PAPERS AND SHORT REPORTS

Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children

BIRMINGHAM REFLUX STUDY GROUP

Abstract

Children with severe vesicoureteric reflux were allocated at random within three age groups (<1, 1-5, and ≥6 years) to either operative or non-operative treatment. In 96 children who completed two years' observation there was no significant difference between treatment groups in either the incidence of breakthrough urinary tract infection, slope clearance of ^{51}Cr-edetic acid, renal length, new scar formation, or progression of existing scars. Ureteric reimplantation was technically successful in 97% of cases, whereas 74% of ureters managed non-operatively still showed significant reflux at two years.

No short term advantage was shown for either form of treatment in this series, but the long term effects of persistent, severe vesicoureteric reflux require further study. The prevention of reflux nephropathy probably demands the identification of vesicoureteric reflux before the advent of urinary tract infection, a goal not attainable with present invasive techniques.

Introduction

The relation between vesicoureteric reflux and renal parenchymal scarring is now firmly established,[1-5] intrarenal reflux evidently having an aetiological role in both man[6] and experimental animals.[7] Although scarring has been produced with sterile urine in pigs with high pressure obstructive reflux,[8] there is little to suggest that human reflux nephropathy occurs in the absence of urinary tract infection. Using chemoprophylaxis to prevent bacteriuria in children with vesicoureteric reflux might therefore seem a logical way of minimising renal scarring. The Cardiff-Oxford Bacteriuria Study Group,[9] however, found that treatment of bacteriuria in schoolgirls with vesicoureteric reflux did not affect either renal growth or progression of scarring. These findings, together with the failure to detect intrarenal reflux after the fifth birthday,[6] imply that the scarring process is initiated early in childhood and that subsequent medical intervention may be ineffective.

Infected urine can be prevented from reaching the renal parenchyma by surgical reimplantation of the affected ureter. Improved renal growth has been reported after reimplantation,[10] but without comparison with patients managed medically. The possible benefits of reimplantation must be weighed against the continuing tendency towards spontaneous resolution observed over a long period.[1 3 11]

We therefore embarked on a prospective trial of operative versus non-operative treatment. This trial, which is described in detail elsewhere,[12] includes clinical, functional, and radiological assessment at entry and again two years and five years after allocation. In this paper we report the main findings in 96 children from whom adequate data were obtained during their first two years of observation.

Patients and methods

GRADING OF VESICOURETERIC REFLUX

The severity of vesicoureteric reflux was graded on cystourethrography as 1 (reflux of contrast medium on filling or micturition which fails to reach the renal pelvis), 2 (contrast medium reaching the renal pelvis but not causing caliceal distension), and 3 (contrast medium distending the calices).

PATIENTS

Of all children considered for the study, just under two thirds were referred by regional paediatricians and the remainder either by general practitioners or via the hospital's accident and emergency

The Children's Hospital, Birmingham B16 8ET

Members of the group were: R Astley (consultant paediatric radiologist), R C Clark (senior paediatric registrar), J J Corkery (consultant paediatric surgeon), P Gornall (consultant paediatric surgeon), K J Shah (consultant paediatric radiologist), C M Taylor (senior paediatric registrar), R H R White (consultant paediatrician and nephrologist), M H Winterborn (consultant paediatrician and nephrologist).

This report was drafted by Drs R H R White and C M Taylor.

Correspondence to: Dr R H R White, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET.

department. The following criteria were required for entry into the study: (*a*) age less than 15 years at time of allocation; (*b*) vesicoureteric reflux diagnosed in the absence of active urinary tract infection less than six months previously; and (*c*) vesicoureteric reflux grade 3 with or without renal scarring, or grade 2 associated with renal scarring.

A patient was considered ineligible for the study if (*a*) the refluxing ureter drained an ectopic or horseshoe kidney or one that was functioning poorly as judged by intravenous urography; (*b*) vesicoureteric reflux was associated with complete duplication, ureterocele, obstructive uropathy, neuropathic bladder, or urinary calculus; or (*c*) operation had previously been performed on the lower third of the ureter or the bladder.

