ORIGINAL ARTICLE

MEDICAL EXPULSIVE THERAPY FOR URETERAL STONES; BEYOND ALPHA BLOCKERS & STEROIDS

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ABSTRACT

Objectives: To Know the Medical Expulsive Therapy for Ureteral Stones; Beyond Alpha Blockers & Steroids.

Material and Methods: This prospective cohort study was carried out to see the effects of adding Serratiopeptidase to the already established drug therapy, 'alpha blockers' in patients with the ureteral stones size from 05mm up to 10mm, for the medical expulsion therapy. It consisted of a total of 80 patients. There were 63 male patients (78.80%) as compared to 17 female patients (21.30%). The mean age of the patients was 25.80 ± 06.43 years (Range = 15 to 41 years).

Results: In our study the stones were cleared in a total of 68 patients (Total stone clearance = 85.00%). IVU was carried out in 12 patients (15%). The stones clearance was achieved in 08 patients (10%) by Extra Corporeal Shock Wave Lithotripsy (ESWL) and four patient needed surgical intervention (5%). A total of 12 (15%) patients had failed attempt at MET.

Conclusion: Majority of the clinicians accept the effectiveness of the anti inflammatory and analgesic properties of serratio-peptidase & this role can be exploited in the medical expulsion therapy of the ureteral stones substituting steroids.

Key Words: Urolithiasis, Alpha blockers, Serratiopeptidase, Steroids, Medical expulsion therapy.

This article may be cited as: Afridi Z, Khan AR, Haleem A, Kamran K, Ahmed I, Tanoli R. Medical expulsive therapy for ureteral stones; beyond alpha blockers & steroids. J Med Sci 2017; 25: (4) 446-451.

INTRODUCTION

Urolithiasis is a worldwide problem andhas been known since ancient times. The management that changes the outcome of this problem has a huge economic burden since in almost half the cases, the stones recur. The first aim of managing these stones is to relieve the patients of the acute painful condition. While at the same time focusing on preserving the kidney function by relieving the obstruction. The spontaneous stone passage rate varies according to various studies but generally those of 2 mm or less pass 100% and only 1% of those 6mm or more. In general the recommendations for ureteral stones of stones smaller than 1cm are of watchful waiting for about a month in those, having no high grade obstruction, sepsis or severe pain. And if the stones do not pass by approximately 2nd month, then they need more aggressive management. The invasive modalities to treat these stones have their own complications and their availability is also a problem at various places. So to aid the stone expulsion during the watchful waiting period, various pharmacological agents have been tried. These are being used since long times, with varying results. These drugs include alpha blockers, steroids, calcium channel blockers and phospho diesterase 5 inhibitors. The steroids have gained attention because of their anti inflammatory and anti edema properties for relieving the inflammatory swelling of the ureteral wall at the stone impaction site. And when combined with the alpha blockers to expedite the rate of stone expulsion, has been found effective. However the results of steroids in isolation for the medical expulsion of ureteral stones have not been validated. Having the same concept and similar anti edema action along with the added benefit of analgesia, the serratiopeptidase can be used in combination with alpha blockers, very effectively in the medical expulsion therapy of ureteral stones without the risk of the many known adverse effects of the steroids.

The urinary tract stones have been known to humanity since the ancient times[1] and the people world-

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Date Received: March 3, 2017
Date Revised: September 18, 2017
Date Accepted: November 20, 2017

wide are affected with a prevalence of up to 5%[2]. The cases are on the increase allover and variations in race and gender are observed. It is estimated that in almost half the cases, the stones may recur in five years, after the first presentation[3]. This usually adversely affects the life of the patients and their productive working days. So considering the trouble and huge financial burden of surgical intervention, the inclination towards the medical treatment becomes an acceptable alternative.[4] Though there has been progress and increasing availability of various interventional modalities, like minimal invasive endoscopic techniques and extra corporeal short wave lithotripsy (ESWL) for the management of ureteral stones but no significant progress in the medical management of urolithiasis has been made.[2]

