Antibiotic prophylaxis in catheter-associated urinary infections

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SUMMARY

This study aimed to assess the usefulness of antibiotic prophylaxis with Levofloxacin (LVFX) in short and medium-term catheterisations. This study was developed to evaluate and confirm the effectiveness and need for prophylaxis in preventing catheter-associated UTIs, using LVFX at a dose of 250 mg administered orally to patients who had been subjected to short and medium-term urinary bladder catheterisation following surgery (3-14 days).
The study was designed as a phase III study with parallel groups, multicentre, randomised, controlled with a placebo in three groups. The study was double-blind in treatment groups A and B and single-blind in group C. The study involved the recruitment of 120 patients, 40 for each treatment group.
We show two types of results, one based on primary effectiveness variables and the other on the secondary effectiveness variables.
The group treated with LVFX displayed a greater tendency toward the negativisation of bacteriuria and pyuria tests than that recorded for the placebo group, and was essentially comparable to that recorded for the group of patients treated with Ciprofloxacin.
We can thus affirm that LVFX may be useful for preventing short and medium-term CAUTIs.

KEY WORDS: Urinary tract infections, Antibiotic prophylaxis, Levofloxacin

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INTRODUCTION

Urinary tract infections (UTIs) and/or catheter-associated urinary tract infections (CAUTIs) are the most common nosocomial infections constituting approximately 40% of all hospital infections. They are often asymptomatic and resolve spontaneously with removal of the catheter (van der Wall *et al.*, 1992; Tambyah *et al.*, 2000; Godfrey *et al.*, 2000). UTIs are caused by opportunistic microorganisms present in the environment, which do not usually damage the infection site (Lautenbach *et al.*, 2001; Doyle *et al.*, 2001). In 30% of patients, however, the infection persists and, particularly in high-risk patients such as elderly persons with urinary tract abnormalities, persons with diabetes or compromised immune systems, this may result in the development of complications such as prostatitis, epididymitis, cystitis and pyelonephritis (Léone *et al.*, 2000; Godfrey *et al.*, 2000). Based on these considerations and the proven benefits of antibiotic prophylaxis in decreasing the risk of infection for certain types of surgeries, it was hypothesized that bladder catheterization could also be accompanied by and benefit from an appropriate antibiotic prophylaxis (Long *et al.*, 2002).
Beginning from this hypothesis a randomised and controlled multicentre phase III study was performed with the goal of assessing the usefulness of antibiotic prophylaxis with Levofloxacin in

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short and medium term catheterisations.
This clinical study, which involved a double-blind treatment in three groups of patients, was conducted in various hospitals throughout the country. In the late 90's various studies (Lee *et al.*, 1998; Saint *et al.*, 1999; Safdar *et al.*, 2002) demonstrated the effectiveness of fluoroquinolone administration in preventing catheter-associated urinary tract infections (CAUTIs); specifically, Levofloxacin (LVFX) was used at a dose of 250 mg administered for 7-10 days in patients who had been catheterised following surgery.
Van der Walls and Salvestrini (van der Wall *et al.*, 1992; Salvestrini *et al.*, 1996) successfully tested Ciprofloxacin (CPFX). Based on these assumptions, this study was developed with the primary goal of evaluating and confirming the effectiveness and need for prophylaxis in preventing catheter-associated UTIs, using LVFX at a dose of 250 mg administered orally to patients who had been subjected to short and medium-term urinary bladder catheterisation following surgery (3-14 days). Secondary goals were also identified including:
- Can LVFX prevent pyuria (>10 leucocytes/cubic mm), bacteriuria (>1000 CFU/ml), symptomatic infections of the urinary tract and nosocomial infections?
- During the follow-up can LVFX prevent pyuria, bacteriuria and symptomatic infections of the urinary tract? Is it possible to identify the distribution of the principal bacterial species involved and the correlation between species isolated in urine samples obtained from the drain tube following catheterisation and bacteria isolated in cultures from the same catheters immediately following removal?
- Which bacterial species are present in the faeces of the three randomisation groups during and after prophylaxis?
- How do age, sex, type of surgery, type of department and hospital, basic clinical conditions, type of concomitant pathologies and the duration of catheterisation influence the clinical outcome?

