A REVIEW OF INJECTABLE MATERIALS IN THE ENDOSCOPIC TREATMENT OF VESICOURETERAL REFLUX

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ABSTRACT

Endoscopic treatment of Vesicoureteral Reflux (VUR) has obvious advantages when compared with open surgery. However, the ideal substance for injection is still not found. An ideal material should have no carcinogenic effect, should not migrate, be free of immunologic reactions, should not be absorbed so that it can preserve its volume after injection and cause a limited local tissue reaction in order to strength its mass effect. Although very high success rates are achieved with Polytetrafluoroethylene (PTFE) both in high grade primary and secondary VUR, it does not seem to be a suitable material for the treatment of VUR in children since it migrates and long term effects are not known. Collagen does not migrate, but it is less effective in the treatment of high grade and secondary VUR because it loses its volume by time. Autologous fat has been found completely unsuccessful in VUR, since more than half of it is absorbed and does not cause granulomatous reaction which is necessary for the posterior support of the terminal ureter. PDMS is a new inert agent with a greater particle size than PTFE and theoretically does not migrate. Early results with PDMS are encouraging but it has been suggested that it carries the potential risk of collagen disease in the long term. In conclusion, urologic world still looks forward for an ideal material for the endoscopic treatment of VUR in children.

Key Words: Endoscopic treatment, injectable materials, vesicoureteral reflux

INTRODUCTION

Vesicoureteral reflux (VUR) is an important cause of end-stage chronic renal failure (1) and has been reported in 29 to 50% of children with urinary tract infection (2). Endoscopic treatment of VUR with Polytetrafluoroethylene (PTFE) was first described by Matouscheck in 1981 and popularized by Puri and O'Donnel (3, 4). This treatment modality has gained worldwide interest and has been used with an increasing trend in the treatment of thousands of children with VUR without any significant complication (5). Endoscopic treatment has the advantages of short duration of anesthesia, day-case operation, very low surgical morbidity and no compromise of open surgery. However, as every prosthetic material, it has been observed that PTFE is not a perfect substitute of natural human tissue with its migration ability and its potential complication of carcinogenesis (5, 6). These drawbacks have forced the researchers to find more ideal substances. Collagen and Polydimethylsiloxane (PDMS) are today new alternatives of PTFE. In this review, we aimed to summarize the advantages and disadvantages of different injectable materials used in the treatment of VUR.

POLYTETRAFLUOROETHYLENE (PTFE)

Since its first report in 1981, many high success rates have been reported from different institutes. With one or two injections, the success rates in primary reflux vary between 70 to 95 percent, in neurogenic bladders between 70 to 75 percent (7-9). Despite these successful results it has a major disadvantage of migration which limited its use in the recent years.

History

PTFE was invented by Dr. Roy Plankett, a chemical engineer, in 1938 (10). It is a chemical inert material; it means that no product can attack PTFE. Therefore, The Statue of Liberty is covered with PTFE in order to

protect it from the corrosion of sulfuric acid (11). PTFE is also resistant to enzymatic and microbiological attacks so that it is considered to be a biologically inert material (11). Its great thermic stability makes the sterilization at high temperatures possible (11). The other important properties of PTFE are very low coefficient of friction equivalent and slippery character that enable its use, in catheters and vascular patches, and in the sky industry (11).

Animal studies began in 1949 with the implantation of PTFE in the dog peritoneal cavity (12). In comparison with other polymers it was found to casue less tissue reaction. Following animal experiments revealed a local inflammation at the site of injection one week after implantation with histiocytes, giant cells, fibroblasts and peripheral collagen. This inflammatory reaction was displaced after 1 to 4 weeks by fibrosis creating a granuloma or fibrous capsule which persisted for 6 years without any histological or biological changes (13).

It has been more than 30 years since PTFE was first used in otorhinolaryngology in 1962 in the treatment of vocal cord paralysis (14). No distant metastasis or malignant tissue proliferation was noted after many following intracordal injections. PTFE was first used in urology in 1973 with its periurethral injection for stress incontinence (15). Periureteral injection of PTFE for the treatment of VUR was pioneered by Puri and O'Donnel in 1984 (4), and has been performed in thousands of children in all over the world without any reported significant complication.

