Comparison of different substances for subureteric injection in the management of vesicoureteric reflux in children

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Introduction: *Endoscopic techniques are becoming increasingly accepted for treatment of vesicoureteric reflux as alternatives to open surgical reimplantation. However, there is some debate about the ideal injectable material. Since we have accumulated experience with several substances, an opportunity existed to compare them.*

Materials and methods: *From 1991 to 2003, 101 children with vesicoureteric reflux were treated by endoscopic subureteric injection either once (74) or twice (27) by either of two pediatric urologists. There were a total of 165 ureteral injections, 83 with polytetrafluoroethylene (Teflon®), 73 with polydimethylsiloxane (Macroplastique®), and 9 with collagen. Each child was evaluated pre-operatively and 3 months post-operatively with a nuclear cystogram and renal ultrasonography.*

Results: *The polytetrafluoroethylene and polydimethylsiloxane groups were not significantly different with respect to sex, age, indication for surgery, severity of reflux or prior surgeries. The collagen group overall did very poorly with only 3 of 9 refluxing ureters cured. The other two substances had much more success with 61% of ureters in the polytetrafluoroethylene group cured on first injection and 75% with polydimethylsiloxane, plus another 19% and 11% cured on second attempt, respectively (total 80% and 86%).*

Conclusions: *Subureteric injections of polytetrafluoroethylene and polydimethylsiloxane are very effective at curing vesicoureteric reflux in children with little morbidity. When comparing individual cases, ureters, and all grades of reflux, polytetrafluoroethylene and polydimethylsiloxane have similar success rates. Collagen injections were less successful, and patients with neurogenic bladders had poor results.*

Key Words: vesicoureteric reflux, Teflon®, Macroplastique®, collagen, endoscopic subureteric injection

Introduction

Vesicoureteric reflux (VUR) is a congenital condition that is the result of a short intramural ureteral tunnel combined with the absence of adequate detrusor support behind the intravesical ureter.[1] It is very common, being found in 30%-50% of all children diagnosed with urinary tract infections[2] and in 17.2 % of children without a history of UTI.[3]

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VUR has significant health consequences. It is the most common cause of severe hypertension in children and young adults[4] and 5% of all people with end stage renal disease have reflux nephropathy as their primary diagnosis.[5]

The treatment goal of VUR is to prevent infected urine from reaching the immature kidneys, thus avoiding pyelonephritis and renal scarring. Conservative treatment with antibiotic prophylaxis until the reflux resolves spontaneously is a popular option, however antibiotics have side effects, parents are often hesitant to give their child long term pharmacotherapy and the child may be at risk for pyelonephritis once antibiotics are stopped. Open surgical repair is highly successful (98.8%),[6] but can have

significant morbidity. Endoscopic subureteric injection is a simple day surgery procedure with minimal morbidity, but is less effective than ureteric reimplants.[6]

The best injectable material has yet to be determined, but polytetrafluoroethylene paste (Teflon®) was the first material used for the endoscopic correction of reflux.[10] However, it causes granuloma formation at the injection site and can migrate to lymph nodes, and possibly to lung and brain with giant granuloma formation.[7] Collagen is gluteraldehyde cross-linked bovine collagen and it is also used for sutures and cardiac valves. It has minimal tissue reaction, but tends to disappear with time.[8]

Macroplastique® is 40% polydimethylsiloxane (silicon particles) suspended in 60% hydrogel. It is an elastomer that has minimal migration, but animal studies show a potential risk of autoimmune reaction or malignancy.[9]

At our centre we initially used polytetrafluoroethylene because it was the only substance available at that time. We then switched to polydimethylsiloxane when it became available in Canada and we also did a small trial of collagen. The switch to polydimethylsiloxane was made because of concerns raised in the literature about polytetrafluoroethylene's long term safety[7] and it had never been approved by Health Protection Branch for the VUR indication, although we did not have any adverse effects specific to this substance.

Materials and methods

From July 1991 to August 2003, 101 children with VUR were treated by endoscopic subureteric injection either once (74) or twice (27) by either of two pediatric urologists at our institution.

