

# Effects of Additional Glycine in Outpatients Being Treated for Urine Storage Disorders

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## Abstract

**Objectives:** This study aimed to determine whether additional glycine can improve urine storage symptoms in outpatients. **Methods:** We recruited 50 outpatients (15 females, 35 males) with an Overactive Bladder Symptom Score (OABSS) of 3 or more. Participants being treated for urine storage disorders took additional glycine for 8 weeks at a dose of 3 g twice a day. Outcome measures included blood pressure, the International Prostate Symptom Score (IPSS), OABSS, Nocturia Quality of Life (N-QOL) score, urination frequency, sleep latency, time until the first void at night, bladder pain, improvement in urinary symptoms assessed with the Global Self-Assessment (GSA), and adverse events. **Results:** In the OABSS, the number of nighttime voids, urgency to urinate, urgent incontinence, and total score were improved. Improvements were also found in the IPSS total score for urine storage items, blood pressure, IPSS-QOL, time to first void, bladder pain, and GSA score, but no changes were seen in the frequency of urination at night, sleep latency or N-QOL score. No adverse events were recorded. **Conclusion:** Oral glycine improves objective and self-assessed urine storage symptoms, blood pressure, and bladder pain.

## Keywords

Chronic Prostatitis, Glycine, Interstitial Cystitis, Overactive Bladder, Urine Storage Symptoms

## 1. Introduction

The amino acid glycine is commonly used not only as a sweetener but also as an over-the-counter supplement for improving the quality of sleep, and it has not been found to have any adverse effects [1]. Endogenous glycine acts as the main inhibitor of neurotransmission in the spinal cord [2], and this inhibition plays an essential role in the micturition reflex [2] [3] and sensitivity to pain [4] [5]. Glycine levels decrease after spinal cord injury, and men with benign prostatic hyperplasia also have lower levels than healthy individuals [6]. Studies in rats showed that, as glycine levels decrease, bladder activity increases, bladder contractions are more frequent, and the maximum bladder contraction pressure is higher [3] [7]. Other studies in rats showed that oral glycine (administered as 1% to 3% of the diet) reduces both the frequency of bladder contractions and the maximum contraction pressure [8] [9] [10].

Previously, in a 4-week study, we compared oral glycine (3 g twice a day) with glucose in 20 patients receiving treatment for urine storage symptoms and found greater improvements by additional glycine in urine storage symptoms, cardiovascular function, bladder pain, and sleep quality [11]. Because this study had a small sample size, we subsequently performed an 8-week study of glycine versus glucose in a larger sample. Unfortunately, the drop-out rate was extremely high in the glucose group because of insufficient symptom improvement; however, an encouraging finding was that no patients in the glycine group discontinued the study at least for 4 weeks. Therefore, we aimed to conduct a single-blind, uncontrolled study to evaluate the effects of oral glycine in ameliorating symptoms of urine storage.

## 2. Materials and Methods

### 2.1. Study Participants

We recruited 50 males and females outpatients being treated at six urological clinics in Japan (Kitakami Central Hospital, Kobe Medical Center, Yamada Urological Clinic, Kitanodai Clinic, Okinawa Hokubu Hospital, and Okinawa Kyodo Hospital) from April 2013 to April 2016. Patients were eligible to participate if they were aged 20 years and older and had urine storage symptoms that showed no improvement after 8 weeks of standard treatment; a diagnosis of overactive bladder, chronic prostatitis, or bladder pain syndrome/interstitial cystitis; and an Overactive Bladder Symptom Score (OABSS) [12] of 3 or more. Exclusion criteria included urinary tract infection; relevant untreated organic diseases, such as benign prostatic hyperplasia with urine voiding symptoms, prostate cancer, bladder neck obstruction (sclerosis), stricture of the urethra, and bladder tumor or stones; 100 mL or more of residual urine after voiding; and a lack of urgency to urinate. Participants were permitted to continue taking all their regular medications.

The study protocol was approved by the Okinawa Kyodo Hospital Ethics Committee (approval no. 2012-005) for all participating institutions. All patients

provided written informed consent to participate.

## 2.2. Study Drug

Although the study was uncontrolled, participants were informed that they would be assigned to receive small pouches containing either glucose or glycine. However, all participants actually received glycine (Nippon Garlic Corporation, Takasaki, Japan) at a dose of 3 g twice a day (morning and evening). The dose was chosen as being equivalent to about 1% of the dry weight of an adult man's daily food intake.

