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Risk of Adverse Effects Using Antibiotic Prophylaxis in Ambulatory Cystoscopy: A Systematic Review

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Abstract

Objective: to determine incidence of adverse effects related to antibiotic prophylaxis compared to other interventions in patients who undergo cystoscopy with sterile urine.

Methods: Search strategy (January 1980-January 2014) in Medline via PubMed, CENTRAL, and EMBASE. Additionally, we searched databases for registered trials and conference abstracts, as well as reference lists of systematic reviews and included studies. Two published randomized placebo-controlled trials (January 1, 1980 and January 31, 2014) were included in qualitative analysis with no language restrictions. Two independent reviewers collected Data. Risk of bias was evaluated with the Cochrane Collaboration recommendations. The primary outcome was incidence of adverse effects (AE).

Results: 2448 patients were found in the studies of García-Perdomo et al., and Jimenez-Cruz et al. The incidence of AE in one study was 0.7% in intervention group (nausea), no AE in control group or in the other study included. A meta-analysis was not performed.

Conclusions: There is a low incidence of adverse effects associated with antibiotic prophylaxis in cystoscopy besides we found inadequate conducting and report of this outcome in studies included.

Keywords: Urinary tract infection; Cystoscopy; Antibiotic prophylaxis; Systematic review; Adverse effects.

Introduction

In Urology, there are multiple indications to perform a cystoscopy, like hematuria, cancer, planning a surgery, and many others [1]. This has many advantages as a diagnostic procedure, however it also has adverse effects like urinary tract infection (UTI) which has been studied frequently in ambulatory and hospital settings, recognizing as the most common nosocomial infection nowadays [2] and it has been associated with higher morbidity for patients [3-5].

An adverse effect is defined as an unfavorable outcome occurred during or after a drug administration or other intervention has been used, with a possible causal relationship. Different definitions are found in literature but this is the one most accepted and it is fundamental to comprehend and analyze the purpose of this systematic review (SR) [6]. According to García-Perdomo et al. (Meta-analysis submitted for publication), post cystoscopy UTI is not prevented by using antibiotic prophylaxis according to low risk of bias studies, however adverse effects were not assessed.

Multiple studies suggest that there are not differences between selecting randomized or not randomized studies to obtain the best information about adverse effects (AE) [7] although others suggest that quasi-experimental and analytical studies must be selected due to they have more chance to describe adverse effects not evidenced in randomized studies [8].

The aim of this study was to determine incidence of adverse effects related to antibiotic prophylaxis compared to other interventions in patients who undergo cystoscopy with sterile urine.

Methods

This study was conducted according to the recommendations of the Cochrane Collaboration and is reported following the PRISMA Statement. The protocol was registered in the International prospective register of systematic reviews (PROSPERO): CRD 42014007341.

Eligibility criteria

- Studies: We included parallel, randomized clinical trials (RCT) conducted between January 1, 1980 and January 31, 2014. We searched for quasi-experimental and analytical studies (cross-sectional, case-control and cohorts) but we did not find any. No language restrictions were imposed.
- Participants: Female and male people older than 18 years old that underwent cystoscopy with sterile urine (negative urine culture). There were no preferences in any other demographic characteristic of participants.
- Interventions: The planned interventions were: Antibiotic vs. placebo; Antibiotic vs. no intervention and Antibiotic vs. any other antibiotic (No articles were found).
- Outcomes: The primary outcome was the incidence of adverse effects in both groups.
- Exclusions: No assessment or description of adverse effects.

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Information sources and search strategy

We designed a search strategy for Medline via PubMed, CENTRAL and EMBASE. The search strategy was specific for each database and included a combination of the medical subject headings and free text terms for urinary tract infection, cystoscopy and adverse effects. No language or publication status restrictions. We included articles between January 1, 1980 and January 31, 2013. The full search strategies are listed in eAppendix 1.

Other electronic sources were used to find additional studies, such as Clinicaltrials.gov, conference abstracts, DARE, PROSPERO and database from the pharmaceutical industries. We looked for additional studies in reference lists of selected articles, contact with authors about knowledge of published or unpublished articles. The results of searches were crosschecked in order to eliminate duplicates.

Study selection

Two investigators independently and blindly screened the titles and abstracts to determine the potential usefulness of the articles. Eligibility criteria were applied to the full text articles during the final selection. When discrepancies occurred, an agreement was made to take a final decision. If they could not agree, a third reviewer made the final decision.

Data collection process

Relevant data were collected by duplicate, using a standardized data extraction sheet, which contains: study design, participants, interventions and comparators and final outcomes details. Reviewers confirmed all data entries and checked at least twice for completeness and accuracy. If some information were missing, we contacted authors in order to get data completed but never returned the communication.

