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The Influence of a Brief Preoperative Illness on Postoperative Healing

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In a study of wound healing at high altitude, subcutaneously implanted PTFE tubes were used to stimulate and measure accumulation of wound hydroxyproline (an index of collagen) in 26 patients who had appendectomy and in 38 patients who had cholecystectomy. Patient age, length of surgery, and postoperative recovery seemed to predict better healing in patients who had appendectomy, but there was a difference in the preoperative illness of the two groups: acute cholecystitis was treated medically and cholecystectomy performed after resolution of the acute phase of illness, whereas patients who had appendectomy were taken to surgery as soon as a diagnosis was made. It was observed that patients who had appendectomy accumulated 20% less hydroxyproline than patients who had cholecystectomy ($p < 0.02$), and that the depression of hydroxyproline accumulation was significantly related to length of preoperative illness ($p = 0.008$). This decrease in wound hydroxyproline accumulation is attributed to the acute preoperative illness. Conceptually, this is a unique situation since the brief illness did not produce lasting debility, and the source of illness, the inflamed appendix, was not present during healing. This indicates that even a brief preoperative illness has a more prolonged influence on postoperative healing than usually anticipated.

PATIENTS ARE AT GREATER RISK for complicated healing after emergency, as opposed to elective, surgery. Generally, poor healing is believed to be related to ongoing sepsis, malnutrition, and/or impaired function of one or more major organs during the healing process. Research efforts have been directed to understanding how these factors relate to healing and host resistance to infection.

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In a recent study of wound healing at high altitude we discovered an unanticipated healing defect in patients who had appendectomy, which we attribute to brief, acute preoperative illness, a factor not usually considered after operation. The basic study was intended to investigate the cause of an infection rate of 33% after appendectomy at the Hospital Carlos Andrade Marin in Quito, Ecuador, which has an elevation of 9650 feet.[1] We designed the study to evaluate the role of altitude-induced hypoxia in collagen deposition, subcutaneous tissue oxygen tension, and infection. Otherwise healthy, acclimatized patients who had appendectomy and cholecystectomy were studied. We used accumulation of hydroxyproline in response to an acute, standard wound stimulus as an index of wound healing capacity.

We expected the patients who had appendectomy and cholecystectomy to be comparable, but if there were to be a difference, patient age, length of surgery, and postoperative recovery seemed to predict better healing in patients who had appendectomy. However, as we later recognized, there was a difference in the level of acute illness immediately before operation. At the Hospital Carlos Andrade Marin, acute cholecystitis is treated medically and cholecystectomy is performed after resolution of the acute phase of illness. Patients who had appendectomy, however, were taken to surgery as soon as a diagnosis was made.

During the study we observed that patients who had appendectomy accumulated 20% less hydroxyproline than patients who had cholecystectomy, and that the depression of hydroxyproline accumulation was significantly related to the length of preoperative illness. We believe the difference in acute preoperative illness can explain the dif-

TABLE 1. *Total Collagen in PTFE Catheters (μg hydroxyproline/cm PTFE tubing)**

	Total Collagen (μg/cm)	p
Breathing ambient air	0.96	>0.20
Breathing supplemental oxygen	0.88	
Appendectomy	0.80	<0.02
Cholecystectomy	1.04	

* Cell means from two-way ANOVA.

ference in wound hydroxyproline accumulation. Conceptually, this is a unique situation since the brief illness did not produce lasting debility, and the source of illness, the inflamed appendix, was not present during healing.

Methods

Measurement of Wound Hydroxyproline as an Index of Collagen Formation

Using a 14-ga, pointed but unsharp needle, a small wound was made in the upper arm, and a 10-cm length of expanded, 90-μ pore size, polytetrafluoroethylene (PTFE) tubing (Gore-Tex, W.L. Gore, Flagstaff, AZ) was threaded through the subcutaneous tissue. This is similar to our previous method of human study,[2] the only change being the simplified method of insertion.

PTFE tubes were placed at the end of surgery and removed after 7 days. Total hydroxyproline per centimeter was measured as previously described.[2] There were no infections and no complications. One patient did not return for catheter removal until the 10th day after operation, and data from one other patient were lost in processing. Twenty-six patients were evaluated after appendectomy and 38 were evaluated after cholecystectomy.

