The importance of osmolality for intermittent catheterization of the urethra

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Objectives: The urethral trauma after catheterization with intermittent catheters was studied histologically using unconscious rabbits.

Setting: The study was performed at Astra Hässle, Mölndal, Sweden.

Materials and methods: Fifteen rabbits were randomized into five groups (three rabbits in each group), one control group and four groups catheterized with four different LoFric[®] catheters (Astra Tech, Mölndal, Sweden): (1) control (not catheterized); (2) salt coated (i.e. high osmolality catheters) with drainage eyes; (3) without salt (i.e. low osmolality catheters) and with eyes; (4) with salt coating but without drainage eyes; and (5) without neither salt coating nor drainage eyes. The urethral injuries were evaluated using a four graded histological scale.

Results: The results showed that salt coated LoFric[®] catheters gave less urethral trauma than LoFric[®] catheters without salt. This was also supported by the significantly lower removal friction measured during withdrawal of the high osmolality catheters. No significant differences either in removal friction or in urethral trauma could be observed between LoFric[®] catheters with or without drainage eyes.

Conclusion: It may be concluded that osmolality is one important factor (there might be others, like e.g. water binding ability) when comparing different hydrophilic catheters, in regards to removal friction and urethral trauma. Furthermore it is suggested that there is no difference in urethral trauma between catheters with eyes or without eyes. To minimize the risk of urethral trauma, high osmolality catheters are recommended, especially when the catheterization times are a few minutes or more.

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Introduction

A number of different diseases and injuries will create problems for the patient to urinate. The common solution for this is catheterization of the urethral bladder via the urethra. In earlier days, this was often done by the use of indwelling catheters, which remained in the urethra for 3–10 days. Today the use of indwelling catheters is reduced, in favour of intermittent catheterization, since this therapy is much more comfortable for the patient.¹ One such catheter is the LoFric[®] catheter (Astra Tech, Mölndal, Sweden), which is a sterile, hydrophilic urinary catheter for intermittent use. The LoFric[®] catheter consists of a PVC (poly vinyl chloride) catheter with a friction reducing PVP (poly vinyl pyrrolidone) coating. It has been on the market since 1983, and during the first years a few incidents with catheters sticking to the urethral wall were observed.² The reason for this might

be that the catheters were drying out during catheterization due to the osmotic gradient. Catheters with a salt layer added to the PVP coating was later developed. The reason for the salt layers was to enhance the osmolality of the coating.^{3,4} After this change there were no further problems with catheters adhering to the urethral wall.⁴ The favourable results with the LoFric[®] catheter are now well documented.^{5–10} Catheters are produced with drainage eyes (the holes close to the tip of the catheter shaft) of different designs, and the question has been raised whether the design/shape of eyes will have any influence on the urethral trauma.

The aim of the study was to examine the urethral trauma after catheterization (compared to uncatheterized urethras), using catheters with different osmolality in the hydrophilic coating. The urethral trauma after catheterization was judged according to a four graded scale (see Figure 2). Furthermore, the effect on the urethra after insertion of catheters with or without drainage eyes was examined.

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Materials and methods

Animals and catheters

Fifteen male New Zealand White rabbits (HB Lidsköpings kaninfarm, Sweden) were randomized into five groups, three rabbits in each group: (1) Control (non catheterized rabbits); (2) LoFric® Nelaton CH08 with drainage eyes and with salt; (3) LoFric Nelaton CH08 without drainage eyes and with salt; (4) LoFric Nelaton CH08 with drainage eyes and without salt; and (5) LoFric Nelaton CH08 without drainage eyes and without salt.

The rabbits were kept individually in cages with perforated floors (EC2, Scanbur A/S, Denmark). A tray was placed under each cage for collection of urine and faeces. The animal room had a temperature of 16–18°C and a relative humidity of 40–60%. The air was changed about 15 times per hour. The animal room was illuminated on a 12 h light/dark cycle with light of early dawn and dusk. The rabbits were fed *ad libitum* with a complete pelleted rabbit diet (K1, Lactamin, Sweden) and they had free access to tap water in drinking bottles.

