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Women require routine opioids to prevent painful colonoscopies: a randomised controlled trial

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ABSTRACT

Background: Women are at high risk for painful colonoscopy. Pain, but also sedation, are barriers to colorectal cancer (CRC) screening participation. In a randomised controlled trial, we compared on-demand with pre-colonoscopy opioid administration to control pain in women at CRC screening age.

Methods: Women, aged 55–79 years, attending colonoscopy at two Norwegian endoscopy units were randomised 1:1:1 to (1) fentanyl on-demand, (2) fentanyl prior to colonoscopy, or (3) alfentanil on-demand. The primary endpoint was procedural pain reported by the patients on a validated four-point Likert scale and further dichotomized for the study into painful (moderate or severe pain) and non-painful (slight or no pain) colonoscopy. Secondary endpoints were: willingness to repeat colonoscopy, adverse events, cecal intubation time and rate, and post-procedure recovery time.

Results: Between June 2017 and May 2020, 183 patients were included in intention-to-treat analyses in the fentanyl on-demand group, 177 in the fentanyl prior to colonoscopy group, and 179 in the alfentanil on-demand group. Fewer women receiving fentanyl prior to colonoscopy reported a painful colonoscopy compared to those who were given fentanyl on-demand (25.2% vs. 44.1%, $p < .001$). There was no difference in the proportion of painful colonoscopies between fentanyl on-demand and alfentanil on-demand (44.1% vs. 39.5%, $p = .40$). No differences were observed for adverse events or any of the other secondary endpoints between the three groups.

Conclusions: Fentanyl prior to colonoscopy provided better pain control than fentanyl or alfentanil on-demand. Fentanyl before colonoscopy should be recommended to all women at screening age.

Trial registration: Clinicaltrials.gov (NCT 01538550). Norwegian Medicines Agency (16/16266-13). EU Clinical Trials Register (EUDRACTNR. 2016-005090-13)

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death [1]. CRC screening is recommended for average-risk adults [2] and successful screening programs depend amongst others on high attendance rates. Anticipation of pain is a major barrier to attend screening colonoscopy [3] and may also jeopardize attendance to colonoscopy for symptoms and surveillance [4,5]. Women feel more anxious about colonoscopy and report pain more often than men [6,7].

Strategies to prevent painful colonoscopies include amongst others improved medication strategy [8]. Moderate

sedation combining opioids and benzodiazepines is generally recommended [9] while unsedated colonoscopy or sedation on-demand has been recommended in selected patients [10]. Nevertheless, deep propofol sedation is the standard in some parts of the world, while in other parts sedation strategies differ widely [11–13]. Most colonoscopies are performed sedation-free in several countries [14–17]. These differences may be due to the challenge to balance the benefits and drawbacks of different sedation strategies as well as regulations concerning the administration of propofol. In addition, cultural differences may influence the endoscopist's attitude and the patient's expectation regarding medication

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 Supplemental data for this article can be accessed [here](#).

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use. A recent review of current sedation recommendations concluded that there is a lack of harmonisation regarding the recommended level of sedation and type of drugs [12].

Deep sedation is associated with adverse events and costs [18–21] and may also influence the effect of screening because it hampers dynamic position change and thus may reduce the adenoma detection rate [22]. Furthermore, sedation has been identified as a barrier to CRC screening, probably because healthy screenees do not accept potential risks and inconveniences of medication [23,24].

If sedation-free colonoscopies are the standard, on-demand medication is commonly offered if pain occurs. Unsedated colonoscopy minimizes complications and costs and enables patients to return to normal daily activities immediately after the procedure [8,20]. Moreover, sedation does not necessarily result in painless colonoscopies and is not correlated with less post-colonoscopy pain [16,25].

Studies comparing pain control provided by on-demand medication to medication before colonoscopy are inconsistent [26,27]. Targeted preemptive medication in individuals at high risk for pain might be more appropriate than medication prior to colonoscopy to everyone [26]. Female sex has been identified as the strongest pre-examination risk factor for painful colonoscopy while the male gender was associated with increased willingness to attend unsedated colonoscopy [28–30]. Thus, routinely given analgesia may be appropriate for women.

Both fentanyl and alfentanil are well tolerated and commonly used during colonoscopies but Alfentanil has a superior pharmacodynamical profile for on-demand administration as it is more potent and has an extremely rapid onset of action [31–34].

The present trial aimed to investigate whether fentanyl administered before colonoscopy in women is more effective in reducing the proportion of painful colonoscopies than fentanyl administered on-demand. Further, in an exploratory setting, we also investigated the effectiveness of a third strategy of analgesia, alfentanil on-demand. Fentanyl on-demand was the standard medication at the two participating units.

Material and methods

Participants and design

From June 2017 to May 2020, all women aged 55–79 years who participated in a CRC screening trial [35] and were referred to colonoscopy after a positive faecal immunochemical test or sigmoidoscopy screening at two Norwegian endoscopy units were eligible for the present randomised trial. To reach the required sample size, women of the same age scheduled for a clinical non-screening outpatient colonoscopy were recruited from May 2018. Exclusion criteria for colonoscopy were (1) multi-morbidity specified as chronic heart-/lung disease New York Heart Association III-IV; (2) previous CRC; (3) respiratory distress; (4) allergy to opioids; (5) use of benzodiazepines, barbiturates, antipsychotic drugs, serotonergic drugs and antifungal drugs on the examination day; and (6) individuals with former or current drug abuse.

