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Original Investigation | Anesthesiology

Effect of Intraoperative Dexmedetomidine on Recovery of Gastrointestinal Function After Abdominal Surgery in Older Adults
A Randomized Clinical Trial

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Abstract

IMPORTANCE Postoperative ileus is common after abdominal surgery, and small clinical studies have reported that intraoperative administration of dexmedetomidine may be associated with improvements in postoperative gastrointestinal function. However, findings have been inconsistent and study samples have been small. Further examination of the effects of intraoperative dexmedetomidine on postoperative gastrointestinal function is needed.

OBJECTIVE To evaluate the effects of intraoperative intravenous dexmedetomidine vs placebo on postoperative gastrointestinal function among older patients undergoing abdominal surgery.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, double-blind, placebo-controlled randomized clinical trial was conducted at the First Affiliated Hospital of Anhui Medical University in Hefei, China (lead site), and 12 other tertiary hospitals in Anhui Province, China. A total of 808 participants aged 60 years or older who were scheduled to receive abdominal surgery with an expected surgical duration of 1 to 6 hours were enrolled. The study was conducted from August 21, 2018, to December 9, 2019.

INTERVENTIONS Dexmedetomidine infusion (a loading dose of 0.5 μg/kg over 15 minutes followed by a maintenance dose of 0.2 μg/kg per hour) or placebo infusion (normal saline) during surgery.

MAIN OUTCOMES AND MEASURES The primary outcome was time to first flatus. Secondary outcomes were postoperative gastrointestinal function measured by the I-FEED (intake, feeling nauseated, emesis, physical examination, and duration of symptoms) scoring system, time to first feces, time to first oral feeding, incidence of delirium, pain scores, sleep quality, postoperative nausea and vomiting, hospital costs, and hospital length of stay.

RESULTS Among 808 patients enrolled, 404 were randomized to receive intraoperative dexmedetomidine, and 404 were randomized to receive placebo. In total, 133 patients (60 in the dexmedetomidine group and 73 in the placebo group) were excluded because of protocol deviations, and 675 patients (344 in the dexmedetomidine group and 331 in the placebo group; mean [SD] age, 70.2 [6.1] years; 445 men [65.9%]) were included in the per-protocol analysis. The dexmedetomidine group had a significantly shorter time to first flatus (median, 65 hours [IQR, 48-78 hours] vs 78 hours [62-93 hours], respectively; $P < .001$), time to first feces (median, 85 hours [IQR, 68-115 hours] vs 98 hours [IQR, 74-121 hours]; $P = .001$), and hospital length of stay (median, 13 days [IQR, 10-17 days] vs 15 days [IQR, 11-18 days]; $P = .005$) than the control group. Postoperative gastrointestinal function (as measured by the I-FEED score) and delirium incidence were similar in the dexmedetomidine and control groups (eg, 248 patients [72.1%] vs 254 patients [76.7%],

(continued)

Key Points

Question Does the intraoperative administration of dexmedetomidine accelerate the recovery of gastrointestinal function among older patients undergoing abdominal surgery?

Findings In this randomized clinical trial of 808 patients aged 60 years and older undergoing abdominal surgery, the time to first flatus among patients who received intraoperative dexmedetomidine was 65 hours, which was significantly shorter than the 78 hours to first flatus observed among those who received placebo.

Meaning This study's findings support the intraoperative use of dexmedetomidine for the recovery of gastrointestinal function among older adults undergoing abdominal surgery.

+ Visual Abstract

+ Supplemental content

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Abstract (continued)

respectively, had I-FEED scores indicating normal postoperative gastrointestinal function; 18 patients [5.2%] vs 12 patients [3.6%] had delirium on postoperative day 3).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, the administration of intraoperative dexmedetomidine reduced the time to first flatus, time to first feces, and length of stay after abdominal surgery. These results suggest that this therapy may be a viable strategy to enhance postoperative recovery of gastrointestinal function among older adults.

