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The Effects of Dexmedetomidine and Midazolam on Gastrointestinal Motility in Septic Rats

Septik Farelerde Deksmedetomidin ve Midazolamın Gastrointestinal Motilite Üzerine Etkileri

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ABSTRACT

Introduction: *Management of gastrointestinal system is a challenge in septic patients. As far as the necessity of sedative drug infusion is concerned it can be a double-edged sword issue in intensive care units (ICU). Dexmedetomidine and midazolam are the drugs used in ICUs for sedation to provide the comfort in mechanical ventilation and optimize patient care. In this study, the effects of these drugs on gastrointestinal motility in an experimental model of sepsis were investigated.*

Materials and Methods: *A cecal ligation and perforation (CLP) method was used to induce sepsis. Following standard laboratory conditions, 48 female Wistar-Albino rats were randomly divided into 6 groups: Group I: Sham-operated and saline, Group II: Sham-operated and dexmedetomidine, Group III: Sham-operated and midazolam, Group IV: CLP and saline, Group V: CLP and dexmedetomidine, Group VI: CLP and midazolam. Gastrointestinal transit was calculated as the ratio of the distance of charcoal from pyloric sphincter to the total length of the small intestine.*

Results: *In sham-operated groups, dexmedetomidine significantly inhibited the gastrointestinal transit (18.13 ± 6.71% in dexmedetomidine-treated rats vs 60.43 ± 7.93% in midazolam-treated rats) In the CLP groups, gastroin testinal transit was significantly less than sham-operated groups because of the sepsis induced alterations in gastrointestinal motility. The effect of both drugs on gastroin testinal transit in septic rats was similar (27.17 ± 11.84% in Group V, 22 ± 7.14% in Group VI, p=1.00).*

Conclusion: *Both dexmedetomidine and midozolam can be used safely as sedation agent in septic patients with a similar clinical profile. Long-term effects of these drugs on gastrointestinal motility must be elucidated.*

Key Words: *Sepsis, Gastrointestinal motility, Dexmedetomidine, Midazolam.*

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ÖZET

Giriş: *Septik hastalarda gastrointestinal sistemin yönetilmesi oldukça karmaşık bir konudur. Sedatif ilaç infüzyonu gereksinimi göz önüne alındığında yoğun bakım hastalarında bu konu iki ucu keskin bıçak haline gelmektedir. Deksmedetomidin ve midazolam mekanik ventilasyon konforunun ve hasta bakımının iyileştirilebilmesini sağlamak için yoğun bakım hastalarında sedasyon amacıyla kullanılan ilaçlardır. Bu çalışmada, bu ilaçların deneysel sepsis modelinde gastrointestinal sistem üzerindeki etkileri araştırılmıştır.*

Materyal ve Metod: *Sepsis oluşturmak için çekal ligasyon ve perforasyon (ÇLP) yöntemi kullanıldı. Standart laboratuvar koşullarını takiben 48 dişi Wistar-Albino fare rastlantısal olarak altı gruba ayrıldı; Grup I: Sham-opere ve salin, Grup II: Sham-opere ve deksmedetomidin, Grup III: Sham-opere ve midazolam, Grup IV: ÇLP ve salin, Grup V: ÇLP ve deksmedetomidin, Grup VI: ÇLP ve midazolam. Gastrointestinal geçiş, aktif kömürün pilorik sfinkterden olan uzaklığının toplam ince bağırsak uzunluğuna oranı (%) olarak hesaplandı.*

Bulgular: *Sham-opere grupta, deksmedetomidin gastrointestinal geçişi anlamlı olarak yavaşlattı (deksmedetomidin uygulanan farelerde %18.13 ± 6.71, midazolam uygulanan farelerde %60.43 ± 7.93). ÇLP grubunda, gastrointestinal sistem üzerinde sepsisin neden olduğu değişiklikler nedeniyle gastrointestinal geçiş sham-opere gruba oranla anlamlı şekilde düşüktü. Septik farelerde her iki ilacın gastrointestinal geçiş üzerine etkisi benzer bulundu (Grup V'te %27.17 ± 11.84, Grup VI'da %22 ± 7.14, p= 1.00).*

Sonuç: *Hem deksmedetomidin hem de midazolam septik hastalarda benzer klinik seyir nedeniyle sedasyon amacıyla kullanılabilir. Bu ilaçların gastrointestinal sistem üzerine uzun dönem etkilerinin aydınlatılması gerekmektedir.*

Anahtar Kelimeler: *Sepsis, Gastrointestinal motilite, Deksmedetomidin, Midazolam.*

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INTRODUCTION

The gut is the largest lymphoid organ and acts as a barrier to prevent abnormal absorption of intraluminal microbes and their products. The digestion and absorption of nutrients and water is the most important function of the gut. The enteric nervous system initiates and regulates the gastrointestinal motility (1,2). Abnormalities of gastrointestinal motility are common in the intensive care unit (ICU) setting, occurring as a consequences of multiorgan dysfunction, medications and metabolic derangements. Sepsis is one of the major causes of gastric stasis in critically ill patients and results with the enteral feeding intolerance (3). Disturbed upper gastrointestinal motility results not only in inadequate nutritional support but also constitutes a major risk factor for gastrooesophageal reflux and aspiration (4).

