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Randomized open label phase II study to compare oxycodone/naloxone vs. oxycodone in early return of gastrointestinal function after laparoscopic colorectal surgery

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Key words: Oxycodone/naloxone, postoperative ileus, enhanced recovery, colorectal surgery, laparoscopic

Comment [PH1]: Changed to past tense

Abstract

Background
Combined oral modified release oxycodone/naloxone (Targinact®) may reduce opioid-induced postoperative gut dysfunction. We examined the feasibility of a randomised trial of oxycodone/naloxone within the context of enhanced recovery for laparoscopic colorectal resection.

Methods
In a single centre open label phase II feasibility study patients received analgesia based on either oxycodone/naloxone or oxycodone. Primary endpoints were recruitment, retention and protocol compliance. Secondary endpoints included a composite endpoint of gut function (tolerance of diet, low nausea/ vomiting score, passage of flatus or faeces).

Results
Eighty-two patients were screened and 62 randomised (76%) with an attrition rate of 19% (12/62), leaving 50 patients who received the allocated intervention with 100% follow-up and retention (modified intention to treat cohort). Protocol compliance was >90%.
Return of gut function (a composite endpoint defined by passage of flatus and tolerance of solid food) by day 3 was similar: 13 of 27 (48%) in the oxycodone/naloxone group and 15 of 23 (65%) in the control group (95% CI -44%, 10%, P=0.264). However, the oxycodone/naloxone group had a shorter time to first bowel movement (mean 87 hours (SD 38) vs. 111 hours (SD 37), 95% CI 2, 45 hours, P=0.03) and reduced total (oral + parenteral) opioid consumption (mean 78 mg (SD 36) vs. 94 mg (SD 56), 95% CI -11, 44 mg, P=0.22).

Conclusions
High participation, retention and protocol compliance confirmed feasibility. Potential benefits of oxycodone/naloxone in reducing time to bowel movement and total opioid consumption could be tested in a randomised trial.

ClinicalTrials.gov: NCT02109640

Introduction

As multimodal enhanced recovery pathways have been implemented in laparoscopic and open colorectal surgery, so there has been recognition that delayed return of gut function represents one of the main barriers to maximising the benefits of modern surgical techniques and perioperative care.[1] Research in this area has increased in recent years, with substantial progress achieved in reaching consensus on definitions and study endpoints.[2, 3]

Postoperative ileus (POI) is a transient impairment of normal gastrointestinal motility after surgery and has complex multifactorial aetiology. It is a frequent cause of delayed discharge from hospital after elective colorectal surgery, affecting up to 40% of patients.[3] POI is poorly defined but manifests as any combination of nausea, vomiting, constipation or abdominal distension sufficient to prevent resumption of adequate postoperative oral nutritional intake. Treatment comprises fasting, prolongation of intravenous fluid therapy and nasogastric tube insertion. Although self-limiting in most cases, it can prolong hospital admission by a number of days despite the absence of other postoperative complications, increasing healthcare costs.[1]

Opioids are the mainstay of postoperative analgesic regimens after abdominal surgery and are highly effective in achieving adequate pain control. However, opioids contribute to impaired gut function by reducing normal forward propulsion and increasing non-propulsive gut spasm.[4, 5] Targinact® (Napp Pharmaceuticals Ltd, Cambridge Science Park, Milton Rd, Cambridge CB4 0AB, UK) is a combination of modified release oxycodone hydrochloride and naloxone hydrochloride (an opioid receptor antagonist) designed to reduce constipation in patients with chronic pain requiring long-term opioids. Oral naloxone has minimal systemic availability (high first-pass hepatic metabolism), confining its local action to the gut to reduce opiate inhibition of gut motility without systemic effects. Oxycodone/naloxone has been shown to provide comparable analgesia to other opioid analgesics in patients with chronic severe pain whilst reducing the unwanted side-effect of constipation.[6, 7] Whether it has the same beneficial effect on constipation in the acute pain setting and whether there would be a more rapid return of overall gastro-intestinal (GI) function in the post-operative setting is not known.

