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Research Article
Qili Qiangxin as an Adjuvant Treatment with Inotrope for Advanced Heart Failure: Retrospective Analysis

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Abstract

Background and Objective: Inotropic treatment is generally used for advanced chronic heart failure. However, a single administration of an inotropic agent is insufficient to produce long-lasting results. The objective of the study was to evaluate the clinical impact of adjuvant treatment of Qili Qiangxin capsules on inotropic agents on N-terminal pro-B-type natriuretic peptide (NTproBNP), hospitalization and quality of life of outpatients with advanced chronic heart failure. **Materials and Methods:** Patients who requiring the optimal medical management have received intermittent intravenous infusions of levosimendan plus oral Qili Qiangxin capsules (LN cohort, n = 67) or that of dobutamine plus oral Qili Qiangxin capsules (DB cohort, n = 62) or oral Qili Qiangxin capsules only (QQ cohort, n = 54). **Results:** At 12 weeks after intervention(s) (EL), NTproBNP was significantly decreased in patients of LN cohort than those of DB ($p<0.0001$, $q = 6.555$) and QQ ($p<0.0001$, $q = 6.612$) cohorts. Patients of LN cohorts had fewer all-cause hospitalization. At EL, only patients of the LN cohort had improved the Euro quality of life five-dimensional-five-level score (0.40 ± 0.27 vs. 0.52 ± 0.25, $p = 0.019$, $q = 3.872$) and the Kansas City Cardiomyopathy Questionnaire score (39.21 ± 11.71 vs. 45.81 ± 12.18, $p = 0.004$, $q = 4.324$) and had higher numbers of patients with normal the 6 min walking distance test value (3 vs. 15) as compared to before intervention(s). **Conclusion:** Qili Qiangxin capsules as an adjuvant treatment with intermittent intravenous infusions of levosimendan could be preferred for optimal medical management of advanced chronic heart failure patients to improve prognosis.

Key words: Six min walking distance test, dobutamine, health-related quality of life, heart failure, inotrope, Kansas City Cardiomyopathy Questionnaire, levosimendan, n-terminal pro-b-type natriuretic peptide, Qili Qiangxin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Heart failure has adverse effects on the health care systems and advanced heart failure has a higher risk of hospitalization, poorer health-related quality of life and death than many other chronic diseases[1,2]. In China, hyperlipidemia, coronary heart disease and hypertension are common than the other developed countries[3]. The incidence of heart failure in Chinese males and females is 1.0 and 0.7%[4].

β-blockers with angiotensin-converting enzyme inhibitors (s) are currently used as the first-line treatment in heart failure patients but patients may develop decompensation[5]. Therefore, to improve hemodynamics in heart failure patients, there may require inotropic agents[1]. However, intermittent or continuous administration of an inotropic agent has increased the risk of proarrhythmic effects and subsequent mortality. Also, a single administration of it is insufficient to produce long-lasting effects[5].

Levosimendan is one of the inotropic agents that stabilizes the open conformation of troponin C and the troponin C-calcium-tropomyosin complex and enhances the calcium sensitivity of cardiac myofilaments[2]. Unlike other inotropic agents, the effects of levosimendan are irrespective of cellular or intracellular calcium concentration. Therefore, levosimendan does not increase intracellular calcium concentration and associated arrhythmias[1]. Also, it opens adenosine triphosphate-dependent potassium channels and provides vasodilatation[6]. Thus, it increases cardiac output without excessive myocardial oxygen requirements[7] and its repetitive and intermittent administration is preferred in advanced chronic heart failure patients[8]. The available studies are also reported that levosimendan reduces the mortality of advanced chronic heart failure patients[9,10] but the evidence is not uniform in those settings[2]. A pulsed or intermittent administration of levosimendan is a beneficial therapeutic option in advanced chronic heart failure patients[6,8]. A retrospective analysis[11] is reported that levosimendan is increased the risk of bleeding after heart valve surgery but this risk might be due to the dose-dependent antiplatelet effect of levosimendan[12].

