Cost-effectiveness of Medical Expulsive Therapy with α-blockers for Large Distal Ureteral Stones in China

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Purpose: To assess the cost-effectiveness of medical expulsive therapy (MET) versus observation for large distal ureteral stones in China and provide preliminary evidence for the determination of the course of MET by mathematical estimation.

Materials and Methods: With linear success rate assumptions, a decision tree was constructed by TreeAge Pro 2011 software. The stones passage rates after observation or receiving 0.4 mg daily tamsulosin were estimated according to a large randomized clinical trial (RCT). The costs of ureteroscopy, drugs and examinations were estimated according to related price from pharmacies or hospitals, or the guidance price published by the government. MET was also compared with observation by the sensitivity analysis. The effectiveness of MET or observation was presented by quality-adjusted life-day. Mathematical estimation of stone expulsion time was made by using a decision-analytic Markov model under the assumption that the daily stone expulsion probability is constant.

Results: In China, the MET was associated with a $295.1 cost advantage over observation. The cost of ureteroscopy has to decrease to $77.8 to reach cost equivalence between observation and MET. Observation is cost-effective only if ureteroscopy is very cheap or the difference of stone expulsion rates is insignificant. The estimated expulsion time was much longer than those reported in above mentioned RCT.

Conclusion: Due to the high cost of ureteroscopy, MET showed a cost advantage over observation in treating distal ureteral stones in China. The daily stone passage rate was inconstant. More studies are needed to find the appropriate duration of MET.

Keywords: cost-effectiveness; medical expulsive therapy; observation; distal ureteral stones; tamsulosin

INTRODUCTION

Urolithiasis affects about 5-10% of the population across the world[1,2]. There are various treatment modalities for ureteral stones, such as percutaneous nephrolithotomy, ureteroscopic lithotripsy (URS), extracorporeal shockwave lithotripsy (ESWL), and medical expulsive therapy (MET). For patients with distal ureteral stones less than 10 mm who do not require immediate invasive intervention, MET is one of optimal treatment modalities. Recently a multicenter, randomized, double-blind, placebo-controlled clinical trial was published and confirmed the advantages of α-blocker over placebo in the treatment of distal ureteral stones, especially large stones. This randomized controlled trial (RCT) was conducted across 30 centers in China including 3296 patients[3]. Although MET has been demonstrated to promote ureteral stone passage, diminish time to stone expulsion, and reduce the need for analgesics, it is still of great importance to minimize cost by applying cost-effective treatment regimens when resolving ureteral stones. However, compared with observation or simple hydration, the cost-effectiveness of α-blocker for the treatment of large distal ureteral stones in Chinese population hasn't been established. We hypothesized that, since MET can increase the probability of large distal ureteral stone passage and reduce the need for URS, then it might have cost-effective advantage over observation. Our study is the first study that aims to compare the cost of MET versus observation for the treatment of large distal ureteral stones in China.

In addition, although MET has been recommended by guidelines from the European Association of Urology (EAU) for the treatment of urolithiasis[4], there is still no consensus on the course of MET. Our study firstly pro-

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Table 1. Data of costs used in the estimation of cost of medical expulsion therapy and observation

Items	Cost ($)
Color Doppler ultrasound	5.2
Blood routine test	3.9
Renal function test	1.6
Tamsulosin per box (0.2mg*10)	9
Surgery related cost	2537

vides preliminary evidence for the determination of the course of MET by mathematical estimation of stone expulsion time according to the RCT mentioned above[4].

MATERIALS AND METHODS

In order to compare the cost of MET versus observation, a decision tree was used to simulate and analyze the expected treatment cost of a patient with large distal ureteral stones. The effectiveness of MET or observation was presented by quality-adjusted life-day (QALD). A Markov model was used to estimate the change of daily stone expulsion rate.