Continuous administration of sedative drugs is a commonly used method for sedation in ICUs especially in mechanically ventilated patients to minimize the patient discomfort, control respiratory rate and optimize patient care (5). Inhibition of intestinal peristalsis is a major side effect of sedative agents so it is important to choose an appropriate drug when treating critically ill patients (6). The present study was designed to determine the effect of midazolam and dexmedetomidine on gastrointestinal transit in septic rats.

MATERIALS and METHODS

We used 48 female Wistar-Albino rats aged 4-5 months and weighing 150-230 g. The study was approved by Istanbul University Faculty of Medicine Institutional Committee on Animal Research. The rats were maintained for four days under standardized laboratory conditions. The rats were housed in a temperature-controlled room with a diurnal cycle consisting of 12-h of light and 12-h of darkness. The animals were fasted for 18 h but allowed to take water until 20 min before procedure. Rats were randomly divided into six groups, each consisting of eight rats and kept to separate cages until the start of the experiment. We used a cecal ligation and perforation model to induce sepsis. This model was introduced by Topcu et al. was modified from Wichterman et al. (7,8). Rats were anesthetized by intraperitoneal 50 mg/kg ketamine. Following aseptic conditions a 2 cm midline abdominal incision was performed. A

sham operation was performed in Group I, II and III by only manipulation of small intestine and cecum with a sterile pad. In Group IV, V and VI, after exposure and ligation of cecum with 3-0 silk, the cecum was perforated twice with a 18-gauge needle. A small amount of feces was extruded into abdominal cavity and then the cecum was replaced in its original position within abdomen. The abdominal incision was closed with sutures in two layers.

Rectal body temperature, body weight and blood leucocyte count were recorded 24 h before (basal values) and at 6-h intervals after operation. Study drugs were administered subcutaneously. Rats in Group I and III received 1 mL saline as control groups, Group II and V received 1 mL saline containing 0.01 mg/kg dexmedetomidine, Group III and VI received 1 mL saline containing 0.01 mg/kg midazolam. Meal containing 10% charcoal was applied via 6F feeding tube. Twenty minutes after the charcoal administration rats were sacrificed by cervical dislocation under anesthesia. Rats were reexplorated and peritoneal inflammation was assessed by using Peritoneal Inflammation Grading of Simon et al. (9). The small intestine was resected and gastrointestinal transit was calculated as the ratio of the distance of charcoal from the pyloric sphincter to the total length of the small intestine as previously used by Topcu et al. (7).

Statistical Analysis

Results were expressed as mean ± standard deviation (SD). Gastrointestinal transit was expressed as percentage (%). SPSS 11.5 for Windows was used for statistical analysis. One-way analysis of variance (ANOVA) was used to compare the continuous variables among groups. Bonferroni's hoc test was used to compare gastrointestinal transit for each drug. Independent samples were compared by using Mann-Whitney U-test. Categorical variables were analyzed using X^2 test. A p value < 0.05 was considered statistically significant.

RESULTS

Mean body weight, body temperature and blood leucocyte count was similar in Groups I,II, III. In cecal ligation and perforation (CLP) groups, these parameters were statistically significant in favor of sepsis (Table 1). Mortality rate was higher in CLP groups 24 h after the procedure (37.5%, 25%, 37.5% respectively in Group IV, V and VI; p= 0.01) (Table 2). Degree of peritoneal inflammation in survivals was significantly higher in CLP groups. There was peritoneal inflammation ranging from Stage 2-4 in 6 rats in CLP groups. Gastrointestinal transit ratio of groups is shown on Table 3. The

Table 1. Changes of body weight, body temperature and blood leucocyte count in CLP groups (mean ± SD)

	Group IV (CLP + S)	Group V (CLP + D)	Group VI (CLP + M)
Body weight (g)			
Basal	175.37 ± 8.84	169.5 ± 24.11	174.25 ± 26.85
24 hour after operation	157.8 ± 17.18	146.5 ± 21.21	158.4 ± 29.41
p values	0.043	0.028	0.042
Body temperature (°C)			
Basal	36.52 ± 0.75	36.4 ± 0.44	36.56 ± 0.33
24 hour after operation	31.50 ± 0.36	31.88 ± 0.41	32.08 ± 0.48
p values	0.043	0.028	0.043
Blood leucocyte count (/mm^3)			
Basal	6825 ± 423.42	6900 ± 329.50	6725 ± 604.15
24 hour after operation	2180 ± 83.66	2000 ± 340.58	2040 ± 336.15
p values	0.043	0.027	0.043

CLP: Cecal ligation and perforation, S: Saline, D: Dexmedetomidine, M: Midazolam, SD: Standard deviation.

