**Management of hemorrhagic pleural effusion with intra-pleural streptokinase in peritoneal dialysis patient on dual anti-platelet therapy**

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**Abstract:**

Pleural effusion is seen in up to 10 percent of patients on peritoneal dialysis (PD). A hemorrhagic pleural effusion is a diagnostic dilemma and a therapeutic challenge. We report a complicated case of 67 years old male with end stage renal disease, with coronary artery disease and stent in situ under dual antiplatelet therapy and continuous ambulatory peritoneal dialysis. The patient presented with left sided loculated hemorrhagic pleural effusion. The effusion was most likely due to uremic pleuritis complicated by dual antiplatelet therapy. He was managed with intrapleural streptokinase therapy. His loculated effusion resolved without any local and systemic bleeding manifestations.

We conclude that intrapleural streptokinase is a therapeutic option in loculated hemorrhagic pleural effusion in resource-poor settings. Nevertheless, its use is individualized in high-risk conditions based on risk-benefit analyses.

Key Words: Peritoneal Dialysis; Hemorrhagic pleural effusion; Intrapleural streptokinase; dual antiplatelet therapy

**Introduction**

Pleural effusion is seen in up to 10 percent of patients on peritoneal dialysis (PD).[[1]](#endnote-1) The differential diagnosis of pleural effusion in PD patients is extensive. It includes general causes of pleural effusion and causes unique to PD patients. Transudative pleural effusions in PD patients may be commonly related to volume overload and cardiac failure, or rarely peritoneal dialysate in the thoracic cavity.[[2]](#endnote-2) Exudative effusions could occur due to infection, inflammation, or hemorrhage. The presence of a hemorrhagic pleural effusion can narrow the differential diagnoses to trauma, tuberculosis, or tumor. Other causes include bleeding diatheses, pulmonary infarction, embolism, or vascular malformations. Unique to end-stage renal disease (ESRD) patients, uremia can lead to a hemorrhagic pleural fluid.[[3]](#endnote-3)

Hemorrhagic pleural effusion is a diagnostic dilemma and a therapeutic challenge. Angioblastic and fibroblastic proliferation can lead to the formation of fibrin clots.[[4]](#endnote-4) Thus, chest tube drainage becomes ineffective due to clots and septations in up to 40 percent of these cases.[[5]](#endnote-5) The management of such septated effusion is debatable. Video-assisted thoracoscopic surgery (VATS) is an effective modality of treatment.[[6]](#endnote-6) Also, the administration of intra-pleural enzymes is a reasonable cost-effective approach, especially in resource-poor settings.[[7]](#endnote-7) Intra-pleural enzymes like streptokinase (IPSK), urokinase, tissue plasminogen activator (tPa), or DNase lyse fibrin adhesions and allow free-flow drainage. Side effects include chest pain, fever, chills, and allergic reactions. In addition, local pleural and systemic hemorrhages are reported adverse events of IPSK.[[8]](#endnote-8)

Nevertheless, the use of IPSK in ESRD patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) has not been reported in the literature. We report a case of successful instillation of IPSK in a hemorrhagic pleural effusion in a patient on CAPD and dual anti-platelet therapy (DAPT). The effusion resolved without any local and systemic bleeding manifestations. We report a case of successful instillation of IPSK in a hemorrhagic pleural effusion in a patient on CAPD and dual anti-platelet therapy (DAPT). The effusion resolved without any local and systemic bleeding manifestations.

**Case Report**

A 67 years old male, non-smoker, with no contact history of tuberculosis, presented with chief complaints of gradually progressive shortness of breath for seven days and left-sided chest pain for three days. He had a past history of systemic hypertension, type 2 diabetes mellitus, chronic kidney disease under CAPD for six months and, coronary artery disease with a stent in-situ for three months. He was under DAPT (aspirin 75 mg and clopidogrel 75 mg), statin, anti-hypertensive, hypoglycemic agents, and other supportive medications. Physical examination revealed pallor, tachycardia, and tachypnea. Chest X-ray showed a left-sided massive pleural effusion. Ultrasonography (USG) chest and Computed Tomography (CT) chest showed effusion with multiple septations. There was no evidence of consolidation, cavitation or lymphadenopathy in CT chest. Pleural fluid analysis revealed an exudative fluid. The adenosine deaminase (ADA) level was 46 IU/L. The pleural fluid culture was sterile. Sputum was negative for acid-fast bacilli (AFB) on three consecutive sputum samples. There were no atypical cells on three malignant cytology samples.

A tube thoracostomy was done. We noted 500 ml of dark red pleural fluid under the water seal bag. The ratio of blood hematocrit to pleural fluid haematocrit was less than 50 percent. On re-evaluation with USG chest, multiple pockets of effusion were persistent. There was no expansion in the lung field. Hence, we administered intrapleural streptokinase 3 million units over 2 hours, once daily for three days. Subsequently, we noted 700 ml, 800 ml, and 600 ml of dark red fluid on three consecutive days. The chest tube was in-situ another seven days and removed on the eighth day after no drainage for two consecutive days. We ensured adequate flushing and correct positioning of the tube on all days. Chest X-ray and USG review after removal of the chest tube showed expansion of lung field. The patient received intravenous antibiotics during the hospital stay. Throughout the hospital stay, the patient remained on his routine peritoneal dialysis and past medications, including DAPT.

