Angioplasty for renovascular hypertension in 78 children

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ABSTRACT

Objectives To evaluate the outcome of percutaneous transluminal angioplasty (PTA) in children with renovascular hypertension (RVH) treated at a single centre over 29 years.

Methods A retrospective study of the medical charts of all children with RVH who underwent PTA between 1984 and 2012. The primary outcome measurement was blood pressure (BP) achieved after the procedure. The BP before the procedure was compared with that at last available follow-up, 6 (range 0.6–16) years after the initial procedure.

Results Seventy-eight children with median (range) age of 6.5 (0.5–17) years were studied. Twenty-three (29.5%) had an underlying syndrome, 35 (44.9%) children had bilateral renal artery stenosis (RAS), 18 (23%) intrarenal disease and 11(14%) showed bilateral RAS and intrarenal disease. Twenty (25.6%) children had mid-aortic syndrome and 14 (17.9%) cerebrovascular disease. One hundred and fourteen PTA procedures were carried out including 31 stent insertions. Following PTA, BP was improved in 49 (62.8%) children and of those 18 (23.1%) were cured. Children with involvement of only the main renal arteries showed improved BP control in 79.9% of the children with cure in 39.5%. BP was intentionally maintained above the 95th centile for age and height in four children with coexistent cerebrovascular disease. No change in BP was seen in 18 children despite observed technical success of the PTA, and in seven children due to technical failure of the procedure.

Conclusions PTA provided a clinical benefit in 62.8% of children with RVH.

What is already known on this topic?

- Percutaneous transluminal angioplasty (PTA) is clinically effective in children with renovascular hypertension due to fibromuscular dysplasia and in stenosed renal transplant arteries.
- Most reports included small numbers or case reports with the largest series of 36 children.

What this study adds?

- This confirms that PTA with or without stent insertion is a safe and effective intervention in children with renovascular hypertension.
- Outcome of PTA in children with neurofibromatosis type 1 is similar to other children.
- Many children benefit from repeated procedures due to the nature of their often progressive disease.

INTRODUCTION

Percutaneous transluminal angioplasty (PTA) was first reported as treatment of renal artery stenosis (RAS) in 1978, in a 61-year-old patient.[1] It was soon shown to be clinically effective in children with renovascular hypertension (RVH) due to fibromuscular dysplasia (FMD)[2] and in stenosed renal transplant arteries.[3]

Renovascular stenotic lesions are frequently accompanied by involvement of the aorta and its visceral branches, which is known as mid-aortic syndrome (MAS). The most common cause of RAS in adult patients is atherosclerosis.[4] In children from Europe and North America the most common cause is FMD[5] and in children from Asia and South Africa it is Takayasu arteritis.[6] Over the last 30 years, many paediatric case reports and case series have been published on the use of PTA.[7–11]

In this study we report on our experience of PTA in 78 children with RVH who were treated over the last three decades at Great Ormond Street Hospital (GOSH) for Children in London.

PATIENTS AND METHODS

We have retrospectively reviewed the medical charts of all children who underwent PTA for treatment of RVH due to RAS at GOSH between January 1984 and December 2012. Children with stenosis of transplant renal arteries or stenosis of small intrarenal branches caused by an inflammatory multisystem disease such as polyarteritis nodosa were not included in this study. Demographic data, underlying syndromes, mode of presentation, blood pressure (BP) and antihypertensive drugs were recorded from the charts.

All children underwent diagnostic digital subtraction angiography.[12] When clinically indicated, cerebral MRI with MR angiography was performed. Children with abnormal findings on the cerebral MR studies or with significant neurological symptoms or signs also underwent cerebral angiography. Our indications for angiography and our treatment protocol for children with RAS have been presented elsewhere.[12 13]

All angioplasty procedures were performed by a paediatric interventional radiologist and radiographer, under general anaesthesia with endotracheal

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intubation and muscle relaxants. Arterial access (usually femoral but also axillary if appropriate) was obtained by ultrasound-guided puncture and insertion of a valved sheath. Diagnostic angiography consisted of abdominal aortography (biplane, or rotational with three dimensional reconstructions), selective angiography of all renal arteries in multiple projections, and selective angiography of other vessels if appropriate.

Other methods of evaluation of any abnormal arterial segment (such as pressure measurements, intravascular ultrasound or optical coherence tomography) were performed before and/or after angioplasty at the operator's discretion.

