Traditional Chinese medicine decreases the obstructive uropathy risk in uterovaginal prolapse: A nationwide population-based study

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Abstract

Traditional Chinese medicine (TCM) is a popular treatment for voiding dysfunction in Eastern countries. However, no previous studies have investigated the effects of TCM on preventing obstructive uropathy in uterovaginal prolapse women. We conducted a large-scale nationwide population-based cohort study to investigate the relationship between TCM and obstructive uropathy in uterovaginal prolapse women. This is a retrospective cohort study with the Taiwan National Health Insurance Research Database (NHIRD). The study population was newly diagnosed uterovaginal prolapse patients between 1997 and 2010 year. Among patients, 762 uterovaginal prolapse patients in this cohort. Significant adjusted HRs of urine retention or hydronephrosis in Cox proportional hazard models were uterovaginal prolapse [HR: 1.74, 95% confidence interval: 1.43–2.14]. The Kaplan-Meier analysis showed a higher incidence rate of urine retention or hydronephrosis in the uterovaginal prolapse cohort compared with that of the without uterovaginal prolapse cohort. The results of this nationwide population-based study support a relationship between TCM and a reduced risk of obstructive uropathy in uterovaginal prolapse women.

Keywords: nationwide population-based study, obstructive uropathy, traditional Chinese medicine, uterovaginal prolapse

1. Introduction

Pelvic organ prolapse (POP), the herniation of the pelvic organs to or beyond the vaginal walls, is a common condition in older women. According to previous studies, 32% to 98% of middle-aged and older women are reported to have some degree of pelvic organ prolapse on examination. Untreated uterovaginal prolapse, also called apical compartment prolapse, means the descent of the apex of the vagina into the lower vagina, to the hynem, or beyond the vaginal introitus. The etiology of uterovaginal prolapse is dependent on patient factors such as age, parity, body mass index, and pelvic floor muscle function. Advanced prolapse may cause anatomic distortion of lower urinary tract including urethral kinking, resulted in impaired urine flow and an elevated postvoid residual. According to previous studies, urinary splinting was reported by 5% to 12% of women with stage II anterior prolapse and 23% to 36% of those with stage III or IV anterior prolapse. This anatomic obstruction leads to dysfunctional voiding, which would increase the obstructive uropathy, including clinical conditions of urinary retention or hydronephrosis. The treatment for uterovaginal prolapse women to prevent obstructive uropathy include alpha-adrenergic blocker medications, vaginal pessary, and pelvic reconstructive surgery. Alpha-adrenergic blocker such as terazosin, tamsulosin might act on the urethra alpha1-adrenergic receptor, thus reducing bladder outlet obstruction. Vaginal pessaries are silicone devices in a variety of shapes and sizes, which support the pelvic organs. The use of pessary was associated with relief of urinary retention in 75% patients. Surgical repair of uterovaginal prolapse is dependent on patient’s condition. There are many different surgeries for uterovaginal prolapse, such as abdominal sacral colpopexy, laparoscopic sacrocolpopexy, vaginal surgical approach with synthetic mesh, and transvaginal apical repair procedures. An elevated preoperative PVR normalizes after surgical correction of prolapse in over 90% of women.
However, alpha-blocker has some side effects including dizziness and rhinitis, pessaries must be removed and cleaned on a regular basis and local infection is one of the contraindications, surgical treatment incurs the risk of complications and recurrence,[20] which reduce the willingness of patients to receive treatment.

Traditional Chinese medicine (TCM) is a popular treatment for voiding dysfunction in Eastern countries, including Taiwan.[21–23] For example, Bu-zhong-yi-qì-táng (BT) is a classical formula for the treatment of spleen-qi descending, visceroposis with hyposplenik qi, and uterovaginal prolapse in TCM and has been identified as an effective drug for the treatment of TCM spleen-qi deficiency in clinical practice. The restorative effects of BT were observed in certain metabolic pathways, such as the energy, protein, and glycolytic metabolisms.[24] In Taiwan, >62% of urolithiasis patients use TCM.[25] Previous studies have reported that several Chinese herbs can be used to treat urolithiasis.[26] Some formulae have been proved that can inhibit the severity of calcium oxalate crystallization,[27] some can suppress the growth of crystals, and reduce the incidence of stones in animal models.[28,29] Furthermore, some formulae demonstrate a nephroprotective effect.[30,31] However, no previous studies have investigated the effects of TCM on preventing obstructive uropathy in uterovaginal prolapse women. Therefore, we conducted a large-scale study, using nationwide population-based cohort study, to investigate the relationship between TCM and obstructive uropathy in uterovaginal prolapse women.