Assumptions

The base case assumption

The base case assumption was patients with a large distal ureteral stone without urinary infection, fever, severe hydronephrosis, renal insufficiency, abnormal anatomy, a history of ureter strictures, diabetes mellitus, hypotension, known or suspected pregnancy for either observation or tamsulosin. If the patients chose observation, they would only receive necessary analgesics, hydration, and examinations. And if the patients chose MET, they would receive 0.4mg tamsulosin daily and also necessary analgesics and examinations. We assumed that these patients may not require emergent hospitalization and would be given an opportunity to receive MET or pass their stone spontaneously as out-patients. This assumption was consistent with results in the above Chinese RCT which compared tamsulosin with placebo in treating large distal ureteral stones[3]. Those patients who did not pass their stones were assumed to undergo an outpatient URS. All the patients would receive computed tomography to confirm stone clearance at the end.

Rate of stone passage

We utilized the data from above-mentioned RCT comprising 2180 patients with distal ureteral stones between 5 and 7 mm to estimate the stones passage rates after receiving placebo or 0.4 mg daily tamsulosin[3]. The stones passage rates after receiving placebo or tamsulosin were 75% and 87% respectively.

Cost

In recent years, China has been committed to promoting the reform of the medical insurance payment system. According to the local economic level, local governments have formulated corresponding standards for diagnosis and treatment payment according to disease types. The cost of surgery and examinations of most patients can be calculated based on these published guidance pricing in relevant government website. According to the reports from national bureau of statistics of China (http://www.stats.gov.cn/english/PressRelease/201802/t20180228_1585666.html), 2017 per capita gross national product was ￥59660, while the 2017 per capita gross national product of Hubei province was ￥60199, which is the closest to the national level among all provinces. Therefore, the data from Hubei province was used on behalf of China. Because some provinces are still formulating their standards and we can't calculate the average cost directly. The costs were converted into US dollars with the exchange rate of 1 US dollar to 6.7 yuan. The cost of 'treatment', whether observation or tamsulosin, included the cost of drugs, examinations, test, and possible surgery after failure. We also assumed that all the patients who were failed to pass their stones would be treated with URS since it has much higher successful rate than ESWL in treating distal ureteral stones. The cost of initial diagnosis was excluded because it would be equal in the two groups. The complications were not included in the cost analysis due to the infrequent need for intervention. Those rare major complications, such as renal function failure, were also excluded from the cost analysis. Treatments were assumed to be performed in outpatient clinics. For MET, tamsulosin was used as assumed at a dosage of 0.4 mg daily. The dosage of analgesic (diclofenac sodium suppository) was less than one box in both groups according to the results of the previous RCT[3]. Therefore, the cost of analgesic in the two groups was equal and was not included. The cost of tamsulosin was calculated as an average of the costs obtained from local health system, including hospitals and pharmacies. Due to the lack of medical knowledge and the backwardness of community medical services, in order to ensure timely treatment for patients in the event of complications such as infection or renal function damage, patients were required to come to our hospital for weekly blood routine test, renal function test and ultrasonography during their treatment period. According to the pre-

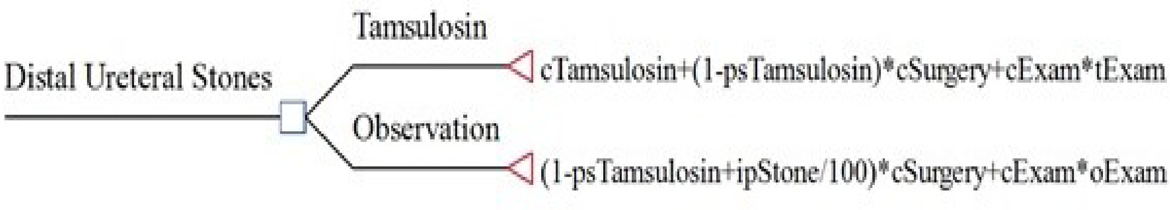

Figure 1: Decision analysis model. Model comparing the expected total cost of medical expulsion therapy (MET) versus observation. psTamsulosin: stone passage rate of MET; cSurgery: the cost of surgery; tExam: expected number of examinations; cTamsulosin_box: cost of tamsulosin per box; cExam: cost of each examination; ipStone: difference between stone passage rate of MET and observation; oExam: expected number of examinations for patients in observation group.

