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Fosfomycin vs. Cefixime on infectious prophylaxis of transrectal prostatic biopsy: Prospective study

(versão final após defesa)

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Dissertação para obtenção do Grau de Mestre em
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CHAVE MÓVEL

Dedicatória

Aos meus pais, aos meus irmãos e ao Bruno

Agradeço por sempre terem acreditado em mim.

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Resumo

Introdução: A profilaxia antibiótica na biópsia prostática transrretal é a chave para o controlo das complicações infeciosas. Este estudo visa investigar a eficácia da fosfomicina versus cefixima como regime único de tratamento profilático da biópsia prostática transrretal.

Material e Métodos: Este estudo prospetivo e randomizado incluiu pacientes com suspeita clínica prévia de cancro da próstata que foram divididos em dois grupos. O Grupo 1 recebeu fosfomicina oral 3g antes e 3g 24h após a biópsia prostática. O Grupo 2 foi tratado com cefixima 400mg via oral, durante 3 dias, com início 24h antes da biópsia. Foi desenvolvido um questionário que quantificou os sintomas urinários e registou os sinais clínicos que comprovavam a ocorrência de infeção. A infeção do trato urinário foi definida pela ocorrência de febre (temperatura igual ou superior a 38ºC), diagnóstico de infeção por profissional de saúde ou prescrição de antibioterapia. Modelos de regressão logística estudaram a frequência de infeção segundo a profilaxia antibiótica prescrita e fatores de risco relacionados com o doente e com o procedimento.

Resultados: Dos 118 doentes incluídos no estudo, 50 (42,4%) receberam fosfomicina e 68 (57,6%) cefixima. A idade média foi de 68,7 anos, a mediana do PSA sérico foi de 16,7 ng/ml e a média do IPSS antes da biópsia foi de 9 pontos. A incidência geral de infeção urinária foi 8,5% (12% no Grupo 1 versus 5,9% no Grupo 2; p=0.238). Nenhuma característica basal esteve significativamente associada à ocorrência de infeção. Não foi documentada necessidade de internamento hospitalar. A cefixima esteve mais associada ao agravamento dos sintomas do trato urinário e da qualidade de vida após a biópsia (Grupo 1: -0,7; Grupo 2: -1,5; p=0,347; Grupo 1: -0,1; Grupo 2: -0,4; p=0,059, respetivamente).

Conclusão: A fosfomicina revelou eficácia semelhante à da cefixima na prevenção de complicações infeciosas resultantes da biópsia prostática transrretal.

Palavras-chave

Profilaxia antibiótica;infeção do trato urinário;biópsia prostátca;resistência antibiótica;complicações infecciosas

Resumo Alargado

Introdução: A profilaxia antibiótica na biópsia prostática transrretal é o pilar essencial no controlo das complicações infeciosas. A crescente resistência às fluoroquinolonas obrigou a que deixasse de ser recomendada na União Europeia. Contudo, ainda não existem estudos que indiquem qual o antibiótico mais eficaz para a prevenção de infeções que ocorrem após a biópsia prostática transrretal.

Objetivo: Avaliar a eficácia da fosfomicina versus cefixima, como regime único de tratamento profilático da biópsia prostática transrretal.

Material e Métodos: O presente estudo longitudinal prospetivo foi realizado no Instituto Português de Oncologia de Coimbra entre setembro de 2021 e julho de 2022. Os participantes foram divididos aleatoriamente em dois grupos. O Grupo 1 recebeu fosfomicina oral 3g antes e 3g 24h após a biópsia prostática. O Grupo 2 recebeu cefixima 400mg via oral, durante 3 dias, com início 24h antes da biópsia. Os pacientes com suspeita clínica prévia de cancro da próstata foram incluídos no estudo. Os critérios de exclusão foram a prescrição de antibioterapia nos 3 meses prévios à biópsia, história de infeção do trato urinário, de algaliação ou de realização de biópsia prostática nos últimos 6 meses, imunossupressão conhecida (excluiu-se a Diabetes Mellitus), anomalias do trato urinário e recolha de núcleos de biópsia superior a 16 ou inferior a 10 unidades. Foi desenvolvido um questionário para quantificar os sintomas urinários e registar os sinais clínicos que comprovavam a ocorrência de infeção. A infeção do trato urinário foi definida pela ocorrência de febre (temperatura igual ou superior a 38ºC, diagnóstico de infeção por profissional de saúde ou prescrição de antibioterapia. O questionário foi preenchido antes, uma semana e um mês após a biópsia prostática transrretal. Posteriormente, os dados dos questionários previamente preenchidos bem como as informações cínicas de cada doente foram registadas. O desfecho primário do estudo foi a eficácia dos antibióticos selecionados. Modelos de regressão logística estudaram a frequência de infeção segundo a profilaxia antibiótica prescrita e fatores de risco relacionados com o doente e com o procedimento.

Resultados: Foram incluídos 118 doentes no estudo, 50 (42,4%) receberam fosfomicina e 68 (57,6%) cefixima. A idade média foi de 68,7 anos, a mediana do PSA sérico foi de 16,7 ng/ml e a média do IPSS antes da biópsia foi de 9 pontos. A incidência geral de infeção urinária foi 8,5% (12% no Grupo 1 versus 5,9% no Grupo 2; p=0.238). Não houve diferença estatisticamente significativa na taxa de infeção entre os grupos. Nenhuma característica basal esteve significativamente associada à infeção. Não foi documentada necessidade de internamento hospitalar. Embora sem significado

estatístico, a cefixima esteve mais associada ao agravamento dos sintomas do trato urinário e da qualidade de vida após a biópsia (Grupo 1: -0,7; Grupo 2: -1,5; *p*=0,347; Grupo 1: -0,1; Grupo 2: -0,4; *p*=0,059, respetivamente).

