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Kareem Elsayed Ageeba
Anesthesiology, Surgical Intensive Care and Pain Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Hesham Ebrahim Eltatawy
Anesthesiology, Surgical Intensive Care and Pain Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Reda Sobhi Salama
Anesthesiology, Surgical Intensive Care and Pain Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Yasser Mohammed Amr
Anesthesiology, Surgical Intensive Care and Pain Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Lobna Mohammed AboAlnasr
Anesthesiology, Surgical Intensive Care and Pain Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Corresponding Author:
Kareem Elsayed Ageeba
Anesthesiology, Surgical Intensive Care and Pain Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Effect of sedation with midazolam versus dexmedetomidine on gastric emptying assessed by gastric ultrasound in mechanically ventilated patients: A randomized control study

Kareem Elsayed Ageeba, Hesham Ebrahim Eltatawy, Reda Sobhi Salama, Yasser Mohammed Amr and Lobna Mohammed AboAlnasr

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Abstract
Background: Sedation remains an essential component of managing those going through mechanical ventilation in the ICU. This work was aimed at assessing the midazolam effect vs. dexmedetomidine on gastric emptying assessed by gastric ultrasound in mechanically ventilated patients receiving enteral nutrition.
Methods: our prospective randomized controlled double-blind study involved 90 individuals whose ages are between twenty-one and sixty years, both genders, expected ICU stay was ≥ 48 h (to permit adequate exposure to the proposed intervention). All participants underwent an even categorization into two groups who were administered sedation with: Midazolam: given as an initial bolus of 0.05 mg/kg loading, then maintenance infusion at 1-2 mg/h, which could be increased by 1-2 mg/h increments till obtaining adequate sedation, or dexmedetomidine: receiving a loading dosage of 0.5 µg/kg over ten min, then maintenance infusion dosage of 0.2 - 0.7 µg/kg/h.
Results: The aspirated GRV correlated significantly with the measured antral cross-sectional area (CSA). In Midazolam group, the aspirated GRV increased linearly with the increasing antral CSA (Spearman correlation coefficient: 0.842, p<0.001). In dexmedetomidine group, the aspirated GRV decreased with the decreased antral CSA (Spearman correlation coefficient: 0.573, p<0.001). Regarding CSA and GRV, a significant variation between patients' measured antral CSA among both groups (p<0.001).
Conclusion: Dexmedetomidine is better than midazolam as a sedative drug for those undergoing a mechanical ventilation administering enteral nutrition in ICU because it has a better effect on gastric emptying.

Keywords: Sedation, midazolam, dexmedetomidine, gastric emptying, gastric ultrasound, mechanical ventilation

Introduction
Sedation remains an essential component of therapy for those undergoing mechanical ventilation in ICU due to its anxiolytic action, sleep facilitation as well as decreased mechanical ventilation resistance [1]. Using sedative drugs for those undergoing mechanical ventilatation in ICU is often associated with delayed gastric emptying, resulting in gastro-oesophageal reflux as well as aspiration pneumonia [2].
Measuring RGV is often advisable for assessing enteral nutrition tolerance for those undergoing mechanical ventilation [3], involving gastric contents sequential suctioning utilizing a RGV cut-off value above which enteral feeding is reduced or ceased [4]. However several studies have shown that continuous gastric suctioning, resulting in caloric intake reduction with no advantages regarding decreasing vomiting and reflux [5]. Therefore, monitoring RGV could be done utilizing other approaches, involving abdominal radiological assessment [6].
Gastric ultrasound represents a simple, non-invasive, bedside method, utilized easily to detect gastric contents [7]. This based on gastric antrum qualitative examination. The gastric antrum ultrasonographic assessment could represent an alternative approach to gastric suctioning regarding monitoring individuals in ICU [6].
Midazolam is a γ-aminobutyric acid (GABA) receptor agonist.

It has been one of the most used sedative drugs in ICU.
Dexmedetomidine represents a highly selective α2-adrenoceptor agonist, used in anaesthesia and ICU. It provides proper sedation and has also analgesic and amnesic effect. It has no respiratory depression action. It`s now established as novel approach to intensive care sedation [8].
This work was aimed at assessing the midazolam effect vs. dexmedetomidine on gastric emptying assessed utilizing gastric ultrasound for mechanically ventilated patients receiving enteral nutrition.