Qili Qiangxin capsules are traditional Chinese medicine extracts of 11 herbs[13] and are approved by the China Food and Drug Administration for the treatment of heart failure in 2004[4] but there is no study available to compare Qili Qiangxin capsules as an adjuvant treatment with inotropic agents for the optimal medical management of patients with advanced chronic heart failure except one randomized trial that compares Qili Qiangxin capsules against inotropic agent[4] and lack of high-quality literature for assessment of Qili Qiangxin capsules as adjuvant treatment in patients with advanced chronic heart failure[13].

The objectives of the non-randomized retrospective study were to evaluate the clinical impact of intermittent intravenous infusions of levosimendan plus oral Qili Qiangxin capsules, intermittent intravenous infusions of dobutamine plus oral Qili Qiangxin capsules and oral Qili Qiangxin capsules only on the level of N-terminal pro-B-type Natriuretic Peptide (NTproBNP), hospitalization, health-related quality of life, social quality of life, physical quality of life and the adverse events of Chinese outpatients with advanced chronic heart failure.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Cardiology, the First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China and Jiangxi Hypertension Research Institute, Nanchang, Jiangxi, China from 14 January, 2017-30 November, 2019.

Ethics approval and consent to participate: The designed protocol (20203097 dated 13 January, 2017) was approved by the Human Ethics Committees of the First Affiliated Hospital of Nanchang University. Also, the protocol was approved by the Nanchang University and the Chinese Society of Cardiology. The study reporting adheres to the law of China and the V2008 Declarations of Helsinki. The informed consent form was signed by care givers of all enrolled patients regarding intervention(s), pathology and publication of anonymized information of patients in the form of the article before the start of the intervention(s). As being retrospective study the registration in the Chinese Clinical Trial Registry is waived by the institutes.

Inclusion criteria: A total of 183 patients (age>18 years) with advanced chronic heart failure (diagnosed as per the Chinese guidelines for the diagnosis and management of chronic heart failure[14]), <35% of the left ventricular ejection fraction (history of 6-months) and who were requiring the optimal medical management included in the analysis.

Exclusion criteria: Among those patients who were put on amrinone, enoximone, dopamine or milrinone but not put on levosimendan or dobutamine or Qili Qiangxin capsules were excluded from the analysis.

Cohort: A total of 67 patients had received 0.2 μg/kg/min intravenous levosimendan (Simenda, Lupin Ltd., Baltimore,

MD, USA) for 6 hrs. The same cycle was repeated at 15 days. These patients had received a total of 6 cycles. If patients were reported hypotension (systolic blood pressure less than 90 mmHg without symptoms or less than 100 mmHg with symptoms) the dose of intravenous levosimendan was reduced to 0.1 μg/kg/min[1]. These patients have also received 4 capsules (0.3 g per capsule) of Qili Qiangxin (Shijiazhuang Yiling Pharmaceutical Co., Ltd., Shijiazhuang, Hebei, China) per day for 12 weeks[15]. These patients were included in the LN cohort. A total of 62 patients have received 10 μg/kg/min intravenous dobutamine (Dobutrex, Abbott Laboratories, Chicago, Illinois, USA) for 6 hrs. The same cycle was repeated at 15 days. These patients had received a total of 6 cycles[16]. These patients have also received 4 capsules of Qili Qiangxin per day for 12 weeks. These patients were included in the DB cohort. A total of 54 patients had received 4 capsules of Qili Qiangxin per day for 12 weeks only[4]. These patients were included in the QQ cohort. Besides, usual care and medications (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers (except those who received dobutamine), digoxin, diuretics, mineralocorticoid receptor antagonists, hydralazine-nitrate combination, antiplatelet, anticoagulant, implantable cardioverter-defibrillator or cardiac resynchronization therapy) those prescribed by cardiologists were also taken by patients. All interventions were given under the supervision of cardiologists.

Data regarding clinical history, physical examinations, hospitalization, mortality and adverse events were retrospectively collected from the institutional medical records of patients and analyzed.