Conclusão: A fosfomicina revelou eficácia semelhante à cefixima na prevenção de complicações infeciosas resultantes da biópsia prostática transrretal.

Abstract

Introduction: Antibiotic prophylaxis in transrectal prostatic biopsy is the key to controlling infectious complications. Our study aims to investigate the efficacy of fosfomycin versus cefixime as a single prophylactic treatment regimen.

Material and Methods: This prospective randomized study included patients with a previous clinical suspicion of prostate cancer that were divided into two groups. Group 1 received oral fosfomycin 3g before and 24 hours after the biopsy. Group 2 was treated with cefixime 400mg orally for 3 days, starting the day before the procedure. A questionnaire quantified urinary symptoms and recorded clinical signs of infection. Urinary tract infection was defined by the presence of fever (temperature equal to or greater than 38ºC), diagnosis of infection by a healthcare professional, or antibiotic prescription. Logistic regression models studied the frequency of infection according to the antibiotic prophylaxis prescribed and patient- and procedure-related risk factors.

Results: Of 118 patients, 50 (42.4%) received fosfomycin and 68 (57.6%) cefixime. The mean age was 68.7 years, and the median PSA value was 8 ng/ml. The overall incidence of urinary infection was 8.5% (12% in group 1 versus 5.9% in group 2; p=0.238). No baseline characteristics were significantly associated with infection. No need for hospital admission was documented. Cefixime was more associated with worsening urinary tract symptoms and quality of life after biopsy (group 1: -0,7; group 2: -1,5; p=0,347; group 1: -0,1; group 2: -0,4; p=0,059, respectively).

Conclusion: Fosfomycin has shown similar efficacy to cefixime in preventing infectious complications resulting from transrectal prostate biopsy.

Keywords

antibiotic prophylaxis;urinary tract infection;prostate biopsy;antibiotic resistance;infectious complications.

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DRE	Digital rectal examination
PSA	Prostate-specific antigen
TRUS-PB	Transrectal ultrasound-guided prostate biopsy
UTI	Urinary tract infection
LUTS	Lower urinary tract symptoms
E.Coli	*Escherichia coli*
FQ	Fluoroquinolones
EAU	European Association of Urology
IPSS	International Prostate Symptoms Score
QoL	Quality of life

1. Introduction

Prostate carcinoma is the fifth leading cause of cancer death and the second most common in men worldwide. Despite clinical suspicion (abnormal digital rectal examination (DRE), altered prostate-specific antigen (PSA) values or modified imaging tests), the gold standard is histopathological verification of carcinoma by prostate biopsy (1–4).

A prostate biopsy can be performed using a transrectal or transperineal approach. Studies argue that transrectal ultrasound-guided prostate biopsy (TRUS-PB) is associated with a 1.81 times higher risk of infection compared to transperineal prostate biopsy, although it's widely used (5,6). TRUS-PB is the most used method worldwide, thus becoming essential to know that it is a technique performed in a non-sterile environment with a high rate of complications that may also be the result of iatrogenesis or the presence of risk factors. Therefore, it is important to prevent and make patients aware of the complications and possible symptoms that may develop (7).

Studies show that the majority of complications are self-limited and that the hospitalization rate varies between 0.5% and 4.8% (8). They are classified into immediate and late. Immediate complications include rectal bleeding, prostatic bleeding, mild hematuria, vasovagal episodes, urinary tract infections (UTIs) and severe urinary retention. Hematospermia, late or recurrent hematuria, persistent pain, fever and, occasionally, urinary baseline sepsis are the most frequent late complications. Hematuria is the immediate complication most frequently reported by patients (7,8). Other complications, such as exacerbation of pre-existing lower urinary tract symptoms (LUTS), anxiety and temporary erectile dysfunction, hurt the patient's quality of life (9).

Infectious complications account for 5-7% of all complications and include asymptomatic bacteriuria, fever, symptomatic UTI, prostatitis, epididymitis and bacteremia (10). Symptomatic UTIs are the most frequently reported infectious complications.

According to Bonkat et al., UTIs in men are always complicated and the most common clinical symptoms should be considered (dysuria, urgency, frequency, flank or suprapubic pain, tenderness at the costovertebral angle or fever >38ºC) (11). The most serious infectious complications include meningitis, epidural abscess and endocarditis, although they correspond only to less than 1% of cases (8). Fatal complications are rare and are usually the consequence of a septic shock (7).

The most frequently isolated agent is *Escherichia coli (E.coli)*. Previous history of sepsis, previous acute prostatitis, recent travel history and recent antibiotic therapy use are documented as risk factors (12).

Unlike non-infectious complications, which have remained stable over time, infectious complications are responsible for the greatest number of hospitalizations (7,8,13). Studies show that the risk of developing infectious complications is 0.56 times lower with the use of antibiotic prophylaxis compared to the use of a placebo. However, although antibiotic prophylaxis has considerably reduced the percentage of associated complications, there has been an increase in these complications, the main cause being the growing resistance to antibiotics, namely to Fluoroquinolones (FQ). This situation is due to the excessive prescription of antibiotic therapy and the limited number of antibiotics available for prophylaxis of TRUS-PB (14,15). Since 2019, it has been recommended to discontinue antibiotic prophylaxis in TRUS-PB with FQ in the European Union, opening the door to other antibiotics classes potentially effective in reducing the high rates of infectious complications. The European Association of Urology (EAU) recommends one of three options: targeted prophylaxis, augmented prophylaxis or alternative antibiotics (fosfomycin, cephalosporins or aminoglycosides). Despite the recommendation, there is insufficient scientific evidence to conclude which approach is most effective (14,16).

