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MEAN URGE INCONTINENCE EPISODES COMPARISON AFTER SOLIFENACIN AND MIRABEGRON TREATMENT IN OVERACTIVE BLADDER PATIENTS: A CASE REPORT

PERBANDINGAN RERATA EPISODE INKONTINENSI URIN URGENSI PASCA TERAPI SOLIFENACIN DAN MIRABEGRON PASIEN *OVERACTIVE BLADDER: LAPORAN KASUS*

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ABSTRACT

Backgrounds: Overactive bladder (OAB) is a syndrome which interferes with the quality of life, especially women quality of life. The pharmacological therapy choice for OAB is antimuscarinic agents (80%), such as solifenacin. Beta-3 agonist agents also a new pharmacological therapy option for OAB, such as mirabegron. Urge incontinence is the most disturbing symptom of OAB, so it is necessary to assess whether solifenacin and mirabegron provide different symptom improvements.
Case: A 50-year-old woman with a diagnosis of overactive bladder (OAB) with symptoms of urgency, urinary frequency 20 times / day, nocturia 3 – 4 times / night, and urge incontinence without any sign of urinary tract inflammation.
Discussion: A literature search was used through the Google Scholar, Pubmed, Embase, clinicaltrials.gov and the Cochrane library. We found total of 532 articles with only two meta-analysis articles was matched and appraised. The meta-analysis validity, importance and applicability was analyzed using oxford CEBM tools systematic review. The meta-analysis shown that solifenacin and mirabegron had no significant differences in terms of mean number of urge incontinence episodes.
Conclusions: Solifenacin and Mirabegron had a similar effect to the number of urge incontinence episodes in OAB patients.

Keywords: *Overactive Bladder (OAB); Solifenacin; Mirabegron; Urge Incontinence; Women*

ABSTRAK

Latar Belakang: *Overactive bladder* (OAB) merupakan sindrom yang mengganggu kualitas hidup, khususnya kualitas hidup wanita. Pilihan terapi farmakologis untuk OAB adalah agen antimuskarinik (80%), seperti solifenacin. Agen agonis beta-3 juga merupakan pilihan terapi farmakologis baru untuk OAB, seperti mirabegron. Inkontinensia urin urgensi merupakan gejala OAB yang paling mengganggu, sehingga perlu dilakukan penilaian

apakah solifenacin dan mirabegron memberikan perbaikan gejala yang berbeda. Kasus: Seorang wanita berusia 50 tahun dengan diagnosis *overactive bladder* (OAB) dengan gejala urgensi, frekuensi berkemih 20 kali/hari, nokturia 3 – 4 kali/malam, dan inkontinensia urgensi tanpa tanda-tanda peradangan saluran kemih. Pembahasan: Pencarian literatur dilakukan melalui *Google Scholar*, *Pubmed*, *Embase*, *clinicaltrials.gov* dan *Cochrane library*. Ditemukan total 532 artikel dengan hanya dua artikel meta analisis yang dicocokkan dan dinilai. Validitas, kepentingan dan penerapan meta-analisis dianalisis menggunakan tinjauan sistematik alat Oxford CEBM. Meta analisis menunjukkan bahwa solifenacin dan mirabegron tidak memiliki perbedaan yang signifikan dalam hal jumlah rata-rata episode inkontinensia urgensi. Kesimpulan: Solifenacin dan Mirabegron mempunyai pengaruh yang sama terhadap jumlah episode inkontinensia urgensi pada pasien OAB.

Kata Kunci : *Overactive bladder* (OAB); Solifenacin; Mirabegron; Inkontinensia Urgensi; Wanita

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INTRODUCTION

Overactive bladder (OAB) is a syndrome that greatly interferes with the quality of life of human(Johnston et al., 2019; Milsom et al., 2012), especially women. The prevalence of OAB is not small, reaching around 10% of the world's population(Marcelissen et al., 2019). This number may not be the actual number because the number may be much higher. This happens because urinary disorders are often considered embarrassing when they are known to other people, especially in Asia, including Indonesia.(Xu et al., 2014) OAB sufferers usually seek treatment if the complaint is very disturbing to their daily activities.