For data protection reasons, we were not allowed to record reasons for non-participation among eligible women.

Participants were randomised 1:1:1 to either of three groups “fentanyl on-demand” (standard medication at the participating units), “fentanyl prior” (fentanyl was administered immediately before colonoscopy), or “alfentanil on-demand”. The block randomisation was performed by a computer-generated true random number (<https://random.org/>) after written informed consent was obtained. For screening trial participants, randomisation was performed in a dedicated computer system. In patients scheduled for clinical outpatient colonoscopy, the assisting nurse performed randomisation by selecting sealed opaque envelopes. Neither the endoscopists, the endoscopy nurses nor the participants were blinded to the group allocation. The study was approved by the Regional Research Ethics Committee of south-east Norway (2011/1272) and registered at clinicaltrials.gov (NCT 01538550). Additionally, this trial was approved by the Norwegian Medicines Agency (16/16266-13) and registered in the EU Clinical Trials Register (EUDRACTNR. 2016-005090-13).

Procedure and analgesia

Split dose bowel preparation (PicoPrep®, Ferring Pharmaceuticals) was recommended. At attendance, medical history and risk factors for a painful colonoscopy (previous painful colonoscopy, expectation of pain, irritable bowel syndrome with pain, previous abdominal surgery, previous diverticulitis, and low body mass index) together with a pain score were registered before starting the colonoscopy. All participants received an intravenous (iv) access cannula. As a standard, the Olympus Exera II/III systems with Olympus CF-H180DL/I, CF-HQ190L/I colonoscopes (CF-colonoscopy) (®, Olympus Europa, Hamburg, Germany) were used. CO₂ was the standard insufflation gas. Water immersion or water exchange technique during insertion was performed at the endoscopist’s discretion. A magnetic position device (ScopeGuide®, Olympus Europa, Hamburg, Germany) was available for all examinations. Changing to small-calibre colonoscopes Olympus PCF-PH190L/I, PCF-H190DL/I (PCF colonoscopy) at the endoscopist’s discretion was possible but was defined as a failure for cecum intubation.

The endoscopists assessed bowel cleansing quality by either a four-point rating scale (good, acceptable, partially poor, or poor) or by the Boston Bowel Preparation scale (BBPS). Reaching good or acceptable bowel cleansing or a score of at least two out of three at BBPS in each of three colonic segments was considered adequate [36]. The calculation of Cohen’s κ showed substantial agreement between these two scales [35]. Twenty-four endoscopists performed the colonoscopies. Most colonoscopies were performed by resident physicians with varied degrees of experience, only 14 of the colonoscopies were performed by gastroenterology consultants.

The starting dose of fentanyl in both fentanyl groups (in the “on-demand group” only given at the participant’s request) was 75 mcg for women <50 kg and 100 mcg for women \geq 50 kg given iv as a split dose, initially 25 mcg and 50 mcg, respectively. After 3 min of uneventful observation of vital parameters, the remaining dose of fentanyl was administered. Dose titrating was applied at the endoscopist’s