TRIAL REGISTRATION Chinese Clinical Trial Registry Identifier: ChiCTR1800017232

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Introduction

Postoperative ileus is characterized by the inability to resume a normal diet, nausea and vomiting, abdominal distension, and constipation.[1] The incidence of postoperative ileus varies between 10% and 30%, depending on the type of abdominal surgery and anatomical site.[2] Moreover, the general decrease in gastrointestinal function among older patients increases their risk of developing postoperative ileus.[3,4] Postoperative ileus is associated with prolonged hospital stay,[5] worse patient experience, increased 30-day readmission rate,[6] and higher hospital costs.[7]

Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist with sedative, analgesic, sympatholytic, and anxiolytic properties.[8] It is widely used as an anesthetic adjuvant in perioperative settings and as a sedative in the intensive care unit. Previous studies have reported that dexmedetomidine compared with other sedatives may be associated with lower incidence of postoperative delirium,[9] prevention of delirium in the intensive care unit,[10] weakening of the intraoperative stress response,[11] and reductions in postoperative mortality for up to 1 year.[12] However, the reported effects of dexmedetomidine on gastrointestinal function have been inconsistent. Two preclinical studies[13,14] and 1 study[15] involving healthy participants found that dexmedetomidine inhibits gastric emptying and gastrointestinal transit. In contrast, dexmedetomidine has been reported to improve gastrointestinal motility after lumbar spinal fusion,[16] colonic resection,[17] and colorectal cancer resection.[18] To address this inconsistency and the relatively small samples included in previous studies, a prospective multicenter, double-blind, placebo-controlled randomized clinical trial was conducted to investigate the effect of low-dose intraoperative dexmedetomidine on the recovery of gastrointestinal function after abdominal surgery among older patients. We hypothesized that intraoperative administration of low-dose dexmedetomidine would accelerate the recovery of gastrointestinal function after surgery.

Methods

Study Design and Settings

This multicenter, double-blind, placebo-controlled randomized clinical trial was conducted at 13 sites in China from August 21, 2018, to December 9, 2019. The study was approved by the ethics committee of the First Affiliated Hospital of Anhui Medical University in Hefei (lead site) and the 12 other ethics committees of participating sites in Anhui Province. Written informed consent was obtained from all participants. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials. The trial protocol and statistical plan are available in Supplement 1.

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Participants

Patients aged 60 years or older who were scheduled to receive elective abdominal surgery (gastric surgery, intestinal surgery, hepatobiliary surgery, pancreatic surgery, or appendectomy) with an expected surgical duration of 1 to 6 hours were screened to assess their study eligibility. Patients were excluded if they had known gastrointestinal motility disorders, previous abdominal surgery, severe hepatic or kidney dysfunction, second-degree or third-degree heart blockage, bradyarrhythmia with a baseline rate lower than 50 beats per minute, mental disorders, history of difficult airway or delayed extubation, opioid medication misuse, allergy to dexmedetomidine or other anesthetic drugs, preoperative gastrointestinal hemorrhage (bleeding volume >800 mL), emergency reoperations, or American Society of Anesthesiologists classification of 4 or 5 (with 4 indicating the patient had severe systemic disease that was a constant threat to life and 5 indicating the patient was moribund and not expected to survive without the surgery) at the time of enrollment.

Randomization and Blinding

Eligible participants were randomized on a 1:1 ratio to receive dexmedetomidine or normal saline placebo (control group) during surgery. Central randomization was performed using a secure web-based system. The randomization sequence was based on computer-generated random numbers. Study statisticians were not involved in patient recruitment or the delivery of medication. An anesthetic nurse who was not otherwise involved in the study prepared the study agents in identical 50-mL syringes according to treatment groups, with the treatment group information contained in sequentially numbered sealed envelopes. The surgeons and other health care personnel, the research staff who assessed the outcomes, and the patients themselves were blinded to treatment group.

Protocol

Standard monitoring, including electrocardiography, heart rate, noninvasive blood pressure, pulse oxygen saturation, and nasopharyngeal temperature, was initiated on arrival in the operating room. Patients in the dexmedetomidine group received an infusion of dexmedetomidine at a rate of 0.5 μg/kg for 15 minutesa followed by 0.2 μg/kg per hour through a continuous pump until approximately 30 minutes before the end of surgery.[16] Patients in the control group received an equivalent volume of saline infused at the same rates. Fifteen minutes after the infusions began, intravenous anesthesia induction was performed using 0.02 to 0.04 mg/kg of midazolam, 0.2 to 0.3 μg/kg of sufentanil, and 1.0 to 2.5 mg/kg of propofol. Cisatracurium, 0.2 mg/kg, was administered after the bispectral index value decreased to less than 60. Volume-controlled ventilation was performed to maintain an end-tidal carbon dioxide concentration between 35 and 45 mm Hg.