N-terminal pro-B-type natriuretic peptide: Immunoassay based on chemiluminescence (Elecsys® method, Roche Diagnostics, Rotkreuz, Switzerland) was used for the evaluation of the serum concentration of NTproBNP. Pathologists (minimum 3 years of experiences) of institutes were evaluated NTproBNP before intervention(s) (BL) and 12 weeks after intervention(s) (EL). Decrease (%) of NTproBNP (% NTproBNP) at EL was calculated as per Eq.[2]:

$$\Delta N_{TproBNP} \text{ at EL}(\%) = \frac{NTproBNP_{BL} - NTproBNP_{EL}}{NTproBNP_{BL}} \times 100 \quad (1)$$

Where:

$\Delta_{ntproBNP}$ at EL (%) = Percentage decrease in NTproBNP 12 weeks after intervention(s)

$NtproBNP_{EL}$ = NTproBNP at 12 weeks after intervention(s)

$NtproBNP_{BL}$ = NTproBNP before intervention(s)

Table 1: Chinese utility value set for the Euro quality of life five-dimensional-five-level health status

Dimension	Mobility	0.345
	Self-care	0.253
	Usual activities	0.233
	Pain/discomfort	0.302
	Anxiety/depression	0.258
Level	L_1	0
	L_2	0.191
	L_3	0.458
	L_4	0.832
	L_5	1

Health-related quality of life

Euroquality of life five-dimensional-five-level (EQ-5D-5L): It comprises Mobility (MO), Self-Care (SC), Usual Activities (UA), Pain/Discomfort (PD) and Anxiety/Depression (AD). Each one has five possible answers (1: No problems, 2: Slight problems, 3: Moderate problems, 4: Severe problems and 5: Extreme problems). A total of 3,125 health states were possible. The utility score ranged from -0.391-1. Where, score less than 0: The health status worse than death, 0: Death, 1: Full health[17]. The score was calculated from Table 1[18] and equation 2[19]. Trained instructors (minimum 3-years of experience) of institutes were evaluated EQ-5D-5L at BL and EL:

$$\text{Utility} = 1-(MO\times L_n)-(SC\times L_n)-(UA\times L_n)-(PD\times L_n)-(AD\times L_n) \quad (2)$$

where, n = 1, 2, 3, 4, 5.

Kansas City Cardiomyopathy Questionnaire (KCCQ) score: This comprises 23-items questionnaires for the physical and social quality of life of patients. The is ranged from 0-100. 0: Death, 1-25: Complete disability and severe symptoms, 26-50: Moderate symptoms, 51-75: Fair symptoms and 76-100: No disability[20]. Trained instructors (minimum 3-years of experience) of institutes were evaluated KCCQ score at BL and EL.

Six min walking distance test (6MWDT): The distance travel by patient in 6 min was considered as the 6 min walking distance. More than 500 m was considered a normal value[4]. Trained instructors (minimum 3-years of experience) of institutes were evaluated the 6MWDTat BL and EL.

Adverse events: Any adverse event reported during 1 year from the start of the intervention(s) were extracted from medical records of institutes and analyzed. The effect was considered an adverse event as per institutional protocol.

Statistical analysis: The study was assumed that the 12 weeks of intervention(s)might be decreased more than 25% of serum NTproBNP level in at least 40±5% of the

population. Also, with 5% two-sided type-I error, 80% power (β = 0.2) and 95% of confidence level, the sample size (minimum patients enrolled in each cohort) was 50[4]. InStat®, 3.01, GraphPad Software, San Diego, CA, USA was used for statistical analyses. Descriptive and ordinal variables are presented as frequency (percentages) and continuous variables are presented as Mean±Standard Deviation (SD). One-way analysis of variance (ANOVA) was used for continuous and ordinal variables and the Chi-squared test for independence was used for constant variables[2]. The Tukey test (considering critical value (q)>3.329 as significant) was used for *post hoc* analysis. All results were significant if the p-value was reported as less than 0.05.

