Local antiseptic therapy for non-gonococcal urethritis: phase II study with Instillagel

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Abstract Non-gonococcal urethritis (NGU) is conventionally treated with oral antibiotics. With this Phase II study, we investigated the action of a locally disinfecting substance, Instillagel, in symptomatic NGU. Instillation treatment was performed twice daily to 32 male patients with symptomatic NGU. To evaluate the therapeutic outcome, a smear was taken from the urethra and an urine examination was performed at baseline as well as at 5 and 8 days after the start of the treatment. Pain and micturition symptoms were determined by a questionnaire with analog scales taken before and after therapy. A pre/post comparison of the urethral smears of the patients with symptomatic NGU showed a significant difference ($P < 0.0001$). The microbial count in the urine did not show a significant difference. The symptoms micturition ($P < 0.0001$) and pain in the urethra ($P < 0.0001$) were significantly improved. This Phase II study confirmed that local antiseptic treatment of NGU can offer an alternative to systemic antibiotic treatment.

Keywords Non-gonococcal urethritis  ·  Local antisepsis  ·  Therapy

Urethritis is characterized by a discharge from the urethra, burning within the urethra and pain during micturition.

Gonococcal and non-gonococcal urethritis (NGU) are distinguished. NGU, in particular, has shown a rapid increase in the last 10 years in sexually transmitted diseases [8]. The principal pathogens responsible for the condition have been identified as _Chlamydia trachomatis_, _Ureaplasma urealyticum_ and _Mycoplasma genitalium_.

In men older than 35 years of age, enterobacteria are often involved in NGU, especially _Escherichia coli_. The prevalence statistics cited for the individual pathogens in the literature vary considerably [4]. _C. trachomatis_ has been detected in 25%–40% of the cases, _U. urealyticum_ in 40%–50% (often in combination with _C. trachomatis_ and other pathogens, such as enterobacteria, in 5%–10%. Bacteria cannot be detected at all in 20%–30% of the patients [9, 14].

The variation of the distributions may be demonstrated in the examples of _Haemophilus influenzae_, parainfluenzae and atrophilus. Joly-Guillou et al. reported detection in 20% of the cases, while, according to other authors, the urethritis is attributed to a _Haemophilus infection_ in only 1.2% and 9.3% [3, 7]. Other cases of urethritis are due to fungal infections or are induced after the urethra has been manipulated and are due to non-sexually transmitted pathogens [10, 13].

The standard therapy for NGU is systemic antibiotic treatment with fluoroquinolones, gyrase inhibitors, aminoglycosides or tetracyclines [4, 10]. Wabroesch has indicated a possible action mechanism of local disinfectant therapy. In five patients with fungicide-resistant Candida urethritis, a complete cure was achieved after repeated instillations of Instillagel for several days [13].
Patients and methods

Following approval of the study protocol by the Ethics Committee of Essen University, 32 male patients suffering from symptomatic non-gonococcal urethritis were given local antiseptic therapy that conforms to good clinical practice (GCP) guidelines.

The inclusion criteria were fully competent patients with symptomatic NGU who had given their informed consent. The exclusion criteria were participation in another therapeutic study using a transurethrally applied medication, detection of gonococcal urethritis, simultaneous systemic antibiotic treatment and an allergy to lidocaine.

The test medication was Instillagel (Farco-Pharma, Cologne, Germany), a local antiseptic and a local anaesthetic. The sterile gel, in sterile disposable syringes, contains the following as the antimicrobial active principle: a combination of disinfectants that consist of chlorhexidine digluconate and propyl 4-hydroxybenzoate, as well as 2% lidocaine as the anaesthetic.

