

The Efficacy of Mirabegron as Medical Expulsive Therapy for Distal Ureteral Stones: A Systematic Review and Meta Analysis

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ABSTRACT

The aim of this study was to determine how good mirabegron is as MET for adults with ureteral stones. The study adhered to the 2020 PRISMA guidelines for Systematic Reviews and Meta-Analyses throughout its duration. Four randomized controlled trial (RCT) studies were included in our analysis, encompassing a total of 369 participants. Our meta-analysis findings indicated that individuals who were administered mirabegron exhibited a statistically significant increase in SER [OR = 2.69, 95% CI 1.16-6.23, p = 0.02] and a reduction in the frequency of pain episodes [MD= -0.18, 95% CI -0.33-(-0.04), p = 0.01] in comparison to those receiving a placebo. However, there was no substantial impact of mirabegron on SET [MD= -3.47, 95% CI -8.65-1.72, p = 0.19] when contrasted with the placebo group. Mirabegron exhibited significantly increased SET levels and reduced pain episodes, although it did not have a significant impact on SER.

INTRODUCTION

Urolithiasis ranks as one of the prevalent urological conditions worldwide, with a prevalence that varies from 1% to 13% on a global scale. The rate shows considerable differences worldwide because of variations in geography, climate, dietary habits, fluid consumption, genetic factors, gender, occupation, and age. Urolithiasis also has a high rate of new and recurrent cases with high morbidity. Ureterorenoscopy (URS) is a well known procedure to treat urolithiasis, especially ureteral stone. The problem is about 5-10% patients require a second procedure after the initial treatment because the operator failed to access the ureter clearly. Another method of intervention is needed to facilitate the stone expulsion and avoid the complication from surgery.

Medical expulsive therapy (MET) represents a non-surgical approach utilized in the management of ureteral stones. MET involves the administration of medication to aid in the natural passage of ureteral stones. The primary goals of MET involve increasing the removal rate of stones from the ureter, reducing ureteral colic, and thus avoiding the need for surgical or more invasive treatments.

Mirabegron is previously used as a treatment for overactive bladder and has shown significant effect. Mirabegron is a β_3 -agonist drug which works by relaxing the ureteral muscle and dilating the lumen for the stone to go through. As a MET for ureterolithiasis, mirabegron works by stimulating β_3 adrenoceptors in the ureteral smooth muscle. The expression of β_1 adrenoceptor, β_2 adrenoceptor, and β_3 adrenoceptor levels decreased in the dilated ureter as compared to the healthy ureter. Research conducted by Cai et al. demonstrated that mirabegron is efficient in facilitating the passage of ureteral stones. They also stated that mirabegron decreases the pain episodes but not the expulsion interval.

The utilization of mirabegron as a medical expulsive therapy (MET) for distal ureteral stones is still not widely understood. This research endeavors to evaluate how effective mirabegron is as MET for distal ureteral stones in adults, with a particular emphasis on enhancing the rate at which stones are naturally expelled (SER), decreasing the time it takes for stones to be expelled (SET), and minimizing the frequency of daily pain episodes.

LITERATURE REVIEW

Urolithiasis is a prevalent urologic disease which varies in occurrence globally (1-13%) due to factors like geography, diet, genetics, and more. As medical expulsive therapy (MET), mirabegron is a β_3 -agonist medication used to treat ureteral stones. Mirabegron works by vitalizing the β_3 adrenoceptors in the ureteral smooth muscle, augmenting the ureteral lumen. The motivation behind this study was to decide how well mirabegron filled in as MET for grown-ups with ureteral stones. The study adhered to the 2020 PRISMA guidelines for Systematic Reviews and Meta-Analyses throughout its duration. A far reaching writing search was acted in data sets including PubMed, Scencedirect, and Scopus up to June 2023. RevMan 5.4 was utilized for information investigation.

METHODOLOGY

This research follows the 2020 Guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Concurring or rejecting your proposed hypothesis.

Eligibility Criteria

In this study, the primary focus was on the examination of randomized controlled trials (RCTs). Two authors (IGYPA and RNHS) reviewed titles and abstracts that met the specified inclusion criteria: (1) RCT from the last 10 years, and (2) the article must be in English. The primary outcomes include Stone Expulsive Rate (SER). The secondary outcomes include the Stone Expulsive Time (SET) and pain episodes per day. The exclusion criteria are research with children population, and urinary stone disease other than ureteral stone.

Search Strategy and Study Selection

Two researchers, namely IGYPA and RNHS, performed a keyword search up until June 2023 to find pertinent articles across multiple databases including PubMed, ScienceDirect, and Scopus. They utilized the following keywords: ("ureterolithiasis" OR "ureteral stone") AND ("mirabegron"). The titles and abstracts were examined separately to pinpoint articles that matched the criteria. Subsequently, these selected articles underwent further evaluation based on their complete content. Any discrepancies among the authors were addressed through discussions that included other contributors, AP, and PAS until a unanimous agreement was reached.