The trial was undertaken as a pilot study for the following reasons: to estimate effect size (having no information *a priori* on which to base a sample size calculation); to refine endpoint definition of return of gut function; and to assess variation in protocol compliance and other practical aspects of running a clinical trial within a complex intervention in a busy NHS hospital. The primary endpoint was feasibility, assessed by recruitment and retention (number of patients screened and/or consented), and compliance with the intervention. The secondary endpoints were regarded as exploratory to inform design of future trials of return of gut function after surgery and included time to tolerance of diet and time to passage of first flatus and faeces.[3, 8]

Methods

Gut function comprises the interaction of many complex physiological functions and there is no universal definition to confirm its return after major abdominal surgery. Resumption of normal gut function requires patients to have the desire to eat, sufficiently low levels of nausea or vomiting to ingest food, and evidence of return of lower GI transit, evidenced by passage of flatus or faeces with the former usually preceding. Thus a number of positive and negative endpoint definitions exist, including tolerance of diet, independence from intravenous (IV) fluids, passage of flatus, bowel movement, absence of severe nausea and vomiting and nasogastric tube insertion.[8-10] None of these measures is satisfactory in isolation. We recorded data to positively and negatively define the return of gut function after laparoscopic colectomy. Our pre-study composite definition of return of gut function was toleration of diet, absence of severe nausea/vomiting (PONV score ≤4[11]), and passage of either flatus or faeces, reflecting seminal work in this area by previous investigators.[3, 8, 13].

Studying the impact on postoperative outcomes of a single component within a complex intervention such as colonic surgery is challenging. Minimising variation by application of a consistent experimental model is fundamental to being able to draw robust conclusions; ideally, all aspects of treatment would be identical for each patient apart from the intervention being studied. This is difficult to achieve across all aspects of patient selection, anaesthesia, surgical intervention and perioperative care within a busy UK National Health Service (NHS) hospital setting. Therefore, the study included only colonic resections that could be carried out by different surgeons with a consistent technique. A standard anaesthetic protocol and perioperative patient care pathway based on Enhanced Recovery After Surgery (ERAS) principles was agreed by anaesthetic and surgical teams and its implementation monitored by the study team.[12]

Study design and participants

A Phase II, randomised, open label trial was conducted (ClinicalTrials.gov: NCT02109640) to compare modified release oxycodone/naloxone (intervention) with modified release oxycodone (control). Patients were recruited between 1st Dec 2014 and 12th August 2015 from patients scheduled for elective laparoscopic segmental colonic resection under the care of one of 11 specialist colorectal surgeons at the Lothian Colorectal Surgery Unit, Western General Hospital, Edinburgh, UK. Patients were identified from all cases being scheduled for elective segmental colonic resection and potential eligibility for study inclusion confirmed with the responsible surgeon. Enrolment and consent to participate was undertaken at hospital visits required as part of the normal patient pathway (outpatient clinics, preoperative assessments).

Exclusions were pregnancy, inability to give informed consent, age <18 years, regular opioid analgesic prescription, opiate dependence, intolerance/allergy to oxycodone/naloxone or oxycodone, total rectal resection, planned stoma, or additional intraoperative procedure.

At baseline patients were assessed in terms of: body mass index (BMI); waist/hip ratio (WHR)[14]; Simplified Nutritional Appetite questionnaire (SNAQ)[15]; Quality of

Recovery Score (QoRS)[16], Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (P-POSSUM)[17] and Apfel score for prediction of postoperative nausea and vomiting.[18]

The protocol was approved by the East of Scotland Research Ethics Service and written informed consent was obtained from all patients. The trial was performed in compliance with ICH-GCP and the Helsinki Declaration.

