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Oral tranexamic acid as a novel treatment option for persistent haematuria in patients with sickle cell disease

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Abstract: Abstract omitted (reviewer's suggestion)

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If you think any imaging may be beneficial to the manuscript please do not hesitate to contact me as I have copies of all the images/ investigations mentioned.

Yours Sincerely,

Mr. Niall Davis

Urology Research Registrar

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Abstract:

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2 **in Patients with Sickle Cell Disease**
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1 A 17 year old Nigerian female (para 1+0) with sickle cell disease (genotype HbSS)
2 presented to the emergency department in sickle crisis with a four day history of gross
3 haematuria with clots. The crisis settled quickly but her haematuria continued
4 unabated. Urine was sterile and serum creatinine was 52mmol/L. This was her first
5 episode of haematuria. She had no other relevant past medical or family history. For
6 fourteen days the patient was treated with intravenous fluids, analgesia and repeated
7 blood transfusion. She underwent a number of investigations during this time.
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14 CT urography and angiography demonstrated bilateral papillary necrosis and
15 thrombus within the bladder. Selective bilateral renal arteriogram showed four renal
16 arteries but no vascular abnormality or active bleeding point. Cystoscopy was
17 performed and thrombus was evacuated. Following administration of furosemide a jet
18 of blood coming from the left ureteric orifice was seen. Both ureters were catheterised
19 and samples taken for culture and sensitivity including tuberculosis and mycoplasma
20 were negative. Non-contrast CT identified a small focus of petechial haemorrhage in
21 the lateral calyx of the midpole of the left kidney. A gradient echo MRI showed no
22 dephasing abnormality to suggest blood product in either kidney. The assumed
23 diagnosis was haematuria secondary to papillary necrosis due to increased fibrinolysis
24 in a patient with sickle cell disease.
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36 Despite sophisticated imaging techniques and invasive investigations no bleeding
37 focus was identified and severe haematuria continued until treatment with oral
38 tranexamic acid (1g QDS) was commenced. The patient's haematuria ceased on the
39 fourth of seven days of treatment and her haemoglobin remained stable. She was
40 discharged 24 days after initial presentation and had no further episodes of gross
41 haematuria at three months follow up.
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1 Patients with sickle cell anaemia are well known to show evidence of microscopic
2 haematuria but severe persistent haematuria is a rare complication with only several
3 small retrospective reviews, case reports and analyses published on the subject.
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5 Severe haematuria is more common in sickle trait rather than disease [1]. This may be
6 due to the higher prevalence of the trait than the disease, or to the higher haematocrit
7 seen in people with sickle trait predisposing to a tendency towards sludging [1]. The
8 haematuria reported is usually painless, however reports of flank pain are most likely
9 due to colic from ureteral obstruction [2].
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16 Bleeding can be continuous or intermittent and may last several months. Interestingly,
17 massive haematuria (as in our case) is mostly from the left kidney [2,3] and can
18 sometimes be identified on cystoscopy at the left ureteric orifice [2] or from the tip of
19 a papilla on ureteroscopy. Explanations for bleeding from the left side include
20 elevated venous pressure due to the many tributaries of the left renal vein. This leads
21 to a relatively greater anoxia in the left renal medulla increasing the likelihood of
22 sickling [4]. Bleeding in the contralateral kidney has been reported in 10-20% of
23 patients [1] and as such nephrectomy as a treatment option [3] has fallen quickly out
24 of vogue.
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34 The focus of treatment in this condition is to inhibit the fibrinolytic system and
35 prevent liquefaction of the clot at the bleeding site, thus promoting haemostasis and
36 healing. Treatment with epsilon-aminocaproic acid inhibits fibrinolytic activity and
37 can stop bleeding within 3-7 days of starting therapy [5]. Aminocaproic acid is an
38 analogue of lysine that competitively inhibits plasminogen activators (streptokinase,
39 urokinase tissue activators). Side effects such as intra-glomerular thrombosis and
40 urinary obstruction [6] as well as convulsions, cardiac and hepatic dysfunction have
41 been described.
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51 Tranexamic acid exerts its anti-fibrinolytic activity primarily by forming a reversible
52 complex with plasminogen which results in inhibition of fibrinolysis. While
53 prolonged treatment may increase the risk of a thrombosis, large scale studies reveal
54 that the incidence of this in women taking tranexamic acid for the treatment of
55 menorrhagia is no different from the spontaneous incidence of thrombosis in women
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[7]. Tranexamic acid is at least seven times more potent than aminocaproic acid when inhibiting fibrinolysis on a molar basis [8].

We report the first use of tranexamic acid in the treatment of persistent haematuria in patients with sickle cell disease. This antifibrinolytic agent should be considered as a treatment option in similar cases with appropriate multidisciplinary involvement.

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