A bispectral index value of 45 to 60 was maintained using continuous intravenous infusions of 50 to 100 μg/kg of propofol per minute and 0.1 to 1.0 μg/kg of remifentanil per minute. Cistracurium was administered at 1 to 2 μg/kg per minute to maintain neuromuscular blockade. Intraoperative nasopharyngeal temperature was maintained at higher than 36 °C using thermal insulation measures. Azasetron, 10 mg, was administered intravenously to prevent postoperative nausea and vomiting. Postoperative analgesia was achieved with an intravenous infusion of a cocktail comprising 3 μg/kg of sufentanil and 100 mg of flurbiprofen axetil in 100 mL of normal saline. The background infusion rate was 2 mL per hour.

Outcome Measures

The primary outcome was the time to first flatus according to patient self-report, corrected to the nearest hour. Secondary outcomes included postoperative gastrointestinal function using the I-FEED (intake, feeling nauseated, emesis, physical examination, and duration of symptoms) scoring system,[1] time to first feces, time to first oral feeding, incidence of delirium (measured twice daily for 3 days using the confusion assessment method, which evaluates acute onset and fluctuating course,

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inattention, disorganized thinking, and altered level of consciousness[19]), pain scores, sleep quality, postoperative nausea and vomiting, hospital costs, and hospital length of stay. The I-FEED scoring system assigns 0 to 2 points for each of 5 components based on clinical presentation, then categorizes patients as having normal gastrointestinal function (scores of 0-2), postoperative gastrointestinal intolerance (scores of 3-5), or postoperative ileus (scores of ≥6). We used a 10-point rating scale to measure severity of pain, postoperative nausea and vomiting,[20] and sleep quality[21] for the first 7 postoperative days, with 0 indicating no pain, no postoperative nausea or vomiting, or deep sleep and 10 indicating maximal pain, postoperative nausea and vomiting, or sleep disturbance. Hospital costs were reported in Chinese yuan (CNY; to convert to US dollars, multiply by 0.1481, which was the mean exchange rate for 2018-2019). Independent trained researchers who were blinded to treatment group were responsible for collecting data through interviews with patients. The physicians caring for patients did not participate in data collection.

Intraoperative, Postoperative, and Adverse Event Assessments

The duration of surgery and anesthesia, total dose of drugs used, fluids administered, and bleeding and urine output (both corrected to the nearest 100 mL) were recorded. A telephone follow-up was conducted at approximately 28 days after surgery, during which the patient was asked about the presence of nausea, vomiting, abdominal distension, constipation, dietary status (categorized as solid or liquid diet), and the estimated amount of food intake.

The occurrence of adverse intraoperative events, including bradycardia (<40 beats per minute), tachycardia (>120 beats per minute), hypertension (blood pressure >20% higher than baseline or systolic blood pressure >160 mm Hg), and hypotension (blood pressure >20% lower than baseline or systolic blood pressure <80 mm Hg), were recorded. Other postoperative complications, such as cerebrovascular events, myocardial infarction, heart failure, and acute kidney injury were assessed until hospital discharge.

Statistical Analysis

Based on pilot data, we estimated the difference in time to first flatus to be 2.5 hours between groups, with a within-group SD of 10 hours. Using an α value of .05 and a power of 0.9, a minimum sample of 674 participants was calculated using the DuPont and Plummer method.[22] Allowing for a 20% withdrawal rate, we enrolled 808 patients.

Statistical analysis was conducted from March 15 to October 10, 2020. For continuous variables, data were reported as means with SDs or medians with IQRs according to the normality of distribution; for categorical variables, data were reported as numbers with percentages. Group differences between the dexmedetomidine and control groups were examined using unpaired *t* tests for normally distributed continuous variables, Mann-Whitney *U* tests for nonnormally distributed continuous variables, and χ^2 tests for categorial variables.

