

—Originals—

Endoscopic treatment of vesicoureteral reflux in children with
glutaraldehyde cross-linked bovine dermal collagen

Short-term results

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Abstract

Background: Endoscopic treatment using glutaraldehyde cross-linked (GAX) collagen was conducted on 4 children with bilateral primary vesicoureteral reflux (VUR) ... a 1-year-old boy and three 5- to 8-year-old girls ... all having a history of repeated hospitalization for fever due to acute pyelonephritis, visiting as pediatric outpatients regularly and receiving antibiotics continuously. By international VUR classification, 4 ureters were grade 3, 2 grade 4, and 2 grade 5.

Methods: After nonallergy to GAX collagen was confirmed intracutaneously, a needle was used through a 9.5 Fr cystoscope channel to puncture bladder mucosa 4 to 5 mm from the affected ureteral orifice at 6 o'clock under general anesthesia; 1.1 to 1.9 ml of GAX collagen was injected immediately below affected orifices.

Results: Three months after surgery, voiding cystourethrography showed reflux had disappeared in 6 ureters, for a short-term success rate of 75%. VUR in the Remaining 2 ureters improved from grade 3 to 1 and from grade 5 to 4. No postoperative urinary tract infection occurred and antibiotics were stopped.

Conclusion: Since GAX collagen is less viscous than Teflon paste, it is easily injected into submucosa, does not form granuloma or migrate to other organs, and is noncarcinogenic. Endoscopic VUR treatment using GAX collagen is indicated when less invasion and shorter hospitalization are considered, although it requires general anesthesia, which itself involves some risk. (J Nippon Med Sch 2000; 67: 9—12)

Key words: VUR, endoscopic treatment, GAX collagen

Introduction

The association between vesicoureteral reflux (VUR) and renal injury has been well established. Reflux nephropathy in association with urinary tract infection has been shown to be the cause of renal insufficiency and hypertension in large numbers of children. VUR is conventionally treated two ways: conservatively, controlling urinary tract infection with antibiot-

ics until reflux disappears, and surgically. Since Teflon paste endoscopically injected into submucosa immediately below the affected ureteral orifice was demonstrated to be successful in eliminating VUR in 1981¹, this has often been used^{2,3}. Teflon, however, involves disadvantages such as the granuloma formation and the migration to other organs^{4,5}. We report favorable short-term (3 months after surgery) results of endoscopic VUR treatment in children using glutaralde-

hyde cross-linked (GAX) bovine dermal collagen.

Materials and Methods

1. Materials

Four Japanese children with bilateral primary VUR ...a 1-year-old boy and three 5- to 8-year-old girls... had a history of repeated hospitalization for fever due to acute pyelonephritis, visiting as pediatric outpatients regularly and receiving antibiotics continuously. By international VUR classification, 4 ureters were classified grade 3, 2 grade 4, and 2 grade 5. ^{99m}Tc -DMSA reno-scintigraphy showed atrophy in 1 kidney and scarring in 4 (Table 1).

2. Methods

Informed consent was obtained from the subjects' representatives after the following were explained: (1) GAX collagen is not approved for use in VUR treatment in Japan; (2) health insurance does not

cover collagen use; and (3) possible benefits and risks of alternative treatments and endoscopic treatment using collagen. The subjects were monitored for 4 weeks after GAX collagen was administered intracutaneously to confirm collagen nonallergy. The bladder's inner surface was observed using a universal operating urethrocystoscope (Wolf Co., Ltd., 9.5 Fr) under general anesthesia. The location, number, and shape of ureteral orifices and presence of vesical diverticulum and/or trabeculation were noted. A 22-gauge needle (Bird Co., Ltd.) filled with GAX collagen was inserted into a cystoscopic instrument channel and punctured bladder mucosa 4 to 5 mm from the affected ureteral orifice at 6 o'clock (Fig. 1). GAX collagen, 1.1 to 1.9 ml, was injected into the submucosa immediately below the orifice. It was injected until the area directly below the orifice swelled into a mountain-like shape and the orifice was blocked (Fig. 2). The needle remained in the injection site about 2 minutes until the collagen set. After needle removal, no

