The Efficacy and Safety of Tamsulosin and Tadalafil Combination Compared to Tamsulosin as Medical Expulsive Therapy: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Medical expulsive therapy (MET) with tamsulosin is generally used for ureteral stones. Tadalafil, a PDE5 inhibitor, has been discussed as a concomitant MET in several studies. However, evidence regarding its efficacy and safety has not been described in detail.

Purpose: To determine the efficacy and safety of tamsulosin-tadalafil combination compared to tamsulosin-only for distal ureteral stones.

Materials and Methods:

Articles were systematically searched through EMBASE, MEDLINE, and Scopus, complying with PRISMA guideline. Qualitative and quantitative data were analyzed using Cochrane RoB II and RevMan 5.4. Significant measures were observed if $p < 0,05$ (95% confidence interval).

Results: Tamsulosin-tadalafil combination significantly improve stone expulsion rate (OR 2.59, 95% CI 1.77 – 3.79, $p < 0.00001$), erectile function (OR 41.31, 95% CI 8.19 – 208.29, $p < 0.00001$), and stone expulsion time (OR -1.05, 95% CI -1.76– -0.34, $p = 0.004$). Colic episodes and hospital visits were also benefited from the combination compared to the monotherapy group. Abnormal ejaculation was significantly lower with combination and no difference on headache, dizziness, backache, and orthostatic hypotension were found between groups.

Conclusion: Tadalafil-tamsulosin combination enhanced efficacy while reducing adverse effects. Sexually active patients with uncomplicated ureteral stones who are sexually active benefit from this combination.

Keywords: tamsulosin, tadalafil, medical expulsive therapy, ureteral stone, stone expulsion

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INTRODUCTION

Urinary tract stone or urolithiasis is one of the most common diseases in the field of urology. The prevalence of urolithiasis is approximately 15%, with men account for twice as high compared to women (Tchey et al., 2011; Puvvada et al., 2016). Twenty percent of all stones are located in the ureter, two-thirds of which are in the distal portion (Alwan, Ajeel and Abd, 2019). Colic

pain is the typical symptom which prompt the patients to seek for treatment (Hollingsworth et al., 2006).

In Asia, patients with urolithiasis are reported to have a recurrence rate of 21% - 53% within three to five years (Liu et al., 2018). Generally, the stone formation process is thought to originate from the kidney through the calyces and the pelvis before shifting to the ureter, whereas primary ureteral stones usually occur in the aftermath of obstructed flow of urine (Papadoukakis, Stolzenburg and Truss, 2006).

Most ureteral stones could pass spontaneously depending on their size, shape, location, and the presence of ureteral wall pathology. Ureteral stones measuring 4 mm, 4-6 mm, and 6 mm have spontaneous expulsion rates of 79%, 59%, and 21%, respectively. Proximal compared to distal ureteral stones have an expulsion rate of 25% versus 75%. Ureteral stones usually pass during voiding within 2-6 weeks from the initial symptoms (Miller and Kane, 1999).

Medical expulsive therapy (MET) is the most frequently used modality for ureteral stones. Application of MET could involve a combination of drugs with different mechanisms. Blockage of α1-adrenergic receptor in distal-third ureter causes reduction on basal contraction of ureteral smooth muscle, propelling antegrade stone expulsion (Porpiglia et al., 2006; Jayant, Agrawal and Agrawal, 2014; Puvvada et al., 2016). It also causes stone expulsion by increasing intra-ureteral pressure difference around the stone. Currently, tamsulosin is an option which has been shown to increase the percentage of stone expulsion while expediting time to expulsion (Wang, Huang and Chang, 2008). Pathological changes in the ureteral wall around the stone are mostly caused by stone impaction. Inflammation with mucosal edema will further result in ureteral obstruction at the level of the stone (Rahman et al., 2018). As with symptoms originating from hollow organs, the obstruction will manifest as colic pain.

Recent studies have investigated that tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, acts on the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) signaling pathway in smooth muscle, causing an accumulation of cGMP which stimulates smooth muscle relaxation (Gratzke et al., 2007; Hari Bahadur et al., 2016). Tadalafil with its pharmacological efficacy is approved by US Food and Drug Administration for use as treatment of choice for diseases of the urinary tract. Combination of tamsulosin and tadalafil could enhance the stone expulsion rate via smooth muscle relaxation and concomitant decreased intramural ureteral pressure. This will ultimately lower the frequency of spastic reactions caused by obstruction of the ureter. Several studies have reported that the administration of tamsulosin and

tadalafil influenced the number of office visit, the incidence of erectile dysfunction (ED) and complications (Jayant, Agrawal and Agrawal, 2014; Goyal et al., 2018; Gnyawali et al., 2020). Accordingly, we conducted a meta-analysis to determine the efficacy and safety of tamsulosin and tadalafil combination compared to tamsulosin alone as MET for distal ureteral stones.