Randomisation

Eligible patients were randomised before surgery to receive intervention or control drug (allocation ratio 1:1) using sealed envelopes stratified by left or right colectomy created independently by the study statistician. The randomisation sequence was generated by using the block method of randomisation, using blocks of 6 and 8 to disguise the pattern. Separate schedules were generated for left and right colonic operations. The number of randomisations generated was slightly larger than the sample size required in order that the last randomisation was not 'guessable'. The statistician was blinded to which group was allocated to intervention and which to control. Randomisation was carried out by the principal or chief investigator opening the next envelope in a numbered sequence in the presence of a research nurse, after informed consent was obtained, approximately 1-7 days before the intended date of operation. The first (preoperative) dose of the study drug or control was then prescribed for the date of surgery and ordered from the hospital pharmacy. Treatment allocation was not blinded to the patient, clinical staff or research study staff as over-encapsulation of the study drugs proved prohibitively expensive.

Protocol

A key feature of the study design was that patients were given the first dose of oxycodone/naloxone (10mg) or oxycodone (10mg) 1-2 hours before induction of anaesthesia. It was postulated that giving oxycodone/naloxone before administration of systemic opioids during anaesthesia would maximise any potential benefit of the gut naloxone component in reducing gut dysfunction. Patients were managed using a standard perioperative care pathway based on enhanced recovery principles in order to maintain consistency of perioperative care.[12] Eleven surgeons and 10 anaesthetists participated in the study. Surgery was undertaken by colorectal specialists, all of whom had undertaken >100 laparoscopic colonic resections prior to the study and perform 30-40 laparoscopic colonic resections per year.

Standard operative technique was agreed between the participating surgeons. Right hemicolectomy was undertaken using a 4-port technique, ligating and dividing the proximal ileocolic/ right colic vessels to achieve radical lymphadenectomy and extracting the colon via a small periumbilical incision to undertake resection and end-to-end sutured anastomosis. Left colectomy was undertaken using a 4- or 5-port technique, with routine splenic flexure mobilisation, high ligation of the inferior mesenteric artery and vein, extraction of the specimen through a short Pfannansteil incision and stapled transanal intracorporeal anastomosis. In order to achieve a

consistent operation for evaluating the study drug, patients converted to open surgery or requiring an unplanned stoma were withdrawn.

Anaesthesia comprised a single intrathecal injection of diamorphine (0.8mg)+ 3mls bupivicaine 0.25%, induction with Propofol (1-2mg /kg) and Remifentanil (0.25 to 1mcg/kg bolus followed by infusion of 1-2mcg/kg/min) and Atracurium (0.5mg/Kg) or Rocuronium (0.6mg/Kg). Maintenance was with oxygen/air (50:50) and Desflurane. Perioperative intravenous lidocaine was given by a bolus of 1.5mg/kg at induction over 20 minutes followed by continuous infusion of 1mg/min if < 70kg or 2mg/min if >70kg for 12 hours. Analgesia comprised intraoperative Remifentanil and postoperative morphine via patient-controlled analgesia (PCA). Oral oxycodone/naloxone (5-20mg) or oxycodone (5-20mg) 12-hourly was continued from the evening of surgery. All patients received oral paracetamol (1g qds). Non-steroidal anti-inflammatory drugs were not used routinely. Pain scores were assessed daily by the Acute Pain team according to existing unit protocols.

Perioperative management was delivered according to a defined protocol including: minimal preoperative fasting time, preoperative oral fluid and carbohydrate loading, early discontinuation of IV fluids (day 1), early discontinuation of systemic and/or oral opioids, immediate resumption of oral nutrition as tolerated and defined daily mobilisation goals. Patients were deemed fit for discharge if they met the following criteria: tolerating diet and fluids without requirement for IV fluids, passage of either flatus or faeces, independently mobile, pain controlled with oral analgesia, no medical contraindication to discharge, and willing to go home.

Outcomes

The objective was to learn about all the parameters required to design a definitive trial if we were persuaded that such a definitive trial was (a) necessary and (b) feasible. Therefore, the primary endpoints were chosen to assess feasibility of studying the effect of a specific perioperative intervention intended to improve return of postoperative gut function (in this case oxycodone/naloxone). Recruitment was assessed by the proportion of patients screened versus those consented. Retention was determined by documenting attrition rate and the reasons for it.