Another problem with the OAB syndrome is its management. The current pharmacological therapy that has been widely used is with antimuscarinic agents and beta-3 agonists.(Hsu et al., 2019) Antimuscarinics are the most widely used medical therapy today, including in Indonesia, with around 80% usage.(Aparasu et al., 2020; Margulis et al., 2018) However, the problem is the cure rate with the use of antimuscarinics is 60%, so it is not satisfactory.(Chughtai et al., 2016) Beta-3 agonist agents have been widely studied recently and are believed to have fewer side effects, some studies have even stated that beta-3 agonists have better efficacy compared to antimuscarinics.(Chapple et al., 2014; O Kane et al., 2022) The OAB syndrome consists of four main symptoms: urgency, frequency, nocturia, and urge incontinence without any sign of other diseases.(D'Ancona et al., 2019) Among these four symptoms, urge incontinence was the most disturbing and became the basis for patients coming for treatment. Thus, it is necessary to prove the difference in the effect of using

antimuscarinics with beta-3 agonists on complaints of urinary urge incontinence objectively. Comparison between the two can be a basis for consideration for the use of pharmacological therapy for OAB sufferers.

CASE REPORT

A 50-year-old woman comes with complaints of urge when she wants to urinate, urinary frequency up to 20 times a day, urinating 3 to 4 times a night, and often accompanied by urge urinary incontinence. The patient did not experience any signs of a urinary tract infection, such as pain when urinating, bloody urine, fever, and others. The patient has no history and no signs of other co-morbidities such as diabetes, pelvic organ prolapses, and others. Laboratory tests showed that there were no abnormalities, indicating that there were no other causes that could cause the symptoms of OAB syndrome in this patient. In Indonesia, the most frequently used pharmacological therapy is solifenacin, and a beta-3 agonist agent has been introduced, namely mirabegron. Thus, it is necessary to study the difference in efficacy of mirabegron compared to solifenacin in reducing the average episode of urge urinary incontinence.

Clinical Question

What is the difference between the efficacy of mirabegron and solifenacin to reduce mean urge incontinence episodes in OAB patients?.

MATERIAL AND METHODS

Search strategy

Literature searches were carried out between 2013 and 2023 using several search systems such as Google Scholar, Pubmed, Clinicaltrials.gov, Embase, and Cochrane Library which used terminology as shown in Table 1. Searches were carried out based on title, abstract, keywords, and availability of full text.

Table 1. Search strategy used in Google Scholar, Pubmed, Clinicaltrials.gov, Embase and Cochrane Library

Location	Terminology	Hits
Google scholar	meta-analysis AND mirabegron AND overactive bladder AND randomized controlled trials AND solifenacin AND monotherapy AND women	532
Pubmed	((((meta-analysis) AND (randomized controlled trial)) AND (mirabegron)) AND (solifenacin)) AND (overactive bladder)	3
Embase	('meta analysis'/exp OR 'meta analysis') AND 'randomized controlled trial' AND mirabegron AND solifenacin AND 'overactive bladder' AND monotherapy	6
Clinicaltrials.gov	Overactive bladder AND Solifenacin AND Mirabegon AND monotherapy	29
Cochrane Library	(overactive bladder):ti,ab,kw AND (solifenacin):ti,ab,kw AND (mirabegron):ti,ab,kw AND (clinical trial):pt	5

Quality assessment

After screening the research, two meta-analysis studies were obtained(Kelleher et al., 2018; Wang et al., 2019). The two meta-analytic studies were reviewed using the Oxford CEBM tools for systematic review.

Inclusion criteria

The inclusion criteria used were:

1. Meta-analysis or clinical trials; 2. Articles obtained from 2013 to 2023 using English.

The Exclusion criteria were all of these articles that did not have the desired outcome (number of episodes of urge urinary incontinence):

1. View point articles; 2. Consensus studies; 3. Review studies

Data extraction

The information extracted from the included studies was the mean number of incontinence episodes per 24 hours.

