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Prolonged gastrointestinal dysfunction in critically ill patients

Disfunção do trato gastrointestinal prolongada em pacientes admitidos na terapia intensiva

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ABSTRACT

Objective: We aimed to investigate the prevalence and independent predictors of prolonged gastrointestinal dysfunction (GID) in critically ill patients admitted to the intensive care unit.

Methods: This was a retrospective and observational cohort study performed in a 24 medical and surgical beds intensive care unit, in a tertiary center. Patients admitted to the intensive care unit between August 2003 and January 2004, who had a length of stay in the intensive care unit greater than 4 days were enrolled. Gastrointestinal function was evaluated daily according to a classification that considered physical examination (bowel sounds or distension) and the nutritional support progress.

Results: Were included 128 patients. The mean age was 56 ± 19 years, 63.3% were male and 77.3% were surgical patients. Prolonged GID occurred in 35% of patients, with prevalence 3.3 times higher

in surgical patients (27%) than in medical patients (8%). Endoscopies were performed in 38 patients (29.7%), and in three quarters of them erosive lesions and or bleeding were observed. Gastrointestinal dysfunction was more frequent in patients presenting moderate or severe edema (51%) than in patients without edema (22.5%) ($p < 0.05$). In the logistic regression analysis, a serum lactate level higher than 5.2 mEq/L (RR 6.69 95%CI 15-38.7, $P = 0.034$) and the presence of a low oxygenation index (RR 12.4 95%CI 2.18-70.8, $p = 0.005$) were predictive of gastrointestinal dysfunction.

Conclusion: Prolonged gastrointestinal dysfunction was highly prevalent in this heterogeneous population of critically ill patients. Admission high serum lactate levels and a low oxygenation index were predictive of GID.

Keywords: Gastrointestinal tract/pathology; Gastrointestinal diseases; Multiple organ failure; Lactate; Ileum

INTRODUCTION

In severely ill patients, while other organs or systems dysfunctions are rapidly progressive, the gastrointestinal system dysfunction (GID) is generally insidious and less valued, due to the dramatic patient's condition.⁽¹⁾ Mucosal injuries and functional gastrointestinal tract (GIT) changes may be a consequence of the circulatory shock, surgical or traumatic stress, and long term broad spectrum antibiotics use.⁽²⁻⁵⁾ GID is associated with

severe discomfort and increased hospitalization time and costs.⁽⁶⁾

GID after traumatic or infective injury may manifest with abdominal distension, adynamic ileum, delayed flatus and stools elimination, and vomiting, frequently causing intolerance to enteral feeding. Disabsorptive syndromes from atrophy, mucosal edema and bacterial overgrowth will lead, in long term, to severe proteic-caloric malnutrition.⁽⁴⁾ Intra-abdominal hypertension and abdominal compartment syndrome are beginning to be valued in the GID context, and are associated to high mortality rates.⁽⁷⁻⁹⁾ Yet gastric mucosa erosions and hemorrhage were described between 24 and 100% of the critically ill patients already in the first 24 hours following admission to the intensive care unit (ICU).⁽²⁾ GID é potentially harmful due to the risk of the intestinal barrier breakage, allowing germs and toxins to enter the blood stream, and additionally due to accompanying severe in-hospital malnutrition, emphasizing the relevance of its characteristics and risk factors acknowledgement, allowing interventional studies to be developed. Our aim was to evaluate the GID prevalence and risk factors in a heterogeneous critically ill patients group.

METHODS

This was a retrospective and observational cohort study. It was developed in a 24 beds clinical-surgical ICU belonging to a university hospital. All patients admitted between August 2003 and January 2004 and staying in the ICU longer than 4 days, were enrolled. The Institution's Ethics Committee exempted the signature of an Informed Consent Form before the data collection.