MATERIALS AND METHODS

This was a phase III study with parallel groups, multicentre, randomised, controlled with a placebo in three groups:
- group A: LVFX, experimental drug;
- group B: control group with placebo, drug in controlled study;
- group C: comparison with CPFX, drug in control study.

The study was double-blind in treatment groups A and B and single-blind in group C. Administration began on the second day post-surgery which corresponded to the second day of catheterisation and ended with the removal of the catheter (minimum duration of prophylaxis: 2 days, maximum duration 13 days); this was followed by a follow-up phase 4-6 weeks after the end of prophylaxis (Table 1). Examinations were performed and data recorded at the following stages (Figure 1):
- baseline or pre-surgical examination (V1): prior to surgery and insertion of the catheter, this included an assessment of all protocol selection criteria and the collection of patients' personal and baseline information (anamnesis, recording of vital signs, concomitant treatments, etc.). Blood and urine samples were also collected so as to establish the baseline blood chemical and urinary parameters and the type of surgery, type of perioperative prophylaxis used and catheterisation data were recorded.
- Start of prophylaxis examination (V2): on the second day post-surgery the data relative to the surgery were recorded (outcome/duration/complications) and the multi-organ dysfunction score was calculated. A urine sample was then taken and subjected to bacteriological testing, and the possible signs and symptoms of UTIs or other nosocomial infections were recorded; all of this was completed prior to beginning treatment with antibiotics.
- End of prophylaxis examination (V3): the physical examination was repeated, vital signs recorded, a urine sample collected for bacteriological testing and any possible signs and symptoms of UTIs or other nosocomial infections recorded. During this examination compliance was evaluated and the response to prophylaxis recorded. Catheterisation data were recorded as well as data covering the post-catheterisation observation period up until discharge. Blood and urine samples were collected again to measure blood chemical and urinary parameters. This examination evaluated the response to prophylaxis and a summary of the study was drawn up.

TABLE 1 - *Methods*.

Views/Activity	*V1*	*V2*	*V3*	*V4*	*VIA**
Informed consent	X				
Include/exclude criteria	X				
Demography	X				
History	X		X	X	X
Concomitant therapies	X	X			
Surgery	X	X		X	X
Physical examination / Concomitant pathology	X	X	X	X	X
Vital signs	X	X	X		X
Catheterization	X	X	X	X	X
IVU/IO signs and symptoms		X	X	X[2]	X
Blood chemistry and urinary parameters		X[1]	X[1]		X[1]
Multiorgan dysfunction score		X			
Randomization /Delivery drug		X			
Bacteriological examination (feces and urine)		X[3]	X[3]	X[3]	X[3]
Response to prophylactic			X	X	X
Observation post-catheterization			X		X
Adverse reactions	X	X	X	X	X
Abstract of the study		X[4]	X[4]	X	X
Withdrawal Card Diary				X	X[5]

*Patients who come from the study after this visit (VIA) shall complete all procedures scheduled for the end of the visit or follow-up prophylaxis (V3 or V4). [1]To be calculated only in case of obvious clinical deterioration of patients after surgery: if it is greater than or equal to 9, the patient must come out from the study. [2]Be carried out only in case of abnormal results in V3. [3]Urine taken from the drainage tube (V2/V3/VIA), midstream urine (V4 or VIA). [4]Only if the break is made at this visit. [5]Only if the break is done before V4 (during the period of follow-up).