2. Materials and methods

2.1. Data sources and study subjects

This is a retrospective cohort study. We used the Taiwan National Health Insurance Research Database (NHIRD) to analysis data. Taiwan launched a compulsory, social insurance program, the NHI program, to provide health care for >99% of the 23.75 million residents in 1995. The longitudinal Health Insurance Database 2000 (LHID2000), which was used in this study, comprises the medical information of 1 million insurer, randomly sampled from the registry of all beneficiaries for the year 2000. The claims data in the LHID2000 was extended to December 31, 2011, and retrospectively collected until January 1, 1996. There were no significant differences in the distributions of sex and age between the original claims data and the sampled data. The diagnosis codes in the NHIRD were in accordance with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2–115). The IRB also specifically waived the consent requirement.

The study population was newly diagnosed uterovaginal prolapse patients between 1997 and 2010 year. Population with uterovaginal prolapse should have at least 2 ambulatory or in-patient’s claims with diagnosis of ICD-9-CM code 618.2 or 618.3 or 618.4. Among patients in the LHID, 762 uterovaginal prolapse patients in this cohort. We used 1:4 frequency match by age and index year to selected random without diagnosis of uterovaginal prolapse as compared cohort group (n = 3048). The index date defined the first diagnosis date of uterovaginal prolapse between 1997 and 2010 year for cohort group; random give the date between 1997 and 2010 years as index date for compared cohort. All subjects were follow-up from the entry date until first diagnosis date of urine retention or hydronephrosis, withdrawal from the database, or December 31, 2011. We excluded who had accepted pelvic reconstructive surgery before the index date.

2.2. Outcome and relevant variables

The primary outcome was the event of obstructive uropathy, including clinical conditions of urine retention (ICD-9-CM 788.20) or hydronephrosis (ICD-9-CM 591) during the follow-up period (1997–2011). Relevant variables were age, drug used, TCM used and comorbidities, including diabetes mellitus (ICD-9-CM: 250), hypertension (ICD-9-CM: 401), cerebrovascular accident (ICD-9-CM: 434.91, 434.11), asthma (ICD-9-CM: 493), constipation (ICD-9-CM: 564.0), and urinary tract calculi (ICD-9-CM: 592.0, 592.1, 592.9, and 594.1). All comorbidities were defined before the index date and should have at least 2 ambulatory or in-patient’s claims.

2.3. Exposure to TCM

The NHIRD records detailed prescription information for both TCM and western medicine codes. Patients using TCM after initial diagnosis of uterovaginal prolapse disease were defined as TCM users, whereas those no treated were considered as TCM non-users.

2.4. Statistical analysis

Difference in demographic characteristics, treatment, TCM used, and comorbidities between the cohort and compared cohort and the reference cohort were tested by chi-square test for categorical variables and t test for continuous variables. We estimated hazard ratio (HR) and 95% confidence intervals (95% CI) by Cox proportional hazard model. The Kaplan–Meier method was used to estimate the obstructive uropathy proportion for the cohort and compared cohort group. All analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC), and the results were considered statistically significant when two-tailed P values were <.05.

3. Results

Baseline sociodemographic factors, comorbidities and treatment between cohort and compared cohort group are shown in Table 1. Uterovaginal Prolapse cohort was linked with the following factors: higher proportions of constipation; urinary tract calculi; TCM used; and alpha-blocker used. The means of age were 55.15 (13.21) and 55.07 (13.28) for uterovaginal prolapse cohort group and compared cohort group, respectively.