Patients and Methods

Our prospective randomized controlled double-blind study involved 90 individuals whose ages are between twenty-one and sixty years, both genders, expected ICU stay was ≥ 48h (To permit adequate exposure to the proposed intervention). The study was done from August 2022 to August 2023 following the Ethical Committee Tanta University Hospitals, Tanta, Egypt approval. All patients' legal guardians were asked to fill an informed consent.
Exclusion criteria were hemodynamic instability, sepsis, or burn, electrolyte disturbances, hepatic failure or renal failure, diabetes, pregnancy, recent major abdominal surgery, gastrointestinal haemorrhage, intestinal obstruction or perforation, inotropes and opioids or prokinetic consumption at forty-eight h before study.

Randomization and blindness

An opaque, sealed envelopes as well as computer-generated number were utilized for randomization. All participants went through an even categorization, then sedation was administered based on each group: Midazolam (group M): midazolam was administered as an initial bolus dosage of 0.05 mg/kg loading, then maintenance infusion dosage of 1-2 mg/h, which could be increased at one to two mg/h till obtaining sufficient sedation. Dexmedetomidine (group D): administering a loading dosage of 0.5 µg/kg within ten min, a maintenance infusion dosage of 0.2 - 0.7 µg/kg/h was then administered.
All participants went through: comprehensive medical history, (APACHE II) score as well as sequential (SOFA) score, gastric antrum ultrasonic evaluation [Gastric US will be utilized for assessing gastric antrum cross sectional area at 1 and 2 hours after test meal], gastric residual volume (GRV) measurement by suctioning after the 2nd hour and gastrointestinal intolerance within initial seven days following enteral feeding initiation.
The sedation efficacy was assessed by using Riker Sedation-Agitation Scale (SAS) [9] sedation level was considered adequate when the SAS score is 3 or 4.
The enteral feeding algorithm was set for achieving 100% of the desired nutritional intake in forty-eight h following the enteral feeding initiation. Enteral feeding was started with 1/2 the calculated amount of Nutrison per each meal bolus and increasing gradually within 48 h to reach full nutrition requirements if no intolerance to enteral feeding was observed as distention, vomiting or aspiration. If intolerance occurred, enteral feeding was held, antiemetic and prokinetic therapy was given provided that the prokinetic had been stopped 48 hours prior to the study, and then enteral feeding was restarted using half the previous amount, increasing gradually until no intolerance observed and full nutrition requirements were achieved. Patients received the enteral feeding through the nasogastric tube in 5 meal boluses at 4 hours interval, with gastrointestinal tract rest from 12 a.m. to 8 a.m. Each feeding ceased in an hour utilizing a gravity-based infusion. Glycemic control was maintained between 140 and 180 mg/dl (at the discretion of the intensivist).
On the day of the study (24 hours after achieving the full nutrition goal and after 8 hours fasting), sedation level, APACHE II and SOFA were assessed. All gastric contents suctioned as well as disposed. A one hundred ml nutrition test meal was administered via NG tube in five minutes, then ultrasonographic gastric antrum imaging was applied after 1 and 2 hours and gastric contents were aspirated after the second hour.

Ultrasonographic gastric antrum imaging

It applied to all participants after 1 and 2 hours following test meal. Gastric antrum images captured utilizing 2 - 5 MHz curvilinear probe which positioned in the epigastric region sagittal plane. The imaging procedures were conducted in supine postures as well as the bed head raised at a 30 degrees. Reference points were utilized for capturing images of gastric antrum - left anterior lobe of the liver anteriorly, inferior vena cava and abdominal aorta posteriorly [9]. Figure 1.

