E-ISSN: 3068-5052
Journal of Regenerative Medicine & Biology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Research Article

Peritoneal FGF-2 as a Potential Marker for Traumatic Gastrointestinal Tract Injury

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Citation: Trinh SM, et al. Peritoneal FGF-2 as a Potential Marker for Traumatic Gastrointestinal Tract Injury. J Reg Med Biol Res. 2025;6(2):1-4.

https://doi.org/10.46889/JRMBR.2025.6207

Received Date: 01-07-2025

Accepted Date: 04-08-2025

Published Date: 11-08-2025

Abstract

Timely recognition of traumatic gastrointestinal tract injuries present a diagnostic challenge. Accurate diagnosis often relies on operative intervention, which harbors risks to the patient and also can be challenging for certain injury patterns. Identifying biomarkers to aid the surgeon in the prompt recognition of traumatic gastrointestinal injuries can facilitate faster diagnosis and adequate management. This study presents data from the peritoneal fluid of 14 trauma patients. A decrease in the level of Fibroblast Growth Factor-2 (FGF-2) in the post-trauma period, a cytokine associated with intestinal stem cell proliferation, might indicate the absence of a traumatic gastrointestinal tract injury. Further research is needed to determine whether peritoneal FGF-2 can be a biomarker to aid in the detection of gastrointestinal tract injuries in trauma patients.

Keywords: Trauma; Gastrointestinal Tract Injury; Peritoneal Fluid

Introduction

Traumatic Gastrointestinal Tract Injuries (GITI) can lead to significant mortality and morbidity when unrecognized1. Timely diagnosis and adequate surgical intervention can be life-saving. Once the necessity of surgery has been established, the patient can either undergo definitive surgical treatment or if the patient is hemodynamically unstable, a Damage Control Laparotomy (DCL) can be performed to explore the abdomen and implement temporizing measures to aid recovery. The decision to perform a DCL must be weighed against the risks of an open abdomen if performed unnecessarily [2]. There is an increased risk of complications such as enterocutaneous fistulae, infections and hernias. Identifying reliable quantitative markers to assess the presence of GI injury can help stratify patients and guide clinical decisions for trauma patients in extremis.

Peritoneal fluid analysis is emerging as a potential tool in the surgeon's armamentarium to understand the dynamic microenvironment of growth factors, cytokines and chemokines in response to stressors such as traumatic injuries and surgery. Monitoring the cytokine response in the peritoneum following trauma may aid the surgeon in evaluating the extent of injury and the associated inflammatory response. If further research can identify peritoneal markers that correlate with different types of abdominal injuries, peritoneal fluid sampling may also be performed during the initial phase of a DCL to provide diagnostic clues. This study aimed to explore the patterns of cytokine responses to traumatic GITI in order to identify significant trends that could facilitate clinical decision-making. We hypothesized that the presence of Fibroblast Growth Factor-2 (FGF-2) in the post-trauma period, a cytokine associated with intestinal stem cell proliferation, may provide important diagnostic information.

Methods

Adult trauma patients who underwent DCL for trauma were included in the study. Peritoneal fluid was collected during the index Laparotomy Procedure (IP) and the subsequent Takeback operation (TB). Institutional Review Board approval (IRB) was obtained from Louisiana State University Health Sciences Center. All patients or their legally authorized representatives were consented to participate in the study and HIPAA authorization was obtained.

Cytokine concentrations in the peritoneal fluid were analyzed using the MILLIPLEX® MAP Human Cytokine/Chemokine/Growth Factor Panel A (HCYTA-60K-PX48, Merck Life Science, LLC, Darmstadt, Germany) multiplex assay, according to the manufacturer's protocol. Patients were stratified into GITI and non-GITI groups to compare cytokine concentrations from the IP, TB and the change between the two procedures [change (Δ) = IP - TB], where Δ was compared to zero. Statistical analyses were performed using the Mann-Whitney U test, Wilcoxon's signed rank test and Pearson's chi-square test. A p value <0.05 was considered to be significant. Data was analyzed using Statistical Package for Social Sciences, version 29.0.1.0 for Macintosh (IBM Inc, Armonk, NY).

