subject of research[8]. We selected the most frequently used criteria found in the work of Chapman et al.[9]: time to passage of first flatus, time to passage of first stool, time to solid food tolerance, number of patients requiring post-operative introduction of nasogastric tube, time to first bowel movement at the auscultation and post-operative length of hospital stay. The following parameters were reported in hours: first gas, first stool, solid food resumption and bowel movement. The duration of hospitalisation was stated in post-operative days and the reintroduction of nasogastric tube was reported in number of patients. Studies were eligible if one or more of these outcomes were reported or provided by the Corresponding Author. The mean age of each individual study population was recorded in addition to the percentage of male participants and the mean operative time. No surgical complications beyond ileus were recorded due to heterogeneity in reporting complications.

Data collection and extraction

A data abstraction form was designed *a priori* with Excel (Microsoft Corp, Redmond Washington, USA) to standardise data collection. Two independent reviewers (E.B and T.P) scanned all abstracts identified by search cross-referencing. The full text was then identified for each study that potentially met the inclusion criteria. Two reviewers (E.B and T.P) independently reviewed the full-text eligibility. If no consensus could

be reached by the two reviewers and after discussion, a third specialist author was consulted and made the decision (J.S and/or C.D). Articles that did not meet the inclusion criteria were excluded (Figure 1). Data extraction included general study information (see details in Table 1 and Supplemental Tables 2 and 3).

Quality assessment

A quality assessment of the studies was performed by two independent reviewers (E.B and T.P) using the Cochrane Collaboration risk of bias tool[7]. Any disagreement was resolved by discussion or by consulting a third investigator (J.S and /or C.D). We recorded the methods used to generate the randomisation schedule and conceal treatment allocation as well as find out whether blinding was implemented for participants, personnel and outcomes assessment and if there was evidence of incomplete outcomes data and selective reporting of outcomes.

Statistical analysis

All statistical analyses were performed in R version 4.0.3. For all outcomes bar post-operative introduction of nasogastric tube, mean difference (MD) was used as a treatment estimate and standard error of the mean was deployed as the standard error of treatment estimate. Since outcomes were reported in widely different ways, we reformatted them to MD when needed using the following rules. If the means in each treatment group were available, MD was calculated as the difference between the two means. If median and range were present, we used the formula proposed by Hozo et al. to calculate the means in each group[10]. If range and IQR were available, we used the formula Mean = (Quartile 1 + Median + Quartile 3) to calculate the means in each group. For post-operative introduction of nasogastric tube, we used the odd ratio (OR) as the unit of treatment effect. When none of the above was available, studies were excluded from analysis in this outcome. Since we aimed to compare pharmacological class treatment size rather than individual treatment or dose, we could not use the multi-arm studies option of network meta-analysis for studies comparing more than one dose of the same treatment to placebo. Therefore, we recalculated a common mean for all treatment arms to calculate the mean difference. The main analysis was a Bayesian network meta-analysis using the packages gemtc, rjags and the software JAGS. We used an identity-link for mean difference and a log-link for the OR. We performed 10e5 iterations with a thinning interval of 10 and a burn-in interval of 5000. Model convergence was assessed using density and trace plots. Results are presented as a network graph, a forest plot comparing each treatment with placebo, ranking probability as well as a surface under the curve cumulative ranking probabilities (SUCRA). As a sensitivity analysis, we performed a frequentist network meta-analysis using the package netmeta. We presented results as comparison to placebo and a matrix presenting both direct and indirect comparisons. Finally, publication bias was assessed for each outcome with a funnel plot and an Egger's test.

RESULTS

Literature search and results

The initial search resulted in 1723 citations. No duplicates were found. After screening, 128 publications were retrieved for full-text review. From the 128 articles, 108 articles were excluded with the reasons detailed in Figure 1. Finally, 38 were included in quantitative synthesis[11–48] (Figure 1).