Table 2. Survival rates of the rats during procedure

	Group I (Sh + S)	Group II (Sh + D)	Group III (Sh + M)	Group IV (CLP + S)	Group V (CLP + D)	Group VI (CLP + M)
Basal	8	8	8	8	8	8
6 hour after	8	8	8	8	8	8
12 hour after	8	8	8	7	8	8
18 hour after	8	8	8	6	8	7
24 hour after	8	8	7	5	6	5

Values represent the number of rats in each group.
Sh: Sham-operated, S: Saline, D: Dexmedetomidine, M: Midazolam, CLP: Cecal ligation and perforation.

Table 3. Data related to GIT values (%)

	n	Length of SI (cm)	Distance of charcoal in SI (cm)	GIT (%)
Group I	8	110.75 ± 9.44	78.37 ± 12.39	72.38 ± 10.85
Group II	8	113.37 ± 10.1	20.38 ± 7.31	18.13 ± 6.71*
Group III	7	114 ± 7.49	69 ± 8.71	60.43 ± 7.93*
Group IV	5	108.2 ± 7.82	28.8 ± 11.94	28 ± 12.19
Group V	6	96 ± 5.21	26.16 ± 12.59	27.17 ± 11.84
Group VI	5	108.2 ± 8.44	24.2 ± 8.17	22 ± 7.14

* p= 0.001; significant difference between groups.
SI: Small intestine, GIT: Gastrointestinal transit.

gastrointestinal transit ratio in Sham-dexmedetomidine group was significantly less than Sham-midazolam group (p= 0.001) but there were no significant difference between CLP groups (p= 1.00).

DISCUSSION

In this study, we found that gastrointestinal transit was significantly inhibited in dexmedetomidine-treated rats in sham-operated group, but in the septic condition the effects of both drugs were similar.

Different experimental models can be used to induce sepsis. Bacterial inoculation, injection of endotoxin/lipopolysaccharide (LPS) and cecal ligation and perforation (CLP) are very frequent methods found in the literature. We chose to use CLP, a simple, economical and widely used method for stimulating polymicrobial sepsis (10). Within 24 h of CLP, there was a significant decrease in leukocyte count, body temperature and body weight compared with baseline values. In addition, the mortality rate and the degree of peritoneal inflammation was significantly higher in CLP groups. Slowing of gastrointestinal transit in the CLP-saline group implied the sepsis induced alterations in gastrointestinal motility in our study as previously reported (11-13).

The enteral nutrition has been the predominant method for nutritional support to preserve gut integrity, though up to 50% of critically ill patients are intolerant to this treatment (14). One reason for intolerance is due to inhibited motility problems. Motility regulation is a complex process involving stimulation and feedback involving many hormones and neuroendocrine pepti-

des (15,16). Sepsis is an important inflammatory process affecting the gastrointestinal tract and results with the inhibition of propulsive intestinal motility and mucosal barrier dysfunction (17). The use of sedatives and opioids can be problematic in intensive care units and can contribute to sepsis. There are many reports about the sedative agents comparing the effects on gastric emptying and intestinal motility but little is known about septic patients. So, the aim of this study was to examine whether midazolam and dexmedetomidine inhibit gastrointestinal transit in experimental septic model.

The effect of midazolam was previously examined in a few reports, and Inada et al. recently demonstrated that both gastric emptying and gastrointestinal transit was inhibited by midazolam in a dose-dependent manner (18). Midazolam affects only the proximal part of the duodenum and had no significant inhibitory effect on the antroduodenojejunal motility in volunteers (19). Dexmedetomidine is an increasingly used α-2 adrenergic drug because of the ability to induce analgosedation and improve sympathoadrenal stability in ICU patients. Unlike midazolam, which acts on the γ-amino butyric acid system and produces a clouding of consciousness, dexmedetomidine produces sedation by reducing sympathetic activity and the level of arousal (6,20). In the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study, the efficacy, safety and pharmacokinetics of both drugs were compared and dexmedetomidine provided several advantages for prolonged ICU sedation, but the effect on gastrointestinal motility was not mentioned (21). In our study, gastrointestinal transit was significantly delayed in Sham-dexmedetomidine group. These data suggest that in the absence of septic conditions, midazolam may be a better choice than dexmedetomidine in ICUs for sedation. On the other hand, both dexmedetomidine and midazolam caused a statistically insignificant slowing of gastrointestinal transit under septic conditions. This reveals that the drug choice must be based on a patient's needs and appropriate individual therapeutic approach.

In conclusion, slowing of gastrointestinal transit is a clinical problem in critically ill patients. If the effect of sepsis on gastrointestinal motility is a concern, it is important to choose an appropriate drug for sedation. Our findings imply that midazolam may be advantageous for sedation because of the little effect on gastrointestinal transit but in the presence of septic conditions both dexmedetomidine and midazolam reveal similar clinical findings. Further prospective studies are required to confirm the effects of dexmedetomidine and midazolam on gastrointestinal motility in septic patients.

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