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Development and first-in-human testing of FLUME urinary catheter with protected tip and relocated drainage holes

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ABSTRACT

Purpose: Evaluation of a catheter design which protects its tip with the retaining balloon when inflated, and has eyeholes at the base of the balloon to improve drainage.

Materials and methods: Preclinical tests included assessment of retaining balloon performance, and microbiological blockage. Clinical testing evaluated short-term use and safety in hospital (stage 1) or the patient's usual residence (stage 2).

Results: The retaining balloon supported static loads of 0.7kg, with reduced trauma when modelling forced evulsion. In vitro time to blockage with P. Mirabilis was significantly slower for FLUME compared with latex Foley catheters, but not the silicone Foley. Stage 1 testing (10 patients) confirmed balloon inflation, drainage, retention and removal, with no serious adverse events caused by catheterisation; one balloon failed to inflate, one patient could not be catheterised. Of five patients at stage 2, one had the catheter for 28 days without complication, one experienced spontaneous balloon deflation (14th day) and three needed early removal (blood clot, bypassing, difficulty connecting the drainage bag). Bacterial profiles of two FLUME catheters retained at least 2 weeks matched the Foley catheters. Acquired catheter colouration (two FLUME, one Foley) was not associated with biochemical change in the material.

Conclusion: FLUME catheter performed well in preclinical blockage and balloon tests. Tests in 15 patients confirmed basic function and additional training was not needed for staff familiar with Foley catheterisation. Clinical issues commonly seen with catheters included failed catheterisation, clot blockage and bypassing. In addition, an unintended balloon deflation and a failure of bag connection occurred.

Plain language summary: This article describes a new catheter design which aims to improve patient comfort and safety, and maximise bladder drainage, by protecting the bladder from the exposed catheter tip and by locating the drainage holes better. Various tests were done to check the catheter retaining balloon was safe and how well the catheter did when exposed to bacteria that could block it. The catheter was also used in people for the first time, to check it could be put in safely and functioned as intended. The results showed the FLUME catheter did well in the balloon and blockage tests. Tests in 15 patients confirmed basic function and showed placement was easy for staff familiar with conventional catheters. There were some clinical issues typical of urinary catheters and some possible improvements were identified.

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Fig. 1. Comparison of the tips of the standard Foley catheter (left) and the FLUME catheter (right). The FLUME catheter has less foreign material in the bladder and places the drainage eyeholes close to the bladder neck. With the retaining balloon inflated, it envelopes the catheter tip, so the bladder wall is protected. The Foley has a prominent tip, which can cause discomfort and places the eyeholes near the bladder wall where they may aspirate the mucosal tissue and get blocked.

1. Introduction

The most widely employed indwelling urinary catheter configuration is the Foley catheter, used by around 100 million patients worldwide, and little changed since 1937, despite significant limitations. The Foley catheter is a tube with drainage holes at the tip, secured in place by a retaining balloon which is inflated once the catheter is fully advanced into the bladder. The external end accommodates the connector to a drainage bag or catheter valve, and the valve for filling or emptying the retaining balloon.

The Foley design places the pointed tip a significant distance into the bladder lumen when in use. Consequently, the tip can impinge on the bladder wall, leading to discomfort and potentially urothelial trauma, aspiration of mucosal tissue and blockage of the drainage holes. Additionally, there is a significant gap between the eye holes and the bladder base, leading to incomplete drainage. In theory, the resulting stagnation of urine may predispose to infection and the formation of bladder stones. The retaining balloon is a robust structure, designed to remain in place even when subjected to the force exerted by dropping a full urine collection bag. Unfortunately, forced catheter removal (evulsion) with the balloon inflated is a traumatic event, which potentially causes bleeding, urethral rupture or subsequent stricture. The distance between the eyeholes and the balloon also mean that urine may pass along the lumen before the balloon is safely inside the bladder, leading to prostatic urethral trauma if inflated prematurely. On other occasions, the balloon may fail to deflate when catheter removal is due, and must be pierced with a needle, either transurethrally or transabdominally with ultrasound guidance.

Advances in materials, design and manufacturing processes enable options to address clinical issues, particularly reconfiguration to protect the bladder wall and improve drainage. In this study, we describe an approach that envelops the tip of the catheter with the balloon when inflated, to reduce discomfort and improve drainage [Fig. 1]. The "FLUME" design uses biomedical materials that also support an increased lumen calibre relative to the external diameter, and greater retaining balloon flexibility to reduce potential trauma in the event of an evulsion incident.