The effects of intervention on secondary outcomes of interest (eg, pain scores, sleep quality, and postoperative nausea or vomiting) over time were assessed using the interaction of group (dexmedetomidine and control) and time (day 1 to day 7) in a repeated-measures analysis of variance. The Greenhouse-Geisser correction was applied if data violated the assumption of sphericity, as determined by the Mauchly test. For measures that showed significant group by time interaction effects, a post hoc analysis of the differences between the dexmedetomidine and control groups was performed using an independent samples *t* test with Bonferroni correction. Statistical analyses were conducted using SPSS software, version 23.0 (IBM SPSS), and 2-sided $P < .05$ was considered statistically significant.

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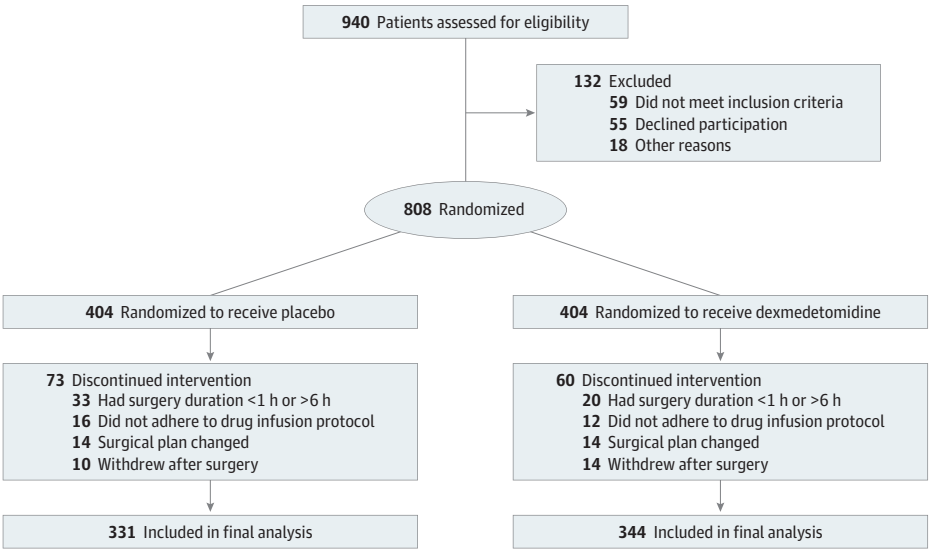
Results

Study Population

Of 940 patients screened for eligibility, 132 were excluded, and 808 proceeded to randomization, with 404 patients randomized to receive dexmedetomidine and 404 randomized to receive placebo (**Figure 1**). A total of 133 patients were excluded because of protocol deviations after randomization, 60 of whom were in the dexmedetomidine group (20 because of surgical duration <1 hour or >6 hours, 14 because of surgical plan changes, 12 because of study drug infusion modifications, and 14 because of study withdrawal after surgery) and 73 of whom were in the control group (33 because of surgical duration <1 hour or >6 hours, 14 because of surgical plan changes, 16 because of study drug infusion modifications, and 10 because of study withdrawal after surgery). The remaining 675 patients (344 in the dexmedetomidine group and 331 in the placebo group) were included in the per-protocol analysis. In total, 445 patients (65.9%) were male and 230 (34.1%) were female, with a mean (SD) age of 70.2 (6.1) years; 485 patients (71.9%) underwent gastrointestinal surgery. Baseline characteristics of the dexmedetomidine and control groups were similar (eg, mean [SD] age, 70.1 [5.8] years vs 70.4 [6.5] years, respectively; 222 men [64.5%] vs 223 men [67.4%]), and there were no significant differences in educational level (eg, 180 patients [52.3%] vs 162 patients [48.9%] had a primary school education), American Society of Anesthesiologists status (eg, 233 patients [67.7%] vs 231 patients [69.8%] had class 2 status [indicating mild systemic disease]), method of surgery (eg, 182 patients [52.9%] vs 194 patients [58.6%] had open surgery), or anatomical site of surgery (eg, 141 patients [41.0%] vs 142 patients [42.9%] had gastric surgery) (**Table 1**). The baseline characteristics of patients who were excluded from the final analysis were comparable to those of patients who were included (eTable 1 in Supplement 2).