Table 2 displays uni- and multivariable Cox proportional hazard models in a cohort of uterovaginal prolapse versus non-uterovaginal prolapse population during 1997 to 2011. Significant adjusted HRs of urine retention or hydronephrosis in Cox proportional hazard models were uterovaginal prolapse (HR: 1.74, 95% CI: 1.43–2.14), age 40–64 years (1.51, 1.01–2.27), >60 years (3.52, 2.32–5.34), DM (1.52, 1.23–1.89), hypertension (1.38, 1.13–1.7), constipation (1.35, 1.05–1.75), urinary tract calculi (1.54, 1.06–2.23), and TCM users (0.34, 0.28–0.41).

Table 3 shows stratified by with and without uterovaginal prolapse, uterovaginal prolapse group using TCM had lower risk of urine retention or hydronephrosis than non-TCM users (aHR:0.2, 95% CI: 0.14–0.29). And non-uterovaginal prolapse
The Kaplan–Meier analysis showed a higher incidence rate of urine retention or hydronephrosis in the uterovaginal prolapse cohort compared with that of the without uterovaginal prolapse cohort (Log rank test, \( P < .001 \)) (Fig. 1). In the uterovaginal prolapse cohort, patients treated with only TCM showed a lower incidence rate of urine retention or hydronephrosis compared with whom treated with non-TCM and alpha-blocker (Fig. 2).

### Table 1
Demographic characteristics and comorbidity in patients with and without uterovaginal prolapse.

| Variables                              | Uterovaginal prolapse | P-value |
|----------------------------------------|-----------------------|---------|
|                                        | No (\( N = 3048 \))   | Yes (\( N = 762 \)) |
| Follow up period (y), mean (median)    | 4.46 (3.64)           | 7.17 (7.24) |
| Age, y                                 |                       |         |
| 18–39 y                                | 384                   | 96      |
| 40–64 y                                | 1860                  | 465     |
| >65 y                                  | 804                   | 201     |
| Mean (SD)                              | 55.07 (13.28)         | 55.15 (13.21) |

### Table 2
Cox model measured hazard ratio and 95% confidence intervals of urine retention or hydronephrosis associated with uterovaginal prolapse.

| Characteristics                        | Urine retention or hydronephrosis | Crude          | Adjusted         |
|----------------------------------------|----------------------------------|----------------|------------------|
|                                        | No. (\( n = 491 \))              | HR (95% CI)    | P-value          | HR (95% CI)    | P-value |
| Uterovaginal prolapse                  |                                  |                |                  |                |         |
| No                                     | 358                              | 1.00 reference |                  | 1.00 reference |         |
| Yes                                    | 133                              | 1.57 (1.28–1.91) | <.0001          | 1.74 (1.43–2.14) | <.0001  |
| Age, y                                 |                                  |                |                  |                |         |
| 18–39 y                                | 27                               | 1.00 reference |                  | 1.00 reference |         |
| 40–64 y                                | 219                              | 1.80 (1.21–2.69) | 0.0039          | 1.51 (1.01–2.27) | .0440   |
| >65 y                                  | 246                              | 5.78 (3.88–8.6) | <.0001          | 3.52 (2.32–5.34) | <.0001  |
| Baseline comorbidity (ref=non-site comorbidity) |          |                |                  |                |         |
| DM                                     | 122                              | 2.15 (1.75–2.64) | <.0001          | 1.52 (1.23–1.89) | .0001   |
| Hypertension                           | 197                              | 2.50 (2.08–2.99) | <.0001          | 1.38 (1.13–1.7) | .0019   |
| Cerebrovascular accident (CVA)         | 1                                | 1.54 (0.22–10.89) | 0.6665          | 0.43 (0.06–3.11) | .4062   |
| Asthma                                 | 42                               | 1.45 (1.06–2)   | 0.0207          | 1.18 (0.85–1.62) | .3247   |
| Constipation                           | 73                               | 1.65 (1.29–2.12) | <.0001          | 1.35 (1.06–1.75) | .0207   |
| Urinary tract calculi                  | 30                               | 1.78 (1.23–2.57) | 0.0023          | 1.54 (1.06–2.23) | .0244   |
| TCM used (after index date)            | 251                              | 1.00 reference |                  | 1.00 reference |         |
| Alpha-blocker used (after index date)  | 240                              | 0.30 (0.25–0.36) | <.0001          | 0.34 (0.28–0.41) | <.0001  |