RESULTS

Two meta-analysis articles were obtained, which were appraised with VIA criteria (validity, importance, and applicability) based on the appraisal test tool from systematic review and prognostic studies by the Centre for Evidence-Based Medicine, University of Oxford, 2010. From the meta-analysis obtained, all were important and valid. However, for the study of Kelleher et al., special note is needed because this article does not only compare mirabegron and solifenacin, but also with other antimuscarinic agents. Table 1 shows the search strategies performed with Google Scholar, Pubmed, Clinicaltrials.gov, Embase, and the Cochrane Library. Table 2 shows the clinical appraisal of the meta-analysis articles obtained, and Table 3 shows the validity analysis of the meta-analyses obtained. Table 4 shows the characteristics of the studies used in this evidence-based case report. Figure 1 shows the process for obtaining the literature search flow used.

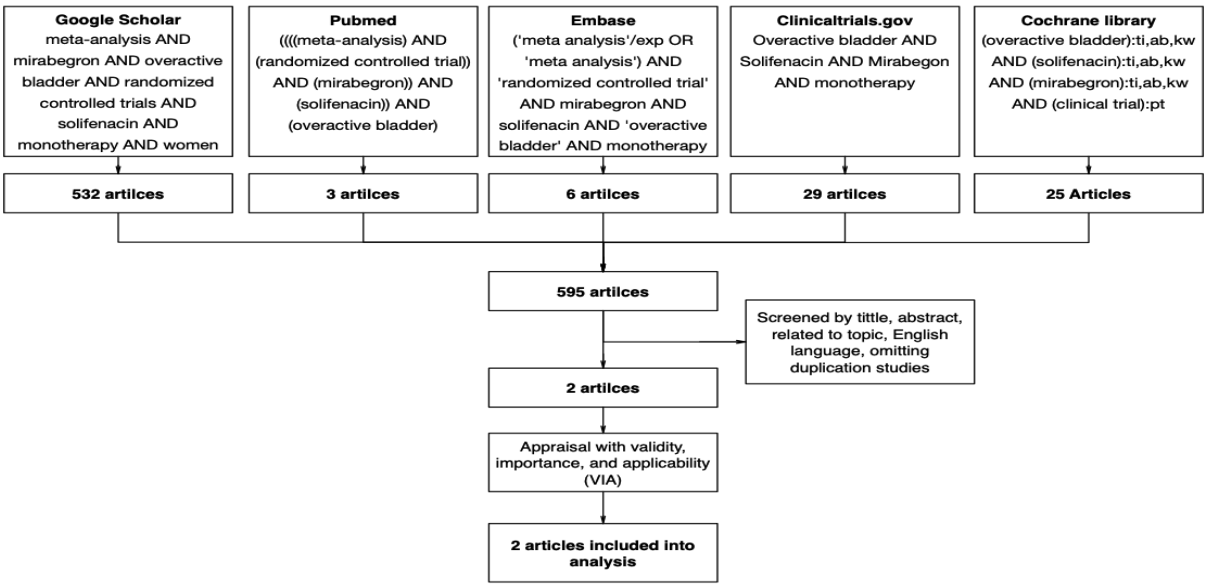

Figure 1. Flowchart of search strategy

Table 2. Clinical Appraisal of The Systematic Review

Study	Validity					Results
	PICO	Relevant studies	Criteria for inclusion appropriate	Include studies valid	Similar from study to study	
Wang et al.(Wang et al., 2019)	Comparison between efficacy of mirabegron and solifenacin for overactive bladder	Yes	Yes	Yes	Clear	Below
Kelleher et al.(Kelleher et al., 2018)	Comparison between efficacy of mirabegron and antimuscarinics for overactive bladder	Yes	Yes	Yes	Unclear	Below

Table 3. Validity of Systematic Review and Meta-analysis Included in this Evidence Based Case Reports

