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Efficacy and Safety of Blood Stasis Based Herbal Medicine for Patients with Traffic Accident : A Prospective Observational Study

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ABSTRACT

Background: Blood stasis (BS) is commonly used for pattern identification in traumatic injuries, including traffic accidents (TAs). Various studies have identified the efficacy of Korean medicine treatments for TA patients, but studies focusing on the BS-based herbal medicine (BSHM), including Tongdo-san (TDS), are rare.
Methods: This was a single-center, prospective observational study, conducted from August 24th, 2018 to December 27th, 2018, which included 40 TA patients. Participants underwent routine Korean medicine treatments including acupuncture, electronic moxibustion, cupping, physical therapy, and herbal medicine. In the herbal medicine treatment, participants took BSHM with more than 3 days including taking TDS. The primary outcome measures were the scores from a 100 mm visual analogue scale (VAS) and numerical rating scale (NRS). Secondary outcome measures included scores from EuroQol-5 dimension (EQ-5D) and EQ-VAS questionnaires, the BS and cold/heat indices, and safety assessments.
Results: There were significant improvements in the VAS, NRS, EQ-5D, EQ-VAS scores, and BS index after treatment. In the sub-analysis, VAS, NRS, EQ-5D, and EQ-VAS scores were higher in groups with a higher BS index. The moderate and severe BS index groups showed more improvement than the minor BS index group, and there was a significant difference in the EQ-5D scores. There was no significant differences observed in cold/heat index groups scores.
Conclusion: BS is associated with TA-related symptoms. BSHM, including TDS, may significantly reduce BS, pain, and discomfort.

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Introduction

Blood stasis (BS) is a significant pathological concept in Korean medicine (KM) [1]. It involves structural and functional slowing of blood circulation leading to characteristic symptoms such as bleeding, chills, fever, abdominal or flank discomfort, and dark-purple signs in the face, tongue, and under the eyes [2]. BS is known to cause pain by obstructing the meridian system and circulatory system of the body.

Furthermore, BS has been used, mainly in KM, to explain the cause of pain sustained during traumatic injury, including traffic accidents (TAs) [3]. Although TA patients have different symptoms due to various factors including collision type and seat position [4], these symptoms are related to traumatic injury, and 94.2% of KM doctors consider these injuries to be related to BS [5]. Therefore, KM doctors aim to treat TA patients by reducing BS by administering various therapies including acupuncture, herbal medicine, and cupping [6]. Among them, the use of various types of BS-based herbal medicines (BSHMs) has been reported [7,8].

BSHMs including Tongdo-san (TDS), which is mentioned

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in Donguibogam [9], is comprised of 11 herbs (Rhei rhizoma, natrii sulfas, angelicae gigantis radix, sappan lignum, persicae semen, carthami flos, glycyrrhizae radix, akebiae caulis, aurantii immaturus fructus, citri pericarpium, and magnolia cortex), which have the potential to relieve pain. Rhei rhizoma and natrii sulfas exert anti-inflammatory effects [10,11], while angelicae gigantis radix and sappan lignum have analgesic effects [12,13]. Additionally, carthami flos and persicae semen reduce BS and have antinociceptive, anti-inflammatory, and anticoagulation effects [14-16], while the other ingredients exert anti-inflammatory activity for alleviating pain [17-21].

However, the efficacy and safety of BSHM has not been studied apart from 1 observational study [22] therefore, a prospective observational study was conducted using BSHM, including TDS.

Materials and Methods

Study design

This study was a prospective observational study conducted at Dongguk University Bundang Oriental Hospital (DUBOH, Korea). This study followed the principles of the Declaration of Helsinki and it was approved by the Institutional Review Board of DUBOH on July 4th, 2018 (IRB no.: DUBOH-2018-0010). This study was registered with the Clinical Research Information Service (CRIS; KCT0004648).

Participants

This study included 40 TA patients, aged > 19 years, who were assessed for eligibility by predefined inclusion and exclusion criteria. All participants were to undergo KM treatments and BSHM at DUBOH (as outpatients or inpatients). Participants were excluded if they had participated in other clinical trials within 3 months of beginning this current trial, were unable to adjust their schedule for this trial, or had difficulty responding to the research questionnaires.