There was little difference in surgical time (mean [SD], 183.39 [69.87] minutes vs 190.14 [73.64] minutes) or anesthetic time (mean [SD], 206.08 [73.12] minutes vs 211.92 [78.44] minutes) between the dexmedetomidine and control groups, respectively (Table 1). The long-acting opioid analgesic sufentanil (mean [SD], 41.2 [10.3] μg vs 43.1 [8.6] μg, respectively; $P = .009$) and the short-acting opioid analgesic remifentanil (mean [SD], 1779.4 [946.7] μg vs 2040 [1172.5] μg; $P = .002$) were administered less often during surgery in the dexmedetomidine group vs the control group, respectively. The volumes of intraoperative bleeding (median, 100 mL [IQR, 50-200 mL] for both groups), crystalloid solution administered (median, 1000 mL [IQR, 850-1500 mL] in the dexmedetomidine group vs 1000 mL [IQR, 1000-1500] in the control group), and colloidal solution

Figure 1. CONSORT Flow Diagram



Patients in the dexmedetomidine group received 0.5 μg/kg of dexmedetomidine for 15 minutes, then 0.2 μg/kg of dexmedetomidine per hour through a continuous pump until 30 minutes before the end of surgery. Patients in the control group received equivalent volumes of normal saline following the same protocol.

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administered (median, 500 mL [IQR, 500-500 mL] for both groups) were the same in the 2 groups. Patients in the dexmedetomidine group had higher urine output than those in the control group (median, 300 mL [IQR, 200-450 mL] vs 250 mL [IQR, 200-400 mL], respectively; $P = .03$).

Primary Outcome

The median time to first flatus according to patient self-report was significantly lower in the dexmedetomidine group than in the control group: 65 hours (IQR, 48-78 hours) vs 78 hours (IQR, 62-93 hours) ($P < .001$) (**Table 2**).

Secondary Outcomes

In the dexmedetomidine and control groups, the proportion of patients with I-FEED scores indicating normal postoperative gastrointestinal function (248 patients [72.1%] vs 254 patients [76.7%], respectively), postoperative gastrointestinal intolerance (85 patients [24.7%] vs 69 patients [20.8%]), and postoperative ileus (11 patients [3.2%] vs 8 patients [2.4%]) were similar (**Figure 2**). The times to first feces (median, 85 hours [IQR, 68-115 hours] vs 98 hours [IQR, 74-121 hours]; $P = .001$) and first oral feeding (median, 76 hours [IQR, 52-112 hours] vs 90 hours [IQR, 72-115 hours];

Table 1. Patient Characteristics and Intraoperative Data

Characteristic	No. (%)	
	Dexmedetomidine group	Control group
Total patients, No.	344	331
Age, mean (SD), y	70.1 (5.8)	70.4 (6.5)
Height, mean (SD), cm	163.3 (11.7)	163.0 (14.6)
Weight, mean (SD), kg	60.0 (9.5)	59.3 (9.6)
BMI, mean (SD)	22.3 (2.9)	22.0 (3.0)
Sex		
Female	122 (35.5)	108 (32.6)
Male	222 (64.5)	223 (67.4)
Educational level		
None	127 (36.9)	115 (34.7)
Primary school	180 (52.3)	162 (48.9)
Secondary school	23 (6.7)	41 (12.4)
College	14 (4.1)	13 (3.9)
ASA classification[a]		
1	18 (5.2)	12 (3.6)
2	233 (67.7)	231 (69.8)
3	93 (27.0)	88 (26.6)
Method of surgery		
Laparoscopic	162 (47.1)	137 (41.4)
Open	182 (52.9)	194 (58.6)
Anatomical site of surgery		
Gastric	141 (41.0)	142 (42.9)
Intestinal	102 (29.7)	100 (30.2)
Other[b]	101 (29.4)	89 (26.9)
Time, mean (SD), min		
Anesthetic	206.08 (73.12)	211.92 (78.44)
Surgical	183.39 (69.87)	190.14 (73.64)
Sufentanil, mean (SD), μg[c]	41.2 (10.3)	43.1 (8.6)
Remifentanil, mean (SD), μg[c]	1779.4 (946.7)	2040.0 (1172.5)
Bleeding, median (IQR), mL[f]	100 (50-200)	100 (50-200)
Crystalloid solution, median (IQR), mL[d]	1000 (850-1500)	1000 (1000-1500)
Colloidal solution, median (IQR) mL[d]	500 (500-500)	500 (500-500)
Urine output, median (IQR), mL[c,d]	300 (200-450)	250 (200-400)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Class 1 indicates normal health; class 2, mild systemic disease; and class 3, severe systemic disease that is not life-threatening.