Drawbacks of PTFE

There are two major potential complications of PTFE which limited its use: Carcinogenesis and distant migration. In 1959, Oppenheimer et al reported sarcomas following implantation of PTFE in the subscutaneous tissue of mice (16). The authors suggested that mechanical irritation rather than a toxic product was the carcinogenic factor. However, in the animal studies of Kirchner and ,Puri and O'Donnel no carcinogenesis or distant migration was observed (17, 19). According to the literature, there are only three cases of malignancy adjacent to a PTFE implant among thousands of injections (5); but no definite cause and effect relationship with PTFE was found in these tumors. Although, the human data in large series would suggest that the carcinogenic risk is low, one should consider that the longest follow up of the human histological response to PTFE is 16 years (18). Therefore, there still remains a question for the children with a long life expectancy.

The other major drawback of this material is distant migration of the particles. In 1984, Malizia et al reported in their animal study migration to the pelvic lymph nodes, lungs, liver and brain after periurethral injection (19). Electron microscopy scanning revealed that the PTFE particles ranged from 4 and 100 μm in greatest dimension and more than 90% of them were between 4 and 40 μm. They found in distant tissues inflammatory granulomas containing PTFE spherules with diameters ranging from 4 to 80 μm. The major drawback in this study was that large amounts of PTFE were injected into the periurethral space where blood supplement was more intensive compared to subureteric region. Although, periurethral injections did not resemble subureteric ones the latter study caused the prohibition of the medical use of PTFE in children by the FDA. Aaronson et al further demonstrated in an animal experiment the migration to the lungs and brain after periureteral injection of PTFE with sting procedure (6). In the latter study, the diameters of the particles found in the brain ranged from 4 to 40 μm which closely resembled PTFE. Since long term consequences of these particles are not known, the authors concluded that endoscopic injection in children of both Teflon paste and any other substance containing small particles which may pass through the pulmonary vascular bed and lodge in the brain should be approached with caution.

Beside the aforementioned animal experiments, migration of PTFE also in humans has been reported in autopsy studies (20, 21). Cleas et al reported a case of persistent fever due to pulmonary migration of PTFE in a 22 year old woman who underwent multiple periurethral injections for her urinary incontinence (22).

As an opposing argument it can be commented that all of these aforementioned complications are very rare compared to the number of PTFE injections performed so far. To our knowledge, there is no medical or surgical procedure free of side effects or complications, and PTFE is surely not more hazardous than any of them.

Collagen

The migration ability and potential carcinogenic effect of PTFE have forced the investigators to find more

stable materials for the endoscopic treatment of VUR. Cross linked bovine collagen has been widely used in dermatology and plastic surgery and documented to be safe and effective (23). It causes minimal local tissue reaction, does not migrate and may be injected easily (23). Shortliffe et al used collagen in the treatment of urinary incontinence in 1989 (24) and Lipsky et al for the treatment of reflux in 1990 (25). Leonard et al reported a cure rate of 75% 1 month after injection for reflux (23), whereas, Frey et al achieved 68% success rate after 1 injection and 89% after 2 (26). Lipsky et al reported their experience in 115 refluxing ureters in 1993 (27). All children were free of reflux immediately after collagen injection. One year later, 45 of them showed recurrence. They observed that ureters with low grade reflux did better than those with a higher grade. This data shows that the outcome of high grade reflux is better with PTFE than collagen. High incidence of recurrence with collagen may be explained by several factors (28). There is no or very mild perifocal inflammatory reaction and no granulomatous formation with collagen. The collagen implant has a lower friction coefficient and is more liquid. As a consequence, it is probably flattened by pressure from the surrounding tissues that makes injection of larger amounts necessary. Additionally, collagen loses volume over time that is another factor for recurrence. Refluxing ureters with extremely short submucous tunnels or laterally positioned orifices, double ureters and ureters with paraureteric diverticula are reported not to be suitable for collagen injection (27).

Immunologic responses to bovine collagen appear in 3% of cases as minor allergic reactions (28). Possible development of autoimmune disease is a potential risk for children.