Intervention

After fulfilling the eligibility criteria and voluntarily signing the informed consent form, participants underwent KM treatments every day for 7 days. During the follow-up period, participants were treated according to their needs.

Acupuncture

After disinfection of the area with an alcohol swab, stainless steel sterilized needles with a diameter of 0.25 mm and a length of 40 mm (Dongbang Medical, Korea) were inserted into the selected acupuncture or ashi points to a depth of 10-20 mm, and electronic stimulation was applied using electro-acupuncture apparatus (STN100, StraTek, Korea) for 15 minutes. Participants received acupuncture treatment once or twice a day for 7 days.

Electronic moxibustion

Rechargeable electronic moxibustions (Cettum, K-medical Co., Korea) were placed on the sites of pain or acupuncture points for 15 minutes.

Cupping

Cupping was conducted once a day. The cups were placed over the painful parts of the body and performed for 5 minutes.

Physical therapy

Transcutaneous electrical nerve stimulation was applied to the painful parts of the body for 10 minutes, once a day.

Pharmacopuncture

Pharmacopuncture (0.1-1 mL) was conducted using a disposable syringe (Shina Cor., 1 mL, 31 G, Korea). Jungsongouhyul (Jaseng, Korea) or bee venom (10,000:1, 20,000:1, Jaseng, Korea) were the most commonly used pharmacopuncture. Each 0.02-0.2 mL was injected at acupuncture or ashi points to the depth of either subcutaneous or intramuscular regions.

Herbal medicine

The participants consumed herbal medicine twice a day for 2 weeks and TDS was the first to be prescribed for at least 3 days (Table 1). Following this, participants consumed the herbal medicine according to their individual clinical symptoms, but BSHM including TDS was the primary medication.

Outcomes

The 100 mm visual analogue scale (VAS) and numerical rating scale (NRS) were used to measure the primary outcome [23]. The participants marked the VAS according to the intensity of pain they were experiencing which was on a scale from 0 (no pain and discomfort) to 100 (the most severe pain and discomfort) on a 100 mm line. Additionally, participants performed the NRS to show the extent of the average pain they felt daily on a scale of 0 (painless at all) to 10 (the most painful condition). Changes in VAS and NRS scores between Visits 1 and 8 were noted.

Secondary outcome measures were indicated using the EuroQol-5 dimension (EQ-5D), EuroQol-VAS (EQ-VAS) questionnaires, the BS index, and the cold/heat index (CH index) during Visits 1, 8, and 9. The EQ-5D was used to measure health-related quality of life and was composed of 5 items (mobility, self-

Table 1. Components of Tongdo-san.

Scientific name	Latin name	Ratio (g)
Rheum palmatum L.	Rhei rhizoma	8
Mirabilite	Natrii sulfas	8
Angelica gigas Nakai.	Angelicae gigantis radix	4
Caesalpinia sappan L.	Sappan lignum	4
Prunus persica (L.) Batsch	Persicae semen	4
Carthamus tinctorius L.	Carthami flos	4
Glycyrrhiza uralensis Fisch.	Glycyrrhizae radix	2
Akebia quinata Decaisne	Akebiae caulis	2
Citrus aurantium L.	Aurantii immaturus fructus	2
Citrus unshiu Markovich	Citri pericarpium	2
Magnolia officinalis Rehder et Wilson	Magnoliae cortex	2

care, usual activities, pain/discomfort, and anxiety/depression). The EQ-VAS used a scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine) for indicating the overall rating of health. In this study, the Korean version of the EQ-5D and EQ-VAS were used [24-26]. The BS index is a questionnaire developed using the Delphi method to estimate the severity of BS. It is composed of 14 items, and participants checked points from 1 to 7. The data were calculated using the pre-defined formula [27]. The CH index comprised of a cold/heat questionnaire including 15 items in 6 categories and was used to estimate the tendency of cold/heat in an individual. The participants scored points from 0 (not at all) to 6 (very). After the pre-defined calculation, the cold score and heat score were compared and the cold/heat tendency was determined [28]. Observations for adverse events and vital signs were made at every visit and were recorded in detail as part of the safety assessment (Table 2).