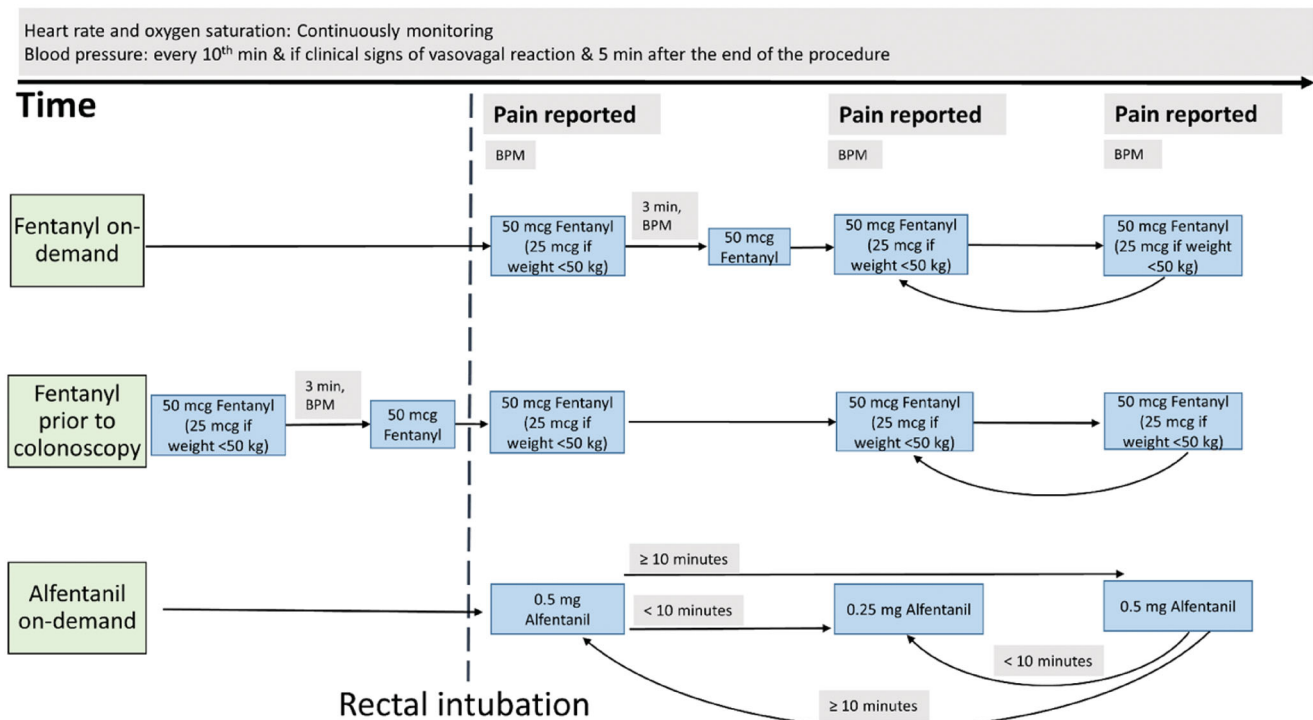


Figure 1. Flowchart medication. BPM = Blood pressure measurement. Curved arrows = Strategies to repeat medication if required.

discretion depending on patients' pain and clinical features in both groups. In the alfentanil on-demand group, a dose of 0.5 mg alfentanil was administered iv if required. Subsequent titrating was applied until required pain relief. The dosage regimen is outlined in Figure 1. Additional use of midazolam during the examination was provided if considered necessary by the endoscopist but was defined as a failure for cecum intubation.

Oxygen saturation and heart rate were monitored continuously. Blood pressure was measured every 10 min. Additional measurements were made immediately before analgesics were given and 5 min after the end of the procedure as well if clinical symptoms consistent with vasovagal reaction occurred. It was recorded whether large polyps (>2 cm) were removed. Cecum intubation was defined as reaching the cecum with a CF colonoscope and without administration of benzodiazepine (midazolam) during the examination. Adverse events with impairment of vital parameters (i.e., systolic blood pressure <100 mmHg, heart rate <50 beats/minute, oxygen saturation <90% without oxygen supplement) were defined as serious adverse events.

For participants not able to leave the endoscopy unit immediately after a colonoscopy, the time elapsed between the end of the colonoscopy and the discharge from the endoscopy unit was defined as recovery time. In the recovery room, vital signs were monitored, and participants were kept under surveillance by a trained endoscopy nurse.

Pain assessment

Baseline pain was indicated by the participants on a validated 100 mm visual analogue scale (VAS) ruler immediately before the examination [37]. After the colonoscopy,

participants were asked for willingness to repeat the examination with identical procedural process (yes, no, unsure). Furthermore, when leaving the endoscopy unit, every participant received the standard questionnaire for the Norwegian colonoscopy quality registry (Gastronet) and was asked to return it completed in a prepaid return envelope the day after the examination [38]. This questionnaire included a question on procedural pain on a validated four-point Likert scale (no, slight, moderate, severe pain) [37].

Endpoints

The primary endpoint was the proportion of women who experienced moderate or severe pain during colonoscopy, defined as painful colonoscopy, recorded within the Gastronet questionnaire the first post-colonoscopy day. Secondary endpoints were; the dose of medication, willingness to repeat the colonoscopy with identical procedural process, adverse effects, cecum intubation time and rate, and recovery time.

Statistical analysis

For the sample size calculation, the proportion of women experiencing painful colonoscopy in the fentanyl on-demand group was assumed to be 35%. This estimate was calculated by analysing the pain scores obtained from 375 women who underwent a colonoscopy in the CRC screening trial in 2015, receiving fentanyl on-demand. The main comparison of interest for this study was between the fentanyl on-demand and the fentanyl prior group: 140 women were needed in each group to achieve 80% power to detect an absolute difference between the group proportions of 15% points. The

proportion in the fentanyl prior group was assumed to be 35% under the null hypothesis and 20% under the alternative hypothesis. The significance level of the two-sided test was targeted at 0.05.

Another group was further added to explore the effectiveness of alfentanil on-demand compared to fentanyl on-demand. Based on the same assumptions formulated for the comparison between fentanyl on-demand and fentanyl prior, we added another 140 women in the alfentanil on-demand group.

Since there was only one primary analysis and all other comparisons were exploratory, no methods for multiple comparisons to avoid type I error were planned.

Based on previous experience, we assumed that 85% of the participants would return the Gastronet questionnaire. Taking the non-response rate of 15% into account the final number was 160 women in each of the three groups.

Pain was analysed as a dichotomous variable: moderate/severe pain versus no/slight pain. Distributions of dichotomous variables were compared by the Chi-squared tests or Fisher's exact test, as appropriate. Continuous variables were compared by Student's *t* tests. Risk ratios (RR) were calculated as the major measure of association and reported with 95% confidence intervals (CI). We also fitted multivariable logistic regression models, adjusted for risk factors for painful colonoscopies. Besides covariates specified in Table 1, we included polypectomy of polyps ≥ 2 cm as a covariate in our model, as we suggested that time-consuming procedures can cause more pain.

We performed a sensitivity analysis on pain experienced in the first and second half of the study period, respectively, using a multivariable logistic regression model.