By the admission were evaluated the demographic data, Acute Physiology And Chronic Health Evaluation II (APACHE II)⁽¹⁰⁾ and Sequential Organ Failure Assessment (SOFA)⁽¹¹⁾ scores, the serum lactate level, and arterial blood gasometry. Infections during the stay, the main infection sites and sepsis diagnosis by the admission were recorded. Use of vasoactive drugs was considered when dopamine was infused in doses above 5 µg/kg.min, or norepinephrine in any dosage. The ratio between partial oxygen pressure and inspired oxygen fraction ($\text{PaO}_2/\text{FiO}_2$) was used as oxygenation index, and was based on the ICU admission arterial blood gasometry. Bodily edema was defined as the presence of abnormal subcutaneous tissue fluid accumulation, and evaluated daily on ankles, legs and

hands by the on duty and resident doctors, during the first 7 days in the unit. A semi-quantitative criterion was used to evaluate the degree of edema, being one mark (+) for mild edema, two (++) for moderate edema, and three (+++) for severe edema.

GID was considered when appropriate enteral or oral feeding was not feasible due to GIT changes such as distension, ileum or vomiting. The GIT function was evaluated daily according to the service's categorization, taking into consideration the physical examination (presence or absence of bowel sounds, or distension) and the nutrition support level and kind (Chart 1). The patients with a degree equal or above three for more than five consecutive days were rated as having prolonged GID.

Chart 1- Gastrointestinal tract dysfunction degree rating

1	Prescribed more than 25 cal/Kg/day via oral or enteral, with hydro-aerial sounds
2	Prescribed less than 25 cal/Kg/day via oral or enteral with hydro-aerial sounds
3	Prescribed less than 25 cal/Kg/day via enteral plus parenteral nutrition
4	Exclusive parenteral nutrition and/or no hydro-aerial sounds
5	No nutrition support

Statistics

The results were expressed as mean and standard deviations or median and 25-75% percentiles. The statistical analyses were performed using the t Student and Fisher tests. A logistic regression analysis was conducted to evaluate for the independent GID predictive factors. For the multivariate analysis, only early admission variables (within the first 24 hours) and with p values below 0.2 were included in the model. The mortality rate was calculated as relative risk. A $p < 0.05$ value was considered statistically significant.

RESULTS

One hundred and twenty eight patients were included. Mean age was 56 ± 19 years, being 63.3% male and 77.3% surgical. The demographic and progression information are shown on Table 1. Of the patients, 51% were admitted with sepsis diagnosis, and infection was documented or presumed based on laboratory tests, physical examination and image tests at any time during the stay in 106 patients (83%). The main infection sites were lungs (39%), abdomen

Table 1 – Clinical and demographic data, tissue perfusion markers and outcomes for all patients

Age (years)	56 ± 19
Male gender	81 (63.3)
Categorization	
Surgical	99 (77.3)
Medical	29 (22.6)
Severity scores	
APACHE II	15.3 ± 7.2
SOFA	9.5 ± 4.3
Main diagnosis	
Sepsis	65 (50.8)
Respiratory failure	38 (29.7)
Polytrauma	14 (10.9)
Infection	13 (10.2)
Others	33 (25.7)
Tissue perfusion markers	
Admission lactate (mEq/L)	4.0 ± 2.9
Day 2 lactate (mEq/L)	3.4 ± 2.0
Maximal lactate (mEq/L)	5.2 ± 3.0
Maximal lactate day (mEq/L)	2 [1-5]
Outcomes	
Hospital stay (days)	16 [9-28]
ICU stay (days)	6 [4-15]
In-Hospital mortality rates (%)	56.2

APACHE II - Acute Physiology and Chronic Health Evaluation II; SOFA - Sequential Organ Failure Assessment; ICU – intensive care unit. Results expressed as mean ± standard deviation, median [25-75%] or number (%). Maximal Lactate: corresponds to the highest observed level.