Sub-group classification

Regarding the BS index, sub-groups were formed to investigate the difference in therapeutic effect according to the degree of BS. Since there was no clear classification criteria according to the BS index, 2 or 3 groups were formed based on the mean, and the distribution of the index. The 40 participants were sub-grouped according to the results of CH index. Regarding the classification of CH index, it was assigned as either a cold or heat tendency according to the prescribed formula [28], based on the CH index at Visit 1.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows version 20.0; SPSS Inc., Chicago, IL, USA). Categorical variables were presented as percentages, and continuous variables were presented as mean ± standard deviation. The chi-square test or Fisher's exact test were performed for categorical variables. The paired t test was used to analyze changes in scores in VAS, NRS, EQ-5D, EQ-VAS, BS index, and CH index. In the sub-group analysis, the changes in continuous variables were analyzed using the independent t test or Mann-Whitney test between 2 groups, and Kruskal-Wallis test or one-way analysis of variance among 3 or more sub-groups. All statistical verification was determined at the 95% confidence interval when $p < 0.05$.

Results

Patient characteristics

This study recruited TA patients from August 24th, 2018 to December 27th, 2018. None of the participants withdrew from the trial (Fig. 1). Among the 40 participants who enrolled, 19 were male and 21 were female, and 11 were outpatients and 29 were inpatients. The most frequent TA was rear collision (n = 18) causing pain in the cervical and lumbar spine. TDS was typically prescribed for 3-5 days, however there were 4 cases in which the participants took TDS for > 1 week (Table 3).

Analysis of outcome measures

In the primary outcome, the changes in VAS and NRS scores showed significant improvement not only between Visits 1 and 8

Table 2. Study Time and Events Schedule.

	Study period									
	Enrollment	Intervention								Follow up
Time point (d)	0	1	2	3	4	5	6	7	8	15
Time point (visit)	0 (screening)	1	2	3	4	5	6	7	8	9
Enrollment:										
Eligibility screen	X									
Informed consent	X									
Interventions:										
KM treatment		X	X	X	X	X	X	X	X	X
TDS (at least)		X	X	X						
Assessments:										
VAS, NRS	X	X	X	X	X	X	X	X	X	X
EQ-5D, EQ-VAS, BS index, CH index		X							X	X
Adverse events, v/s, change of medication		X	X	X	X	X	X	X	X	X

BS, blood stasis; CH, cold/heat; EQ-5D, EuroQol-5 dimension; EQ-VAS, EuroQol-visual analogue scale; KM, Korean medicine; NRS, numerical rating scale; TDS, Tongdo-san; VAS, visual analogue scale; v/s, vital sign.

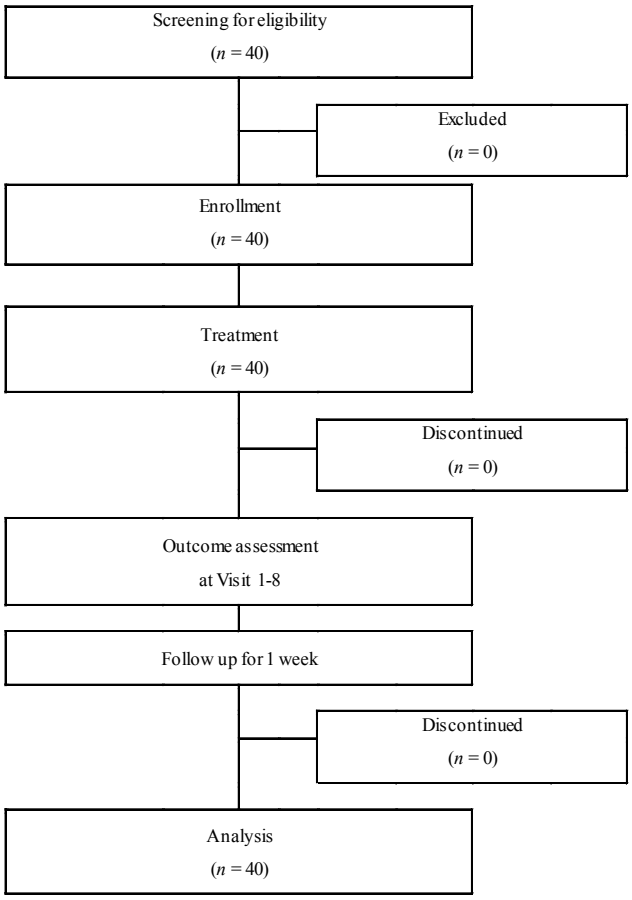

Fig. 1. CONSORT flow diagram of the study.

