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Is scurvy a 21st century diagnosis? Implications on surgical patients

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Abstract

Objective: Scurvy, vitamin C deficiency, is seldom reported in the modern era. We sought to determine the morbidity and mortality of gastrointestinal surgery in patients with scurvy.

Methods: Patients admitted to Indiana University Health University Hospital between 2012-2013 who underwent surgery and were identified to have scurvy (serum vitamin C≤1.0 mg/dL), were included in this study. Data regarding demographics, surgical procedures, post-operative course, and relevant biochemical markers were collected and a descriptive analysis was performed using SPSS version 15®.

Results: Nineteen patients were included in this study; median age was 65 years. Diagnoses included GI tract malignancy (31%), pancreatic necrosis (26%), and debridement of decubitus ulcers (11%). All patients were of poor functional status (ECOG score≥3) and had protracted hospital courses (median length of stay for index admission was 14 days). Morbidity included superficial/deep surgical site infection (52%), organ space infection (63%), and post-operative fistulae (52%). Multiple (≥2) readmissions were seen in 14 patients (73%). Excluding scurvy, biochemical markers indicative of poor nutrition were also present in all 19 patients and these included: albumin ≤3.0 mg/dL (78%), deficiencies of vitamin A (16%), vitamin B (16%), vitamin D (26%), zinc (37%), and magnesium (11%). Of these, a feeding jejunostomy was used postoperatively in 10 patients (58%). The median follow up period for this study was 15 months.

Conclusion: Scurvy was found in a contemporary series of surgical patients. Scurvy was frequently associated with other vitamin (A, B, D) and micronutrient (Zn, Mg) deficiencies. Therefore, patients with scurvy after major surgery, are prone to infectious complications and fistulae, should be aggressively screened and treated preoperatively for vitamin C and other nutrient deficiencies in order to decrease severe surgical morbidity and readmissions.

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Introduction

Scurvy, first described by Hippocrates in 4th century BC is a state of vitamin C avitaminosis. This was a cause of significant morbidity and mortality in the 18th and 19th centuries. After the pioneering work of James Lind and others investigating the etiopathogenesis and treatment of scurvy, there has been a significant reduction in the incidence and outlook after diagnosis [1]. Furthermore, recent National Health and Nutrition Examination Surveys (NHANES) have indicated that between 1988 and 2004 the incidence of scurvy has declined stepwise from 14% to 3% [2,3]. This has created a sense of security with regards to vitamin C deficiency, and a relative lack of interest in scurvy, which is hence seldom reported in the current era.

Populations at risk for vitamin C deficiency include those consuming fad diets, mentally challenged, and institutionalized individuals. Another high-risk population includes cancer patients [4)]. Cancer associated dysphagia, dysgeusia and abdominal pain can lead to decreased oral intake, lack of enteral nutrition, and GI mucosal atrophy; this can lead to decreased absorption, and increased energy expenditure are some of the mechanisms that result in avitaminosis C. After major gastrointestinal surgery, patients experience some of the same risk factors. However, there are no reports concerning the association of vitamin C and post-operative morbidity and mortality in patients after major surgery. Therefore, the aim of this study was to describe the post-operative morbidity, mortality, and nutritional parameters, in patients diagnosed with scurvy who underwent major gastrointestinal surgery at a quaternary academic medical center.

Materials and methods

The National Surgical Quality Improvement Program patient repository at Indiana University Health-University Hospital was queried for patients who underwent surgery between 2012-2013 and had a serum vitamin C level ≤ 50 µmol/L. This time period correlated with the increased recognition of nutritional and/or vitamin/micronutrient deficiencies, but just prior to the creation of the preoperative screening program in the outpatient setting for nutritional disorders. The patients in this series were suspected and thus underwent a biochemical analysis that confirmed the diagnosis. A review of electronic medical records was conducted to review laboratory parameters, operative notes, discharge summaries, and pertinent notes. These data were transformed into a dataset with demographic data, operative details, post-operative morbidity, mortality and follow up information.

Statistical analysis

The patient data were analyzed in a descriptive pattern. All variables were defined as either continuous or categorical. Age at diagnosis, length of hospital stay, serum albumin, and serum vitamin C were deemed continuous variables. The diagnoses, surgical procedure performed, presence of associated deficiency of vitamin A, D, E, zinc, magnesium, calcium, need for feeding jejunostomy, post-operative enterocutaneous fistula, superficial or deep surgical site infection, organ space infection, post-operative pneumonia, post-operative acute renal failure, and immediate post-operative death (≤30 days) were labelled as categorical variables and analyzed across the entire dataset.

