

Lian-Sheng Ma
Science Editor, Company Editor-in-Chief
Editorial Office
Baishideng Publishing Group Inc.
World Journal of Clinical Cases

Dear Editor,

We appreciate the opportunity to respond to the reviewers' comments. We have addressed them point-by-point in the attached letter and revised manuscript. We thank the reviewers for their constructive criticism. We hope that you will find the revised manuscript suitable for publication in ***World Journal of Clinical Cases***.

Thank you for your consideration.

Sincerely,

Co-authors: Jae Young Lee, Ho Seok Lee, Si-Bog Park

Corresponding author:

Kyu Hoon Lee, MD, PhD, Professor of Medicine, Department of Rehabilitation Medicine,
Hanyang University Hospital, 222-1, Wangsimni-ro, Seongdong-gu, Seoul, 04763, Korea
dumitru1@hanyang.ac.kr

Response to Reviewers' Comments

Manuscript: 77193

To Reviewer #1:

Specific Comments to Authors: Neurogenic bladder due to suprasacral spinal cord injury (SCI) is characterized by detrusor-sphincter dyssynergia (DSD) or sphincter dis-relaxation. Such neurogenic lower urinary tract dysfunction (NLUTD) can lead to renal dysfunction and urinary tract infection due to increased bladder pressure and decreased voiding efficiency. Alpha-blockers are usually used in patients with NLUTD to reduce the resistance at out of the bladder (bladder neck or prostatic urethra). Although a variety of alpha-blockers are used, randomized controlled trials using tamsulosin (0.4 mg and 0.8 mg) have shown no significant difference in the reduction of maximum intraurethral pressure after 4 weeks of treatment compared to placebo. The frequency of side effects was also not significantly different in the placebo group. Few countries have insurance approval for the use of tamsulosin in women with NLUTD. Therefore, it is difficult to say that tamsulosin is widely used worldwide for NLUTD. In this paper, the authors report a 59-year-old woman with NLUTD who experienced life-threatening hypotension after using tamsulosin (0.4 mg to 0.2 mg administration), which improved with withdrawal. The authors emphasize that this is the first report of its kind, but as noted earlier, it is not a useful report for clinicians because of the lack of practice of using tamsulosin for women worldwide. This reviewer's main concern is whether alpha-blocker administration was necessary for this patient. The directives of micturition for her are the combination self-voiding and CIC four times per day to reduce residual urine. What is the reason for considering tamsulosin administration? In general, video urodynamic study (VUDS) should be needed to determine the appropriate micturition management in SCI patients, and the selection to administer tamsulosin without VUDS in this case is questionable. It seems that the patient refused, but then tamsulosin administration is not considered essential if the patient is able to void on her own and does not have an extremely large amount of residual urine. In addition, what is the rationale for using a cholinergic agonist for dysuria as a definitive treatment? As long as AEs of tamsulosin are observed, the authors should administer VUDS with the patient's understanding. The rationale for recommending fluid intake at 2000 ml/day is also unclear. Since dyspareunia and dizziness were observed prior to the hypotension event, this reviewer still thinks that vasovagal syncope is likely. The possibility that autonomic neuropathy due to myelopathy

and diabetes mellitus (DM) contributed to this event cannot be ruled out. Since it is well known that the duration of DM is involved in the unconscious progression of neuropathy, we would like to know the details of the diabetes including the blood glucose value.

Author response: We appreciate your in-depth review, which has assisted us in revising our manuscript. Please see our line-by-line responses to the comments below.

Comment 1: Few countries have insurance approval for the use of tamsulosin in women with NLUTD. Therefore, it is difficult to say that tamsulosin is widely used worldwide for NLUTD. In this paper, the authors report a 59-year-old woman with NLUTD who experienced life-threatening hypotension after using tamsulosin (0.4 mg to 0.2 mg administration), which improved with withdrawal. The authors emphasize that this is the first report of its kind, but as noted earlier, it is not a useful report for clinicians because of the lack of practice of using tamsulosin for women worldwide. This reviewer's main concern is whether alpha-blocker administration was necessary for this patient. The directives of micturition for her are the combination self-voiding and CIC four times per day to reduce residual urine. What is the reason for considering tamsulosin administration?