Data Extraction

Relevant information was independently collected using a structured format that included details such as the primary author, publication year, study methodology, country of origin, sample size, participant demographics (age and gender), the standard treatment or control group, intervention details, SER (Standard Error of the Mean), SET (Standard Error of the Treatment), daily pain episode frequency, and the duration of the follow-up period.

Quality Assessment

Two creators (IGYPA and RNHS) autonomously assessed the systemic meticulousness of each study utilizing the Cochrane ROB2 device. The research was divided into three groups: "low risk of bias," "some concerns," or "high risk of bias." Moreover, the evaluation of detailing predisposition will be directed as per the Cochrane Handbook, incorporating variables, for example, distribution, delay, numerous distributions, concentrate on the spot, reference, language, and result announcing inclination.

Statistical Analysis

All information examinations were led utilizing Survey Supervisor variant 5.4, created by The Cochrane Coordinated effort at The Nordic Cochrane Center in Copenhagen, Denmark. The impact measures utilized were Mean Contrast (MD) for ceaseless information and Chances Proportion (OR) for

dichotomous information. The 95% confidence intervals (CIs) and p-values were both provided. For each outcome, meta-analyses were only conducted when there were at least two studies with comparable data. Cochran's Q and I² statistics were used to assess the studies' heterogeneity. A fixed-effects model was chosen for the meta-analysis if there was no significant heterogeneity (p-value > 0.1, I² 50%); A random-effects model was used otherwise. Conceivable distribution predisposition was assessed through visual review of Begg's channel plots. For all analyses, a p-value of less than 0.05 was considered statistically significant.

RESULTS

Study Selection

The search yielded 67 records, with 2 of them being excluded because they were either duplicates or irrelevant. Following a review of titles and abstracts, 45 articles that appeared to meet the criteria were identified. Subsequently, after a thorough evaluation of the full texts, 4 studies were deemed suitable for inclusion in this systematic review and meta-analysis. A graphical representation of this study selection process can be found in Figure 1 of the PRISMA flowchart.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

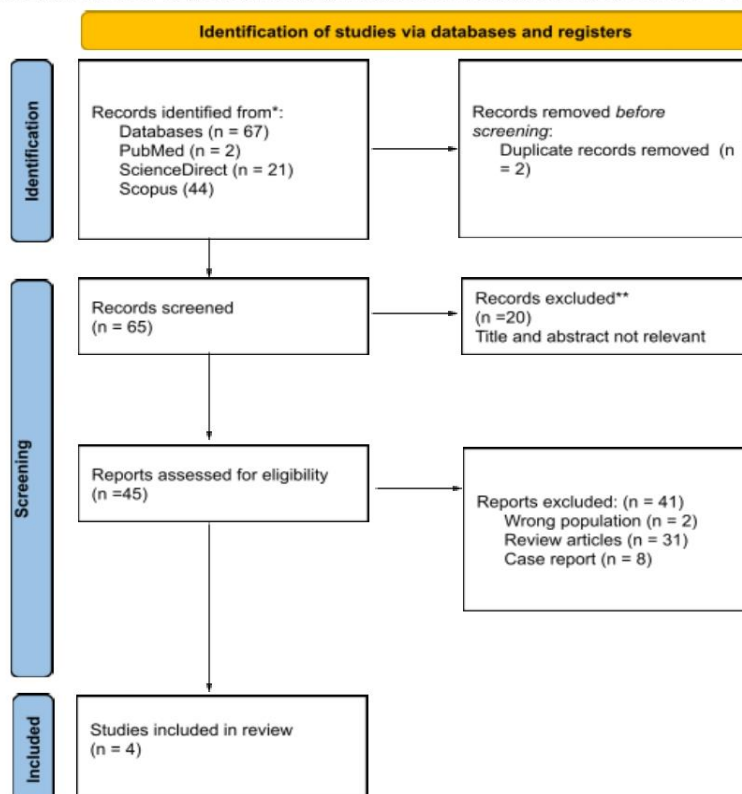


Figure 1. The PRISMA 2020 Flow Chart

Quality Assessment

Based on the Cochrane Risk of Bias 2 (RoB2) evaluation, four Randomized Controlled Trials (RCTs) were determined to possess a minimal risk of bias. Additional information regarding the assessment's quality can be found in the Supplementary Material (Figure 2).