Risk of Bias of adverse effects

We assessed the quality of conducting and reporting adverse effects according to recommendations of Higgins & Green, and Loke et al. We used the next questions:

On conduct

- Are definitions of reported adverse effects given?
- Were the methods used for monitoring adverse effects reported? Use of prospective or routine monitoring; spontaneous reporting; patient checklist, questionnaire or diary; systematic survey of Patients?

On reporting

- Were any patients excluded from the adverse effects analysis?
- Does the report provide numerical data by intervention group?
- Which categories of adverse effects were reported by the investigators?

Statistical Analyses

No Meta-analysis was performed due to lack of data.

Results

Study selection

87 articles were found with the search strategies designed, after exclusions, 2 studies were included in qualitative analyses [9,10] (Figure 1).

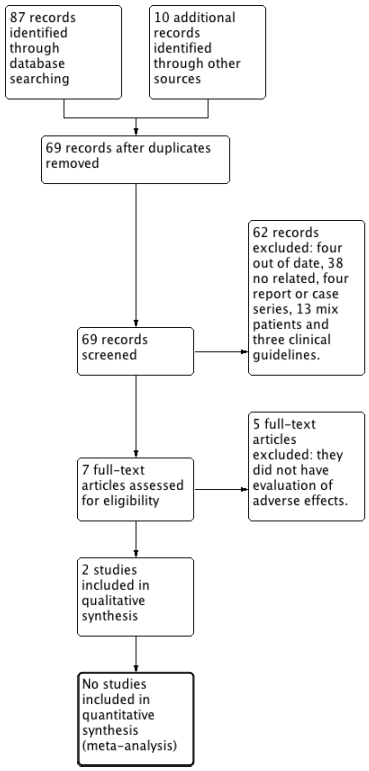

Figure 1: Assessment of cough severity.

Characteristics of included studies

2448 patients were found in the studies of García-Perdomo et al. and Jimenez-Cruz et al. Both studies measured adverse effects and the general characteristics are shown in Table 1.

The study of García-Perdomo et al., described the possible adverse effects but finally only one event was shown in the intervention group and no events were seen in control group.

The study of Jimenez-Cruz et al., described no adverse effects during the experiment in both groups.

Characteristics of excluded studies

We excluded the studies of Cam, Jimenez-Pacheco, Karmouni, Rane and Tsugawa because they did not describe adverse effects.

Risk of bias of included studies

We evaluated the quality in conduction and reporting of adverse effects of the two included studies according to the recommendations of Higgins and Green; Loke et al.

García-Perdomo et al., described the assessment of adverse effects in intervention and placebo groups both for antibiotic use and the procedure itself. It described the events that never happened such as emesis, diarrhea, headache, delirium, hallucinations, convulsions, and rash and they show how nausea was the only one that happened in intervention group (n=138). On the other side, Jimenez-Cruz et al. did not describe correctly the adverse effects, neither methodologically or in the result section. They only described there were no adverse effect in both groups (Tables 2 and 3).

Source	Setting	No of patients	Mean age	Inclusion criteria	Intervention	Control	Outcome	Follow up
García-Perdomo et al. [9]	Colombia	276	58	Any non urgent indication of cystoscopy. Exclusion: no follow up, allergy, interaction with antibiotic, permanente urethral catheter, inmunossupression, intermitent catheterization.	Levofloxacin 500 mg	Placebo	UTI and Bacteriuria	Up to 10 days
Jimenez-Cruz et al. [10]	Spain	2284	NA	Older than 16 years old, negative urine culture, diagnostic cystoscopy. Exclusion: indwelling urethral catheter, antibiotics, UTI.	Ceftriaxone 1 gr	No intervention	UTI and Bacteriuria	Up to 30 days

Table 1: Characteristics of included studies.

Conducting:		Report:	
Question	**Assessment**	**Question**	**Assessment**
Are definitions of reported adverse effects given?	Yes, however, there is a description overlapping about procedure and antibiotic prophylaxis adverse effects.	Were adverse effects reported adequately?	It is not clear. They just described adverse effects that never happened and only one that happened in the intervention group.
Were the methods used for monitoring adverse effects reported? Use of prospective or routine monitoring; spontaneous reporting; patient checklist, questionnaire or diary; systematic survey of Patients?	A checklist was used to recollect data (we asked the author).	Were any patients excluded from the adverse effects analysis?	No, there were 6 lost to follow up patients in placebo group and 3 patients in intervention group. They did not report any adverse effect.
• Were the methods to detect AE rigorous?	No, they just described variables and the checklist they used. No other data to support this item.	Does the report provide numerical data by intervention group?	Yes, one patient had nausea (n=138)
		Which categories of adverse effects were reported by the investigators?	They were not described. They just described the variables.
		Did the researchers report all important or serious adverse effects? How were these AE defined?	Yes, they were reported but definitions were by event not by category. The events were: emesis, diarrhea, delirium, hallucinations, headache, seizures and rash.
		Were reported the adverse effects considered for monitoring?	Yes, all of them were reported.