The main secondary outcome was the return of gut function on the third post-operative day. Protocol definition of return of gut function was a composite endpoint measured on the third postoperative day comprising each of the following: tolerating diet (3 consecutive light meals), Postoperative Nausea and Vomiting (PONV) score ≤4 and passage of either flatus or faeces. Outcomes were documented by study nurses or a research fellow at a daily morning visit to each patient. Prior to the first randomised patient, data collection was tested on 5 “dummy” patients to evaluate study documentation and review utility of data recording and definitions.

The day of operation was day 0; day 3 was the third day after the day of operation.

Other secondary outcome measures comprised the following patient-reported outcome measures: Overall Benefit of Analgesia score,[19] PONV score,[11] Quality of Recovery score,[16] oral nutritional intake (patient diary), daily opioid consumption, time to first flatus and time to first bowel movement. The study team did not

participate in deciding on date of discharge, which was left to the clinical team. Complications were recorded using a severity scale until 30 days after surgery.[20]

Protocol compliance was measured based on implementation of the following core perioperative interventions: single spinal dose of diamorphine; 12 hour lidocaine infusion; cessation of morphine PCA on day 1 (the first postoperative day); cessation of intravenous fluids on day 1.

Statistical analysis

Since this was a pilot study, a power calculation was not performed. A sample size of 50 evaluable patients was chosen as an achievable recruitment target within the specified study duration of 1 year, and it was felt that this would be sufficient to reliably estimate the study performance metrics (e.g. recruitment rate) and likewise give adequate insight into the parameters needed (e.g. the variability, and the prevalence of delayed return of gut function and prolonged postoperative ileus) to inform a sample size calculation for a definitive full multicentre UK-wide clinical and cost-effectiveness study.

Analyses of the data included Fisher's Exact test for categorical data (due to the small numbers in some of the cells), and Student's t-test, with log transformation where appropriate. Estimates of differences in proportions and means have also been calculated. We compared the randomised groups for a number of clinical measures, and have in general commented where there is little or no difference between the groups. However, as a pilot/feasibility study the sample size was insufficient to rule out what might be important clinical differences, as evidenced by the large width of the 95% confidence intervals around the point estimates between randomised group differences. As all these analyses are descriptive we have made no adjustment for multiple comparisons, hence the reader should exercise caution in not over interpreting these data as a result. Statistical analysis was performed using SPSS 19.0. The trial statistician was blinded to treatment allocation for data analysis. Two-sided 5% significance level was applied throughout. All data for the variables included in this article were complete for all patients. However, unless demonstrated otherwise, data would have been assumed to be missing at random.

Results

Primary outcomes

Eighty-two patients were screened over an eight month period resulting in 62 patients being randomised (Figure 1). Recruitment rate (screened versus consented) was 76% (62/82). The main reason for non-recruitment was failure to meet eligibility criteria. Patients randomised but not analysed were withdrawn due to:

a) development of protocol-specified ineligibility (change of planned operation in 3 patients; emergency surgery before the planned date of elective surgery in 1 patient); conversion to open surgery in 3 patients; eligibility violation in 1 patient (chronic opioid use)

b) decision by anaesthetist to deviate substantially from defined protocol (e.g. epidural) in 3 patients.

c) a fundamental protocol violation (first dose of the study drug not given pre-operatively) in 1 patient

These patients are all detailed in the CONSORT flow diagram under the 'Allocation' heading. Study data was **not** collected on these patients. Thereafter, all patients that received the allocated intervention (27 in the oxycodone/naloxone arm, 23 in the oxycodone arm) had 100% follow up and were included in the analysis, referred to hereafter as the modified intention to treat population (mITT). Demographic and clinical characteristics of the mITT population are shown in Table 1.

Secondary outcomes

The number of patients achieving return of individual components of gut function by postoperative day 3 and 4 is shown in Table 2. Day of return of gut function based on the prespecified composite endpoint definition of tolerating diet, passage of either flatus or faeces and PONV ≤4 is shown in Figure 2. The quality of analgesia and overall recovery assessed by OBAS and QoR scores were similar (Figure 3). The time to first bowel movement was reduced in the oxycodone/naloxone group (Table 3). Time to first flatus and time to first bowel movement are shown in Figures 4 and 5 respectively. Total opioid consumption was approximately 20% less in the oxycodone/naloxone group than controls: mean 78 mg (SD 36) oxycodone/naloxone vs. 94 mg (SD 56) controls; 95% CI -11-44 mg; p=0.22.