1.1 Aim

This study aimed to compare fosfomycin's efficacy with that of cefixime in preventing infectious complications in patients undergoing transrectal prostate biopsy.

2. Materials and Methods

This is a randomized controlled prospective longitudinal study that included patients undergoing TRUS-PB between November 2021 and July 2022. All patients had prior clinical suspicion of prostate cancer. Patients were randomly divided into two groups according to their clinical process number (odd clinical processes belonged to Group 1 and even clinical processes belonged to Group 2).

The procedure included the prescription of antibiotic prophylaxis to be taken just before the time of the biopsy, the initial application of a local anesthetic and subsequently the collection of systematic and echo-guided double-sextant biopsy cores or more cognitive fusion biopsy fragments when indicated.

Group 1 participants received a prophylactic regimen of oral fosfomycin 3g before and 24h after TRUS-PB, while Group 2 participants received a three-day regimen of oral cefixime 400mg 1id, starting 24h before biopsy.

Between ten and sixteen biopsy fragments were collected. Individuals on antibiotic therapy for less than three months or with a history of UTI, use of an indwelling catheter or prostate biopsy in the last six months were not eligible for the study. In addition, individuals with known immunosuppressive factors (except Diabetes Mellitus) or with urinary tract abnormalities were also excluded.

A self-questionnaire on clinical urinary symptoms and other data related to the period after the biopsy was prepared (appendix 1). It included seven closed-answer questions based on the Portuguese version of the International Prostatic Symptoms Score (IPSS), one question on the impact of these on the patient's quality of life (QoL) and three questions that allowed the clinical evaluation of the presence of UTI. The IPSS value ranged from 0 to 35 points. UTI occurrence was defined by the occurrence of at least one of the following signs or symptoms self-reported by the patient: fever 38ºC, antibiotics intake or diagnosis of UTI by a healthcare professional. Patients filled in the questionnaire before the biopsy, one week and one month after the biopsy. Other relevant clinical data were collected from the patient file.

The bibliographic research was conducted in the PubMed database with the association of the terms "prostate biopsy" with each of the following: "infectious complications", "antibiotic resistance", "prophylaxis" and "prostate cancer". There were no limitations in the choice of the official language of the papers, however, only papers published in the last 15 years were consulted, and the ones older than 20 years were not used.

The study was approved by the Ethics Committee of the institution (attachment 1). Each participant signed an Informed Consent (appendix 2) form before the transrectal prostate biopsy was performed.

The data obtained was treated with IBM SPSS software version 28.0.1.1® (IBM Corporation, New York, USA) and statistically significant associations were considered for a significance level of 5% ($p \leq 0.05$). T-Tests and the Mann-Whitney Test were used for independent samples. The Chi-Square Independence Test was used for categorical variables.

3. Results

A total of 124 patients were eligible for the study. Six were excluded. The remaining 118, 50 (42.4%) were randomly distributed to Group 1 and 68 (57.6%) to Group 2 (Figure 1). A patient's follow-up was lost.

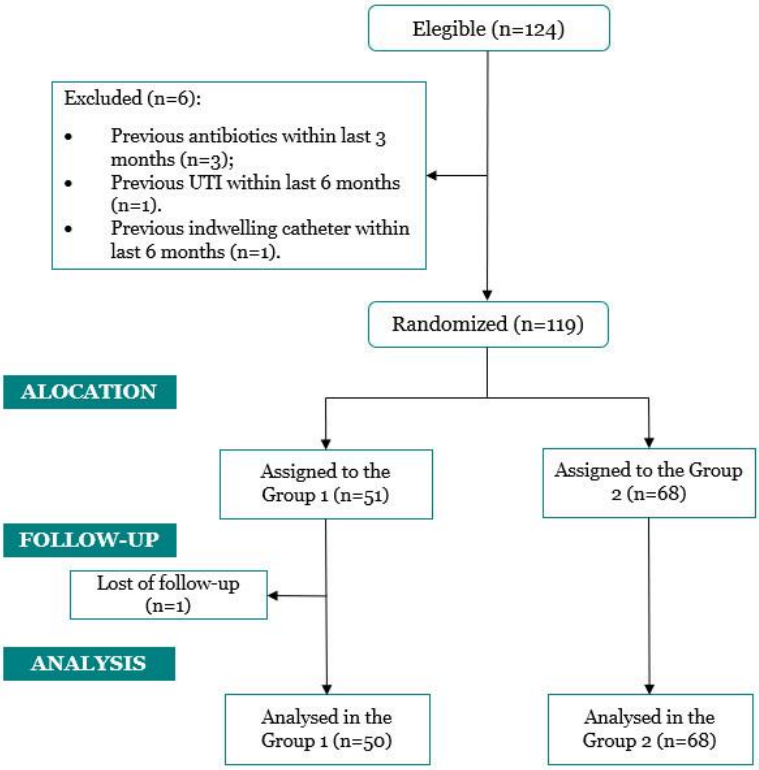

Figure 1. Flow-chart of study enrollment and follow-up.

The mean age of patients was 68.7 years old (range: 54-86) and the median value of the PSA serum was 8 ng/ml (range 1.3-331). The mean value of transrectal ultrasound volume was 47.7 ml (range 19-186). In comparison, the mean number of biopsy cores collected was 12.6 units (range 11-16). Fifty (42.4%) patients had suspicious DRE. The mean value of IPSS and QoL before the biopsy was 9.3 (moderately symptomatic) and 1.7 (not very satisfied), respectively. There was no statistically significant difference between the two groups, except in the median value of serum PSA and in the mean value of IPSS and QoL before biopsy (Table 1).