Due to administrative errors, 11 women did not receive the allocated intervention (4 in fentanyl on-demand, 2 in fentanyl prior, 5 in alfentanil on-demand). In accordance with an intention-to-treat approach, these individuals were included in the analysis in their allocated group.

There was an administrative loss of data for the secondary endpoints "willingness to repeat examination" and information about "recovery time" if one of the following events occurred: (1) the endoscopist switched to PCF colonoscope; (2) midazolam was given during colonoscopy; (3) the allocated intervention was not given; (4) the examination was incomplete. We, therefore, performed a per-protocol analysis

for "willingness to repeat examination" and "recovery time" limited to participants who had undergone a complete colonoscopy with standard colonoscope and without additional midazolam. The proportion of data loss belonging to these two secondary endpoints was not different between the fentanyl on-demand group and the fentanyl prior group (28 participants vs. 17 participants, $p = .20$), while there was a lower frequency of data loss in the alfentanil on-demand group (15 participants, $p = .04$) compared to fentanyl on-demand. The majority of missing values can be assigned to those who completed colonoscopy with a PCF colonoscope (fentanyl on-demand 20, fentanyl prior 14, alfentanil on-demand 11). Those women reported more often a painful colonoscopy than the average of their respective group (fentanyl on-demand 69.2%, fentanyl prior 66.7%, and alfentanil on-demand 71.4%).

All statistical analyses were performed independently by ALS using Stata statistical software version 16.1 (StataCorp, College Station, TX, USA), and EB using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Discrepancies were discussed and resolved.

Results

A total of 1819 women were invited to participate, of whom 568 consented and were randomised (Figure 2). After randomisation, 29 individuals were excluded because exclusion criteria were detected, they withdrew their consent or colonoscopy could not be carried out due to insufficient bowel cleaning. A total of 539 participants were included in the intention-to-treat analysis, of whom 60 had a clinical non-screening outpatient colonoscopy (183 patients in the fentanyl on-demand group, 177 in the fentanyl prior to colonoscopy group, and 179 in the alfentanil on-demand group). Both mean ages, vital parameters, and risk factors for painful colonoscopy were similarly distributed between the three groups (Table 1).

Fentanyl prior vs. fentanyl on-demand

In the intention-to-treat analysis, 38 patients (25.2%) reported painful colonoscopies in the fentanyl prior group, compared to 71 patients (44.1%) in the fentanyl on-demand group (RR 0.57, 95% CI 0.41–0.79, $p < .001$) (Table 2,

Table 1. Baseline participants' characteristics in the three groups; fentanyl on-demand (the reference), fentanyl prior to colonoscopy or alfentanil on-demand.

	Fentanyl on-demand ($n = 183$)	Fentanyl prior ($n = 177$)	Alfentanil on-demand ($n = 179$)
Age, mean (95% CI), years	66.8 (65.9–67.7)	66.7 (65.8–67.5)	67.1 (66.2–67.9)
Heart rate (pre-procedure), mean (95% CI), beats per minute	75.8 (73.8–77.7)	74.9 (73.0–76.8)	75.0 (73.1–76.9)
Oxygen saturation (pre procedure), mean (95 % CI),%	97.1 (96.8–97.4)	97.0 (96.7–97.3)	96.8 (96.5–97.1)
Adequate bowel cleansing, n (%) ^a	165/181 (91.2)	161/175 (92.0)	162/176 (92.1)
Body mass index, mean (95% CI), kg/m ²	26.0 (25.3–26.8)	26.5 (25.7–27.3)	26.4 (25.6–27.2)
Expectation painful colonoscopy, n/N (%)	89/152 (58.6)	88/159 (55.4)	96/161 (59.6)
Previous painful colonoscopy, n/N (%) ^b	34/58 (58.6)	44/77 (57.1)	49/69 (71.0)
Previous abdominal surgery, n/N (%)	96/161 (59.6)	91/159 (57.2)	86/168 (51.2)
Previous diverticulitis, n/N (%)	9/157 (5.7)	12/156 (7.7)	7/164 (4.3)
IBS with pain, n/N (%)	12/152 (7.9)	9/151 (6.0)	14/159 (8.8)
VAS before colonoscopy, mean (95% CI), mm	0.5 (0.3–0.7)	0.3 (0.2–0.4)	0.3 (0.2–0.5)

IBS: irritable bowel syndrome; VAS: visual analogue scale.

^aJudged as good/adequate or BBPs ≥ 2 in each segment.

^bOnly among those who reported a previous colonoscopy.