MATERIALS AND METHODS

This study is a systematic review and meta-analysis that followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol (Page et al., 2021). We determine the criteria for eligible studies using PICO (Participant, Intervention, Comparison, Outcome) analysis. The search strategies were performed in the medical database, such as EMBASE, MEDLINE, and Scopus using relevant keywords ("Tamsulosin") and ("Tadalafil") and ("ureter stone" or "ureteral stone" or "ureteric stone" or "ureter calculi" or "ureteral calculi" or "ureteric calculi" or "ureterolithiasis"). The supplementary materials table is provided for detailed information regarding the search strategy (Table 1).

Table 1. The supplementary materials of the search strategy

Database	Keywords
EMBASE, MEDLINE, SCOPUS	((TITLE-ABS-KEY (tamsulosin) AND TITLE-ABS-KEY (tadalafil) AND TITLE-ABS-KEY (ureter AND stone) OR TITLE-ABS-KEY (ureteral AND stone) OR TITLE-ABS-KEY (ureteric AND stone) OR TITLE-ABS-KEY (ureter AND calculi) OR TITLE-ABS-KEY (ureteral AND calculi) OR TITLE-ABS-KEY (ureteric AND calculi) OR TITLE-ABS-KEY (ureterolithiasis))

Inclusion and Exclusion Criteria

The inclusion criteria of this study are Randomized Controlled Trial (RCT) studies, adult patients with distal ureteral stones as targeted participants, include treatment comparison between the combination of tamsulosin-tadalafil and tamsulosin only, and accessible via MEDLINE, Embase, and Scopus. On the other hand, the exclusion criteria of this study are non-English journals, experimental research on animals, unpublished articles, and abstract-only articles.

Data Extraction

Two independent authors carried out data extraction by filling out the templates. The extracted data in Research characteristics and methodology includes the name of the first author, year of publication, number of patients, patient age, and study design; intervention includes the type of intervention and stone size; outcome and other data include stone expulsion rate, average stone exclusion time, the average number of colic episodes, number of hospital visits, improvement in erectile dysfunction, and complication. The risk of research bias was assessed using the Cochrane Risk of Bias Tools for Randomized Trials. If there are differences during the data extraction process, the third author will help with decision-making.

Statistical Analysis

Continuous outcome data were analyzed to produce a Mean Difference, while the outcome of dichotomous data was analyzed to produce Odds Ratio (OR). Both were analyzed with a Confidence Interval of 95%, and a P-value below 0.05 was determined as statistically significant. Heterogeneity between studies was calculated using I2. If I^2>50%, heterogeneity between studies was considered statistically high, and random effect model analysis would be used. However, if I^2 < 50%, the fixed-effect model will be applied to the meta-analysis. RevMan 5.4 software was used as a data analysis tool. The analysis results are presented in forest plots and descriptive narratives.

RESULTS

Systematic search results

The PRISMA flowchart was used to guide the selection of included studies for the meta-analysis (Figure 1). The initial research using Medline, EMBASE, and Scopus revealed 81 potential articles. However, eleven studies were excluded in duplication removal. Screening of titles and abstracts then excluded 30 articles. After thorough research on journal full-text, five studies are chosen to be the included in qualitative analysis, while 4 studies included in quantitative analysis. Reporting on the selection of studies in this meta-analysis follows the PRISMA rules.

