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Olson M[1]
1. University of Calgary, Calgary, Alberta, Canada

CANINE BLADDER TISSUE RESPONSES TO INJECTABLE NASHA/DX GEL

Hypothesis / aims of study

Non-animal stabilised hyaluronic acid/dextranomer (NASHA/Dx) gel (Q-Med AB, Uppsala, Sweden) is an injectable, biocompatible material. It was originally developed for the endoscopic treatment of vesicoureteral reflux in children (Deflux™), and it has been utilised for over a decade without any safety problems. NASHA/Dx gel is also used for the treatment of stress urinary incontinence (SUI) in women (Zuidex™), where it is administered using a device called the Implacer™. Moreover, promising results have been obtained for the treatment of post-prostatectomy SUI in men. Other injectable agents have been investigated for the treatment of these conditions, but several have safety concerns. These include migration of the injected material from the implantation site to other organs in the body, and inflammatory or allergic reactions. This study used a canine model to investigate long-term tissue reactions and particle migration following injection of NASHA/Dx gel.

Study design, materials and methods

This study was conducted in compliance with Good Laboratory Practice and according to our institution's standard operating procedures. NASHA/Dx gel was injected into the submucosa of healthy, adult female dogs (n=12) at 5 sites: right and left bladder neck, right and left bladder wall, and the bladder apex. The actual amount of injected material was determined by weighing the syringes before and after each injection. The bladder was removed at 2 weeks, 3, 6 and 12 months (n=2, at each timepoint), and 24 months (n=4) post-implantation. The implant sites, bladder tissue and distant organs (pancreas, kidney, liver, lung, draining lymph nodes and brain) were examined for gross abnormalities. Tissue samples were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with haematoxylin and eosin. Histological cross-sectional diameters of the implants were measured. The stained sections were also examined for inflammation, infection, irritation, foreign body responses, tissue necrosis and scarring.

Results

The mean amount of NASHA/Dx gel injected was 2.35 g, 2.34 g, 2.37 g, 2.36 g and 2.37 g for the right and left bladder neck, right and left bladder wall, and the bladder apex, respectively.
No complications were observed during the 24-month follow-up period, and the implants were well tolerated. No gross abnormalities or infections were detected at any implant site. Furthermore, all distant organs were normal, with no NASHA/Dx gel detected. Implant material was visually identified in 17/20 deposits after 24 months. The mean implant cross-sectional diameter was 7.9 mm at week 2 and 5.13 mm at month 24, representing a reduction of approximately one-third. Dextranomer microspheres were detected by histopathology in the majority of implant tissue sections. These were surrounded by 100–600 µm of fibrous tissue (consisting predominantly of collagen), fibroblasts and fibrocytes, indicative of a local fibrous tissue reaction. Early after implantation, whole implants were surrounded by a well-defined fibrous capsule, which became less pronounced after 12–24 months. There was no evidence of infiltration of inflammatory cells (neutrophils or lymphocytes), or of deleterious inflammatory reactions, necrosis or irritation, either at the implant sites or in the surrounding tissues.

Interpretation of results

A 28-day study using a rabbit model has shown that dextranomer microspheres do not migrate to distant organs (1).The present study extends these results by showing that there is no evidence of migration after at least 24 months, though in a different animal model. Moreover, the tissue response observed in the canine model was generally consistent with that observed in pigs following submucosal injection of NASHA/Dx gel into the bladder, and in rats, where NASHA/Dx gel was subcutaneously injected into the abdomen (2). Indeed, the data presented here support the previous observations that in-growth of endogenous connective tissue stabilises the implants as the NASHA is degraded.

Concluding message

These results show that submucosal injection of NASHA/Dx gel produces an implant that remains *in situ* for at least 24 months without any complications. Furthermore, NASHA/Dx gel has no deleterious effects on the surrounding tissue and does not migrate to distant organs. These results support the clinical use of NASHA/Dx gel in VUR, SUI and post-prostatectomy incontinence.

1 Lack of distant migration after injection of a ^{125}Iodine labeled dextranomer based implant into the rabbit bladder. *J Urol* 1997; **158**: 1937–41.
2 Injectable dextranomer-based implant: histopathology, volume changes and DNA-analysis. *Scan J Urol Nephrol* 1999; **33**: 355–61.