204

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PROOF OF PRINCIPLE FOR A TEMPORARY PATIENT-OPERATED INTRAURETHRAL VALVE DEVICE IN MANAGEMENT OF INCONTINENCE AFTER RADICAL PROSTATECTOMY

Hypothesis / aims of study

It was hypothesised that a valve placed at the bladder neck would allow urine containment in the bladder, and that valsalva straining could serve to initiate flow through the valve for voiding, with containment returning once flow has ceased. Proof of this hypothesis required development of a device designed for restoring continence to post-prostecomy patients suffering from stress urinary incontinence.

Vysera Biomedical has developed novel biomaterials that can mimic the mechanical properties of soft biological tissues and are demonstrated biocompatible, biostable in urine, resistant to encrustation and can be sterilised easily. A trifoliate valve design was developed, the function of which is to remain closed during bladder filling cycles and during short duration pressure spikes (e.g. cough), and to open automatically when a more sustained pressure increase (strain) is applied. The valve which traverses the bladder neck is opened by the application of abdominal strain and closes again automatically once flow has ceased. Operation of this valve has been previously verified by attaching it to the end of an indwelling catheter on the premise that bladder pressure is transferred hydrostatically through the catheter lumen and directly onto the valve thus mimicking the pressures the valve would encounter in-vivo [1]. In tandem, urodynamics and more specifically urethral pressure profilometry was used to assess the magnitude and temporal variation of pressures generated within the bladder and urethra during normal everyday activities and during straining and cough episodes. This information was essential in order to select the valve performance required to address this specific clinical need. Coupled to the valve, a shape- memory scaffold was designed to contour to the relevant anatomical location where the valve needs to be deployed. The scaffold also has the function of preventing proximal and distal displacement of the valve and also of acting as a frame which prevents deformation of the valve in-vivo thus maintaining valve function even with typical anatomical variations. The valve-scaffold device is deployed at the bladder neck using a 21F custom catheter delivery using endoscopic and fluoroscopic guidance. The device can be sheathed using a custom 23F catheter and removed under local anaesthetic. Design of the scaffold, catheter systems and insertion/removal were informed by several cadaver studies.

The aims of this phase 1 human study were to confirm safe insertion and removal of the device, to assess device tolerability in short-term use and to verify urine containment in the bladder under a range of conditions.

Study design, materials and methods

This study was a non-randomised, historical control, treatment based feasibility study conducted in 2 stages, with up to 14 patients. Stage 1 objective was to confirm safe and effective delivery and retrieval of the device with a minimum of 2 and a maximum of 4 male patients attending the clinical site, for routine general anaesthetic cystoscopy. Insertion and removal took place immediately after the patient's cystoscopy, during the general anaesthetic. Stage 2 objectives were to confirm delivery, retrieval, functionality and tolerability of the device in up to 10 patients invited to participate in the study. Inclusion criteria were; male patients, at least 3 months post-radical prostatectomy, and aged 18 years or and older. Insertion took place under general anaesthetic with removal under local anaesthetic. The device was inserted for no longer than 8 hours. One week post-removal, a follow-up to ascertain the patient's experience of the invasive device was completed. Endpoints were defined as follows: ***Primary***: Demonstrate that the patient has the ability to activate the device to void the bladder. ***Secondary:*** Evaluate the delivery, retrieval and tolerability of the device and to assess urinary containment and residual urine post-void. Each participant in Stage 2 was monitored for up to 8 hours in the controlled environment of the clinical site. All measurements taken within the monitoring period were recorded on the study case report forms by the Clinical Investigator and/or the Clinical Study Nurse. Patients who were woken up with the device in-situ were questioned as to their experience of the device. Patients were asked to rate the experience on a scale of 1 to 5 with ratings described as follows: 1=Very Poor; 2=Less than acceptable; 3=Acceptable; 4=Good and 5=Very Good. The study was approved by the regional ethics committee, and the valve was approved by the UK Medicines and Healthcare Regulatory Agency (MHRA).

Results

Four patients were enrolled in Stage 1 of which one was deemed unsuitable on the day of the procedure. The three patients enrolled during stage 1 showed clinical suitability of the insertion and removal catheters and procedures. It was identified that accurate device delivery required measurements placed on the insertion catheter, coupled with fluoroscopic guidance. During stage 1, ability to retrieve of devices deployed too proximally (within the bladder) was verified and it was also demonstrated that the device could feasibly be removed without sheathing due to the soft and compliant nature of the device.

Seven patients were enrolled in stage 2. In one patient, the procedure was abandoned due to a urethral stricture which had not previously been diagnosed. Five of the remaining six patients were woken up with the device inserted and one patient had the device inserted and removed while still under general anaesthetic (as a test of the scaffold configuration in situ). "Patient experience" results are summarised in the following table.

	Pt1	Pt2	Pt3	Pt4	Pt5	Average
Overall Impression	5	5	5	4	2	4.4
Tolerability (stationary)	5	5	5	5	3	4.6
Tolerability (Ambulatory)	5	5	5	5	4	4.8
Ease of voiding	4	5	4	5	3	4.2
Speed of voiding	5	3	5	5	3	4.2
Bladder Emptyness	5	5	5	4	3	4.4

In addition, case report forms measured various relevant clinical outcomes from the study which are summarised in the following table.

	Pt1	Pt2	Pt3	Pt4	Pt5
Insertion time (mins)	30	20	25	15	15
Ease of insertion	Challenging	Acceptable	Acceptable	Easy	Easy
Leakage (ml/min)	0.5	n/a	0	0.15	0.10
Volume voided	394	350	950	400/200	300/400
Time to void (secs)	60	n/a	n/a	120/25	60/85
Removal time (mins)	3	15	10	6	4
Ease of removal	Challenging	Acceptable	Acceptable	Acceptable	Challenging

Observations: Accurate placement is critical to device tolerability. Catheter markings, fluoroscopic guidance and the ability to re-position make this possible. Scaffold design may need to be adapted to provide a greater level of tolerability. A withdrawal tether extending past the urethral meatus provides a significantly improved means of device removal and shortened the removal time dramatically.

Interpretation of results

All patients were able to open the valve by straining and achieve bladder emptying. Safe delivery and removal and accurate placement has been demonstrated. Containment has been demonstrated with a bladder volume of up to 950ml with resultant relatively low leakage. The device is tolerable but design improvements for the scaffold are needed.

Concluding message

Urinary containment and voiding using a strain-activated intraurethral valve is feasible. Leakage is low and the device is relatively well tolerated. Opening pressures of the valve match intravesical pressures measured for the target population and have been shown to impart the desired clinical benefits to the patient.

References

1. Proof of principle for a non-manual catheter valve; voiding and storage function using a valve opened by voluntary straining. Drake M, Gammie A, Edwards J, Parke S, Ward K, Devery D, Timothy M. International Continence Society annual meeting 2014, Abstract 320.

Disclosures

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