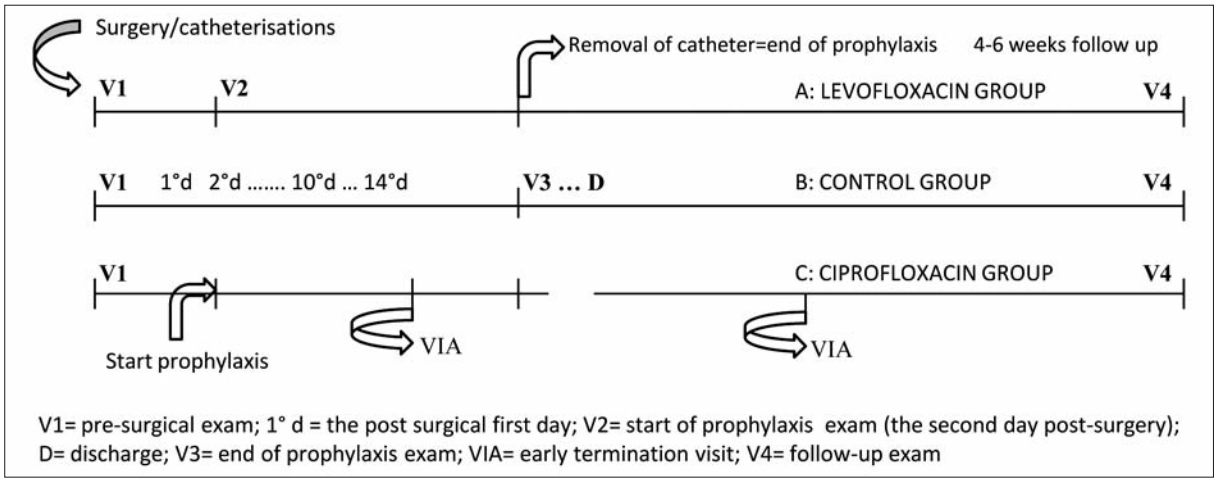
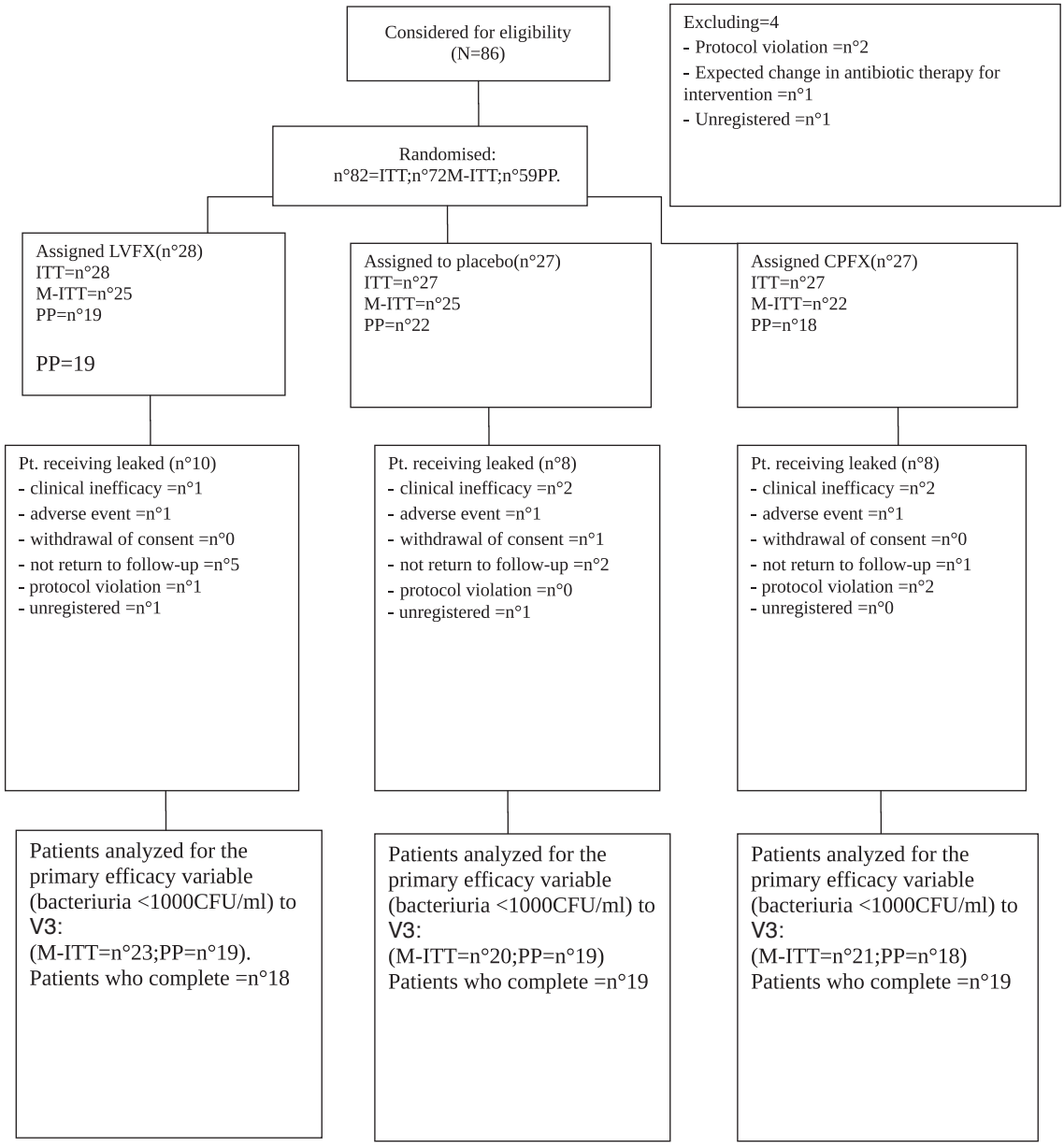