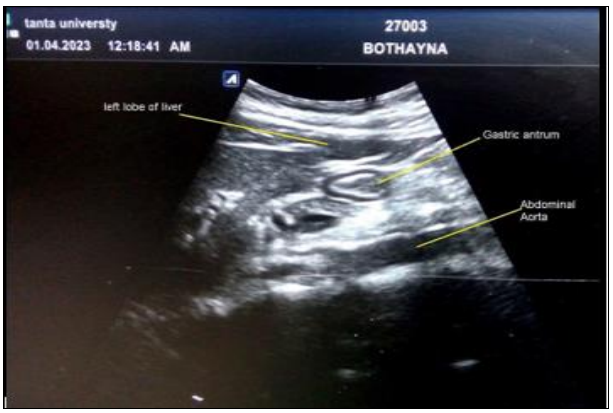

Fig 1: Ultrasound showing gastric antrum

The empty stomach is characterized by the sonographic presence of certain appearances in the antrum, involving the anterior as well as posterior walls extremely close together (flat antrum), round or oval antrum, known as bull's eye, with no visible contents [10]. If the antrum appeared to have an endo cavitary lumen with hypoechoic content and distended walls, it was assigned to contain fluid. Figure 2.

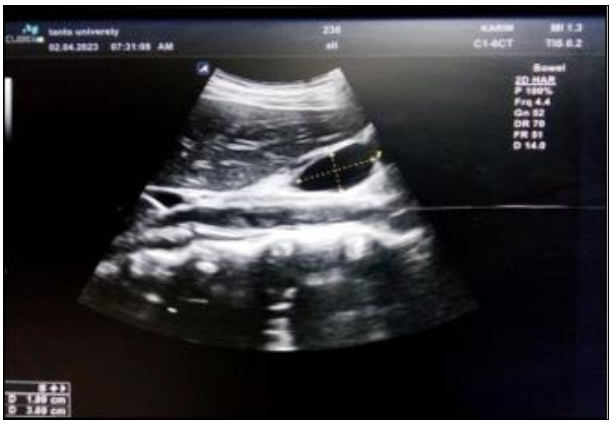

Fig 2: (1) Anteroposterior diameter (dAP), (2) Craniocaudal diameter (dCC)

Sedation infusions and feeding formulae were prepared by the ICU nursing staff while assessment of the outcome measures was performed by an anesthesiologist blinded to the assigned group.

The primary outcome was gastric antrum cross sectional area as assessed by gastric U/S. The secondary outcomes were GRV and incidence of gastrointestinal intolerance (Distention, vomiting, reflux, and aspiration).

Sample Size Calculation

The sample size as well as power analysis were measured utilizing Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. We utilized criteria for calculating sample size involving: 95% confidence limit, 80% power of the study, expected better gastric emptying measured by cross section of gastric antrum less than 360 mm^2 in the best-treated group at 90% as opposed to 65% within least favourable treatment one. The sample size, determined by the previous criteria, proved to be more than 44 in each group (N>44). To compensate for the incomplete findings, the sample size will be increased to 45 by researchers.

Statistical analysis

The data wen through a statistical analysis utilizing SPSS v26 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks test as well as histograms were utilized for assessing the normality of the distribution of data. Quantitative parametric variables were displayed as mean as well as standard deviation then underwent a comparison between the two groups utilizing unpaired Student's t- test. Quantitative non-parametric data were displayed as median as well as interquartile range (IQR) then went through analysing utilizing Mann Whitney-test. Qualitative variables were displayed as frequency as well as percentage (%) then went through analysis utilizing the Chi-square test or Fisher's exact test when appropriate. Calculating Pearson correlation coefficient (r) was done for indicating strength as well as direction of association among two numerical variables, both are continuous and at least one of them is normally distributed. A two tailed P value < 0.05 deemed to be statistically significant.

Results

Regarding age, sex, height, weight, APACHE as well as SOFA, no significant variation was documented among both groups. Table 1.

Table 1: Comparison among both studied groups based on demographics, APACHE as well as SOFA

		Midazolam (n = 45)	Dexmedetomidine (n = 45)	P
Age (years)		37.69 ± 9.50	39.67 ± 10.04	0.340
Sex	Male	31 (68.9%)	33 (73.3%)	0.642
	Female	14 (31.1%)	12 (26.7%)	
Height (cm)		171.09 ± 5.12	171.87 ± 6.08	0.513
Weight (kg)		72.42 ± 6.60	73.09 ± 7.05	0.644
APACHE		1.0 (0.0-3.0)	1.0 (0.0-2.0)	0.841
SOFA		1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.748

Data are exhibited as mean ± SD or frequency (%) or median (IQR), *significant p value<0.05, APACHE II: Acute physiology and chronic Health Evaluation II, SOFA: Sequential sepsis related organ failure Assessment

Regarding CSA and GRV, a significant variation between patients' measured antral CSA in both groups (p<0.001). Table 2.