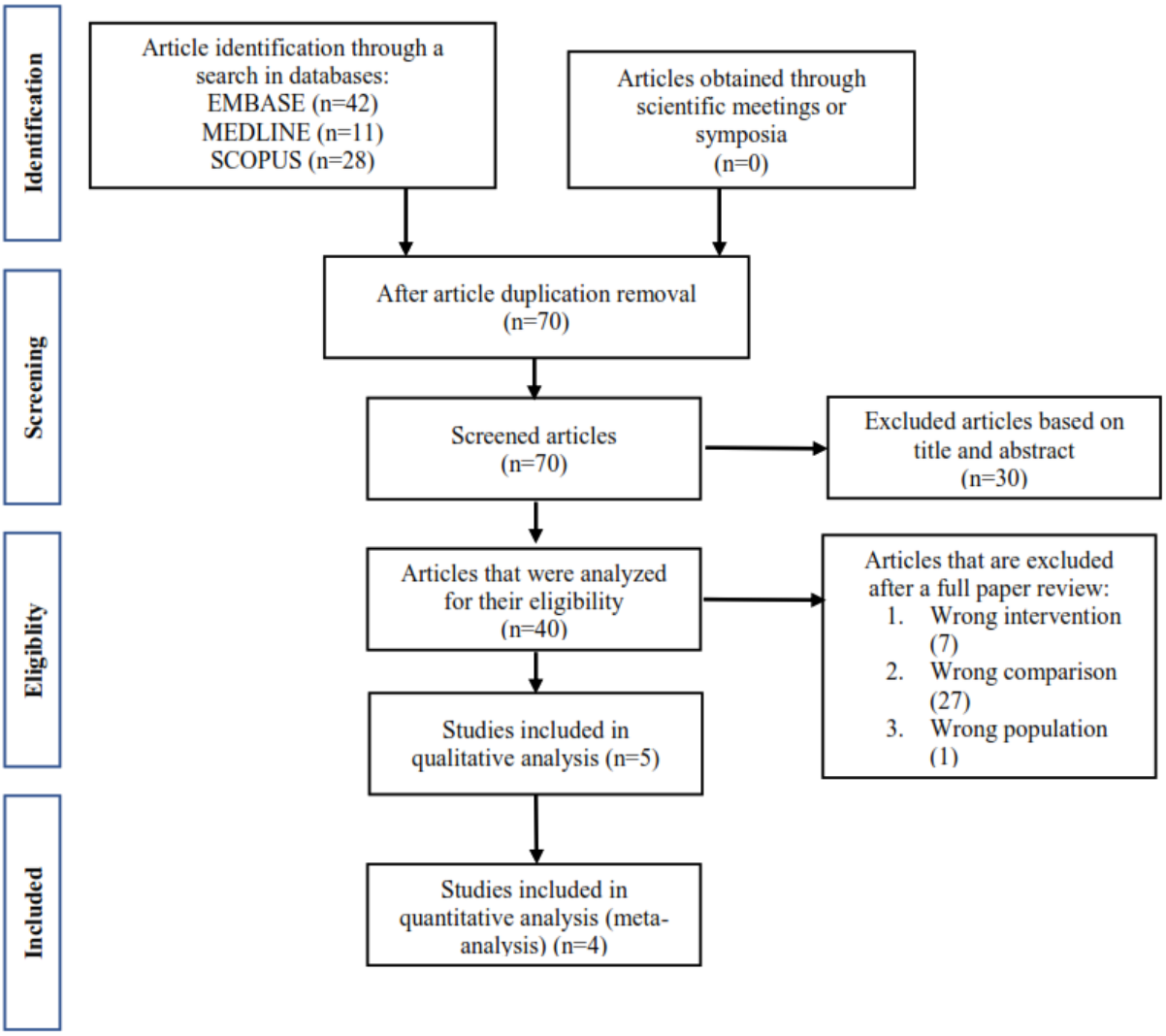

Figure 1. The PRISMA flowchart for study selection

Baseline characteristics of the included studies

All studies that have been selected for qualitative and quantitative analysis are then presented in tabulated form. The presented data consist of the author, publication year, the number of patients in the tamsulosin-tadalafil combination group and tamsulosin only group, the mean age, and several assessed outcomes (Table 2). Overall, 790 patients were analyzed in this study.

Table 2. Baseline characteristics of the included studies

Studies	Study Design	Treatment Arm	Age (years)	N (male/female)	Stone size	Outcomes					Complication					
						Stone expulsion rate %	Stone expulsion time	Mean colic episode	Mean hospital visit	Improved erectile function %	Headache %	Dizziness %	Backache %	Orthostatic hypotension %	Abnormal ejaculation %
(Gnywali *et al.* 2020)[14]	RCT	Tamsulosin + Tadalafil	33.75 ± 10.01	81 (58/23)	7.43 ± 1.23	79	1.66 ± 0.87 (weeks)	2.02 ± 0.80	1.48 ± 0.61	NA	10 (12.4)	9 (11.1)	11 (13.6)	4 (4.9)	5 (6.2)
		Tamsulosin	32.85 ± 10.36	80 (50/30)	7.34 ± 1.13	62.5	2.32 ± 0.76 (weeks)	2.34 ± 0.67	1.70 ± 0.60	NA	8 (10)	7 (8.8)	7 (8.8)	3 (3.8)	6 (7.5)
(Abdulameer *et al.*, 2019)[3]	RCT	Tamsulosin + Tadalafil	34.25 ± 10.50	100 (65/35)	7.75 ± 1.30	91	11.5 ± 5.3 (days)	NA	NA	30	16.1	17.1	NA	5.4	13.1
		Tamsulosin	32.45 ± 9.36	100 (72/28)	7.15 ± 1.62	75	18.6 ± 5.2 (days)	NA	NA	0	14	13.9	NA	2	21.1
(Goyal *et al.*, 2018)[15]	RCT	Tamsulosin	42.13 ± 13.8	61 (43/18)	7.54 ± 1.11	73.77	9.38 ± 6.66 (days)	NA	NA	NA	6 (9.8)	4 (6.6)	3 (4.92)	2 (3.28)	6 (9.8)
		Tadalafil	42.61 ± 14.93	62 (41/21)	7.60 ± 0.91	69.35	9.61 ± 7.47 (days)	NA	NA	NA	7 (11.3)	6 (9.7)	3 (4.8)	2 (3.2)	1 (1.6)
(Jayant *et al.*, 2014)[8]	RCT	Tamsulosin + Tadalafil	37.23 ± 12.54	122 (67/55)	7.05 ± 1.62	83.6	14.9 ± 4.4 (days)	0.45 ± 0.68	2.2 ± 1.0	12.3	15.6	15.6	15.6	5.8	12.3
		Tamsulosin	36.45 ± 10.36	122 (65/57)	6.72 ± 1.44	65.5	16.7 ± 4.8 (days)	1.60 ± 1.0	2.85 ± 0.90	0	12.3	12.3	9.8	3.0	18.3
(Kumar *et al.*, 2014)[17]	RCT	Tamsulosin + Tadalafil	35.23 ± 13.54	31 (25/6)	6.67 ± 1.44	83.9	15.15 ± 5.40 (days)	0.45 ± 0.68	2.90 ± 0.90	12.9	16.1	16.1	16.1	6.4	12.9
		Tamsulosin	32.45 ± 9.36	31 (19/12)	7.05 ± 1.62	74.2	18.90 ± 8.71 (days)	1.60 ± 1.00	3.85 ± 0.99	0	12.9	12.9	9.6	3	19.4

