ELEVATED UROKINASE PLASMINOGEN ACTIVATOR-1 LEVELS IN WOUND FLUID AFTER COLORECTAL RESECTION LIKELY ACCOUNTS FOR THE ELEVATED PLASMA LEVELS NOTED FOR TWO WEEKS AFTER SURGERY

SAGES 2023
Abstract ID: 124094
P674

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Introduction

Urokinase-type Plasminogen Activator-1 (uPA) is a secreted protease that converts plasminogen to plasmin (1,2). Activated plasmin catalyzes many physiopathological processes requiring extracellular matrix (ECM) remodeling (3). uPA binds to the widely expressed uPA receptor (uPAR) and uPA-uPAR complexes can be inhibited by Serpin E1/ Plasminogen activator inhibitor-1(PAI-1) (4)uPA together with the uPA receptor (uPAR) and PAI-1 plays a wide regulatory role as regards tumor cell proliferation, adhesion, migration, and metastasis(5-7). uPA and uPAR promote immune cell activation at sites of matrix remodeling during wound healing(4,8-10).uPA directly and via plasmin leads to activation of angiogenic growth factors including VEGF and IGF. uPA over expression has been noted in colorectal cancer (CRC); high tumor levels correlate with a poor prognosis (11-12). Persistently elevated postop plasma uPA levels (11-66% over baseline) after CRC resection (CRCR) has been noted previously. We believe wound uPA levels will be high and account for much of the postop uPA plasma elevations. This study's purpose was to determine perioperative uPA blood and wound fluid (WF) levels after CRCR.

Methods

Consenting CRCR patients (pts) enrolled in an IRB approved tissue/data bank in whom a pelvic drain had been placed for whom adequate plasma and wound fluid samples were available were studied. Demographic, Clinical and pathologic data were collected. Preoperative (preop) blood , postoperative blood and WF samples were taken simultaneously on postoperative day (POD) 1, 3, and a late time point between POD7-13. Plasma were collected from blood via centrifugation at 450 G, and clear WF collected via centrifugation at 16,000G for 10 min at 60^{0}C ; samples were stored at -80^{0}C as aliquots until further used. The POD 7-13 samples were bundled and considered as a single time point. uPA levels were determined in duplicate via ELISA and reported as median and 95% CI. The Wilcoxon and Mann and Whitney test were used for analysis ($p<0.05$).

Parameter	Result
Demographic & Operative Data	N =29 patients
Age, years (mean ± SD)	66.2± 12.3
Sex: Male	12 (41.0%)
Female	17 (59.0%)
Incision size :cm (mean ±SD) LAP/Hand Open procedures	9.3±3.7 23.8±7.7
Surgery time, min (mean ± SD)	459.8± 108.1
Length of stay, days (mean ± SD)	9.6± 6.3

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

Time	Plasma (ng/ml)	(n)	Wound fluids (ng/ml)	(n)	*p*
PreOp	690.8; 95% CI: 553.9- 828.2	29	N/A	N/A	N/A
POD1	709.5;95%CI: 621.9- 955.3	29	8421; 95% CI: 5285.5- 12191.7	28	< 0.001
POD3	799.2;95%CI: 648.5- 946.8	27	5735;95% CI: 4367.3- 6428.8	25	< 0.001
POD 7-13	782.3;95%CI: 726.5- 1233.9	16	4921;95% CI: 3999.3- 10849.8	17	< 0.001

Figure 1: Surgical procedure

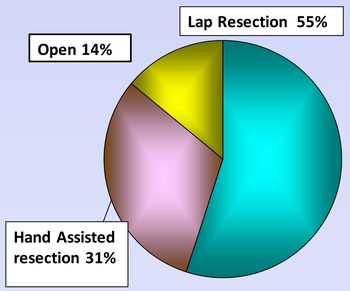
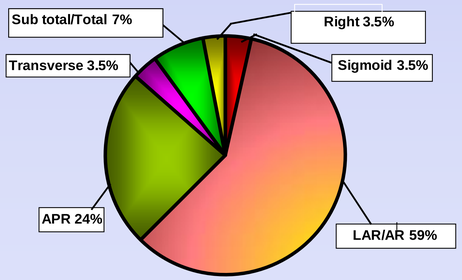


Figure 2: Types of Resection



Results

Plasma and wound fluid samples from 29 CRC patients (male: 12, female: 17; mean age 66.2± 12.3 years; colon 5, rectal 24) were studied; the surgical methods used were minimally invasive in 25 and open in 4 pts. Surgical methods were used (mean incision length (cm) for laparoscopic & hand assisted, 8.3±3.4, 11.5±3.6; for open 23.8.0±7.7). The majority of patients underwent LAR/AR colectomy (59%) followed by APR resection (24%) and subtotal/total resection (7%) (Figure 2). The mean length of stay was 9.6± 6.3 days and mean surgery time was 459.8± 108.1(min). Significantly higher plasma uPA levels were found on POD1, 3, and 7-13 ($p=0.02$ to $p<0.01$) versus preop levels Also, wound fluid uPA levels were many times higher than the corresponding plasma levels at each postop time point ($p<0.001$Table 1).

Conclusion

Median postop plasma uPA levels were again noted to be significantly elevated over baseline. Wound fluid levels were 529-1086% higher than the corresponding plasma levels. The wounds may account for much of the plasma elevations noted post colorectal cancer resection. Although unproven, uPA, by promoting angiogenesis, may facilitate growth of residual tumor deposits postop. Further study with larger patient group is warranted.

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