FIGURE 1

- Follow-up examination (V4): 4-6 weeks following the end of prophylaxis, the physical examination was repeated, vital signs recorded and urine samples collected (midstream urine samples) for bacteriological testing (bacteriuria, pyuria, isolation and identification of microorganisms, antibiogram and possible faeces examination).
  Any signs and symptoms of UTIs that developed during or upon completion of the follow-up period were also recorded. During this examination the response to prophylaxis was assessed and, if necessary, blood and urine samples were collected (midstream urine samples) in order to measure blood chemical and urinary parameters. The study summary was updated during this examination.

TABLE 2 - *Results*.



- Intermediate examination (IE): this examination may be performed for any reason prior to the end of catheterisation (prior to V3) or upon completion of the follow-up period (prior to V4).

RESULTS

The study involved the recruitment of 120 patients, 40 for each treatment group, who were hospitalised for planned surgery in the departments of gynaecology, surgery, urology or orthopaedics in 4 hospitals in Campania and two in Sicily (Table 2).
The following centres participated in the study:
- Urology Department.
  University Hospital at II University of Naples.
  1 patient enrolled;
- Surgery Department
  University Hospital at II University of Naples.
  2 patients enrolled;
- Vascular Surgery Department
  "Maurizio Ascoli" Cancer Hospital, Palermo.
  5 patients enrolled;
- Gynaecology Department
  Civil Hospital of Caserta. 6 patients enrolled;
- Gynaecology Department
  University Hospital at II University of Naples.
  14 patients enrolled;
- Urology Department
  Civil Hospital of Caserta. 14 patients enrolled;
- A.R.N.A.S. Civico
  Lithotripsy Department, Palermo. 11 patients enrolled;
- Surgery-Orthopaedics Department
  Santa Maria delle Grazie Civil Hospital, Pozzuoli. 15 patients enrolled;
- Gynaecology Department
  Santa Maria delle Grazie Civil Hospital, Pozzuoli. 15 patients enrolled;
- Vascular Surgery Department
  Civil Hospital of Caserta. 17 patients enrolled.

Of the 120 initially planned, the study actually included a total of 86 patients who underwent the screening examination (exam 1), and a total of 82 patients were randomised (exam 2) and then subdivided into:
- group A: 28 patients receiving the treatment of 250 mg of LVFX administered p.o. every 24 h + placebo;
- group B: 27 patients receiving the placebo administered p.o. every 24;
- group C: 27 patients receiving the treatment of 500 mg of CPFX administered p.o. every 12 h.

