Tumour-shrinking decoction for symptomatic uterine fibroids: a double-blind, randomised, two-dose trial (abridged secondary publication)

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KEY MESSAGE

Both low-dose and high-dose tumour-shrinking decoction could improve the uterine fibroid–related symptoms and reduce the fibroid size after 16 weeks of treatment.

Hong Kong Med J 2021;27(Suppl 2):S8-10
HMRF project number: 11121841

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Background

Uterine fibroids (UFs) are the most common benign tumours in women in the middle and later reproductive ages.[1] These women may experience irregular vaginal bleeding, heavy or painful periods, abdominal discomfort or bloating, painful defecation, back ache, urinary frequency or retention, miscarriage, premature labour, and even infertility, depending upon the location, size, and number of UFs. A formula called tumour-shrinking decoction (TSD) was developed for the treatment of UFs. The preliminary results from experimental and clinical studies[2,3] and the empirical evidence from clinical practice have warranted a controlled trial to examine the effectiveness of TSD for treating UFs.

We hypothesised that TSD could effectively reduce the fibroid size and improve the symptoms associated with UFs, and its greater anti-tumour potency was associated with higher therapeutic doses. We aimed (1) to evaluate the efficacy and safety of TSD in the treatment of UFs, including alleviating the UF-related symptoms and reducing the fibroid size, (2) to verify if high dose is more effective than low dose, and (3) to explore the effect of the quality control of TSD on the clinical research.

Methods

This was a double-blind randomised controlled trial. A total of 78 women with symptomatic UFs were recruited and randomised to receive either low (69 g/day) or high (217 g/day) dose daily TSD for 16 weeks. The severity of UF-related symptoms and the quality of life were evaluated using the 37-item Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire (UFS-QOL). Blood loss, pelvic pain, traditional Chinese medicine (TCM) syndrome, magnetic resonance imaging (MRI) findings, serum concentrations of follicle-stimulating hormone, oestradiol, and haemoglobin were also assessed. Adverse events were closely monitored and recorded. The quality of the herbs in TSD was established using the ultra-performance liquid chromatography and high-performance liquid chromatography.

Results

Between May 2014 and May 2016, five (6.4%) of the 78 women dropped out. All the tested samples fulfilled the Hong Kong Chinese Materia Medica Standards. The linear mixed effects model showed no significant difference between the low-dose and high-dose groups in terms of symptom severity, health-related quality of life, pictorial blood assessment chart, and pelvic pain. Similar results were obtained after controlling for age, duration of illness, and co-medication. Therefore, high-dose group was not more efficacious than low-dose group in reducing UF symptoms, blood loss, pelvic pain, or improving quality of life across study time points.

There was significant within-group improvement from baseline to end-point in terms of UF-related symptoms, with the strongest effect on pelvic pain, followed by symptom severity, pictorial blood assessment chart, and quality of life. There was no significant between-group difference in follicle-stimulating hormone, oestradiol, haemoglobin, or pelvic MRI data (Table 1).

Both low-dose and high-dose groups had

reduction in the fibroids size. The low-dose group had significantly higher reduction of TCM syndrome score than the high-dose group (P<0.01), even after adjusting for age, duration of illness, and co-medication (Tables 2 and 3).

TABLE 1. Results of Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire, pictorial blood assessment chart, and pelvic pain across study time points