Eligible patients were stratified into three age groups (<1, 1-5, and $\geqslant 6$ years) and then allocated at random within each group (fig 1) to either operative or non-operative treatment. In the case of bilateral

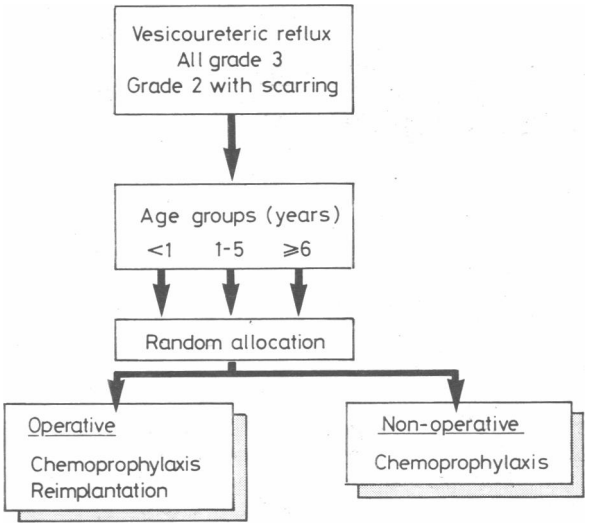

FIG 1—Flow diagram illustrating allocation procedure.

vesicoureteric reflux one or both ureters were included in the study depending on whether they met the inclusion criteria. For example, in a child admitted to the trial on the basis of grade 3 reflux in the right ureter but who also had left sided grade 2 reflux without scarring the analysis of radiological data was confined to the right kidney and ureter.

All patients received chemoprophylaxis in single nightly dosage throughout the two year period. Children who drew operative management underwent reimplantation of their affected ureters within six months after the diagnosis of reflux. Operations were performed by one of two surgical teams, using either a modified Leadbetter-Politano method (JJC) or the Cohen technique (PG).

On allocation each child was assessed clinically by one of us and the blood pressure recorded. A midstream urine sample was cultured. Renal excretory function was assessed by determining the slope clearance of chromium-51 labelled edetic acid (^{51}Cr-EDTA).[13] Intravenous urograms were reviewed by the radiologists, who, at the time of allocation, noted the presence or absence of caliceal distortion and cortical loss. Measurement of renal length was deferred until the results of the trial were analysed.

Regular hospital attendance, either at this hospital or at the referring hospital, was requested every three months and parents instructed to report sooner if symptoms of urinary tract infection developed. Blood pressure was recorded and the urine screened for infection at each visit.

All patients underwent reassessment of renal function together with repeat intravenous urography and cystourethrography two years after allocation. Children treated surgically had an additional intravenous urogram and cystourethrogram performed six months postoperatively to exclude ureteric obstruction and ensure that reflux had been abolished, but these films were not included in the radiological analysis. Most of the children referred from other hospitals had their radiographic examinations carried out locally, although all films were reviewed by our radiologists.

ANALYSIS OF RESULTS

The intravenous urograms were returned to the radiologists after obliteration of identification labels, to permit documentation of renal length and scarring without knowledge of the mode of treatment. Renal length was related to the intervertebral distance L1-3 and expressed as a standard deviation (SD). The formula SD = renal length $-[2{\cdot}6+0{\cdot}98\ (L1\text{-}3)]/0{\cdot}72$ was derived from the nomogram of Eklöf and Ringertz.[14]

The radiological workload was shared between RA and KJS. Preliminary tests showed that measurement of renal length was reproducible for each radiologist and that interobserver error was negligible. When difficulty arose independent interpretation was made by both radiologists; and when, despite this, there was still any difficulty a joint discussion was held between the two radiologists and RCC. If agreement could not be reached the patient was withdrawn. In all infants, and in all children showing new or progressive scars, both radiologists made independent assessments.

