

Facilitative Effects of Add-on Therapy with Tadalafil in Stone Passage After Shockwave Lithotripsy; A Randomized Clinical Trial

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Research Article

Keywords: SWL, urolithiasis, Tadalafil, Tamsulosin

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11142891/v1>

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Additional Declarations: No competing interests reported.

Abstract

Objective

Extracorporeal shock wave lithotripsy (SWL) is a key treatment for urinary stones, breaking them into fragments that can be naturally passed. Our goal was to evaluate the effectiveness of adding tadalafil to Tamsulosin for improving stone expulsion after SWL.

Methods

After SWL, 160 patients with kidney or proximal ureter stones were randomly divided into two groups. One group received Tamsulosin and a placebo, while the other received Tadalafil and Tamsulosin. They were compared based on stone-free status, pain duration and intensity, hematuria, analgesic use, and remaining stone size.

Results

160 patients (mean age 47.16 ± 14.37 years; mean stone size 11.87 ± 3.88 mm), the mean stone passage time after shock wave lithotripsy (SWL) was 2.56 ± 1.05 days in the treatment group and 2.80 ± 1.17 days in the control group ($P = 0.180$). Pain duration post-SWL was similar, with the treatment group experiencing 2.66 ± 1.68 days and the control group 2.07 ± 3.03 days ($P = 0.226$). The total pain score was significantly lower in the treatment group (5.80 ± 5.02) than in the control group (8.57 ± 8.44) ($P = 0.019$). Patients taking tadalafil had hematuria for 2.55 ± 1.52 days, compared to 3.13 ± 1.54 days in the control group ($P = 0.018$). There were no significant differences in analgesic use duration, residual stone size, or other side effects ($P = 0.207$ and $P = 0.408$). Stone-free status was achieved in 49 patients (61.3%) in the control group and 53 patients (66.3%) in the treatment group ($P = 0.511$).

Conclusion

Adding Tadalafil to Tamsulosin does not affect stone passage; however, it decreases pain and hematuria after SWL with negligible additional side effects.

Clinical Trial Registry:

The study was registered in the Iranian Registry of Clinical Trials (IRCT) with registry number of IRCT20240515061806N1 on 2024/08/07.

Introduction

Urinary stones or urolithiasis affects one in every 11 people in the United States, hence, is accounted as a prevalent disease that can present with significant pain and dangerous sequelae [1]. This condition imposes an annual DALY (Disease-Adjusted Life Years) of 0.6 million years [2]. The migration of renal stones is accompanied by flank pain that usually prompts medical management with analgesics [3, 4]. However, in case of larger stones medical expulsive therapy can be utilized. The most commonly used agent for Medical Expulsive Therapy (MET) is oral Tamsulosin [5, 6]. For stones larger than 10 mm procedural interventions are required [3].

There are multiple procedures such as Extracorporeal Shockwave Lithotripsy (SWL), ureteroscopy, and Percutaneous Nephrolithotomy. SWL is commonly used in stones smaller than 15 mm, with a density less than 800 Hounsfield Units (HU), and a Stone-to-Skin Distance (SSD) of less than twelve centimeters. [7]. In this method, high-energy shock waves are exerted on the stone breaking it into smaller fragments that are then spontaneously expelled from the urinary tract [8]. In some centers, alpha-blockers like Tamsulosin are prescribed after SWL [9]. Novel studies have shown that Phosphodiesterase inhibitors (PDEIs) can also be used. [10–13].

Tadalafil, (a Phosphodiesterase-5 Inhibitor) has shown efficacy in distal ureteral stone expulsion [10]. Previous literature has revealed that this drug combined with Tamsulosin can enhance SWL results in stones less than 20 mm located in lower calyx, reducing further surgical interventions and complications [14]. However, to implement such results in clinical guidelines, further research is needed; Herein, we aim to compare the efficacy of Tamsulosin and Tadalafil versus Tamsulosin alone in stone expulsion after SWL.

Methods and materials

This study followed a double-blinded, placebo-controlled parallel randomized clinical trial protocol with 1:1 ratio. The target population was patients with urinary stones referred to urology clinics or emergency departments of Kerman University of Medical Sciences.

