Effect of Dexmedetomidine on Intestinal Barrier in Patients Undergoing Gastrointestinal Surgery - A Single-Centre Randomized Clinical Trial

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Research

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Abstract

Background: Gastrointestinal failure accounts for death in critically ill patients. This study aimed to explore the effect and mechanism of dexmedetomidine (DEX) in intestinal barrier function in critically ill patients undergoing gastrointestinal surgery.

Methods: Patients undergoing gastrointestinal surgery were randomized into a DEX group (n=21) or an MID group (n=21). Sufentanil was used in both groups for analgesia. In the DEX group, DEX was loaded (1 μg/kg) before sedation and was infused (0.7 μg/kg/h) during sedation. The mean arterial pressure (MAP), heart rate (HR), borborygmus resumption time (BRT), first defecation time (FDT), stay of ICU and hospital were observed. The DAO, D-LAC, TNF-α, IL-6 and α7nAChR levels in plasma or haemocytes were detected before the start of the sedation (0 h) and after the sedation (24 h).

Results: There were no significant differences in age, sex, BMI, APACHE II score, SOFA (P>0.05). The MAP between 0 and 24 h presented no significant difference between the groups (P > 0.05), but HR was significantly slower in the DEX group (P=0.042). The recovery time of bowel sounds was significantly earlier in the DEX group (P=0.034). Both of the stay of ICU (P=0.016) and hospital (P=0.031) were significantly shorter in the DEX group. The expression of α7nAChR in the DEX group was significantly higher at 24 h than at 0 h (P=0.002). The D-LAC decreased significantly in the DEX group than MID group at 24 h (P=0.016).

Conclusions: DEX maintained the integrity of the intestinal barrier in patients undergoing gastrointestinal surgery through the cholinergic anti-inflammatory pathway.

Trial registration: ChiCTR1900024367. Registered 7 July 2019-Retrospectively registered, http://www.chictr.org.cn/showproj.aspx?proj=40832

Introduction

The gastrointestinal tract provides the largest storage of bacterial organisms and endotoxins,and also the most sensitive to ischaemia and hypoperfusion of the human body. Intestinal epithelial tissue can resist the invasion of pathogens, produce and secrete antimicrobial peptides, and maintain homeostasis[1, 2]. Because of mechanical injury, intestinal surgery can lead to Intestinal barrier function dysfunction[3]. A large number stress factors can destroy the intestinal barrier, disturb the intestinal flora's homeostasis, disrupt immune function, and release intestinal bacteria. At the same time, the bacterial metabolites enter the blood, causing gut origin sepsis (GOS)[4, 5].

The gastrointestinal tract is the largest organ innervated by nerve fibres. The inflammatory reflex formed by the vagus nerve could play an important role in intestinal immune regulation. Studies[6, 7] have shown that upregulation of vagal nerve activity could improve the intestinal permeability barrier. Dexmedetomidine (DEX) can improve the activity of the vagus nerve and activate the expression of α7nAChR[8–10]. Studies[11–17] have shown that DEX has a definite anti-inflammatory effect, and this

effect is similar to that of direct electrical stimulation of the vagus nerve, but whether it can further improve intestinal permeability in patients with gastrointestinal surgery is unclear[18]. Therefore, our study was conducted to investigate whether DEX could improve intestinal permeability in intestinal surgery and to explore its possible mechanism.

Methods

2.1. Study subjects

This randomized,double-blinded□prospective□controlled study was performed in accordance with the Declaration of Helsinki, approved by the Institutional Review Board of the First Affiliated Hospital of Wannan Medical College (approval number: WAN 2015-18) and registered with the Chinese Clinical Trial Registry at www.chictr.org(registration number: ChiCTR1900024367).

Patients were included according to the following criteria: 1) patients undergoing gastrointestinal surgery; 2) patients who received ventilator-assisted ventilation intubated through the oral trachea for 12 h and an estimated ventilation time of more than 24 h; 3) patients who needed analgesia and sedation; and 4) an informed consent form signed by the patient or family member. Patients who met any of the following criteria were excluded: 1) women who were pregnant or lactating; 2) patients younger than 18 years old; 3) patients with heart rates (HRs) lower than 55 bpm; 4) patients with a high atrioventricular block without a cardiac pacemaker; 5) patients diagnosed with acute liver failure; 6) patients diagnosed with cerebrovascular accident; and 7) patients diagnosed with dementia.