The stones in the ureter, can get impacted at the three anatomically narrow portions; 1). At the uretero-vesical junction 2) at the pelvic brim and 3) Uretero-pelvic junction, causing obstruction and severe colicky pain.[5] This is the time to relieve the patients of pain first and then further manage the stones to aid their expulsion. Narcotics analgesics and non steroidal anti-inflammatory agents are the routine drugs used during the acute attack of colic.[6] But these drugs have to be used with caution to avoid their undesirable effects. Moreover, the obstruction also needs to be relieved for preservation of the renal function. While the pathophysiological mechanism is that the impaction of these ureteral stones also cause to increase the local production of lactic acid and impaired ureteral smooth muscle contraction causing localized edema of its walls, aggravating the obstruction even further and hence severe pain.[7] Generally stones of one millimeter size spontaneously pass in 87% while those of 5-7 millimeter in 60% and the up to 9 millimeter in 25% cases.[8] Whereas some sources mention the spontaneous stone clearance rate to be 100 % for those up to 02 millimeter size and only 1% for those larger than six millimeter size.[9]

Various methods and drugs have been suggested after trials to aid ureteral stone expulsion for long times. One of these being drinking of increased water and other liquids since ages. The increased amount of urine production was believed to increase the ureteral pressure forcing the stones to pass out.[10] And the current medical literature also advocates the role of various other drugs to aid expulsion of the ureteral stones in the early management as a part of non surgical treatment options. The agents studied so far are, alpha and the calcium channel blocking drugs, the steroids, and others like phosphodiesterase-5-inhibitors. But of all these agents, the alpha blockers have so far been the only and most commonly proposed drug, which can be used alone. While the role of steroids has gained more popularity recently as a possible addition to it to help the ureteral stones to pass spontaneously.[11]

However, the cases of the failed Medical expulsion therapy (MET) have to be referred for the more aggressive interventional modalities. But the most suitable method to treat these ureteral stones has yet to be defined.[12] Though, it has been observed that ESWL can safely tackle the stones up to 1 cm size and is more safe and less invasive as compared to the endourological methods. But if the stone size is larger or multiple, the ureteroscopy (URS) seems to be more effective.[12]

Whereas, our study is an attempt to identify the role of other agents beyond alpha blockers and steroids in the medical management of ureteral stone expulsion therapy. No other study to date has tested Serratiopeptidase in the medical expulsion therapy of Ureteral stones.

MATERIAL AND METHODS

This prospective cohort study was conducted in Khyber Teaching Hospital (KTH), Peshawar, Fauji Foundation Hospital (FFH), Rawalpindi and Institute of Medical Sciences (PIMS), Islamabad, Pakistan, between April, 2009 until December, 2015. One hundred, otherwise healthy patients from 15-45 years of age were randomly selected on the basis of their diagnosis of unilateral Ureteral stones from Pelvi-ureteric junction(PUJ) until Vesico-ureteric junction (VUJ) with the size of stones from 05 mm to 10mm as diagnosed X-ray- KUB (kidney, ureter and bladder) and on ultrasound (US) scanning.

Bilateral normal renal cortical thickness on U/S and normal urea/creatinine levels were regarded as selection criteria. All the patients with sepsis, previous urological surgery or history of urolithiasis, deranged renal function, high grade obstruction, no stone visualization on Ultrasound and X-ray KUB, hypertension, ischemic heart disease, diabetes mellitus, solitary kidneys, peptic ulcer disease and those with no second visits or subsequent follow ups were excluded along with those who could not tolerate the pain.