Measurement of Subcutaneous Tissue Oxygen Tension

A through-and-through wound was made in the upper arm using a #19 spinal needle, and a oxygen-permeable Silastic tube was threaded into the wound.[3,4] Once daily, starting in the recovery room, the tube was filled with normal saline to maintain electrical contact; oxygen tension in the central portion of this tube (Psc02) was measured directly by placing platinum and reference electrodes in the tube. We have previously shown that changes in such a standardized arm needle wound reflect changes in an operative wound in the same patient, although the arm needle wound has slightly higher oxygen tensions.[5] Catheters for measuring subcutaneous oxygen tension were placed in the same arm location as the PTFE catheters for measuring hydroxyproline accumulation, so that we directly measured Psc02 at the site of the healing test. Psc02 was measured in a sample of seven patients after cholecystectomy and in three patients after appendectomy.

Patients were assigned to receive supplemental oxygen using cards prepared with the odd-even assignment from a random number table. At the conclusion of surgery, after insertion of the PTFE catheter, a card was drawn. Assigned patients received oxygen at 5 L/min by nasal prongs for 18 hours a day as long as they were in the hospital, an average of 5.2 days for patients who had cholecystectomy and 3.8 days for patients who had appendectomy. Other than supplemental oxygen, all postoperative care was routine. Patients with abscesses found at surgery were excluded.

Data were collected prospectively on the length and severity of preoperative illness, operative findings, antibiotic use, and infection. Amount of fluid administration and postoperative advancement of diet were collected by retrospective chart review. Patients were examined 3 weeks after operation to check for late infection.

Study protocols were reviewed and approved by the Committee on Human Research at the University of California, San Francisco (UCSF), and again by appropriate officials of the Hospital Carlos Andrade Marin in Quito.

Statistics

Hydroxyproline values were analyzed according to whether or not supplemental oxygen had been administered and according to type of surgery: appendectomy or cholecystectomy. Since the experiment design was unbalanced with respect to number of patients in each group, the least squares, or cell means, model of analysis was used (Statistical Analysis Systems procedure GLM, type III analysis). Two-way analysis of variance provides a cell mean for each cell group, which is an index using the correction for effects of other factors (in this instance, type of operation or supplemental oxygen). In this system, standard deviation does not have the same implication as for description of a single sample so only cell means are listed in Table 1. (Mean ± SD of hydroxyproline/cm PTFE tubing is listed for individual groups in Table 3.) The relationship of length of preoperative illness to hydroxyproline accumulation in patients who had appendectomy was determined using Kendall's tau test. Two-way analysis of variance and Kendall's tau test were done by the statistics unit in the Computer Department of UCSF.

Results

Wound Hydroxyproline in Human Subjects

Two-way analysis of variance found a significant effect of type of operation on hydroxyproline accumulation, with lower values after appendectomy ($p < 0.02$). Supplemental oxygen did not have a significant effect on wound hydroxyproline accumulation in this study (Table 2), but the inclusion of the oxygen-treated patients does not influence the results of the study. Wound hydroxyprolines for all four subgroups were within a range comparable to patients at sea level measured previously.

The patients who had appendectomy were younger and had shorter operations. However, they were sicker in the immediate preoperative period: 80% had nausea and/or vomiting for an average of 34 hours. Postoperative fluid requirements, titrated to the customary criterion of adequate urine output, were similar in both groups, and the time until normal diet was taken was only slightly greater in patients who had appendectomy (Table 2). The length of time that patients actually received oxygen reflects the length of hospital stay, which was shorter in patients who had appendectomy (Table 3).

Thirty-four per cent of the patients who had cholecystectomy were admitted to the hospital more than 24 hours before surgery for care until resolution of acute symptoms. The four patients listed as having acute cholecystitis had also passed the acute phase by clinical criteria.