Autologous fat

Autologous fat injection has been used for many years in plastic surgery. It has several advantages: it is easy to obtain, has no immunologic reactions, is cost effective, and is not carcinogenic (29, 30). The major disadvantage of this material is the problem of resorption. Many studies found that no more than 30% of the fat survives after injection (29). Palma et al performed lipoinjection in 17 refluxing ureters of renal transplant candidates in which reflux disappeared only in one ureter (30). The authors suggested that autologous fat do not induce foreign body reaction and granuloma formation which is mandatory for increasing the posterior support of the terminal ureter. This fact, besides its high resorbtion rate, makes autologous fat inappropriate for the treatment of reflux.

Polydimethyisiloxane (PDMS)

This polymer has been successfully used in plastic surgery since 1960's and recently proposed to treat incontinence and reflux by endoscopic injection (31). These microimplants are biphasic polymers consisting of textured PDMS particles suspended in a lubricating carrier gel. Ninety - nine per cent of these chemically inert particles are reported to be greater than 100 μm in diameter with a mean particle size of 156.5 μm (range: 35 - 540 μm). The big particle size of PDMS disables ingestion by macrophages and distant migration (32). It shows less tissue reaction than PTFE and there is no difference between the inflammatory response seen at 1, 3 or 6 months (7). Sites of injection show a well-encapsulated foreign - body reaction with an organized collagen capsule. Contrary to PTFE, there is no chronic inflammation causing progressive fibrosis. Azmy achieved 91% complete cessation of reflux in 54 high grade refluxing ureters with injection of PDMS (33). PDMS seems today to be the most promising subject for subureteric injection. However, in an animal experiment, Aaranson et al found silicone containing macrophages at remote sites and suggested that children injected with silicone may carry the same long term risk of collagen disease as patients with other silicone implants (34). Studies are going on to elucidate this issue.

Other materials

Patient's own heparinized blood as an injection material in the endoscopic treatment of VUR was reported by Kohri et al in 1989 (35). They treated 16 low grade refluxing ureters (Grade I-III), in which 9 showed complete absence of VUR. Reflux disappeared in 1 of 3 ureters with Grade III, in 6 of 10 ureters with Grade II and in all with Grade I VUR. Although it seemed to be free of complications, the disadvantage of this material was the decrease in success rates with increasing grade of reflux.

Polyvinyl alcohol foam was first used in medicine in 1940 as a prosthesis after pneumonectomy (36). This inert and biocompatible material has been widely used for embolization of different neoplastic and vascular lesions (37). Subureteric injection of this material was performed by Merguarian et al in 1990

in 10 rabbits (38). Polyvinyl alcohol foam remained in a submucosal location after 3 months and all were surrounded by a fibrotic reaction. The authors suggested that the possibility of distant migration was low because the particles were measuring between 150 to 250 µm. However, more studies are needed to decide on the long term effects of this material.

There are other trials with injectable alginate seeded with human blader muscle cells (39), dextranomer in hyaluronic acid (40), bioglass (41), chondrocyte - alginate suspension (42) and small intestinal submocosa (43), but there is little data available about the biocompatibility and long term effects of these materials.

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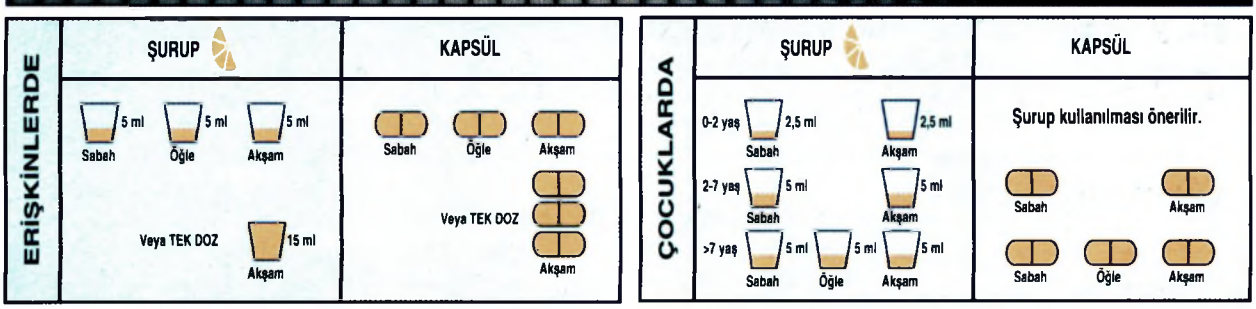

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