[b] Includes surgery of the liver, gallbladder, pancreas, and appendix.

[c] Intraoperative characteristics with significant differences between 2 groups.

[d] Values were rounded to the nearest 100 mL.

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P < .001) were shorter for patients in the dexmedetomidine group compared with the control group, respectively (Table 2). The dexmedetomidine group had significantly lower median hospital costs (CNY: ¥40 632 [IQR, ¥34 106-¥47 502]; US dollar equivalent: $6018 [IQR, $5051-$7035]) vs the control group (CNY: ¥43 764 [IQR, ¥37 102-¥50 880]; US dollar equivalent: $6481 [IQR, $5495-$7535]; *P* < .001) and a shorter median length of stay (13 days [IQR, 10-17 days]) vs the control group (15 days [IQR, 11-18 days]; *P* = .005). The incidence of delirium was comparable between the dexmedetomidine and control groups in the first 3 postoperative days (day 1: 41 patients [11.9%] vs 43 patients [13.0%], respectively; day 2: 25 patients [7.3%] vs 19 patients [5.7%]; day 3: 18 patients [5.2%] vs 12 patients [3.6%]).

Postoperative pain scores decreased in the first 7 days after surgery, with patients in the dexmedetomidine group having lower pain scores than those in the control group on postoperative days 1 and 4 (eFigure panel A in Supplement 2). Patients in the dexmedetomidine group had better sleep quality than those in the control group on postoperative days 2 and 5 (eFigure panel B in Supplement 2). The postoperative nausea and vomiting scores in the dexmedetomidine group were significantly lower than those of the control group on postoperative days 1 and 3 (eFigure panel C in Supplement 2).

Adverse Events

The incidence of hypotension (30 patients [8.7%] vs 45 patients [13.6%]) or hypertension (14 patients [4.1%] vs 15 patients [4.5%]) requiring treatment was similar between the dexmedetomidine and control groups, respectively (eTable 2 in Supplement 2). Moreover, the incidence of bradycardia that required treatment (22 patients [6.4%]) and did not require treatment (28 patients [8.1%]) in the dexmedetomidine group was comparable with that in the control group

Table 2. Clinical Postoperative Outcomes

Outcome	Median (IQR)		*z* Score or χ^2 value	*P* value
	Dexmedetomidine group	Control group		
Total patients, No.	344	331	NA	NA
Primary end point				
Time to first flatus, h[a]	65 (48-78)	78 (62-93)	7.02[b]	<.001
Secondary end points				
Time to first feces, h[a]	85 (68-115)	98 (74-121)	3.47[b]	.001
Time to first oral feeding, h[a]	76 (52-112)	90 (72-115)	4.55[b]	<.001
Delirium, No. (%)[c]				
Postoperative day 1	41 (11.9)	43 (13.0)	1.13[d]	.57
Postoperative day 2	25 (7.3)	19 (5.7)	0.65[d]	.42
Postoperative day 3	18 (5.2)	12 (3.6)	1.03[d]	.31
Hospital cost, Chinese yuan[e]	40 632 (34 106-47 502)	43 764 (37 102-50 880)	3.81[b]	<.001
Length of stay, d	13 (10-17)	15 (11-18)	2.82[b]	.005

Abbreviation: NA, not applicable.

[a] Values were rounded to the nearest hour.

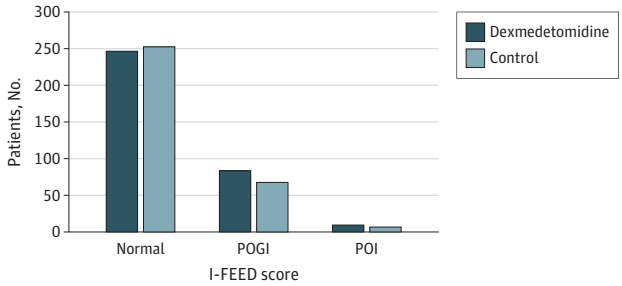
[b] *z* Score.

[c] Measured twice daily using the confusion assessment method, which evaluates acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness.

[d] χ^2 Value.

[e] Mean exchange rate for 2018-2019 (years of study period): 1 Chinese yuan = 0.1481 US dollars. Equivalent median for dexmedetomidine group: $6018 (IQR, $5051-$7035). Equivalent median for control group: $6481 (IQR, $5495-$7535).