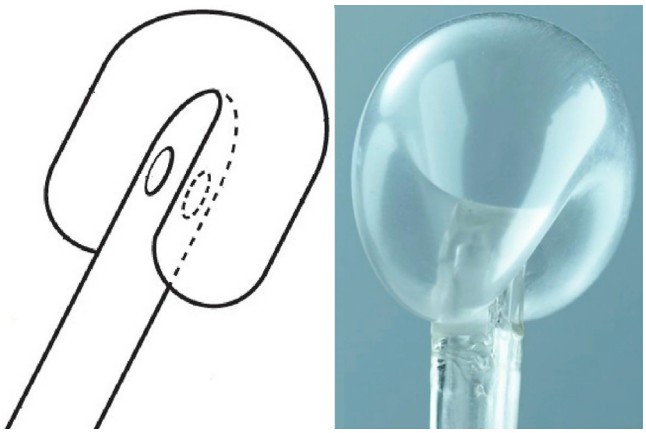

Fig. 2. FLUME design drawing (left) and prototype catheter (right) illustrating use of the balloon to cover the catheter tip and place the drainage holes close to the bladder base when in use.

2. Methods

Design specifications required drainage holes close to the bladder base and a covered catheter tip when deployed [Fig. 2]. The design also required that clinical placement would be methodologically like current techniques, with the retaining balloon accessed by a valve compatible with standard clinical syringes. Reduced urethral trauma when modelling an evulsion incident, and a contingency manoeuvre to deal with balloon non-deflation, were considered desirable. The design solution resembles a standard Foley catheter when removed from the packaging, but the balloon is folded over the catheter tip. Hence, placement is undertaken in the same way as a Foley catheter, without retraining of the healthcare professionals. The retaining balloon is inflated with a 5 ml volume from a prefilled clinical syringe using a standard valve. Inflation is safe once urine is seen to flow from the external end of the catheter. In the event of balloon non deflation, a puncture manoeuvre of the FLUME balloon can be accomplished with a sharp mandrel advanced within the catheter lumen. The mandrel should be housed in a sheath to prevent the sharp tip from penetrating the catheter wall until it is advanced fully along the lumen, right to the innermost end.

The materials used in the catheter have undergone biocompatibility, biomechanical and sterility testing according to ISO 10993, ISO 20696:2018 and ISO 11737-2:2009 respectively. Preclinical tests of the catheter *in vitro* included performance assessment of the retaining balloon in the flexible elastomer bladder base model, using static and impact force tests while measuring internal retention balloon pressure, as previously described [1]. *In vitro* microbiological blockage testing used a validated model [2] to evaluate FLUME catheters and marketed Foley catheters (Bard Biocath, Bardex IC and Rüsch Brillant Aquaflate 100% silicone). Sets of 4 bladder models were assembled with size 14 Charriere (Ch) catheters and inoculated with a clinical isolate *P. mirabilis* NSM6 (approximately 3×10^7 colony forming units/ml in 60 ml artificial urine) capable of generating alkaline urine and rapidly blocking catheters. The inoculum was drained via the catheter, leaving a sump in the model proportionate to the distance of the eyeholes above the base. After inoculation, artificial urine was perfused at 0.5 ml/min. Five experimental replicates were performed for deriving time to blockage, where models were run until crystalline biofilm occluded the lumen. Statistical analysis (Graphpad Prism 6) utilised a one-way Anova with Tukey post hoc test.

First-in-human clinical testing evaluated short-term use and safety in a hospital setting, using devices for which U.S. 510(k) regulatory clearance was granted in November 2021 and an MHRA 'no objection' to clinical trial in February 2022. The stage 1 primary objective was

to confirm placement and removal, ability to drain and remain indwelling (healthcare professional) and with acceptable comfort (user). Secondary objectives were: To identify any problems with the FLUME design or manufacture, resulting from its use, that could cause clinical and/or safety problems; To identify adverse events; To identify specific training needs for healthcare professionals. The first group of 5 patients had the device placed and removed whilst still under anaesthetic in the operating theatre, as an additional element of a routine endoscopic urological procedure (Stage 1a). The second group of 5 patients had the catheters placed in theatre as part of an endoscopic procedure and removed post-operatively as clinically scheduled for the procedure, with a maximum of up to 72 h (Stage 1b). Inclusion criteria were: adults (≥18 years) of any gender, who are willing to participate in the study and give their written informed consent. In addition, for stage 1a, subjects who are due to undergo planned general anaesthetic endoscopic bladder inspection. For stage 1b, subjects who are due to undergo a procedure where an indwelling catheter is routinely used. Exclusion criteria were: Urinary tract infection (UTI) at time of assessment; Systemic antibiotics within 48 h prior to enrolment; Allergy to any catheter materials; Urinary tract anatomic abnormality that would prevent catheter placement; Informed consent cannot be obtained; Breast feeding or pregnant; Transurethral resection of the prostate (TURP) within the last 3 months.