Wound hydroxyproline accumulation in patients who

TABLE 2. *Comparison of Composite of Patients who had Appendectomy and Cholecystectomy Showing Major Variables*

	Appendectomy N = 26*	Cholecystectomy N = 38
Age (years)	33 ± 13	39 ± 15
Male	23	11
Female	3	27
Length of acute preoperative illness (hours)	34 ± 18	NA
Preoperative nausea, vomiting	21 (80%)	0
Admitted over 24 hours for preoperative stabilization	NA	13 (34%)
Length of surgery (minutes)	46 ± 14	75 ± 24
Fluids first 24 hours (mL)	3074 ± 1149	2617 ± 1327
Eating solids postoperative day 2	20 (83%)	33 (94%)
Test wound hydroxyproline (μg/cm)	0.80	1.04

* Note two fewer patients in hydroxyproline analysis than in infection analysis since one did not return for tube removal on correct day and data from one patient were lost during processing.

TABLE 3. *Summary of Data on All Patients by Subgroups*

	Appendectomy		Cholecystectomy	
	Ambient O_2	Supplemental O_2	Ambient O_2	Supplemental O_2
No. of patients	12	16	16	22
Male	9	15	6	5
Female	3	1	16	17
Age (years)	33 ± 14	31 ± 14	37 ± 13	42 ± 14
Numbered days with O_2	0	3.8 ± 1.8	0	5.2 ± 1.6
Condition of appendix				
Normal	1 (8.3%)	0	NA	NA
Phlegmatic	6 (50%)	12 (75%)		
Gangrenous	3 (25%)	3 (18.7%)		
Perforated	2 (16%)	1 (6.2%)		
Condition of gallbladder				
Acute	NA	NA	0	4 (18%)
Simple lithiasis			13 (81%)	14 (64%)
With common duct stones			3 (18.7%)	3 (14%)
With duodenal fistula			0	1 (5%)
Length of operation (minutes)	46 ± 12	43 ± 16	77 ± 20	73 ± 28
Infection				
Wound	2 (16.5%)	1 (6.25%)	0	1 (4.5%)
Intra-abdominal abscess	1 (8.3%)	1 (6.25%)	2 (12.5%)	0
Total	3 (25%)	2 (12.5%)	2 (12.5%)	1 (4.5%)
Length of illness before surgery				
Hours	33 ± 18	33 ± 19	NA	NA
Months	NA	NA	17 ± 28	15 ± 21
Postoperative fever (38 C or more)	3 (25%)	0	2 (12.5%)	4 (18%)
Postoperative antibiotics	10 (83%)	11 (69%)	2 (12.5%)	0
Preoperative nausea, vomiting	10 (83%)	11 (69%)	0	0
Admitted for preoperative medical care	NA	NA	6 (37%)	6 (27%)
First 24-hour fluid requirement (based on "adequate urine output") (mL)	2595 ± 1061	3516 ± 1063	2328 ± 1289	2880 ± 1310
Incidental appendectomy	NA	NA	2 (12.5%)	2 (9%)
Eating solids postoperative day 2	10/11 (91%)	12/16 (75%)	16 (100%)	19 (90%)
Wound collagen (μg/cm)	0.89 ± 0.34	0.71 ± 0.20	1.10 ± 0.73	1.05 ± 0.31

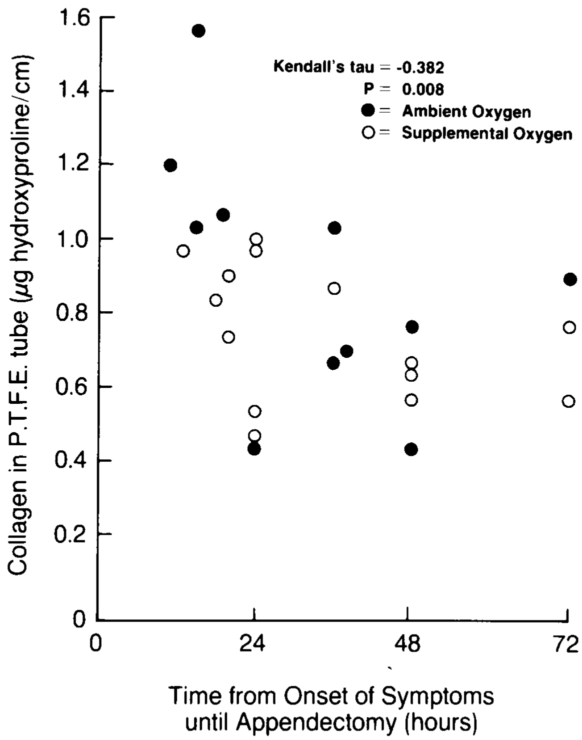

FIG. 1. Effect of length of illness before appendectomy. There is a significant negative correlation between the length of untreated, acute preoperative illness and collagen accumulation (Kendall's tau = −0.385, p < 0.008).

had appendectomy decreased as length of acute preoperative illness increased (Kendall's tau = −0.385; p = 0.008) (Fig. 1).