Study and patient characteristics

Study descriptions are provided in Table 1. Study endpoint details for each study are stated in the Supplementary Data. The quality of studies evaluation was assessed, using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2), into two categories: some concerns and low risk of bias (Supplemental Figures 4.6, 5.6, 6.6, 7.6, 8.6 and 9.6). Seventeen RCT compared prokinetics to placebo[29–45]. Seven compared peripheral µ-opioid receptor antagonists to placebo[22–28]. Four compared non-steroidal anti-inflammatory drugs to placebo[11–14]. One study compared glucocorticoids (dexamethasone) to placebo[17]. Two compared erythromycin to placebo[18,19]. Two studies compared gastrograffin to placebo[20,21]. Three compared probiotics to placebo[46–48]. One study compared colloid infusion to placebo[16] and one study compared oral carbohydrates to placebo[15]. Erythromycin has a dual antibiotic and prokinetic effect, which is why this

treatment is analysed separately [49]. We have classified erythromycin in a category outside the prokinetic treatments with regard to its reference therapeutic class. Indeed, erythromycin being a macrolide antibiotic, it has a potential effect on the balance of the microbiota.

The 38 included studies covered 6,371 patients: 2,091 patients for prokinetic studies (including 860 receiving placebo), 3,118 patients for μ-opioid receptor antagonist studies (including 1151 receiving placebo), 276 patients for non-steroidal anti-inflammatory drug studies (including 137 receiving placebo), 302 patients for glucocorticoid studies (including 151 receiving placebo), 156 patients for erythromycin studies (including 80 receiving placebo), 129 patients for gastrografin studies (including 65 receiving placebo), 169 patients for probiotics studies (including 85 receiving placebo), 80 patients for colloid infusion studies (including 42 receiving placebo) and 50 patients for oral carbohydrate studies (including 25 receiving placebo). Pooled baseline characteristics are displayed in Table 2.

Study endpoints

The outcomes of each study are detailed in Supplemental Table 3. The main findings of the studies are summarised in Supplemental Tables 4.1, 5.1, 6.1, 7.1, 8.1 and 9.1. Visual inspection of the funnel plots for the main and secondary outcomes of interest as well as the non-statistically significant Egger's test for each suggested the absence of publication bias in our study (Supplemental Figures 4.5, 5.5, 6.5, 7.5, 8.5 and 9.5).

Time to passage of first flatus

From the literature, 33 studies reporting the time to first flatus were included although 27 give useable data for statistical analysis[11,13–25,27–29,32,36–41,44,45,48]. A total of 27 studies with 4,351 patients and 9 pharmacological treatments are reported. The extracted data are detailed in Supplemental Table 4.1. The following treatments were studied and included in the network analysis: opioid antagonists, NSAIDs, gastrografin, erythromycin, dexamethasone, colloid infusion, oral carbohydrates, prokinetics and probiotics. Figure 2.A reports the network map for the 9 pharmacological treatment classes analysed. The main results are reported in Figure 2: network map, relative effect Bayesian plot, rankogram and the surface under the cumulative ranking curve (SUCRA).

Of the 9 treatments studied, prokinetics showed a significantly faster onset of first flatus compared to the control treatments (Mean difference (MD) (hours) – 16; credible interval - 30, - 3.1 (Figure 2.B); SUCRA 0.418 (Figure 2.C)). Dexamethasone was the best treatment for the duration of flatus recovery with a probability of P=0.33. The ranking (rank1+rank2+rank3) in descending order of the top three treatments from the best to the third was as follows: dexamethasone had a 62% (0.33+0.17+0.10) probability of being among the top three therapies followed by colloid infusion at 59% (0.28+0.19+0.12) and then prokinetics with 23% (0.01+0.07+0.15). Considering the relative effect, there was no significant difference between dexamethasone and colloid infusion and between dexamethasone and prokinetics. The bias studies are summarised in Supplemental Figure 4.6. The overall bias was rated low risk in 96.3% of studies and of some concern in 3.7% of studies. The highest ratio of some concern was for deviation from intended intervention (18.5%) and measurement outcomes (18.5%).

Time to passage of first stools

According to the literature, 19 studies reporting post-operative time to first stools were included although 13 give useable data for statistical analysis[15–17,20,21,36,37,40,44–48]. A total of 13 studies with 1,125 patients and 6 pharmacological treatments are reported. The extracted data are detailed in Supplemental Table 5.1. The following treatments were studied and included in the network analysis: gastrografin, dexamethasone, colloid infusion, oral carbohydrates, prokinetics and probiotics. Figure 3.A reports the network map for the 6 pharmacological treatment classes analysed. The main results are reported in Figure 3: network map, relative effect Bayesian plot, rankogram and the surface under the cumulative ranking curve (SUCRA).