Table 2 – Clinical and demographic data, tissue perfusion markers and time of stay in patients with and without gastrointestinal tract dysfunction

	Without GID (N=83)	With GID (N=45)	P value
Age, years	54 ± 20	56 ± 18	0.504
Surgical/Medical (%)	61 (73.5)/22 (26.5)	38 (84.4)/ 7 (15.6)	0.341
Severity scores			
APACHE II	14.8 ± 6.8	16.9 ± 7.6	0.112
SOFA (admission)	8.4 ± 3.9	11.7 ± 4.1	<0.001
SOFA (day 2)	7.7 ± 4.1	10.6 ± 3.9	<0.001
SOFA (maximal)	10.0 ± 3.8	13.4 ± 3.9	<0.001
Tissue perfusion			
Admission lactate (mEq/L)	3.6 ± 2.3	4.8 ± 3.4	0.019
Day 2 lactate (mEq/L)	3.3 ± 2.2	3.4 ± 1.5	0.786
Maximal lactate (mEq/L)	4.7 ± 2.9	6.0 ± 3.1	0.020
Maximal lactate Day (mEq/L)	2 [1-4]	2 [1-7]	0.688
PO ₂ /FiO ₂ < 200 ratio	42 (50.6)	37 (82.2)	<0.001
Outcome			
Vasopressors required	31 (73.5)	29 (64.4)	0.380
Vasopressors use (days)	3.0 [2-6]	5.5 [2-8]	0.008
ICU stay (days)	6 [4-15]	15 [8.5-23]	0.002
Hospital stay (days)	14 [8-27]	23 [15-34]	0.014

GID – gastrointestinal system dysfunction; APACHE II - Acute Physiology and Chronic Health Evaluation II; SOFA - Sequential Organ Failure Assessment; ICU – intensive care unit. Results expressed as number (%), mean ± standard deviation or median [25-75%]. Maximal Lactate: corresponds to the highest observed level.

(31%) and urinary tract (18%). Vasoactive drugs were required for 47% of the patients (Table 1).

In 38 patients (29.7%) an upper endoscopy was conducted for suspected digestive hemorrhage. Erosive (25 patients, 66%) and/or hemorrhagic (10 patients, 26%) lesions were seen in three quarters of the examinations.

Prolonged GID was identified in 35% of the patients (level 3: 1; level 4: 4; level 5: 40), with a 3.3 times higher prevalence in surgical patients (27%) versus medical patients (8%). The mean GID duration was 14 days for level 3, 10.5 ± 4.3 days for level 4, and 6.3 ± 2.7 days for level 5. Table 2 shows the demographic, severity, serum lactate levels and time of stay data for the patients with or without prolonged GID. Patients with GID were more ill, as shown by the higher severity scores, had more vasopressor support days, and stayed longer in the ICU and hospital (Table 2).

The prolonged GID frequency was significantly higher in patients with moderate or severe edema (51%) in comparison to patients without or with mild edema (22.5%) (RR 2.26; 95%CI 1.36-3.72; p<0.05). The mortality rate was 53% for the group without GID, and 62% for the GID group (RR 1.17; 95%CI 0.86-1.59; non-significant).

The variables from the first 24 hours after admission, and used for the multivariate analysis, were APACHE II and SOFA scores, sepsis, vasoactive drugs use, serum lactate level and oxygenation ratio. In the logistic regression analysis, a serum lactate level above 5.2 mEq/L (RR 6.69 95%CI 1.15-38.7; $p=0.034$) and a low oxygenation ratio (RR 12.4 95%CI 2.18-70.8; $p=0.005$) were predictive of GID.

DISCUSSION

GID is a relevant medical condition in ICU patients. It is associated with longer stays and probably increased mortality.⁽⁶⁾ Our results have shown that prolonged GID is largely prevalent in a heterogeneous intensive care patients population. As anticipated, it was more frequent in surgical versus medical patients, and was associated to infection and longer hospitalizations. We detected high admission serum lactate levels and low oxygenation ratios as independent predictors of GID. In addition, moderate or severe bodily edema patients had a two fold GID prevalence.