## 2.3. Outcome Measures

The following variables were assessed at baseline and after 4 and 8 weeks of treatment: overall clinical status; blood pressure and pulse rate; number of daytime voids; sleep latency; time until first nighttime void; and number of nighttime voids. At the same visits, patients also completed the following self-assessment tools: International Prostate Symptom Score (IPSS) (**Appendix 1**) [13]; IPSS quality of life (IPSS-QOL); OABSS (**Appendix 2**); nocturia quality of life (N-QOL) (**Appendix 3**) [14]; and visual analogue scale for bladder pain.

Transabdominal ultrasonography was performed at baseline to assess prostate volume and at baseline and the end of the study to assess the volume of residual urine after voiding. After 4 and 8 weeks, patients completed a global self-assessment (GSA) scale to assess changes in symptoms, as follows: 0, excellent improvement; 1, good improvement; 2, fair improvement; 3, no change; 4, worse. Adverse events were recorded at weeks 4 and 8.

## 2.4. Statistical Analysis

Results are reported as the mean  $\pm$  standard deviation. Higher scores corresponded to worse outcomes in all self-assessment tools except the N-QOL, in which a higher score corresponded to a better outcome. Changes over time were analyzed by Student's *t*-test for paired data, and significance was set as a *p* value of less than 0.05.

## 3. Results

The 50 participants comprised 35 males and 15 females with a mean body mass index of  $23.4 \pm 3.2$  and a mean age of  $66 \pm 15$  years. Diagnoses were as follows: chronic prostatitis with overactive bladder (15 males); mild benign prostatic hyperplasia with overactive bladder (9 males); bladder pain syndrome/interstitial cystitis with overactive bladder (5 males and 12 females); and overactive bladder (6 males and 3 females) (**Table 1**). Concomitant diagnoses were hypertension in 12 patients and type 2 diabetes in 7. The mean prostate size was  $21.9 \pm 7.8$  mL (range, 12.3 - 35.7 mL). Concomitant medication included anti-muscarinic drugs for overactive bladder (*n* = 39) and anti-muscarinic tricyclic antidepressants for bladder pain syndrome/interstitial cystitis (*n* = 11). Nine patients with benign

**Table 1.** Characteristics of patients.

Sex	Diagnosis	Number of cases
Male	Chronic prostatitis with overactive bladder	15
	Benign prostatic hyperplasia with overactive bladder	9
	Bladder pain syndrome/interstitial cystitis with overactive bladder	5
	Overactive bladder	6
		total 35
Female	Bladder pain syndrome/interstitial cystitis with overactive bladder	12
	Overactive bladder	3
		total 15

prostatic hyperplasia were also receiving an alpha-1 blocker, and fifteen with chronic prostatitis, an anti-inflammatory botanical preparation.

At 4 weeks, we found a decrease in diastolic blood pressure compared with baseline (baseline:  $67.2 \pm 10.5$  mmHg vs 4 week after:  $65.1 \pm 10.5$  mmHg,  $p < 0.05$ ), but no change in systolic blood pressure ( $124.7 \pm 17.3$  mmHg vs  $123.3 \pm 17.3$  mmHg, respectively) or pulse rate ( $75.0 \pm 13.2$ /min vs  $73.3 \pm 12.5$ /min, respectively) (**Table 2**). The IPSS showed an improvement in total score, urgency to urinate, and total score of items related to urine storage. The OABSS showed improvements in total score, number of nighttime voids, urgency to urinate, and urge incontinence. Regarding quality of life, the IPSS-QOL score improved, as did the total score and total score of items about worries on the N-QOL. The number of day- and nighttime voids, bladder pain, and sleep latency showed no changes, but the time until the first void at night improved.

At 8 weeks, we found a decrease in systolic (baseline:  $124.7 \pm 17.3$  mmHg vs 8 week after:  $121.2 \pm 15.5$  mmHg,  $p < 0.05$ ) and diastolic blood pressure compared with baseline ( $67.2 \pm 10.5$  mmHg vs  $65.1 \pm 10.5$  mmHg, respectively,  $p < 0.05$ ) but no change in pulse rate ( $75.0 \pm 13.2$ /min vs  $73.4 \pm 14.2$ /min, respectively). The IPSS showed an improvement in total score, frequency of urination, nocturia, and total score of items related to urine storage. In the OABSS, the same improvements from baseline were seen at 4 weeks. IPSS-QOL score was higher than at baseline, but neither the N-QOL total score nor any of the individual items showed an improvement from baseline. Neither the number of day- and nighttime voids nor sleep latency showed an improvement from baseline. The time until the first void at night was still higher than at baseline, and bladder pain improved slightly, but significantly. The volume of residual urine after voiding showed no change from baseline to 8 weeks ( $27.8 \pm 26.6$  mL vs  $28.6 \pm 25.9$  mL, respectively).