Based on a similar study by Neeli et al. [14] for comparison of Tamsulosin alone or in combination with Tadalafil in stone expulsion after SWL, considering a type I error of 0.05 and a study power of 80%, and a drop-out rate of 5%, the minimal sample size for the study to be statistically reliable would be 80 in each group (160 patients in total). The following formula was used in this calculation:

$$\left(Z_{\frac{\alpha}{2}} + Z_{\beta} \right)^2 \left[\frac{p_1(1 - p_1) + p_2(1 - p_2)}{(p_1 - p_2)^2} \right]$$

$$p_1=0.725, p_2 = 0.901$$

The inclusion criteria were: Patients above 18 years old, with urinary stones of 5–20 mm in the kidney or the proximal ureter, having a normal renal function tests and coagulation panel. The exclusion criteria in our study were: Patients younger than 18 years old, pregnancy, coagulation disturbances, creatinine

clearance less than 50 mL/min, hepatic impairment, need of emergent surgical intervention for urinary obstruction, having a positive urine culture, patients with coexistent multiple ureteral stones, Stone-to-Skin distance more than 12 cm, previous history of unsuccessful SWL, history of uncontrolled hypertension, ischemic heart disease, use of nitrates, having a systolic blood pressure less than 90 mmHg at the time of presentation, cataract, history of hypersensitivity to Tamsulosin or Tadalafil, severe back pain or gastrointestinal problems during treatment, priapism, unwillingness to participate in the study or lack of adequate cooperation.

After proper explanation of the study course, a written consent including statements about anonymity, voluntary participation, and the right to withdraw from the study was sought from the patients, those who fulfilled the study criteria entered the study. The patients were informed that they could exit the study as they wished and it was asserted that the authors would be responsible for any adverse reaction to the treatment. The patients were asked to collect their urine in translucent containers and evaluate their urine regarding color and stone expulsion. The patients were also asked to register their pain level and use of analgesics in a form.

Participants were instructed how to use a visual analogue scale and for assurance of complete and correct filling of the forms frequent calls were made with the patients. Patients were instructed to visit the urology clinic in case of any adverse effects including fever, headache, hypotension, fatigue, dermatologic rash, intractable nausea and vomiting, decreased urinary volume, severe flank pain, and possibility of pregnancy.

The Dornier HM3 Lithotripter (Dornier MedTech, Wessling, Germany) was used. Shockwaves were delivered at a rate of 60–90 shocks/min to a maximum of 3000 shocks per session. The therapeutic power was started from 12 kV and increased stepwise up to 18 kV. Stones were fragmented under fluoroscopic/ultrasonic guidance.

After SWL, participants were randomly divided into two groups using www.randomization.org website and by a permuted blocks method using blocks of eight-patient size. The sequences for the patient groups were written on paper and placed in envelopes to ensure allocation concealment. One of the groups received 0.4 mg of Tamsulosin every night and 5 mg of Tadalafil every day and the other group received 0.4 mg of Tamsulosin every night and a placebo every day. All of the drugs were handed over to patients in containers labeled A and B. The placebo was made by the Pharmacy School of Kerman University of Medical Sciences with physical attributes the same as Tadalafil. Only the pharmacist knew about the ingredients of each container and the patients and urologist were ignorant of this matter.

After two weeks, the patients were asked to visit the clinic once again as their follow-up visit. The patients were evaluated again using renal function tests and spiral abdominopelvic CT scan to assess Stone-free status. Stone-free status was defined as a lack of stones larger than 3mm in patients as assessed by a CT scan. The forms of pain level and stone expulsion were collected in the follow-up visit.

The data were then entered into IBM SPSS version 24.0 for statistical analysis. The qualitative variables were reported as frequency and percentage and the quantitative variables were reported as mean and standard deviation. Comparison was done using chi-squared test for qualitative variables and independent two-sample T test or Mann-Whitney U test for quantitative variables as appropriate. P-values less than 0.05 were considered statistically significant.