Adjusted HR: adjusted for uterovaginal prolapse, age, DM, hypertension, cerebrovascular accident, asthma, constipation, TCM used and Alpha-blocker used in Cox proportional hazards regression. CI = confidence interval; HR = hazard ratio.
Table 3
Cox model measured hazard ratio and 95% confidence intervals of urine retention or hydronephrosis associated with TCM used stratified by stage of uterovaginal prolapse.

| Characteristics Urine retention or hydronephrosis no. (n=491) | Crude HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
|----------------------------------------------------------|------------------|--------|---------------------|--------|
| Non-uterovaginal prolapse TCM used (after index date) No | 177   | 1.00    | reference           | 1.00   |
| Yes           | 181   | 0.34 (0.28–0.42)               | <.0001 | 0.41 (0.33–0.50)    | <.0001 |
| Age, y 18–39 y | 18    | 1.00    | reference           | 1.00   |
| 40–64 y      | 160   | 1.98 (1.22–3.23)               | .0058  | 1.71 (1.05–2.80)    | .0319  |
| >65 y        | 180   | 6.47 (3.98–10.51)              | <.0001 | 4.14 (2.50–6.85)    | <.0001 |
| Baseline comorbidity (ref= non-site comorbidity) DM     | 84    | 2.10 (1.64–2.68)               | <.0001 | 1.47 (1.14–1.90)    | .0334  |
| Hypertension  | 142   | 2.53 (2.05–3.14)               | <.0001 | 1.46 (1.15–1.85)    | .0016  |
| Cerebrovascular accident (CVA) 1                     | 2.70 (0.38–19.25)   | .3217  | 0.82 (0.11–5.99)    | .8449  |
| Asthma       | 28    | 1.36 (0.92–2.0)                | .1211  | 1.11 (0.75–1.65)    | .5945  |
| Constipation  | 46    | 1.65 (1.21–2.29)               | .0017  | 1.38 (0.99–1.90)    | .0504  |
| Urinary tract calculi 20                               | 1.79 (1.14–2.81)               | .0118  | 1.69 (1.01–2.52)    | .0445  |
| Alpha-blocker used (after index date) No              | 356   | 1.00    | reference           | 1.00   |
| Yes          | 2     | 0.97 (0.24–3.89)               | .9635  | 0.77 (0.19–3.11)    | .7138  |
| Uterovaginal prolapse TCM used (after index date) No   | 74    | 1.00    | reference           | 1.00   |
| Yes          | 59    | 0.18 (0.13–0.26)               | <.0001 | 0.20 (0.14–0.29)    | <.0001 |
| Age, y 18–39 y | 9    | 1.00    | reference           | 1.00   |
| 40–64 y      | 59    | 1.45 (0.72–2.92)               | .2999  | 0.99 (0.48–2.03)    | .9742  |
| >65 y        | 65    | 4.51 (2.24–9.07)               | <.0001 | 2.11 (0.99–4.52)    | .0534  |
| Baseline comorbidity (ref= non-site comorbidity) DM     | 38    | 2.17 (1.49–3.17)               | <.0001 | 1.63 (1.09–2.44)    | .0173  |
| Hypertension  | 55    | 2.34 (1.65–3.51)               | <.0001 | 1.08 (0.71–1.65)    | .7169  |
| Cerebrovascular accident (CVA) 0                      | -   | -                       | -      | -      | -      |
| Asthma       | 14    | 1.66 (0.95–2.89)               | .0751  | 1.55 (0.87–2.73)    | .1340  |
| Constipation  | 27    | 1.47 (0.96–2.24)               | .0749  | 1.27 (0.82–1.98)    | .2891  |
| Urinary tract calculi 10                               | 1.54 (0.81–2.93)               | .1919  | 1.36 (0.71–2.62)    | .3522  |
| Alpha-blocker used (after index date) No              | 132   | 1.00    | reference           | 1.00   |
| Yes          | 1     | 0.31 (0.04–2.23)               | .2455  | 0.26 (0.04–1.86)    | .1783  |

Adjusted HR: adjusted for uterovaginal prolapse, age, DM, hypertension, cerebrovascular accident, asthma, constipation, TCM used and Alpha-blocker used in Cox proportional hazards regression. CI = confidence interval, HR = hazard ratio, TCM = Traditional Chinese medicine.