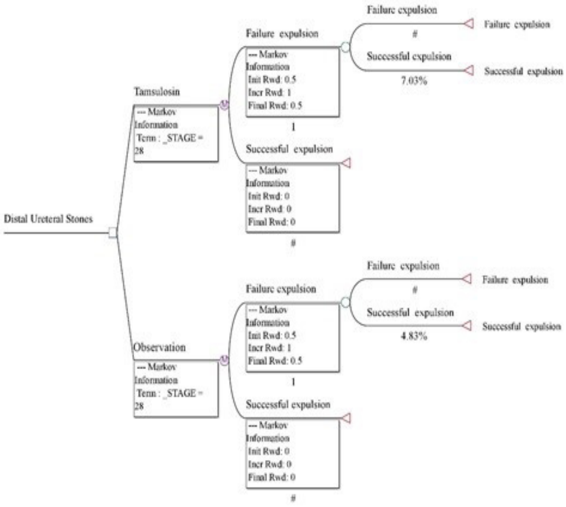

Figure 2: Markov model for estimation of stone expulsion time. Init Rwd: initial reward; Incr Rwd: increase reward.

viously mentioned RCT(3), the patients in MET group were expected to receive weekly examinations for 1 time (average stone expulsion time: 152.5h) and the patients in MET group were expected to receive weekly examinations for 2 times (average stone expulsion time: 299.5h). The indirect costs including travel and lost wages were not included. Because patients could go to hospital by local public bus and the fare is only $0.3. In addition, patients could continue working when colic pain could be tolerated by using analgesics. Therefore, the indirect costs were omitted.

Cost analysis

A decision analysis model was made to compare the costs of MET and observation for large distal ureteral stones (5 - 7 mm) (**Figure 1**). According to the assumption, the estimated costs of drugs, surgery, and examinations are included in the cost estimation. With linear success rate assumptions, a decision tree was constructed by TreeAge Pro 2011 software. For each arm of the model, the probability of stone passage and the costs associated with treatment including examination, MET, and URS was utilized.

Effectiveness analysis

The effectiveness of MET or observation was presented by QALD during a 28-day period and adjusted according to the study about health-related quality of life (HRQOL) of patients with ureteral stones treated by MET(5). After stone expulsion, HRQOL of patients was considered as normal. The HRQOL in that study(5) was evaluated by EuroQol-5D (EQ-5D), which is the most widely used multi-attribute utility (MAU) instrument for measuring HRQOL in cost-effectiveness analysis. The descriptive system of EQ-5D consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D index in that study(5) was used as HRQOL index in our study. The QALD equals to index of HRQOL times days with stone un-expulsed plus days with stone expulsed. The HRQOL index for patients in MET group and observation group during treatment was 0.8 and 0.72, respectively. According to the previously mentioned RCT(3), the average stone expulsion time of patients in MET group and observation group was 6.35 days and 12.48 days respectively.

Sensitivity analysis

By holding other parameters fixed, a one-way sensitivity analysis was performed to evaluate the effect of varying the cost of surgery on the expected total cost for both treatment modalities. It can also determine the point at which MET and observation were of equivalent cost in China.

Two-way sensitivity analysis was performed by evaluating the difference between the stone passage rate of MET and observation and the cost of surgery over a wide range of values to determine the most cost-effective therapy.

Tornado diagram was utilized to assess the effect of some parameters on the expected total cost of MET. These parameters included stone passage rate of MET, the cost of surgery, expected number of examinations, expected dosage of tamsulosin for a patient who succeeded in expelling stone, expected dosage of tamsulosin for a patient who failed to expel stone, and cost of