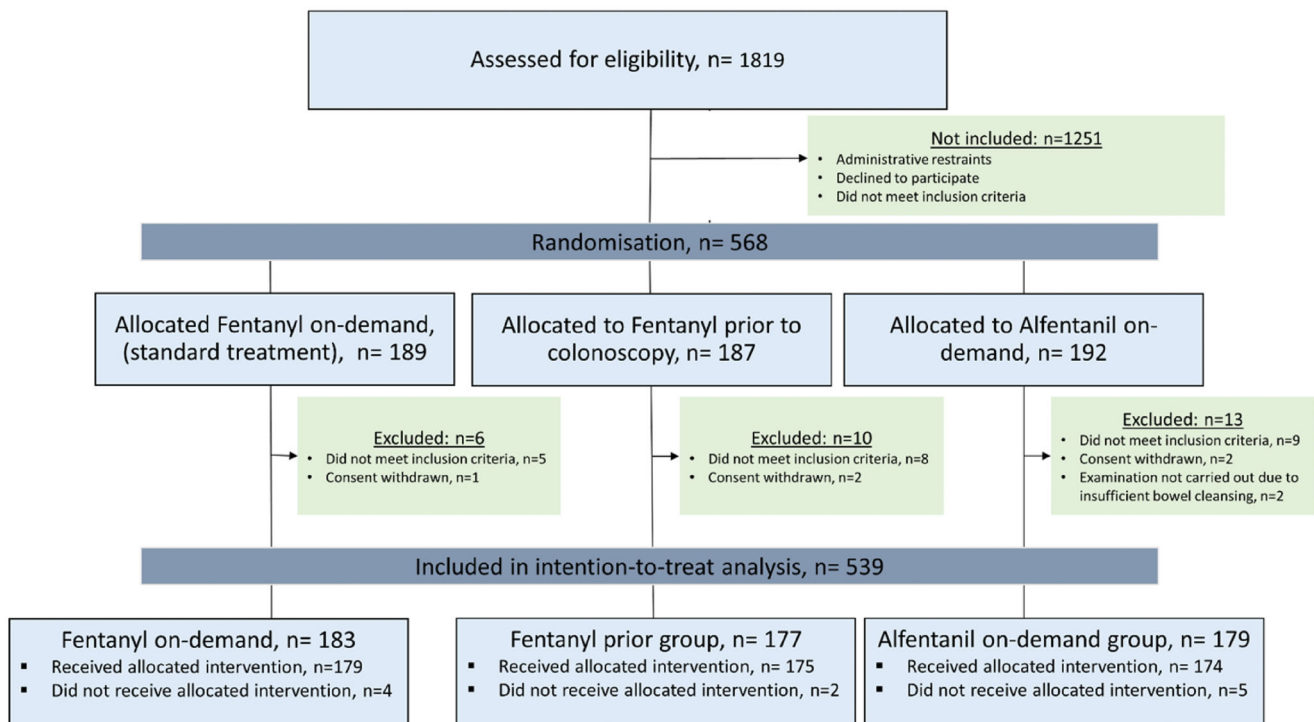


Figure 2. Flowchart trial.

Table 2. Colonoscopy variables in participants of the three groups; fentanyl on-demand (the reference), fentanyl prior to colonoscopy or alfentanil on-demand.

	Fentanyl on-demand (n = 183)	Fentanyl prior (n = 177)	P ^a	Alfentanil on-demand (n = 179)	P ^a
Questionnaire response rate					
1 st post-colonoscopy day, n/N (%)	161/183 (88.0)	151/177 (85.3)	.46	162/179 (90.5)	.44
Procedural pain score, recorded 1 st post-colonoscopy day, Likert scale					
No pain, n/N (%)	33/161 (20.5)	59/151 (39.1)	<.001	38/162 (23.5)	.83
Slight pain, n/N (%)	57/161 (35.4)	54/151 (35.8)		60/162 (37.0)	
Moderate pain, n/N (%)	46/161 (28.6)	20/151 (13.3)		40/162 (24.7)	
Severe pain, n/N (%)	25/161 (15.5)	18/151 (11.9)		24/162 (14.8)	
Completeness of colonoscopy					
Cecal intubation rate, n/N (%) ^b	159/179 (88.8)	160/175 (91.4)	.41	166/176 (94.3)	.06
Cecal intubation time, mean (95% CI), minutes	17.3 (15.8–19.1)	15.6 (14.2–17.1)	.11	17.5 (15.6–19.1)	.91
Medication					
Analgesics given, n/N (%)	102/183 (55.7)	175/177 (98.9)	<.001	95/179 (53.1)	.61
Administration of additional opioid dose, n/N (%)	30/183 (16.4)	39/177 (22.0)	.17	40/179 (22.4)	.15
Dose, mean (95%CI), mcg (fentanyl)/mg (alfentanil)	59.8 (51.35–68.3)	107.8 (103.4–112.2)	<.001	0.3 (0.3–0.4)	–
Dose in medicated persons, mean (95%CI), mcg (fentanyl)/mg (alfentanil)	107.3 (101.1–113.5)	109.0 (104.9–113.1)	.63	0.68 (0.63–0.73)	–
Adverse events					
Adverse events, n/N (%) ^c	13/183 (7.1)	21/177 (11.9)	.12	16/179 (8.9)	.52
Serious adverse events, n/N (%) ^d	5/183 (2.7)	6/177 (3.4)	.72	5/179 (2.8)	1.00

^aCompared to Fentanyl on-demand.^bSwitching to small-calibre colonoscope or administering of benzodiazepine during examination was defined as intubation failure even if cecum was reached.^cEvents requiring intravenous antiemetics, intravenous fluids, intravenous spasmolytics, elevating lower extremities.^dSystolic blood pressure < 100 mmHg and/or heart rate < 50 beats per minute and/or oxygen saturation < 90% without supplemental oxygen.