Of the 6 treatments studied, prokinetics (Mean difference (MD) (hours) - 23; credible interval - 43, - 4.3 (Figure 3.B); SUCRA 0.424 (Figure 3.C)) and dexamethasone (Mean difference (MD) (hours) - 47; credible interval - 88, - 6.0 (Figure 3.B); SUCRA 0.113 (Figure 3.C)) showed a significantly faster onset of first

stools compared to the control treatments. Dexamethasone was the best treatment for the duration of flatus recovery with a probability of P=0.67. The ranking (rank1+rank2+rank3) in descending order of the top three treatments from the best to the third was as follows: dexamethasone had a 90% (0.67+0.16+0.07) probability of being among the top three therapies followed by prokinetics at 50% (0.28+0.18+0.03) and then probiotics with 41% (0.05+0.17+0.18). The bias studies are summarised in Supplemental Figure 5.6. The overall bias was rated low risk in 92.3% of studies and of some concern in 7.7% of studies. The highest ratio of some concern was due to the randomisation process and deviations from intended interventions (23.1%) as well as deviation from intended intention (23.1%).

Time to solid food tolerance

In line with literature, 31 studies reporting post-operative time to solid food tolerance were included although 29 give useable data for statistical analysis[13,16,18–34,36,38,40–45,47,48]. A total of 29 studies with 5,683 patients and 7 pharmacological treatments are reported. The extracted data are detailed in Supplemental Table 6.1. The following treatments were studied and included in the network analysis: NSAIDs, gastrografin, opioid antagonists, colloid infusion, erythromycin, prokinetics and probiotics. Figure 4.A reports the network map for the 7 pharmacological treatment classes analysed. The main results are reported in the SUCRA and rankogram in Figures 4.C and 4.D.

Of the 7 treatments studied, opioid antagonists (Mean difference (MD) (hours) - 19; credible interval - 26, - 14 (Figure 4.B); SUCRA 0.163 (Figure 4.C)) and colloid infusion (Mean difference (MD) (hours) - 22; credible interval - 38, - 5.5 (Figure 4.B); SUCRA 0.138 (Figure 4.C)) showed a significantly faster onset of solid food tolerance compared to the control treatments. Colloid infusion was the best treatment for the duration of flatus recovery with a probability of P=0.41. The ranking (rank1+rank2+rank3) in descending order of the top three treatments from the best to the third was as follows: opioid antagonists had a 97% (0.20+0.46+0.31) probability of being among the top three therapies followed by colloid infusion at 92% (0.41+0.31+0.2) and then gastrografin with 75% (0.36+0.17+0.22). The bias studies are summarised in Supplemental Figure 6.6. The overall bias was rated low risk in 100% of studies and of some concern in 0% of studies. The highest ratio of some concern was for deviations from intended interventions (13.8%).

Time to first bowel movement

From the literature, 28 studies reporting post-operative first bowel movement were included although 21 give useable data for statistical analysis[11–16,18,19,22,23,25,27–29,31,35,36,39,41,42,46]. A total of 21 studies with 3,584 patients and 7 pharmacological treatments are reported. The extracted data are detailed in Supplemental Table 7.1. The following treatments were studied and included in the network analysis: prokinetics, erythromycin, opioid antagonists, NSAIDs, probiotics, oral carbohydrates and colloid infusion. Figure 5.A reports the network map for the 7 pharmacological treatment classes analysed. The main results are reported in Figure 5: network map, relative effect Bayesian plot, rankogram and the surface under the cumulative ranking curve (SUCRA).

Of the 7 treatments studied, prokinetics (Mean difference (MD) (hours) -25; credible interval - 39, - 11 (Figure 5.B); SUCRA 0.25 (Figure 5.C)) and opioid antagonists (Mean difference (MD) (hours) - 21; credible interval - 39, - 3.5 (Figure 5.B); SUCRA 0.355 (Figure 5.C)) showed a significantly faster onset of first stools compared to the control treatments. Probiotics were the best treatment for the duration of flatus recovery with a probability of P=0.56. The ranking (rank1+rank2+rank3) in descending order of the top three treatments from the best to the third was as follows: probiotics had a 75.7% (0.56+0.11+0.07) probability of being among the top three therapies followed by prokinetics at 75.1% (0.13+0.33+0.27) and then opioid antagonists with 53% (0.06+0.19+0.26). The bias studies are summarised in Supplemental Figure 7.6. The overall bias was rated low risk in 90.5% of studies and of some concern in 9.5% of studies. The highest ratio of some concern was for deviations from intended interventions (23.8%).