Apart from pain around the chest tube site, there were no other side effects or complications. There were no local and systemic bleeding manifestations during the hospital stay. The patient improved symptomatically and was hemodynamically stable at discharge. During follow-up, the patient was asymptomatic, and chest X-ray and USG review showed an expanded lung field.

**Discussion**

Patients with chronic kidney disease on PD may develop hemorrhagic effusion due to various aetiologies. Common causes such as parapneumonic effusion, tuberculosis, malignancy were ruled out in our patient. In addition, our patient did not have a history of smoking, connective tissue diseases, bleeding diasthesis or a history of trauma to the chest.

Unique to ESRD, uremic pleuritis leads to an exudative fibrous hemorrhagic pleural fluid.[[9]](#endnote-9) A study reported uremic pleural effusion as the second most common cause of effusion in ESRD patients. It was second only to heart failure with volume overload.[[10]](#endnote-10) Reportedly; pleural effusions can occur with BUN ranging from 30 to 240 mg/dl. The pathogenesis of hemorrhagic fibrinous effusion in uremia is multifactorial. It is thought to be due to uremic toxins leading to serosal inflammation and pleuritis with increased capillary permeability, exudation of proteins and fibrin deposition.[[11]](#endnote-11) In addition, altered hemostasis in patients with renal failure could contribute to hemorrhagic effusion in uremia. There is alteration in the platelet surface glycoprotein GPIIb/IIIa in patients with uremia, which is a receptor for von willibrand factor and fibrinogen. It leads to decreased platelet function. Also nitric oxide, an inhibitor of platelet aggregation is increased in uremic pleuritis.[[12]](#endnote-12)

Similarly, our patient was under DAPT (aspirin and clopidogrel) for post-stent coronary artery disease for three months. So, the hemorrhagic nature of fluid could be drug-related. The association between hemorrhagic fluid and dual anti-platelet therapy has not been reported in literature yet. Nevertheless, aspirin at a dose of 100 mg per day can increase bleeding time in renal failure patients.[[13]](#endnote-13) Also, a metanalysis concluded glycoprotein IIb/IIIa inhibitors or clopidogrel may increase major bleeding in CKD.[[14]](#endnote-14) In our patient, dual anti-platelet therapy could be major additive contributing factor to altered platelet function associated with renal failure and uremic pleuritis. In addition, presence of anemia in our patient is an important clinical factor that predisposes uremic patients to bleed.[[15]](#endnote-15)

For the management of loculated hemorrhagic effusion, we used intrapleural streptokinase. A trial concluded that IPSK is beneficial after failed tube drainage and favors lung expansion in hemothorax.[[16]](#endnote-16) Nevertheless, higher success rates have been observed with intrapleural tPA/DNase treatment with decreased likelihood of invasive interventions and shortened hospital stay. [[17]](#endnote-17), [[18]](#endnote-18) In our patient, we used intrapleural streptokinase as tPA/DNase and Video Assisted Thoracoscopic Surgery were unavailable in our setting.

The safety of intrapleural streptokinase is also debatable. Studies document it to be safe.[[19]](#endnote-19),[[20]](#endnote-20) While in a multi-center randomized control trial involving 427 participants, seven percent in the streptokinase group demonstrated local pleural or systemic bleeding.[[21]](#endnote-21) Although systemic absorption of intra-pleural administered streptokinase is low, cumulative doses of intra-pleural streptokinase may cause systemic fibrinolysis.[[22]](#endnote-22) Case reports of fatal hemorrhage from aortic dissection[[23]](#endnote-23) and diffuse alveolar hemorrhage following intrapleural streptokinase have been reported.[[24]](#endnote-24) Risk for hemorrhage is high in those on systemic anti-coagulation.[[25]](#endnote-25) Absolute contraindications to intrapleural fibrinolysis include any trauma, surgery, or major hemorrhage within 48 hours, a bronchopleural fistula and history of allergic reaction to the drug.[[26]](#endnote-26)

Our patient had chronic kidney disease on CAPD, a state of altered platelet function. Patients with CKD have increased risk of thrombosis. Paradoxically, these patients also have increased risk of hemorrhage.[[27]](#endnote-27) Increased bleeding occurs due to platelet hyporeactivity to adenosine diphosphate (ADP). And, increased platelet cyclic adenosine monophosphate (cAMP) and decreased thromboxane A2 formation contribute to bleeding.[[28]](#endnote-28) Furthermore, our patient was under dual antiplatelet therapy (aspirin and clopidogrel). Hence, he was at a higher risk of severe bleeding post pleural procedures.[[29]](#endnote-29) Use of intrapleural streptokinase in ESRD patients on CAPD with DAPT has not been reported in literature yet.

**Conclusion**

Our patient's hemorrhagic effusion was probably related to dual antiplatelets and uremic pleuritis in the background of renal failure on CAPD. Our patient was at increased risk of further bleeding complications with pleural procedures due to the presence of anemia, renal failure, and dual antiplatelet therapy. Nevertheless, the use of intrapleural streptokinase (IPSK) was not contraindicated in our patient. We instilled 3 million units of streptokinase daily for three days. Its administration was not associated with local or systemic bleeding manifestations in our patient. There was resolution of septations which facilitated adequate drainage. Radiographically, the lung field expanded, and clinically, our patient improved.

Intrapleural streptokinase is a therapeutic option in loculated hemorrhagic pleural effusion in resource-poor settings. Its use is individualized in high-risk conditions based on risk-benefit analyses by the treating clinician.

**Conflict of Interest:** Authors declare no conflict of interest.

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