Table 1. Patient baseline characteristics.

Patients characteristics		Overall (n=118)	Group 1 - fosfomycin (n=50)	Group 2 - cefixime (n=68)	*p*-value
Age in years, Mean (range)		68.7 (54 - 86)	68.9 (55 - 86)	68.5 (54 - 86)	0.793
PSA in ng/ml, Median (range)		8 (1.3 - 311)	9.5 (1.3 - 311)	7.1 (1.6 - 54.3)	0.004*
Ultrasound prostate volume in ml, Mean (range)		47.7 (19 - 186)	49.5 (19 - 186)	46.4 (20 - 90)	0.766
Prostate volume on MRI in ml, Mean (range)		49.2 (23 - 127)	54 (26 - 127)	44.1 (23 - 96)	0.211
Cores per biopsy, Mean (range)		12.6 (11 - 16)	12.8 (12 - 16)	12.6 (11 - 16)	0.266
Diabetes, n (%)		28 (23.7%)	9 (18%)	19 (27.9%)	0.21
Arterial hypertension, n (%)		51 (43.2%)	22 (44%)	29 (42.6%)	0.883
Smoker, n (%)		13 (11%)	8 (16%)	5 (7.4%)	0.138
Previous prostate MRI, n (%)		31 (26.3%)	16 (32%)	15 (22.1%)	0.225
Suspicious DRE, n (%)		50 (42.4%)	20 (40%)	30 (44.1%)	0.655
ISUP, n (%)	0	38 (32.2%)	18 (36%)	20 (29.4%)	0.571
	1	16 (13.6%)	4 (8%)	12 (17.6%)	
	2	10 (8.5%)	4 (8%)	6 (8.8%)	
	3	30 (25.4%)	9 (18%)	21 (30.9%)	
	4	16 (13.6%)	11 (22%)	5 (7.4%)	
	5	8 (6.8%)	4 (8%)	4 (5.9%)	
Positive biopsy, n (%)		80 (67.8%)	32 (64%)	48 (70.6%)	0.449
IPSS before biopsy, Mean (range)		9.3 (0-33)	11.4 (0-33)	7.8 (0-28)	0.031*
QoL before biopsy, Mean (range)		1.7 (0-6)	2.1 (0-6)	1.5 (0-6)	0.011*

*p<0,05; Abbreviations: MRI - magnetic resonance imaging; ISUP: International Society of Urological Pathology.

During the follow-up period, a total of 10 patients were reported with urinary tract infections (8.5%) (Group 1: 6 (12%) patients; Group 2: 4 (5.9%) patients) (Table 2).

Table 2. Infectious complications after prostate biopsy.

Infectious complications	Overall (n=118)	Group 1 - fosfomycin (n=50)	Group 2 - cefixime (n=68)	*p*-value
Post-TRUS-PB UTI, n (%)	10 (8.5)	6 (12)	4 (5.9)	0.238

According to the UTI criteria defined, 6 patients had fever and 6 reported the diagnosis of UTI in the post-biopsy period by a health professional. Only 7 patients self-reported that were treated for the infection. Of these seven, only 2 were asked for uroculture to characterize the infection and the pattern of resistances. One patient had a positive culture for *E. coli* sensitive to amoxicillin, cefuroxime and ciprofloxacin. The other patient had a positive culture for *E. coli* with resistance to cotrimoxazole. The treatments recommended in the management of UTI were cefuroxime, levofloxacin or ciprofloxacin. Two patients with infection required recourse to the emergency department for symptomatic control, but none required hospitalization during the study.

No patient characteristics or particularities of the procedure were statistically significant as potentiators for the development of UTI (Table 3).

Table 3. Factors associated with post-TRUS-PB UTI occurrence.

Patients characteristics		Post-TRUS-PB UTI (n=10)	*p*-value
Age in years, Mean (range)		70.1 (62 - 83)	0.578
PSA in ng/ml, Median (range)		7.34 (2.6 - 39.9)	0.499
Ultrasound prostate volume in ml, Mean (range)		51.52 (26.2 - 88)	0.501
Prostate volume on MRI in ml, Mean (range)		49.5 (23 - 70)	0.658
Cores per biopsy, Mean (range)		12.6 (12 - 16)	0.869
Diabetes, n (%)		3 (10.7%)	0.626
Arterial hypertension, n (%)		7 (13.7%)	0.074
Smoker, n (%)		0 (0%)	0.245
Previous prostate MRI, n (%)		4 (12.9%)	0.302
Suspicious DRE, n (%)		3 (6%)	0.408
ISUP, n (%)	0	4 (10.5%)	0.426

	1	0 (0%)	
	2	2 (20%)	
	3	4 (13.3%)	
	4	0 (0%)	
	5	0 (0%)	
Positive biopsy, n (%)		6 (7.5%)	0.581
IPSS before biopsy, Mean (range)		11.2 (0-27)	0.581
QoL before biopsy, Mean (range)		2.5 (1-5)	0.063

When comparing the results of patients who did not have a UTI with those who did, we may consider that patients with infection had a higher IPSS and in most cases had moderately high symptoms (without UTI: 10.6 points in the first week and 9.7 points between the second and fourth weeks; with UTI: 18.8 and 18.4; p=0.016 and 0.019, respectively). The differences between IPSS before and after the first week and before biopsy and between the second and fourth weeks after biopsy were also higher in the infected (without UTI: -1.5 points in the first week and -0.6 points between the second and fourth weeks; with UTI: -7.6 and -7.2; p=0.002 and 0.004, respectively). The same logic was also observed in individual assessment of their QoL, with patients without infection considering themselves as not very satisfied with their lives and infected patients as dissatisfied with their lives. Statistical significance was found in the abovementioned variables between patients with and without UTI.