Length of hospital stay

On the basis of the literature, 30 studies reporting post-operative length of hospital stay were included

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although 25 give useable data for statistical analysis[12,13,15,16,18–23,25,27–29,31,36,38–43,45,46,48]. A total of 25 studies with 3,958 patients and 8 pharmacological treatments are reported. The extracted data are detailed in Supplemental Table 8.1. The following treatments were studied and included in the network analysis: NSAIDs, gastrografin, colloid infusion, oral carbohydrates, prokinetics, probiotics, erythromycin and opioid antagonists. Figure 6 reports the network map for the 8 pharmacological treatment classes analysed. The main results are reported in Figure 6: network map, relative effect Bayesian plot, rankogram and the surface under the cumulative ranking curve (SUCRA).

Of the 8 treatments studied, prokinetics (Mean difference (MD) (hours) – 1.9; credible interval – 3.8, - 0.040 (Figure 6.B); SUCRA 0.34 (Figure 6.C)) showed a significantly faster onset of first stools compared to the control treatments. Gastrografin was the best treatment for the duration of flatus recovery with a probability of P=0.41. The ranking (rank1+rank2+rank3) in descending order of the top three treatments from the best to the third was as follows: gastrografin had a 73% (0.41+0.20+0.11) probability of being among the top three therapies followed by colloid infusion at 50% (0.21+0.17+0.11) and then prokinetics with 47% (0.05+0.17+0.25). The bias studies are summarised in Supplemental Figure 8.6. The overall bias was rated low risk in 92% of studies and of some concern in 8% of studies. The highest ratio of some concern was for deviations from intended interventions (24%).

Number of patients requiring post-operative nasogastric tube placement

According to the literature, 18 studies reporting the number of patients requiring post-operative nasogastric tube placement were included although 13 give useable data for statistical analysis[17–19,21,23,26,28,32,33,36,41,45,47]. A total of 13 studies with 2,803 patients and 6 pharmacological treatments are reported. The extracted data are detailed in Supplemental Table 9.1. The following treatments were studied and included in the network analysis: gastrografin, prokinetics, erythromycin, opioid antagonists, probiotics and dexamethasone. Figure 7.A reports the network map for the 6 pharmacological treatment classes analysed. The main results are reported in Figure 7: network map, relative effect Bayesian plot, rankogram and the surface under the cumulative ranking curve (SUCRA).

None of the studies reached significance for the 6 treatments (Figure 7.B). Erythromycin was the best treatment with a probability of P=0.32. The ranking (rank1+rank2+rank3) in descending order of the top three treatments from the best to the third was as follows: erythromycin had a 63% (0.323+0.18+0.127) probability of being among the top three therapies followed by gastrografin at 59% (0.281+0.183+0.126) and then opioid antagonists with 51% (0.08+0.18+0.25). The bias studies are summarised in Supplemental Figure 9.6. The overall bias was rated low risk in 100% of studies. The highest ratio of some concern was for measurement of the outcomes (23.1%).

DISCUSSION

Many treatments have been the subject of randomised controlled trials to decrease the rate of post-operative ileus. Nevertheless, our previous descriptive analysis of the literature did not allow us to draw clear conclusions as to the superiority of one treatment over another[5]. This finding led us to perform this network meta-analysis. We included in this meta-analysis only randomised controlled trials that reported the criteria commonly used in the return to normal transit. This network meta-analysis shows that prokinetics significantly reduce the duration of first gas, duration of first bowel movements and duration of post-operative hospitalisation. This treatment is ranked (SUCRA and rankogram) among the three best ones apart from food tolerance and the number of patients requiring a nasogastric tube. For food tolerance, opioid antagonists are the treatment that significantly improve the duration of food recovery.