RESULTS

Study population: A total of 244 patients (age>18 years) were diagnosed with advanced chronic heart failure with <35% of the left ventricular ejection fraction (history of 6 months) and were requiring optimal medical management. Among them 25 patients were put on amrinone, 13 patients were put on enoximone, 11 patients were put on dopamine and 12 patients were put on milrinone treatment. Therefore, data of these patients (n = 61) were excluded from the analysis. Data regarding clinical history, physical examinations, hospitalization, NTproBNP level, the adverse events, EQ-5D-5L, KCCQ score and 6MWDT of a total of 183 patients who requiring optimal medical management for advanced chronic heart failure were included in the analysis. The flow diagram of the optimal medical management for advanced chronic heart failure patients is presented in Fig. 1.

Clinical history and physical examinations: Patients of the LN cohort were received 25.12±1.22 mg per patient intermittent intravenous levosimendan and 300±20 oral Qili Qiangxin capsules per patient during 12 weeks. Patients of the DB cohort were received 1.01±0.75 g per patient intermittent intravenous dobutamine and 295±18 oral Qili Qiangxin

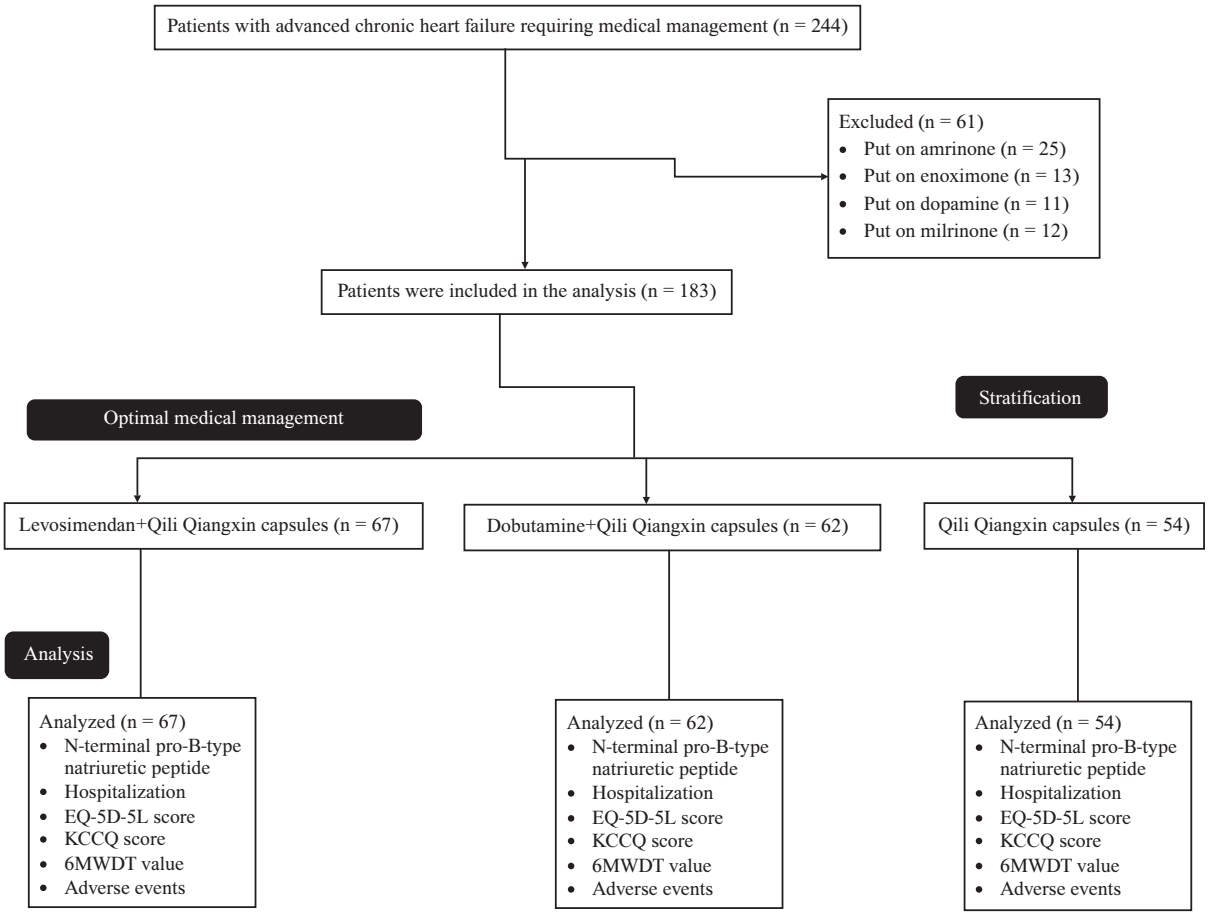

Fig. 1: Flow diagram of the optimal medical management for advanced chronic heart failure patients

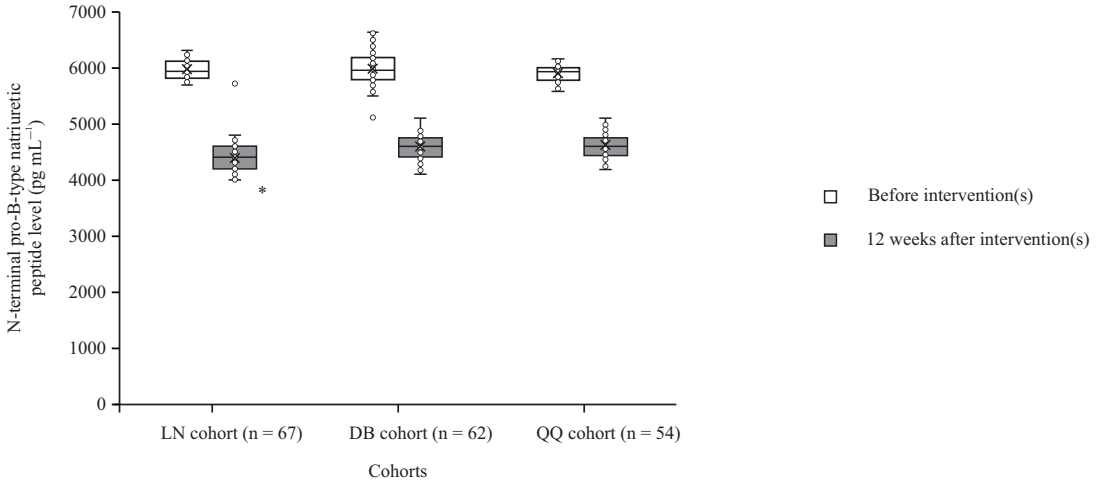

Fig. 2: N-terminal pro-B-type natriuretic peptide analysis

Immunoassay was performed for evaluation of N-terminal pro-B-type natriuretic peptide. *Significantly higher decrease in patients than those of DB and QQ cohort

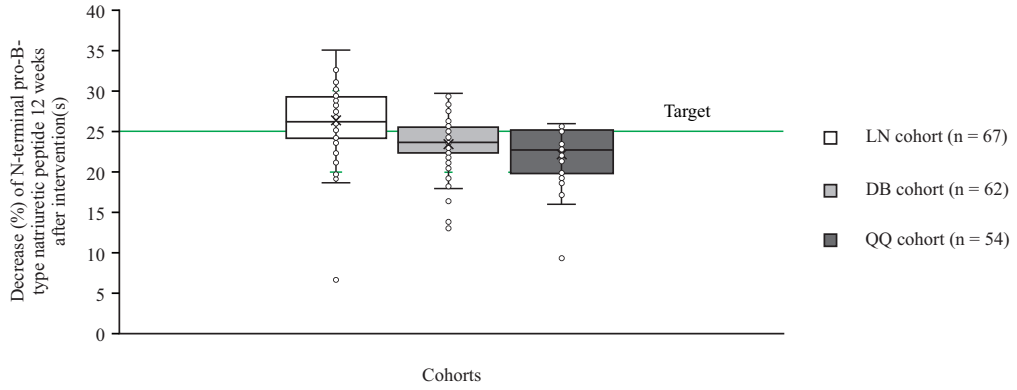

Fig. 3: Decrease (%) of N-terminal pro-B-type natriuretic peptide 12 weeks after intervention(s)