There was no clinically notable or statistically significant difference in other secondary outcome measures.

Comment [PH2]: The previous version paragraph below has been moved to table 2: Thirteen of 27 (48%) in the oxycodone/naloxone group versus 15 of 23 (65%) in the oxycodone group had achieved return of gut function by day 3 (Δ= -17%; 95% CI -44%, 10%; P=0.264). By day 4, 23 of 27 (85%) in the Oxycodone/naloxone group versus 17 of 23 (74%) in the control group had achieved return of gut function (Δ= 11%; 95% CI -11%, 34%; P=0.48).

Complications

There were no Suspected Unexpected Serious Adverse Reactions (SUSARs) or Serious Adverse Events (SAEs) attributable to the study drug. Three patients were readmitted urgently. There were 2 major complications in the intervention arm of the study: one intra-abdominal collection was drained percutaneously and one (day 4) anastomotic dehiscence required reoperation, repair and proximal diversion. There were no major complications in the control arm.

Protocol compliance

Forty-seven patients (94%) received the single-shot spinal analgesia. Overall 46 patients (92%) received IV lidocaine, IV fluid was withdrawn per protocol in 45 of 50 patients (90%) and had to be re-instituted due to excessive nausea, or intolerance of

oral intake in 16 of 50 patients (32%); there was no difference in distribution of these cases between the study arms (Table 4). Urinary catheter was removed per protocol in 37 of 50 patients (74%) and delayed for medical reasons in most of the remainder (prostatic hypertrophy, traumatic catheter insertion). Five patients (5/50, 10%, 4 males 1 female) required re-catheterisation for acute urinary retention.

Discussion

The trial demonstrated that it is feasible to assess a novel perioperative intervention in the context of post-operative gut function using a consistent multimodal enhanced recovery pathway. The rate of recruitment and retention was good. The main reason for ineligibility was regular opioid use, reflecting the relatively elderly patients typical of colorectal practice. The attrition rate was an unanticipated consequence of the study design, in which the first dose of the study drug was given preoperatively to maximise benefit. A more conventional design in which patients were randomised after completion of the operation might have resulted in lower attrition. In a future definitive study using the current design, all patients randomised would be included in analysis (testing the policy of treating rather than the drug itself).

Overall length of stay, gut function recovery times, event rate (postoperative ileus) and complications were comparable with contemporary laparoscopic colectomy data.[21, 22] In contrast, the cohort was a decade older and cancer was the indication for surgery in a much greater number than in these reports. Excessive intravenous fluid administration was avoided, most patients were converted to oral analgesia on day 1 and independent mobilisation was restored by day 2. The surgical intervention in the mITT population was consistent with protocol. Minor deviations from the anaesthetic protocol reflected the 'real world' nature of the study e.g. spinal osteoarthritis preventing spinal analgesia injection or early termination of IV lidocaine infusion due to lack of high-dependency monitoring.

No patient relapsed once the composite endpoint definition of return of gut function had been achieved, and no patient was discharged before it was fulfilled. However, the PONV score did not provide additional discrimination to a definition of return of gut function comprising tolerance of diet and passage of flatus or faeces. Hence this study supports the GI-3 definition of return of gut function (tolerance of diet plus passage of flatus OR bowel movement) as the appropriate endpoint for future studies.[13, 23-25]