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Solakhan, 2018	Mirabegron	Placebo	Stone Expulsion Rate	1	+	+	+	+	+	+
Bayar, 2020	Mirabegron	Placebo	Stone Expulsion Rate	1	+	+	+	+	+	+
Tang, 2021	Mirabegron	Placebo	Stone Expulsion Rate	1	+	+	+	+	+	+
Sayed, 2022	Mirabegron	Placebo	Stone Expulsion Rate	1	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
 D2 Deviations from the intended interventions
 D3 Missing outcome data
 D4 Measurement of the outcome
 D5 Selection of the reported result

Figure 2. Cochrane ROB2 Assesment

Patients Characteristics

There are 4 studies included with a total of 369 adults with distal ureteral stone, with 255 male and 114 female. There are 183 patients in the mirabegron therapy group, and 186 patients in the placebo group. The participants' mean age was xx years old. In this review, the studies were conducted in Turkey, China, and Saudi Arabia.

Efficacy of Mirabegron on Stone Expulsion Rate

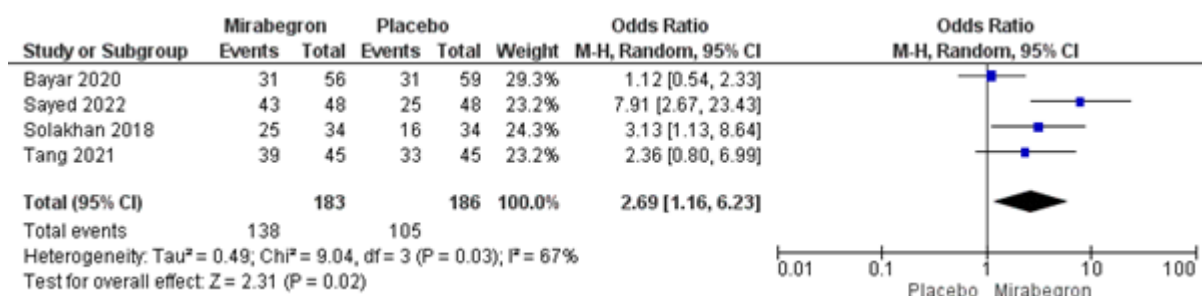


Figure 3. Efficacy of Mirabegron on Stone Expulsion Rate

The analysis of SER [figure 3] incorporated a sum of 4 trials, with 183 participants assigned to the mirabegron group and 186 assigned to the placebo group. The forest plot employing the fixed-effects model revealed a notable increase in SER among patients who received a daily dosage of 50 mg mirabegron compared to those in the placebo group, with an odds ratio of 2.69 (95% CI 1.16-6.23, P = 0.02).

Efficacy of Mirabegron on Stone Expulsion Time

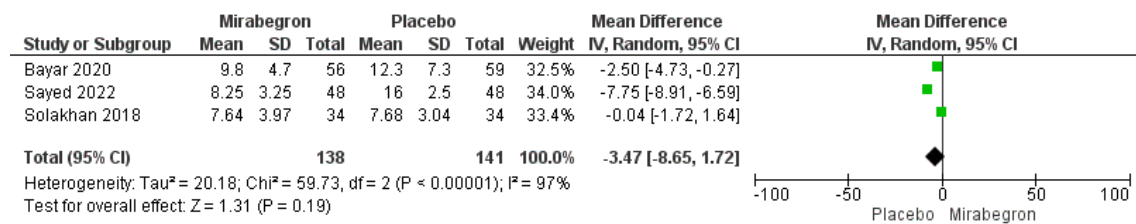


Figure 4. Efficacy of Mirabegron on Stone Expulsion Time

Three experiments were considered in the SET analysis shown in Figure 6, involving 138 participants in the mirabegron group and 141 participants in the placebo group. The forest plot, employing a fixed-effects model, indicated that administering 50 mg of mirabegron per day did not yield a significant impact on SET when compared to the placebo group [MD= -3.47, 95% CI -8.65-1.72, P = 0.19].

Efficacy of Mirabegron on Duration of Pain Episodes Per Day

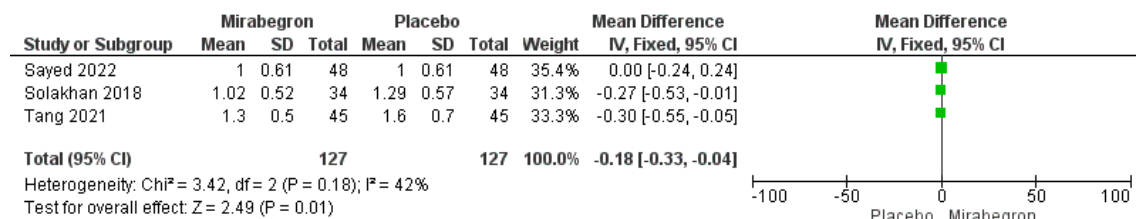


Figure 5. Efficacy of Mirabegron on Duration of Pain Episodes Per Day

Three experiments were utilized in the evaluation of daily pain episodes [figure 5], involving 127 participants assigned to the mirabegron group and 127 to the placebo group. The forest plot, employing the fixed-effects model, illustrated that individuals receiving 50 mg of mirabegron daily experienced a notable reduction in daily pain episodes compared to the placebo group [MD= -0.18, 95% CI -0.33-(-0.04) P = 0.01].