Table 2: Comparison among both studied groups based on CSA, GRV as well as intolerance

		Midazolam (n = 45)	Dexmedetomidine (n = 45)	P
CSA (mm^2)	1 hour	349.0 (316.5-510.6)	303.6 (263.5-325.0)	<0.001*
	2 hours	316.2 (289.6-412.9)	268.2 (229.0-296.6)	
Z (p°)		5.841* (<0.001*)	5.333* (<0.001*)	
GRV		27.80 ± 12.93	17.44 ± 7.39	<0.001*
Intolerance	0	28 (62.2%)	38 (84.4%)	0.071
	1	10 (22.2%)	5 (11.1%)	
	2	4 (8.9%)	2 (4.4%)	
	3	3 (6.7%)	0 (0%)	

Data are exhibited as mean ± SD, median (IQR) or number (%), *significant p value<0.05, p: p value to compare between 1 hour and 2-hour CSA in each group. P°: p value to compare between the two studied groups. CSA: cross sectional area of gastric antrum, GRV: gastric residual volume

The aspirated GRV was linked significantly to measure antral CSA. In group M, the aspirated GRV increased linearly with the increasing antral CSA (: Spearman correlation coefficient: 0.842, p<0.001). In group D, the aspirated GRV decreased with the decreased antral CSA (Spearman correlation coefficient: 0.573, p<0.001). Table 3.

Table 3: Association between GRV as well as CSA in each group and total sample

		Total (n =90)		Midazolam (n = 45)		Dexmedetomidine (n = 45)	
		r_s	p	r_s	p	r_s	p
CSA	1 hour	0.796*	<0.001*	0.845*	<0.001*	0.596*	<0.001*
	2 hours	0.778*	<0.001*	0.842*	<0.001*	0.573*	<0.001*

rs: Spearman coefficient, *significant p value<0.05, CSA: cross sectional area of gastric antrum, GRV: gastric residual volume

Discussion

Gastrointestinal intolerance represents a primary complication linked to early enteral feeding for those in ICU. It is often accompanied by gastroparesis with prolonged stomach emptying, resulting in regurgitation, vomiting as well as pulmonary aspiration. Intolerance to enteral nutrition is often linked to decreased dieter intake, poor clinical outcomes as well as higher mortality rates [11].

The present study showed that as regard APACHE II score; no significant variation was documented regarding the patients' APACHE II score among both groups, in group M, the patients' score with mean 1.42±1.32 while in group D with mean 1.31±1.08, P value = 0.841. Regarding SOFA score; no significant variation regarding the patients' SOFA score was documented among both groups. In group M, the patients' score with mean 0.96±0.90 while in group D with mean 1.0 ± 0.83, P value = 0.748. Our results supported by study of Memiş *et al*. [1] reported that about 24 critically ill individuals who were enteral fed; they were administered enteral feeding utilizing a nasogastric tube at a dosage of fifty mL h-1 within the study's period of five hours. Either propofol at a dosage of two mg kg-1 h-1 (n 12, Group P) or dexmedetomidine at a dosage of 0.2 µg kg-1 h-1 (n 12, Group D) were IV administered over a duration of five h. Baseline APACHE II (16.10 4.8 and 17 4.72, Group P as well as D, respectively) exhibiting no statistically significant difference between them.

Our study addressed, the gastric antrum measured CSA for group M with mean 426.71±161.28 after the 1st hour and with mean 359.27±111.84 after the 2nd hour which was significantly higher. While the CSA in group D with mean 306.43±56.22 after the 1st hour with mean 310.33±263.54 after the 2nd hour which was significantly lower, P value <0.001. As regard GRV (GRV in ml): a significant variation regarding the patients' measured GRV was documented among both groups, in group M the GRV was increased and with mean 27.80±12.93 while in group D the GRV was decreased with mean 17.44±7.39, P value <0.001.

Regarding correlation between the measured antral CSA and aspirated GRV in each group; the aspirated GRV correlated significantly with the measured antral CSA. In group M, the aspirated GRV increased linearly with the increasing antral CSA (Spearman correlation coefficient: 0.842, p<0.001). In group D, the aspirated GRV decreased with the decreased antral CSA (Spearman correlation coefficient: 0.573, p<0.001).