A subset analysis was also performed. The entire dataset was divided into three subsets using the serum prealbumin concentrations. A cut-point of ≥10 mg/dL was determined to identify the best division of patients concerning protein malnutrition. The above descriptive analysis of post-operative morbidity was repeated in the highest subgroup of patients with regards to serum prealbumin concentrations. Mean and median values were calculated. Group comparisons were made with the t-test of means, and χ^2 test as appropriate, and $p<0.05$ was used as a test of significance. All data were analyzed in SPSS version 15.0 software (SPSS Inc, Chicago, IL). All components of this study were approved by the Indiana University School of Medicine Institutional Review Board.

Results

Patient characteristics

During the study period 21 patients were found to have vitamin C deficiency. There was one immediate post-operative death. This was caused due to a technical complication of placing a central line and was otherwise unrelated to the surgical procedure. Additionally, very little data was available for analysis in one other patient and these were both censored from the study population. Nineteen patients were therefore included in the final analysis (Table 1). Of the nineteen patients who were included in this study, 12 (63%) were female. The median age of the patient population was 65 years. The median length of stay in the hospital for these patients was 14 days following the index surgical procedure.

Diagnoses and surgical procedures performed

The patients in this analysis were heterogeneous concerning their diagnoses and these patients underwent diverse major operations. Indications for surgery (Table 2) included colon adenocarcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, and pancreatic necrosis.

The surgical procedures performed (Table 3) included procedures such as regional and total pancreatectomy, splenectomy, abdominal wall reconstruction, colectomy, and colonic diversion with decubitus ulcer debridement. This dataset therefore consisted of a heterogeneous patient population (Figure 1) having undergone a wide variety of surgical operations.

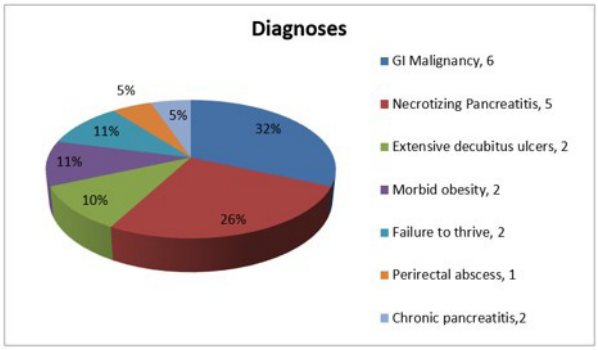

Figure 1: Surgical diagnoses for patients with scurvy. This figure illustrates the varied diagnoses of patients with scurvy who underwent major surgery at an academic referral center.

Nutritional parameters

All patients in this study population had biochemical parameters indicative of poor nutrition. A majority of the patients in this population had protein malnutrition. The majority (78%) of patients had an albumin level less than 3.0 mg/dL and a corresponding median serum albumin concentration was 2.9 mg/dL. Importantly, the median best prealbumin at the time of surgery was 9 mg/dL demonstrating the overall protein-depleted state in these patients (Table 4).

In addition to hypovitaminosis C, there were deficiencies of other vitamins in excess to that prevalent in the general U.S population. Of the patients, 16% each had deficiencies of vitamin A, and B, and 26% had deficiencies of vitamin D. Finally, deficiencies of micronutrients were also noted in this patient population; Manganese and Zinc deficiencies were seen in 11% and 37% of the patients respectively (Table 4). Therefore, the patients in this study not only had other vitamin deficiencies associated with hypovitaminosis C, but also had evidence of protein malnutrition and micronutrient deficiencies.

Post-operative morbidity

A large number of patients in this population had post-operative morbidity resulting in multiple readmissions. The overall morbidity was 84%. The median number of readmissions was 4 and the majority (73%) had more than two readmissions.

More than half of the patients in this population had infectious complications after surgery. These included both superficial/deep Surgical Site Infection (SSI) (52%) and Organ Space Infection (OSI) (63%) (Table 5). These patients had poor pre-operative nutritional status leading to a 58% of patients requiring a feeding tube for alimentation after surgery. Furthermore, 59% of these patients had a clinically relevant fistula from the surgical procedure performed, which included pancreatic fistula, chyle leak, or enterocutaneous fistula (Table 5). Finally, there was an increased incidence of post-operative non-surgical site morbidity such as pneumonia and acute renal insufficiency in 11% each.