Results

Fourteen patients were enrolled (GITI: n=7, non-GITI: n=7). No significant differences in age, gender, mechanism of injury or body mass index were observed between the two groups ($p > 0.05$). Four patients in the GITI group experienced wound complications, compared to none in the non-GITI group ($p = 0.05$). A statistically significant decrease in Fibroblast Growth Factor 2 (FGF-2) concentrations was observed between the initial and takeback operations in the non-GITI group (ΔnGITI = 1121 pg/mL; $p = 0.016$), indicating a significant change over time within the group (Table 1,Fig 1). This could indicate that in the absence of GI trauma, the FGF2 concentration in the peritoneal fluid should be expected to decrease. In other words, the absence of a downward trend in the peritoneal fluid FGF-2 level quantification could point towards the presence of a possible GI tract injury [1-4].

Cytokine	N	nGITI (pg/mL)	N	GITI (pg/mL)	p-value
At initial laparotomy					
IL 6	7	3758 (1771,13707)	7	6833 (4458,13372)	0.160
IL 1-beta	7	72.6 (7.5,2431)	7	112 (65.2,3540)	0.443
IL 8	7	1990 (71.1,12510)	7	8381 (750,13350)	0.443
IL 4	6	52.7 (0.2,3612)	6	38.1 (0.1,112)	0.575
IL 10	7	295 (29.3,1419)	7	1039 (383,5448)	0.074
FGF-2	7	1745 (511,4619)	7	3033 (700,5411)	0.898
MCP-1	7	5820 (4867,9623)	7	6822 (5297,9425)	0.443
VEGF	6	93.8 (6.5,358)	7	204 (101,510)	0.175
At first takeback to the OR					
IL 6	7	5091 (204,10201)	7	7703 (4205,14361)	0.055
IL 1-beta	7	85.8 (1.7,1480)	7	455 (98.4,2681)	0.097
IL 8	7	8859 (948,11014)	7	9557 (7651,13256)	0.443
IL 4	6	38.7 (0.1,2794)	7	4.0 (0.3,199)	0.617
IL 10	7	132 (7.8,725)	7	636 (5.8,1271)	0.125
FGF-2	7	624 (65.6,2307)	7	915 (279,3659)	0.250
MCP-1	7	5602 (1731,6810)	7	6752 (5477,8775)	0.074
VEGF	7	233 (9.7,314)	6	377 (137,2278)	0.074
Δ (Initial - Takeback)					
IL 6	7	1406 (-3466,4598)	7	98 (-7529,2486)	0.443
IL 1-beta	7	3.5 (-1021,2429)	7	-102 (-2577,1913)	0.799
IL 8	7	-2440 (-9543,9548)	7	94 (-11174,1175)	0.702
IL 4	6	29.1 (-17.8,817)	6	-1.5 (-113,64)	0.174
IL 10	7	8 (-363,1345)	7	663 (-732,4177)	0.160
FGF-2	7	**1121 (446,3399)**	7	723 (-2011,5100)	0.609

MCP-1	7	888 (-735,3790)	7	52.8 (-754,2214)	0.250
VEGF	6	-20.4 (-239,199)	6	-224 (-2158,363)	0.379
Δ=0					
IL 6		0.469		0.688	
IL 1-beta		0.938		0.813	
IL 8		0.688		0.578	
IL 4		0.156		0.563	
IL 10		0.578		0.109	
FGF-2		0.016		0.156	
MCP-1		0.156		1.000	
VEGF		0.844		0.313	
GITI: Gastrointestinal Tract Injury; nGITI: no Gastrointestinal Tract Injury; FGF-2: Fibroblast Growth Factor- 2; MCP-1: Monocyte Chemoattractant Protein-1; VEGF: Vascular Endothelial Growth Factor					

Table 1: Median cytokine concentrations (min,max) of patients in the Gastrointestinal Tract Injury (GITI) and nGITI (no GITI) groups.