The definition of return to normal transit is an important point to discuss. Indeed, not all segments are affected to the same extent. Small bowel motility is disturbed within 24 hours, gastric motility within 24 to 48 hours and colonic motility within 48 to 72 hours post-surgery[4,50]. The difference in time for recovery of motor function explains why the passage of the first stool and gas is most often used to define return to normal function. The complexity of the definition lies in the fact that the return of the migrating motor complex is not synonymous with a return to normal function, i.e. the perception of peristalsis

on auscultation is not indicative of a return to normal transit. A recent literature review of 215 articles identified a total of 73 criteria defining return to normal transit[9]. Thus, in descending order of frequency, the criteria are: passage of first gas (140 studies out of 217, 64.5%), passage of first stool (69 studies out of 217, 31.8%) followed by first bowel movements (65 studies out of 217, 30%)[9]. The commonly accepted outcome for assessing the pharmacological effects of treatment for POI is the presence of first gas [9]. Some studies have proposed composite scores but this is variable across studies. The COMET-registered core outcome set aims to standardise the reporting of outcomes in clinical studies of post-operative ileus[8]. Among recent work, the American Society for Enhanced Recovery After Surgery (ERAS) and Perioperative Joint Consensus have considered a more functional definition of POI and a classification system for post-operative gastrointestinal transit disorders[51]. Classification was proposed on a pathophysiological and functional basis using the following criteria: tolerance to oral ingestion, nausea, vomiting and physical signs of ileus (intake, sensation of nausea, vomiting, physical examination and duration of "I-FEED" symptoms). A three-category classification system was therefore established. This recent score has never been evaluated in a prospective cohort of GI tract surgery patients. This score would allow a reproducible evaluation of the return to normal transit and therefore have comparable criteria for pharmacological studies[51].

Adding duration of hospitalisation (a reproducible criterion) to the criteria commonly used and reported in the literature made two pharmacological principles stand out: prokinetics and opiate antagonists (as reported above). Prokinetics are made up of active principles used in clinical practice to treat nausea and vomiting. Their action on peristalsis supported an interesting approach in POI[52,53]. Among this class of potential active molecules, 5HT3 receptor antagonists (metoclopramide), selective 5HT4 receptor agonists (mosapride, prucalopride, cisapride) and ghrelin receptor agonists (ulimorelin) were the most evaluated. The results of our meta-analysis show that prokinetics are among the three best treatments for commonly used criteria (time for first bowel movement and for first stool) to characterise POI as well as the post-operative length of stay. Nevertheless, these results do not show a real superiority.

One way to optimise the post-operative recovery of bowel function after surgery would be to antagonise peripheral opioid receptors without negating their central analgesic action. The most commonly used drug for analgesia and anaesthesia is morphine which is a central and peripheral μ receptor agonist[54]. This central and peripheral action contributes to the prolongation of post-operative ileus although it is gastrointestinal receptors that have a predominant role in inhibiting post-operative gut motility. Morphine and other opioid analgesics inhibit the release of acetylcholine from the mesenteric plexus, thereby increasing colonic muscle tone and reducing propulsive activity in the gastrointestinal tract. There are several types of opioid receptors, the three main ones being μ, δ, and ϰ receptors with each class having several subtypes as well[54]. Opioid receptors are stimulated exogenously by agonists such as morphine and codeine. Both alvimopan and methylnaltrexone are the main peripheral opioid antagonists used that do not cross the blood-brain barrier[55]. Since the early 2000s, randomised controlled trials have been conducted in North America on cohorts of patients who have undergone bowel resection and hysterectomy[23,26,28]. Compared to placebo, patients treated with alvimopan had a significant reduction in time to transit recovery as evidenced by clinical functional signs such as first gas, first bowel movements or first stools. These encouraging results were not confirmed in a large clinical trial involving 70 hospitals in 10 countries on the European continent (Austria, Belgium, France, United Kingdom, Germany, Greece, Poland, Portugal, Spain and Sweden) and New Zealand[22].

Despite the lack of a strict definition for POI resulting in discrepancies regarding the endpoints reported across studies, the current analysis provides the first Bayesian network analysis focused on pharmacological intervention of POI. This analysis is based on 6 robust endpoints, with nasogastric tube placement being the weakest endpoint because it is not included in all studies.

In conclusion, based on our meta-analysis, the two most consistent pharmacological treatments in terms of effectiveness for reducing POI after abdominal surgery are prokinetics and opioid antagonists. The absence of clear superiority of one treatment over another highlights the limits of the pharmacological principles available. It therefore appears necessary to act on other pathways. Indeed, there is a need to study and

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develop new pharmacological approaches that target the intimate mechanisms of intestinal damage involved in inflammation and/or neuroinflammation observed during post-operative ileus. New research approaches are required to help understand this phenomenon and develop new pharmacological treatments.