When both antibiotics in the study were compared, we found that in patients without UTI after biopsy, there was only statistical significance between the two groups in the differences between QoL before biopsy and after the first week and between QoL before and between the second and fourth weeks after biopsy (Group 1: 0 and 0.1; group 2: -0.4 and -0.3; p=0.003 and 0.017). In this case, it was found that group 1 remained poorly satisfied with quality of life and that, on the other hand, the cefixime group transitioned from satisfied to poorly satisfied with quality of life. However, we point out that, although there were no statistically significant differences between the two groups, the IPSS value was higher in the first and between the second and fourth weeks in the cefixime group and, in turn, the difference between the IPSS values was always higher in the cefixime group. On the other hand, there was no statistically significant difference between the two groups in this study in patients who had infections. Only patients with UTI in the cefixime group had urinary tract symptoms considered severe (Table 4).

Table 4. Evolution of IPSS and Quality of life.

Patient's IPSS and QoL	Overall (n=18)			Antibiotic (n=118)			Post-TRUS-PB without UTI (n=108)			Post-TRUS-PB UTI (n=10)		
	Post-TRUS-PB without UTI (n=108)	Post-TRUS-PB UTI (n=10)	*p*	Group 1 (n=50)	Group 2 (n=68)	*p*	Group 1 (n=50)	Group 2 (n=68)	*p*	Group 1 (n=50)	Group 2 (n=68)	*p*
	Mean (range)			Mean (range)			Mean (range)			Mean (range)		
IPSS before biopsy (A)	9.1 (0 - 33)	11.2 (0 - 27)	0.581	11.4 (0 - 33)	7.8 (0 - 28)	0.031*	11.4 (0 - 33)	7.6 (0 - 28)	0.045*	12 (0 - 21)	10 (4 - 27)	0.914
IPSS at 1st week (B)	10.6 (0 - 33)	18.8 (6 - 35)	0.016*	12.4 (0 - 33)	10.5 (0 - 35)	0.218	11.7 (0 - 33)	9.9 (0 - 28)	0.287	17.8 (6 - 32)	20.3 (6 - 35)	0.762
IPSS between 2nd and 4th weeks (C)	9.7 (0 - 33)	18.4 (1 - 33)	0.019*	12.1 (0 - 33)	9.3 (0 - 32)	0.12	11.3 (0 - 33)	8.7 (0 - 28)	0.15	18 (1 - 33)	19 (6 - 32)	0.914
Δ (A-B)	-1.5 (-22 - 9)	-7.6 (-31 - 0)	0.002*	-1 (-15 - 8)	-2.7 (-31 - 9)	0.334	-0.3 (-10 - 8)	-2.2 (-22 - 9)	0.145	-5.8 (-15 - - 1)	-10.3 (-31 - 0)	1
Δ (A-C)	-0.6 (-21 - 17)	-7.2 (-28 - 3)	0.004*	-0.7 (-16 - 8)	-1.5 (-28 - 17)	0.347	0.1 (-9 - 8)	-1 (-21 - 17)	0.181	-6 (-16 - 3)	-9 (-28 - 0)	0.914
QoL before biopsy (D)	1.7 (0 - 6)	2.5 (1 - 5)	0.063*	2.1 (0 - 6)	1.5 (0 - 6)	0.011*	2.1 (0 - 6)	1.4 (0 - 6)	0.008*	2.3 (1 - 4)	2.8 (1 - 5)	0.762
QoL at 1st week (E)	1.9 (0 - 6)	4.2 (1 - 6)	0.000*	2.3 (0 - 6)	2 (0 - 6)	0.337	2.1 (0 - 6)	1.8 (0 - 6)	0.442	4 (1 - 6)	4.5 (3 - 6)	0.762
QoL between 2nd and 4th weeks (F)	1.9 (0 - 6)	3.9 (1 - 6)	0.001*	2.2 (0 - 6)	1.9 (0 - 6)	0.246	2 (0 - 6)	1.8 (0 - 6)	0.284	3.8 (1 - 6)	4 (3 - 5)	0.762
Δ (D-E)	-0.3 (-5 - 5)	-1.7 (-5 - 0)	0.005*	-0.2 (-5 - 3)	-0.5 (-5 - 5)	0.010*	0 (-5 - 3)	-0.4 (-5 - 5)	0.003*	-1.7 (-5 - 0)	-1.8 (-3 - 0)	0.762
Δ (D-F)	-0.2 (-5 - 5)	-1.4 (-5 - 0)	0.001*	-0.4 (-5 - 3)	-0.4 (-5 - 5)	0.059	0.1 (-2 - 3)	-0.3 (-5 - 5)	0.017*	-1.5 (-5 - 0)	-1.3 (-3 - 0)	1

*p<0,05.

4. Discussion

Antibiotic prophylaxis is recommended in transrectal prostate biopsy to reduce the risk of biopsy-associated infection (17). Studies report that non-antibiotic strategies should be used with antibiotics to control post-biopsy infections (6,18). However, only povidone-iodine preparation (6,19–21) and rectal culture research to identify resistant microorganisms (22) have promising results.

Our analysis confirms that both fosfomycin and cefixime are effective for antibiotic prophylaxis in candidate patients for TRUS-PB. In the current evidence, the rates of infectious complications vary between 2.2% and 11.7% and this difference depends on the variety of study methods and the different types of UTI classification available (7,10,13,23). Similar results were presented in our study, as the urinary tract infection rate was 8.5%. The UTI rates obtained are within the expected values, but a value closer to the lower limit was expected since factors such as previous antibiotic therapy or previous prostate biopsy were excluded and previous studies with similar results did not exclude them and proved that they influence the increase of infections (24,25). However, our UTI criterion was broad, which may explain the infection rate.