This prospective study respected the principles of the Helsinki Declaration of Ethics in Biomedical Research. The study was conducted with the approval of the ethics committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1403.050). The trial was also registered in the Iranian Registry of Clinical Trials (IRCT) with registry number of IRCT20240515061806N1.

Results

In the study period from March 2023 to March 2024, 893 patients with urinary stones were evaluated, of whom 249 patients needed SWL. From these 249 patients 38 patients were excluded due to comorbidity, concomitant infection, obstructive uropathy, young age, pregnancy, or morbid obesity. Furthermore, 48 patients did not consent to participate in the study, and three patients did not refer for their follow-up visit. Figure 1 shows the flowchart of the study population. A total of 160 patients entered the study of whom 98 patients (61.3%) were male and 62 (38.8%) were female. The mean age of the participants was 47.16 ± 14.37 years old. eight patients in the Tamsulosin group and nine patients in the Tamsulosin and Tadalafil group had two stones. Table 1 summarizes the baseline characteristics of the study population.

Table 1
Basic variables compared between the two study groups

variable		Tamsulosin	Tamsulosin and Tadalafil	P-value
Gender	Male	51 (63.7%)	47 (58.8%)	0.516
	Female	29 (36.3%)	33 (41.3%)	
Number of stones	One	71 (88.8%)	70 (87.5%)	0.807
	Two	9 (11.2%)	10 (12.5%)	
Stone location	Upper calyx	3 (3.4%)	4 (4.4%)	0.942
	Middle calyx	12 (13.5%)	13 (14.4%)	
	Lower calyx	20 (22.2%)	18 (20.2%)	
	Renal pelvis	33 (37.1%)	28 (31.1%)	
	Proximal ureter	25 (27.8%)	23 (25.8%)	
Side of stone	Right	44 (49.4%)	34 (37.8%)	0.116
	Left	45 (50.6%)	56 (62.2%)	
Previous operation		15 (18.8%)	20 (25.0%)	0.339
History of hypertension		9 (11.3%)	12 (15.0%)	0.482
History of diabetes		8 (10.0%)	9 (11.3%)	0.798
Age		46.85 ± 14.562	47.46 ± 14.252	0.788
Stone size		11.56 ± 3.665	12.18 ± 4.079	0.289

After SWL, multiple components were compared. The duration of pain was lower in patients receiving Tadalafil, but the difference was not statistically significant ($P = 0.226$); however, the sums of the pain levels in the visual analog scale was significantly lower in patients receiving Tadalafil (8.44 ± 8.57 vs. 5.80 ± 5.02 , $P = 0.019$). Those patients also experienced hematuria for shorter courses (3.13 ± 1.54 days vs. 2.55 ± 1.52 , $P = 0.018$). 49 patients out of the 80 patients receiving Tamsulosin (61.3%, 95%CI: 49.7%-71.9%), 53 cases out of the 80 cases receiving Tamsulosin and Tadalafil (66.3%, 95%CI: 54.8%-76.4%) reached stone-free status in their follow-up visit. These two groups did not differ significantly in this regard ($P = 0.511$). Table 2 summarizes the comparison of post-procedure complaints of the patients.

Table 2
Outcomes compared between the two study groups

Variable	Tamsulosin	Tamsulosin and Tadalafil	P-value
Duration of pain	3.03 ± 2.07	2.66 ± 1.68	0.226
Severity of pain	8.44 ± 8.57	5.80 ± 5.02	0.019
Duration of hematuria	3.13 ± 1.54	2.55 ± 1.52	0.018
Duration of analgesic use	1.04 ± 1.50	0.78 ± 1.09	0.207
Residual fragments size	4.93 ± 4.25	4.42 ± 3.98	0.408
Stone-free status	49 (61.3%) (95%CI: 49.7%-71.9%)	53 (66.3%) (95%CI: 54.8%-76.4%)	0.511

A subgroup analysis was performed to compare stone expulsion in the two groups based on stone size and location. Stone expulsion was not significantly different in the two groups in various locations. Regarding various stone sizes, all stones less than 5 mm were passed. In the group of stones between 6–10 mm, stones expelled in the Tamsulosin group were more, yet the difference was not statistically significant (P = 0.431). In stones larger than 10 mm, 37 stones (72.5%) in Tamsulosin and Tadalafil and 28 stones (56.0%) in the Tamsulosin group were passed. This difference was more prominent but still not statistically significant (P = 0.083). Table 3 summarizes the subgroup analysis.