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Authorship:

Guarantor of the article: Etienne Buscail

Authors' contributions :

Each author has made substantial contributions to all of the following: (1) the conception and design of the study, acquisition of data or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript including related data, figures and tables has not been previously published and is not under consideration elsewhere.

All authors approve the final version of the manuscript including the authorship list and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Conceptualisation and Design: Etienne Buscail, Thibault Planchamp, Jason Shourick and Celine Deraison. Acquisition of Data: Etienne Buscail, Thibault Planchamp and Celine Deraison. Analysis and Interpretation of Data: Etienne Buscail, Thibault Planchamp, Guillaume Le Cosquer Jason Shourick and Celine Deraison. Writing Original Draft: Etienne Buscail, Thibault Planchamp, Guillaume Le Cosquer Jason Shourick, Celine Deraison and Nathalie Vergnolle. Writing Review and Editing: Manon Bouchet, Julie Thevenin, Nicolas Carrere, Fabrice Muscari, Olivier Abbo, Charlotte Maulat, Laurent Ghouti, Ariane Weyl, Jean Pierre Duffas, Jean Paul Motta, Antoine Philis, Cindy Canivet and Nathalie Vergnolle.

Figure legends

Figure 1. PRISMA 2020 Flow Diagram Showing the Search Strategy.*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Figure 2: Results for the Intervention to Reduce POI Measured by Time to Flatus:

A-Network map, the width of each line corresponds to the number of RCTs comparing the two treatments. B-Relative effect Bayesian plot. C-Treatments reported in order of efficacy ranking according to surface under the cumulative ranking curve (SUCRA). D- Rankogram demonstrating relative ranking of each treatment to reduce POI.

Figure 3: Results for the Intervention to Reduce POI Measured by Time to Passage of First Stools:

A-Network map, the width of each line corresponds to the number of RCTs comparing the two treatments. B-Relative effect Bayesian plot. C-Treatments reported in order of efficacy ranking according to surface under the cumulative ranking curve (SUCRA). D- Rankogram demonstrating relative ranking of each treatment to reduce POI.

Figure 4: Results for the Intervention to Reduce POI Measured by Time to Solid Food Tolerance:

A-Network map, the width of each line corresponds to the number of RCTs comparing the two treatments. B-Relative effect Bayesian plot. C-Treatments reported in order of efficacy ranking according to surface under the cumulative ranking curve (SUCRA). D- Rankogram demonstrating relative ranking of each treatment to reduce POI.

Figure 5: Results for the Intervention to Reduce POI Measured by Time to Bowel Movement:

A-Network map, the width of each line corresponds to the number of RCTs comparing the two treatments. B-Relative effect Bayesian plot. C-Treatments reported in order of efficacy ranking according to surface under the cumulative ranking curve (SUCRA). D- Rankogram demonstrating relative ranking of each treatment to reduce POI.

Figure 6: Results for the Intervention to Reduce POI Measured by Time to Length of Hospital Stay:

A-Network map, the width of each line corresponds to the number of RCTs comparing the two treatments. B-Relative effect Bayesian plot. C-Treatments reported in order of efficacy ranking according to surface under the cumulative ranking curve (SUCRA). D- Rankogram demonstrating relative ranking of each treatment to reduce POI.

Figure 7: Results for the Intervention to Reduce POI Measured by Number of Patients Requiring Post-Operative Nasogastric Tube Placement:

A-Network map, the width of each line corresponds to the number of RCTs comparing the two treatments. B-Relative effect Bayesian plot. C-Treatments reported in order of efficacy ranking according to surface under the cumulative ranking curve (SUCRA). D- Rankogram demonstrating relative ranking of each treatment to reduce POI.