(VAS: 25.825 ± 17.027, p = 0.000; NRS: 2.475 ± 1.552, p = 0.000), but also between Visits 8 and 9 (VAS: 5.350 ± 15.647, p = 0.037; NRS: 0.550 ± 1.551, p = 0.031). In the secondary outcomes, the changes in EQ-5D, EQ-VAS, and BS index scores showed significant improvement between Visits 1 and 8 (EQ-5D: 0.375 ± 1.352, p = 0.000; EQ-VAS: 4.475 ± 15.914, p = 0.000; BS index: 2.839 ± 1.953, p = 0.000), but not between Visits 8 and 9 (Table 4). During the administration of TDS, diarrhea (n = 8) and abdominal pain (n = 5) were reported.

Sub-analysis according to the BS index

The BS index at Visit 1 showed a range of 3 to 13 points. There were no guidelines or studies to classify BS severity according to the BS index. Hence, the mean BS index of 40 participants (9.041) was calculated and the 3 groups were assigned accordingly whilst attempting to match the numbers in each group thus, BS indexes 3-7 were classified as the minor group, 8-9 as the moderate group, and 10-13 as the severe group.

In the baseline, the close relationship between BS index and VAS, NRS, EQ-5D, and EQ-VAS scores was confirmed by showing that the VAS, NRS, EQ-5D, and EQ-VAS scores in the 3 groups worsened as the BS score increased. Particularly, among the 3 groups, there were significant differences in VAS, EQ-5D, and EQ-VAS scores (Kruskal-Wallis; $p < 0.05$), in which significant

Table 3. Patient Characteristics at Visit 1.

Characteristics	Male (n = 19)	Female (n = 21)	Total (n)
Age (y)			
10-19	1	0	1
20-29	1	6	7
30-39	6	2	8
40-49	5	7	12
50-59	3	2	5
60-69	3	2	5
70-79	0	2	2
Collision type			
Front	3	5	8
Rear	8	10	18
Left side	2	4	6
Right side	1	2	3
Multiple	4	0	4
Other	1	0	1
Treatment			
Outpatient	6	5	11
Inpatient	13	16	29
Taking TDS period			
3	6	6	12
4	5	5	10
5	4	7	11
6	1	2	3
≥ 7	3	1	4
BS index			
3	1	0	1
4	1	1	2
5	0	1	1
6	2	2	4
7	2	1	3
8	4	2	6
9	2	6	8
10	2	6	8
11	3	2	5
12	1	0	1
13	1	0	1

BS, blood stasis; TDS, Tongdo-san.

Table 4. The Change in Scores Between Visit 1, 8, and 9.

	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
VAS	62.650 ± 18.131	36.825 ± 19.763	31.475 ± 20.394	-25.825 ± 17.027	-5.350 ± 15.647
p				0.000**	0.037*
NRS	6.300 ± 1.727	3.825 ± 1.838	3.275 ± 1.921	-2.475 ± 1.552	-0.550 ± 1.551
p				0.000**	0.031*
EQ-5D	12.250 ± 4.049	8.675 ± 2.324	8.300 ± 2.138	-3.575 ± 3.201	-0.375 ± 1.352
p				0.000**	0.087
EQ-VAS	44.050 ± 16.025	63.850 ± 13.390	68.325 ± 17.279	19.800 ± 15.960	4.475 ± 15.914
p				0.000**	0.083
Blood stasis index	9.041 ± 2.256	6.652 ± 1.998	6.513 ± 2.136	-2.839 ± 1.953	-0.139 ± 1.609
p				0.000**	0.587

* $p < 0.05$, ** $p < 0.01$ by paired *t* test in group.
EQ-5D,EuroQol-5 dimension; EQ-VAS, EuroQol-visual analogue scale; NRS, numerical rating scale; VAS, visual analogue scale; V, visit.