Analgesia using oxycodone/naloxone appeared to be at least equivalent in efficacy to modified release oxycodone; indeed, total opioid consumption was 20% less in the oxycodone/naloxone group. In addition, the oxycodone/naloxone group had a shorter time to first bowel movement. These observations are biologically plausible: reduced inhibition of lower GI function is the *modus operandi* of the study drug. Earlier defecation may have contributed to lower total opioid consumption in the oxycodone/naloxone arm; it appeared that most of the difference in opioid consumption between the groups occurred after day 3 (Table 3). Based on this data, in order to detect a difference of around 16 mg assuming a common standard of around 40 mg (an effect size of 0.4) within this population, one would need a study of around 300 participants (using a two sample t-test with 90% power at a 5% level of significance, and allowing for 15% loss to follow up). A study of approximately 300 patients would also be required to detect the difference observed in this study in time to first bowel movement (Figure 4: by 100 hours (i.e. day 4) approximately 40%

in the control group vs 60% in the intervention group had defecated, effect size of 20%, using a comparison of proportions with 90% power at a 5% level of significance, and allowing for 15% loss to follow up).

We did not undertake blinding as the study budget would not extend to commercial over-encapsulation of controlled drugs. Investigator bias was minimised by the majority of outcome measures being patient-reported and non-involvement of the study team in clinical care (including analgesic assessment and prescription). The statistician was blinded to treatment allocation throughout. Double-blinding of a future study would be achievable within this model.
There was a considerable interval between passage of flatus and first bowel movement. Routine laxation was not part of the study protocol and might have shortened this interval, but adequate consensus on this point could not be agreed by participating surgeons, reflecting the limited evidence.[26]

Despite consistently implementing a modern enhanced recovery study protocol in one of the more straightforward colorectal surgery subgroups (laparoscopic segmental colectomy, no stomas, no low rectal dissection) gut function had not returned by day 3 in a substantial number of patients. Although there was a possible beneficial effect of oxycodone/naloxone on analgesia and time to first bowel movement, oxycodone/naloxone did not alter the overall postoperative return of gut function in this study.

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Disclosure
The authors declare no conflict of interest.

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Table 1 Demographic characteristics of patients who were randomised and received their allocated treatment (modified intention to treat cohort)

	Control (n=23)	***Intervention (n=27)***
Age (years)	68 (50-87)	71 (30-83)
Sex ratio (F:M)	12:11	12:15
Right / Left colectomy (n)	10 / 13	14 / 13
BMI	25.75 (20.07-43.58)	27. 50 (19.12-42.46)
WHR	0.96 (0.80-1.14)	0.96 (0.76-1.12)
SNAQ	16 (10-19)	16 (14-19)
Baseline QOR score	129 (97-140)	130 (112-140)
Apfel score 1 2 3 4	 1 10 10 2	 3 11 13 0
P-POSSUM	27 (18-48)	28 (16-42)

Values are median(range). BMI: body mass index (kg/m^2); WHR: waist/hip ratio; SNAQ: Simplified Nutritional Appetite questionnaire; QoR: Quality of Recovery Score; P-POSSUM: Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity; Apfel score: prediction of postoperative nausea and vomiting. Indication for surgery was colorectal cancer in 49 patients and diverticular disease in one patient.

Table 2 Cumulative numbers of patients achieving individual elements of the composite endpoint of return of gut function by postoperative days 3 and 4

		Control (n=23)	Intervention (n=27)	Difference in % (95% CI)	p
Day 3	**Composite endpoint***	**15**	**13**	**-17 (-44, 10)**	**0.264**
	PONV ≤4	*20*	*26*	*-9.3 (-28.6, 7.5)*	*0.322*
	Tolerance of diet	*18*	*20*	*4.2 (-20.0, 26.5)*	*1.000*
	Passage of flatus	*19*	*17*	*19.7 (-5.5, 41.1)*	*0.206*
	Passage of faeces	*3*	*7*	*-12.9 (-33.5, 10.1)*	*0.308*
Day 4	**Composite endpoint***	**17**	**23**	**11 (-11, 34)**	**0.481**
	PONV≤4	*22*	*25*	*3.1 (-14.4, 19.4)*	*1.000*
	Tolerance of diet	*19*	*24*	*-6.3 (27.3, 13.6)*	*0.689*
	Passage of flatus	*22*	*25*	*3.1 (-14.4, 19.4)*	*1.000*
	Passage of faeces	*8*	*16*	*-24.5 (-47.2, 3.0)*	*0.098*