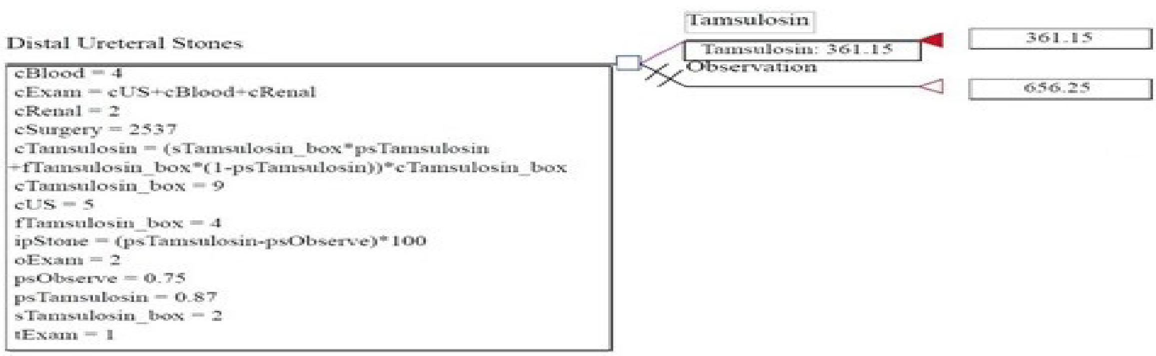

Figure 3: Cost analysis by decision model. cBlood: cost of routine blood test; cRenal: cost of renal function test; cUS: cost of ultrasonography; cExam: cost of each examination; cSurgery: the cost of surgery; tExam: expected number of examinations for MET; oExam: expected number of examinations for observation; cTamsulosin: cost of tamsulosin; sTamsulosin_box: dosage of tamsulosin(box) for patient who succeeded in expelling stone; cTamsulosin_box: cost of tamsulosin per box; fTamsulosin: dosage of tamsulosin(box) for patient who failed to expel stone; ipStone: difference between stone passage rate of MET and observation; psTamsulosin: stone passage rate of MET; psObserve: stone passage rate of observation.

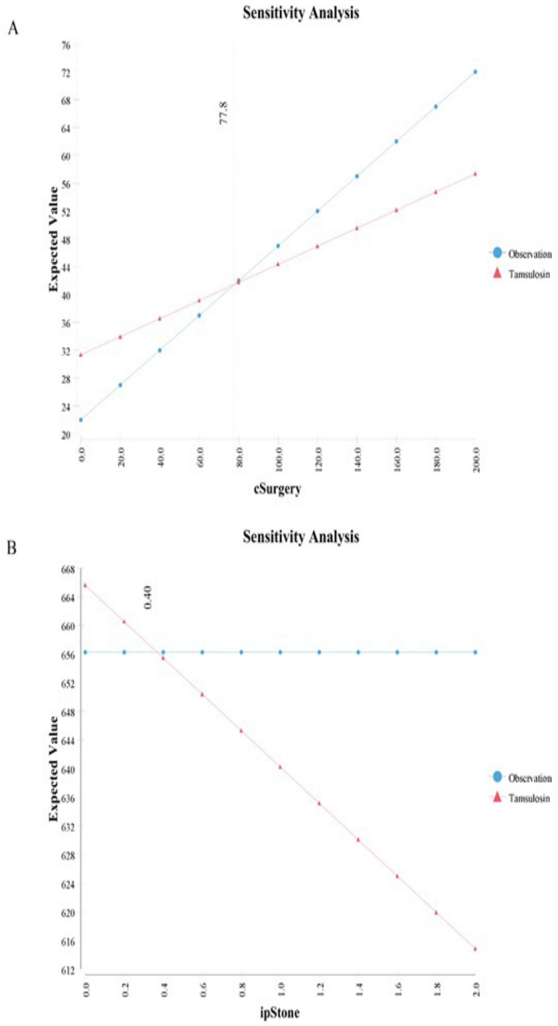

Figure 4: One-way sensitivity analysis. **A:** One-way sensitivity analysis varying costs of ureteroscopy. cSurgery: total cost of surgery. **B:** One-way sensitivity analysis varying difference between stone passage rate of MET and observation with constant stone passage rate of the observation group. ipStone: difference between stone passage rate of MET and observation.