All data were transferred to computer cards and stored in an ICL 1906A computer, which was programmed to evaluate the observations recorded at entry, two years, and five years using Student's *t* test, Fisher's exact test, and Yates's corrected χ^2 test as appropriate. Our analysis is confined to the first two years of observation.

Results

CLINICAL FINDINGS

During July 1975 to December 1981, 109 children completed two years of observation; however, 13 were withdrawn on account of inadequate radiographs or failing to comply with the study protocol, leaving 96 patients for analysis. These comprised 15 infants (11 boys, four girls) and 81 children (32 boys, 49 girls) aged 1 year or more.

Table I shows the distribution of patients and resulting allocation of ureters between the two treatment groups. Similar proportions of patients in each treatment limb and age group were allocated for unilateral or bilateral reflux. Grade 3 vesicoureteric reflux was present in 130 ureters and grade 2 reflux in five. All five grade 2 ureters were associated with contralateral grade 3 reflux and, by chance, four were allocated to operative and only one to non-operative treatment.

One child with bilateral scarring and reduced glomerular filtration rate was found at allocation to have hypertension, as defined by the National Heart, Lung, and Blood Institute,[15] but no other child developed hypertension during the observation period. Of the 49 patients in the operative group and 47 in the non-operative group, 12 and 11 respectively had at least one episode of urinary tract infection, giving an overall incidence of 24%.

RENAL FUNCTION

Clearance of ^{51}Cr-EDTA showed no significant difference between treatment modalities at any age. Figure 2 shows the mean clearance (and standard error (SE)) in each age and treatment group at entry and at two years. The rise in clearance of ^{51}Cr-EDTA observed in patients aged under 1 year reflected the physiological increase in glomerular filtration rate related to body surface area in the first two years of life.[16]

RADIOLOGICAL DATA

The 96 patients yielded 135 kidneys drained by severely refluxing ureters, referred to here as the allocated kidneys (table II). At alloca-

TABLE I—*Randomisation of patients and ureters*

		Operative	Non-operative
No of patients:			
Total		49	47
Allocated for one ureter		29	28
Allocated for both ureters		20	19
No of ureters:			
Total		69	66
Vesicoureteric reflux grade	3	65	65
	2	4	1
Age (years)	<1	10	13
	1-5	33	26
	≥6	26	27

TABLE II—*Radiological data in allocated and unallocated kidneys at entry and after two years' observation*

	Allocated			
	Operative	Non-operative	Total	Unallocated
At allocation:				
No of ureters	69	66	135	55
Existing scarring	34	39	73	5
Renal length < −2·0 SD	12	18	30	0
After two years:				
Progression of scarring	7	11	18	2
Renal length decrease ⩾1·0 SD	22	20	42	5
New scars	2	2	4	1

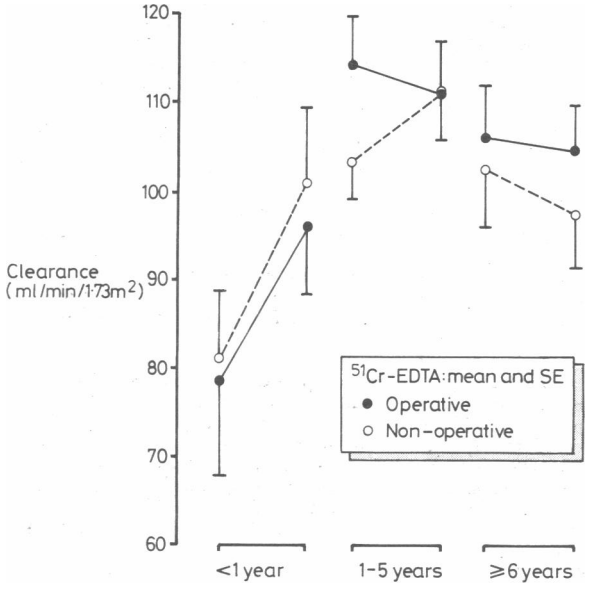

FIG 2—Clearance of ^{51}Cr-edetic acid (^{51}Cr-EDTA) for each age group, at allocation and after two years' observation.