**Composite endpoint= tolerating diet, passage of either flatus or faeces and PONV ≤4*
Difference calculated as Control - Intervention

Table 3: Secondary outcome measures

	Control (n=23)	*Intervention (n=27)*	*Difference (95% CI)*	*P*
OBAS day 3 (median (range))*	2 (0-10)	2 (0-11)	-0.09 (-0.60, 0.57)	0.68
PONV day 3 (median(range))†	1 (0-6)	1 (0-5)	0.48 (-0.31, 1.27)	1.0
QoR score day 3	117 (20)	119 (23)	-1.44 (-13.7, 10.8)	0.81
Opioid consumption up to day 3 (mg of morphine equivalent)	79 (42)	70 (31)	8.5 (-12.3, 29.2)	0.42
Total opioid consumption (mg of morphine equivalent)	94 (56)	78 (36)	16.3 (-10.2, 42.8)	0.22
Time to first flatus (hours)	51 (26)	57 (26)	-6.3 (-21.3, 8.7)	0.40
Time to first bowel movement (hours)	111 (37)	87 (38)	23.8 (2.3, 45.4)	0.03
Intraoperative IV fluids (mls)	1756 (814)	1575 (738)	179.7 (-262.1, 621.6)	0.42
Total IV fluid up to day 3 (mls)*	1887 (1228)	1946 (1747)	0.03 (-0.33, 0.39)	0.86
Total oral fluids up to day 3 (mls)	4627 (1864)	4134 (1452)	493.0 (-450.5, 1436.5)	0.3
Day of discharge (median(range)) †	4 (3-10)	5 (3-14)	-0.02 (-0.27, 0.23)	1.0

Data is shown as mean (SD) and analysed by T-test unless otherwise stated; * T-test following log transformation, difference is the difference in the log scale; †Fisher's exact test, difference applies to logged data

OBAS: Overall Benefit of Analgesia score; PONV: Postoperative Nausea and Vomiting Score; QoR: Quality of Recovery Score

Total opioid consumption comprises in-hospital and post-discharge oral and intravenous medication until cessation

Table 4: Protocol compliance

	Control (n=23)	***Intervention (n=27)***	***Difference in % (95% CI)***	***P (Fisher's Exact test)***
Single shot spinal	20	27	-13.0 (-32.1, 2.0)	0.090
IV lidocaine infusion	21	25	-1.3 (-20.2, 15.9)	1.000
IV removed day 1	21	24	2.4 (-17.1, 20.5)	1.000
PCA removed day 1*	21	25	-1.3 (-20.0, 15.9)	1.000
IV replaced	7	9	-2.9 (-26.9, 22.3)	1.000