Study	Validity			Applicability		
	Representative sample	Follow-up sufficiently long and complete	Outcome applied in "blind" fashion	Adjustment for prognostic factors	Different patient	Clinically important to patient
Wang et al.(Wang et al., 2019)	Yes	Yes	Yes	Yes	Yes	Yes
Kelleher et al.(Kelleher et al., 2018)	Unclear	Unclear	Unclear	Yes	Yes	Yes

Table 4. Characteristic of Studies and Summary Included in the Evidence-Based Case Report

Article	Design	Intervention	Included Studies	Number of patients	Outcomes
Wang et al.(Wang et al., 2019)	Meta-analysis	Oral mirabegron versus oral solifenacin with the treatment duration of 12 weeks	Five studies (Abrams et al.(Abrams et al., 2015), Batista et al.(Batista et al., 2015), Scaldazza et	3620 patients (1773 in mirabegron group and 1847 in solifenacin group)	No significant differences between the mirabegron group and solifenacin group for the mean number of

			al.(Vecchioli Scaldazza and Morosetti, 2016), Herschorn et al.(Herschorn et al., 2017), Gratzke et al.(Gratzke et al., 2018))		incontinence episodes per 24 hours.
Kelleher et al.(Kelleher et al., 2018)	Meta-analysis	Various antimuscarinics versus mirabegron	Thirty-seven studies	25494 patients	No significant difference between mirabegron and all other active treatments.

DISCUSSION

It is well known that overactive bladder (OAB) has a negative impact on sufferers' quality of life, including negative effects on work productivity, social and family relationships, and sleep patterns. In fact, OAB can negatively affect self-confidence, self-esteem and can lead to anxiety and depression. This disorder occurs in both men and women and increases with age. It is a fact that only about 52% of OAB sufferers seek treatment from healthcare professionals.(Milsom et al., 2012) That is, the current prevalence of OAB, which is at 10% may in fact be much higher.(Marcelissen et al., 2019)

Urinary incontinence is a problem that is often found in men and especially women, and is divided into stress urinary incontinence, urge urinary incontinence, and mixed urinary incontinence. The most common type is stress urinary incontinence. Urge urinary incontinence increases in incidence over the age of 40, and is the most common type in old age, especially in women. Urge-type urinary incontinence is known to have a prevalence of approximately 0.7% in Asian women, especially those with a parity of more than two and postmenopausal age. In addition, in populations with diabetes mellitus, a higher prevalence of urge urinary incontinence (10.5%) was found.(Minassian et al., 2013)

Evidence from a meta-analysis study showed that solifenacin significantly reduced the 24-hour rate of incontinence episodes. Compared to placebo, in more than 1300 OAB patients, solifenacin has been shown to reduce episodes of urgency symptoms, reduce the number of micturitions per 24 hours, reduce episodes of urge urinary incontinence, and significantly reduce voiding volume. The commonly used dose of solifenacin is an oral dose of 5 mg. With a higher dose, namely the oral solifenacin dose of 10 mg, it was shown that there was a decrease in the number of voids per 24 hours. However, the 10 mg dose of solifenacin did not have a better effect than the 5 mg dose in reducing episodes of urgency and nocturia symptoms per 24 hours, and episodes of urinary incontinence. As for the side effects, related to its nature as an antimuscarinic agent, the use of solifenacin has been shown to increase the incidence of symptoms of dry mouth (OR 5.57), constipation (OR 2.87), and blurred vision (OR 2.15).(Luo et al., 2012)

The weakness of solifenacin as an antimuscarinic agent has led to efforts to find other pharmacological agents for the treatment of OAB, namely beta-3 agonists, such as

mirabegron. In Indonesia, the currently available beta-3 agonist agent is mirabegron, while other agents, such as virabegron, are not yet available. Compared with placebo, in more than 4900 patients, it was found that mirabegon was better at reducing the average urgency urinary incontinence episodes per 24 hours and the number of voids per 24 hours, regardless of the dose given. Studies on the side effects of mirabegron show that the most common side effects are headaches and hypertension. However, when compared, it turned out that there were no significant changes in the side effects caused by mirabegron compared to placebo.(Wu et al., 2014)