Progress and safety reports were reviewed by the steering committee before stage 1b and stage 2 could commence. Adverse events prespecified in the protocol related to patient outcomes were: urethral trauma requiring emergency surgical or endoscopic treatment (infrequent, defined as <10% and >0.1%); urethral false passage (infrequent), unable to catheterise (infrequent), visible haematuria (infrequent), urinary infection (CAUTI) requiring hospital systemic treatment (infrequent), urinary infection (CAUTI) requiring antibiotic treatment (common, defined as ≥10%). Adverse events prespecified in the protocol related to device outcomes were: failure to remove FLUME catheter, resulting in interventional radiology or surgical intervention (<10% and >0.1%); device fragmentation necessitating endoscopic removal from bladder (rare, defined as ≤0.1%); blockage, leading to acute urinary retention requiring acute intervention (≥10%); adherence to urethra compromising catheter removal (rare).

Stage 2 evaluated the device in long-term catheter users at the patient's usual residence. The primary objectives were to confirm catheter function for up to 30 days and to investigate the incidence of adverse events. The secondary objectives were to identify any design or manufacturing problems, resulting from its use, and to gather patient and healthcare experiences. Inclusion criteria were: adult patients who need an indwelling urinary catheter for at least one month/ established catheter users (at least the last 6 months and anticipate continuing to use one for at least the next 3 months); Willing and able to participate and give informed consent. Exclusion criteria were: catheter-associated UTI at time of assessment; Systemic antibiotics within 48 h prior to enrolment; Suprapubic catheter user; Allergy to polyurethane or silicone; Anatomical abnormality that would prevent catheterisation; Pregnant; New catheter users; Patients scheduled for catheter changes more frequently than monthly; Cognitive impairment affecting ability to complete outcome assessments; TURP within the last 3 months.

Clinical study data was collected using paper Case Report Forms (CRFs) or electronically into a REDCap (Research Electronic Data Capture [3]) database. CRFs were managed by a qualified Research Nurse or a member of the Investigator team. Favourable ethical opinion was obtained on 08 November 2021 from UK Health and Social Care Research Ethics Committee A (HSC REC A), reference 21/NI/0150.

3. Results

Retaining balloon performance during *in vitro* testing showed that the model could hold a catheter with static loads up to 0.7 kg. Impact forces from dropped weights caused the balloon to elongate and pass along the modelled urethra, evulsing the catheter with lower trauma severity than a Foley. The diameter of the FLUME balloon during passage through the model decreased to 14 mm, which was 61% of the diameter of a Foley during passage (23 mm). *In vitro* time to blockage data is given in Table 1. Anova indicated there was a significant difference in time to blockage between the FLUME catheter and the latex Foley catheter models ($p < 0.0001$ for both), but there was no significant difference between the FLUME catheter and the silicone Foley [Fig. 3]. To deal with the eventuality of balloon non deflation, sheathed cystoscopic injection needles, for example needles used for intravesical injections, met the requirements for safe access to the balloon via the catheter lumen. For the 14 Ch FLUME a 5 Ch mandrel within a 7 Ch sheath was used, with an 8 mm needle projection once deployed; ability to deflate the balloon with this approach was bench-tested with two catheters.