Table 5. Analysis of Scores for VAS, NRS, EQ-5D, and EQ-VAS at Visit 1 Classified by the BS Index.

Classification	VAS at V1	NRS at V1	EQ-5D at V1	EQ-VAS at V1
Minor group ($n = 11$)	51.363 ± 17.089	5.454 ± 1.634	7.727 ± 1.555	55.454 ± 15.794
Moderate group ($n = 14$)	62.785 ± 16.446	6.285 ± 1.489	12,857 ± 3.880	44.000 ± 13.067
Severe group ($n = 15$)	70.800 ± 16.874	6.933 ± 1.830	15.000 ±2.329	35.733 ± 14.225
Total	62.650 ± 18.131	6.300 ± 1.727	12.250 ± 4.049	44.050 ± 16.025
p (KW)	0.017*	0.146	0.000**	0.014*
Minor versus Moderate group	0.183	0.272	0.000††	0.049†
Minor versus Severe group	0.006††	0.057	0.000††	0.006††
Moderate versus Severe group	0.101	0.325	0.071	0.201

* $p<0.05$, ** $p<0.01$ by Kruskal-Wallis (KW) test between 3 groups.
† $p<0.05$, †† $p<0.01$ by Mann-Whitney test between 2 groups.
EQ-5D,EuroQol-5 dimension; EQ-VAS, EuroQol-visual analogue scale; NRS, numerical rating scale; VAS, visual analogue scale; V, visit.

differences between the minor and moderate or severe groups could be confirmed (Table 5).

Additionally, this close relationship, even in the change in the 4 scales between Visits 1 and 8 were observed. While each group showed significant improvement, except for EQ-5D scores in the minor group, the most improvement was noted in the moderate and severe groups. Among the 3 groups, there was no significant difference in VAS, NRS, and EQ-VAS scores, but we observed significant differences in the EQ-5D scores. Changes observed in the 4 scales between Visits 8 and 9, gave uncertain results. While each group showed improvement, there was no significant difference in the VAS scores between the severe and moderate groups. There was no tendency for a particular group to show the most improvement, and there was no significant difference among the 3 groups (Table 6).

Sub-analysis according to the CH index

Based on the CH index, the proportion of cold and heat tendencies at Visit 1 was 24:16. This proportion was maintained at Visit 8, and participants with a cold tendency increased from 24 to 27 at Visit 9. In a few cases, changes to a cold tendency were confirmed. The 40

Table 6. The Change of VAS, NRS, EQ-5D, and EQ-VAS Scores Classified by the BS Index.

VAS	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Minor group (n = 11)	51.363 ± 17.089	32.636 ± 22.874	24.818 ± 19.456	-18.727 ± 18.133	-7.818 ± 12.464
p				0.014*	0.074
Moderate group (n = 14)	62.785 ± 16.446	31.071 ± 12.079	28.357 ± 17.176	-31.714 ± 19.148	-2.714 ± 22.584
p				0.001**	0.124
Severe group (n = 15)	70.800 ± 16.874	45.266 ± 21.345	39.266 ± 22.467	-25.533 ± 12.569	-6.000 ± 9.235
p				0.001**	0.030*
p (KW)				0.190	0.985
NRS	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Minor group (n = 11)	5.454 ± 1.634	3.454 ± 2.252	2.545 ± 1.809	-2.000 ± 1.843	-0.909 ± 1.446
p				0.007**	0.076
Moderate group (n = 14)	6.285 ± 1.489	3.357 ± 1.008	3.000 ± 1.519	-2.928 ± 1.591	-0.357 ± 2.097
p				0.001**	0.144
Severe group (n = 15)	6.933 ± 1.830	4.533 ± 1.995	4.066 ± 2.153	-2.400 ± 1.242	-0.466 ± 0.990
p				0.001**	0.112
p (KW)				0.297	0.637
EQ-5D	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Minor group (n = 11)	7.727 ± 1.555	6.909 ± 1.700	7.000 ± 2.000	-0.818 ± 1.401	0.090 ± 0.700
p				0.084	0.655
Moderate group (n = 14)	12.857 ± 3.880	9.000 ± 1.754	8.428 ± 1.452	-3.857 ± 3.738	-0.571 ± 1.222
p				0.003**	0.068
Severe group (n = 15)	15.000 ± 2.329	9.666 ± 2.554	9.133 ± 2.416	-5.333 ± 2.193	-0.533 ± 1.767
p				0.001**	0.216
p (KW)				0.000††	0.380
EQ-VAS	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Minor group (n = 11)	55.454 ± 15.794	71.090 ± 17.688	74.000 ± 23.558	15.636 ± 17.385	2.909 ± 11.978
p				0.013*	0.202
Moderate group (n = 14)	44.000 ± 13.067	61.857 ± 11.766	71.357 ± 11.766	17.857 ± 17.797	9.500 ± 13.760
p				0.007*	0.030*
Severe group (n = 15)	35.733 ± 14.225	60.400 ± 9.462	61.333 ± 14.573	24.666 ± 12.522	0.933 ± 19.663
p				0.001**	0.392
p (KW)				0.253	0.109