The 35% prolonged GID prevalence found in our series including surgical and medical patients who stayed in the ICU for longer than 4 days, is similar to the findings of other studies in severely ill patients. In enteral nutrition patients staying in a mixed ICU, 32% of them had enteral diet intolerance (high gastric residue), which was an independent predictor of nosocomial pneumonia, longer ICU stay and increased mortality.⁽¹²⁾ In a mixed mechanical ventilation patients population, the authors identified GID, signs of enteral diet intolerance and/or signs of intra-abdominal hypertension in 58.3% and 27.3%, respectively.⁽⁹⁾ These rates were reduced in lower risk populations. A prospective multicenter Brazilian study in 21 ICUs used the same definition as we used in this study, and showed prolonged GID as the third most frequent post-operative complication in non-heart major surgeries, in 8% of the patients.⁽¹³⁾ Gastrointestinal complications were seen in only 2.5% of heart surgery patients.⁽¹⁴⁾

Serum lactate levels above 5.2 mEq/L increased by almost 7 times the risk of GID. High admission lactate levels suggest shock, although moderately increased lactate levels may be seen in already appropriately resuscitated severe sepsis patients.⁽¹⁵⁾ Accordingly, the presence of acidosis, diagnosed based on base excess and pH, tissue perfusion indicators, in addition to prolonged surgery time and large blood losses, were associated with GID in elective midsize surgery.⁽¹⁶⁾ GIT mucosa is particularly

sensitive to blood flow or oxygenation changes. This is due to peculiar microcirculation architectural features, presenting a complex network where arterioles and effluent venules proximity at the vilum base may result in a diffusion shunt from arterioles to venules, subjecting the vilum tip to hypoxia.⁽¹⁷⁾ Maintenance of the blood flow is the most relevant aspect to keep intestinal oxygen consumption.⁽¹⁸⁾ This set of data suggests that tissue perfusion is a relevant point for development of GID, in agreement with several physiological studies.⁽¹⁸⁻²¹⁾

A low admission oxygenation index, i.e., lower than 200 PaO₂/FiO₂, increased the risk of GID by more than 12 times. Acute lung injury (ALI) is a common cause for ICU admission, and was seen in 42% of the patients within the first 48 hours following admission.⁽²²⁾ In this study involving 1,038 patients in a medical-surgical ICU, ALI was associated with increased rates of infection, severity, cardiovascular dysfunction and longer mechanical ventilation, vasopressor drugs use and renal replacement therapy. ALI correlates with the injury and inflammatory response degrees, as indicated by higher C reactive protein levels in these patients.⁽²²⁾ There are several indications from experimental trials that intestinal lesions may take place few hours after tracheal bacteria instillation or endotoxins injection.⁽²³⁾ Our studies suggest that GID is part of the spectrum of organs affected in systemic inflammatory response syndromes and MODS, and should be valued in future trials.

Gastrointestinal complications prevalence, particularly a longer post-GIT surgery time to intestinal function recovery, increases proportionally with the amount of fluids given, and weight increase.⁽²⁴⁻²⁶⁾ In our study, moderate or severe bodily edema was evaluated as indicative of positive fluid balance. In our series, prolonged GID frequency more than doubled in patients with moderate or severe bodily edema. Edema reflects a local rupture of the relationship which keeps fluids within the intravascular space, and is almost always associated with a positive water and sodium balance, and increased weight. Hypoalbuminemia has been associated with prolonged gastric emptying and intestinal transit times, and post-operative ileum.⁽²⁷⁾ It is unknown whether the effect is due to hypoalbuminemia *per se*, or a result of the positive fluid balance, as these conditions are difficult to be distinguished.

Erosive and/or hemorrhagic esophageal or gastric mucosa lesions were seen in three quarters of the endoscopies. In other studies, these lesions were described in 24% to 100% of critical patients' procedures within the first 24 hours after ICU admission.⁽²⁾ As main GIT

lesions triggering mechanisms, cell hypoxia and inflammatory mediators release, apoptosis and necrosis, specially in sepsis, in addition to acid and pepsin secretions changes are discussed.^(28,29)

This study has several limitations, but probably the most important regards the lack of a more objective GID definition.⁽⁹⁾ However, the data available are still controversial; there is no consensus on this subject, and no objective measurements are available. In our definition were included physical examination data and information related to enteral or oral diet tolerance. The retrospective design has limited the analysis of important data, such as fluid balance and the impact of drugs which may influence the intestinal transit, such as morphine derivatives or prokinetic drugs. The sample size and the single center design, and being a medical-surgical ICU also suggest that these results couldn't likely be applicable for other ICUs. Nevertheless, our data are important as draw attention to GID increased prevalence and impact, and risk factors.