Table 3
comparison of patients receiving Tamsulosin or combination of Tamsulosin and Tadalafil in stone passage in different locations or sizes.

Comparing variable		Total	Tamsulosin	Tamsulosin+Tadalafil	P-value
Location	Upper calyx	7 (100%)	3 (100%)	4 (100%)	N/A
	Middle calyx	18 (72.0%)	10 (83.3%)	8 (61.5%)	0.378
	Lower calyx	20 (52.6%)	7 (38.9%)	13 (65.0%)	0.107
	Renal pelvis	40 (65.6%)	19 (57.6%)	21 (75.0%)	0.153
	Proximal ureter	36 (75.0%)	19 (82.6%)	17 (68.0%)	0.243
size	0–5 mm	9 (100%)	6 (100%)	3 (100%)	N/A
	6–10 mm	47 (68.1%)	24 (72.7%)	23 (63.9%)	0.431
	> 10 mm	65 (64.4%)	28 (56.0%)	37 (72.5%)	0.083

The two groups were also compared regarding adverse effects to evaluate the safety of this medication. No severe adverse effect was observed in the two groups. Nonetheless, mild adverse events such as

headache, fatigue, and vertigo were present in both groups. None of which was statistically significant. Table 4 summarizes the adverse events of treatment in the two groups.

Table 4
Treatment side effects in the two groups

Adverse event	Tamsulosin	Tamsulosin+Tadalafil	P-value
Headache	3 (3.8%)	4 (5.0%)	> 0.99
Vertigo	1 (1.3%)	4 (5.0%)	0.367
Fatigue	0 (0.0%)	2 (2.5%)	0.497

Discussion

In this double-blinded placebo-controlled randomized clinical trial, we attempted to assess the efficacy of adding Tadalafil to Tamsulosin in patients with urolithiasis undergoing Extracorporeal Shockwave Lithotripsy (SWL). In this study, we found that adding Tadalafil to Tamsulosin was not effective in increasing stone-free status; however, this alteration in the therapeutic regimen decreased the patients' pain and duration of hematuria.

The efficacy of phosphodiesterase-5 inhibitors was first described after the publication of a study by MS Abdel-Kader. He showed that male patients who have sexual intercourse three to four times per week have higher rates of stone expulsion; Therefore, suggesting that such outcome might be through the release of release Nitric Oxide (NO). The author speculated that the drugs that increase NO release might have beneficial effects on stone expulsion [15].

In a study by Gnyawali et al. the efficacy of Tamsulosin was compared with Tamsulosin and Tadalafil combined in treatment of patients with distal ureteral stones. They found that patients with a mean stone size of near seven millimeters using Tamsulosin and Tadalafil combined, have a stone-free status of 64%, while only 50% of the cases receiving Tamsulosin alone reached stone-free status, a statistically significant difference [13]. In our study, the difference between the two groups was not statistically significant which might be due to different stone locations and stone sizes.

Although the difference in stone expulsion in various stone sizes was not statistically significant, the difference was more prominent in larger stones suggesting the need for further research with larger stones. In a study by Neeli and colleagues in 2021, the difference in stone expulsion in patients receiving Tamsulosin alone or Tamsulosin and Tadalafil combined after SWL was significant in stone sizes larger than 12 mm. They also concluded that adding Tadalafil minimizes the likelihood of stone street formation [14].

To the best of our knowledge a study designed by Mahapatra et al. was the only study comparing the efficacy of adjuvant Tadalafil and adjuvant Tamsulosin in patients undergoing SWL. It should be Although low in sample size, The study demonstrated that stone expulsion was more significant in

patients receiving Tadalafil, yet with more colic episodes [16]. In contrast, in our study, the simultaneous use of Tamsulosin and Tadalafil did not enhance the patients' stone-free status, however the patients experienced less pain for stone expulsion. This difference in results might be due to the smaller sample and mean stone size in the study conducted by Mahapatra et al.