Angioplasty was performed with various types of balloons over this time period, with monorail 0.014-inch systems being used for most recent renal angioplasty procedures. Shaped guiding catheters or sheaths were used in larger children (over about 25 kg) if the aorta was not so narrow as to prevent the shape from being useful.

A stent was inserted in certain patients at the operator's discretion (see discussion), and always in the presence of flow-limiting dissection or occlusion that was not improved by reinflation of the angioplasty balloon.

Poor angiographic result of angioplasty was an indication early in the series, but with increasing recognition that this does not necessarily indicate a poor clinical response we no longer stent for this reason. Similarly, early recurrence of high BP after clinically successful angioplasty was regarded as an indication early in the series, but we now consider that repeat angioplasties are more appropriate in this setting.

Outcome categorisation was based on the criteria suggested by Ellis *et al*:[14] (1) 'cured,' with normal BP (<95th centile for age, gender and height) on no antihypertensive treatment; (2) improved BP with same or reduced treatment; (3) no change in BP despite angiographic success; or (4) technical failure (ie, unable to pass balloon catheter or unable to dilate vessel with balloon). Similar to our previous report we have added a fifth category; BP intentionally maintained above the 95th centile because of concerns that achieving too low a BP could impair the cerebral blood flow in children with cerebrovascular disease. The Schwartz formula was used to calculate estimated glomerular filtration rate (eGFR).[15] Short-term outcome was defined within 3 months from the procedure.

Statistical analyses

Results have been expressed as median and range. χ^2test was used when comparing outcomes.

RESULTS

Presentation

Seventy-eight children (who underwent 114 procedures) were included in this study. The median age at referral to our unit was 6.5 years (range 0.5–17 years). There were 51 boys (65.4%). Forty-six children were referred from within the UK (59%), 28 patients were referred from units elsewhere in Europe (35.9%) and four children from the Middle East (5.1%).

The median systolic BP at referral to GOSH was 160 mm Hg (range 90–240 mm Hg). This was 45 mm Hg (range 0–131 mm Hg) above the 95th centile for age, gender and height. The children were prescribed between one and eight antihypertensive drugs (median three).

In 36 children (46%) the elevated BP was discovered as an incidental finding without any symptoms suggestive of hypertension, while other children presented with severe cerebral or cardiac symptoms (table 1). Most of the younger children (<5 years of age) presented with severe symptoms while more than 50% of older children were discovered incidentally to be hypertensive (table 1).

Twenty-three children (29.5%) had an underlying syndrome: neurofibromatosis type 1 (NF1) in 19 children (24.3%), Williams syndrome in two, and one patient each with velocardiofacial syndrome and Alagille syndrome.

Left ventricular hypertrophy was diagnosed in 40 children out of 60 (66.7%) with available echocardiogram results. Eleven out of 47 investigated children (23.4%) showed evidence of hypertensive retinopathy. The median serum creatinine at presentation was 50 μmol/L (range 24–99 μmol/L) and the median eGFR was 104.1 mL/min/1.73 m^2 (range 44–144 mL/min/1.73 m^2). Nineteen children (24.4%) had an eGFR below 90 mL/min/1.73 m^2.

Findings on angiography

Thirty-five children (44.9%) had bilateral RAS, 18 (23%) showed intrarenal disease and 11 children (14%) had bilateral RAS and intrarenal disease. MAS was found in 20 (25.6%) children and was associated with bilateral RAS in 14 patients. Twenty-two children (28.2%) had mesenteric vessel involvement and 17 of those (77.3%) also had MAS. All 14 children (17.9%) with cerebrovascular involvement had bilateral RAS, including 8 with MAS (57%) and 9 (64.3%) with mesenteric involvement. Isolated stenosis of a segmental renal vessel was found in five children.

Angioplasty

One hundred and fourteen procedures were performed in 78 children, of which 15 were done on renal artery grafts. The median age at first PTA was 8.4 (range 1.0–17.9) years with median interval between referral and PTA of 0.4 (range 0–11) years. Some children required further procedures because of restenosis or inadequate results of the first procedure. Fifty-six patients needed only one treatment, 14 had two, 5 had three procedures and 3 children needed more than three procedures. The median duration between the first and the second

Table 1 Presenting features in all children and according to the age at presentation: <5 years, 5–11 years and 12–17 years