Mean GSA scores showed a fair improvement at both 4 ( $2.4 \pm 0.8$ ) and 8 weeks ( $2.2 \pm 1.1$ ), and no adverse events were recorded at either visit.

**Table 2.** Comparison of parameters and self-assessed questionnaires between before and after glycine treatments.

	Before		4 weeks after		8 weeks after	
Number of cases	50		50		40	
<b>Blood pressure (mmHg)</b>						
Systolic	124.7	± 17.3	123.3	± 17.3	121.2	± 15.5*
Diastolic	67.2	± 10.5	65.1	± 10.5*	65.1	± 10.5*
Pulse rate (/min)	75.0	± 13.2	73.3	± 12.5	73.4	± 14.2
<b>IPSS</b>						
Incomplete emptying	1.2	± 1.2	1.0	± 1.1	1.1	± 1.2
Frequency	2.8	± 1.6	2.6	± 1.5	2.3	± 1.6*
Intermittency	1.3	± 1.6	1.2	± 1.4	1.1	± 1.3
Urgency	1.9	± 1.5	1.3	± 1.2**	1.6	± 1.4
Weak stream	2.0	± 1.7	1.9	± 1.7	1.9	± 1.5
Straining	1.0	± 1.4	0.8	± 1.2	0.8	± 1.3
Nocturia	2.1	± 1.2	2.0	± 1.3	1.8	± 1.3*
Voiding Total	4.3	± 3.9	3.9	± 3.5	3.7	± 3.2
Storage Total	6.6	± 3.1	5.8	± 2.8**	5.6	± 3.4**
Total score	12.3	± 6.2	10.8	± 6.2**	10.4	± 6.9*
IPSS-QOL	4.7	± 1.2	4.1	± 1.5**	3.6	± 1.6**
<b>Urinary frequency (times)</b>						
Diurnal	10.5	± 3.4	10.8	± 6.7	10.6	± 7.3
Nocturnal	2.1	± 1.3	1.9	± 1.6	1.7	± 1.7
<b>OABSS</b>						
Diurnal urination	1.2	± 0.9	1.1	± 0.5	1.0	± 0.6
Nocturnal urination	2.0	± 0.8	1.8	± 0.9**	1.5	± 0.9**
Urgency	2.5	± 1.6	2.0	± 1.5**	1.8	± 1.4**
Incontinence	1.3	± 1.6	1.1	± 1.5*	0.9	± 1.3*
Total score	7.0	± 3.6	6.0	± 3.4**	5.3	± 3.4**
<b>N-QOL</b>						
Q1	2.9	± 0.9	3.1	± 0.9*	3.1	± 1.1
Q2	2.9	± 1.0	2.8	± 1.0	2.9	± 1.2
Q3	2.4	± 1.2	2.6	± 1.2	2.5	± 1.2
Q4	2.9	± 1.0	3.0	± 0.9	2.9	± 1.1
Q5	2.7	± 1.2	3.3	± 3.2	2.9	± 1.2
Q6	2.4	± 1.3	2.7	± 1.0	2.7	± 1.1
Q7	2.2	± 1.1	2.3	± 1.2	2.4	± 1.2
Q8	3.6	± 1.0	3.7	± 0.8	3.6	± 0.9
Q9	3.1	± 1.1	3.2	± 0.9	3.2	± 1.1

**Continued**

Q10	2.4	±	1.3	2.6	±	1.2	2.7	±	1.0
Q11	2.4	±	1.2	2.5	±	1.3	2.8	±	1.3
Q12	2.3	±	1.2	2.6	±	1.1	2.6	±	1.3
Q13	3.9	±	2.7	3.4	±	2.7	3.3	±	3.0
Vitality Total	16.0	±	5.2	17.2	±	6.1	16.8	±	5.9
Worries Total	16.1	±	5.5	17.3	±	4.9*	17.4	±	5.4
Total score	35.9	±	7.6	37.9	±	8.1*	37.5	±	8.3
Sleep latency (min)	24.6	±	20.6	23.3	±	19.5	21.2	±	19.6
First nocturia latency (min)	181.5	±	93.9	203.9	±	93.2**	206.5	±	94.8*
Bladder pain (VAS)	2.3	±	2.9	1.8	±	2.5	1.8	±	2.8*
Global self-assessment				2.4	±	0.8	2.2	±	1.1

The larger is the number, the better is the N-QOL, but the worse is the other questionnaires. Mean ± standard deviation. \*:  $p < 0.05$ , \*\*:  $p < 0.01$  vs before.