Since using Tamsulosin and tadalafil together, decreased the pain level in patients, despite not affecting stone expulsion, adding this agent to the therapeutic plan is recommended. As previously shown, phosphodiesterase isoenzymes are scattered through the urinary tract from the ureters to the detrusor muscles of the bladder and smooth muscle cells of the urethra [17–20]. This enzyme hydrolyses cyclic adenylyl monophosphate (cAMP) and guanylyl monophosphate (cGMP) [21]. Thus, inhibition of phosphodiesterase increases the cytosolic concentration of cGMP and cAMP which in turn relaxes the smooth muscles and decreases the friction between the stone and ureteral or urethral wall which can further decrease the pain level. This effect can also increase the likelihood of stone expulsion for larger stones.

Regarding the safety of using Tadalafil, it is worth noting that the first generation of phosphodiesterase-5 inhibitors like Sildenafil and Vardenafil could inappropriately inhibit phosphodiesterase 5 enzymes in eyes and cause functional decreased visual acuity, blurred vision, and hypersensitivity to light. Such complications were not observed in cases using Tadalafil [22, 23]. Moreover, the long half-life of Tadalafil (17.5 hours) and its long duration of action (36 hours) makes this agent superior compared to other phosphodiesterase-5 inhibitors [22]. Prescribing this drug should be with caution in patients taking other medications that induce or inhibit cytochrome 4A3 [24]. Cytochrome inhibitors such as Antibiotics, e.g., Ciprofloxacin, Clarithromycin, and Erythromycin, as well as Isoniazid (anti-TB), antineoplastic drugs such as Tamoxifen, Irinotecan, anti-HIV agents such as Ritonavir and Delavirdine, antifungal drugs including Ketoconazole, Itraconazole, and Fluconazole, as well as Calcium channel blockers like Verapamil and Diltiazem, as well as grapefruit juice can increase the efficacy and adverse effects of Tadalafil [25]. On the other hand, cytochrome inducers like Phenytoin, Phenobarbital, Carbamazepine, Rifampin, and glucocorticoids can increase Tadalafil metabolism and decrease its efficacy [26]. Also, the potentially dangerous interactions of phosphodiesterase-5 inhibitors with nitrates should be considered and its prescription should be limited in those taking drugs like nitroglycerines [27].

In preclinical studies on rat models of prostatic hypoxic injury, Tadalafil could decrease the oxidative stress in the prostate and help with repair mechanisms [28]. Thus, considering the role of Tadalafil in repair pathways, it is speculated that using this agent can increase blood flow to the mechanical injury site help with better repair, and decrease further adverse events like meatal stenosis; however, this hypothesis needs further investigation.

A major drawback in our study is the lack of assessment of daily lab data especially inflammatory markers. Also, further studies with Tamsulosin or Tadalafil alone can be performed in patients undergoing SWL.

Conclusion

Adding Tadalafil to Tamsulosin in patients undergoing SWL for renal and proximal ureteral stones can reduce pain levels and hematuria. however, it does not influence the duration of stone passage.

Declarations

Acknowledgments:

This article was derived from dissertation of MH for degree of specialty in urology. The authors would like to thank the vice chancellor of research and technology of Kerman University of Medical Sciences for their financial support of the study.

Authors' Contributions:

AK and HP conceptualized the study. MH and MHA collected the data. AHH analyzed the data. AHH wrote the first manuscript of the study. All of the authors read and reviewed the manuscript and made the necessary changes. The final format of the manuscript is accepted by all of the authors.

Funding:

This work was solely financed by Kerman University of Medical Sciences.

Availability of Data and Materials:

The datasets analyzed during the current clinical trial are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate:

The protocol of the current study was approved by the ethics committee of the Kerman University of Medical Sciences (approval code: IR.KMU.AH.REC.1403.051). Also, written informed consent was obtained from the patients before study begun. The study is also registered to Iranian Registry of Clinical Trials by the code IRCT20240515061806N1 on August 7th 2024.