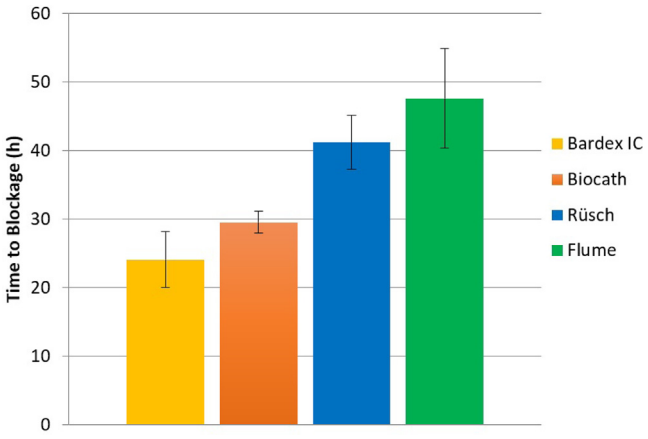

Fig. 3. Time to blockage in five replicates evaluating FLUME catheter (green) and three Foley catheters, two of which were latex (yellow and orange) and one silicone (blue). All catheters were size 14 French gauge. Error bars represent the standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Five patients participated in stage 1a clinical testing (placement and removal by a urologist during the general anaesthetic of an endoscopic procedure). Catheter placement was straightforward, with normal balloon inflation, retention, deflation and removal. 1 patient reported bloodstaining of the first void after the procedure. No serious adverse events (SAE) caused by catheterisation occurred. There was one unrelated SAE (problems with the removal string of a ureteric stent after return home). There were no complications or infections in the week following. Five different patients participated in stage 1b clinical testing (placement by a urologist during the general anaesthetic of an endoscopic procedure and removal as scheduled for the procedure). In one case, balloon non-inflation meant the catheter was not retained in situ. In one case, placement failed due to bladder neck configuration preventing full catheter advancement into the bladder lumen. Three catheters were sited without difficulty and removed as scheduled the following day. No adverse patient issues were reported.

Five male patients participated in stage 2 clinical testing (placement by a nurse at scheduled change for a long-term catheter user). Catheter placement was straightforward in all five cases. One patient had the catheter in place for 28 days without complication or difficulty. One patient experienced spontaneous deflation of the retaining balloon, with the catheter falling out painlessly on the 14th day. The other three patients had the FLUME catheter for less than a day. One patient experienced blockage because of a blood clot, necessitating change back to a Foley catheter; this was something he had previously experienced with his usual Foley catheter. One patient experienced bypassing and requested change back to a Foley catheter. For one patient, once placed, the external end of the catheter did not accommodate the drainage connector.

Table 1
Summary of time to blockage data (minutes displayed as decimal, apart from the last row).

	Foley			Flume
	Bardex IC *latex*	Bard Biocath *latex*	Rüsch Brillant *silicone*	
Run 1	22.85	31.78	35.92	39.75
Run 2	30.42	27.42	38.72	57.68
Run 3	19.73	29.87	44.55	44.38
Run 4	25.42	29.55	45.12	43.88
Run 5	22.00	28.87	41.70	52.38
Mean	24.08	29.50	41.20	47.62
Mean *(hours:mins)*	24:05	29:30	41:12	47:37

Bacterial colonisation profiles of the two FLUME catheters retained for 2 weeks or longer matched the bacteria present in the respective patients' Foley catheters. In both cases *E. coli* and *Enterococcus* were present, and one patient also had *Pseudomonas aeruginosa* in their FLUME and Foley catheters. None of the catheters had visible biofilm on the internal lumen or external surface. Catheter materials acquired colouration in both these FLUME catheters and one Foley catheter. Fourier transform infrared spectral analysis confirmed no biochemical change in the catheter material; no new small molecules or impurities were identified to suggest changes from the materials with completed biocompatibility testing.

4. Discussion

This paper describes a process from fundamental design, through *in vitro* testing, and first-in-human testing for the new FLUME urinary catheter. The design shields the tip of the catheter with the retaining balloon, aiming to reduce impingement of the bladder wall into the drainage eyeholes, and places the eyeholes closer to the bladder neck to improve drainage. Placement, retention and connections of the FLUME catheter use the same principles as the Foley design. As the FLUME configuration resembles the Foley catheter when the retaining balloon is deflated, placement and removal is expected to be familiar to users, and the first-in-human tests support that assumption; no specific training needs for healthcare professionals were identified. There is also a potential safety benefit, as about 1% of male catheterisations result in injuries [4,5]. The Foley catheter allows urine flow while the balloon is in the urethra, so further advance is needed to avoid premature inflation. In contrast, urine flow along the FLUME catheter means the balloon is in the bladder, so it can safely be inflated.

Secondary objectives were to identify any problems with the FLUME design or manufacture, and adverse events. The clinical study identified two out of 15 used catheters where balloon deflation was an issue (one in Stage 1b, one in Stage 2). All catheters used in clinical testing had passed a test of balloon integrity during manufacture, but this issue led to retesting under in vitro conditions designed to simulate clinical use, specifically by incorporation of flexion of the catheter and additional weight challenge. This confirmed a possibility of leakage on prolonged manipulation and is the basis for enhanced testing that has been adopted for future production. There is potential to improve the drainage bag connector fit and usability. Additional problems reflect the challenges experienced in studies with long-term catheter users, for example early blockage due to a blood clot (one patient), inability to catheterise past the male bladder neck (one patient) and catheter bypassing (one patient). The blood clots and bypassing issues were noted in the respective patients' prior Foley catheter usage.