All of the patients were put on alpha blocker (Tamsulocin 0.4mg) once a day initially for two weeks and later continued until 04 weeks, serratio-peptidase (10mg TID) for 05 days and later prescribed for another 05 days if needed. Non-steroidal anti-inflammatory (Diclofenac Sodium with the maximum dose up to 150mg daily. Paracetamol (500 mg to 01 gram TID) was advised in case the patient needed additional analgesia. All patients included in the study were put

on Quinolone group of anti-biotics for 02 weeks and dose adjusted accordingly. The patients were advised not to take anti-cholinergics until the pain was not relieved by the above remedy. They were advised to take normal fluid for three days and then increase the fluids intake until the stone passed or 3 weeks initially and then review. The patients were also counseled and encouraged for sports, jolting or skipping from 4th day onwards to facilitate the stone passage. The patients' statement of experiencing the stone passage or no visualization of stone on U/S scan on the subsequent visits were regarded as stone clearance. IVU was done only if there was no stone passage in the follow up, as observed on US. The results were compared with those in the literature.

RESULTS

There were 80 patients, who completed the study and follow up of 04 weeks. The results were gathered and compiled. 63 were male patients (78.80%) as compared to 17 female patients (21.30%). The mean age of the patients was 25.80 ± 06.43 years (Range = 15 to 41 years). In our study the stones were cleared in a total of 68 patients (Total stone clearance = 85.00%). Whereas, Intra Venous Urogram (IVU) was carried out in 12 patients, stone clearance was achieved in 08 (10%) patients with extra corporeal shock wave lithotripsy (ESWL) and in four (5%), the stone clearance was achieved by URS. Hence, a total of 12 patients required referral for further intervention.

Left sided stones were more commonly encountered in the current study. A total of 56 patients had left sided stones (70.00%) whereas 24 patients had right sided stones (30.00%). The mean size of the stone was 07.20 ± 01.35 mm (Range = 05mm to 10 mm). Most of the patients presented with solitary stone, 45 patients (56.30%). Two stones were noted in a total of 33 patients (41.30%) whereas only two patients had three stones (2.5%). Analysis of stone location demonstrated that in 59 patients (73.80%) the stones were located in the upper ureter while in 19 patients (23.80%) the stones were in the lower ureter. The middle ureteric stones were seen in only two patients (2.5%). The average time to stone expulsion was 02.12 ± 0.18 weeks.

DISCUSSION

Ultrasound has a definite role in the preliminary assessment of patients with suspected obstructing urinary calculi. And once the obstruction is diagnosed, IVP may be substituted as an elective investigation or even omitted13, if no other problem. Since Pakistan, being a developing country has poor health facilities with an over burdened health system and IVP and other modalities have their own cost and effects. Therefore, we reserved it for those cases in which the stone passage or movement was not observed on ultrasound in the subsequent follow up visit. The European and American urological associations recommend to wait and watch all those stones less than 1 cm in size who have well controlled pain.[14] Since most of the lesser size stones pass in almost a month time and those which do not pass in two months times are usually unable to pass spontaneously.[15] Whereas, all those patients who have poor renal function, severe infection, uncontrolled pain, and high grade obstruction should be put off the watchful waiting list and referred for urgent surgical intervention.[16] Moreover, the open surgical techniques, though have been largely substituted by the now considered gold standards minimally invasive methods like extracorporeal shock wave lithotripsy (ESWL) and endourological procedures. However, these invasive modalities have their own cost and complications along with their availability, which is also a problem in the countries with poor health facilities.[17] Therefore, medical expulsion therapy is still being evaluated and studied during the watchful waiting period to aid the expulsion of ureteral stones. But the results of these agents are usually unpredictable and variable. And since edema and spasm of the ureter is thought to block the stone movement, so to overcome this hindrance, various drugs abolishing these effects have been studied. In this regard, the most common drugs studied and evaluated so far are; alpha and calcium channel blockers, steroids and non steroidal anti-inflammatory drugs.[18]

As far as the role of the steroids is concerned, some authors have studied their effectiveness in combination with alpha blockers or calcium channel blockers in medical expulsion therapy (MET) of ureteral stones. The steroids are used for their anti-inflammatory and anti edema action for reducing the swelling of the ureteral walls at the stone impaction sites. But a problem with steroids is that, these cannot be used for prolonged periods because of their adverse effects. Since these can cause stomach ulcers, aggravate diabetes, and suppress the immune system with chances of aggravating urosepsis. Though found beneficial in combination with other agents, the effects and benefits of the steroids used alone are still not clear.[11] And because of their potential of causing the side effects, makes them a choice in MET for very limited and selective patients.