Figure 2. Postoperative Gastrointestinal Function



I-FEED indicates intake, feeling nauseated, emesis, physical examination, and duration of symptoms; POGI, postoperative gastrointestinal injury; and POI, postoperative ileus.

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(12 patients [3.6%] required treatment and 20 patients [6.0%] did not require treatment). None of the patients developed postoperative stroke, myocardial infarction, or heart failure.

28-Day Outcomes

Most patients (321 [93.3%] in the dexmedetomidine group and 309 [93.4%] in the control group) resumed a normal solid diet by postoperative day 28; a small proportion still required a liquid diet (23 patients [6.7%] in the dexmedetomidine group and 21 patients [6.3%] in the control group) (**Table 3**). One patient in the control group was unable to resume any oral diet by day 28. Among the 2 groups, there was no significant difference in dietary status, and the incidence of nausea, vomiting, abdominal distension, and constipation was similar. One patient in the dexmedetomidine group and 0 patients in the control group died within 28 days after surgery.

Discussion

This randomized clinical trial investigated the effects of the intraoperative administration of dexmedetomidine on the recovery of gastrointestinal function in older adults. The study's findings demonstrated that dexmedetomidine decreased the time to first flatus and feces compared with saline placebo but did not find any statistically significant difference in postoperative gastrointestinal function as measured by the I-FEED score. Notably, the use of intraoperative dexmedetomidine had no effect on the incidence of delirium in the first 3 postoperative days. However, opioid medication use, pain scores, hospitalization costs, and hospital length of stay were significantly lower in the dexmedetomidine group compared with the control group.

Our results are consistent with those of previous studies[16,18] in which the intraoperative use of dexmedetomidine was associated with a shorter time to first flatus than saline placebo. Li et al[16] randomized 66 patients undergoing lumbar spinal fusion surgery to receive dexmedetomidine (a loading dose of 0.5 μg/kg infused over 15 minutes, followed by a maintenance dose of 0.1 μg/kg per hour) or normal saline and found that patients in the dexmedetomidine group had a shorter time to first flatus and lower overall use of sufentanil analgesic medication. In a randomized clinical trial examining laparoscopic resection of colorectal cancer, Chen et al[18] also found that intraoperative use of dexmedetomidine (a loading dose of 1 μg/kg over 10 minutes, followed by a maintenance dose of 0.3 μg/kg per hour) was associated with reductions in time to first flatus, first feces, and return to a regular solid diet. However, several studies have reported contradictory results. In a study of 20 healthy participants who received 1 μg/kg of dexmedetomidine over 20 minutes followed by a continuous infusion of 0.7 μg/kg per hour for 190 minutes,[15] dexmedetomidine markedly inhibited gastric emptying and gastrointestinal transit compared with normal saline. In a study involving critically ill patients,[23] no difference in gastric emptying time was observed after receipt of intraoperative dexmedetomidine vs propofol. Two preclinical studies reported that

Table 3. Follow-up Outcomes at Postoperative Day 28

Outcome	No. (%)		χ^2 value	*P* value
	Dexmedetomidine group	Control group		
Total patients, No.	344	331	NA	NA
Dietary status				
Regular/solid	321 (93.3)	309 (93.4)	NA	.82
Liquid	23 (6.7)	21 (6.3)		
No eating	0	1 (0.3)		
Nausea	11 (3.2)	14 (4.2)	0.50	.48
Vomiting	5 (1.5)	3 (0.9)	0.09	.76
Abdominal distension	38 (11.0)	40 (12.1)	0.18	.67
Constipation	13 (3.8)	22 (6.6)	2.82	.09
Death	1 (0.3)	0	NA	>.99

Abbreviation: NA, not applicable.