*No patients required PCA to be reinstated

Figure 1: CONSORT flow diagram

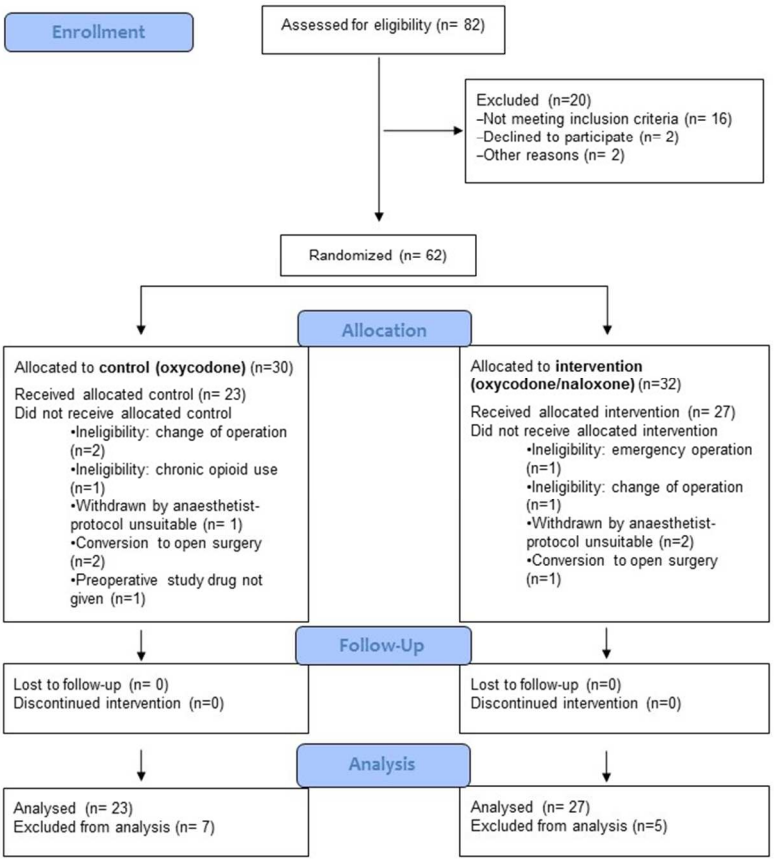

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Figure 3: Comparison of oxycodone/naloxone with oxycodone on Overall Benefit of Analgesia Score (OBAS) and Quality of Recovery (QoR) score on postoperative days 1, 2 and 3

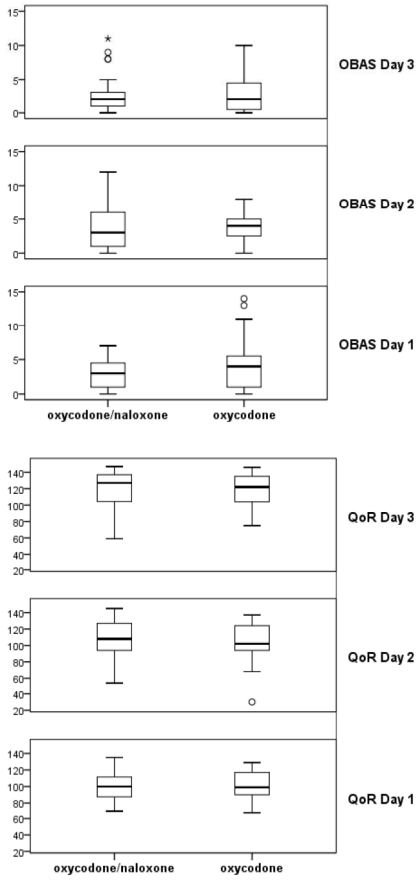

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Figure 4: Time to first flatus (hours). Median time to first flatus was 52 hours for the oxycodone/naloxone group and 43 hours for the oxycodone group; P=0.337 (Mantel –Cox log rank test)

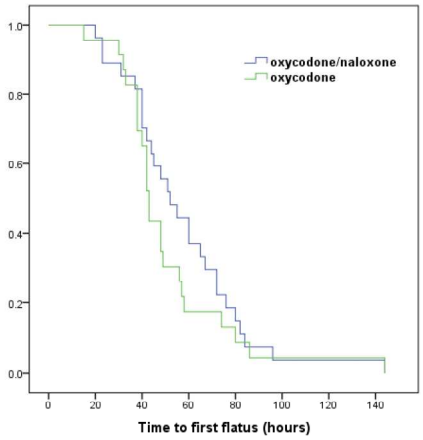

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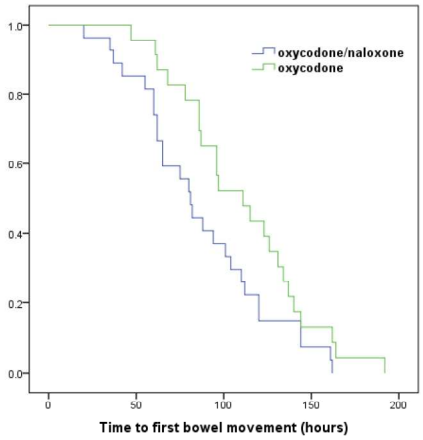
Figure 5: Time to first bowel movement (hours). Median time to first bowel movement was 81 hours in the oxycodone/naloxone group and 111 hours for the oxycodone group; P=0.062 (Mantel –Cox log rank test)



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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6/7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1 and p8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1;
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 2-4
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Tables 2-4
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.