Figure 3). The adjustment for covariates (adequate bowel cleansing, body mass index, expectation of painful colonoscopy, previous painful colonoscopy, previous abdominal surgery, previous diverticulitis, irritable bowel syndrome with pain, removal of polyps \geq 2 cm, and baseline pain score) did not change the results (crude odds ratio [OR] 0.43, 95% CI 0.26–0.69; adjusted OR 0.42, 95% CI 0.25–0.70).

No difference in cecum intubation rate (CIR) was observed between the fentanyl prior group (91.4%) and the fentanyl on-demand group (88.8%, $p = .41$). Adverse events, mainly nausea, dizziness or vasovagal reactions, occurred in 21 women (11.9%) in the fentanyl prior group and 13 women (7.1%, $p = .12$) in the fentanyl on-demand group. Serious adverse events occurred with similar frequencies (fentanyl

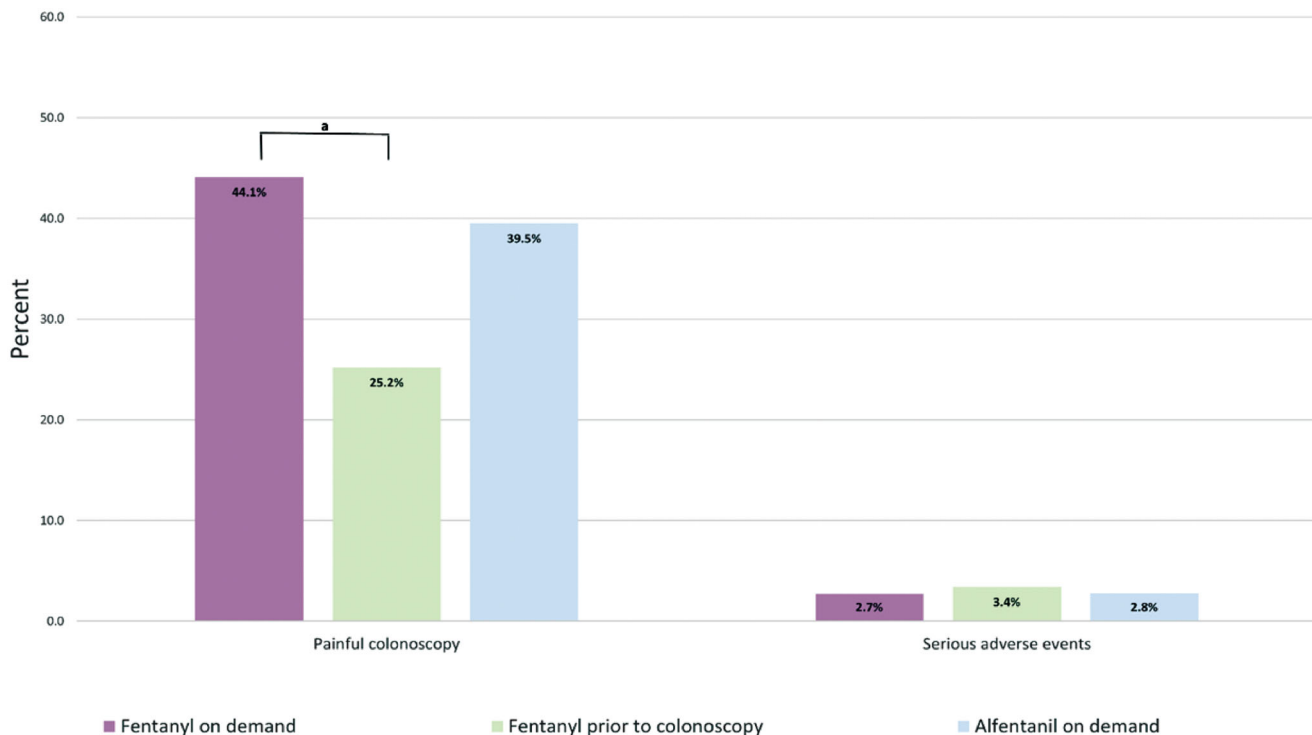


Figure 3. Outcomes in the fentanyl on-demand group (the reference) compared to fentanyl prior to colonoscopy and alfentanil on-demand. ^a $p < .001$. Painful colonoscopy = moderate or severe pain. Serious adverse event = Systolic blood pressure < 100 mmHg and/or heart rate < 50 beats per minute and/or oxygen saturation < 90% without supplemental oxygen.

prior 3.4% vs. fentanyl on-demand 2.7%, $p = .72$). Perforations did not occur.

In the per-protocol analysis, there was no difference between the groups regarding the willingness to repeat colonoscopy. In participants reporting painful colonoscopies, the willingness to repeat examination decreased, but still, there was no difference between the groups (Supplementary Table 1). The proportion of participants able to leave the endoscopy unit immediately after the colonoscopy and the mean recovery time were similar (Supplementary Table 1).