* p<0.05, ** p<0.01 by Wilcoxon signed-rank test in group.
† p<0.05, †† p<0.01 by Kruskal-Wallis (KW) test between 3 groups.
BS, blood stasis; EQ-5D,EuroQol-5 dimension; EQ-VAS, EuroQol-visual analogue scale; NRS, numerical rating scale; VAS, visual analogue scale; V, visit.

participants were assigned a cold or heat tendency group according to the CH index at Visit 1. At baseline, there was no significant difference in the 4 scales between the 2 groups.

With respect to the changes in the 4 scales between Visits 1 and 8, each group showed improvements, but there was no significant difference between the 2 groups. On the other hand, between Visits 8 and 9, the cold tendency group showed significant improvement in VAS, NRS, and EQ-VAS scores, but there was no significant difference between the 2 groups (except for the EQ-VAS scores; Table 7).

Table 7. The Change of VAS, NRS, EQ-5D, and EQ-VAS Scores Classified by the CH Index.

VAS	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Cold (n = 24)	62.791 ± 19.624	36.041 ± 19.813	26.541 ± 18.077	-26.750 ± 13.904	-9.500 ± 8.551
p				0.000**	0.000**
Heat (n = 16)	62.437 ± 16.252	38.000 ± 20.278	38.875 ± 21.978	-24.437 ± 21.307	0.875 ± 21.344
p				0.001**	0.670
p (MW)				0.868	0.070
NRS	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Cold (n = 24)	6.375 ± 1.974	3.708 ± 1.921	2.750 ± 1.621	-2.666 ± 1.522	-0.958 ± 0.907
p				0.000**	0.000**
Heat (n = 16)	6.187 ± 1.327	4.000 ±1.751	4.062 ± 2.112	-2.187 ± 1.600	0.062 ± 2.080
p				0.001**	0.836
p (MW)				0.516	0.066
EQ-5D	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Cold (n = 24)	11.833 ± 3.679	8.291 ± 2.274	8.041 ± 2.136	-3.541 ± 2.604	-0.250 ± 1.224
p				0.000**	0.267
Heat (n = 16)	12.875 ± 4.602	9.250 ± 0.588	8.687 ± 2.151	-3.625 ± 4.031	-0.562 ± 1.547
p				0.006**	0.116
p (MW)				0.760	0.395
EQ-VAS	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Cold (n = 24)	45.166 ± 18.400	65.333 ± 14.813	73.458 ± 14.992	20.166 ± 15.544	8.125 ± 15.712
p				0.000**	0.009**
Heat (n = 16)	42.375 ± 11.982	61.625 ± 10.996	60.625 ± 18.062	19.250 ± 17.066	-1.000 ± 15.055
p				0.002**	0.633
p (MW)				0.890	0.010†
BS index	V1	V8	V9	The change between V1 and 8	The change between V8 and 9
Cold (n = 24)	8.869 ± 2.156	6.679 ± 2.208	6.366 ± 2.305	-2.189 ± 1.726	-0.313 ± 1.353
p				0.000**	0.372
Heat (n = 16)	9.301 ± 2.446	6.612 ± 1.703	6.733 ± 1.906	-2.689 ± 2.278	0.121 ± 1.951
p				0.001**	0.796
p (MW)				0.362	0.782

* p<0.05, ** p<0.01 by Wilcoxon signed-rank test in group.
† p<0.05, †† p<0.01 by Mann-Whitney (MW) test between 2 groups.
CH, cold/heat; EQ-5D,EuroQol-5 dimension; EQ-VAS, EuroQol-visual analogue scale; NRS, numerical rating scale; VAS, visual analogue scale; V, visit.