#### 4. Discussion

The current study found that 8 weeks' administration of oral glycine improved urine storage symptoms such as nocturia, urgency to urinate, and urge incontinence; patient quality of life; and bladder pain. These findings are in line with our earlier 4-week study that compared glycine with glucose, although that study also found improvements in sleep [11]. Both studies also found a decrease in blood pressure but no change in pulse rate. Taken together, these findings indicate that oral glycine has positive effects on urine storage symptoms, blood pressure, and bladder pain.

Oral glycine given at a dose of 1% to 3% of food weight was found to increase the time between bladder contractions in healthy rats [8] and in those with pelvic vein congestion [10] and to reduce the strength of bladder contractions in rats with spinal cord injury [8]. Another study in rats found that orally administered glycine increased glycine levels in brain tissue, indicating that glycine can cross the blood-brain barrier [15]. Both our earlier [11] and the present study found that symptoms improved in patients receiving anti-muscarinic drugs for urine storage symptoms. These drugs usually have a peripheral action [16], and our findings indicate that concomitant treatment with centrally acting glycine may result in further improvement of symptoms.

Although both the IPSS and OABSS showed improvements in nighttime urinary parameters in the current study, the number of nighttime voids did not improve significantly. This result is in contrast to our previous study, where the number of nighttime voids decreased significantly after 4 weeks' administration of glycine [11]. The maximum possible score for nighttime voids is 5 on the IPSS and 3 on the OABSS, even if the actual number of voids is higher. Therefore, any reduction in the number of nighttime voids to a number that is still above 5 (IPSS) or 3 (OABSS) will not be recorded, even though the change may be sig-

nificant. The large standard deviation in our data may also explain why our current study found no significant improvement in the number of nighttime voids.

Glycinergic interneurons in the spine may help regulate neurotransmission of pain and reduce neuropathic pain [5] and may also decrease sensitivity to pain [4]. Consequently, glycine probably can also reduce bladder pain, which may explain our respective findings.

Glycine is widely used at a dose of 3 g as an over-the-counter supplement for sleep and has no known side effects [1]. It inhibits orexin neurons, which stimulate active wakefulness, and increases the duration of non-rapid eye movement sleep [17]. In addition, it binds to N-methyl-D-aspartate receptors in the suprachiasmatic nucleus shell, leading to dilation of peripheral blood vessels, which promotes sleep [18]. Our earlier study confirmed the sleep-promoting effects of glycine [11]; however, the current study did not, which may be a chance finding related to the time of glycine administration: Participants were instructed to take the two doses of glycine at different times (morning and evening) each day, but the exact times were not specified. Future studies need to evaluate whether administering glycine at bedtime has positive effects on sleep.

The finding in the present study that systolic and diastolic blood pressure decreased after 4 to 8 weeks' administration of glycine may be related to the peripheral vasodilation caused by binding of glycine to N-methyl-D-aspartate receptors in the suprachiasmatic nucleus shell [18]. Glycine also binds to these receptors in the rostral ventral medulla, an area involved in the maintenance of arterial baroreceptor reflex [19]. Furthermore, a study in rats with diabetes showed that oral glycine leads to an increase in blood nitric oxide levels, resulting in vasodilation [20]. These central and peripheral effects of glycine may act together to reduce blood pressure.

There are limitations of the current study. Although our previous 4-week study comparing oral glycine with glucose as a placebo found greater improvements by additional glycine in urine storage symptoms, cardiovascular function, bladder pain, and sleep quality [11], this study had a small sample size. In the current study, we started an 8-week study of glycine versus glucose in a larger sample. However, the drop-out rate was extremely high in the glucose group. Therefore, it was not possible to compare the effects of glycine and placebo, and we conducted a single-blind, uncontrolled study but not double-blind, controlled study to evaluate the effects of oral glycine.

Nighttime urination has a negative effect on the quality of life, but the frequency of voiding is not the only related issue reported by patients [21] [22]. Other problems include time to first nighttime voiding and bladder pain, both of which improved in the present study, as did the OABSS, which reflects many related symptoms. These positive changes may explain the increase in IPSS-QOL and GSA scores.