In our study, we used Serratiopeptidase instead of the steroids and achieved the stone clearance of 85% with the mean size of the stone being 07.20 ± 01.35 mm, and the average time to stone expulsion being 02.12 ± 0.18 weeks. While Hwang and colleagues,[19] used steroids in combination with alpha blockers, in

ureteral stones of less than 10 millimeter by randomizing their patients into two groups; One group with 10 mg Alfuzosin and 8 mg Methylprednisolone and the other control group with pain killers only. And they concluded that the former regimen was more effective by increasing the stone passage rate and decreasing the time to expulsion significantly. While in an effort to find an ideal agent for MET, a study by Dellabella M et al[20] in a trial used three different agents in 210 patients. These were Nifidipine, Tamsulocin and Phloroglucinol. And to enhance the efficacy, they categorically gave steroids to all of their patients. Their stone clearance rates were; 97.1% in the Tamsulocin group in comparison to the Nifidipine (77.1%) and Phloroglucinol (64.3%) respectively. In another study, during the watchful waiting period, the patients were randomly divided in three groups. One received Tamsulocin, the second group was put on Deflazocort plus Nifidipine, while the third placebo group was used as control. They observed stone clearance of 85% in group one (Tamsulocin only), 80% in group two and 43% in the third group. While the average stone sizes in the study were; 5.42mm (group 1), 4.7mm (group 2) and 5.35mm (group 3) respectively.[21] Interestingly, the mean stone size in the Tamsulocin group was larger than the rest of the two groups but much smaller, as compared to ours.

And when it comes to choosing among the alpha blockers, Agarwal M and associates[22] compared two alpha blockers; Tamsulocin and Alfuzoscin with a placebo in 102 patients. The average stone size in group one (6.17mm), group two (6.70mm) and the placebo group (6.35mm). While they achieved stone clearance of 82.3%, 70.5% and 35.2% and the average stone expulsion time was 12.2, 14.5 and 24.5 days, respectively. Comparing with our results, we had almost the same average time of stone expulsion but with a relatively larger average size of the stones (07.20 ± 01.35 mm) in our patients, when Serratiopeptidase was combined with Tamsulocin. Moreover, the stone clearance was achieved in 82% of Tamsulocin group Vs 61% in the placebo controls by Al-Ansari A and associates23. They observed that the chances of stone expulsion were three times higher with the alpha blocker. In addition, they concluded that the alpha blocker was more effective in the stones smaller than 5 mm as compared to those of the larger size. And De Sio M et al,[24] in a series of 96 patients, compared Diclofenac plus Aescin with alpha blocker (Tamsulocin) and found the later much superior with 90% stone clearance as compared to 58.7% in the former. While in a study by Porpiglia F and colleagues,[25] they examined the effects of steroids in combination with alpha blockers. The patients were put on Tamsulosin + Deflazacort daily and they found the stone expulsion rate to be 84.8%. While the mean stone size in their study ranged from 5.71 to 5.96 mm. Interestingly, the average stone size in our study is yet again larger than the study mentioned. But their stone clearance rate was almost the same as ours. This shows that, a proper drug combination with an alpha blocker (Tamsulocin) can be really effective in the clearance of less than 10 mm sized ureteral stones. Interestingly, in another meta analysis of 55 randomized controlled trials, comparing a placebo with alpha blocking drug, found evidence favoring the role of the role of the later in facilitating the expulsion of these ureteral stones.[26] And they observed more benefit among those patients, with relatively larger size stones. Hence, these results support the current clinical practice of MET, advocating an effective role of pharmacological agents in patients with ureteral stones to aid expulsion.