The dataset was then divided using the serum prealbumin concentration with a cut point of >10 mg/dL as being of better nutrition. We then reanalyzed the subset of patients in order to identify whether the high rates of post-operative morbidity were the result of protein malnutrition or low vitamin C levels (Table 5). Our analysis indicated that patients with good pre-operative nutrition also had a high rate of post-operative morbidity; all patients had at-least one complication. There were no significant differences between the two populations with regards to incidence of readmissions, SSI, OSI, post-operative fistula, pneumonia, and renal failure. However, as expected, patients in the subgroup with prealbumin ≥ 10 mg/dL were less likely to have undergone the placement of a feeding tube. Only 33% of the patients required the placement of a feeding tube compared with 58% in the entire population, p=0.02.

Discussion

Vitamin C has largely been ignored in the past few decades in the surgical community. This may have been a result of our more detailed understanding of the mechanisms and physiologic functions of vitamin C. This manuscript demonstrates that patients can have clinically significant vitamin C deficiency. These patients have high rates of protein malnutrition, post-operative infectious and non-infectious morbidity.

The patients were predominantly older with age and gender distribution comparable to those in contemporary series of patients susceptible to vitamin C deficiency [5]. This was a heterogeneous dataset consisting of varied diagnoses and having undergone major general surgical procedures. The relative importance of vitamin C affect wound healing and immune responses regardless of the type of surgery performed, the heterogeneous group of patients makes the results of our analysis more readily applicable.

All patients had nutritional markers of poor nutrition. Although the initial inclusion criteria for this study were low levels of vitamin C, all nineteen patients had additional markers of poor nutrition, namely albumin and prealbumin. The majority (80%) patients in this study had a low albumin level. In one of the largest prospective trials on preoperative risk factors for surgical outcomes, low preoperative albumin level was one of the strongest risk factors for post-operative complications [6]. A large inflection point in the rate of 30-day mortality was noted at a serum albumin level <3.0 mg/dL, which was the cut-off point used in this study. Moreover, this association was independently demonstrated in subsets of general, orthopedic, and thoracic surgical patients. In addition to low albumin levels, a low overall pre-operative prealbumin level was found. Although, some studies have demonstrated an inferiority of prealbumin over albumin in predicting post-operative complications after major surgery [7], prealbumin has previously been shown to be specifically associated with increased infectious complications after general and GI surgery [8]. Therefore, from a perspective of protein malnutrition, the patients in our dataset were at high risk for post-operative infectious complications after surgery.

In addition to protein malnutrition, other vitamin deficiencies were evident. The prevalence of deficiencies in vitamin A and vitamin B in the general US population is <1% and 8% respectively [3]. The deficiencies of the corresponding vitamins in this dataset were much higher than the population at large. Similarly, 25% of patients were deficient in vitamin D in this study as compared to 8% for the general US population. Furthermore, the deficiency of zinc was four times more prevalent compared to the general US population. Therefore, patients with scurvy were significantly more likely to have protein, vitamin, and micronutrient deficiencies.

A large proportion of these patients suffered a major or minor complication resulting in a high readmission rate. 75% of patients were readmitted at least two times, which is significantly higher in comparison to readmission rates reported between 5-15% for general surgery patients [9-10]. This is high even when compared with a readmission rate of 13% for small/large intestine surgery and 16% for HPB surgery [9]. The discrepancy in readmission rate in this study with our institutional data appears to be in stark contrast to each other. This fact may be directly attributable to the especially poor nutritional status seen in patients with scurvy.

The most common reason for readmission was wound and infectious complications and more than half of the patients in this study faced surgical site infections and wound complications. Large academic referral centers have reported superficial and deep SSI in a wide range. The incidence of SSI ranges from 5-45% [11,12]. SSI after elective abdominal surgery have been reported to be between 11-26% [13]. Peri-incisional moisture skin damage in many cases greatly contribute to this incidence [14]. Yet, the prognostic factors for organ space infection also include poor albumin, prealbumin, other nutritional deficien-

cies, and complex GI surgery, all of which were present in this patient population. The deficiency of vitamin C in these patients likely contributed to the post-operative morbidity.