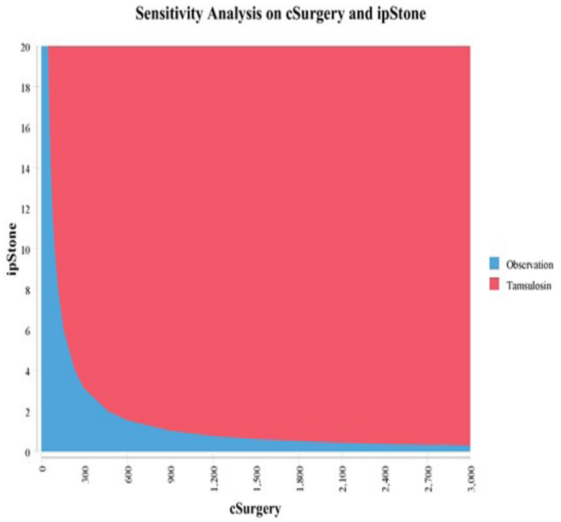

Figure 5: Two-way sensitivity analysis varying cost of ureteroscopy and the increased likelihood of stone expulsion with medical expulsion therapy. Blue area represents points at which observation is more cost-effective than medical expulsion therapy. cSurgery: cost of ureteroscopy. ipStone: difference between stone passage rate of MET and observation.

each examination and cost of tamsulosin per box.

Mathematical estimation of stone expulsion time

A decision-analytic Markov model was used to estimate the expected stone expulsion time mathematically, under the assumption that the daily stone expulsion probability was constant. The structure of the model is shown in **Figure 2**. Two discrete health states reflecting different characteristics of the disease were identified: failure stone expulsion and successful stone expulsion. In the Markov model, the cycle length was 1 day and the entry state was failure stone expulsion. During each 1-day cycle, the patients either remained in their assigned health state or progressed to a new health state, successful stone expulsion. The estimation of stone expulsion probability for treatment with tamsulosin or placebo was based on the results of our previous RCT[3]. Based on the Weibull model, stone expulsion rates for these treatment modalities were calculated at each cycle. With the assumption that the daily stone expulsion rate was constant, the daily stone expulsion rate p was defined as p = 1-exp{Pt}=1-e$^{\wedge(-Pt)}$

, where P is the instantaneous stone expulsion rate after t-day treatment duration. The rates are also shown in Figure 2. The estimated stone expulsion time was adjusted by applying half-cycle correction to achieve accurate estimation, which was performed by setting the reward in the initial and final cycle to 0.5.

RESULTS

Related data on cost is shown in **Table 1**. The cost of surgery was estimated to be $2537. Based on the assumption and the decision model, MET was associated with a $295.1 cost advantage over placebo ($361.15 vs $656.25 respectively) (**Figure 3**). Due to the dramatically high cost of URS ($2537) and the low cost of tamsulosin ($9), even a 1% greater likelihood of stone passage with MET made this strategy cost advantages. On the other hand, under the existing stone passage rates for MET and observation, the cost of URS had to decrease to $77.8 to reach cost equivalence ($41.45) between observation and MET (**Figure 4A**). The difference between the spontaneous stone expulsion rate of the two groups needed to decrease to 0.40% to reach the cost equivalence, when the spontaneous stone expulsion rate of patients in the observation group remained still. And the costs of the two treatment schemes would reach $656.25 (see **Figure 4B**). Therefore, due to the high cost of URS and the extremely low price of tamsulosin, the MET with tamsulosin had a cost advantage even if it only increased the stone expulsion rate by 1% compared with observation.

According to the effective analysis, during 28 days after the beginning of treatment, MET produced an average of 26.7 QALDs, compared to 24.5 QALDs receiving observation.