The procedure was done endoscopically as an outpatient procedure under general anesthetic with intravenous antibiotic coverage using 2 mg/kg gentamicin. The technique did not differ with the various injectable substances; the material was injected subureterically at the six o'clock position using a needle specifically designed for this purpose, with the goal being to convert the orifice into a slit-like crescent appearance. The children were continued on their oral antibiotic prophylaxis until their return visit at 3 months.

There were a total of 165 ureteral injections as follows: polytetrafluoroethylene - 83, polydimethylsiloxane - 73, collagen - 9. Each child was evaluated 3 months post-operatively with a nuclear cystogram and renal ultrasonography.

Pre-existing bladder anomalies, indications for the procedure, cure rate, need for further treatments and complications were evaluated with a retrospective chart review.

Our institution began subureteric injections in 1990, however the first year of our experience was excluded from analysis to allow for adequate mastery of the technique.

Results

The 80 girls and 21 boys were a mean age of 90 months at the time of operative intervention. The indications for intervention included one or more of the following: breakthrough UTI (52%), non-compliance with antibiotics (10%), un-resolving reflux approaching puberty (37%), severe grade reflux (7%), and renal scarring (51%). Ongoing reflux approaching puberty was never a solitary indication for surgery. In evaluating for other associated conditions 13% of the children had neurogenic bladders and 14% had had prior bladder surgery, half of those surgeries were for reflux. Reflux grade was defined based on the nuclear cystogram with grade I: reflux only into the ureter, grade II: reflux filling ureter and renal pelvis, Grade III: as with II, but with dilatation of either the ureter or pelvis. Improvement in reflux was not evaluated since this is not the desired outcome. Only complete absence of reflux on repeat nuclear cystogram was considered to be a cure. The polytetrafluoroethylene, polydimethylsiloxane and collagen groups were not significantly different with respect to sex, age, indications for surgery, severity of reflux or prior surgeries, Table 1. Preoperative reflux was grade I or II in 44% of ureters and grade III in 66% and cure rate was significantly better with grade I or II reflux regardless of material used for injection, Table 2.

The collagen group overall did very poorly with only 2 of the 6 children being cured of their reflux (3/9 ureters cured). One of these "cured" children had his reflux recur 2 years later and was ultimately cured with a polytetrafluoroethylene injection. Collagen was only briefly used at our institution because of these very poor results.

When comparing renal units: the polytetrafluoroethylene group was 61% cured on first injection and another 19% cured on second attempt for an overall success rate of 80%. Polydimethylsiloxane had slightly better results with 75% of ureters cured on first injection and a further 11% cured with a second (86%), but this did not reach statistical significance ($P>0.05$). Table 2

The group with neurogenic bladders did poorly regardless of material used for injection with a cure rate of 29% and 40%. Grades I - II reflux had a cure rate of 84% with both polytetrafluoroethylene and polydimethylsiloxane, but higher grade reflux had a

TABLE 1. **Demographics**

Material	Polytetra-fluoroethylene	Polydimethyl-siloxane	Collagen	Total	P**
Children	49	49	6*	101	-
Age (months)	91	86	139	90	0.35
Female	42	36	2	80	0.17
Ureters	83	73	9	165	-
Prior bladder surgery	3	5	0	8	-
Prior open reflux surgery	4	3	0	7	-
Neurogenic bladder	9	4	0	13	-
Pre-op grade mean	2.5	2.4	2.0		0.14

*3 of these children subsequently had injections with polytetrafluoroethylene.
**One way ANOVA test comparing polytetrafluoroethylene and polydimethylsiloxane

cure rate of only 50% with polytetrafluoroethylene and 63% with polydimethylsiloxane, Table 2.

The polytetrafluoroethylene and polydimethylsiloxane groups each had 16 children fail subureteric injection. Eight of these children were continued on antibiotics, 8 underwent open surgical repair while 8 others were given a trial off antibiotic prophylaxis. The remaining eight cases had incomplete documentation of their subsequent management.