Analgesics were administered to 55.7% of participants in the fentanyl on-demand group (Table 2). Similar proportions of women received an additional dosage of opioids in the fentanyl prior and the fentanyl on-demand groups, respectively (22.0% vs. 16.4%, $p = .17$) (Table 2). The mean fentanyl dose was 59.8 mcg (95% CI 51.3 – 68.3 mcg) in the fentanyl on-demand group vs. 107.8 mcg (95% CI 103.4 – 112.2 mcg) in the fentanyl prior group. The first dose of analgesics in the fentanyl on-demand group was mainly given before or at the same time as the splenic flexure was reached (85.5%). The proportion of painful colonoscopies among those not receiving analgesia in the fentanyl on-demand group was similar to the fentanyl prior group (16.9% vs. 25.2%, $p = .17$).

Alfentanil on-demand vs. fentanyl on-demand

The proportion of painful colonoscopies in the alfentanil on-demand group was similar to the fentanyl on-demand group (39.5% vs. 44.1%; RR 0.90, 95% CI 0.69–1.16, $p = .40$) (Table 2,

Figure 3). The adjustment for covariates did not change the results (crude OR 0.83, 95% CI 0.53–1.29; adjusted OR 0.80, 95% CI 0.50–1.30).

There was no difference in CIR between alfentanil on-demand and fentanyl on-demand (94.3% vs. 88.8%, $p = .06$). The proportion of women experiencing adverse events was similar in these two groups (alfentanil on-demand 8.9% vs. fentanyl on-demand 7.1%, $p = .52$). Serious adverse events occurred in 5 women in each group (2.8% in alfentanil on-demand vs. 2.7% in fentanyl on-demand, $p = 1.00$). Perforations did not occur.

In the per-protocol analysis, willingness to repeat colonoscopy and the mean recovery time, as well as the proportion of women who were able to leave the endoscopy unit immediately, were similar (Supplementary Table 1).

Analgesics were given to 53.1% of participants in the alfentanil on-demand group (Table 2) and 22.4% received additional dosage (vs. 16.4% in the fentanyl on-demand group, $p = .15$). The mean alfentanil dose was 0.3 mg (95% CI 0.3 – 0.4 mg). The first dose of alfentanil on-demand was given before or at the same time as the splenic flexure was reached in 93.7% of cases. There was no difference in the proportion of painful colonoscopies between the alfentanil on-demand and fentanyl on-demand group if only women not receiving analgesia were taken into account (alfentanil on-demand 15.4% vs. fentanyl on-demand 16.9%, $p = .80$).

Sensitivity analysis showed a similar proportion of painful colonoscopies in the alfentanil on-demand group in the first and second half of the study period, respectively.

Discussion

In this randomised trial, we showed that, in women aged 55–79, fentanyl prior to colonoscopy provided better pain relief than fentanyl on-demand. Furthermore, there was no difference in pain relief between alfentanil on-demand and fentanyl on-demand. Importantly, the cecum intubation rate, frequency of adverse events, recovery time, and willingness to repeat the examination with an identical procedural process did not differ between the groups.

Although anxiolytics during colonoscopy have been suggested to be unnecessary when analgesia is effective [39], a combination of a benzodiazepine and an opioid is most frequently used [9]. Consequently, studies assessing the pain-relieving effect of opioids in monotherapy are rare [31,32,40]. To the best of our knowledge, this trial is the first randomised trial assessing alfentanil in colonoscopies with pain as the primary endpoint.

In both on-demand groups, about four out of ten women experienced a painful colonoscopy. This is in line with a previous trial demonstrating that on-demand analgesia was associated with painful colonoscopies in one out of two women [28]. Three further studies reported painful colonoscopies in about a third of patients given on-demand sedoanalgesia [16,26,27]. We showed that the proportion of painful colonoscopies was reduced by 43% when fentanyl was given before the examination compared to on-demand and this is in line with a previous trial comparing midazolam plus meperidine administered before colonoscopy to on-demand medication [27]. However, the administration of midazolam triggers retrograde amnesia in 80% of the patients [41]. Therefore, our results may be more reliable as we can exclude amnesia as a cause for the lower proportion of painful colonoscopies. In contrast to our findings, a previous trial comparing fentanyl on-demand to fentanyl before colonoscopy showed the same frequency of painful colonoscopies in both groups. However, the initial fentanyl dose was only half of the one used in the present trial and may have been too low and the inclusion of men may also have disguised any difference between the strategies to ease colonoscopy for the more pain-prone female patients [26]. Consequently, it may be preferable to offer analgesics before the examination to those at high risk for painful colonoscopy, such as women.

Despite the relatively high proportion of painful colonoscopies, the willingness to repeat the examination with the same procedural process was high in all groups and not higher in the fentanyl prior group. This indicates that willingness to return may be associated with other factors than pain, like organisation, premises and facilities at the endoscopy unit and waiting time [42]. Another reason for the high willingness to return for another colonoscopy may be that the reported high pain scores reflect only short spells of pain and that the participants did not experience pain during most of the colonoscopy. This assumption is supported by the fact that medication was mainly administered before the passage of the splenic flexure since the sigmoid colon often is the most challenging segment where looping and stretching of the mesentery can cause short spells of pain. The high

willingness to repeat colonoscopy may also reflect the local Norwegian expectations and acceptance of pain during colonoscopy. This also fits that, according to the Norwegian colonoscopy quality registry, about 60% (45% among women aged 55–79 [personal communication with Gert Huppertz-Hauss, leader of Gastronet]) of outpatient colonoscopies in Norway are performed without any sedation or analgesia [43].

