Cell-free deoxyribonucleic acid as a prognostic marker of bowel ischemia in patients with small bowel obstruction

Uri Netz, MD,[a,d] Zvi Perry, MD,[a,d] Solly Mizrahi, MD,[a,d] Boris Kirshtein, MD,[a,d] David Czeiger, MD, PhD,[b,d] Gilbert Sebbag, MD,[b,d] Avraham Reshef, MD,[b,d] *and* **Amos Douvdevani, PhD,[c,d]** *Beer-Sheva, Israel*

Background. *Patients with strangulation small bowel obstruction are at a high risk for serious morbidity and mortality due to ischemic bowel. Measuring serum, cell-free deoxyribonucleic acid levels could help recognize early cell death. Our hypothesis was that small bowel ischemia or necrosis is associated with increases in serum cell-free deoxyribonucleic acid and that recovery is associated with a decrease in cell-free deoxyribonucleic acid levels.*

Methods. *A prospective cohort study in addition to standard treatment of patients admitted with a diagnosis of small bowel obstruction. The participants were divided into groups depending on the presence of ischemic or necrotic bowel according to operative and clinical outcome. Clinical data and serum-based cell-free deoxyribonucleic acid levels were compared. Cell-free deoxyribonucleic acid levels from these 2 groups also were compared with a third group of healthy controls.*

Results. *In the study, 58 patients were enrolled, and 18 patients (31%) underwent operation. During the operative procedure, ischemic or necrotic bowel was found in 10 cases (17%). Serum levels of cell-free deoxyribonucleic acid at the time of admission in the ischemic/necrotic bowel group were increased compared with patients with well perfused or spontaneously recovered bowel (*$P = .03$*). Cell-free deoxyribonucleic acid levels decreased on the day after admission in 88% of the nonoperated patients. No significant differences were found in demographics, medical background, imaging performed, and cause of obstruction nor in clinical admission data.*

Conclusion. *Surgeons currently rely on imprecise clinical parameters, including degree of pain, abdominal tenderness, leukocytosis etc to decide when operative intervention is needed. The association of cell-free deoxyribonucleic acid with small bowel obstruction, ischemia, and recovery supports our hypothesis and suggests that this biomarker is a potential surrogate of small bowel perfusion. (Surgery 2017;■:■-■.)*

From the Departments of Surgery A,[a] B,[b] and Clinical Biochemistry and Pharmacology,[c] Soroka University Medical Center; and Faculty of Heath Sciences,[d] Ben-Gurion University of the Negev, Beer-Sheva, Israel

Patients with small bowel obstruction (SBO) can be divided into those with a simple obstruction, and those with a strangulation obstruction. Simple SBO involves mechanical blockage of luminal contents without compromise of the vascular perfusion of the small bowel (SB). In contrast, strangulation obstruction usually involves a closed loop with a compromised vascular supply, and can lead ultimately to SB ischemia and necrosis.[1] Strangulation is associated with increased morbidity and mortality, stressing the importance of early recognition and early operative intervention. To differentiate between simple and strangulation obstruction, parameters, such as tachycardia, fever, leukocytosis, increased blood lactate, and unrelenting pain, have been considered indicative of strangulation SBO. Addition of imaging studies, especially abdominal computed tomography (CT), increases the likelihood of early

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Reprint requests: Uri Netz, MD, Department of Surgery A, Soroka University Medical Center POB 151, Beer Sheva, 84101. E-mail: urinetz@gmail.com.

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recognition of patients requiring urgent intervention[2,3]; however, despite this ability, an accurate and timely diagnosis still is elusive. In addition, current clinical and basic laboratory parameters do not identify strangulating obstruction accurately.[4,5] Accordingly, one must understand that a calculated risk is being taken with a possible avoidable delay in operative treatment when patients are treated conservatively or when operative intervention is delayed.

Strangulation SBO is a complex clinical problem with regard to diagnosis, timing, and type of treatment. Considering this, there is an ongoing interest in biomarkers of bowel ischemia that may improve the decision-making process. Some serologic markers have correlated with strangulation obstruction, such as intestinal fatty acid binding protein[6] and histidine decarboxylase.[7] To date, these markers have shown mixed results and are expensive, time-consuming impractical tests. Another marker, procalcitonin (PCT),[8] also has been shown to be associated with strangulation obstruction. PCT is generally a sensitive marker of infection and inflammation; however, PCT is not specific for bowel nor to recognize necrosis and apoptosis,[9] its half-life is very long (24 hours), and its serum levels probably will remain increased after successful, nonoperative intervention.

Cell-free deoxyribonucleic acid (cfDNA) has the potential to be a good biomarker for SBO. CfDNA is DNA that has been released into the circulation after cellular necrosis, apoptotic cell death, and inflammatory reactions. In contrast to PCT, cfDNA has a short half-life of 15 minutes and its concentration may be a real-time integrative reflection of the degree of inflammation, necrosis, and/or apoptosis. Recent published data demonstrate an increase of serum cfDNA in autoimmune and cardiovascular diseases, cancer, and trauma.[10-12] Studying patients with myocardial infarction, Shimony et al[13] demonstrated that increased serum levels of cfDNA correlated with established markers of myocardial necrosis. Other studies have shown a correlation between cfDNA levels and mortality from traumatic head injury[14] and sepsis.[15]

A sensitive, rapid, direct fluorescent assay has been developed for quantifying cfDNA levels in biologic fluids.[16] This rapid, simple, and inexpensive assay has been used successfully in several animal and human studies.[17-19] Because of the difficulty in recognizing closed loop obstruction requiring operative intervention, measuring cfDNA levels in the blood of patients with SBO could help identify early cell death and could be used as an additional tool in the decision of whether or not to operate on a patient with a SBO.

The aim of this study was to evaluate blood levels of cfDNA as a prognostic biomarker for patients admitted with a diagnosis of SBO. Our working hypothesis was that small bowel necrosis causes cfDNA levels in peripheral blood to increase and that recovery from SBO is associated with a decrease in cfDNA levels.

MATERIALS AND METHODS

Data were collected prospectively from patients with a diagnosis of SBO admitted to both general surgery departments at Soroka University Medical Center, Beer-Sheva, Israel during the years 2014–2015. Patients with both partial and complete SBO were included in the study.

Exclusion criteria included patients with large bowel obstruction, active malignant or infectious disease, severe chronic diseases, abdominal wall hernias that reduced spontaneously immediately after initial treatment in the emergency room (morphine administration, nasogastric tube insertion, urinary catheter placement), and patients who could not give informed consent (dementia, decreased level of consciousness, etc).

The study was approved by the institutional review board of Soroka University Medical Center (0173-12-SOR). Written informed consent was obtained from each participant.

This was a prospective cohort study. All patients with SBO were treated according to generally adopted parameters, and operative treatment was pursued in accordance with the Bologna guidelines for diagnosis and management of SBO[20] and attending physician discretion. The treating staff was blinded to cfDNA levels during patient hospitalization, so as not to affect treatment decisions.

Collected data included patient demographics, past medical and operative history, imaging data, degree of obstruction (partial versus complete), etiology of obstruction, admission clinical and laboratory data, and inpatient management and outcomes.

The participants were divided into groups depending on the presence of ischemic or necrotic bowel according to operative and clinical outcome. Group 1 included patients in whom ischemic or necrotic bowel was identified during operation. Patients who recovered without requiring operative intervention or in whom well-perfused bowel was found during operation were included in group 2. Data were compared between groups. To establish a baseline, cfDNA levels from these 2