Mode of presentation	All children 78 (%)	Age< 5 years 26 (%)	Age 5–11 years 39 (%)	Age 12–17 years 13 (%)
Incidental finding	36 (46%)	6 (23%)	23 (59%)	7 (54%)
Headache with vomiting, lethargy or excessive screaming	14 (17.9%)	3 (11.5%)	8 (20.5%)	3 (23.1%)
Cardiac features (palpitations, congestive heart failure or murmurs)	8 (10.3%)	4 (15.3%)	3 (7.7%)	1 (7.7%)
Neurological manifestations (seizure or ptosis and eye movement disorder)	7 (9%)	4 (15.3%)	2 (5.1%)	1 (7.7%)
Facial palsy	6 (7.7%)	5 (19.2%)	1 (2.6%)	0 (0%)
Cerebrovascular accident	3 (3.9%)	1 (3.8%)	1 (2.6%)	1 (7.7%)
Poor feeding and failure to thrive	2 (2.6%)	2 (7.7%)	0 (0%)	0 (0%)
Hyponatraemic-hypertensive syndrome (HHS)	1 (1.3%)	1 (3.8%)	0 (0%)	0 (0%)
As part of investigations for neurofibromatosis type 1	1 (1.3%)	0 (0%)	1 (2.6%)	0 (0%)

procedures was 13 (0.4–60) months and between the second and the third procedures 40 (0.9–60) months. Thirteen procedures involved PTA of arterial grafts.

Angioplasty in single kidneys

Eight children had single kidneys at presentation to us (seven had previous nephrectomies and one a congenital single kidney). They had PTA at a median age of 7.6 (3.5–16.2) years, with a stent inserted in one child.

Complications

Complications of PTA occurred in 13 (11.4%) of the 114 procedures, including a procedure-related death. One patient, 8 years of age, with severe bilateral RAS, developed a fatal haemorrhage from a graft tear after repeat angioplasty of a synthetic graft to a solitary kidney which was placed after nephrectomy of the contralateral kidney.

Four procedures were complicated with a thrombosis; in one child a clot was seen in a branch of the renal artery after successful PTA. The second child had angioplasty with insertion of a stent, which occluded very rapidly after the procedure. Renal perfusion was markedly reduced (to 8%) on a technetium-99m dimercaptosuccinic acid (DMSA) scan. The third was a 15-year-old girl who had a thrombosis of a covered stent in an upper pole renal artery (following inappropriate discontinuation of antiplatelet therapy for elective surgery); this was successfully treated with angioplasty. All three children were treated by heparin and aspirin, in addition to clopidogrel in the third child. This was successful in the first and third patients only. The fourth child was a 4-year-old boy who underwent PTA and insertion of a flow-diverting stent for otherwise untreatable aneurysmal disease. He had a postoperative ultrasound study that suggested decreased perfusion to the kidney. This was treated with heparin and tissue plasminogen activator infusion. DMSA subsequently showed no uptake in the kidney and it was removed after stopping antiplatelet agents.

One child with pulmonary artery stenosis and atrial septal defect developed congestive cardiac failure, right pleural effusion and tender hepatomegaly following angioplasty and stenting of the abdominal aorta. He also developed a self-limiting pseudoaneurysm in his left axilla. One child developed a small groin haematoma and another had groin pain. Both resolved spontaneously.

Short-term outcome

After their first procedure 14 children (17.9%) were cured (achieved normal BP on no treatment) and another 31 children (39.7%) achieved improved BP on the same or reduced medication (table 2). The outcome improved with further procedures. An improvement in BP control was observed in 79.9% (30 out of 38) of the children when only the renal arteries were stenosed (cure in 39.5%, table 3). Eighteen children remained hypertensive despite radiologically adequate dilatation and the angioplasty was unsuccessful in seven children, in some more than one procedure was unsuccessful (table 3). None of the children with mid-aortic syndrome or cerebral involvement achieved cure, but 7 out of 12 (58%) showed improvement.

There was a non-significant tendency that children below the age of 5 years more often were improved or cured compared with those older than 5 years, 65% versus 42% (p=0.09). One of the eight children with a solitary kidney was cured and stopped all antihypertensive medications, five children achieved improvement in their BP with control on fewer medications and two children did not benefit from the procedure.

The median (range) of last eGFR was 97.4 (40–189.4) with 17 children <90 mL/min/1.73 m^2. Results of DMSA scans were available for 70 children at presentation; 16 had a normal DMSA scan with equal uptake, two children with a solitary kidney had normal uptake and 54 children had an abnormal DMSA scan with reduced uptake or focal lesions. Of those with an initial abnormal DMSA scan, 30 had a follow-up scan: 13 showed improvement and 6 developed a normal DMSA with equal uptake, while 3 children had worsening of their scans. The remaining 11 children had static DMSA scan appearances.