Wound disruption can present in the form of fistula formation. Examples of these include colonic anastomic leak, pancreatic fistula, chyle leak, and enterocutaneous fistula. Each of these represents the same phenomenon of wound disruption and poor tissue healing. Overall colonic anastomotic leak rates are 1-5% [15], pancreatic fistula 10– 30% [16], chyle leak after thoracoscopic or open decortication <5% [17], and enterocutaneous fistula after GI surgery <5% [18]. Although an expected total fistula rate is difficult to determine for such a heterogeneous surgical population, the relevant fistula rate in this vitamin C deficient and malnourished population was 60%. This demonstrated an alarmingly higher incidence of fistula formation than would be expected in vitamin and nutritionally replete patients. These data indicate that a population with protein and micronutrient malnutrition is exceedingly high-risk for any surgical procedure. After undergoing major surgery, these patients have almost a prohibitive post-operative complication rate including superficial/deep SSI, OSI, and fistulae formation.

These poor complication rates were observed even after controlling for prealbumin and nutritional status. The results of our analysis show that even in the higher prealbumin subgroup of patients, the incidence of post-operative superficial SSI, deep SSI, and OSI were the same. As can be expected, the only difference that was demonstrated was the decreased need for the placement of a feeding tube for nutrition. The underlying common denominator in these patients is significant vitamin C deficiency. Although our numbers do not allow us to perform multivariate analysis, this subset analysis of patients with good protein nutrition and yet poor wound and infectious outcomes indicates that vitamin C may play a more significant role in post-operative complications, than has been postulated previously. Furthermore, our analysis also indicates that the role of vitamin C nutrition may have deeper associations with poor post-operative complications than that of low albumin and/or pre-albumin levels.

It is difficult to estimate the best doses for replacement of the body's vitamin C stores before surgery. It has been estimated that the mean body pool size of adult males is 1500 mg [4]. This can be maintained with a daily intake of 100 mg. A 100% safety margin being assumed for GI losses and increased metabolism in patients with cancer, and a 50% safety margin returns a dose of 250 mg. In order to maintain vitamin C levels in the body, it has to be consumed several times during a day and dosing should be repeated between 8-12 hours. Therefore, the recommended treatment program is 250 mg IV vitamin C in 2-3 divided doses two weeks in the perioperative period. Additionally, patients after major surgery should also be discharged home with supplementation which contains vitamin C in order to maintain vitamin C levels even in the presence of decreased PO intake as is common after surgery.

Limitations of the current study are varied. The overall small sample size is a result of a retrospective review of only documented vitamin C deficiency. Likely more patients existed in the same study time period for which were not captured; subsequent to the study time period a prospective evaluation of preoperative surgical patients occurred in the outpatient setting with the confirmed treatment of deficiencies with compliance documentation. This specific data may not be applicable to procedure-specific or diagnosis-specific outcomes due to the varied diagnoses. Many of these limitations will be more readily addressed after years of prospective diagnosis and treatment of deficiencies prior to surgery.

In summary, the important finding of this study was that in addition to protein and micronutrient deficiency, there is a significant deficiency of vitamin C seen in surgical patients at a quaternary academic medical center. This deficiency is under appreciated. The prevalence of these nutritional deficiencies is significantly higher than the general population. Reasons contributing to this poor nutritional profile possibly include, dysgeusia, nausea, vomiting, lack of appetite, diarrhea, and in patients with cancer-chemotherapy and radiation therapy which also results in increased metabolic demand, and decreased intake due to the aforementioned factors.

Conclusion

1. In this series of surgical patients, Vitamin C deficiency carried a significant prevalence of protein malnutrition as well as micro-nutrient and other vitamin deficiencies.
2. Patients with vitamin C deficiency have significantly higher post-operative complication rates compared to historic controls and patients with complex general surgery procedures.
3. Subset analysis indicates that vitamin C deficiency has a significant correlation with post-operative infectious complications, even after controlling for protein malnutrition.
4. A screening program based on history, exam, and biochemical evaluation for major elective general surgery 14 days prior to anticipated date of surgery or, immediately prior to surgery in semi-elective settings will identify patients at risk. If confirmed, the recommended treatment consists of intravenous doses and then oral dosing of vitamin C in doses of 250 mg in two to three divided doses daily for two weeks pre-operative may replenish the vitamin C levels stores of the body (21*).