So far, no studies compared these two antibiotics. The available ones are used fluoroquinolones as a control group (25–27). In this study, the infection rate in the fosfomycin group was 12% which is slightly higher than a previous study conducted in France, where the UTI rate was 9% (27). In the same study, Delory et al. reported that fosfomycin reduces the risk of UTI by 40% and may be an alternative to FQ.

On the other hand, a greek study confirmed the similarity of cefixime's efficacy to that of a FQ, showing severe infection rates with cefixime of 1.67% (25). The same study reported that it is a safe antibiotic in settings where there are high rates of resistance to FQs. Our infection rate with cefixime was 5.9%. The difference in infection rates between these two studies is mainly because in our study UTIs were not classified by severity criteria.

In comparison to the available literature, despite the different criteria for UTI, our results were similar, as low rates of infection were found. Similarly, the literature showed the efficacy of these antibiotics in antibiotic prophylaxis of the biopsy, like ours did. These results allow the medical community to have therapeutic options with equivalent efficacy.

The literature suggests that the presence of comorbidities or procedures performed in the biopsy directly influenced the incidence of infections. Regarding this, a German study revealed that the number of biopsy cores or the presence of diabetes mellitus were associated with a higher number of infectious complications (28). On the contrary, in our univariate analysis, no factor was associated with an increase in infections.

Due to the increasing resistance of fluoroquinolones, the EAU recommends against their use in perioperative antibiotic prophylaxis and suggests alternatives. This choice should be based on the local prevalence of the pathogens, their susceptibility profile and accessibility by the patient. The duration of treatment varies between one and three days and can be administered orally, intramuscularly, or intravenously (11).

The prophylactic regimen is still controversial as there is no consensus on whether a single dose is enough to guarantee efficacy or whether if an intravenous approach is more effective than the oral one. A recent German study tested the efficacy of a single-dose intravenous cephalosporin and cephalosporin in multiple doses orally (26). Wenzel et al. observed no significant differences between the groups supporting both monoprophylaxis and oral administration are effective, well tolerated and are more convenient options for antibiotic prophylaxis.

In this study, only oral antibiotics were chosen for the patient's greater convenience. Fosfomycin is a beta-lactam with low antimicrobial resistance, a good safety profile and reaches the prostate at minimal concentrations for the desired (29). Cefixime is the only third-generation cephalosporin that can be administered orally, it is safe and is used in the routine treatment of prostatitis (25,30). Since they have similar efficacy, the deciding factors are the number of doses, when the prophylaxis begins and the cost for the patient. Since the number of doses is similar (2 for fosfomycin and 3 for cefixime), it's important to understand whether the patient prefers to start the treatment immediately or 24h before the biopsy and should be taken into account that in Portugal fosfomycin costs twice as much as cefixime.

Transrectal prostate biopsy is an invasive technique and therefore, in the post-biopsy period, a worsening of LUTS was expected (7). Our study confirmed this hypothesis since the IPSS value was always higher after biopsy compared to the baseline value of each patient. In addition, the IPSS value was expected to be higher in those who had UTI which was also confirmed in our study. Similar studies analyzing the impact of antibiotic prophylaxis on the management of LUTS were not found. We point out that, although they do not differ statistically, cefixime may imply a greater worsening of lower urinary tract symptoms both in the first week and in the following three weeks compared with Fosfomycin. However, bigger studies are necessary to draw conclusions.

When we evaluate individuals with UTI vs. individuals without UTI, there is also a tendency for the IPSS to be higher with cefixime in both cases. Thus, it suggests that cefixime implies a more extended and difficult recovery of patients after biopsy. Quality of life was a variable with a subjective value that we decided to include in our study to understand the patient's perception of the presence of LUTS and the impact of the biopsy and the antibiotic selected on their life. In conjunction with the worsening of the IPSS, the

quality of life was also lower after the biopsy. This worsening tended to be more associated with cefixime after the first week. It should also be noted that cefixime was associated with lower quality of life mainly in individuals who had no infection.

Studies evaluating alternatives to TRUS-PB have shown that transperineal prostate biopsy is the procedure with the lowest risk of complications (5,10,31–35). Some defend it is a safe method (36), without the need for antibiotic prophylaxis (11) and allows the collection of better-quality samples (37). However, it is more time-consuming and expensive and requires selected equipment, so it is still not widely used in health services with limited access to resources (38,39). Therefore, despite the superiority of the transperineal approach, TRUS-PB is still the most widely used, low-cost, easily accessible and rapid diagnostic method (39,40) making sense to continue to study this method.

The main limitations of this study were the use of prophylactic antibiotics with few references in the literature in the light of current knowledge and the calculated values for sample size equating to a smaller sample than expected. Since healthcare is decentralized and questionnaires were self-completed there was a risk of omission of information. The fact that UTI diagnosis was not centralized and that not all patients with suspected infection were submitted to urine culture constitutes additional limitations of our study. However, being a prospective study with appealing results, it should be noted that a new door has been opened for future research with a larger sample size.

This study proved that both alternatives of antibiotic prophylaxis are safe and associated with low rates of post-biopsy urinary tract infections. Similar multicenter studies and further meta-analyses are needed to confirm the promising results presented.

5. Conclusion

Prophylaxis with fosfomycin revealed similar efficacy to cefixime in the infectious prophylaxis of transrectal prostate biopsy.

6. Conflicts of interest

The author declares no conflicts of interest.