Our study confirms the favourable safety profile and short recovery time with both fentanyl and alfentanil shown in previous studies [40,44]. In addition, the administration of opioids in monotherapy reduces the risk of deeper sedation than intended and thus the risk of more adverse events. About two-thirds of all participants left the endoscopy unit immediately after the examination and the mean recovery time was less than 10 min even in the Fentanyl prior group.

Almost half of the individuals in the on-demand groups did not ask for medication. Consequently, about 50% in the fentanyl prior group received unnecessary drugs, possible to prevent by improved selection of high-risk individuals. However, selecting women who may benefit most from analgesia prior to colonoscopy is challenging and in our trial, opioids given on-demand seemed less pain-relieving and may support the theory that painful stimuli trigger central sensitization which in turn lowers the pain threshold [45] or that the administered on-demand doses were insufficient. Furthermore, it takes two to five minutes for fentanyl to reach its peak effect [46]. The busy endoscopy schedule may discourage an appropriate halt in the procedure to allow time to reach the optimal effect of the medication, in contrast to medication administered before rectal intubation.

Theoretically, alfentanil is the perfect on-demand medication, due to its rapid onset and short duration of action. However, we could not demonstrate a lower frequency of painful colonoscopies in alfentanil on-demand compared to fentanyl on-demand. This may be caused by insufficient titration of alfentanil. Nurses and endoscopists administering alfentanil in our trial had limited experience with this drug and may have been too restrictive to up-titrate the dose as alfentanil on-demand was not repeated more frequently than fentanyl on-demand. Given the short half-life of alfentanil, boluses must be given every three to five minutes to maintain the effect [47]. However, our sensitivity analysis, performed to figure out if variable experience influences outcome, showed no difference between pain experienced in the first or second half of the study period.

In our trial, the proportion of painful colonoscopies was still high, possibly partly explained by the limited experience of the endoscopists. However, data from the screening trial showed that these endoscopists and gastroenterology consultants had similar rates of patient-reported pain [35]. Improved pain relief could, besides improved administration of moderate sedation, include either deeper sedation or better colonoscopy technique, like improved intubation technique (keeping straight scope), use of water-exchange technique and small-calibre, more flexible colonoscopes [48,49]. Though, deep sedation is not recommended for routine colonoscopies according to current consensus-based

recommendations for clinical practice [12], propofol is widely used and has been shown to be associated with high patient satisfaction and short recovery[50]. Still, deep sedation has major drawbacks. It is expensive as it requires additional staff for administration and monitoring [18,19] and increases the overall risk for serious adverse events, including aspiration pneumonia and perforation [20,21].

The strength of this trial is the randomised design with participants from two endoscopy units and several endoscopists. Furthermore, we also assessed the frequency of painful colonoscopies directly without an endoscopy nurse as an intermediate. Another strength is that midazolam was only given to three out of 529 participants. Thus, the analgesic effect was not biased by the amnesic effect of midazolam. Some may consider the un-blinded design to be a weakness of this trial as participants assigned to fentanyl prior to colonoscopy may have benefitted from both the effect of the drug and a placebo effect [51]. However, the present trial aimed to test the effectiveness of treatment alternatives in a real-life scenario where blinded administration of analgesics is no option.

This trial has also some limitations. First, only a third of invited women participated in the trial. Many women had a preferred medication strategy before the colonoscopy, either a request for medication or a wish not to receive medication. Several were not included due to administrative restraints. However, the internal validity of the trial is not jeopardized.

Missing data for the secondary endpoints, “willingness to repeat examination” and “need for observation after colonoscopy”, is another limitation. The loss of data was similar in the two fentanyl groups, but lower in the exploratory alfentanil group. The majority of missing data was restricted to cases that required switching to small-calibre colonoscope and those women experienced more often painful colonoscopies. In each of the three groups, those who experienced painful colonoscopies were less willing to repeat the examination. Therefore, we cannot rule out that the result was biased towards a lower rate of willingness to repeat the examination in the alfentanil on-demand group. Finally, the results from this trial can only be generalized to women at age 55–79 years willing to accept an on-demand approach.

Conclusion

Participants given fentanyl before colonoscopy reported less painful colonoscopies with no difference in adverse events, recovery time, or willingness to repeat examination compared to fentanyl on-demand. Fentanyl before colonoscopy should be recommended to women aged 55–79. Alfentanil is theoretically a better on-demand analgesic agent. However, we could not demonstrate a beneficial effect and further trials with better-defined titration of the dose and improved information to the staff to pause the procedure until the effect of the medication are achieved are required to finally conclude whether alfentanil in monotherapy should be the preferred choice for women who prefer on-demand medication during colonoscopy.

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Author contributions

Study concept and design: ALS, GH, ØH, MB, TdL; Acquisition, analysis, or interpretation of data: ALS, EB, GH, ØH, MB, KRR, EHG, BE, IB, CM, LRN, HMS, TdL; Drafting of the manuscript: ALS, EB, TdL; Critical revision of the manuscript for important intellectual content: ALS, EB, GH, ØH, MB, KRR, EHG, BE, IB, CM, LRN, HMS, TdL; Statistical analysis: ALS and EB; All authors approved the final report and are accountable for all aspects of this work.

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