Using a computer-generated random number table, patients were randomly assigned to the DEX group or the MID group (control group). DEX was loaded (1 mg/kg) before sedation and was infused (0.3 mg/kg/h) during sedation. Analgesia and sedation were performed according to the following procedure: (the RASS score was maintained at -2 to 1) [19] (Figure 1).

2.2. Sample size

Fifty patients who provided written consent were enrolled between June 2017 and May 2019.

2.3. Procedure

To eliminate any possible effects of surgical technique, all of the procedures were performed by the same surgical group. To maintain blinding, the clinicians who prepared and performed the sedation and analgesia were not involved in management or assessments unless an emergency occurred. The investigators and patients were blinded to the intervention.

The patients of gender, age, weight, diagnosis, APACHE II score, SOFA score, hourly heart rate and blood pressure, recovery time of bowel sounds, first defecation time, length of ICU hospital stay and length of hospital stay were recorded.

The patients' sex, age, weight, diagnosis, APACHE II score, SOFA score, hourly HR and blood pressure, recovery time of bowel sounds, first defecation time, length of ICU hospital stay and length of hospital stay were recorded.

Blood was collected 0 h and 24 h. The blood was centrifuged at 3000 rpm for 15 min. The supernatant was carefully absorbed into a 2-ml EP tube with a transfusion gun (avoiding absorbing blood cells) to detect TNF-α, D-Lac, and IL-6. The contents of D-Lac, DAO, TNF-a and IL-6 in blood were detected strictly using ELISA kit instructions. Blood cells were collected to detect the changes in α7nAChR mRNA using real-time PCR (total RNA extraction, total RNA reverse transcription into cDNA, and quantitative analysis of α7nAChR mRNA, with β-actin as an internal reference).

2.4. The outcomes

The primary outcomes included the DAO, D-LAC, and α7nAChR levels in plasma or haemocytes.

The secondary outcomes included the mean arterial pressure (MAP), HR, borborygmus resumption time (BRT), first defecation time (FDT), length of ICU hospital stay and length of hospital stay.

2.5. Statistical analysis

SPSS software, version 22.0 (Chicago, IL, USA), was used for data analysis. All of the data were tested by normal distribution and homogeneity of variance. The measurement data with normal distribution are expressed as the mean ± standard deviation (x ± s). The Mann-Whitney U nonparametric test was used to compare the data and rates of non-normal distribution. $P < 0.05$ was considered statistically significant.

Results

A total of 50 patients were included in this study. Four patients refused to be followed up in the middle of the study. Four patients were excluded because of incomplete follow-up data. Finally, the remaining 42 patients were included in the statistical analysis(Figure 2).

2.1 Demographic and clinical characteristics of the DEX and MID groups

There were no significant differences in age, sex, BMI, APACHE II score, SOFA score or RASS score between the DEX and MID groups ($P > 0.05$).

There was no significant difference in blood pressure between the two groups ($P > 0.05$), but the HR in the DEX group was significantly lower than that in the MID group ($P = 0.042$). The recovery time of bowel sounds in the DEX group was significantly shorter than that in the MID group ($P = 0.034$), and there was no significant difference in the first defecation time between the two groups ($P > 0.05$). Compared with the MID group, the DEX group had a significantly shorter length of ICU hospital stay ($P = 0.016$) and length of hospital stay ($P = 0.031$). (Table 1).

Table 1
Demographic and clinical characteristics of the DEX and MID groups

	DEX Group (n = 21)	MID Group (n = 21)	F	P
Age(years)	69.19 ± 8.52	69.38 ± 9.18	0.242	0.945
Sex (male/female)	16/5	16/5	-	-
BMI(kg/m^2)	20.40 ± 2.77	21.70 ± 3.60	0.627	0.196
APACHE II score	15.86 ± 3.62	15.67 ± 4.07	0.712	0.323
SOFA score	9.15 ± 2.35	9.25 ± 3.02	2.500	0.91
RASS score	-0.33 ± 1.11	-0.48 ± 1.08	0.003	0.675
MAP (mm Hg)	87.20 ± 9.70	87.98 ± 9.66	0.458	0.795
HR(bpm)	72.63 ± 8.21	81.51 ± 17.31	6.867	0.042
BRT(d)	2.95 ± 0.97	3.76 ± 1.37	7.290	0.034
FDT(d)	6.24 ± 2.10	7.38 ± 2.00	0.000	0.077
Length of hospital stay(d)	18.86 ± 8.12	24.74 ± 8.91	0.350	0.031
Length of ICU stay (d)	2.76 ± 0.77	3.71 ± 1.56	3.910	0.016