Catheterization and perfusion fixation

After at least 1 week of acclimatization each rabbit (except group 1) was anaesthetized by intravenous injection, using an ear vein (xylazine, 10 mg/kg body weight and ketamine, 2 mg/kg body weight) and catheterized once for 5 min. The catheter was withdrawn and the removal friction (in N) was measured by an electronic force gauge (Mecmesin AFG-25N). After removal of the catheter the rabbits were deeply anaesthetized, the thorax was opened and the thoracic aorta was catheterized (infusion catheter, Ø~1.5 mm, Venflon®) through the left ventricular wall. Sodium chloride, (9 mg/ml, Pharmacia), and heparin 2000 IU per litre added (Löwen) was infused by a constant perfusion pressure of 80 mmHg. The right atrium was cut for drainage and the rabbit was euthanized. After the saline and heparin perfusion the perfusate was switched over to fixation in 4% buffered formaldehyde (Labassco, Mölndal). The urethra was dissected free from surrounding tissues, removed and the distal end was marked with 'Tissue marking dye' (Histolab, Västra Frölunda, Sweden). The urethra was placed in 4% buffered formaldehyde overnight for final fixation.

Tissue preparation for histology

The urethra was divided into three parts of about 30 mm each. The first part, close to the bladder was marked 'proximal', the one from the middle of the urethra, was marked 'middle' and the most distal, third part was marked 'distal'. Each part was marked distally using tissue marking dye. The three parts of urethra were further divided into four,

about 5 mm long parts. These were identified by the letters a–d, where d was the most distal part (Figure 1), 12 samples were received from each urethra.

The different parts of urethra were then dehydrated and embedded in paraffin. Three to five µm thick sections were cut, using a Leica rotary microtome (HistoCenter, Västra Frölunda, Sweden) and routinely stained with Hematoxylin and Eosin for paraffin sections.

Histological analysis

The sections were analyzed for epithelial cell damage by using a light microscope (Zeiss, Axioskop). A range of objectives from 2.5–40× were used. The lower magnification was used to get an overview of the tissue damage and the higher magnifications for a more detailed analysis. The epithelial cell damage was graded from 0–3, according to the following scale: 0=no damage (Figure 2a); 1=light damage, with only the superficial epithelial cell layer slightly damaged (Figure 2b); 2=moderate damage, one to two cell layers of the urethral epithelium is damaged (Figure 2c); and 3=severe damage, the entire urethral epithelium is severely damaged and partly non-existing (Figure 2d).

All the histological analyses were randomized and blind.

Figure 1 Schematic picture of urethra, showing positions for histological samples

Figure 2 Typical illustrations of the urethral mucosa morphology after catheterization. The mucosa was scored with respect to damage using a scale of four degrees, 0, 1, 2 and 3 respectively. (a) Shows a normal undamaged ('control') epithelium, scored 0 (◆ indicate epithelium). The epithelial cell layer is intact and is three cells thick. (b) Shows a slightly damaged mucosa, scored 1. The outer epithelial cell layer has disappeared, and the epithelium is now two cells thick. In addition, the blood vessels (●) are slightly dilated. Note that occurrence of a few red blood cells outside of the epithelium (arrows). This degree of 'damage' can sometimes also be seen in uncatheterized control animals. (c) Shows a mucosa with a damage score of 2. The epithelium has disintegrated further and is two cells thick, note that the outermost cells have a loose appearance (arrow head). The blood vessels (●) are still dilated. (d) Shows examples of mucosa with the highest damage grade, scored 3. The epithelium is focally totally absent (arrow head). Blood vessels are still dilated (●). (a–d) have all the same magnification as indicated by the bar in (a). The bar represents 50 μ m

Results

Analysis of removal friction

Removal friction (N) was observed in all three rabbits in each group except for group 3 (with salt, without drainage eyes), where one rabbit was excluded due to technical problems when withdrawing the catheter. The means for the groups with salt (2 and 3) were 0.129 N and 0.314 N, whereas the means for the groups without salt (4 and 5) were 0.790 N and 0.711 N respectively (Figure 3). The data were analyzed with two-way ANOVA (Proc Mixed, SAS 6.12) with factors salt, eyes and their interaction. The effect of salt was statistically significant at a 5% level (P value 0.0079), whereas the difference between catheters with and without drainage eyes was not significant (P value 0.723). The interaction between the factors salt and eyes was not

significant (P value 0.391), i.e. there is no evidence that the effect of salt is different in catheters with or without eyes.