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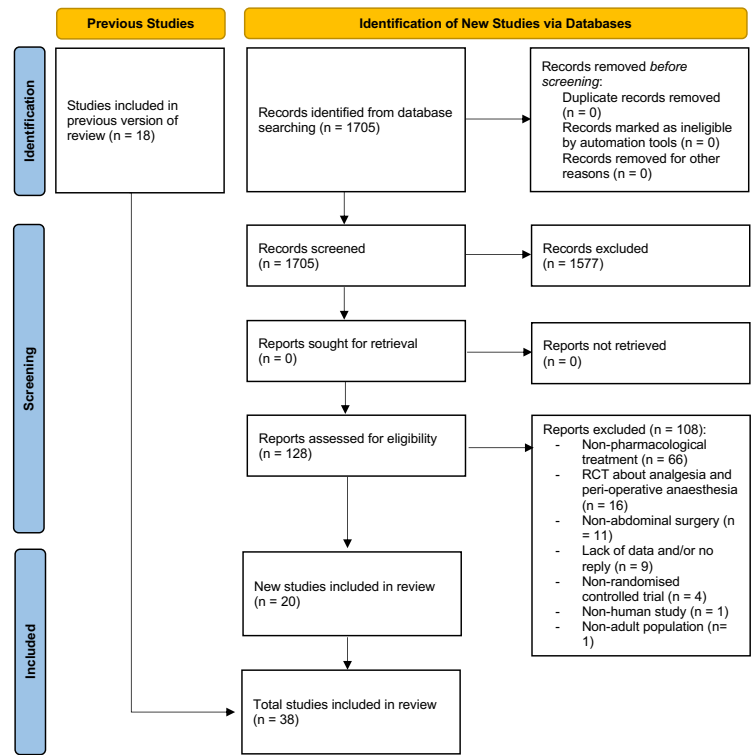
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Figure 1 Flow diagram of assessment of studies identified in the systematic review

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Table 2_Proofread_Sumita.docx available at https://authorea.com/users/600715/articles/632210-

post-operative-ileus-after-digestive-surgery-network-meta-analysis-of-pharmacological-intervention

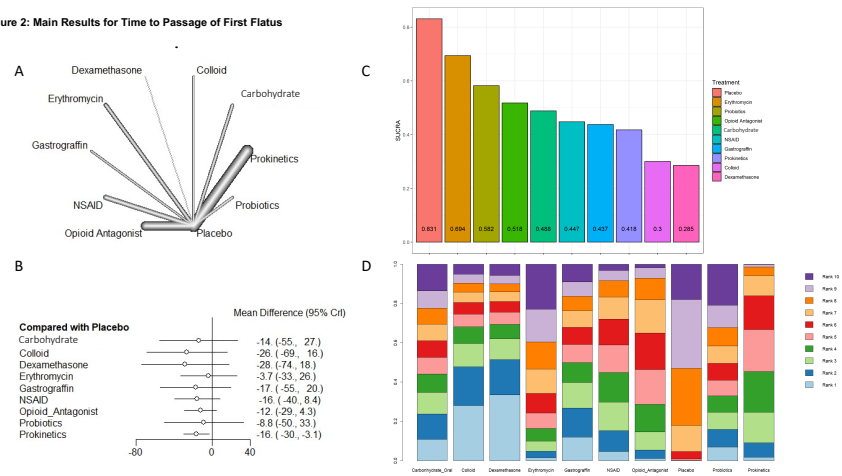**Figure 2: Main Results for Time to Passage of First Flatus**