Variables	Low-dose group (n=39)*	Within-group effect size	High-dose group(n=39)*	Within-group effect size	P value for group by time interaction
Symptom severity					
Baseline	47.60±18.49		42.71±18.49		
2nd treatment	40.53±18.67	0.38	37.48±18.67	0.28	0.88
3rd treatment	38.77±18.86	0.47	35.86±19.05	0.36	0.75
4th treatment	36.39±18.86	0.60	29.11±19.17	0.72	0.71
5th treatment	33.54±18.86	0.75	29.39±19.30	0.70	0.40
End-point	33.30±19.30	0.76	28.99±19.11	0.73	0.96
Health-related quality of life					
Baseline	49.04±10.12		49.04±10.05		
2nd treatment	51.44±10.18	-0.24	49.73±10.12	-0.07	0.44
3rd treatment	52.70±10.30	-0.36	47.64±10.49	0.14	0.83
4th treatment	54.21±10.30	-0.51	52.78±10.55	-0.36	0.33
5th treatment	55.30±10.30	-0.61	52.93±10.68	-0.38	0.70
End-point	55.10±10.62	-0.58	52.74±10.55	-0.36	0.99
Pictorial blood assessment chart					
Baseline	471.49±316.43		397.64±316.43		
2nd treatment	338.69±321.12	0.42	345.39±319.68	0.16	0.31
3rd treatment	337.08±323.55	0.42	313.44±328.30	0.26	0.75
4th treatment	314.55±322.30	0.49	364.93±326.68	0.10	0.85
5th treatment	309.62±322.18	0.51	309.18±330.36	0.27	0.28
End-point	321.43±329.30	0.46	309.09±327.55	0.27	0.82
Pelvic pain					
Baseline	17.00± 10.80		14.49±10.80		
2nd treatment	11.30±10.99	0.52	7.98±10.99	0.60	0.38
3rd treatment	10.15±11.12	0.62	7.33±11.43	0.64	0.24
4th treatment	8.71±11.12	0.76	6.83±11.37	0.69	0.33
5th treatment	7.72±11.18	0.84	7.45±11.55	0.63	0.51
End-point	7.03±11.49	0.89	6.86±11.37	0.69	0.97

* Data are presented as mean ± standard deviation adjusted for last assessment time

Discussion

Both low-dose and high-dose groups could effectively improve UF symptom severity, pelvic pain, TCM syndrome, and fibroids size after 16 weeks of treatment. Surprisingly, there was no significant difference in efficacy between the two groups; the low-dose TSD had similar efficacy as the high-dose one. There was significant improvement in quality of life and blood loss in the low-dose group. The dose-effect relationship of TSD was not proportional because the efficacy of the formula depends on the proper usage and combination of herbs according to the TCM theory of 'Jun-chen-zuo-shi' (ie, monarch, minister, assistant, and emissary) and syndrome differentiation. Reduction on routine drug dosage may be cost-effective by saving medicinal resource and decreasing the potential adverse reactions.

The amount of blood loss was counted using the pictorial blood assessment chart. After the treatment, the irregular bleeding condition was significantly improved. Most women had built up the menstrual cycle, with the menstrual period for about 7 days. Moreover, most women reduced the in-take amount of haemostatic Western medicine or even stop taking it. Therefore, with the function of tonifying Qi, resolving blood stasis, and reducing blood loss, TSD was effective in treating the symptomatic UFs.

About one-third of the women had menstrual pain and chronic pelvic pain. The causes of pain included oppression from UFs and complicating adenomyosis. Both low-dose and high-dose TSD could reduce the pelvic pain effectively. This indicated that the function of resolving blood stasis and dissipating binds of TSD played an important role in improving the pelvic microenvironment.

After the treatment, the UFs shrank or the rate of growth reduced, which was closely related to resolving blood stasis, softening the hardness, and dissipating binds of TSD. We speculate that the TSD has a regulatory role in cell signalling, cell cycle, gene transcription, and gene encoding of protein kinase activity in UFs, such as up-regulation of genes CYCS (which might be associated with apoptosis of leiomyoma), up-regulation of genes KLF6 (which inhibits the proliferation of leiomyoma cells), and regulation of cells proliferation and apoptosis of UFs through the pathways mediated by OP18.[4]

The treatment continued during the menstruation period as the efficacy of TSD was not achieved by suppressing the hormonal activity. This mechanism in treating UFs differs from that of Western medicine. TSD does not cause menopause, hot flashes, irritability, insomnia, or other adverse reactions. This study was an interdisciplinary collaboration between clinical researchers and basic science researchers. It demonstrates that it is possible to establish a quality-control programme to monitor the quality of polymedicinal preparations using botanical and chemical methods.