Analysis of epithelial cell damage

The normal rabbit urethra consists of two outer smooth muscle layers orientated circularly and longitudinally, the lumen is lined with an epithelial cell layer that is three cells thick (see Figure 2a). A lamina propria is found between the epithelium and the smooth muscle.

The control (non-catheterized) rabbits normally had an intact epithelium, however in a few cases a small damage was observed (scored 1, see Figure 2b) and in one sample the epithelium showed a severe damage (scored 3, see Figure 2d). Urethras catheterized with salt-coated catheter were generally

Figure 3 Plot of removal friction. The averages observed for the two groups with salted catheters are distinctly lower than averages of the groups without salt. The averages of groups with and without drainage eyes are similar

slightly damaged and were often scored 1 (see Figure 2b), single samples were scored 2 (see Figure 2c) and 3 (see Figure 2d). Urethras catheterized with catheters with no salt-coating were frequently scored 2 (see Figure 2c) and 3 (see Figure 2d).

The average of the scale assessments of the four subparts (a–d) within each part ('proximal', 'middle' and 'distal') constituted one observation for the statistical analysis, giving a total of nine observations from the three rabbits in each of the four groups (Figure 4). As the variation between rabbits was small compared to the variation between the three urethral parts from each rabbit, it was motivated to treat the data from one group as nine independent observations.

To assess the difference between catheters with and without salt, the data were analyzed with exact Wilcoxon-Mann-Whitney test stratified by presence or absence of drainage eyes, in StatXact 3.1 (Cytel Software Corporation). The degree of injury was found to be significantly lower (P value 0.0031) in catheters with salt. The differences between individual groups were also assessed using the Wilcoxon-Mann-Whitney test. The comparisons of groups with salt versus groups without salt were significant in all cases except the comparison of 2 versus 5, which resulted in a P value slightly above the 5% significance limit (P values; 2 vs 4: 0.0378, 2 vs 5: 0.0616, 3 vs 4: 0.0341, 3 vs 5: 0.0381). No significant difference was found when comparing presence vs absence of drainage eyes for catheters with or without salt (P values: 2 vs 3: 0.803, 4 vs 5: 0.439).

The analysis shows that the presence of salt significantly reduces removal friction and epithelial cell damage, and it is suggested that the effect of presence or absence of drainage eyes, is small compared to the effect of salt.

Epithelial Cell Damage

9 observations per group

Boxplot: A=max, B=75th percentile,
C=median, D=25th percentile, E=min

Figure 4 Box plot of the assessments of epithelial cell damage on a four-graded (0–3) scale. The plotted data are the averages of the measurements on each part (proximal-middle-distal) in each rabbit, treated as nine independent observations per group (this treatment is motivated in 'Results'). The medians of groups without salt are distinctly higher than groups with salt, which in turn are distinct from the control group (median 0). The medians for groups with and without drainage eyes are similar

Discussion

Repeated catheterization has been suspected to affect the urethral wall for some time.⁷ The investigations have been hampered by the fact that the urethral wall cannot be easily studied in patients. Some prospective studies exist however¹ showing a stricture of the urethral wall. Earlier studies using cytology have shown that urethral inflammation is a typical response to repeated catheterization with PVC catheters. The use of self lubricating hydrophilic catheters on the other hand show a significantly lower inflammatory response.⁷ Catheterization with a variety of Silastic and latex rubber catheters produces mainly inflammatory responses.¹¹ None of the human studies mentioned above report any loss of epithelial cells, which was the main injury that we observed in the present study using rabbits.

Animal studies have the advantage that the histology of the urethral wall can easily be studied. The histology of cats, dogs, and rabbits have been studied.^{12–16} The urethra consists of a muscle layer, a submucosa and an epithelial cell layer. The thickness of the layers change with the region of urethra. The distal part of urethra in female dogs, for instance, have a thicker muscle layer than the proximal end.¹³ On the other hand, the epithelial layer was similar along the entire urethral length. Comparisons between female

and male urethra are complicated by the presence of the prostate, but the epithelium was relatively thinner in the males.^{13,14} The epithelial cell layer ranges from 2 to 5 cells.