Tables

Table 1: Demographics of the patient population.

Parameter	Value
Demographics	
Data, n	19
Median age	65
Gender distribution, female	12 (63%)
Median length of stay	14 days

Table 2: Summary of diagnoses and surgical history.

1	Colon cancer	Right hemicolectomy, total gastrectomy, splenectomy
2	Pancreatic cancer	Total pancreatectomy, SMV reconstruction
3	Esophageal cancer	Esophagectomy at OSH with TE fistula, gastric conduit takedown, colonic interposition, multiple relaparotomy, washout, feeding jejunostomy placement, multiple revisions
4	Necrotizing pancreatitis	Pancreatic debridement in 5/2011 preceded by Whipple in 12/2008, Multiple relaparotomies for fistula closure, repeated debridement. Over 30 surgical interventions
5	Failure to thrive	GERD with previous Nissen fundoplication, revision x 3 (2008,2009), Gastrectomy (2010) for bezoar, Jejunostomy placement, with multiple revisions
6	Infected mesh with colocutaneous fistula	Roux-en-Y bypass with incisional hernia (remote past), Incisional hernia repair for infected mesh and colocutaneous fistula takedown (present admission)
7	Gastrocutaneous fistula	Previous gastrojejunostomy placement for gastroparesis, since removed
8	Non healing abdominal wounds	Abdominal ulcerations with cellulitis, surgical debridement in 12/2012
9	Esophageal cancer	MIS Ivor Lewis Esophagectomy, jejunostomy with multiple revisions
10	Eyelid melanoma	Panniculectomy, Breast reduction, peptic ulcer disease with antrectomy, vagotomy, gastrojejunostomy (< 2008)
11	Necrotizing pancreatitis	Severe Acute pancreatitis, readmitted with necrotizing pancreatitis < 15 days post discharge, Pancreatic debridement, feeding jejunostomy placement
12	Chronic non-healing wounds, malnutrition	Local wound care, no surgical debridement was performed
13	Duodenal adenomas with h/o FAP	Pylorus-preserving pancreaticoduodenectomy
14	Paresthesia, decubitus ulcers	none
15	Chronic pancreatitis	feeding jejunostomy, PPPD
16	Multiple perianal fistula	Diverting colostomy, SCC of the anus with diverting colostomy
17	Necrotizing pancreatitis	Pancreatic debridement, feeding jejunostomy
18	Abdominal wall ulcer	Split-thickness skin graft to abdominal wall ulcer, incision hernia repair, Whipple for pancreatic mass, s/p wound dehiscence
19	Incarcerated incisional hernia	Incarcerated incisional hernia repair with high output enteric fistula, subsequent transverse colectomy and end colostomy for perforated diverticulitis.

Table 3: Surgical procedures performed.

Surgical Procedures
Colectomy and diversion
Total Pancreatectomy
Splenectomy
Esophagectomy
Whipple
Feeding tube placement
Abdominal wall reconstruction
Pancreatic necrosectomy
Decubitus ulcer debridement
Roux-en-Y bypass
Panniculectomy

Table 4: Biochemical markers of nutritional status.

Parameter	Value
Poor nutritional parameters	19/19 (100%)
Albumin ≤ 3.0 mg/dL	78%
Median preoperative albumin (mg/dL)	2.9
Median best perioperative prealbumin (md/dL)	9
Vitamin Deficiencies	
Vitamin A	3 (16%)
Vitamin B	3 (16%)
Vitamin C	19 (100%)
Vitamin D	5 (26%)
Micronutrient	
Magnesium	2 (11%)
Zinc	7 (37%)

Table 5: Post-operative complications.

Parameter	Overall (n=19)	Prealbumin >10 mg/dL	p value
Overall Morbidity	16/19, 84%	6/6, 100%	0.7
Superficial/Deep SSI	10/19 (52%)	4/6, 67%	0.21
Organ Space Infection	12/19 (63%)	5/6, 83%	0.8
Feeding tube placement	11/19 (58%)	2/6, 33%	0.02*
Post-operative fistula	10/17 (59%)	5/5, 100%	0.67
Post-operative pneumonia	2/19 (11%)	1/6, 16%	0.2
Post-operative renal failure	2/19 (11%)	0/6, 0%	-
> Two Readmissions	14/19 (73%)	5/6, 83%	0.79
Readmissions (median)	4	2	0.42

*p value <0.05

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