Complications were minor. One polytetrafluoroethylene case developed renal colic post-operatively which resolved spontaneously and there was one polydimethylsiloxane case of extrusion of injected material 2 years after treatment with urethral irritative symptoms. There were no cases of postoperative UTI or of long-term hydronephrosis.

Discussion

According to published literature subureteric injection is not as successful as open ureteric reimplantation (91.6% versus 96%) in treating pediatric VUR.[6] However, this is a minimally invasive technique that is performed as day surgery with low morbidity. There is no consensus on the ideal injectable material to treat VUR and there are several substances that have been used for these injections. The use of polytetrafluoroethylene particles suspended in glycerine paste (Teflon®) was pioneered by Puri and O'Donnell in 1984 with a success rate of 77% in their trial with 13 girls.[10] Since then, several studies with large numbers have been published with success between 44% and 90%[11] for cure with first injection and 66% to 94% with additional injections.[12,13] The largest survey to date with 6216 refluxing ureters in a European multicenter study showed cure in 76% with one injection and 86% with additional injections.[14] This is in keeping with our results of 61% on first attempt and 80% on second.

Cross-linked bovine collagen has also been used in the past with varying success. Capozza et al reported 78% cure with one injection and 81% success with multiple injections. They did however find a recurrence rate of 18% at only 18 months.[15] Our poor results indicated that we should not continue using this substance.

TABLE 2. **Cure rate**

Cure with:	Polytetrafluoroethylene	Polydimethylsiloxane
First injection	51/83 (61%)	55/73 (75%)
Second injection	15/32 (47%)	8/18 (44%)
Total cure	66/83 (80%)	63/73 (86%)
Neurogenic bladder	4/14 (29%)	4/10 (40%)
Grade I-II	31/37 (84%)	27/32 (84%)
Grade III	23/46 (50%)	26/41 (63%)

P> 0.05 comparing polytetrafluoroethylene versus polydimethylsiloxane using one way ANOVA test.

Macroplastique®, polydimethylsiloxane (silicon rubber) particles suspended in a hydrogel,[4] is an elastomer that minimizes the risk of migration and prevents retraction of the substance once injected.[9] Success has been reported from 80.6% to 81%[6,16] with one injection, and 90% to 93.3%[16,17] with multiple injections. The success rate of 75% with one injection and 86% with two in our patients is consistent with these results.

Of the 32 children who ultimately failed endoscopic treatment, eight went on to have open ureteric reimplantation and 5/8 (63%) were cured. The surgeons did not experience any greater difficulty in performing the surgery in comparison to children who had never had any endoscopic injection.

Although it has been our practice to obtain a renal ultrasonographic examination at the 3 month follow up visit to assess for evidence of ureteric obstruction, it should be noted that new hydronephrosis was not observed in any of our cases. Therefore, we question the utility of this investigation in the absence of any clinical indications, and have recently adjusted our approach to omit the test in the majority of cases.

Although safe in the short-term, the major concern with these injections is the long-term risk of particle migration, granuloma formation, and the future unknown risk of malignancy or other problems in this pediatric population.[7]

This retrospective study shows that polydimethylsiloxane provides as good results as the product originally used for the endoscopic treatment of VUR, polytetrafluoroethylene. The safety issue prevented us from performing a direct head to head comparison of the two substances, as polytetrafluoroethylene has now been relegated to a position of historical interest at our institution.

A new substance is now available on the Canadian market for subureteric injection: Deflux® is dextranomer microspheres suspended in a sodium hyaluronic acid solution. It may be as efficacious as polydimethylsiloxane[9] although a large direct comparison of the two substances remains to be reported. We have added Deflux® to our armamentarium in the management of VUR.

Conclusion

Subureteric injections of polytetrafluoroethylene and polydimethylsiloxane are very effective at curing vesicoureteric reflux in children with little morbidity. When comparing individual cases, renal units, and all grades of reflux, polytetrafluoroethylene and polydimethylsiloxane have similar success rates. Regardless of substance used, children with neurogenic bladders had poor results with subureteric injection. □

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