Risk of bias analysis

Research bias assessment was analyzed qualitatively and quantitatively on seven studies. The randomized controlled trial (RCT) was assessed using the Cochrane Risk of Bias Tools for Randomized Trials 2 in this study. The observational study was assessed using the Newcastle Ottawa Scale research bias assessment. All included studies had a low risk of bias in terms of sample randomization. However, the study conducted by Ahmad Abdulameer et al., Diwas et al., Santosh Kumar et al., and Suresh Kumar et al. has the possibility of bias blinding because the studies did not explain in detail the blinding process of participants and researchers in their study (Figure 2).

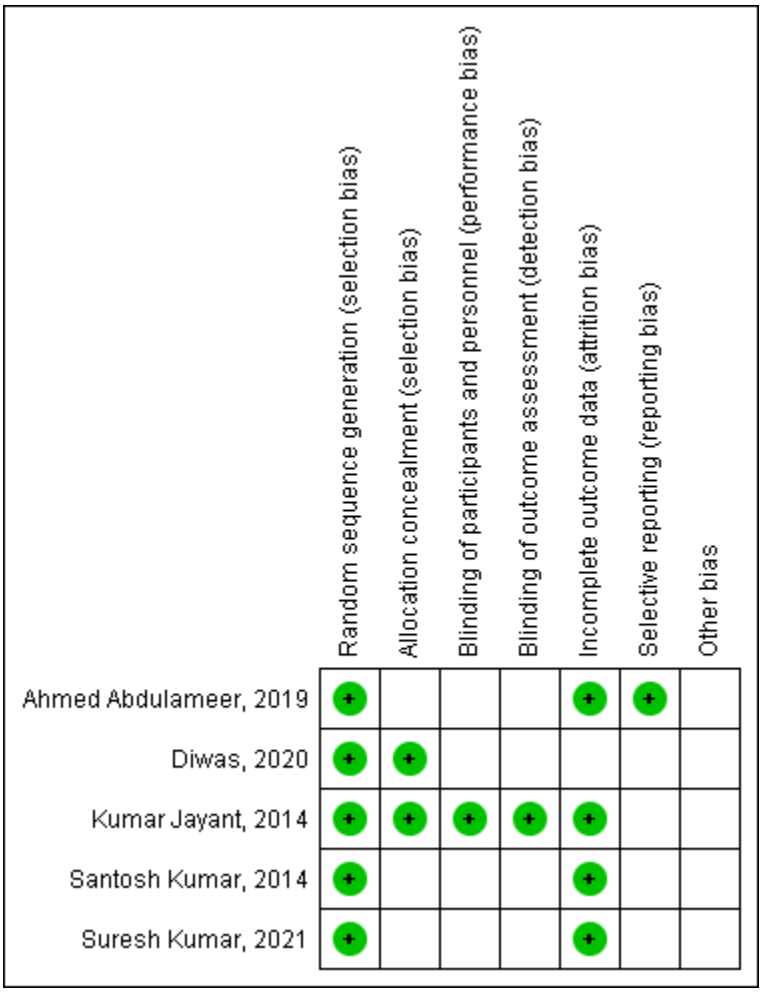

Figure 2. Bias analysis on relevant studies

Meta-analysis results on stone expulsion rate

The forest plot analysis that assessed the difference in the outcome of stone expulsion rate between the combination of tamsulosin-tadalafil and tamsulosin-only is presented in Figure 3

showed a statistically significant result where the combination of tamsulosin and tadalafil group was superior to tamsulosin-only group (OR 2.59, 95% CI 1.77 – 3.79, p < 0.00001). The analysis of this outcome used a fixed-effects model due to low heterogeneity (I^2 < 50%).