In the presence of symptomatic NGU, and after the inclusion and exclusion criteria had been checked, instillations were carried out twice daily; an action time of 30 min was ensured on each occasion by applying a penis clamp. The primary objective of the study was to examine the antimicrobial action of Instillagel in confirmed microbial NGU by taking urethral smears and by microbiological investigations of the urine before and after the therapy. The secondary objective was to establish the therapeutically determined side effects, which were classified by nature, frequency, severity and reversibility. In addition, the patients’ subjective feelings concerning discomfort during urination and within the uretra during treatment were to be evaluated by a questionnaire with an analog scale.

The statistical evaluation was carried out using Testmate Version 5.1 (from IDV, Gauting, Germany), adopting a significance threshold of 0.05.

A two-tailed McNemar binary data test was used as the standard test for intergroup comparisons of nominal data, employing two categories (urethral smears and the urine) to investigate the antimicrobial action of Instillagel.

The data forming part of the secondary study objective, which were on the ordinal scale level, were investigated by Friedman’s test.

Results

The local disinfectant action of Instillagel was investigated in 32 male patients who suffered from symptomatic non-gonococcal urethritis and who had worn an indwelling catheter for an average of 2.6 days (1–3 days). As had been specified within the framework of the Phase II study, an interim evaluation was carried out on 14 patients and, on the basis of the therapeutic outcomes achieved, the investigation was completed with a maximum number of 32 patients.

An urethral smear, taken after the catheter had been removed, was examined in all patients before local disinfectant therapy was started so as to check for the presence of non-gonococcal urethritis, which confirmed the existence of NGU in all 32 cases. The pathogens detected were E. coli, Staphylococcus epidermidis, enterococci and Proteus. In the subjective sensations questionnaire, all 32 patients reported symptoms before the treatment began.

A concomitant urinary tract infection was found in 8 of 32 patients in the urine sediment and during the subsequent microbiological processing. Systemic antibiotic treatment was given to 14 of 32 patients for an average of 2.9 days (1–3 days). None of the patients had been given antibiotics for at least 24 h before the beginning of the local applications of Instillagel.

No bacteria could be detected in the post-therapeutic urethral smears of 26 of 32 patients, while the findings were positive in 4 of 32 cases. Urine cultures carried out at the same time were negative in 28 of 32 cases (see Table 1).

In two cases, further treatment with Instillagel was discontinued at the patients’ wish because of subjective discomfort, such as burning and pain in the urethra that remained constant during the course of the observation period.

The subjective findings questionnaires that referred to sensations during urination showed an improvement in 23 of 32 cases; in none of the cases did the condition worsen, and there was no change in 7 of 32 patients.

The “findings in the urethra” were given by 16 of 30 patients as improved and by 14 of 32 as unchanged. There were no deteriorations in the subjective sensations in the urethra (see Table 2).

Statistical evaluation of the data obtained for 32 patients by the standard test for within group comparisons (pre/post comparison) showed the following:

1. A significant difference in the pre/post comparison of bacteriological findings in the urethral smear: $P < 0.0001$, according to the McNemar chi-squared (two-tailed) test.
2. No significant difference in the pre/post comparison of bacteriological findings in the urine: $P = 0.5$, according to the McNemar chi-squared (two-tailed) test.
3. A significant difference in the pre/post comparison of subjective sensations during urination: $P < 0.0001$, according to a Friedman analysis.

Table 1. Antimicrobial action after topical therapy

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative urethral smear</td>
<td>26/32</td>
<td>0/32</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>No urinary-tract infection</td>
<td>28/32</td>
<td>32/32</td>
<td>$&gt; 0.05$</td>
</tr>
</tbody>
</table>

Two patients dropped out because of local discomfort in the urethra

Table 2. Patients’ symptoms

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findings in the urethra</td>
<td>Better</td>
<td>16/32</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td></td>
<td>Unchanged</td>
<td>14/32</td>
<td>$&gt; 0.05$</td>
</tr>
<tr>
<td>Findings during micturition</td>
<td>Better</td>
<td>23/32</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td></td>
<td>Unchanged</td>
<td>7/32</td>
<td>$&gt; 0.05$</td>
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