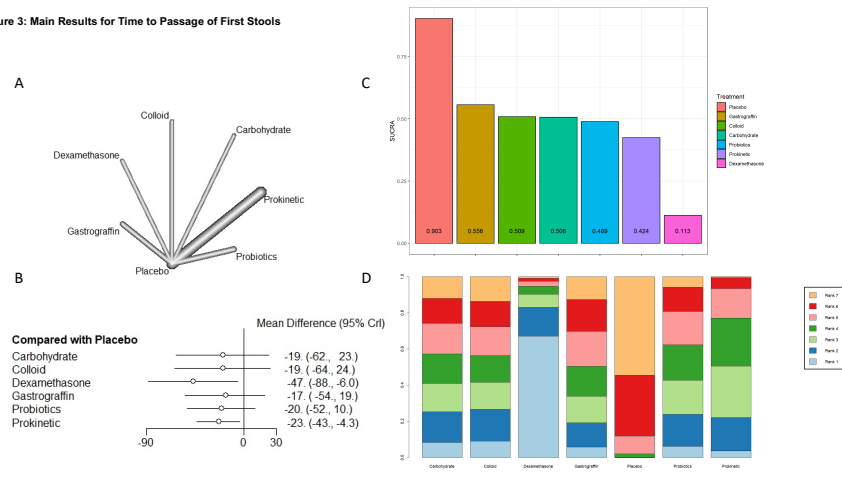**Figure 3: Main Results for Time to Passage of First Stools**
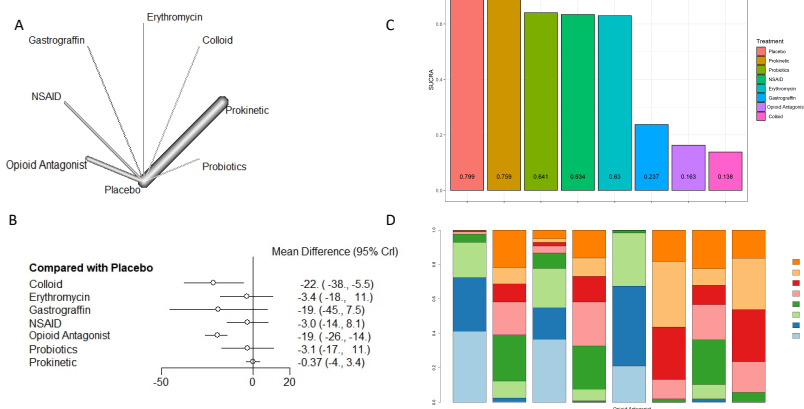

15

Figure 4: Main Results for Time to Solid Food Tolerance

A

B

Compared with Placebo — Mean Difference (95% CrI)

Colloid	-22. (-38., -5.5)
Erythromycin	-3.4 (-18., 11.)
Gastrograffin	-19. (-45., 7.5)
NSAID	-3.0 (-14., 8.1)
Opioid Antagonist	-19. (-26., -14.)
Probiotics	-3.1 (-17., 11.)
Prokinetic	-0.37 (-4., 3.4)

C

D

Figure 5: Main Results for Time to Bowel Movement

A

B

Compared with Placebo — Mean Difference (95% CrI)

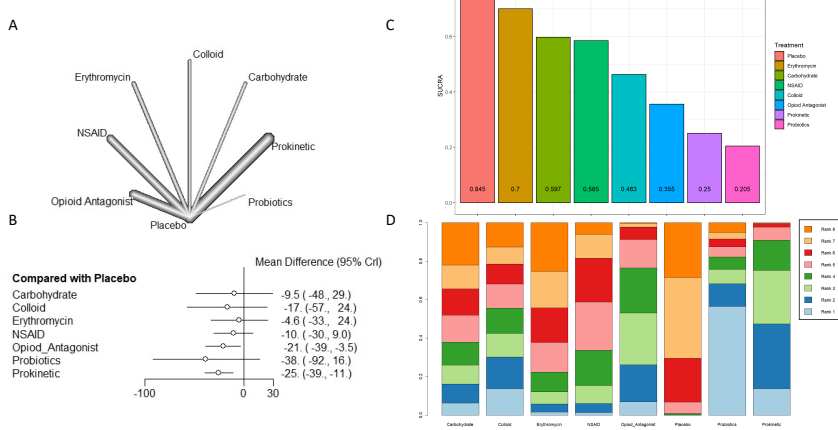|	
Carbohydrate	-9.5 (-48., 29.)
Colloid	-17. (-57., 24.)
Erythromycin	-4.6 (-33., 24.)
NSAID	-10. (-30., 9.0)
Opiod_Antagonist	-21. (-39., -3.5)
Probiotics	-38. (-92., 16.)
Prokinetic	-25. (-39., -11.)

C

D

Figure 6: Main Results for Length of Hospital Stay

A

B

Compared with Placebo — Mean Difference (95% CrI)

Carbohydrate	-1.1 (-7.2, 4.9)
Colloid	-2. (-8.0, 4.0)
Erythromycin	0.097 (-4.2, 4.4)
Gastrograffin	-3.5 (-8.7, 1.6)
NSAID	-1.3 (-5.6, 2.9)
Opioid Antagonist	-0.69 (-3.4, 2.)
Probiotics	-0.61 (-5.1, 3.8)
Prokinetic	-1.9 (-3.8, -0.040)

C

D

Figure 7: Main Results for Number of Patients Requiring Post-Operative Nasogastric Tube Placement