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8. Appendices

8.1 Appendix 1 - Questionnaire

"Fosfomicina vs. Cefixime na profilaxia infeciosa da biópsia prostática transrretal: estudo prospetivo"

IPO COIMBRA

FACULDADE CIÊNCIAS DA SAÚDE

Questionário a preencher antes da biópsia prostática transrretal:

	Nenhuma	Menos de 1 vez em 5	Menos de ½ das vezes	Metade das vezes	Mais de ½ das vezes	Quase sempre	TOTAL
Recentemente, quantas vezes ficou com a sensação de não esvaziar completamente a bexiga?	0	1	2	3	4	5	
Recentemente, quantas vezes teve de urinar novamente menos de 2 horas após ter urinado?	0	1	2	3	4	5	
Recentemente, quantas vezes observou que, ao urinar, parou e recomeçou várias vezes?	0	1	2	3	4	5	
Recentemente, quantas vezes observou que foi difícil conter a urina?	0	1	2	3	4	5	
Recentemente, quantas vezes observou que o jato urinário estava fraco?	0	1	2	3	4	5	
Recentemente, quantas vezes teve de fazer força para começar a urinar?	0	1	2	3	4	5	
	Nenhuma	1 vez	2 vezes	3 vezes	4 vezes	5 vezes ou mais	
Recentemente, quantas vezes, em média, teve de se levantar de noite para urinar?	0	1	2	3	4	5	
Total de sintomas							

Qualidade de vida	Muito satisfeito	Satisfeito	Pouco satisfeito	Confuso	Insatisfeito	Infeliz	Muito infeliz
Se tivesse que passar o resto dos seus dias com esse padrão miccional como se sentiria?	0	1	2	3	4	5	6

Nas seguintes perguntas, colocar uma X:

	Sim	Não
Recentemente, teve febre alta >38ºC?		
Recentemente, foi diagnosticado com Infeção do Trato Urinário (ITU) por um médico nos cuidados de saúde primários ou hospitalares?		
Recentemente, tomou algum antibiótico após terminar a medicação prescrita para a profilaxia?		

Se respondeu SIM à última questão, diga qual foi o Antibiótico prescrito:

_____

Obrigada pela sua colaboração!

prospetivo

IPO COIMBRA FACULDADE CIÊNCIAS DA SAÚDE

Questionário a preencher 1 semana após a biópsia prostática transrretal:

	Nenhuma	Menos de 1 vez em 5	Menos de ½ das vezes	Metade das vezes	Mais de ½ das vezes	Quase sempre	TOTAL
Na última semana, quantas vezes ficou com a sensação de não esvaziar completamente a bexiga?	0	1	2	3	4	5	
Na última semana, quantas vezes teve de urinar novamente menos de 2 horas após ter urinado?	0	1	2	3	4	5	
Na última semana, quantas vezes observou que, ao urinar, parou e recomeçou várias vezes?	0	1	2	3	4	5	
Na última semana, quantas vezes observou que foi difícil conter a urina?	0	1	2	3	4	5	
Na última semana, quantas vezes observou que o jato urinário estava fraco?	0	1	2	3	4	5	
Na última semana, quantas vezes teve de fazer força para começar a urinar?	0	1	2	3	4	5	
	Nenhuma	1 vez	2 vezes	3 vezes	4 vezes	5 vezes ou mais	
Na última semana, quantas vezes, em média, teve de se levantar de noite para urinar?	0	1	2	3	4	5	
Total de sintomas							

Qualidade de vida	Muito satisfeito	Satisfeito	Pouco satisfeito	Confuso	Insatisfeito	Infeliz	Muito infeliz
Se tivesse que passar o resto dos seus dias com esse padrão miccional como se sentiria?	0	1	2	3	4	5	6

Nas seguintes perguntas, colocar uma X:

	Sim	Não
Na última semana, teve febre alta >38ºC?		
Na última semana, foi diagnosticado com Infeção do Trato Urinário (ITU) por um médico nos cuidados de saúde primários ou hospitalares?		
Na última semana, tomou algum antibiótico após terminar a medicação prescrita para a profilaxia?		

Se respondeu SIM à última questão, diga qual foi o Antibiótico prescrito:

_____

"Fosfomicina vs. Cefixime na profilaxia infeciosa da biópsia prostática transrretal: estudo prospetivo"

IPO COIMBRA FACULDADE CIÊNCIAS DA SAÚDE

Questionário a preencher 1 mês após a biópsia prostática transrretal:

	Nenhuma	Menos de 1 vez em 5	Menos de ½ das vezes	Metade das vezes	Mais de ½ das vezes	Quase sempre	TOTAL
No último mês, quantas vezes ficou com a sensação de não esvaziar completamente a bexiga?	0	1	2	3	4	5	
No último mês, quantas vezes teve de urinar novamente menos de 2 horas após ter urinado?	0	1	2	3	4	5	
No último mês, quantas vezes observou que, ao urinar, parou e recomeçou várias vezes?	0	1	2	3	4	5	
No último mês, quantas vezes observou que foi difícil conter a urina?	0	1	2	3	4	5	
No último mês, quantas vezes observou que o jato urinário estava fraco?	0	1	2	3	4	5	
No último mês, quantas vezes teve de fazer força para começar a urinar?	0	1	2	3	4	5	
	Nenhuma	1 vez	2 vezes	3 vezes	4 vezes	5 vezes ou mais	
No último mês, quantas vezes, em média, teve de se levantar de noite para urinar?	0	1	2	3	4	5	
Total de sintomas							

Qualidade de vida	Muito satisfeito	Satisfeito	Pouco satisfeito	Confuso	Insatisfeito	Infeliz	Muito infeliz
Se tivesse que passar o resto dos seus dias com esse padrão miccional como se sentiria?	0	1	2	3	4	5	6

Nas seguintes perguntas, colocar uma X:

	Sim	Não
No último mês, teve febre alta >38ºC?		
No último mês, foi diagnosticado com Infeção do Trato Urinário (ITU) por um médico nos cuidados de saúde primários ou hospitalares?		
No último mês, tomou algum antibiótico após terminar a medicação prescrita para a profilaxia?		