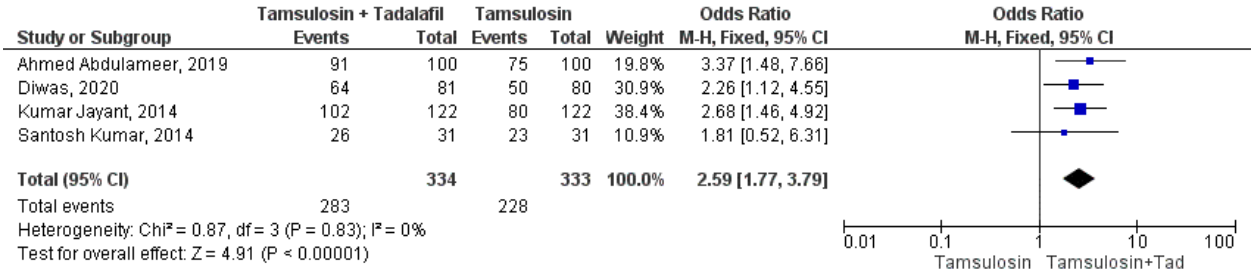

Figure 3. Meta-analysis results on stone expulsion rate

Meta-analysis results on stone expulsion time

The outcome analysis of the stone expulsion time that presented in Figure 4 revealed a statistically significant difference where the mean outcome of stone expulsion time in the tamsulosin-tadalafil combination group was shorter than tamsulosin-only group (OR -1.05, 95% CI -1.76– -0.34, p = 0.004). Analysis of this outcome used a random-effects model due to low heterogeneity (I^2 > 50%).

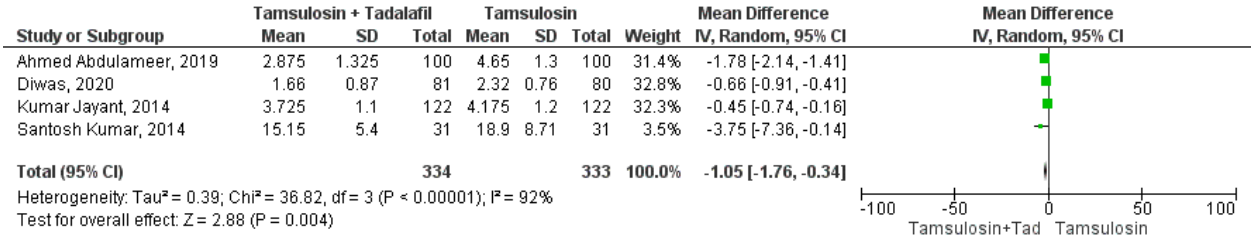

Figure 4. Meta-analysis results on stone expulsion time

Meta-analysis results on mean colic episode

The difference in the mean number of colic episodes revealed a statistically significant outcome, where the number of colic episodes in the tamsulosin and tadalafil combination group was lower than in the tamsulosin-only group (MD -0.86, 95% CI -1.47– -0.26, p < 0.005) (Figure 5). The analysis of this outcome also used a random-effects model due to high heterogeneity (I^2 > 50%).

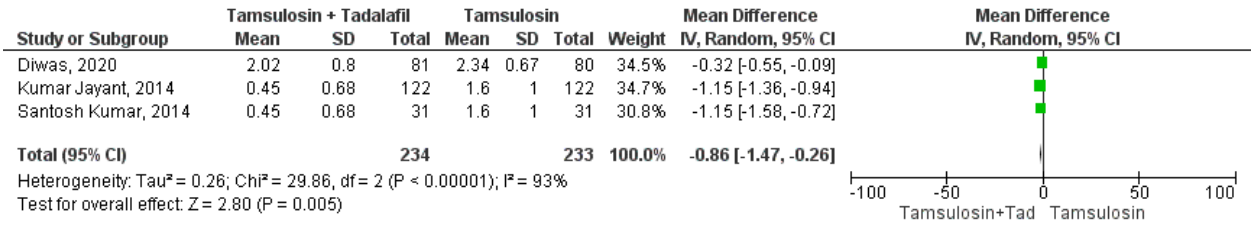

Figure 5. Meta-analysis results on mean colic episode

Meta-analysis results on mean hospital visit

The forest plot analysis that assessed the difference in the mean number of hospital visits between the combination of tamsulosin-tadalafil and the tamsulosin-only group showed no statistically significant result. However, this analysis displayed that the mean number of hospital visits tended to be lower in the tamsulosin-tadalafil combination group than in the tamsulosin group (MD – 1.62, 95% CI -3.93 – 0.69, p = 0.17) (Figure 6). The analysis of this outcome used a random-effects model due to high heterogeneity (I^2 > 50%).