BRT: borborygmus resumption time, FDT: first defecation time, BMI: body mass index, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, RASS: Richmond Agitation and Sedation Scale, MAP: mean arterial pressure HR: heart rate, Length of hospital stay: duration of postoperative hospitalization stay, Length of ICU stay: duration of ICU hospitalization stay

2.2 Changes in indicators of intestinal inflammation and permeability in the DEX and MID groups

TNF-α decreased significantly in the DEX group at 0 h compared with 24 h, but IL-6 levels did not change significantly in the DEX group. TNF-α and IL-6 levels did not change significantly in the MID group at 0 h compared with 24 h. There was no significant difference in TNF-α and IL-6 levels between the DEX and MID groups at 0 h ($P > 0.05$). Compared with the MID group, the DEX group decreased the production of TNF-α ($P = 0.044$) at 24 h, but there was no significant difference in IL-6 between the two groups.

The serum levels of DAO and D-LAC in the DEX group were significantly different at 0 h than at 24 h ($P < 0.05$), but there was no significant difference between the MID group at 0 h and at 24 h ($P > 0.05$), and the serum levels of DAO and D-LAC in the DEX group showed no significant differences compared with those in the MID group at 0 h ($P > 0.05$), while DEX reduced the production of D-LAC more than MID at 0 h than at 24 h ($P < 0.05$) (Table 2).

Table 2
Changes in the indicators of intestinal inflammation and permeability in the DEX and MID groups

		DEX Group	MID Group	F	P
IL-6	0 h	69.18 ± 19.14	64.23 ± 10.76	8.774	0.312
(ng/l)	24 h	67.97 ± 18.28	64.21 ± 13.34	7.767	0.429
TNF-α	0 h	124.61 ± 36.98	105.52 ± 28.14	2.499	0.067
(ng/l)	24 h	99.03 ± 30.49*	116.24 ± 22.67	1.106	0.044
D-LAC	0 h	40.35 ± 8.00	40.22 ± 8.23	0.003	0.960
(μmol/ml)	24 h	34.00 ± 5.68*	39.13 ± 7.39	0.928	0.016
DAO	0 h	72.91 ± 14.54	67.15 ± 17.70	0.034	0.209
(ng/l)	24 h	63.06 ± 15.08*	63.06 ± 15.08	6.359	0.072
Note: * Represents an intra-group comparison (P < 0.05)					
IL-6: interleukin-6; TNF-α: tumour necrosis factor alpha; D-LAC: D-lactate; DAO: diamine oxidase					

2.3 Comparison of α7nAChR levels between the two groups at 0 h and at 24 h

The level of α7nAChR in the DEX group was significantly higher than that in the MID group (P < 0.05), but there was no significant change in the level of α7nAChR in the MID group between 0 h and 24 h (P > 0.05). There was no significant difference in the level of α7nAChR between the DEX and MID groups at 0 h, and the level of α7nAChR in the DEX group was significantly higher than that in the MID group at 24 h (P = 0.015) (Table 3).

Table 3
Changes in α7nAChR levels before and after treatment in the two groups

		DEX Group	MID Group	*P*
α7nAChR	0 h	0.25 (0.18–0.63)	0.52 (0.15–0.92)	0.308
	24 h	0.62 (0.43–1.20)	0.22(0.10–0.79)	0.015
Note: * Represents an intragroup comparison (P < 0.05). α7nAChR: α7-nicotinic acetylcholine receptor				

Discussion

The gastrointestinal mucosa is very sensitive, and gastrointestinal surgery always destroy the intestinal mechanical barrier. At the same time, the gastrointestinal muscle layer is filled with macrophages, many of which are released when stimulated,further promoting the release of cell factors, prostaglandins and

other factors. Therefore, when mucosal injuries occur, they can cause local and systemic inflammatory responses and even sepsis, resulting in postoperative gastrointestinal dysfunction[20].

In recent years, an increasing number of scholars have proposed that the intestinal tract plays an important role in the development of sepsis. Some scholars[21] have proposed that the intestinal tract is not only the first organ involved in sepsis but also the "initiating organ" of sepsis. Approximately 30% of sepsis patients who die of multiple organ dysfunction syndrome (MODS) do not clinically exhibit a primary infection focus, but bacteria similar to intestinal bacteria can be found in their blood cultures[22-25].