In vitro, the alternative design of the FLUME catheter performed well in comparison with control catheters in time to blockage tests after exposure to uropathogenic infection organisms. In the clinical testing, the catheters were not present for sufficiently long to be able to identify differences between FLUME and Foley catheters. For the two FLUME catheters used for two weeks or more, the same bacterial species were identified on both the Foley and FLUME catheters from each individual. The bacteria identified were common urinary tract organisms. Colouration of the internal lumen was observed on both FLUME catheters and one of the Foley catheters. Colouration has been observed in catheters of long-term catheter users previously and the colonising bacteria could contribute. For example, a green tinge is commonly associated with Pseudomonas species [6] and this organism was isolated from a FLUME catheter with green colouration after use.

Evulsion of a catheter with the retaining balloon still inflated is a well-recognised adverse event [5], commonly resulting if catheter tubing becomes tangled in a fixed object when the patient is moving. The Foley catheter design and device assessment standards make no provision to mitigate urethral injury, in prioritising retention despite a high-force challenge. Consequently, when evulsion of an inflated Foley catheter balloon does occur, it is potentially a significant trauma, carrying risk of urethral rupture or subsequent urethral stricture. Hence, a new assessment standard which balances retention with low-trauma evulsion [1] may be clinically advantageous. When evulsion was modelled *in vitro*, the FLUME balloon elongated with reduced urethral dilation; if it burst, the balloon ruptured without leaving fragments (which might require removal from the bladder if occurring in clinical use). Another balloon-related problem is non-deflation at time of planned removal, which is rare but may necessitate ultrasound-guided percutaneous balloon puncture. Because the FLUME balloon is in line with the catheter lumen, advancing a needle to the end of the lumen and puncturing the tip would deflate the balloon without the need for imaging guidance. The wall thickness of the tip of the FLUME catheter has been deliberately constrained during manufacture to facilitate the advancement of a sharp mandrel through the tip to rupture the balloon safely, a manoeuvre successfully demonstrated *in vitro*.

The study is limited by the small sample size. Nonetheless, the preclinical and phase 1 clinical testing suggest the design is intuitive for healthcare professionals familiar with catheterisation, that retention and drainage are achieved, and that there are no safety issues of concern. Enhanced testing was developed for the possibility of balloon leaks on prolonged manipulation. There is also potential to improve the fit and usability of the drainage bag connector. Once these are confirmed, there is a suitable basis for phase 2 testing.

5. Conclusions

The FLUME catheter performed well in preclinical blockage and balloon evulsion tests. Evaluation in 15 patients confirmed basic function and showed FLUME placement did not require additional training for healthcare professionals. Clinical issues were observed in three cases (failed catheterisation, clot blockage, bypassing). In addition, two unintended balloon deflations and one failure of bag connection were reported.

CRediT authorship contribution statement

Marcus J. Drake: Conceptualization, Design, Research, Writing, Manuscript review. **Katherine Anderson:** Research, Manuscript review. **Andrew Gammie:** Conceptualization, Design, Research, Writing, Manuscript review. **Nicola Morris:** Design, Research, Writing, Manuscript review. **Tony Timlin:** Research, Manuscript review. **Nikki Cotterill:** Writing, Manuscript review. **John Duff:** Design, Writing,

Manuscript review. **Mandy Fader:** Design, Research, Manuscript review. **Hazel Taylor:** Design, Manuscript review. **Roger Holmes:** Conceptualization, Design, Research, Writing, Manuscript review. **John Havard:** Conceptualization, Design, Research, Writing, Manuscript review.

Declaration of competing interest

Marcus Drake has received personal fees from Astellas Pharma, and is a Trustee of the International Continence Society. Andrew Gammie undertook consultancy work for The Flume Catheter Company Ltd (TFCC). Katherine Anderson, Nicola Morris, Nikki Cotterill, John Duff, Mandy Fader, Tony Timlin and Hazel Taylor declare no conflict of interest. Roger Holmes is Co-Founder, CEO, and a shareholder of TFCC. John Havard, is Founder, Chairman and a shareholder of TFCC.

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