MARKEDLY ELEVATED LEVELS OF PAI-1 IN WOUND FLUID AFTER COLORECTAL RESECTION ARE LIKELY A MAJOR SOURCE OF PAI-1 IN THE PLASMA FOR TWO WEEKS AFTER SURGERY

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Introduction

Plasminogen activator inhibitor-1 (PAI-1), also known as Serpin 1, is an inhibitor of urokinase type plasminogen activator (uPA) and tissue-type plasminogen activators (tPA), which convert plasminogen to plasmin(1). Plasmin breaks down the fibrin clots initially laid down in wounds, and facilitates macrophage and fibroblast entry into the wounds and the subsequent generation of collagen(2). PAI-1 as well as the plasminogen/plasmin system play an important roles in the regulation of extracellular matrix (ECM) remodeling, angiogenesis, wound healing, and tumor cell invasion(3). PAI-1 influences VEGF induced changes such as pericellular proteolysis that increases vascular permeability and supports endothelial cell proliferation and migration(4). PAI-1 over expression has been reported in colorectal cancer (CRC) patients and elevated expression levels in rectal cancer patients were found to be directly associated with cancer stage(5). Elevated preop plasma levels of PAI-1 have also been associated with worse outcomes in lung, breast, and stomach cancer, as well as CRC(6-11). After CRC resection, persistently elevated plasma PAI-1 levels have been noted(12); we hypothesize that the healing wounds are a source of the added PAI-1 in the blood. This study's purpose is to determine perioperative PAI-1 levels in wound fluid (WF) and blood taken after CRC resection.

Methods

Consented CRC resection patients (pts) in an IRB approved tissue /data bank in whom an intra-abdominal Jackson Pratt (JP) drain had been placed and for whom adequate plasma and WF samples were available made up the study population. Demographic and clinical data were collected. Preoperative (preop) and postoperative blood and WF samples were simultaneously collected on postoperative day (POD) 1, POD 3, and between POD 7-13 (for most pts). Samples collected pod 7-13 were bundled and considered as a single time point. Plasma was isolated via centrifugation at 450 G and clear WF samples were collected via centrifugation at 16,000G for 10 min at 60^{0}C. Samples were stored at -80^{0}C. Plasma PAI-1 levels were determined in duplicate via ELISA and reported as median and 95% CI. Mann Whitney and Wilcoxon signed rank tests were used for analysis (Significance p<0.05).

Parameter	Result
Demographic & Operative Data	**N =29 patients**
Age, years (mean ± SD)	**66.1± 12.3**
Sex: Male	**12 (41.0%)**
Female	**17 (59.0%)**
Incision size: cm (mean ±SD) **Surgical Methods: LAP/Hand or Open**	**9.3±3.7 (Lap/hand)** **26.0±8.3 (Open)**
Surgery time, min (mean ± SD)	**459.8± 108.1**
Length of stay, days (mean ± SD)	**9.6± 6.3**

Table 1: PAI-1 protein levels in preop and post op Plasma vs. postop Wound fluids

Time	Plasma (ng/ml)	(n)	Wound fluids (ng/ml)	(n)	*p*
PreOp	3.83; 95% CI: 3.4-5.2	29	N/A	N/A	N/A
POD1	6.82;95%CI: 4.97-9.34	29	27.16; 95%CI: 20.35-45. 31.5	28	< 0.0001
POD3	6.01;95%CI: 4.35-6.90	27	18.65;95%CI: 15.03-33.15	25	< 0.0001
POD 7-13	5.50;95%CI: 3.99-9.25	17	24.55;95%CI: 19.8-50.05	17	< 0.0001

Figure 1: Surgical procedure

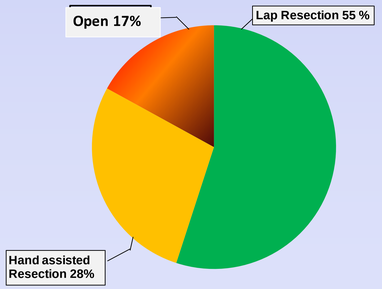
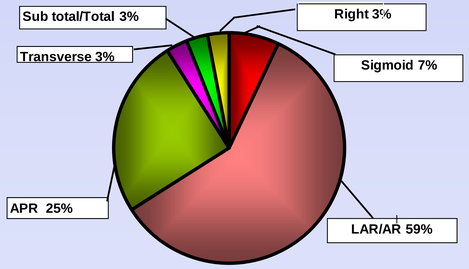


Figure 2: Types of Resection



Results

The study population was comprised of 29 CRC pts (rectal 24, colon 5) who underwent laparoscopic (55%), hand-assisted (28%), or open (17%) resections. See the adjacent table for the demographics. The mean incision length for the lap + hand assisted pts was 9.3. ± 3.7 and for the Open pts was 26.0 ± 8.3 cm. The majority of patients underwent LAR/AR colectomy (59%) followed by APR resection (25%) and sigmoid/recto-sigmoid resection (7%) (Figure 2). The mean length of stay was 9.3± 3.7days and mean surgery time was 459.8± 108.1(min). Postop plasma PAI-1 levels were significantly elevated (p<0.01) over preop baseline at all postop time points (Table 1). In turn, WF PAI-1 levels were 3 to 4.4 times higher than the corresponding plasma levels (also elevated from baseline) at all time points (p<0.0001)(Table 1).

Conclusion

After CRC resection, median plasma PAI-1 levels were 32 to 78% higher than preop levels (p<0.01). Further, WF levels were 205-302% higher than the corresponding elevated postop plasma levels (p<0.0001). These results support the hypothesis that the healing wounds, via diffusion along the concentration gradient, contribute to the plasma PAI-1 elevations noted post CRC. Although not addressed in this study, elevated plasma PAI-1 levels postop, via several mechanisms, may promote the growth of residual tumor deposits after surgery. Further study is warranted.

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