Table 1 Patient's back ground and results

Case	Age	Sex	Pre-operative VUR grade		Post-operative VUR grade	Renal scar	Post-operative UTI
1	7	F	Rt	3	0	+	-
			Lt	3	0	+	-
2	8	F	Rt	5	0	atrophic	-
			Lt	4	0		
3	5	F	Rt	3	1	+	-
			Lt	3	0		
4	1	M	Rt	5	4	+	-
			Lt	4	0		



Fig. 1 The needle perforates the bladder mucosa 4 to 5 mm distal to the refluxing ureteral orifice, at the 6 o'clock position



Fig. 2 Ureteral orifice after GAX collagen injection



Fig. 3 Preoperative voiding cysturethrogram showed grade 5 VUR on the right side and grade 4 on the left



Fig. 4 Post-operative voiding cysturethrogram showed disappearance of bilateral VUR

GAX collagen leakage or hemorrhage from the injection site was found. As the affected ureters were treated bilaterally in 1 session, urinary flow from the treated orifices was confirmed before endoscopic treatment was terminated.

Results

Posttreatment VUR and urinary tract infection

were studied in 8 ureters of 4 children. Voiding cystourethrography 3 months after treatment showed VUR had disappeared in 6 (Fig. 3, 4)-a 3-month success rate of 75%. Observation was, however, too short for 1-year or long-term results. VUR remaining in 2 ureters improved from grade 3 to 1 and from grade 5 to 4. Urinalysis showed no evidence of urinary tract infection (Table 1). As no subjects suffered from fever due to acute pyelonephritis after treatment, antibiotic therapy was stopped.

Discussion

GAX collagen (Contigen: BIRD) has advantages over Teflon paste; lower viscosity eliminates the need for a high-pressure injector; the use of a fine needle in a cystoscope enables surgeons to pinpoint the target mucosa and inject the desired amount of collagen easily into the submucosa, which support the ureteral floor of the uretero-vesical junction; and this is no formation of granuloma or migration to other organs after injection. Injected GAX collagen was reported not to affect surgery even in open operation⁶. Some surgeons avoid use of Teflon paste in children because of possible migration and granuloma⁷. GAX collagen stability in long-term use remains to be confirmed. GAX collagen cannot be used in patients allergic to it, although such cases are rare. As a result of endoscopic VUR treatment in children, Frey et al⁸ achieved on 85 to 90% success rates using Teflon paste and 65 to 85% using GAX collagen. Results using GAX collagen appear to be slightly less satisfactory than those using Teflon paste.

Since reflux may disappear naturally in patients with lower-grade VUR^{9,10}, surgical treatment remains controversial. Children having VUR with persistent urinary tract infection and repeated acute pyelonephritis tend to develop renal scars even if VUR is low-grade¹¹. Conservative treatment with the expectation of natural reflux disappearance may require years of continuous antibiotic administration, which itself tends to cause adverse drug reactions. Ongoing hospital visits disturb both patients and families in daily life. Low-grade VUR is reported to be a good candidate for endoscopic treatment, but high-grade VUR is seldom eliminated by this treatment^{12,13}. Endoscopic treatment

was also reported less effective for grade 5 VUR although no correlation between the efficacy of treatment and VUR grade was seen¹⁴. In our study, 75% of grade 3 VUR, 100% of grade 4 VUR, and 50% of grade 5 VUR disappeared in an average of 75% three months after a single injection of GAX collagen. In the remaining two ureters, remaining VUR improved from grade 3 to 1 and from grade 5 to 4. Postoperative urinalysis showed no urinary tract infection in any of the patients and antibiotics were stopped. No second sessions of endoscopic treatment have been performed and the patients are being followed up. Endoscopic VUR treatment using GAX collagen in children is thus indicated when less invasion and shorter hospitalization are considered, although this requires general anesthesia, which itself involves some risk. Even if VUR remains after treatment, retreatment is possible. VUR was reported to have disappeared during follow-up¹⁵, indicating that endoscopic treatment with GAX collagen does not interfere with natural reflux disappearance. The number of patients undergoing this treatment is expected to increase and long-term results to be reported.

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(Received, September 9, 1999)

(Accepted, October 15, 1999)