Author response 1: We appreciate the reviewer's valuable comments and revised the manuscript accordingly. In Korea, tamsulosin is approved by insurance in both men and women who have neurogenic bladder as well as BPH. A review article shows that tamsulosin improves the average flow rate and post-void residual volume of women^[5]. We used alpha-blocker to prevent urinary tract infection (UTI) and autonomic dysreflexia due to bladder retention based on cervical myelopathy. We agree that we controlled urinary retention too strictly and mentioned this limitation in the DISCUSSION.

We changed the above contents as follows.

INTRODUCTION

Before Tamsulosin is a selective $\alpha 1$ -adrenergic receptor antagonist that is widely used for benign prostatic hypertrophy (BPH). Moreover, it is effective against and commonly used for treating neurogenic bladder in patients with spinal cord injury (SCI). The usual dosage of tamsulosin is 0.2, 0.4, or 0.8 mg per day^[1-3].

After Tamsulosin is a selective $\alpha 1$ -adrenergic receptor antagonist that is widely used for benign prostatic hypertrophy (BPH). It also is effective against and commonly used for treating neurogenic bladder in patients with spinal cord injury (SCI). The usual dosage of tamsulosin is 0.2, 0.4, or 0.8 mg per day^[1-3]. In Korea, tamsulosin is approved by insurance in both men and women who have neurogenic bladder as well as BPH. Furthermore, tamsulosin is an effective treatment for relief of lower urinary tract symptoms in women by improving the average flow rate and the residual volume after voiding^[4-5].

[references]

4. **Meyer LE, Brown JN.** Tamsulosin for voiding dysfunction in women.

Int Urol Nephrol. 2012 Dec;44(6):1649-56.[PMID: 22983886 DOI:

10.1007/s11255-012-0275-0]

5. **H L Zhang , Z G Huang , Y Qiu , X Cheng , X Q Zou , T T Liu.**

Tamsulosin for treatment of lower urinary tract symptoms in women: a systematic review and meta-analysis. *Int J Impot Res.* 2017 Jul;29(4):148-

156.[PMID: 28424499 DOI: 10.1038/ijir.2017.12]

DISCUSSION

Before

After There were some limitations in this case report. First, we tended to manage urinary retention too strictly using tamsulosin. The patient was able to self-void, and residual urine was in the range of 160-200 mL. Though we could have managed her symptoms with self-voiding and timed CIC, considering her cervical myelopathy, we thought that strict management of urinary retention with tamsulosin was needed to prevent urinary tract infection and autonomic dysreflexia.

删除[admin]: (page 10, lines 297-302)

Comment 2: In general, video urodynamic study (VUDS) should be needed to determine the appropriate micturition management in SCI patients, and the selection to administer tamsulosin without VUDS in this case is questionable. As long as AEs of tamsulosin are observed, the authors should administer VUDS with the patient's understanding.

Author response 2: We agree with the reviewer. We planned urodynamic study for the voiding difficulty, but the patient refused it. In general, after urodynamic study, appropriate treatments should be selected to manage voiding difficulty of SCI patients. The reason why we prescribed tamsulosin is mentioned above in Author response 1. We described this limitation in the DISCUSSION.

CASE PRESENTATION

Before Considering her completeness of injury (AIS D), we removed her Foley catheter to identify residual urine using clean intermittent catheterization (CIC). On the day of removal, she was able to self-void, but residual urine was in the range of 160-200 mL. On suspicion of voiding difficulty due to neurogenic bladder, a complication of her SCI, we prescribed the recommended dose of 0.4 mg tamsulosin once daily^[1,2].