The intestinal tract is often involved earlier and recovers later in the disease course. The study found that abdominal distension, intra-abdominal pressure and the time to recovery of intestinal function were significantly delayed in patients with sepsis. The mechanism of injury might be that the gastrointestinal mucosa and villi are rich in blood flow, sensitive to ischaemia and hypoxia, and vulnerable to damage under hypoperfusion. When sepsis occurs, the circulatory blood volume decreases, and the intestinal blood flow decreases significantly. When the systemic circulatory blood volume decreases by 10%, gastrointestinal blood perfusion decreases by nearly half. Long-term hypoperfusion can cause intestinal mucosal cell oedema, villous degeneration and necrosis, damage or even loss of tight junctions between cells, and increased intestinal permeability. If not controlled in time, this condition will eventually result in MODS[1, 2, 21]. Therefore, controlling inflammatory reactions, maintaining intestinal function, protecting the intestinal barrier integrity and avoiding intestinal bacteria and endotoxin release into the blood are the key points for preventing MODS[26].

Recent studies have found that the “cholinergic anti-inflammatory pathway” (CAP) is a neuroimmune regulatory pathway with obvious anti-inflammatory effects[27]. The CAP is composed mainly of the vagus nerve, α7nAChR and muscarinic receptors，it's play different anti-inflammatory roles. Activation of the CAP can effectively reduce the release of TNF-α, IL-6, IL-1β and other inflammatory factors and can significantly inhibit the inflammatory reaction caused by various local and systemic causes[28, 29]. α7nAChR is an important target in the CAP, and it has been a popular research topic in recent years.

Compared with other nicotinic acetylcholine receptors, α7nAChR can be activated rapidly by agonists. The permeability of these receptors to calcium ions increases when activated and can allow for the inflow of calcium ions without causing the depolarization of cell membranes. Therefore, α7nAChR can participate in the regulation of calcium-related events conveniently and quickly. Research have shown that the CAP mainly plays a role through α7nAchR[30]. Directional knockout of the α7nAChR gene or vagotomy can reduce the activity of the CAP and aggravate the inflammatory reaction in various inflammatory model animals. A preliminary study based on clinical sepsis patients showed that high expression of α7nAChR in peripheral blood mononuclear cells was associated with reduced inflammatory status and improved prognosis[31].

DEX is a new type of α2-adrenergic receptor agonist that can simultaneously act on the central and peripheral nervous systems, regulate autonomic nervous activity, and produce dose-dependent sedative,

hypnotic and anti-anxiety effects. At the same time, DEX can reduce the incidence of delirium in patients , and it was widely used in the sedative treatment of critically ill patients [26, 32-34]. Our study found that, compared to MID, DEX had no significant effect on blood pressure at the depth of shallow sedation, At the same time, DEX can also shorten the length of ICU stay.

Several animal experiments on acute inflammation have shown that DEX significantly inhibits the over-release of TNF-α, IL-1β, IL-6 and other inflammatory factors. Clinical studies have also found that DEX use in general anaesthesia can significantly reduce the levels of plasma inflammatory factors in perioperative patients. Especially in patients with severe sepsis caused by intestinal obstruction, DEX treatment can not only reduce the release of inflammatory factors but also reduce the increased intra-abdominal pressure of sepsis patients[14, 15]. Our study found that the borborygmus resumption time (BRT) in the DEX group was significantly shorter than that in the control group. At the same time, our study found that the level of TNF-α in the DEX group was significantly lower, showing that the clinical sedative dose of DEX could produce an obvious anti-inflammatory effect and block the cascade reaction of inflammation.

Many studies have shown that DEX exerts its anti-inflammatory effects by activating the CAP of the vagus nerve and the α-2 adrenergic receptor, and its activation of the CAP is achieved mainly by activating α7nAChR.[35]. In our study, we found that DEX increased the expression of α7nAChR in peripheral blood mononuclear cells.