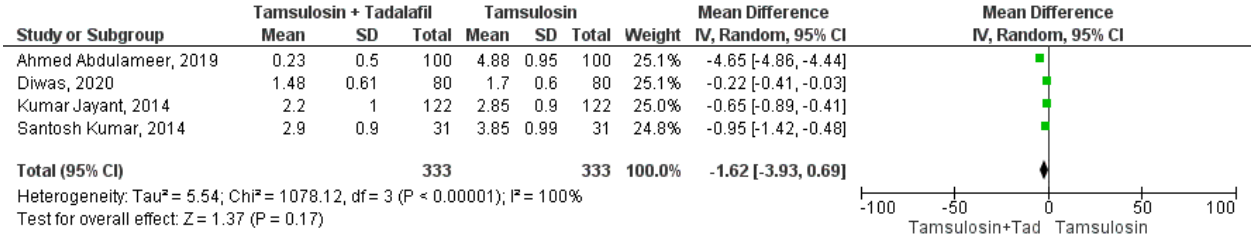

Figure 6. Meta-analysis results on mean hospital visit

Meta-analysis result on improved erectile function

A statistically significant result in improved erectile function between the tamsulosin-tadalafil combination group and the tamsulosin-only group is presented in Figure 7, where the outcome was better in the tamsulosin-tadalafil combination group (OR 41.31, 95% CI 8.19 – 208.29, p < 0.00001). A fixed-effects model was used in the analysis due to low heterogeneity (I^2 < 50%).

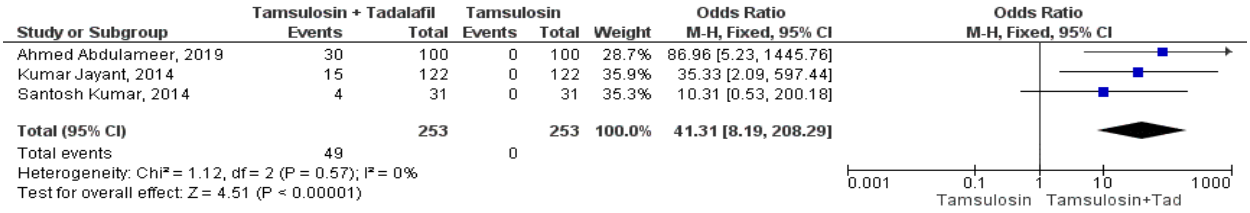

Figure 7. Meta-analysis result on improved erectile function

Detailed analysis of relevant complications

The forest plot analysis that assesses the outcome in the form of drug complications is presented in Figure 8.

Headache complication subgroup

The forest plot analysis that assessed the headache complications between the tamsulosin-tadalafil combination group and the tamsulosin-only group showed no statistically significant result (Figure 8). However, this analysis revealed that the outcome of headache complications tended to be higher in the tamsulosin-tadalafil combination group (OR 1.26, 95% CI 0.81 – 1.96, p = 0.31). A fixed-effects model was used to analyze this outcome due to low heterogeneity (I^2 < 50%).

Dizziness complication subgroup

The forest plot analysis on dizziness complications between the tamsulosin-tadalafil combination and the tamsulosin-only groups showed no statistically significant difference (Figure 8). However, this analysis showed that the outcome of dizziness complications tended to be higher in the tamsulosin-tadalafil combination group than in the tamsulosin group (OR 1.30, 95% CI 0.83 – 2.03, p = 0.26). Due to low heterogeneity, a fixed-effects model was used (I^2 < 50%).

Backache complication subgroup

Although backache complications between the administration of the tamsulosin-tadalafil combination and the tamsulosin-only group showed no statistically significant difference, it tended to be higher in the tamsulosin-tadalafil combination group (OR 1.75, 95% CI 0.97 – 3.14, p = 0.06) (Figure 8). The analysis of this outcome used a fixed-effects model due to low heterogeneity (I^2 < 50%).

Orthostatic hypotension complication subgroup

The analysis results revealed no statistically significant difference between the complications of orthostatic hypotension in the tamsulosin-tadalafil combination group and the tamsulosin-only group. It also showed that orthostatic hypotension complications tended to be higher in the tamsulosin-only group (OR 0.54, 95% CI 0.25 – 1.19, p = 0.13) (Figure 8). A fixed-effects model was used in the analysis due to low heterogeneity (I^2 < 50%).

Abnormal ejaculation complication subgroup

Our analysis result showed a significant difference between the tamsulosin-tadalafil combination group and the tamsulosin-only group, where abnormal ejaculation complications were recorded more in the tamsulosin-only group (OR 0.59, 95% CI: 0.37 – 0.97, p = 0.02) (Figure 8). A fixed-effects model was used in the analysis due to low heterogeneity (I^2 < 50%).