Restenosis

Restenosis occurred in 12 native arteries out of 69 that underwent only balloon dilatation (17.4%), and in 11 of 31 arteries that required stent insertion (35.5%) (p=0.046). Ten patients needed surgical revascularisation later, there were four nephrectomies and two children required surgical removal of aneurysms with autotransplantation.

Children with neurofibromatosis type 1

Of the 19 children with NF1, 6 (31.6%) were cured and 10 (52.6%) had an improvement in their BP, while 3 children continued to have high BP (table 4). This is not different from the results in the whole group. The best outcome was observed in children with main RAS, as all of them showed improvement of their BP with two-thirds cured. None of the 10 children with aortic or cerebrovascular involvement achieved cure, but seven improved.

Long-term follow-up

The median duration of follow-up from the first procedure was 6 (range 0.6–16) years and from the last procedure 3 (0.1–14) years. At the time of last available data 28 children were still followed at GOSH, 32 were treated at their referring centre, 16 had made the transition to adult units and there were 2 deaths. One death was procedure-related, in early years, and one was due to a fatal dysrhythmia secondary to myocardial fibrosis resulting from severe hypertension at 16.8 years of age.

At this last assessment in the study, 23 (82.1% of the 28 followed at GOSH) had improvement in their BP, including 6

Table 2 Outcome of 114 angioplasty procedures

Procedure	Total	Cured	BP improved on same or ↓ treatment	BP>95% + cerebrovascular disease	BP unchanged or increased treatment	Technical failure
First PTA	78	14	31	2	17	14
Second PTA	22	4	11	2	1	4
Third PTA	8		2	2	4	
>3 PTAs	3			1	2	

BP, blood pressure; PTA, percutaneous transluminal angioplasty.

Table 3 Outcome in the children according to pattern of stenosis

Pattern of stenosis	Total	Cured	BP improved on same or ↓ treatment	BP>95%+cerebrovascular disease	BP unchanged or increased treatment	Technical failure
Main RAS	38 (8 bilateral)	15 (39.5%)	15 (39.5%)		7 (18.2%)	1 (2.6%)
RAS and intrarenal disease	14 (6 bilateral)	3 (21.4%)	4 (28.6%)		3 (21.4%)	4 (28.6%)
RAS (±intrarenal disease) and MAS	12 (8 bilateral)		7 (58.3%)		4 (33.3%)	1 (8.3%)
RAS (±intrarenal disease) with cerebrovascular disease	6 (5 bilateral)		3 (50%)		3 (50%)	
RAS (±intrarenal disease) with MAS and cerebrovascular disease	8 (8 bilateral)		2 (25%)	4 (50%)	1 (12.5%)	1 (12.5%)
Total	78 (35 bilateral)	18 (23.1%)	31 (39.7%)	4 (5.1%)	18 (23.1%)	7 (9.0)%

BP>95% signifies a blood pressure higher than the 95th centile for age, gender and height centile; MAS, mid-aortic syndrome; RAS, renal artery stenosis.

(21.4%) who did not need antihypertensive medication. Three patients (10.7%) remained hypertensive on either the same or increased medications and two children (7.1%) had uncontrolled hypertension.

DISCUSSION

We present our experience of 78 children who were treated with PTA for RVH over a 29-year period. We confirm our previous results, and those of others, that PTA is a relatively safe and effective way to improve BP in children with RAS and related vascular problems. All these children were initially medically treated but had not achieved adequate BP control.

There was no mortality related to the procedure in recent years. This is encouraging as we have, over time, been treating children with increasing disease severity, referred to us from many different countries.

Since our last report in 2006, many case reports and a few case series have been published.[16–25] Srinivasan *et al* from Philadelphia reported 19 children, with cure in 39% and improvement in BP in 17%.[11] Similar to our experience, their highest success rate (9 out of 10) was in those with single or discrete lesions of less than 10 mm in length. A high success rate has also been reported by other authors in children with involvement of only the main renal arteries, without intrarenal or extrarenal stenosis, with success rates ranging from 60% to 82%.[16 18]

Bayrak *et al*[19] from Turkey reported their experience of using PTA in 20 children with RAS, with a success rate of 100%. The underlying aetiologies in their children were Takayasu arteritis in 12, FMD in 5 and NF1 in 3 cases. This confirms the previous observation by Tyagi *et al* that PTA is safe and effective in RVH caused by arteritis, which is the most common cause of RAS in Asian children.[9]

Many centres use angioplasty, like we do, as first-line treatment of renovascular disease in children. We use surgery as second-line treatment when angioplasty has failed or when it is not technically possible. Some other centres instead advocate surgery as the preferred first-line treatment, with seemingly good results.[20] It is however quite common that the angioplasty needs to be repeated several times to get a full response and also to repeat the treatment as the arteries narrow down again after an initial good response.