Sub-analysis according to each BS index and questionnaire EQ-5D

The 5 questions of the EQ-5D showed significant improvement between Visits 1 and 8. The most improved items were the third and fourth questions that assessed the pain/discomfort and usual activities by showing a decrease of > 0.8 points. There was no significant improvement between Visits 8 and 9. In the above results, TDS improved the overall quality of life. It was clinically confirmed that there were significant improvements in daily activities based on the original objective of reducing pain and discomfort (Fig. 2).

Significant improvements were observed in 10 out of 15 questions of the BS index between Visits 1 and 8. The most improved item was the fourth question that assessed stabbing pain by showing a decrease of > 1.5 points. Between Visits 8 and 9, only the 6th question assessing flank pain showed significant improvement. Questions 11-14 showed low scores during Visit 1, and assuming the non-changeable question (number of operations), it has been clinically confirmed that TDS may improve overall BS and may effectively reduce pain and inflammation-related symptoms (Fig. 3).

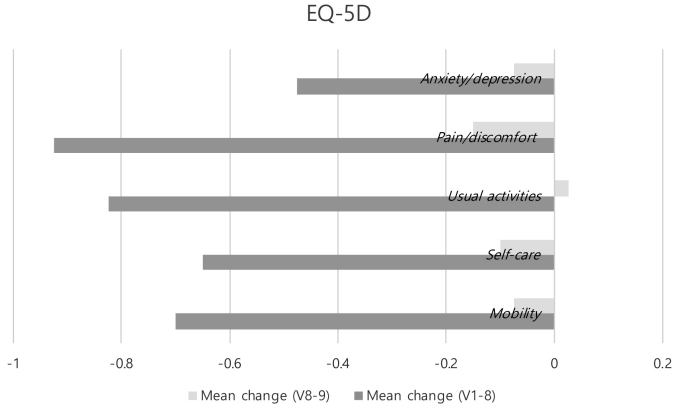

Fig. 2. The change of each questionnaire of EQ-5D.
EQ-5D, EuroQol-5 dimension; V, visit.

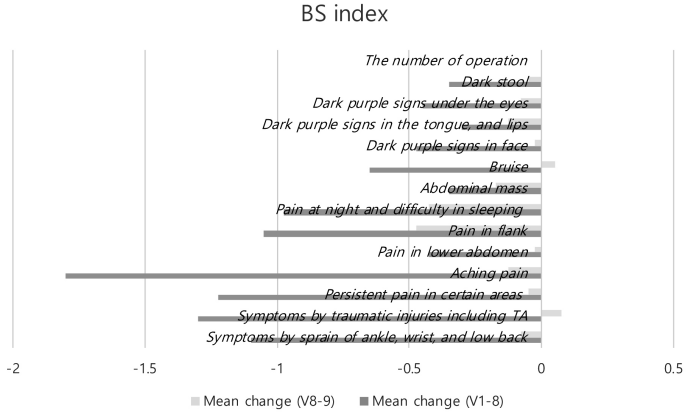

Fig. 3. The change of each questionnaire of BS-index.
BS, blood stasis; V, visit.

Safety assessment

During the course of administration of TDS, diarrhea (n = 8) and abdominal pain (n = 5) were reported, but with no serious consequences.

Discussion

BS is one of the common pattern identifications of KM and has various manifestations, of which pain is the most representative [6,29]. In KM, the mechanism of pain is recognized by the inhibition of blood flow, reduction of signal transduction, and accumulation of secretions by other factors such as inflammation, qi stagnation, BS, and cold [30]. Accordingly, the Yellow Emperor's Inner Classic (Huang Di Nei Jing) has suggested that poor circulation causes pain, and improvement of circulation eliminates the pain [31].