capsules per patient during 12 weeks. Patients of the QQ cohort had received 305±25 oral Qili Qiangxin capsules per patient during 12 weeks. A total of 9 (13%), 7 (11%) and 7 (13%) patients from the LN, the DB and the QQ cohorts respectively had EQ-5D-5L scores less than 0 (the health status worse than death). Clinical history and physical examinations for patients had no significant differences among cohorts before intervention(s) ($p>0.05$ for all parameters, Table 2).

N-terminal pro-B-type natriuretic peptide: At EL, NTproBNP was significantly decreased in all cohorts, i.e., LN cohort (5991.81±170.14 vs. 4415.10±272.59 pg mL^{-1}, $p<0.0001$, $q = 52.527$), DB cohort (6018.05±281.58 vs. 4607.16±203.34 pg mL^{-1}, $p<0.0001$, $q = 50.032$) and QQ cohort (5932.17±145.17 vs. 4616.15±218.26 pg mL^{-1}, $p<0.0001$, $q = 42.921$). At EL, NTproBNP was significantly higher decreased in patients of the LN cohort than those of DB ($p<0.0001$, $q = 6.555$) and QQ ($p<0.0001$, $q = 6.612$) cohorts (Fig. 2). At EL, significantly higher numbers of patients were reported with more than 25% in LN cohort than the DB (45 (67%) vs. 24 (39%), $p = 0.0006$, $q = 4.723$) and QQ (45 (67%) vs. 20 (37%), $p = 0.0006$, $q = 4.719$) cohorts. At EL, higher average (%) was reported in the patients of the LN cohort than those of DB (26.30±4.29 vs. 23.37±3.29 pg mL^{-1} per patient, $p<0.0001$, $q = 6.403$) and QQ (26.30±4.29 vs. 22.18±3.45 pg mL^{-1} per patient, $p<0.0001$, $q = 8.669$) cohort. Also, at EL, average (%) of the patients of only the LN cohort (26.30±4.29 pg mL^{-1} per patient) was higher than 25%. Values of % at EL of different cohorts are presented in Fig. 3.

Hospitalization: Intermittent intravenous infusions of levosimendan plus Qili Qiangxin capsules were reduced

Table 2: Clinical history and physical examinations of the enrolled patients before intervention(s)