Tissue Oxygen Tension and Perfusion

Tissue oxygen tension, measured in seven patients who had cholecystecomy and in three patients who had appendectomy, confirmed that supplemental oxygen increased tissue oxygen delivery. Immediately after operation, while they breathed room air, mean Psc02 was 37 ± 7 torr and 40 ± 5 torr, for the two groups, respectively. With supplemental oxygen this increased to 54 ± 12 torr and 58 ± 13 torr, respectively (Table 4).

These Psc02 measurements can also be used to estimate relative subcutaneous perfusion, which is important because decreased blood flow to tissue can cause decreased healing. We have shown that Psc02 varies according to inspired oxygen, and in healthy persons we can establish "control" values of Psc02 for a given level of inspired oxygen.[4,6] Piasecki, working with isolated tissue, demonstrated that with constant arterial oxygen tension tissue oxygen tension is *also* directly proportional to measured rate of blood flow.[7] We have measured Psc02 in humans with a variety of methods known to decrease subcutaneous perfusion: large-vessel occlusion,[6,8] hypovolemia,[4] and cutaneous vasoconstriction.[9] All cause a drop in Psc02: tissue oxygen tension drops when blood flow decreases.[10]

In the current study either the appendectomy or the cholecystectomy group can be taken as the control for postoperative patients at 9650 feet above sea level because they are interchangeable. The similarity of Psc02 with the same inspired oxygen would not exist if either group had decreased perfusion. That group's Psc02 would be lower. The fact that both patients who had appendectomy and patients who had cholecystectomy had similar Psc02 at both of two different levels of inspired oxygen concentration demonstrates that neither had a decrease in subcutaneous perfusion relative to the other.[11] Therefore, we conclude that a postoperative decrease in perfusion did not cause the decreased test-wound hydroxyproline accumulation in the patients who had appendectomy.

Wound Infection Rates

Wound infection was more frequent in patients who had appendectomy (17.8%) than in patients who had cholecystectomy (7.8%). Lower infection rates would be expected at sea level,[12] but since many factors vary from one institution to another this does not prove that infection rates increase at high altitude. In the original protocol results from patients who had appendectomy and cholecystectomy with and without supplemental oxygen were to be pooled. When this was done the infection rate for patients breathing air was 17.8% and for those breathing supplemental oxygen was 7.8% within the same institution (Tables 3 and 5).

Discussion

Patients who had appendectomy and who were ill during the immediate preoperative period accumulated less

TABLE 4. *Tissue Oxygen Tension (torr) in a Small Subcutaneous Wound*

Group	Breathing	Day of Surgery	Postoperative Day 1	Postoperative Day 2
Cholecystectomy (N = 7)	Ambient air	36 ± 7	36 ± 6	29 ± 9
	Supplemental O_2	52 ± 12	51 ± 10	37 ± 13
Appendectomy (N = 3)	Ambient air	40 ± 5	31 ± 7	26 ± 3
	Supplemental O_2	58 ± 13	44 ± 17	41 ± 10

TABLE 5. *Patients with Postoperative Infection*

Patient	Age/Sex	Time of Preoperative Illness	No. of Postoperative Days on O_2	Type of Infection	Postoperative Day of Infection	Hydroxyproline (μg/cm)	Comment
A2	24/m	24 hr	4	Retrocecal abscess	12	0.47	Gangrenous appendix
A13	44/m	20 hr	3	Wound	17	0.73	Gangrenous appendix
A19	25/f	48 hr	0	Abdominal abscess	3	0.56	Abdominal ectopic pregnancy with normal appendix
A22	51/m	19 hr	0	Wound	7	1.06	Inflamed appendix
A27	68/m	48 hr	0	Wound	7	0.43	Perforated appendix
V6	55/m	72 mo	6	Wound	7	0.51	Cholecystoduodenal fistula
V30	56/m	12 mo	0	Subphrenic abscess	7	1.52	Cholecystectomy with common duct exploration
V35	32/f	12 mo	0	Pouch of Douglas and RLQ abscess	12	0.60	Cholecystectomy with incidental appendectomy