Consent for Publication:

Not Applicable.

Competing Interests:

The authors declare that they have no competing interests.

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Figures

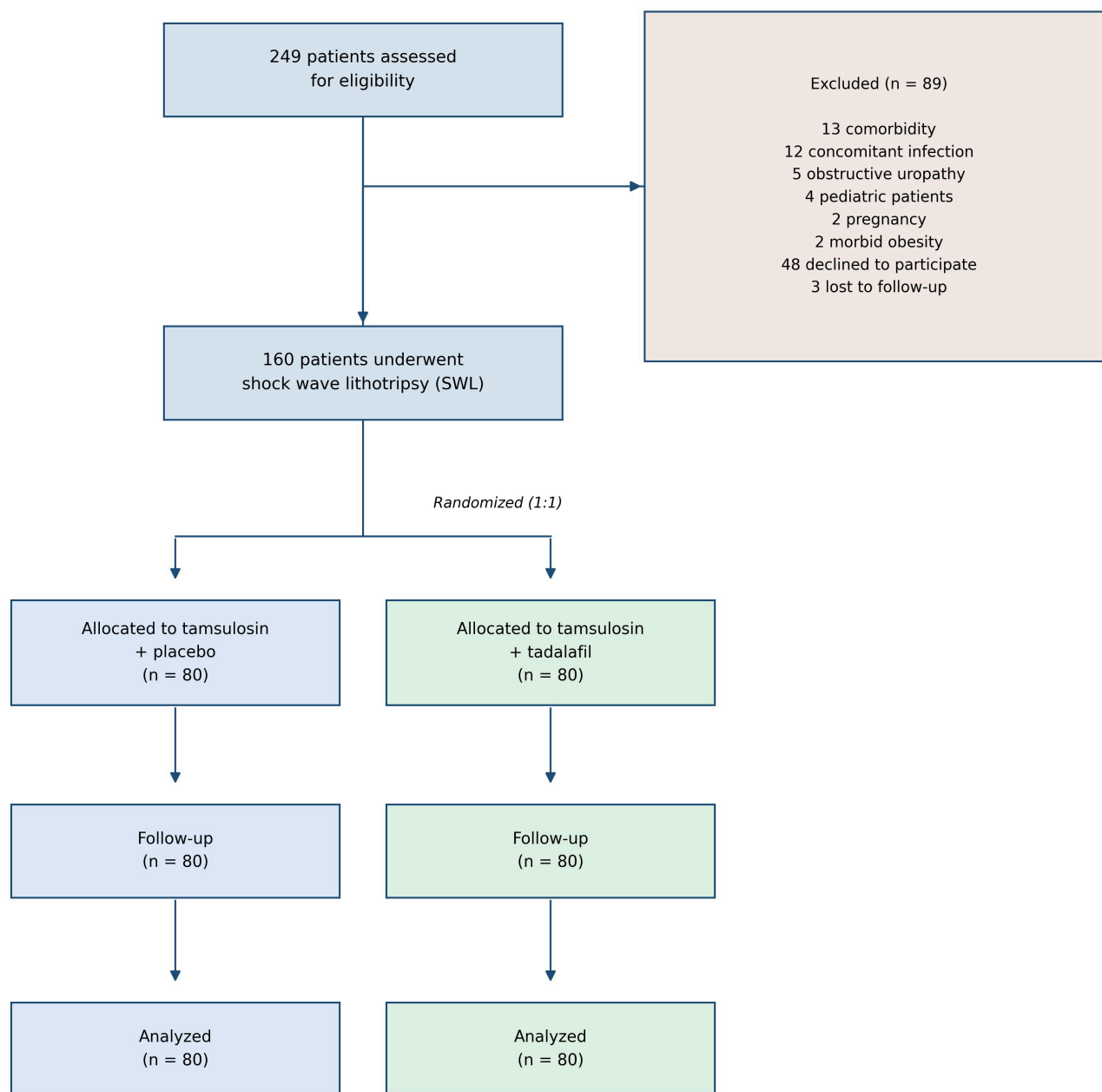


Figure 1

flowchart of the study population