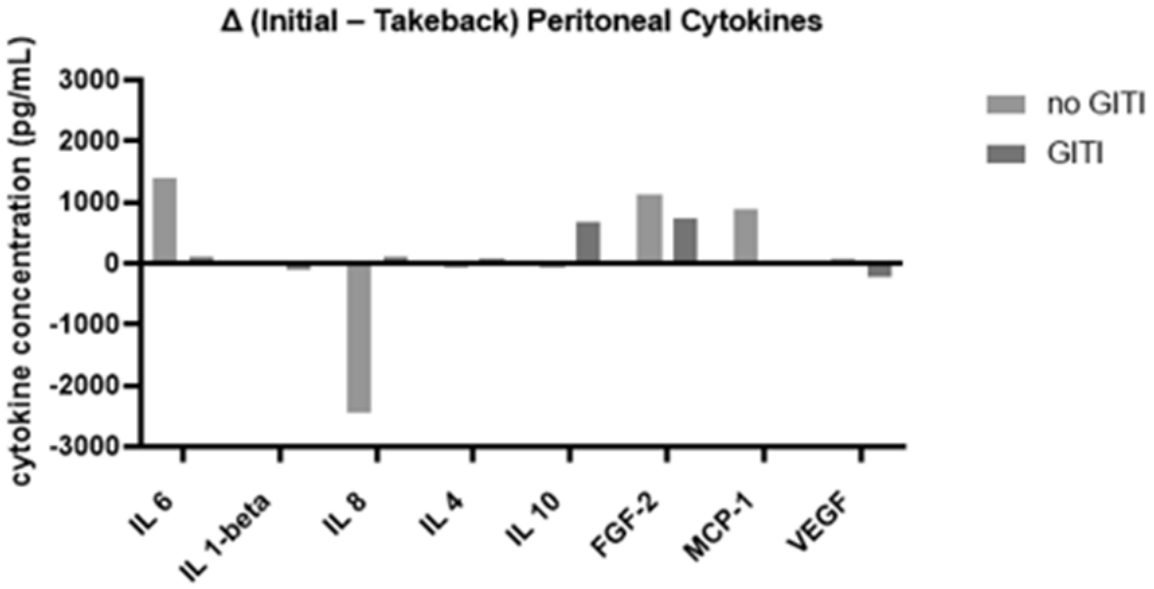

Figure 1: Change in cytokine concentrations between the initial procedure and the takeback [change (Δ) = IP - TB]. GITI: Gastrointestinal Tract Injury; nGITI: no Gastrointestinal Tract Injury; FGF-2: Fibroblast Growth Factor- 2; MCP-1: Monocyte Chemoattractant Protein-1; VEGF: Vascular Endothelial Growth Factor.

Discussion

FGF-2 enhances intestinal stem cell survival following radiation injury and has been shown to maintain intestinal stem cells in a pluripotent, undifferentiated state *in-vitro* [3]. FGF-2 has also been identified as the initiator and key driver of intestinal healing across various types of injury [4]. Our study identified a significant decrease in peritoneal FGF-2 concentrations in the no GITI group between the initial and takeback operations amongst patients who underwent DCL. This decrease might be an indication of a reduced need for intestinal regeneration in these patients.

The reduction in peritoneal FGF-2 levels over time could potentially serve as a marker to rule out GI Injury. Future studies with larger sample sizes and a longer evaluation period may provide enough data to support the utility of FGF-2 levels as a diagnostic tool. This could pave the way for less invasive methods such as peritoneal fluid aspirations to rule out GI tract injury in patients who would otherwise require laparotomies.

To establish FGF-2 as a clinical tool, a physiologic range for FGF-2 and how it is impacted by environmental and individual factors, such as alcohol consumption, diabetes and presence of infections, need to be determined. A major limitation of our study is that FGF-2 were obtained following trauma and there was not a baseline level for these patients. Future studies could monitor FGF-2 over a longer period of time, preferably until complete anatomical recovery is reached. Additionally, assays with higher sensitivities such as Enzyme Linked Immunosorbent Assays (ELISA) can be performed to eliminate the potential interference from cross reacting chemicals. Future studies should also monitor blood FGF-2 concentrations over time and determine the relationship between blood and peritoneal fluid FGF-2 levels.

In conclusion, a decrease in peritoneal fluid FGF-2 levels in trauma patients might suggest an absence of GI tract injuries. If further studies confirm the sensitivity of FGF-2 as a clinical marker in abdominal trauma, it could potentially aid in the prompt recognition of injuries in need of urgent treatment.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate

Not applicable.

Declaration

We hereby declare that no artificial intelligence technology or software was used in the creation, drafting or editing of this literature review and that all the information contained in this literature review was created using information from credible sources in my own words, without deliberately plagiarizing information from said sources.

Funding

None.

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