With varying differences between stone passage rate of

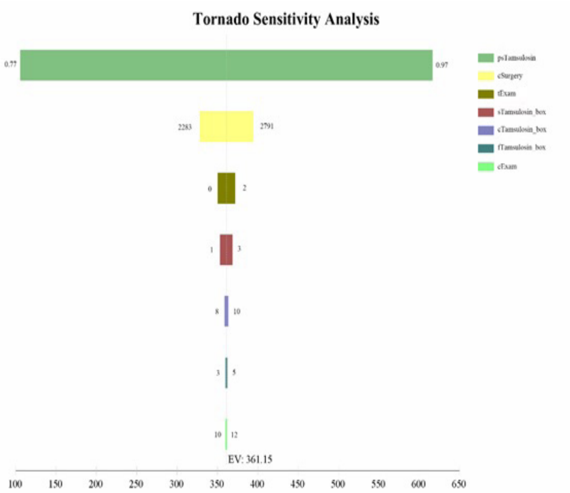

Figure 6: Tornado diagram representing the expected cost of medical expulsion therapy (MET). The vertical dotted line shows the baseline value of these parameters with expected cost of medical expulsion therapy equal to $361.15. psTamsulosin: stone passage rate of MET; cSurgery: cost of surgery; tExam: expected number of examinations; sTamsulosin_box: dosage of tamsulosin(box) for patient who succeeded in expelling stone; cTamsulosin_box: cost of tamsulosin per box; fTamsulosin: dosage of tamsulosin(box) for patient who failed to expel stone; cExam: cost of each examination.

MET and observation and the cost of surgery (Figure 5), observation was cost-effective only if URS was very cheap or the difference of stone expulsion rates between MET and observation was insignificant.

The tornado diagram (**Figure 6**) revealed that the expected total cost of MET was sensitive to some of the relevant parameters. These parameters varied within about 10% range from the baseline value. According to the diagram, the successful stone expulsion rate of MET was the most influential factor. Changing the dose of tamsulosin for patients expulsing stone successfully or the cost of URS could also influence the expected total cost of MET significantly. Other parameters, such as total dose or cost of diclofenac, showed little impact. Under the assumption that the daily stone expulsion probability was constant, the expulsion time, estimated by Markov model, was 11.94 days and 15.15 days for MET and placebo respectively (see supplementary **Figure 1**). Both of them were longer than those reported in above-mentioned RCT(3) (6.35 days and 12.48 days respectively).

DISCUSSION

Nearly 95% of distal ureteral stones would be expulsed spontaneously within 40 days if the stone is less than 4 mm, and a distal ureteral stone has a possible spontaneous expulsion rate of 25%–60% if its size is between 4 mm and 7 mm[6,7]. Obviously, it's necessary to find effective approaches to promote the stone expulsion, such as MET, ESWL, and URS. The optimal treatment of ureteral stones depends on the composition, size, location, number, and structure of the stone, as well as the presence of symptoms. For example, the spontaneous passage rate of stones less than 4 mm is far higher than stones larger than 6 mm[8]. In addition, the spontaneous rate of distal ureteral stones was the highest (45%), followed by the middle ureteral stones (22%), and finally the proximal ureteral stones (12%). Presence of mucosal edema, ureteral spasm or abnormal ureteral anatomy, and inflammation also affects stone expulsion[8,9]. URS is an invasive procedure that might cause more complications and costs than ESWL[10]. ESWL represents the least-invasive surgical procedure for stone management, but it is limited by shock wave-resistant stones (calcium oxalate monohydrate, brushite, or cystine), steep infundibular-pelvic angle, long skin-to-stone distance (> 10 cm) and narrow infundibulum (< 5 mm)(11-13). A meta-analysis including the publications addressed above assessed stone passage as the primary outcome[14]. It concluded that ARBs promote spontaneous stone expulsion of large stones (> 5mm) located in any part of the ureter. Therefore, MET might be a feasible treatment when the size of the stone was between 4 mm and 7 mm. Even some studies reported that MET is suitable for patients when the size of the stone was between 5 mm and 10 mm[15,16].