After Considering her completeness of injury (AIS D), we removed her Foley catheter to identify residual urine using clean intermittent catheterization (CIC). On the day of removal, she was able to self-void, but residual urine was in the range of 160-200 mL. On suspicion of voiding difficulty due to neurogenic bladder, a complication of her SCI, we scheduled a urodynamic study, but the patient refused due to discomfort. In the absence of a urodynamic study, we prescribed the recommended dose of 0.4 mg tamsulosin once daily^[1,2].

DISCUSSION

Before	
After	<p>There were some limitations in this case report. First, we tended to manage urinary retention too strictly using tamsulosin. The patient was able to self-void, and residual urine was in the range of 160-200 mL. Though we could have managed her symptoms with self-voiding and timed CIC, considering her cervical myelopathy, we thought that strict management of urinary retention with tamsulosin was needed to prevent urinary tract infection and autonomic dysreflexia. Second, we could not perform urodynamic study because the patient refused. In general, urodynamic study should be performed and used as the basis for appropriate treatments to manage voiding difficulty of SCI patients. We should have persuaded the patient to proceed with the urodynamic study.</p>

Comment 3: In addition, what is the rationale for using a cholinergic agonist for dysuria as a definitive treatment?

Author response 3: We appreciate your comment. We added references for using a cholinergic agonist for dysuria.

OUTCOME AND FOLLOW-UP	
Before	We prescribed bethanechol chloride for voiding difficulty, and the patient was discharged 10 days after the first event.
After	We prescribed bethanechol chloride for voiding difficulty, and the patient was discharged 10 days after the first event ^[10,11] .
	[references]
	10. Gaitonde S, Malik RD, Christie AL, Zimmern PE. Bethanechol: Is it

still being prescribed for bladder dysfunction in women? *Int J Clin Pract.* 2019 Aug;73(8):e13248.
[PMID: 30112787 DOI: 10.1111/ijcp.13248]

11. **Diokno AC, Koppenhoefer R.** Bethanechol chloride in neurogenic bladder dysfunction. *Urology.* 1976 Nov;8(5):455-8.[PMID: 982732 DOI: 10.1016/0090-4295(76)90274-0]

Comment 4: The rationale for recommending fluid intake at 2000 ml/day is also unclear.

Author response 4: We appreciate the valuable comment. To prevent urinary tract infection due to urinary retention, fluid restriction is recommended. However, we encouraged fluid intake to prevent orthostatic hypotension, which is a frequent occurrence in cervical cord myelopathy. In order to clarify, we revised the manuscript in CASE PRESENTATION.

CASE PRESENTATION

Before For bladder management, we planned approximately 2000 mL/ day of total fluid intake and CIC at least 4 times/ day, followed by self-voiding. To confirm the exact bladder pathology, we scheduled a urodynamic study, but the patient refused due to test discomfort.

After For bladder management, we planned CIC at least 4 times/ day, followed by self-voiding. Because she had been diagnosed with cervical spinal cord myelopathy, we encouraged fluid intake of approximately 2000 mL/ day to prevent orthostatic hypotension^[8].
[reference]

8. **Snapper H, Cheshire WP.** Oral and intravenous hydration in the treatment of orthostatic hypotension and postural tachycardia syndrome. *Auton Neurosci.* 2022;238:102951.[PMID: 35123367 DOI:

Comment 5: Since dyspareunia and dizziness were observed prior to the hypotension event, this reviewer still thinks that vasovagal syncope is likely.

Author response 5: We appreciate your helpful comment. The patient experienced dizziness and nausea prior to the hypotension event, but later to tamsulosin administration. Cervical myelopathy can cause orthostatic hypotension because of damage to the autonomic nervous system. Considering prevalence of orthostatic hypotension in SCI and the fact that these symptoms had been relieved after stopping tamsulosin, we thought that tamsulosin provoked orthostatic hypotension due to underlying cervical myelopathy. We revised the manuscript in CASE PRESENTATION.

CASE PRESENTATION

Before After administering tamsulosin for 6 days, we reduced the dose to 0.2 mg once daily as her residual urine remained less than 200 mL. In addition to voiding difficulty, she had a few other symptoms. Though her blood pressure (BP) remained stable, she experienced occasional dizziness, likely due to orthostatic hypotension. She also experienced constipation and post-defecation symptoms such as nausea, lightheadedness, and sweating.