However, to know the effectiveness of medical expulsion therapy, some recent large scale studies[27,28] conducted, showed that there is a growing skepticism about the role of Alpha and Calcium channel blockers. In one of these two trials, Pickard R and associates[27] in their multicentre, randomized, placebo-controlled trial, evaluated 1136 adult patients having a single stone. They used selective alpha and calcium blocker and found them to be ineffective in clearing the stones after waiting for a month. Whereas, the Suspend28 trial also concluded that there was no benefit to using tamsulosin or nifedipine in MET, compared to placebo. The primary outcome to look into the effectiveness of MET was spontaneous passage of stone, confirmed radiologically or the patient declaring that a stone was passed per urethra. The Suspend trial used lack of surgical intervention as a proxy for its primary outcome. But to refute these two trials, yet another systemic review of 47 Randomized Control Trials of MET by Seitz C et al10 found out strong evidence in favor of alpha and calcium channel blockers in expediting the stone expulsion and decreasing the analgesic requirements especially for stone less than 10mm size. Moreover, they also observed that combining alpha blockers with steroids showed better results than using the alpha or calcium channel blockers alone.

Stone is a three dimensional structure and its passage depends not only upon its maximum size but its shape and location, as well as the associated ureteral wall edema, which is likely to depend upon as for how long it has remained impacted.[29] And when measuring the size of the stone, only its maximum dimension is considered, ignoring it being a three dimensional structure. In the same context, we also observed in our study that even the relatively larger stones passed with MET. And we have the opinion that, it is not only the overall size but the shape is also an important factor in determining the expulsion

or impaction of the ureteral stones. However, our regimen seemed less effective in clearance rate, when the stones were two or more. And most of the cases which needed intervention were from these patients. In the same context, it is noteworthy to mention that the Serratiopeptidase is being used in many clinical disciplines for its anti-inflammatory, anti-edemic and analgesic effects.[30] Although it is not licensed for the MET of ureteral stones, but the concept of the use of Serratiopeptidase was adapted from the use of steroids for the same purpose, with the added advantage of analgesia and reduced risks of aggravating urosepsis. Since it has potent anti inflammatory action and can reduce the post traumatic swellings. In addition, it has the ability to dissolve the blood clots, plaques and dead tissues. And these roles of Serratiopeptidase have been exploited in many clinical trials showing it to be very beneficial by mobilizing the scar tissue and reducing the post surgical and traumatic edema. More over it can also decrease the release of chemical mediators of pain by the inflamed tissues. In addition, there are no major adverse effects noted with its use.31 Whereas, we observed that the Serratiopeptidase, if combined with alpha blocker (Tamsulocin) may give very encouraging results and it can be used safely for the MET of the ureteral stones instead of steroids without facing the undesirable effects of the later.

The ureteral colic is a very painful and common condition, so simpler remedies that would alter the course of the disease, saving the patients from the trouble and making spontaneous expulsion of the stones more likely are still required. And there is strong a urge to identify other alternative pharmacological agents.[32] While the debate on the efficacy of the various agents goes on, it has been established that the MET not only expedites the stone expulsion, but are safe as well. And in addition significantly reducing the need for analgesia in these patients, as shown by various studies.[20-24]

LIMITATIONS

The present study has some limitations. First, the exact and precise measurement of stone size could to be validated, as we relied on the simple visual estimation of the largest stone size as measured on Ultrasound and simple x-ray KUB. Second, we did IVU only if the stone movement or passage was not observed on Ultrasound. And lastly no randomization was done as case controls.

CONCLUSION

Serratiopeptidase can be very useful addition to the already established alpha blocking agents for the increased ureteral stone clearance, if used instead of steroids or any other agents.

RECOMMENDATIONS

This is the first study to test the Serratiopeptidase in MET of the ureteral stones and showed encouraging results. We therefore recommend further evaluation of the drug (Serratiopeptidase) in MET of the ureteral stones through more randomized controlled trials.

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CONFLICT OF INTEREST: Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE NIL

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Afridi Z: Planned the study.
Khan AR: Statistical analysis.
Haleem A: Manuscript writing.
Kamran K: Data collection.
Ahmad I: References.
Tanoli R: Biblopgraphy.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.