TABLE III—*Radiological changes in kidneys exposed to breakthrough urinary tract infection related to mode of treatment and compared with unexposed kidneys*

	Exposed to urinary tract infection			Not exposed to urinary tract infection
	Operative	Non-operative	Total	
Total	17	18	35	100
Scarred at allocation	8	11	19	54
Progression of scarring	2	2	4	14
Renal length decrease ⩾1·0 SD	8	5	13	28
New scars	0	1	1	3

tion 73 (54%) of the kidneys were already scarred and 30 (22%) were also small (less than −2·0 SD in length), with an even distribution between treatment groups. After two years of follow up there were no significant differences between the two modes of treatment in the proportion of kidneys showing new or progressive scars (table II). Poor renal growth, which we defined as a decrease of renal length ⩾1·0 SD, was equally distributed between both treatment groups. Figure 3 shows the changes in mean renal growth in the three age groups. Renal growth was retarded at all ages and did not differ between treatment groups.

Table II compares the radiographic changes in allocated kidneys with those of the 55 contralateral kidneys for which the criteria for inclusion in the study were not met. These unallocated kidneys were of significantly greater mean length ($p < 0{\cdot}0005$), showed less existing scarring ($p < 0{\cdot}0005$), and grew better ($p < 0{\cdot}01$). The proportions of kidneys showing new or progressive scars, however, did not differ from those of the allocated kidneys.

Thirty five allocated kidneys were exposed to breakthrough urinary tract infection during the observation period. Table III shows that there were no radiological differences between the treatment groups. Table III also gives radiological details of the 100 allocated kidneys not exposed to breakthrough infection, and again these did not differ significantly from those of the exposed kidneys. Five kidneys developed new scars under observation; four are shown in table III. The fifth was in an unallocated kidney exposed to urinary tract infection but drained by a non-refluxing ureter. Two of the five children were more than 5 years old at entry.

Operative management was successful in abolishing vesicoureteric reflux in 67 out of 69 ureters (97%). The two failures continued to show significant reflux; there were no cases of postoperative ureteric obstruction. On the other hand, 48 (74%) of the 65 grade 3 ureters managed non-operatively still showed grade 2 or 3 reflux after two years.

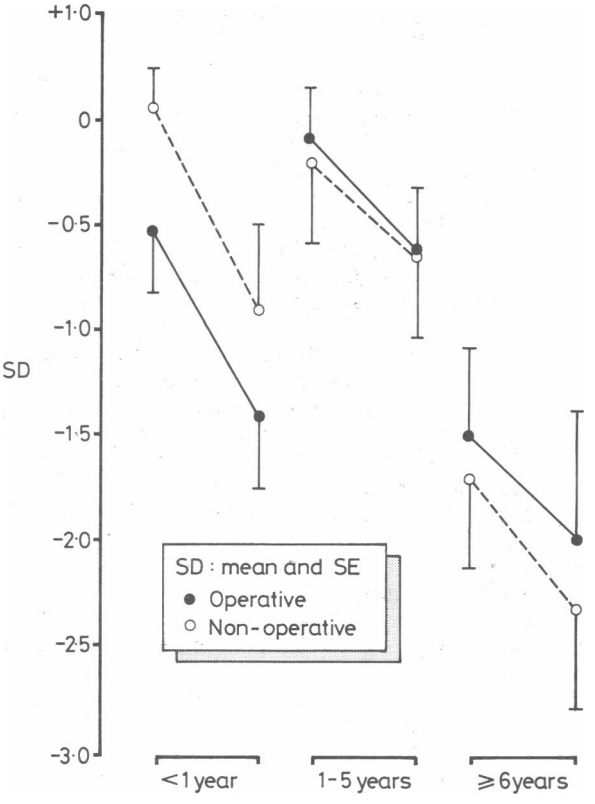

FIG 3—Renal length standard deviation (SD) for each age group at allocation and after two years' observation.