RLQ = right lower quadrant.

collagen than patients who had cholecystectomy. The degree to which this depression occurred was proportional to the length of preoperative illness. The healing defect amounted to approximately 20% less collagen accumulation in patients who had appendectomy. Apparently, a brief preoperative illness has a much greater effect than is usually assumed, a surprising finding in a disease as common as appendicitis.

Our test of healing is like other models using subcutaneous implants: there are multiple holes in the PTFE tubing, and the host tissue responds to wounding with infiltration of inflammatory cells, followed by an ingrowth of granulation tissue. The PTFE material has 90-μ pores, three times the 30-μ pore size of commercial vascular graft material, and it is not reinforced, as is vascular graft material. Materials with smaller pore size and reinforced coating have been evaluated and found unsatisfactory. The important features of this test are: (1) a standard body location, the upper arm; (2) a standard stimulus, the needle wound and the PTFE implant; and (3) a standard method of sample collection, removal of the tube. Norms for collagen accumulation can be created for periods of 7 days (or less).[2] In fact, peak collagen formation in animal studies occurs at about 5 days, which is before the peak of collagen accumulation.[13] This is similar to other studies of rates of collagen formation in wounds.[14] Results with the PTFE tube method correlate with closure of experimental open skin-defect wounds,[15] and this method has already distinguished poor healing in long-term disability,[2] uremia,[16] and malnutrition,[17] and satisfactory healing in well-controlled diabetics.[18]

We use total hydroxyproline as an index of wound collagen. Accumulation of hydroxyproline corresponds to increased tissue strength[19] and vice versa.[20] There are specific situations in which wound hydroxyproline is normal, but wounds do not heal well (beta amino proprionitrile, which prevents collagen cross-linking, is an excellent example) but we are unaware of a situation in which there is a decrease in hydroxyproline without a decrease in strength. Fortunately, a decrease in wound hydroxyproline accumulation (collagen) does not usually mean that clinical wound failure will automatically follow. For example, it is established that wound healing is depressed in chronic uremia,[14,21] but most kidney transplants heal without infection or dehiscence, even with the added effects of immunosuppression. The implication is that there is a margin of safety in most healing circumstances, and usual postoperative activity does not fully test the strength of wounds.

The immediate question is why were there not more complications of incisions in the patients who had appendectomy if healing was depressed? There are at least three explanations: (1) the usual approach to appendectomy is to split muscle. The incision closes itself when the patient strains; thus, only minimal strength of repair is required. (2) Slower healing at 7 days probably does not mean healing is permanently depressed: it reflects a slower start. The ultimate tensile strength of all these wounds would probably be comparable. (3) A 20% reduction in collagen deposition may not necessarily, by itself, lead to complications.

Defects in postoperative healing after trauma or major surgery have been described in a setting of *ongoing* infection, stress, or major organ failure.[22] Our findings show that *post*operative healing is influenced by the *pre*operative status of the patient in ways not included in the usual considerations of severe malnutrition (greater than 20% weight loss), continuing sepsis or drainage, or organ failure. That 34% of the patients who had cholecystectomy were admitted with acute illness but did not have a defect in wound collagen formation suggests that preoperative control of acute disease can ameliorate this defect. What aspects of resuscitation and care are most important and how long they should be continued were not defined by this study. The list of potential causes ranges from acute starvation to unreplaced fluid loss or the catabolic effects of stress-induced high levels of steroids and/or catecholamines, *etc.*

Conclusions

Preoperative illness causes a depression in postoperative healing. Other studies of postoperative depression of healing have included circumstances of ongoing sepsis, ongoing organ failure, or ongoing malnutrition, in which the problem continued during healing. In our study, wound collagen was depressed even when the source of stress, the appendix, was removed after acute appendicitis without abscess formation. This indicates that even a brief preoperative illness has a more prolonged influence on postoperative healing than usually anticipated.

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