Characteristics	Cohorts			
	LN	DB	QQ	
Treatment(s) during 12 weeks	25.12±1.22 mg per patient intermittent intravenous levosimendan+300±20 oral Qili Qiangxin capsules/patient	1.01±0.75 g per patient intermittent intravenous dobutamine+295±18 oral Qili Qiangxin capsules/patient	305±25 oral Qili Qiangxin capsules/patient	Comparisons
Patients included in the analysis	67	62	54	p-value
Age (years)				
Minimum	62	63	61	0.402
Maximum	72	73	74	
Mean±SD	65.12±7.15	66.14±8.15	67.51±9.45	
Sex				
Male	52 (78)	48 (77)	42 (78)	0.998
Female	15 (22)	14 (23)	12 (22)	
Body mass index (kg m^{-2})	25.12±2.01	24.89±2.12	25.15±3.14	0.813
Ethnicity				
Han Chinese	60 (90)	55 (88)	48 (89)	0.972
Mongolian	4 (6)	5 (8)	5 (9)	
Tibetan	1 (2)	1 (2)	1 (2)	
Uighur Muslims	1 (2)	1 (2)	0 (0)	
Systolic blood pressure (mmHg)	115±12	113±14	116±9	0.384
Heart rate (beats min^{-1})	75±11	76±12	73±14	0.415
New York heart association functional class				
III	61 (91)	56 (90)	46 (85)	0.547
IV	6 (9)	6 (10)	8 (15)	
Left ventricular ejection fraction	30±6	29±6	31±7	0.237
Previous cardiovascular hospitalization in 1 year	31(46)	20 (32)	19 (35)	0.225
Co-morbidities				
Anemia	7 (10)	7 (11)	7 (13)	0.997
Diabetes	15 (22)	15 (24)	14 (27)	
Atrial fibrillation	17 (25)	18 (29)	14 (27)	
Dyslipidemia	16 (24)	15 (24)	16 (30)	
Hypertension	20 (30)	20 (32)	14 (27)	
N-terminal pro-B-type natriuretic peptide (pg mL^{-1})	5991.81±170.14	6018.05±281.58	5932.17±145.17	0.083
Hemoglobin (g dL^{-1})	12.01±1.91	11.91±1.82	11.81±1.93	0.845
Serum creatinine (mg dL^{-1})	1.51±0.41	1.41±0.35	1.43±0.37	0.287
Serum potassium level (mEq L^{-1})	4.23±0.22	4.21±0.25	4.26±0.26	0.541
Serum sodium level (mEq L^{-1})	125±10	127±12	126±5	0.501
Euro quality of life five-dimensional-five-level score	0.40±0.27	0.44±0.27	0.43±0.25	0.667
Numbers of patients with Euro quality of life five-dimensional-five-level score less than 0	9 (13)	7 (11)	7 (13)	0.931
Kansas city cardiomyopathy questionnaire score	39.21±11.71	40.21±11.63	39.67±13.74	0.899
Patients with a complete disability and severe symptoms (Kansas city cardiomyopathy questionnaire score: 1-25)	7 (10)	6 (10)	6 (11)	0.969
Six min walking distance test	405.15±60.67	398.10±52.88	404.85±66.17	0.761
Patients with normal 6 min walking distance test value (>500 m)	3 (5)	3 (5)	5 (9)	0.492

Table 2: Continued

Characteristics Treatment(s) during 12 weeks	Cohorts LN 25.12±1.22 mg per patient intermittent intravenous levosimendan+300±20 oral Qili Qiangxin capsules/patient	DB 1.01±0.75 g per patient intermittent intravenous dobutamine+295±18 oral Qili Qiangxin capsules/patient	QQ 305±25 oral Qili Qiangxin capsules/patient	Comparisons
Patients included in the analysis	67	62	54	p-value
Other medication(s)				
Angiotensin converting enzyme inhibitors	41 (61)	34 (55)	37 (69)	0.994
Angiotensin-receptor blockers	12 (18)	18 (29)	16 (30)	
β-blockers	17 (25)	15 (24)	14 (26)	
Digoxin	10 (15)	11 (18)	11 (20)	
Diuretics	22 (33)	22 (35)	22 (41)	
Mineralocorticoid receptor antagonists	20 (30)	16 (26)	16 (30)	
Hydralazine-nitrate combination	10 (15)	11 (18)	13 (24)	
Antiplatelet	18 (27)	15 (24)	16 (30)	
Anticoagulant	15 (22)	19 (31)	19 (35)	
Implantable cardioverter-defibrillator	21 (31)	20 (32)	12 (22)	
Cardiac resynchronization therapy	21 (31)	16 (26)	14 (26)	

Descriptive variables are presented as frequency (percentages) and continuous and ordinal variables are presented as Mean±Standard deviation (SD), one-way ANOVA was used for continuous and ordinal variables and the Chi-squared test for independence was used for constant variables, all results were significant if the p-value was reported as less than 0.05

Table 3: Hospitalization during 12 weeks from the start of the intervention(s)

Patients Treatment(s)+usual care+medications	Cohorts LN Intermittent intravenous levosimendan+oral Qili Qiangxin capsules	DB Intermittent intravenous dobutamine+oral Qili qiangxin capsules	QQ Qili qiangxin capsules	p-value	Comparisons q-value LN vs. DB	LN vs. QQ	DB vs. QQ
Patients included in the analysis	67	62	54				
Heart failure hospitalization	11 (16)*	12 (19)	20 (37)	0.018	0.564	3.814	3.213
Cardiovascular hospitalization	15 (22)	16 (26)	18 (33)	0.396	N/A	N/A	N/A
Non-cardiovascular hospitalization	10 (15)	12 (19)	14 (26)	0.321	N/A	N/A	N/A
All cause hospitalization	36 (54)*	40 (65)*	52 (93)	<0.0001	2.028	7.714	5.658