Conclusions

Both low-dose and high-dose TSD could improve the UF-related symptoms and reduce the fibroid size. There was significant improvement from baseline

TABLE 2. Results of traditional Chinese medicine syndrome, biomarkers, and magnetic resonance imaging (MRI) findings at baseline and end-point

Variables	Low-dose group (n=39)*	Within-group effect size	High-dose group (n=39)*	Within-group effect size	P value for group by time interaction
Traditional Chinese medicine syndrome					
Baseline	20.44±4.06		18.90±4.12		
End-point	12.22±4.12	2.01	12.64±4.18	1.51	0.024
Follicle-stimulating hormone, mIU/mL					
Baseline	9.51±9.06		11.24±9.06		
End-point	8.79±8.93	0.08	11.75±9.18	-0.06	0.61
Oestradiol, pg/mL					
Baseline	76.94±75.00		73.95±76.00		
End-point	78.51±75.00	-0.02	72.28±77.06	0.02	0.89
Haemoglobin, g/dL					
Baseline	10.54±2.25		10.79±2.25		
End-point	10.24±2.31	0.13	10.50±2.31	0.13	0.99
MRI fibroid, cm^3					
Baseline	154.39±273.28		258.83±277.03		
End-point	108.18±273.28	0.17	197.55±277.03	0.22	0.36
MRI uterus, cm^3					
Baseline	863.74±587.34		972.53±595.40		
End-point	735.85±587.34	0.22	875.79± 595.40	0.16	0.29

* Data are presented as mean ± standard deviation

to end-point in terms of UF-related symptoms, with the strongest effect on pelvic pain, followed by symptom severity, pictorial blood assessment chart, and quality of life.

Acknowledgements

Many thanks to Dr Joyce Chai and Ms Joanne Ng of the Queen Mary Hospital for the recruitment of patients. Special thanks go to Prof Vivian Taam Wong JP, Prof Bian Zhao-xiang, Prof Tang Jin-ling, and Dr Carlos Wong for being members of the Data and Safety Monitoring Board. We also thank the Chinese medicine dispensers for preparing the TSD preparations and all research assistants. Finally, we thank the patients who participated in this study.

Funding

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11121841). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

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TABLE 3. Change from baseline to end-point in the low-dose and high-dose groups

Variable	Low-dose group					High-dose group				
	Baseline*	End-point*	*t*	df	P value	Baseline*	End-point*	*t*	df	P value
Symptom severity	44.82±16.59	30.96±16.71	4.42	31	<0.001	40.71±17.16	28.04±20.48	4.15	34	<0.001
Health-related quality of life	46.07±17.08	52.37±16.95	-3.06	31	0.004	53.45±15.82	56.87±22.57	-1.34	34	0.19
Pictorial blood assessment chart	474.91±391.28	322.84±279.62	3.22	31	0.003	336.41±227.07	264.21±227.67	1.67	33	0.11
Pelvic pain	17.69±14.96	7.28±9.33	4.34	31	<0.001	15.29±15.10	7.29±8.72	3.52	33	0.001
Traditional Chinese medicine syndrome	20.30±3.25	12.14±4.62	13.28	36	<0.001	18.44±3.98	12.35±4.40	10.21	33	<0.001
Follicle-stimulating hormone, mIU/mL	9.66±5.91	8.96±8.20	0.49	34	0.63	10.59±9.63	12.08±9.77	-0.74	31	0.47
Oestradiol, pg/mL	77.73±66.83	76.80±86.78	0.06	34	0.95	78.75±73.85	73.73±68.16	0.29	31	0.78
Haemoglobin, g/dL	10.48±2.11	10.19±2.49	1.20	36	0.24	10.81±2.21	10.51±2.31	1.41	34	0.17
MRI fibroid, cm^3	154.39±148.40	108.18±118.88	6.75	36	<0.001	258.83±391.07	197.55±311.88	4.05	35	<0.001
MRI uterus, cm^3	863.74±516.77	735.85±456.61	5.62	36	<0.001	972.53±675.11	875.79±618.72	5.22	35	<0.001

* Data are presented as mean ± standard deviation

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