Among the various ingredients of BSHM, angelicae gigantis radix (Danggui), persicae semen (Taoren), and carthami flos (Honghua) are representative and known to activate blood circulation, promote blood circulation, and regulate the proteins related to inflammation and pain including tumor necrosis factor, hypoxia inducible factor-1, and neurotrophin signaling pathways in experimental studies [32-34]. Since TDS includes these ingredients and was recorded at Manbyeonghoichun as a treatment for severe or moderate degree of BS [35], and reportedly increases the blood flow and inhibits platelet aggregation [36], TDS was considered in the treatment of TA patients.

In this study, 40 TA patients were treated using general KM treatments and the change in TA-related symptoms was investigated whilst adjusting BSHM from the baseline. To be more objective and reliable diverse outcome measures were used and analysis using the BS index and EQ-5D was used. Each outcome measure showed statistically significant improvements between baseline and Visit 8. These results could indicate that there was a therapeutic effect of the KM treatments on TA-related symptoms and it was in accordance with the results of previous studies that showed improvement in TA patient symptoms following KM treatments [37,38]. Between Visit 8 and 9, however, significant improvements were only observed in pain reduction (VAS and NRS) and not in other secondary assessments. It could be inferred that KM treatments had the effect of continuous pain reduction and that the participants were satisfied with the improvement in health and quality of life through early improvement. It could also be possible that there were many participants in this study with rapid enhancement of secondary outcomes due to the small proportion of participants with severe injuries such as fractures. Nevertheless, this study gave an opportunity to gauge the degree of improvement in symptoms over time.

The sub-analysis revealed interesting results. Firstly, BS severity at baseline had a strong relationship with outcome measure. A greater degree of BS showed worse VAS, NRS, and EQ-5D scores. This result could be because BS can affect other areas such as quality of life as well as the pathology of TA-related symptoms. Furthermore, VAS, NRS, EQ-5D, and EQ-VAS scores could be predictive using the BS index in primary clinical practice. Secondly, the degree of improvement differed according to the severity of BS. While general KM treatments were administered, the herbal medicine focused on the BS, and this study showed a higher degree of improvement in higher BS index groups (moderate and severe groups). It would be reasonable that the more severe BS shows more improvements, but the results of this study could indicate that TDS may be effective in treating severe BS, which was similar to the statement of Manbyeonghoichun.

Moreover, the items that showed more improvement were identified in detail. This study showed marked improvements in pain and discomfort scores in the BS index and EQ-5D questionnaire. This was similar to previous studies that referred to the analgesic mechanism of BSHM [6]. In the CH index, BSHM showed statistical significance in the cold group, but no noticeable difference in the cold/heat tendency. Rhei rhizoma and natrii sulfas, the major constituents of TDS, are known as cold and cool herbal medicines in KM, and can cause gastrointestinal adverse effects [39]. Rhei rhizoma has been used as a purgative [40], and natrii sulfas has a laxative effect [41]. Rhei rhizoma acts as a cathartic, while natrii sulfas acts as a stool softener when used together [42]. However, there was no effect according to the CH index tendency, and there were no contraindications for using TDS. However, some participants with lower pain levels (lower VAS, NRS, and EQ-5D scores) than average, showed adverse events such as abdominal pain and diarrhea. Therefore, it is necessary to consider the reaction to and control the amount of rhizoma and natrii sulfas.

There were some limitations in this study. Firstly, with short-term and observational studies in a single institution, it was difficult to represent the efficacy of BSHM. Secondly, while the KM treatments were administered, we investigated the effects of TDS and BSHM. The KM treatments could have had a role in the improvement of symptoms, and a comparison was not made with other herbal medicines that could be used in the TA treatment. Thirdly, various scales were used, but we did not use objective indicators such as blood tests. Although well-designed studies are recommended in the future, this study was the first to investigate the efficacy of KM and BSHM in treating TA cases, and TDS may be an effective treatment for TA patients. We expect to provide reliable raw data that can be used in future clinical practice.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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