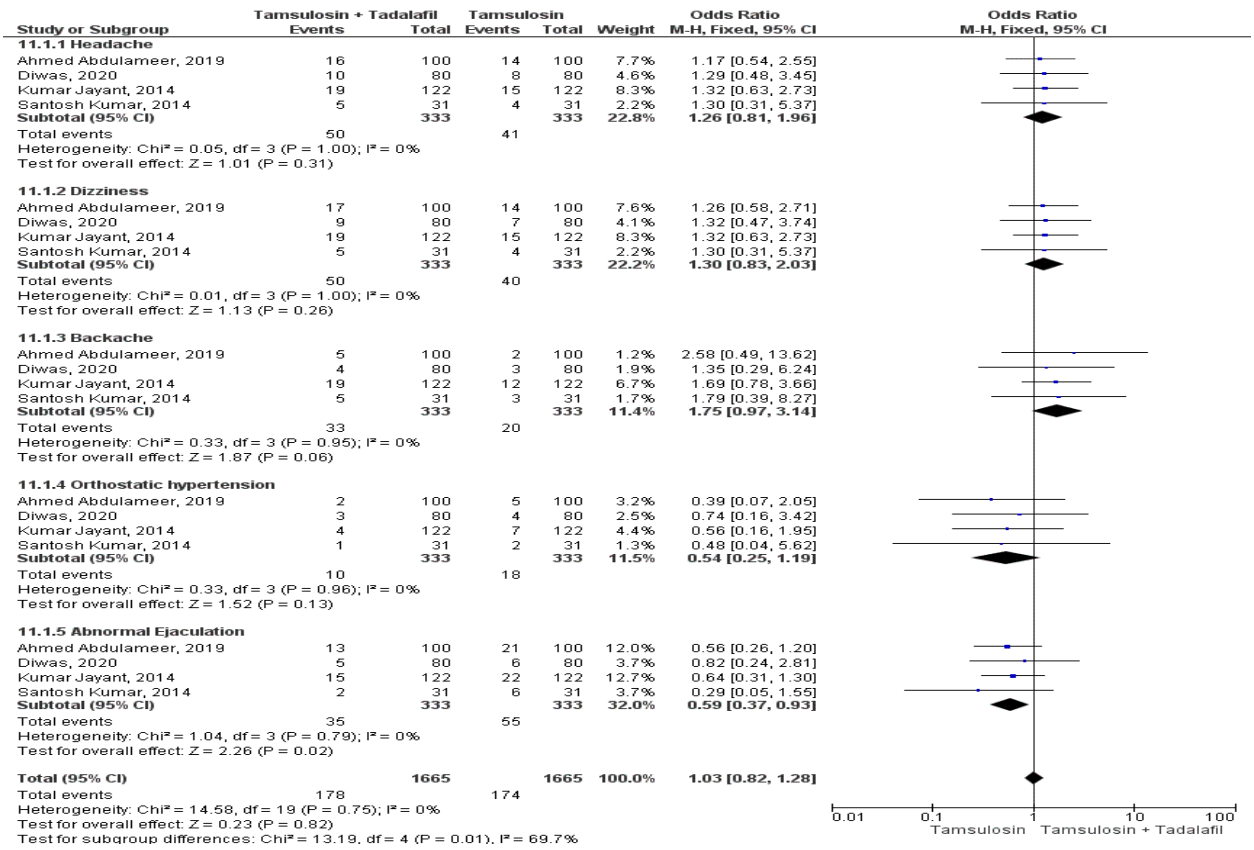

Figure 8. Detailed analysis of relevant complications.

DISCUSSION

Stone expulsion rate analysis indicated that the combination of tamsulosin and tadalafil gave superior results compared to the tamsulosin group with an OR of 2.59 (95% CI 1.77-3.79). Previous reports affirmed that superior stone expulsion rates were achieved in the group of tamsulosin plus tadalafil. Double spasmolytic effect mediated through different pathways of the two drugs on the ureteral smooth muscle and the lower urinary tract may lead to easier passage of distal ureteral stone (Jayant, Agrawal and Agrawal, 2014; Gnyawali et al., 2020). Secondary outcome of the study on average stone expulsion time showed a significant difference was observed in tamsulosin and tadalafil combination, in comparison to tamsulosin monotherapy. The mean stone expulsion time was lower in favor of the combination group with OR -1.05 (95% CI -1.76– -0.34, p = 0.004). Several previous studies have also reported comparable outcomes which support this finding. Emphasize on complementary biomechanisms of α1-blocker and PDE5 inhibitor may give an explanation to the spontaneous passage of distal ureteral stone (Jayant, Agrawal and

Agrawal, 2014; Kumar et al., 2014; Gnyawali et al., 2020).

Considerable outcome regarding the administration of tamsulosin and tadalafil for the patients also included the number of colic episodes. The combination yielded lower mean number of colic relative to tamsulosin alone with MD -0.86 (95% CI -1.47– -0.26, p < 0.005). Prior investigation by Kumar *et al*. reported the mean number of colic episodes in the tamsulosin-tadalafil combination group of 0.45 ± 0.68, whereas the tamsulosin group averaged an occurrence of 1.60 ± 1.0 (Kumar et al., 2014). To some extent, the alleviated colic sensation is associated with the blockade of C-fibers, which are known for mediating pain. As with current advantage, the amount of analgesic use for the management of the patients could be limited and thus avoiding additional cost and adverse effects (AEs) (Jayant, Agrawal and Agrawal, 2014; Kumar et al., 2014; Gnyawali et al., 2020).

