

THE ROLE OF BLADDER FILLING AND VOIDING IN MAINTAINING BLADDER HEALTH: URINARY AND PLASMA CYTOKINES IN CATHETERISED PATIENTS USING VALVES OR ON FREE DRAINAGE

Hypothesis / aims of study

Long-term urinary bladder catheterisation is a common procedure but is associated with frequent complications including urinary tract infection, bladder spasm, recurrent catheter blockage and neoplastic changes [1]. These may be linked to inflammatory changes in bladder tissue. Indeed, the release of inflammatory cytokines may modulate the immune and inflammatory response and promote progression from inflammation to cancer. Recent studies suggested that IL-6, IL-8 and IL-1 stimulate cancer stem cells replication [2]. Catheters can be managed by free drainage or by cyclical bladder filling and voiding using a catheter valve (e.g., flip-flo® valve). The importance of normal physiological stretching and relaxation to bladder health has not been adequately investigated to date [3]. Our working hypothesis was that inflammatory cytokine levels would be higher in those patients with continually empty bladders on free drainage compared to those managed by bladder cycling. Such outcomes would reflect both (1) anecdotal experience that cycling the bladder is associated with less complications than free drainage and (2) an intuitive belief that the bladder which closely mimics its natural action will be "healthier" than its static, empty counterpart. The aim of the study was to investigate whether such cyclical stretching and relaxation of urothelium affects its functional or biochemical integrity. Results would inform the clinical use of catheters and provide a rationale for best practice in terms of their management.

Study design, materials and methods

A case-controlled design was used with index patients (catheter valve users) matched for age, sex and length of catheterisation with patients on free drainage and with a further group of healthy un-catheterised volunteers. Ethical approval was granted for the study. Informed consent was sought from all participants and the relevant clinical details were collected. Between-group continuity corrected Chi-Square tests with a 0.05 two-sided significance level would have 82% power to detect differences of at least 0.33 between any paired groups (odds ratio of 0.00) when the sample size in each group was 20. Accounting for subjects' dropout, the sample size was increased by 25%; therefore we recruited >25 subjects in each group. The three groups were: non-catheterised healthy volunteers (G1; n=26) and catheterised patients either using a catheter valve (G2; n=29) or on free-drainage (G3; n=23). Inflammatory cytokines in urine and blood were compared between these three management regimens. Enzyme-linked immunosorbent assays were used to measure urinary and plasma levels of IL-4, IL-6, IL-8, IL-10, IL-1 β , IFN- γ , TNF- α , TGF- β 1, and tissue factor (TF). Urine microscopy and microbiological cultures were performed on all subjects. Patients' daily living activities and mobility were evaluated using the Barthel-Index. Exclusion criteria common for the 3 groups were current symptomatic urinary tract infection, haematuria of unknown origin, impaired renal function, bladder cancer or any other condition that was likely to influence the outcome. Data was not normally distributed and so results are presented as box and whisker plots showing medians, interquartiles and ranges. Differences between two groups were assessed using the Mann-Whitney test. The level of statistical significance was set at $p < 0.05$.

Results

Urinary IL-6, IL-8 and IL-1 β , as well as plasma TNF- α were significantly reduced in the valve group (G2), compared to free drainage cohort (G3, $p=0.015$, 0.011 , 0.005 and 0.047 , respectively). The urinary IL-1 β is illustrated using a box-and-whisker plot (Fig. 1, below); this cytokine was undetectable in plasma. The other five cytokines measured showed only non-significant trends between G1 and G2. TNF- α , yielding a significant effect in plasma was not detected in urine. While the Barthel-Index showed significant differences between the 3 groups (Chi-square = 22.665, $df = 2$, $p < 0.001$; $G1 > G2 > G3$), there was no significant relationship between this and the levels of the inflammatory cytokines measured. Furthermore, the frequency of asymptomatic bacteriuria did not differ significantly within the 3 groups (Chi-square=0.857, $df=2$, $p=0.651$).

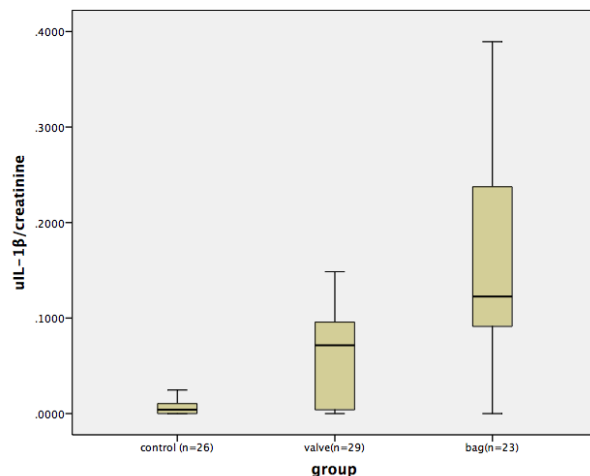
Interpretation of results

The results demonstrate quantitative alterations in inflammatory cytokines detected in urine and plasma which may be linked to the system of managing urinary catheters. These are, in urine (after adjustment for creatinine concentration), consistently towards raised levels in G3 compared to G2. Addressing the objective of the study, comparing catheter management regimens, we observed a trend for cytokines to be reduced in subjects managed with catheter valves compared to those on free-drainage. This reached statistical significance in four of the nine inflammatory cytokines studied. Plasma results, more removed from the site of interest and subject to other influences, are less consistent, but follow the same trend.

Concluding message

This is the first empirical study which investigates objectively whether bladder filling and voiding is important in maintaining bladder health. It provides evidence supporting the concept that maintaining cyclical filling and voiding of the bladder could be important in limiting local inflammatory responses in patients with long-term indwelling catheters and provides some indication that the use of catheter valves may be better for maintaining bladder health.

Figure 1: Urinary IL-1 β /creatinine ratios in non-catheterised healthy volunteers and catheterised patients on cyclical (G2) and free-drainage regimens. Results are shown as Box and Whisker plot. The bottom and top of the 'box' represent the 25th and 75th centile, respectively, while the line within the box represents the median value. The 'whiskers' represent the range.



References

1. Inflammatory; Cytokines; Mana
2. 1. Getliffe K.A. The characteristics and management of patients with recurrent blockage of long-term urinary catheters. *J Adv Nursing* 1994; 20:140-9. 2. Sordillo PP, Helson L. Curcumin and cancer stem cells: curcumin has asymmetrical effects on cancer and normal stem cells. *Anticancer Res* 2015;35:599-614. 3. Feneley RC, Hopley IB, Wells PN. Urinary catheters: history, current status, adverse events and research agenda. *J Med Eng Technol* 2015;39:459-70.
3. None declared.

Disclosures

Funding: Internal **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** Southampton and South West Hampshire Research Ethics Committees (Version 4.0; Reference 05 / Q1704 / 33; Date 02 / 03 / 2005) **Helsinki:** Yes **Informed Consent:** Yes