Discussion

We emphasise the interim nature of this report. Whereas reimplantation offers a technically successful corrective procedure, a high proportion of ureters managed non-operatively for two years showed persistent reflux of significant degree. Longer follow up,[3 11] however, indicates a continuing tendency to resolution of vesicoureteric reflux. Two years of observation is a brief period, and caution is therefore necessary in interpreting the results, especially since the long term effects of persistent, severe reflux are still unknown. Longer follow up of these patients is required.

In designing the trial we decided that, in order to eliminate the risk of introducing a variable owing to uncontrolled antibiotic administration, patients in the operative as well as the non-operative group should receive chemoprophylaxis against urinary and other infections. Nevertheless, breakthrough urinary tract infection occurred in a quarter of our patients. We did not, however, attempt to monitor compliance with medication, nor did we consider it reasonable to expect children without symptoms to attend the clinic at intervals of less than three months. The rate of infection was similar in patients in the operative and non-operative groups, confirming previous observations.[10]

We were unable to show any differences in renal excretory function between the treatment groups; however, ^{51}Cr-EDTA measures only total renal function. By means of ^{99m}Tc-pentetic acid renograms, Verrier Jones *et al*[17] have confirmed that impaired individual renal function is directly related to the presence of parenchymal scarring and is not affected by the persistence of either vesicoureteric reflux or urinary tract infection.

One uncontrolled study[10] reported improved renal growth after ureteric reimplantation, but we cannot confirm this. New scars and progression of existing ones were seen equally among operative, non-operative, and unallocated kidneys and bore no apparent relation to either persistent reflux or breakthrough infection. This confirms and extends the findings of the Cardiff-Oxford Bacteriuria Study Group[9] in schoolgirls. Although most of the few fresh scars reported develop before 5 years of age,[18] they may rarely appear later,[4 18] as our study confirms. The radiologically apparent scar represents the late result of fibrous contraction[19] and, with conventional imaging techniques, we could not state with confidence that the scarring process in our patients had not been initiated before the study.

Though severe bilateral reflux nephropathy is comparatively rare, it is nevertheless a common cause of end stage renal failure.[20] Moreover, even patients with unilateral scarring are at increased risk of developing hypertension,[21] so the prevention of reflux nephropathy must continue to be the main aim of management.

Controlled trials in this subject are few[22] and have an important contribution to make, but it is already apparent from our preliminary results that neither chemotherapy nor surgical intervention is likely to diminish the scarring process once initiated. Table II shows a disturbingly high prevalence of small, scarred kidneys before treatment began; moreover, fig 3 suggests that poor renal growth continues throughout childhood irrespective of treatment, so that the kidneys of many older children are reduced to less than $-2{\cdot}0$ SD in length and may never resume normal growth.[23]

Were the acquisition of renal scarring due to vesicoureteric reflux a continuing process, we could expect to find a higher prevalence in older children than in infants; table IV shows that this is not the case. This early occurrence of scarring perhaps parallels the rapid development of segmental inflammation and fibrosis shown in pigs when infected urine is refluxed into compound papillas.[24] Once the child has presented clinically it may already be too late to influence subsequent events. To prevent reflux nephropathy it may therefore be essential to identify vesicoureteric reflux before the advent of urinary tract infection. Until a non-invasive technique of cystourethrography has been evolved, however, this goal remains unattainable except in the at risk younger siblings of patients with known reflux, in whom screening by conventional methods may be justified.[25]

TABLE IV—*Prevalence of existing renal scarring related to age of patient at allocation*

	Scarred		Unscarred	
	Age < 1	Age ≥ 1	Age < 1	Age ≥ 1
No of kidneys	13	60	10	52

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