Four patients were not randomised due to protocol violations in 2 cases, for specific antibiotic treatment undertaken following a variation in the type of surgery in one case and a lack of records in another. During examination 3 (end of prophylaxis) a total of 74 patients were evaluated, 27 in the LVFX group, 26 in the placebo group and 21 in the CPFX group; during examination 4 (follow-up) a total of 66 patients were evaluated, 23 in the LVFX group, 24 in the placebo group and 19 in the CPFX group.
Each patient participated in the study for a minimum of 31 days and a maximum of 56 days depending on the actual duration of catheterisation.
Of the ITT population (intent-to-treat: patients who received at least one dose) a total of 26 patients were prematurely dropped from the study, 10 of whom were in the LVFX group, 8 in the placebo group and 8 in the CPFX group. The principal reasons for prematurely dropping patients from the study included clinical ineffectiveness in 6 patients (2 in each group); failure to appear at return check-ups in 8 (5 in the LFVX group, 2 in the placebo group and 1 in the CPFX group); adverse events in a total of 3 (1 in the LVFX group, 1 in the placebo group and 1 in the CPFX group); withdrawal of consent in only 1 patient (in the placebo group); protocol violations in a total of 5 patients (1 in the LVFX group, 2 in the placebo group and 2 in the CPFX group); a lack of records for 1 patient (in the LVFX group); another 2 reasons in 2 patients both of whom were in the CPFX group.
The drug was correctly administered to a total of 70 patients, 24 in the LFVX group, 24 in the placebo group and 22 in the CPFX group, and incorrectly administered to a total of 2 patients, 1 in the LVFX group and 1 in the placebo group.

Primary effectiveness variable

The results of the analysis of the primary variable (patients with bacteriuria <1000 CFU/ml in the urine samples collected from catheters at the end of prophylaxis) in the M-ITT population (modified ITT: the ITT population not including the patients whose samples displayed positive bacteriuria during exam 2) were the following:

- a negative bacteriuria test was recorded for 64 patients, 23 in the LVFX group, 20 in the placebo group and 21 in the CPFX group, while a positive response was recorded for a total of 7 patients, 2 in the LVFX group and 5 in the placebo group.

An analysis of the primary variable in the M-ITT population was also performed using the value <100000 CFU/ml to define bacteriuria at the end of prophylaxis: a negative bacteriuria test was recorded for a total of 66 patients, 24 in the LVFX group, 21 in the placebo group and 21 in the CPFX group, while a positive response was recorded for a total of 5 patients, 1 in the LVFX group and 4 in the placebo group.

The results in the PP population (Per-protocol: the M-ITT population not including patients with serious protocol violations) were the following:

- a negative bacteriuria test was recorded for a total of 56 patients, 19 in the LVFX group, 19 in the placebo group and 18 in the CPFX group, while a positive response was recorded for a total of 3 patients, all of whom were in the placebo group.

Secondary effectiveness variables:

- Collection bag bacteriuria: a negative bacteriuria test (<100000CFU/ml) at exam 3 was recorded for a total of 60 patients, 22 in the LVFX group, 19 in the placebo group and 19 in the CPFX group, while a positive response was recorded for a total of 6 patients, 2 in the LVFX group and 4 in the placebo group.
- Bacteriuria at follow-up: a negative response was recorded for a total of 49 patients, 15 in the LVFX group, 16 in the placebo group and 18 in the CPFX group, while a positive response was recorded for 1 patient in the placebo group.
- Bacteriuria in the urethrovesical section of the catheter: a total of 59 bacterial strains were isolated in the population at the end of prophylaxis, 17 in the LVFX group, 22 in the placebo group and 20 in the CPFX group; the most frequently recorded bacteria were Enterococcus faecalis (in a total of 11 patients) and Pseudomanas aeruginosa (in a total of 7 patients).
- Pyuria at the end of prophylaxis and follow-up: at the end of prophylaxis (exam 3) a negative pyuria test was recorded for a total of 67 patients, 25 in the LVFX group, 21 in the placebo group and 21 in the CPFX group, while a positive response was recorded for 3 patients, all of whom were in the placebo group. At the follow-up, a negative pyuria test was recorded for a total of 50 patients, 16 in the LVFX group, 16 in the placebo group and 18 in the CPFX group, while a positive response was recorded for 3 patients, 1 in the LVFX group and 2 in the placebo group.
- Symptomatic urinary infections: no cases of symptomatic urinary infections were recorded at the end of prophylaxis (exam 3) in any treatment groups, while in the follow-up (exam 4) one symptomatic urinary infection was recorded for one patient in the placebo group.
- Local complications associated with the catheter: no local complications associated with the catheter were recorded for any treatment groups.
- Nosocomial infections: 1 case of nosocomial infection was recorded (infection of the surgical wound) in 1 patient in the placebo group.
- Post-discharge symptoms: the number of patients with symptoms was very low in all treatment groups (1, 2 and 2, respectively in the LVFX, placebo and CPFX groups).