Table 2: Risk of Bias for Adverse effects García-Perdomo, [9].

Conducting:		Report:	
Question	**Assessment**	**Question**	**Assessment**
Are definitions of reported adverse effects given?	They were not described.	Were adverse effects reported adequately?	It is not clear. They just described that there were not AE.
Were the methods used for monitoring adverse effects reported? Use of prospective or routine monitoring; spontaneous reporting; patient checklist, questionnaire or diary; systematic survey of Patients?	They were not described.	• Were any patients excluded from the adverse effects analysis?	There is not a description. 75 patients were excluded for UTI before cystoscopy and 30 patients for absence of urine culture after procedure.
Were the methods to detect AE rigorous?	There is not a description.	Does the report provide numerical data by intervention group?	No patient had any AE.
		• Which categories of adverse effects were reported by the investigators?	There is not a description.
		• Did the researchers report all important or serious adverse effects? How were these AE defined?	There is not a description.
		Were reported the adverse effects considered for monitoring?	There is not a description.

Table 3: Risk of Bias for Adverse effects Jiménez-Cruz, [10].

Results of individual studies by outcome

Adverse effects: We noticed for this SR, how the studies of García-Perdomo et al., and Jimenez-Cruz et al., conducted and reported superficially the adverse effects during these clinical trials. We only found one adverse effect (nausea) in intervention group representing 0.7% but no evidence of AE in control group in the study of García-Perdomo et al. The study of Jimenez-Cruz et al., had not AE in both groups. Due to these results and the risk of bias assessment, an evidence synthesis (Meta-analysis) was not performed.

Discussion

Adverse effects are a fundamental topic in conducting clinical trials. A real balance must be between benefits to the patients and the risks around the intervention, so physicians and patients might choose the best intervention possible. Showing only the intervention´s effectiveness might overestimate its impact [6].

Different strategies have been used to assess AE of interventions, some authors suggest its assessment in the same effectiveness´ SR

however it is possible to under evaluate different kind of studies or clinical trials without AE evaluation, rarely two outcomes in the same clinical trial are assessed. This is why the Cochrane Collaboration suggests to assess AE in a separate SR, stating a clear research question, an specific search strategy and including observational analytical studies that frequently report AE of interventions [6,8]. This SR followed Cochrane´s recommendations, tried to include quasi-experiments, case-control, cohort and cross-sectional studies but only clinical trials assessing AE of this antibiotic prophylaxis in cystoscopy, even lacking well conducting and report of these.

Both studies [9,10] had poor description of methods to assess AE: there was not a detailed description about an active search strategy for AE and both just showed that no AE were found in different groups, except for one patient in intervention group in García-Perdomo et al., study. Currently, there are studies supporting that If AEs are not actively searched, the incidence showed is lower than expected, and then it is underestimated [11].

On the other side, adverse effects related to antibiotic prophylaxis are variable, about 10% of patients might show systemic symptoms like: malaise, abdominal pain, diarrhea and paresthesias [7], even some specific symptoms might present like: hypersensitivity (anaphylaxis), bronchospasm and maculo-papular eruption (Cephalosporines); cutaneous rash, nausea, vomiting, mild jaundice, headache, depressive disorder and anemia (TMP/SMX) and nauseas, vomiting, hypersensitivity, fever, leucopenia and anemia (Nitrofurantoin) [7]. The current SR is focused on presentation of AE in patients who underwent a cystoscopy and received antibiotic prophylaxis so its assessment was determined by the effectiveness evaluation although most of the AE are shown during the first 48 hours due to the hypersensitivity reaction [7]. Only one patient with nausea in intervention group using levofloxacin as prophylaxis was found in the study of [1] neither in the control group nor in the study of [2]. This finding have two main implications: the incidence of AE related to antibiotic prophylaxis is low or since their inadequate methods (conducting and report) there is an underestimation of results, then we find difficult to recommend something specific about this topic.

Additionally, clinical trials and the related adverse effects are not well-reported in general scientific literature. Right now, there are worldwide movements to promote well-reported scientific research for journals and researchers (IDEAL collaboration-Equator Network) but there is still lack of high-quality reporting [12,13]. It is important to notice that we need more research about AE of this intervention by well-designed clinical trials or analytical studies due to its implications in clinical practice.

Conclusion

There is a low incidence of adverse effects associated with antibiotic prophylaxis in cystoscopy however we found inadequate conducting and report of this outcome in studies included. We suggest well-developed clinical trials or analytical studies to assess AE correctly.

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