As regard gastrointestinal intolerance (Such as distension, vomiting and reflux), a significant variation was documented among both groups regarding GIT intolerance occurence. In group M, GIT intolerance occurred in about 37.8% of patients with an incidence of: once in 22.2%, twice in 8.9% and 3 times in 6.7% of patients. In group D, GIT intolerance occurred in 15.6% of patients with an incidence of: once in 11.1% and twice in 4.4% of patients. While, in the study of Memiş *et al*. [1] found that no variation among groups regarding gastric emptying duration was documented (AUC120 894.53 499.39 and 1113.46 598.09, Groups P as well as D, respectively). Dexmedetomidine, an α2-adrenoceptor agonist, is utilized in anaesthesia as well as ICUs for its sedative, amnesic, analgesic, as well as anesthetic effects. Its impact on intestinal peristalsis remains uncertain due to suitable models absence. Herbert *et al*. [12] addressed, clonidine as well as dexmedetomidine strongly inhibit the guineas pig ileum peristalsis as a result of interaction with α2-adrenoceptors. Clonidine also activates small conductance Ca2-activated potassium channels along with endogenous opioid pathways.

The pharmacological mechanisms behind the dexmedetomidine peripheral antiperistaltic activity were examined utilizing an approach evaluating transmitter antagonists in parallel with vehicle. More precisely, dexmedetomidine may hinder peristalsis by stimulating inhibitory α1adrenoceptors on the smooth muscle as well as activating inhibitory α2adrenoceptors on excitatory cholinergic pathways, involving opioid, purinergic, as well as nitrergic neurons [13]. Herbert *et al*. [12] addressed, α2-adrenoceptor agonists decrease intestinal peristalsis by acting on enteric neurons in the gut via a peripheral site of action. A prior study of Nguyen *et al*. [2] proposed that the sedation selection could influence gastric emptying in critical illness. They found that propofol-based sedation may be more advantageous, particularly for patients who cannot tolerate gastric feeding. The observed negative impacts of Morphine and midazolam on gastric emptying and intra-gastric meal distribution in the present investigation align with the established motor effects of morphine.

Developing motor impairments in the distal stomach is remains essential as well, since there have been studies suggesting a positive correlation between the motor abnormalities in the distal stomach as well as delayed emptying among those having critical illnesses who are sedated with M and M. Conversely, the propofol effect on stomach motility as well as emptying in humans are not well understood. Although propofol has been shown to hinder gastric emptying in mice in a dosage-dependent manner [14]. Propofol administration at a dosage of five mg/kg/h within one to three h doesn't impact gastric emptying for both healthy individuals [15], and those gone through minor surgeries [16]. In the Nguyen *et al*.'s research [2] it was shown that 56% of patients who were administered propofol, at an average dosage of around 2 mg/kg/h, had delayed stomach emptying. In the absence of control group receiving no sedation, it could be impossible to know if propofol causes delayed gastric emptying for those having critical illness. However, our study revealed that the delayed gastric emptying occurrence for those administering propofol was significantly less as opposed to others sedated with M and M. McArthur *et al*. [17] addressed, for individuals having head injuries, replacing M and M in addition to propofol for sedation did not exhibit improvements regarding gastric emptying. Among these patients, increased intra-cranial pressure rather than sedation had a higher impact on gastric emptying.

Midazolam suppresses the impulses transmission in the CNS synapses (specifically the cerebral cortex as well as reticular formation), resulting in an inhibition in the frequency of excitatory impulses to the autonomic centers in the hypothalamus, which in turn reduces the frequency of excitatory impulses to the central vagal nuclei in the medulla oblongata. As a result, there is a decrease in local muscular paralysis as well as gastric motility, leading to an improvement in gastric mucosal ischaemia, necrosis, and gastric ulceration reduction [18].

Limitations: involved modest sample size as well as single-centered study. Lack of previous similar studies to be

compared with also another limitation.

Conclusion

Dexmedetomidine is better than midazolam as a sedative drug for those undergoing mechanical ventilation and administering enteral nutrition in ICU because it has a better effect on gastric emptying.

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Nil.

Conflict of Interest

Nil.

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