The next question is, although at first glance it seems that mirabegron is better and newer than solifenacin, how do these two drugs compare to complaints of urge urinary incontinence in patients. The complaint of urge urinary incontinence was chosen among the three other symptoms of OAB because, indeed this complaint is the culmination of all the disturbing complaints in OAB patients that greatly affect the patient's quality of life. Solifenacin and mirabegron were chosen because they are currently as available antimuscarinic agents and beta-3 agonists in Indonesia. The doses compared were the smallest doses, namely solifenacin 5 mg and mirabegron 50 mg, although from the previous explanation it was known that there was no significant difference in increasing the doses of solifenacin and mirabegron. To answer the above questions, a literature search was conducted, and two meta-analysis articles were obtained with a total thousands of patients. Even so, research on the comparison of solifenacin and mirabegon in terms of efficacy is still limited. The meta-analytic study that fits the clinical questions in this article is Wang et al.(Wang et al., 2019) because it really fits the clinical questions of this article. However, a meta-analysis by Kelleher et al.(Kelleher et al., 2018) can also be included, although this article compares mirabegron with other antimuscarinics, not only solifenacin.

In Wang et al.'s study (Wang et al., 2019), it was found that mirabegron did not have significantly better efficacy than solifenacin in terms of its efficacy in reducing the average number of incontinence episodes per 24 hours, the average number of voids per 24 hours, the number of urgency symptoms per 24 hours, and voiding volume (mean difference (MD) 0.12, 0.15, 0.12 and -5.85, $p > 0.05$). When compared in terms of side effects, as previously mentioned, solifenacin has the side effect of dry mouth, while mirabegron has the effect of increasing heart rate, but has not proven to increase the incidence of hypertension and tachycardia.

Kelleher et al. (Kelleher et al., 2018)'s study compared the efficacy of mirabegron 50 mg with various antimuscarinics, including solifenacin 5 mg, solifenacin 10 mg, fesoterodine 4 mg, fesoterodine 8 mg, tolterodine 4 mg, oxybutin 10 mg, imidafenacin 0.2 mg, propriverine 20 mg monotherapy. In fact, this study also compared mirabegron 50 mg with a combination of solifenacin 5 mg and mirabegron 25 and 50 mg, although the results could not be applied to this clinical question. This meta-analysis by Kelleher et al.(Kelleher et al., 2018) showed that mirabegron did not have significantly better efficacy in reducing the incidence of urge urinary incontinence than solifenacin monotherapy. However, when mirabegron doses of 25 mg and 50 mg were combined with 5 mg solifenacin, their efficacy was better in reducing the average number of episodes of urge urinary incontinence than 5 mg solifenacin monotherapy.

Although it is clear from the two meta-analysis studies that there is no significant difference in efficacy between solifenacin and mirabegron in reducing episodes of urge urinary incontinence, there are still various limitations in this article that might affect the

results of the analysis. The first thing that is felt is the limitations of clinical trials, let alone the meta-analysis that can be used to answer our clinical research. In fact, in the meta-analysis of Wang et al.(Wang et al., 2019), the population is relatively heterogeneous between male and female populations, so its applicability to male and female populations is still questionable. Due to these limitations, we decided to add analysis to our clinical question by adding an article by Kelleher et al. (Kelleher et al., 2018)that compared mirabegron with other antimuscarinics in general. Consequently, the meta-analysis did not focus on solifenacin. In addition, this article also does not explain which studies were used for the comparison of mirabegron and solifenacin or the number of samples. However, this study can be more convincing that it has not proven a significant increase in efficacy from using mirabegron compared to antimuscarinic agents. Even though its applicability still needs to be sharpened, this analysis should be proof that, so far, mirabegron has not really proven its superiority and that further extensive clinical trials need to be carried out.

CONCLUSION

There is no significant difference in the efficacy of mirabegron compared to solifenacin in reducing mean urge incontinence episodes for patients with overactive bladder.

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