Grade of tissue damage can be examined in a number of different ways. A simple, often used method is a scoring system. A semiquantitative scale ranging from zero to three, four or five grades are often used.^{11,12,16} Our four grade scale was based on the thought to observe mild, moderate and severe erosions of epithelium. Most of our sections show only mild or moderate erosions, although severe focal areas were observed in some sections from rabbits catheterized with a low osmolality LoFric[®] catheter. The results demonstrate that the high osmolality LoFric[®] is gentle to the urethral epithelium. Furthermore, the gentility of the LoFric[®] catheter was demonstrated by the removal friction data, as lower removal friction was indicated in the high osmolality LoFric[®] catheters. Comparisons of the findings with histology and the removal friction, showed a correlation of 0.62 (Kendall-correlation), supporting that the results we obtain can be corroborated with more than one technique.

Catheterization studies have been performed in dogs, cats, ferrets and rabbits.^{12,15,17} Some of the studies involve balloon catheters (CAD catheters). Haemorrhages were observed, with microscopic lesions at the site of the balloon inflation.¹² There was no difference between female or male dogs or cats. We observed no signs of haemorrhage in the urethras used in our study, indicating that blood capillaries were mainly intact. Few red blood cells can however be observed in the lumen, and in the sub mucosa, indicating some impairment of the urethral wall. Examinations of rabbit urethra after catheterization or injury (urethrotomy) showed increased inflammation and fibrosis.¹⁵ In that study rabbits were studied on day 1, 4, 7, 14 and 21, while we studied our rabbits immediately after catheterization. This time difference may explain why we do not see any inflammatory processes. It is also possible that the LoFric[®] catheters used in our study are less traumatic, due to its hydrophilic surface layer. Erosions in the epithelial layer were observed focally.^{15,16} On the other hand, in this study we observed a difference in erosions with the different catheters. Rabbits that were catheterized with low osmolality LoFric[®] catheters, had a higher scoring (erosion) than rabbits that were catheterized with high osmolality LoFric[®] catheters. We used the erosion of the urethral epithelium to study the effect of catheterization, while most previous studies have concentrated on the inflammatory cells and consequently a later response.

The friction of the catheter has a great influence on the trauma, and for hydrophilic catheters the water binding ability is crucial for the friction reduction, since it is the adhered water that creates the low friction (and *not* the hydrophilic polymer itself). The water binding ability depends on a number of factors,

like the chemistry of the hydrophilic polymer and the way it is attached to the surface. In contact with an osmotic environment, the water binding will also depend on the osmolality of the hydrophilic coating, so a certain degree of synergism between these two factors cannot be excluded.

It has been shown in dogs that PVP-salt coated catheters are less erosive than ordinary uncoated catheters³ and that the friction was lower for the LoFric[®] catheters compared to a PVC catheter with gel (lubricant like e.g. chlorhexidine gel),^{3,7} but very similar for LoFric[®] catheters with low or high osmolality. This is true for insertion friction and, if the catheterization time is very short, also for withdrawal friction. Simultaneously Carlsten *et al*³ also investigated the histological changes and found only mild superficial inflammation in the two LoFric[®] catheters compared to frequent erosions, ulcerations, oedema and bleeding with the ordinary catheters. In our study we examined erosions of the rabbit urethral wall and found results corroborating the earlier findings.³ The difference between Carlsten *et al* and our study, is the longer catheterization time in our study (5 min *vs* 1 min). Due to this difference, we could also observe differences in withdrawal friction and urethral trauma between hydrophilic catheters with high and low osmolality respectively.

Our studies indicate that the importance of withdrawal friction (which to some extent depends on osmolality) can be verified through studies of histological changes.

Conclusion

It may be concluded that the osmolality is one very important factor (there might be others, like e.g. water retention ability) when comparing different hydrophilic catheters, both in regard to removal friction and urethral trauma. Furthermore it is suggested that there is no difference in urethral trauma between catheters with or without eyes. To minimize the risk of urethral trauma, high osmolality catheters are recommended, especially when the catheterization times are a few minutes or more.

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