After After administering tamsulosin for 6 days, we reduced the dose to 0.2 mg once daily as her residual urine remained less than 200 mL. In addition to voiding difficulty, tamsulosin use produced other symptoms. Though her blood pressure (BP) remained stable, she experienced occasional dizziness, likely due to orthostatic hypotension. She also experienced constipation and post-defecation symptoms such as nausea, lightheadedness, and sweating. We attributed these symptoms to

orthostatic hypotension due to cervical myelopathy aggravated by tamsulosin^[9]. We reduced the dose of tamsulosin to 0.2mg and expect resolution of the symptoms.

[reference]

9. **Bushkov FA.** Orthostatic hypotension in patients with posttraumatic cervical myelopathy. *Zh Nevrol Psikhiatr Im S S Korsakova.* 2019;119(6):9-13.[PMID: 31407676 DOI: 10.17116/jnevro20191190619]

Comment 6: The possibility that autonomic neuropathy due to myelopathy and diabetes mellitus (DM) contributed to this event cannot be ruled out. Since it is well known that the duration of DM is involved in the unconscious progression of neuropathy, we would like to know the details of the diabetes including the blood glucose value.

Author response 6: We appreciate the comment. As the reviewer mentioned, the patient had past history of diabetes mellitus (DM), which can cause autonomic neuropathy. In addition, DM-associated cardiovascular autonomic neuropathy affects the autonomic nerve that innervates the heart and blood vessels and can lead to cardiovascular shock like this case^[18]. However, in this case, the blood glucose level of the patient had been well-controlled. We did not examine hemoglobin A1c level. We described this limitation and added the above contents on autonomic neuropathy caused by DM in the DISCUSSION and mentioned blood glucose level in LABORATORY FINDINGS.

LABORATORY FINDING	
Before	At the first hypotensive event, the laboratory test results showed WBC of 8,500/mm3, CRP of 0.77 mg/dL, and procalcitonin of 0.04 ng/mL; troponin-I, lactate dehydrogenase, and creatinine levels were normal.

After	Her blood glucose level was 74, 84, 94, 74, and 75 mg/dl pre-meal and 122, 133, 102, 106, and 140 mg/dl 2 hours after a meal. We did not examine hemoglobin A1c because we thought that her blood glucose level was well-controlled. At the first hypotensive event, the laboratory test results showed WBC of 8,500/mm ³ , CRP of 0.77 mg/dL, and procalcitonin of 0.04 ng/mL; troponin-I, lactate dehydrogenase, and creatinine levels were normal.
-------	---

DISCUSSION

Before	
--------	--

After	Furthermore, considering her history of DM, her shock might have been due to autonomic neuropathy. Diabetes-associated cardiovascular autonomic neuropathy (CAN) affects the autonomic nerve that innervates the heart and blood vessels and can cause multi-organ failure ^[18] . However, autonomic neuropathy due to DM was less likely because her blood glucose level had been well-controlled. [reference] 18. Agashe S, Petak S. Cardiac Autonomic Neuropathy in Diabetes Mellitus. Methodist Debaquey Cardiovasc J. 2018 Oct-Dec;14(4):251-256.[PMID:30788010 DOI: 10.14797/mdcj-14-4-251]
-------	---

DISCUSSION

Before	
--------	--

After

Third, we did not examine the hemoglobin A1c level of the patient.

However, in DM patients, hemoglobin A1c level should be measured

because it reflects the mean blood sugar over the previous weeks to

months^[21].