When the gut was damaged, IFN-γ, TNF-α and IL-1β inflammatory factors, through the CAP, activate myosin light streptokinase within intestinal epithelial cells, resulting in myosin light chain phosphorylation, promoting a variety of proteins (such as adhesion molecule-1, occludin, and claudin) in the closely connected intestinal epithelial cells, thereby inducing functional changes and eventually damaging the integrity of tight junctions[36, 37]. Therefore, the key to maintaining intestinal barrier function is inhibiting the inflammatory response. The serum D-Lac level are often used as important reference indicators for evaluating intestinal barrier function[38]. Our study showed that the level of D-Lac decreased significantly in the DEX group, indicating that DEX could significantly improve intestinal permeability in patients undergoing gastrointestinal surgery. At the same time, combined with the increased expression of α7nAChR in peripheral blood mononuclear cells, it can be inferred that mechanism might be related to the activation of α7nAChR, increased CAP activity and inhibition of the intestinal inflammatory response

Conclusions

DEX is more suitable to patients undergoing gastrointestinal surgery. as a sedative, due to the protection of intestinal barrier. The mechanism might be related to the activation of α7nAChR, increased CAP activity and inhibition of the intestinal inflammatory response.

Declarations

Authors' contributions

WHL and ZW conceived and designed the study. YPQ,YYC and WJM performed the experiments and wrote the paper.XS,QC and YYC contributed essential materials, and YPQ and YYC analysed and interpreted the data. All of the authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the local ethics committee (Ethics Committee of the First Affiliated Hospital of Wannan Medical College, protocol number 201518, date of approval 18 November 2015).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

