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Persistent renin-angiotensin system activation after anti-reflux surgery and its management

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Glomerular filtration rate

Abstract *Purpose:* To study renin-angiotensin system activation and the role of angiotensin-converting enzyme inhibition (ACE-I) after anti-reflux surgery.
Material and Methods: Thirty nine children underwent anti-reflux surgery for high grades of primary VUR. Plasma renin activity (PRA), urinary microalbumin, renal scars, split renal function (SRF), glomerular filtration rate (GFR), serum creatinine, blood pressure and episodes of breakthrough urinary tract infection were monitored in the early (5.9 ± 3.9; range 3—9 months) and late (27.1 ± 6.5; range 15—36 months) postoperative phase, before and after therapy with ACE-I (mean period 13.6 ± 2.5; range 10—24 months).
Results: The early postoperative improvement in renal parameters (rise in SRF and GFR by 11.2% and 7.3%, respectively, and fall in PRA by 68.8%), was not sustained subsequently (minimal improvement in SRF, 7.4%, and GFR, 0.14%, was accompanied by a rise in PRA by 92.3%). After ACE-I therapy, improvement was noted in SRF and GFR by 0.5% and 7.5%, respectively, and there was a fall in urinary microalbumin by 52.3%.
Conclusions: Significant down regulation of rennin-angiotensin system activation and the accompanying improvement in renal function seen early after surgery is not sustained during follow up. ACE-I aids renal recovery.

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Introduction

Anti-reflux surgery is indicated for the treatment of vesico-ureteric reflux (VUR) once renal function shows signs of deterioration on non-operative management. However, new postoperative renal scarring has been observed, as reported from two previous prospective studies using excretory urography [1,2] as well as 99^{m}technitium dimercapto-succinic acid (DMSA) scan [3]. The pathophysiologic events which lead to renal scarring are mediated by renin-angiotensin system (RAS) activation resulting in apoptosis and renal scarring [4].

We recently reported high plasma renin activity (PRA) in patients with VUR which, although downgraded, persisted after anti-reflux surgery [5,6].

Proteinuria is an important indicator of poor prognosis and microalbuminuria the most sensitive and specific test for early identification of renal injury [7,8]. In this prospective study we have serially recorded tests of renal function as well as plasma renin activity (PRA) and urinary microalbumin levels before and after RAS blockade in patients who had successfully undergone an anti-reflux procedure. The aim of our study was to evaluate the role of early induction of angiotensin-converting enzyme inhibitor ACE-I (enalapril) after anti-reflux surgery in retarding the pace of renal damage.

Material and methods

Thirty nine children who underwent anti-reflux surgery formed the study group. Their mean age at presentation was 30.1 $\pm$ 19.8 (median 24.0) months (range 6—96 months), with a male-to-female ratio of 3:1, and various grades of primary VUR: grade III = 15, grade IV = 17 and grade V = 7. Fourteen (35.9%) patients had unilateral reflux and 25 (64.1%) bilateral reflux, totaling in all 64 refluxing ureters. These patients included direct referrals after the diagnosis of VUR was made, as well as those who developed indications for surgery after a period of non-operative management. Patients with GFR below 50 ml/min/1.73 m^2 and severely scarred kidneys were excluded from the study.

The salient features of this management included: low-dose antibiotic prophylaxis, triple micturition and management of urinary bladder by pharmacotherapy if any urodynamic abnormalities were present. Patients with dysfunctional voiding were excluded from the study.

During this period we monitored urinary microalbumin, renal scars, split renal function (SRF), glomerular filtration rate (GFR), serum creatinine, high blood pressure, episodes of breakthrough urinary tract infection (UTI) at regular intervals, as well as plasma renin activity (PRA). PRA was measured by radioimmunoassay using commercially available kit SB REN-2. Renal scars were evaluated by DMSA scan.

All the samples were taken with the patient in a sitting posture. These patients were on a normal diet which they had been taking on a routine basis. Each patient acted as their own control as far as comparison of subsequent values was concerned.

Blood pressure was measured by mercury sphygmomanometer using pediatric size cuffs at all times. When UTI occurred, therapeutic doses of antibiotics were used based upon culture and sensitivity reports. Data were collected only when urine had become sterile.

Grade of reflux was recorded by micturating cystourethrogram using the international criteria (Grade I to V). SRF was measured by L,L-ethylnyl cysteine radionuclide study to monitor any deterioration of function in individual units. GFR was measured by a multiple blood sampling technique following diethylene tetra-amine penta-acetic acid injection. Percentage change in GFR was calculated by the formula adopted by Smellie et al. [9] (Final GFR—Initial GFR/Initial GFR—100). Microalbuminuria was measured by enzyme immunoassay (normal range 2—20 mg/l).

Children with an increase in scar grade, decline in SRF, rise in serum creatinine, decline in GFR and recurrent breakthrough UTI (more than two episodes in the last 6 months) were identified, and ureteric reimplantation was performed by the same surgeon (MB) based on established international criteria. The level of RAS activation was recorded by measuring PRA. Parameters of renal function as well as PRA were recorded before and after surgery as well as after treatment with ACE-I. Urinary microalbumin levels were documented before and after RAS blockade using ACE-I. ACE-I was given to patients who had microalbuminuria whether or not they had renal scarring at a dose of 0.14 mg/kg/day and continued for a mean duration of 13.6 $\pm$ 2.5 months (minimum 10 months). While serum creatinine, GFR and DMSA scan were taken at 6 months and 1 year after surgery and then yearly, PRA was repeated every 6 months and microalbumin at 3 monthly intervals.

Analysis of data for patients who required anti-reflux surgery was done according to the phase of treatment (Table 1 and Fig. 1). Phase 1 covers the duration of time (mean 21.0 $\pm$ 6.9; range 12—34 months) when patients were on non-operative management and phase 2 indicates the period after surgery.

Phase 2 was further stratified into three sub-phases:

2a: early postoperative period without ACE-I therapy (mean duration 5.9 $\pm$ 3.9; range 3—9 months),
2b: late postoperative period without ACE-I therapy (mean duration 27.1 $\pm$ 6.5; range 15—36 months), and
2c: late postoperative period with ACE-I therapy (mean duration 13.6 $\pm$ 2.5; range 10—25 months).

Phase 2 data were also analyzed according to whether scarring was present (n = 23) or not present (n = 16).

Serum potassium levels were periodically monitored and none of the patients were found to have hyperkalemia. Parental consent was required for participation. Clearance was also obtained from the institutional ethical committee. This was a longitudinal observational study and not a randomized controlled trial.

Statistical analysis

Statistical analysis was carried out using STATA 9.0 (College Station, TX, USA) Data are presented as means (SE). Renal