Ureteral stones usually cause severe colic pain as a consequence of increased intra-ureteral pressure proximal to the level of obstruction. NSAIDs and anti-spasmodic medication are generally used to relieve pain caused by acute ureteral obstruction. Analysis concerning the frequency of hospital visits showed that tamsulosin-tadalafil combination for ureteral stones gave a modest difference, although this was not statistically significant (MD: -1.62, 95% CI -3.93 – 0.69, p = 0.17). Previously, several studies have figured that the combination of tamsulosin and tadalafil were able to reduce colic episodes among patients with ureteral stone (Coll, Varanelli and Smith, 2002). Well-regulated pain control observed with the use of tamsulosin-tadalafil combination was attributed to the decreased frequency and amplitude of peristaltic contractions in the state of ureteral obstruction (Kumar et al., 2014).

The addition of tadalafil to tamsulosin showed a concurrent benefit in regard to erectile function. Improvement of erectile function while treating patients with the combination therapy had an OR of 41.31 (95% CI; 8.19-208.29). PDE5 inhibitor prevents the degradation of cAMP and cGMP, causing an accumulation of cAMP and cGMP which in turn facilitates smooth muscle relaxation. The proposed mechanism of this compound as an aid for stone expulsion is through moderation of ureteral spasm (Coll, Varanelli and Smith, 2002). Tadalafil, a selective PDE5 inhibitor, was previously approved by FDA for the treatment of erectile dysfunction, owing to its s efficacy in reducing of smooth muscle tone along the urogenital system (Setter et al., 2005; Shabsigh et al., 2006).

Several intervention-related AEs were encountered with the use of tamsulosin and concomitant tadalafil. Reported AEs include headache, dizziness, backache, orthostatic hypotension, and ejaculatory problems. The statistical analysis of AEs did not show a

significant difference in terms of headache, dizziness, backache, and orthostatic hypotension. Moreover, abnormal ejaculation was significantly lower in the tamsulosin and tadalafil combination group. Generally, the administration of tamsulosin in combination with tadalafil for ureteral stones were well-tolerated and did not cause bothersome side effects. In comparison to sildenafil, tadalafil has more selectivity towards PDE5 receptors and inhibits PDE6 in the retina so that ophthalmic disturbances are less. Compared to all PDE5 inhibitors, tadalafil has a longer duration of action (36 hours with a half-life of 17.5 hours) and its bioavailability is not affected by food. Unlike vardenafil which has a configuration similar to sildenafil, tadalafil has a notably different structure (Taher *et al.*, 1994). Prior studies reported that AEs in PDE5 inhibitors were almost the same. Moderate to severe AEs affecting patients' quality of life were seldom. This could be partially due to the proportion of enrolled patients that were among young adults age group (Jayant, Agrawal and Agrawal, 2014; Kumar et al., 2014; Gnyawali et al., 2020).

CONCLUSION

A better outcome in stone expulsion rate and improved erectile function, shorter stone expulsion time, and fewer colic episodes were significant in patients with distal ureteral stones in the tamsulosin-tadalafil combination group. However, there was no significant difference between the two groups in the number of hospital visits and drug complications or side effects in patients with distal ureteral stones. Our future research recommendation is to include RCT studies with larger populations, similar intervention protocols, and group analysis based on stone location and ureteral stone size.

SUMMARY AND OUTLOOK

- Tadalafil, a PDE5 inhibitor, has been discussed as a concomitant MET in several studies.
- Tamsulosin-tadalafil combination significantly improve stone expulsion rate, erectile function and stone expulsion time.
- Colic episodes and hospital visits were also benefited from the Tamsulosin-tadalafil combination compared to the Tamsulosin monotherapy group.
- Abnormal ejaculation was significantly lower with Tamsulosin-tadalafil combination and no difference on headache, dizziness, backache, and orthostatic hypotension were found between groups.
- Tadalafil-tamsulosin combination enhanced efficacy while reducing adverse effects. Sexually active patients with uncomplicated ureteral stones who are sexually active benefit from this combination.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest

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AUTHOR CONTRIBUTION

DAW and TD researched literature and conceived the study. FH and YPK were involved in protocol development and data analysis. DAW wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

ABBREVIATION LISTS

MET : Medical expulsive therapy

RCT : Randomized Controlled Trial

OR : Odds Ratio

CI : Confidence Interval

MD : Mean Difference

PRISMA : Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PDE5 : Phosphodiesterase-5

AEs : Adverse effects

NSAIDs: Non-steroidal anti-inflammatory drugs

cAMP : Cyclic adenosine monophosphate

cGMP : Cyclic guanosine monophosphate

FDA : Food and Drug Administration

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