Hypovolemia, and consequent tissue hypoxia are correlated with the multiorgan dysfunction syndrome (MODS). However, fluids excess is also harmful. In an intestinal ischemia animal model, a larger volume replacement with Ringer versus smaller volumes of crystalloid and colloid solutions determined significant drop in colloid osmotic pressure and more intestinal edema.⁽³⁰⁾ In surgical patients, studies comparing more restrictive fluid strategies during colorectal surgery have demonstrated reduction in the number of complications, and a shorter mean time for flatus and stools elimination start.⁽²⁴⁻²⁶⁾ On the other hand, in high-risk patients, target driven post-operative hemodynamic optimization has shown improved gastric mucosa acidosis, and reduced post-operative gastrointestinal complications.⁽³¹⁻³⁴⁾ In view of the GID impact on the clinical outcomes and costs, studies should be encouraged on this subject. Multi-modal approaches, including measures to reduce the mechanic trauma, early mobilization and enteral feeding, more accurate volume replacement and treatment of shock with visceral region monitoring should be investigated in prospective multicenter trials.

CONCLUSION

For the exposed, we conclude that prolonged gastrointestinal tract dysfunction is highly prevalent in this

heterogeneous intensive care patients' population. Admission high serum lactate levels and oxygen ratio below 200 were predictive of gastrointestinal tract dysfunction.

RESUMO

Objetivos: Em pacientes gravemente enfermos, enquanto as disfunções de outros órgãos ou sistemas são rapidamente progressivas, os sinais de disfunção do trato gastrointestinal são frequentemente sutis e pouco valorizados. Contudo, a região esplâncnica tem muito provavelmente um papel importante no desenvolvimento e ou manutenção da resposta inflamatória e disfunção de múltiplos órgãos e sistemas. O objetivo deste estudo foi avaliar a prevalência e os fatores preditivos de disfunção prolongada do trato gastrointestinal.

Métodos: Estudo de coorte, retrospectivo e observacional. Foi realizado na unidade de terapia intensiva clínico - cirúrgica de 24 leitos de um hospital universitário. Foram incluídos todos os pacientes entre agosto de 2003 e janeiro de 2004 e que tiveram tempo de permanência na unidade de terapia intensiva superior a 4 dias. A função do trato gastrointestinal foi avaliada diariamente de acordo com uma classificação que considera o exame físico (presença ou ausência de ruídos hidro-aéreos ou distensão) e o nível e tipo de suporte nutricional ofertado.

Resultados: Foram incluídos 128 pacientes. A média de idade foi até 56 ± 19 anos, 81 pacientes (63,3%) eram do sexo masculino e 91 pacientes (77,3%) cirúrgicos. Disfunção do trato gastrointestinal prolongada ocorreu em 35 % dos pacientes, com uma prevalência 3,3 vezes maior em pacientes cirúrgicos (27%) do que em pacientes clínicos (8%). Em 38 pacientes (29,7%) foi realizada endoscopia digestiva alta. Lesões erosivas e/ou hemorrágicas foram observadas em $\frac{3}{4}$ do total das endoscopias digestivas altas. A frequência de disfunção do trato gastrointestinal foi significativamente mais alta em pacientes com edema moderado a grave (51%) do que em pacientes sem edema (22,5%) ($p < 0,05$). Na análise de regressão logística, uma concentração sérica de lactato na admissão acima de 5.2 mEq/L (RR 6,69 IC 95% 1,15-38,7, $p = 0,034$) e um índice de oxigenação inferior a 200 (RR 12,4 IC 95% 2,18-70,8, $p = 0,005$) foram preditivos de disfunção do trato gastrointestinal.

Conclusões: Disfunção do trato gastrointestinal prolongada foi altamente prevalente nesta população heterogênea de pacientes de terapia intensiva. Níveis séricos elevados de lactato e índice de oxigenação inferior a 200 na admissão foram preditivos de evolução com disfunção do trato gastrointestinal.

Descritores: Trato gastrintestinal/patologia; Doenças gastrintestinais; Insuficiência de múltiplos órgãos; Lactato; Íleo

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