The role of ARBs in MET was well described[17-20]. Current best practice guidelines recommend ARBs for the expulsion of distal ureteral stones > 5mm. Both the EAU and American Urological Associations (AUA) guidelines outline the role of ARBs as a viable option for distal ureteral stones. Patients treated with ARBs had a 65% greater likelihood of spontaneous stone passage and a pooled risk ratio of 1.54 (95% CI = 1.29–1.85) compared to those not given ARBs ($P < .0001$) when the mean stone size ranged from 3.9 to 7.8 mm[18]. Tamsulosin was the most studied ARBs in MET. Moreover, a RCT demonstrated that tamsulosin, terazosin, and doxazosin were equally effective in distal ureteral stones expulsion in comparison to hydration[21]. But more large-scale studies are needed to further validate this conclusion. Three α1-adrenoceptor subtypes have been identified, α1a, α1b, and α1d, by functional, radioligand-binding, and molecular biological techniques. In 2011, Sasaki showed that expressions of α1-adrenoceptor messenger ribonucleic acid are different in the distal ureter (α1d > α1b >α1a), middle ureter (α1d > aα1a > α1b) and proximal ureter (α1d > α1a > α1b) (22). Furthermore, the distal ureter expressed a higher density of alpha1-receptor than other ureteral regions. As α1-adrenoceptor is likely to maintain ureteral tonus and resistance to stop ureteral calculus from being expulsed, blocking α1a and α1d with tamsulosin might account for the impressive expulsion rate of ureteral stones. In addition, a study by Itoh Y and colleagues showed α1a, α1b and α1d subtypes in Japanese accounted for about 38%, 8%, 54% of total AR mRNA in the ureteral region, respectively[23]. However, another study by Sigala et al. showed three α1-adrenoceptor subtypes in Italians accounted for about 28%, 24%, and 48%, respectively[24]. It means that the distribution of α1-adrenoceptor subtypes in human ureter varies among different populations. Therefore, it is of great significance to analyze the cost-effectiveness of MET with ARBs in different populations.

In 2008, Karim Bensalah et al. published a study on European Urology about the cost-effectiveness of MET using ARB for the treatment of distal ureteral stones in Euro-American countries[25]. They made a meta-analysis of relevant studies in these countries to obtain the rate of spontaneous stone passage. And the cost of URS

($4773) in the United States was derived as the mean cost of 121 consecutive cases at a large metropolitan hospital. The rate of spontaneous stone passage in our study came from a large RCT with high quality and cost estimation was close to the reality of most patients because of our pricing policy. According to our results, even in the developing country with a lower cost of URS and medical examination, MET still has cost advantage over observation even with 1% stone expulsion rate enhancement.

With the rapid rise of health care expenditures in China, more and more people are paying attention to cost-effectiveness. Therefore, medical decision-making is increasingly affected by economic factors. Conservative treatment seems cheap, but it may be more expensive than first-line URS because of the loss of more workdays or the need for more frequent office or hospital visits. The 2017 daily average per capita gross national product of China was about $35.6. Therefore, the lost income is also significant.

In the current study, we found that MET has more cost advantages over observation. In addition, the presence of ureteral stones will affect HRQOL of patients, making the patient unable to work properly. Nowadays, Wisconsin Stone Quality of Life questionnaire (WISQOL) is widely used in evaluating HRQOL of patients who are attacked by urolithiasis. It is designed for patients with urolithiasis to measure their disease-specific, health-related quality of life[26]. A study including 1609 samples at 8 geographically diverse centers in the United States and Canada demonstrated that WISQOL is internally consistent and externally valid(27). WISQOL should be utilized in the assessment of HRQOL of patients treated with MET in the future.

Our study, like most studies, set the duration of therapy as 28 days. But there is also various duration, such as 14 days, 21 days, and so on. In the Markov model, we calculated the expected stone expulsion time under the assumption of constant daily stone expulsion probability. However, we found there was a great difference between the actual average stone expulsion time and what we calculated. Therefore, the daily probability of stone expulsion is not constant, most patients expulsed stones at the front half of the treatment duration. Ibrahim et al. also reported that half of the stones in patients received tamsulosin passed within 2 weeks while the stone expulsion rate was only 35% in the next two weeks[28]. Therefore, it may be of great significance to make cost-effective analysis weekly.

There were several limitations in our study. First, we did not include the cost associated with complications of URS. However, this additional cost would also favor MET because it is associated with a reduced need for surgery. Second, costs vary enormously among different provinces depending on the country's healthcare system. Third, all patients were assumed to receive URS after MET failure, while some of them might have received ESWL. Finally, the assessment of HRQOL involved in our study was based on a study in Turkey, not China.

CONCLUSIONS

In China, due to the high cost of URS, MET showed a cost advantage over observation in treating distal ureteral stones. By applying Markov model, the daily stone passage rate was proved to be inconstant, most patients expulsed stones at the front half of treatment duration. More studies are needed to find the appropriate duration of MET.

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