## 5. Conclusion

Glycine appears to improve symptoms of urine storage, blood pressure, and

bladder pain. It does not cause any adverse events or increase the volume of residual urine after voiding. Furthermore, it is inexpensive. Therefore, we suggest that glycine is a safe concomitant treatment for urine storage symptoms and bladder pain and may be particularly useful in patients with hypertension.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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### Abbreviations

BPH = benign prostatic hyperplasia  
 BPS/IC = bladder pain syndrome/interstitial cystitis  
 GSA = global self-assessment  
 IPSS = international prostate symptom score  
 N-QOL = nocturia quality of life  
 OAB = overactive bladder  
 OABSS = overactive bladder symptom score  
 QOL = quality of life  
 SCI = spinal cord injury

### Appendix 1. International Prostate Symptom Score (IPSS)

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score	
<b>1. Incomplete Emptying</b>								
How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5		
<b>2. Frequency</b>								
How often have you had to urinate less than every 2 hours?	0	1	2	3	4	5		
<b>3. Intermittency</b>								
How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5		
<b>4. Urgency</b>								
How often have you found it difficult to postpone urination?	0	1	2	3	4	5		
<b>5. Weak Stream</b>								
How often have you had a weak urinary stream?	0	1	2	3	4	5		
<b>6. Straining</b>								
How often have you had to strain to start urination?	0	1	2	3	4	5		
	<b>None</b>	<b>1 Time</b>	<b>2 Times</b>	<b>3 Times</b>	<b>4 Times</b>	<b>5 Times</b>		
<b>7. Nocturia</b>								
How many times did you typically get up at night to urinate?	0	1	2	3	4	5		
<b>Total IPSS Score</b>								
<b>Score:</b>	<b>1 - 7: Mild</b>		<b>8 - 19: Moderate</b>		<b>20 - 35: Severe</b>			

## Continued

## Quality of Life Due to Urinary Symptoms

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

0                      1                      2                      3                      4                      5                      6

## Appendix 2. Overactive Bladder Symptom Score (OABSS)

	Score	Frequency
How many times do you typically urinate from waking in the morning until sleeping at night?	0	7 or less
	1	8 - 14
	2	15 or more
How many times do you typically wake up to urinate from sleeping at night until waking in the morning?	0	0
	1	1
	2	2
	3	3 or more
How often do you have a sudden desire to urinate, which is difficult to defer?	0	not at all
	1	less than once a week
	2	once a week or more
	3	about once a day
	4	2 - 4 times a day
	5	5 times a day or more
How often do you leak urine, because you cannot defer the sudden desire to urinate?	0	not at all
	1	less than once a week
	2	once a week or more
	3	about once a day
	4	2 - 4 times a day
	5	5 times a day or more

OABSS (sum of scores) =

### Appendix 3. Nocturia Quality of Life Questionnaire (N-QOL)

The following statements are about the impact of “having to get up at night to urinate”. For each item, please mark an (X) in the box next to the response that best describes how you have felt. Please mark only one box for each statement.

OVER THE PAST 2 WEEKS, HAVING TO GET UP AT NIGHT TO URINATE .....

score	4	3	2	1	0	
1	Has made it difficult for me to concentrate the next day	<input type="checkbox"/> Every day	<input type="checkbox"/> Most days	<input type="checkbox"/> Some days	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
2	Has made me feel generally low in energy the next day	<input type="checkbox"/> Every day	<input type="checkbox"/> Most days	<input type="checkbox"/> Some days	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
3	Has required me to nap during the day	<input type="checkbox"/> Every day	<input type="checkbox"/> Most days	<input type="checkbox"/> Some days	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
4	Has made me less productive the next day	<input type="checkbox"/> Every day	<input type="checkbox"/> Most days	<input type="checkbox"/> Some days	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
5	Has caused me to participate less in activities I enjoy	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all
6	Has caused me to be careful about when or how much I drink	<input type="checkbox"/> All the time	<input type="checkbox"/> Most of the time	<input type="checkbox"/> Some of the time	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
7	Has made it difficult for me to get enough sleep at night	<input type="checkbox"/> Every night	<input type="checkbox"/> Most nights	<input type="checkbox"/> Some nights	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never

OVER THE PAST 2 WEEKS, I HAVE BEEN .....

8	Concerned that I am disturbing others in the house because of having to get up at night to urinate	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all	
9	Preoccupied about having to get up at night to urinate	<input type="checkbox"/> All the time	<input type="checkbox"/> Most of the time	<input type="checkbox"/> Some of the time	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never	
10	Worried that this condition will get worse in the future	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all	
11	Worried that there is no effective treatment for this condition (having to get up at night to urinate)	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all	
12	Overall, how bothersome has having to get up at night to urinate been during the past 2 weeks?	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all	
13	Overall, I would rate my quality of life to be .....	Very good 0 1 2 3 4 5 6 7 8 9 10 Very poor					