4. Discussion

Uterovaginal prolapse is known to be a cause of obstructive uropathy that can result in urine retention or hydronephrosis. According to previous studies, urinary splitting was reported by 5% to 12% of women with stage II anterior prolapse and 25% to 36% of those with stage III or IV anterior prolapse. The prevalence of hydronephrosis in women with advanced POP was 10.3% to 30.6%. Consistent with our findings that uterovaginal prolapse cohort has higher incidence rate of urine retention than non-uterovaginal prolapse patients, using TCM had similar effect but no side effects including dizziness and rhinitis. The use of pessary was associated with relief of urinary retention in 67% to 84% patients, using TCM had less effect but no side effects. Pelvic reconstructive surgery was associated with relief of urinary retention in 90% patients, using TCM had less effect but no side effects.

Chronic urine retention has the potential to cause renal damage if accompanied by high-pressure storage through the transmission of elevated bladder pressures to the upper urinary tract. Hydronephrosis may lead to renal dysfunction and even progress to irreversible renal damage. Hence, chronic urine retention or hydronephrosis from chronic ureteral kinking are indications for uterovaginal prolapse treatment. To our knowledge, this is the first study using a nationwide database to investigate the relationship between TCM use and obstructive uropathy in patients with uterovaginal prolapse.
Figure 1. The estimated cumulative incidence of urine retention or hydronephrosis between the cohort and compared cohort group by Kaplan–Meier analysis.

Figure 2. The estimated cumulative incidence of urine retention or hydronephrosis between those treated with TCM or alpha-blocker in the patients with uterovaginal prolapse cohort by Kaplan–Meier analysis.
In the present study, obstructive uropathy was significantly associated with a diagnosis of diabetes mellitus (HR: 1.52, 95% CI: 1.23–1.89), similar to previous studies’ findings that diabetes mellitus (DM) is clearly seen in a high percentage of women with obstructive uropathy.[32,34] DM patients may have peripheral neuropathy complications and subsequently impair bladder function, hence cause urine retention.[35,36] Furthermore, as diabetes mellitus is associated with glomerulosclerosis and microvascular renal changes, these patients may be at increased risk for complications from the obstructive uropathy caused by POP.[32]

In the present study, obstructive uropathy was significantly associated with a diagnosis of hypertension (HR: 1.38, 95% CI: 1.13–1.7). One reason was that patients with obstructive uropathy may be present with hypertension. The mechanisms of elevated blood pressure may be that acute unilateral obstruction can cause hypertension via activation of the renin-angiotensin system whereas bilateral obstruction may elevate blood pressure through volume expansion.[40,41] Another reason was that half the number of patients with obstructive uropathy were older than 65 years; the incidence of hypertension is associated with advancing age.

There are some limitations of the present study. First, many important information from uroterovaginal prolapse patients such as serum biochemical data regarding stone disease, diet habits, cigarette or alcohol consumption, body weight, and family history of systemic disease was not disclosed in the NHIRD. Also, image data, including x-rays, urodynamic evaluation, and ultrasound, are not available in the NHIRD database, despite that these techniques are valuable techniques for investigating the progression of obstructive uropathy of uroterovaginal prolapse. Second, the severity and disease duration of uterovaginal prolapse could not be evaluated simply by using the ICD-9-CM coding. Third, the relationship between TCM and obstructive uropathy of uroterovaginal prolapse patients was not included in this study, and we were unable to incorporate this information in our study. Finally, the retrospective data generally has more confounding variables than the prospective clinical trials, further prospective studies are warranted to evaluate the relationship between TCM use and obstructive uropathy in uterovaginal prolapse patients.

In conclusions, the results of this nationwide population-based study support a relationship between TCM and a reduced risk of obstructive uropathy in uterovaginal prolapse women.

**Author contributions**

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**Funding acquisition:** Wen-Chi Chen, Yung-Hsiang Chen, Huey-Yi Chen.

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