Tolerability results

Adverse events: there were 8 adverse events in the LVFX group, 7 in the placebo group and 8 in the CPFX group, while there were 5 patients with at least one adverse event in the LVFX group, 6 in the placebo group and 5 in the CPFX group. No patient experienced an adverse event correlated with the duration of the drug. No serious adverse events were recorded in any patients during the study. The number of patients with adverse events who were dropped from the study included 1 in the LVFX group (temperature increase), 1 in the placebo group (temperature increase) and 1 in the CPFX group (infection of the surgical wound).

Laboratory parameters: clinically significant individual abnormalities in laboratory parameters during post-treatment exams (exam 3 or 4) were recorded for one patient in the LVFX group (elevated transaminases), in one patient in the placebo group (elevated transaminases, gamma-GT, albumin and bilirubin), and in 3 patients in the CPFX group (elevated ESR, abnormalities in urinary sediment analysis, elevated glycaemia).

Vital signs: no clinically significant variations in

arterial pressure (systolic and diastolic) or heart rate were recorded for any of the treatment groups during the various examinations.

Experimental conclusions

The data from this study displayed the following:

- no significant difference was found between LVFX and the placebo in terms of effectiveness. However, a higher percentage of subjects without bacteriuria at the end of antibiotic prophylaxis was recorded for those treated LVFX as compared with the placebo,
- two elements may have influenced the above outcome: a high percentage of subjects with a negative bacteriuria test in the placebo group, much higher than the initial hypothesis, and the recruitment of a smaller number of patients than planned; this may have contributed to the failure to find a statistical difference between the compared groups.
- the effectiveness of prophylaxis with LVFX was essentially comparable to that recorded for the group of patients treated with CPFX.

CONCLUSIONS AND DISCUSSION

Despite the usefulness of antibiotic prophylaxis with quinolones during medium and long-term catheterisation, as demonstrated in the United States (Lee *et al.*, 1998; Saint *et al.*, 1999; Safdar *et al.*, 2002), the present study was not able to confirm these data, most likely due in part to the small number of patients recruited (86 vs. the 120 planned). We were thus unable to draw any definitive conclusions on the usefulness of antibiotic prophylaxis with LFVX during short and medium-term catheterisation. The results for the primary variable displayed a negative bacteriuria test in a greater percentage of the placebo group than expected in the experimental hypothesis, which anticipated 30% of patients to be significantly free of bacteriuria. This contributed to precluding the possibility of recording statistically significant differences between the two active treatments and the placebo treatment.

The results relative to a negative bacteriuria analysis at the end of treatment, performed on urine samples collected from bags upon the completion of prophylaxis, confirmed the absence of significant differences between the active treatments as compared with the placebo group, with a positive response recorded for a total of 6 patients, 2 in the LVFX group and 4 in the placebo group.

Compared with the study conducted by van der Walls in the late 80's (van der Wall *et al.*), the present study displayed a much higher percentage of subjects treated with a placebo who were free of bacteriuria. One possible explanation for this difference is the improvement in catheterisation techniques that have occurred over the years following the study by van der Walls, which could cause a reduction in the frequency of catheter infections (Winter *et al.*, 2009; Rhodes *et al.*, 2009). In any case, the group treated with LVFX displayed a greater tendency toward the negativisation of bacteriuria and pyuria tests than that recorded for the placebo group, and was essentially comparable to that recorded for the group of patients treated with CPFX (Poisson *et al.*, 2010; Hameed *et al.*, 2010).

We can thus affirm that LVFX may be useful for preventing short and medium-term CAUTIs (van der Wall *et al.,* 1992; Lautenbach *et al.*, 2001; Salvestrini *et al.*, 1996; Roghmann *et al.*, 2006; Kuster *et al.*, 2010), but additional studies are needed confirm these results and specifically in order to indicate the need for antibiotic prophylaxis during bladder catheterisation. This hypothesis may prompt additional investigation and boost scientific research.

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