It is, however, important to realise that not all children are helped by PTA. There are several reasons for this. The most important is that many children have multiple stenosed vessels. Additionally, in a quarter of our patients MAS was also present and usually associated with severe, widespread disease including bilateral RAS and intrarenal vascular pathology.[21] In the children who also had significant intrarenal disease, seemingly successful treatment of main artery stenoses might fail to improve the BP.

It is not clear whether children with NF1 are more difficult to treat than children with FMD. In our present study the results for children with NF1 were similar to those of the children without NF1. This is similar to the experience of Srinivasan *et al*.[11] Other authors have, however, reported more disappointing results in children with NF1.[22 23] The good results in children with NF1 could perhaps be explained by more frequent use of cutting balloon angioplasty in recent years, as NF1 lesions have been noted to be particularly fibrotic.[8 22] Cutting balloon angioplasty has been reported to be effective in resistant RAS.[24]

Our success rate of PTA in single kidneys was high (75%), indicating that PTA should be considered as a viable option in

Table 4 Outcome according to pattern of stenosis in children with neurofibromatosis type 1

Pattern of stenosis	Total	Cured	BP improved on same or ↓ treatment	BP>95% +cerebrovascular disease	BP unchanged or increased treatment	Technical Failure
Main RAS	6	4 (66.7%)	2 (33.3%)	0	0	0
RAS and intrarenal disease	3	2 (66.7%)	1 (33.3%)	0	0	0
RAS (±intrarenal disease) and aortic stenosis	5		4 (80%)		1 (20%)	0
RAS (±intrarenal disease) with cerebral vascular disease	2		1 (50%)	0	1 (50%)	
RAS (±intrarenal disease) with aortic and cerebral disease	3		2 (66.6%)	0	1 (33.3%)	0
Total	19	6 (31.6%0	10 (52.6%)	0	3 (15.8%)	0

BP>95% signifies a blood pressure higher than the 95th centile for age, gender and height centile; MAS, mid-aortic syndrome; RAS, renal artery stenosis.

children with hypertension due to RAS in a solitary kidney, since it has the potential of improving hypertension while preserving renal function. Successful PTA in single kidneys has also been previously reported.[26 27]

A third of patients who had a stent inserted experienced restenosis. This is similar to our previous report and higher than that seen in adult patients with atherosclerosis.[10] The experience with stent implantation in RAS in children is limited to very few reports with a small number of patients (10 patients in 8 reports).[7 16 26 28–31] Stent placement can be particularly helpful in children with severe or recurrent lesions and to manage iatrogenic dissection.[10 32]

Potential acute complications of PTA include dissection with renal artery occlusion and perforation with the potential for a severe bleed. We therefore always have a vascular surgeon on standby.[33]

In conclusion, our preferred therapy at this moment in time is to start with medical therapy. This treatment is however only successful in a small minority of children with RAS. As our second step we use PTA with or without stent insertion. This has proven to be a safe and effective intervention for many children with RVH. We recommend surgery in the small group of children where the combination of PTA and medical treatment is not enough to control the BP and/or preserve kidney function. There is a small subgroup of children where neither PTA nor surgery is enough to achieve a good BP. Some of these children respond well to treatment with an ACE inhibitor or angiotensin II receptor blocker. The family does, however, in those cases need to be thoroughly informed that this treatment is likely to damage the kidney/part of the kidney that has its blood supply from the affected blood vessel/s.

Contributors JAK: Coordination of the study, collecting the data and writing up the manuscript. DJR: Performing the procedures, providing and reviewing the data and editing the manuscript. CAML: Performing the procedures, providing the data and editing the manuscript. MD: Discussing all patients and performing surgery, providing the data and editing the manuscript. MJD: Leading on the service during the first time period, providing the data and editing the manuscript. GH: Discussingall patients and performing surgery,providing the data and editing the manuscript. SM: Looking after patients, providing the data and editing the manuscript. RS: Providing the data and editing the manuscript. KT: Leading on the service and looking after the patients during the later time period, supervising the study, providing the data and editing the manuscript.

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