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dexmedetomidine markedly enhanced the inhibitory effect of morphine on gastrointestinal transit and substantially inhibited gastrointestinal transit.[13,14]

Two possible explanations may account for the inconsistent data. First, the effects of dexmedetomidine are likely dose dependent. Adverse effects were found after receipt of high-dose dexmedetomidine in the study of healthy participants.[15] In contrast, favorable results were found in the study of lumbar spinal fusion,[16] the clinical trial of laparoscopic colorectal cancer surgery,[18] and the present randomized clinical trial of abdominal surgery using low-dose intraoperative dexmedetomidine. Low-dose dexmedetomidine may improve gastrointestinal transit by acting on central α_2-adrenergic receptors to reduce sympathetic tone.[24] High-dose dexmedetomidine may inhibit transit via inhibitory α_2-adrenergic receptors along excitatory cholinergic pathways in the enteric nervous system.[25] The second possible explanation is that the effects of dexmedetomidine may differ according to the pathophysiological status of participants. Under physiological conditions, dexmedetomidine inhibited gastrointestinal motility in both preclinical studies[13,14] and in the study of healthy participants.[15] In contrast, dexmedetomidine improved gastrointestinal motility in rats with peritonitis[26] and patients undergoing lumbar spinal fusion[16] and laparoscopic gastrectomy.[24] In the present study, the intraoperative administration of low-dose dexmedetomidine in patients undergoing open and laparoscopic abdominal surgeries did reduce the time to first flatus, suggesting the dose and context of administration are relevant in determining the benefits of dexmedetomidine associated with return of gastrointestinal function.

The pathophysiological mechanism of postoperative ileus involves complex processes in which inflammation, ischemic reperfusion injury, fluid administration, and pharmacological factors interact. Opioid medications have been associated with impairment of gastrointestinal motility through a dose-dependent inhibitory effect.[27] The κ, μ, and δ opioid receptor subtypes have been identified on neurons of submucosal and myenteric plexuses.[28] Therefore, the decreased use of sufentanil and remifentanil medications after the receipt of intraoperative dexmedetomidine, which was observed in the present study, may have beneficial effects on the postoperative recovery of gastrointestinal function. Furthermore, dexmedetomidine has the ability to attenuate ischemic reperfusion injury, inhibit inflammatory response, and improve stress response,[29,30] and these benefits may also provide plausible explanations for the reduced time to gastrointestinal recovery. The use of intraoperative dexmedetomidine was associated with improved kidney function in one study[31] and higher urine output among patients in the dexmedetomidine group in the present study, both of which may improve gastrointestinal function by reducing the chance of developing intestinal edema.

Postoperative recovery of gastrointestinal function is often a decisive factor in length of stay after abdominal surgery, especially gastrointestinal surgery, which comprised 71.9% of the surgeries performed in this study. In China, one of the major hospital discharge criteria after abdominal surgery is the restoration of gastrointestinal function.[32] Despite the absence of a protective effect of dexmedetomidine on the I-FEED score, reductions were found in the time to first flatus, length of stay, and hospital costs, and the quality of sleep was improved. Therefore, intraoperative dexmedetomidine may be useful for enhanced recovery after abdominal surgery. Adverse reactions to dexmedetomidine are mainly restricted to hemodynamic alterations, such as bradycardia, transient hypertension, and hypotension.[33] In the current study, which used a low dose of dexmedetomidine, there was no significant difference in these adverse events between the 2 groups.

Limitations

This study has several limitations. First, the precise effects of dexmedetomidine on gastrointestinal function have not been fully elucidated. Additional research, including comparisons of inflammatory factors and intestinal ischemia reperfusion injury, is warranted. Second, during daily delirium assessments, the incidence of delirium may be underestimated because of short-term fluctuations. Third, we assessed postoperative delirium during the first 3 postoperative days only. Previous studies have assessed delirium among older patients in the first 7 postoperative days[10] or over the course of

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a hospital stay.[34] Fourth, further studies are needed to investigate the relationship between dexmedetomidine dose and enhanced recovery of gastrointestinal function.

Conclusions

Among older patients undergoing abdominal surgery, intraoperative dexmedetomidine significantly reduced the time to first flatus, time to first feces, and hospital length of stay without affecting the I-FEED score. Consideration of the use of intraoperative dexmedetomidine as part of the overall strategy for enhanced recovery after abdominal surgery is warranted.

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SUPPLEMENT 1.
Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
eTable 1. Baseline Characteristics of Patients Lost to Follow-up
eTable 2. Intraoperative Serious Events
eFigure. Assessment of Postoperative Pain, Sleep Quality, and Postoperative Nausea or Vomiting

SUPPLEMENT 3.
Nonauthor Collaborators. The POGF Study Collaborators

SUPPLEMENT 4.
Data Sharing Statement

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