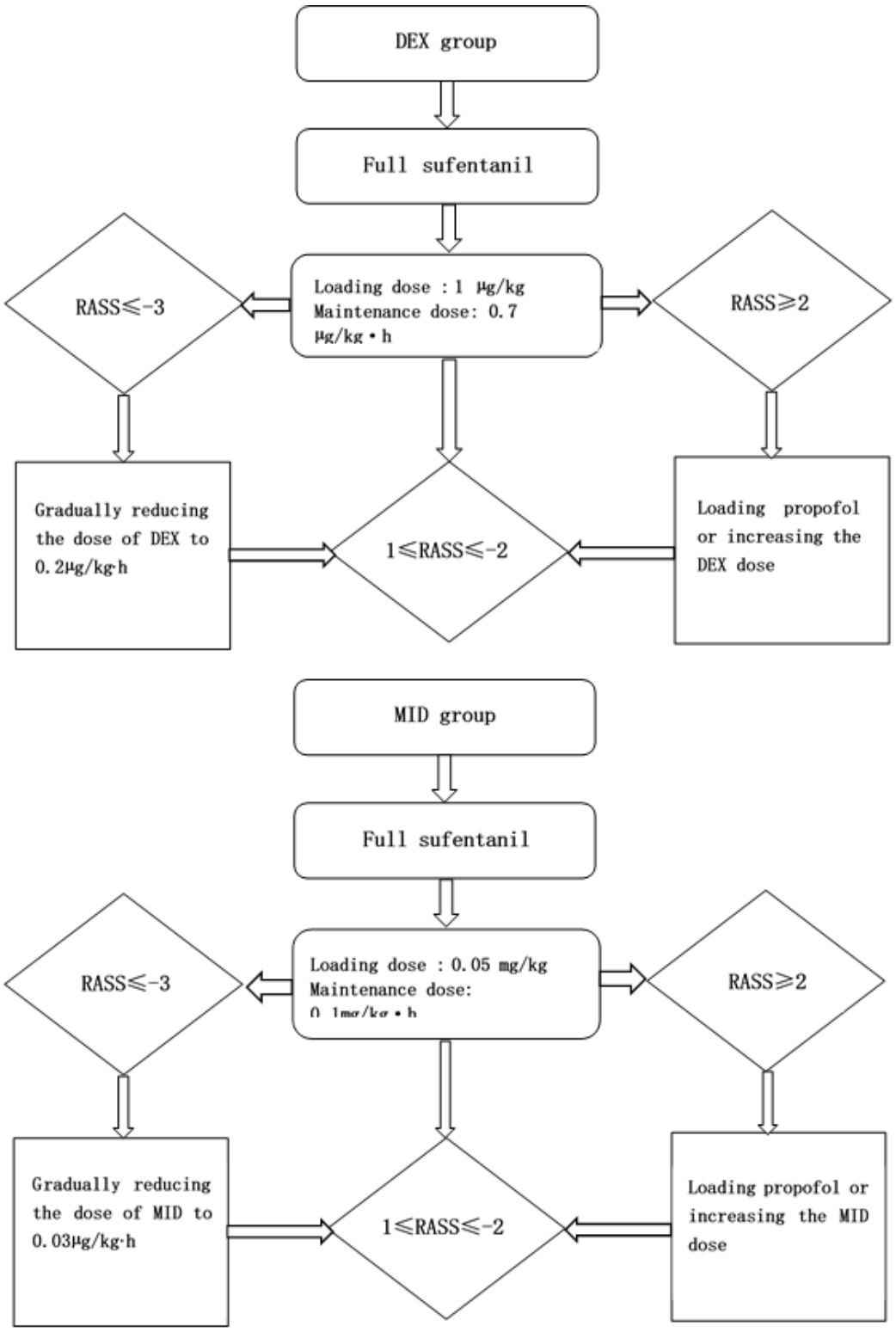

Figure 1

Sedative flow of the DEX and MID groups

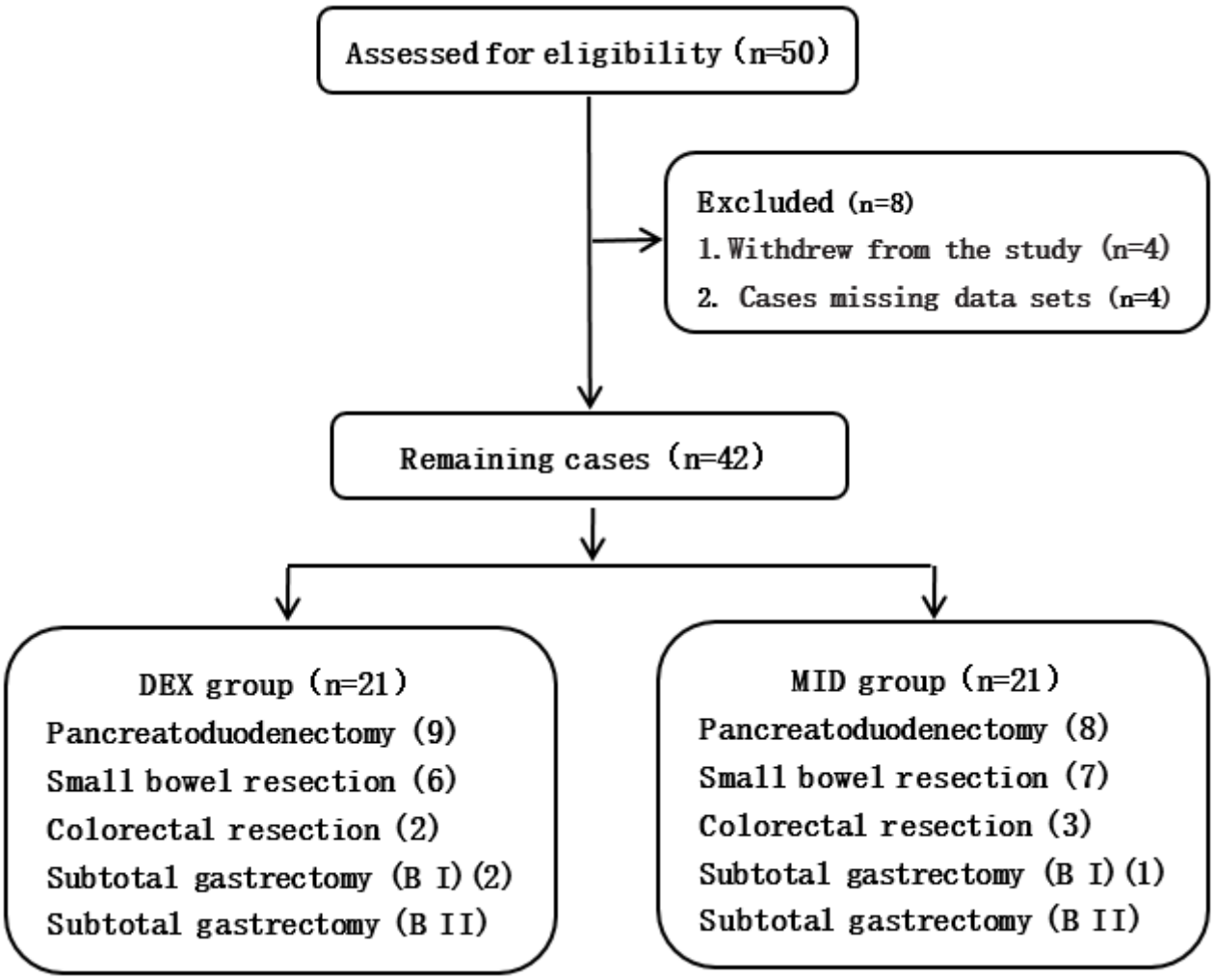

Figure 2

Flow chart of patient inclusion