[reference]

21. Saudek CD, Brick JC. The clinical use of hemoglobin A1c. *J Diabetes*

Sci Technol. 2009 Jul 1;3(4):629-34. [PMID: 20144304 DOI:

10.1177/193229680900300402]

To Reviewer #2:

Specific Comments to Authors: The authors submitted a manuscript presenting one case of severe hypotension induced by tamsulosin in a female patient with spinal cord injury. Tamsulosin, a selective α 1-adrenergic receptor (α 1-AR) antagonist, is a widely prescribed first-line agent for benign prostatic hypertrophy (BPH). Tamsulosin was introduced in 1996 and marketed as a major innovation among α blockers because it was associated with a lower frequency of orthostatic hypotension than other drugs in this class. Tamsulosin now dominates the global drugs market for the treatment of benign prostatic hyperplasia and is the most commonly prescribed treatment for lower urinary tract (LUT) symptoms worldwide. Although tamsulosin is indicated for the treatment of the signs and symptoms of BPH, it has also been assessed in clinical studies for other conditions/symptoms and in other populations such as women and children. The functions of the LUT, such as voiding and storing urine, are dependent on complex central neural networks located in the brain, spinal cord, and peripheral ganglia. Thus, the functions of the LUT are susceptible to various neurologic disorders including spinal cord injury (SCI). SCI at the cervical or thoracic levels disrupts voluntary control of voiding and the normal reflex pathways coordinating bladder and sphincter functions. Oral tamsulosin should be administered with caution in patients with orthostatic hypotension. As the authors mentioned that this patient with SCI has the symptom of orthostatic hypotension, is it reasonable for the patient to take tamsulosin in this case? Some of the authors' explanations and discussions are a bit far-fetched. The English needs to be improved to a certain extent. There are some errors in grammar and format in the whole manuscript: single and plural expressions; the use of prepositions and definite/indefinite articles; superscript and subscript.

Author response: We appreciate the reviewer's valuable comments and have revised the manuscript accordingly. Please see our responses to your comments below.

Comment 1: As the authors mentioned that this patient with SCI has the symptom of orthostatic hypotension, is it reasonable for the patient to take tamsulosin in this case?

Author response 1: We appreciate the reviewer’s comments. The patient experienced orthostatic hypotension after taking tamsulosin. We attributed the orthostatic hypotension to tamsulosin and reduced the dose. We agree that we managed the urinary retention too strictly and mentioned this limitation in the DISCUSSION.

We described the precise history of tamsulosin use in CASE PRESENTATION.

CASE PRESENTATION

Before	After administering tamsulosin for 6 days, we reduced the dose to 0.2 mg once daily as her residual urine remained less than 200 mL. In addition to voiding difficulty, she had a few other symptoms.
After	After administering tamsulosin for 6 days, we reduced the dose to 0.2 mg once daily as her residual urine remained less than 200 mL. In addition to voiding difficulty, she developed other symptoms <u>after tamsulosin administration</u> .

DISCUSSION

Before	
After	<u>There were some limitations in this case report. First, we tended to manage urinary retention too strictly when using tamsulosin. The patient was able to self-void, and residual urine was in the range of 160-200 mL. Though we could have managed her with self-voiding and timed CIC, considering her cervical myelopathy, we thought that strict management of urinary retention with tamsulosin was needed to prevent urinary tract</u>

infection and autonomic dysreflexia.

Comment 2: The English needs to be improved to a certain extent. There are some errors in grammar and format in the whole manuscript: single and plural expressions; the use of prepositions and definite/indefinite articles; superscript and subscript.

Author response 2: We appreciate the reviewer's comment. We revised the whole manuscript for English as you mentioned.

To Reviewer #3:

Specific Comments to Authors: This is an interesting and well written case report on spinal cord injury. In this study, the authors highlighted that tamsulosin can cause severe life-threatening hypotension. They also alert clinicians to be aware of this possible condition when treating neurogenic bladder in a patient with SCI. In general, this paper is clear and is suitable for publication in this journal.

Author response: We appreciate your thoughtful and helpful review. Thank you for the opportunity to respond to your comments.

To Editor-in-chief

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

Author response: We appreciate the opportunity to respond to your comments. We revised our manuscript based on the reviewer's comments and added the original figure documents

and copyright information as PowerPoint files.