DISCUSSION

Medical expulsive therapy (MET) stands as a non-surgical approach for addressing ureteral stones. It is done by administering drugs to get the expulsion of the stone. MET encompasses the dispensation of medication to assist in the spontaneous passage of ureteral stones. The primary goals of MET includes amplifying the rate at which stones are expelled through the ureter, mitigating ureteral colic, and thereby sidestepping the requirement for more invasive interventions.

Mirabegron is previously used as a treatment for overactive bladder and has shown significant effect . Mirabegron, a β₃-agonist medication, functions by relaxing the smooth muscle in the ureter, thereby expanding the ureter's inner

diameter, facilitating the passage of the stone. Earlier research has affirmed the existence of β_1 , β_2 , and β_3 adrenoceptors in the smooth muscle and urothelial layers throughout the entire length of the ureter, encompassing its proximal, middle, and distal segments. In the dilated ureter as opposed to the normal ureter, there was a reduction in the expression of β_1 adrenoceptor, β_2 adrenoceptor, and β_3 adrenoceptor in both the mucosa and muscular layers. The potential compensatory mechanism involves an ureteral contraction as indicated by the downregulation of β_1 and β_3 adrenoceptors, especially within the muscular layer, was subsequent to ureter dilation.

In this analysis, all of the studies included found that mirabegron had a significant effect on increasing the SER. In a study by Solakhan et al., it was stated that mirabegron works significantly in increasing the stone expulsive ratio in the intervention group compared to the control group (73.5% vs 47.1%; $P = 0.026$). Sayed et al. also found that mirabegron increased the SER in the intervention group compared to the control group significantly (89.6% vs 52.1%; $P < 0.001$). Meanwhile, a study by Bayar et al. in 2020 stated that mirabegron does not significantly increase the SER compared to the control group ($P = 0.391$). Based on research conducted by Tang and colleagues in 2021, it was found that there is a notable contrast in terms of Stone Elimination Rate (SER) between mirabegron and a placebo for stones of size ≤ 5 mm ($p < 0.001$). However, there is no substantial distinction between mirabegron and a placebo for stones larger than 5 mm ($P = 0.887$).

Solakhan et al. reported that there was no substantial variance in SET (Spontaneous Ejaculation Time) when comparing mirabegron to a placebo (7.64 days versus 7.68 days; $P = 0.979$). Conversely, investigations by Bayar et al. demonstrated a notable contrast in SET between mirabegron and placebo (9.8 days versus 12.3 days; $P = 0.003$). Furthermore, Sayed et al. affirmed the existence of a significant SET discrepancy between mirabegron and placebo (8.25 days versus 16 days; $P = 0.004$).

Studies conducted by Solakhan et al. found that mirabegron exhibited a notable impact in diminishing the frequency of pain episodes in comparison to the control group (1.02 vs. 1.29 per day; $P = 0.049$). Similarly, Tang et al. reported that mirabegron significantly lowered the occurrence of pain episodes when contrasted with the control group (1.3 vs. 1.6 per day; $P = 0.022$). This observation aligns with the research carried out by Sayed et al., where mirabegron demonstrated a substantial effect on pain episodes in contrast to the control group (1 vs. 1 per day; $P < 0.001$).

There are several drawbacks to this review. The first one is the restricted number of studies that have investigated the utilization of mirabegron as a medical expulsive therapy (MET) for ureteral stones. Second, the RCTs included have a low number of samples which potentially compromises the reliability of results and susceptibility to minor discrepancies. In the forthcoming years, further investigation is required to delve into mirabegron's potential as an alternative MET for treating ureteral stones. The development of more powerful MET agents, which can improve SER and relieve colic pain, would provide

substantial advantages to individuals suffering from ureteral stones, reducing the need for more invasive treatments.

CONCLUSIONS AND RECOMMENDATIONS

A significantly higher SET and lower pain episodes was found in patients who received mirabegron as compared to those who did not. There was no significant effect on SER in the mirabegron group.

FURTHER STUDY

This study still has limitations, so it is necessary to conduct further research related to the topic "Efficacy of Mirabegron as Medical Expulsive Therapy for Distal Ureteral Stones: A Systematic Review and Meta-Analysis". Future research can use different objects of Medical Expulsive Therapy to add insight for readers.

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