Se respondeu SIM à última questão, diga qual foi o Antibiótico prescrito:

_____

Obrigada pela sua colaboração!

8.2 Appendix 2 – Informed Consent

CONSENTIMENTO LIVRE, INFORMADO E ESCLARECIDO

IPO COIMBRA

FACULDADE CIÊNCIAS DA SAÚDE

Comissão de Ética Universidade da Beira Interior

Sou a Mariana Gaspar Pedrosa, aluna do 5º ano do Curso de Medicina da Universidade da Beira Interior, nº de aluno 39622 e investigadora principal do estudo **"Fosfomicina vs. Cefixime na profilaxia infeciosa da biópsia prostática transrretal: estudo prospetivo"** que pretende comparar a eficácia clínica do uso de Fosfomicina Trometamol com a Cefixime, na prevenção de complicações infeciosas após a realização da biópsia prostática transrretal e destina-se a realizar um projeto de investigação no âmbito da Tese de Mestrado.

Venho pedir a sua colaboração, pois sem a sua participação não será possível concretizar com êxito este projeto. O que solicito é que integre um dos dois grupos de investigação, no qual é-lhe prescrito um antibiótico como uma medida de profilaxia a ter em conta para a prevenção de complicações infeciosas decorrentes da biópsia. É de salientar que ambos os antimicrobianos são recomendados pela Associação Europeia de Urologia, não existindo evidência de que um é mais eficaz que o outro, não existem riscos ou complicações associadas, nem despesas adicionais para o próprio doente.

Este estudo envolve, como investigadores, a equipa do departamento de Urologia do Instituto Português de Oncologia de Coimbra, estando incluídos médicos, enfermeiros e auxiliares de saúde, sendo por isso inviável a identificação de toda a equipa. O estudo não contempla qualquer apoio financeiro. Os investigadores envolvidos não serão privilegiados a nível financeiro, na medida em que os resultados obtidos no estudo servem exclusivamente para enriquecer a evidência científica e obter novos dados relevantes para se escolher qual o antimicrobiano mais aconselhado como profilaxia.

A sua confidencialidade está garantida já que o seu número de processo clínico será o critério para a aleatorização dos dados, pelo que o seu nome e informações pessoais não serão alvo de estudo nem constarão nos resultados disponibilizados à comunidade científica. Apenas eu, Mariana Gaspar Pedrosa, terei acesso aos seus dados pessoais, os quais, em todo o caso, não serão divulgados, pois serão utilizados sob codificação.

A participação que solicito é voluntária, isto é, não se sinta obrigado a participar, e pode decidir não participar desde o primeiro momento ou noutro qualquer, sem que daí advenham quaisquer prejuízos para si em qualquer perspetiva.

Uma vez que a sua decisão de participar é voluntária, livre, e informada pelo presente documento, mas também esclarecida em tudo o que tiver dúvidas, qualquer pergunta, dúvida ou informação adicional de que necessite para a sua decisão poderá ser-me colocada ou transmitida através do endereço de correio eletrónico a39622@fcsaude.ubi.pt.

Assinado por: **Mariana Gaspar Pedrosa**
Num. de Identificação Civil: BI15807651
Data: 2022.01.05 00:29:10 Hora padrão de GMT

CHAVE MÓVEL

	05/01/2022
(Mariana Gaspar Pedrosa)	**(data)**

Ao assinar este documento confirmo que transmiti toda a informação nela contida, e expliquei e dei resposta a todas as questões e dúvidas apresentadas pelo participante.

(participante)	**(data)**

Ao assinar esta declaração assumo que irei colaborar livremente, que li e compreendi a informação e os esclarecimentos que me foram dados, e a meu contento, acerca da minha participação, e tive tempo suficiente para me decidir e neles ponderar.

Aceito participar nas tarefas que me são solicitadas, sabendo que nada me impede de mudar de posição, sendo que poderei manifestar o desejo de não colaborar, sem que tal implique quaisquer perdas de direitos ou acarrete prejuízos pessoais. Tenho conhecimento de que um original deste documento, assinado por ambos os subscritores, fica em minha posse.

9. Attachments

9.1 Institutional ethics committee approval

Pedido de autorização para realização de Projeto de Investigação Externos Caixa de entrada ×

Secretariado do Conselho de Administração do IPOCoimbra <secad@ipocoimbra.min-saude.pt> sexta, 7/01, 16:35

para MÁRIO, mim, Fátima, ANA

Exmo.(a) Senhor(a)
Dr. Mário Lourenço
Mariana Gaspar Pedrosa

Em resposta ao V. pedido de autorização para realização do Projeto de Investigação intitulado: "Fosfomicina vs. Cefixime na profilaxia infeciosa da biópsia prostática transrretal: estudo prospetivo", incumbe-me o Conselho de Administração do IPO de Coimbra de informar que o mesmo foi autorizado.

Mais se informa que, qualquer publicação ou divulgação deverá fazer referência à colaboração do IPO de Coimbra.

Após a sua conclusão, os resultados do estudo deverão ser comunicados ao Gabinete Coordenador da Investigação.

Com os melhores cumprimentos,

Irene Cardoso
Assistente Técnica /Secretariado do Conselho de Administração

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