Variables are presented as frequency (percentages), one-way ANOVA was used for statistical analysis, Tukey test was used for statistical analysis, all results were significant if the p-value was reported less than 0.05 and the q-value was reported more than 3.329, *Significantly lower numbers of patients than those of the QQ cohort, N/A: Not applicable

Table 4: Adverse events and mortality reported during 1 year from the start of the intervention(s)

Event Treatment(s)+usual care+medications	Cohorts LN Intermittent intravenous levosimendan+oral Qili qiangxin capsules	DB Intermittent intravenous dobutamine+oral Qili qiangxin capsules	QQ Qili qiangxin capsules	p-value	Comparisons q-value LN vs. DB	LN vs. QQ	DB vs. QQ
Patients included in the analysis	67	62	54				
Infections and infestations	14 (21)*	2 (3)	2 (4)	0.0006	4.923	4.615	0.126
Cardiac disorders	29 (43)*	10 (16)	3 (6)	<0.0001	5.558	7.442	2.049
Gastrointestinal disorders	10 (15)*	7 (11)	7 (13)	0.831	N/A	N/A	N/A
Hypokalemia	8 (12)*	1 (2)	1 (2)	0.013	3.704	3.487	0.081
Skin disorders	5 (7)*	0 (0)	0 (0)	0.011	3.735	3.599	N/A
Death	21 (31)	13 (21)	4 (7)	0.005	2.096	4.659	2.594

Patients had reported one or more events, variables are presented as frequency (percentages), one-way ANOVA was used for statistical analysis, Tukey test was used for statistical analysis, all results were significant if the p-value was reported less than 0.05 and the q-value was reported more than 3.329, N/A: Not applicable, *Levosimendan-emergent adverse effects

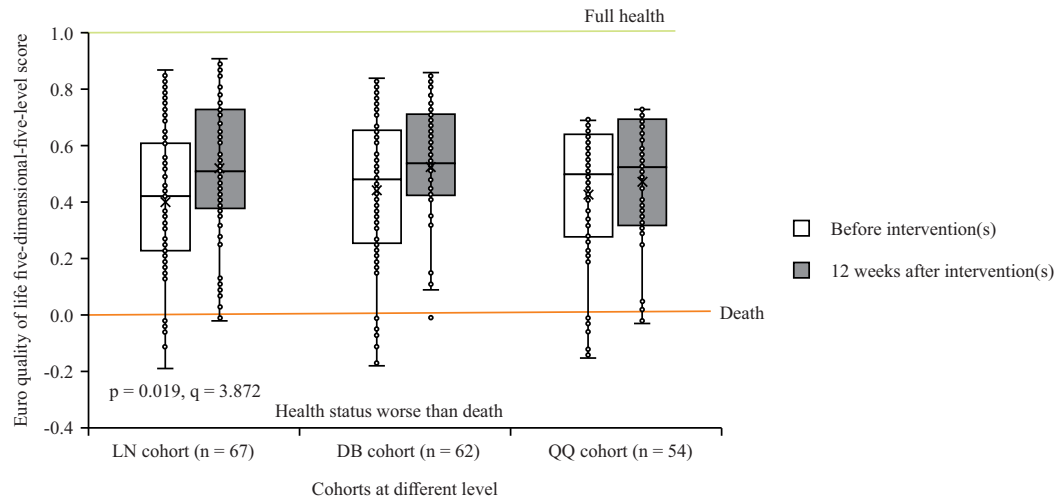

Fig. 4: Euro quality of life five-dimensional-five-level evaluation

Chinese utility value set was used for the evaluation of the EQ-5D-5L score. 1: Full health, 0: Death and <0: Health status worse than death

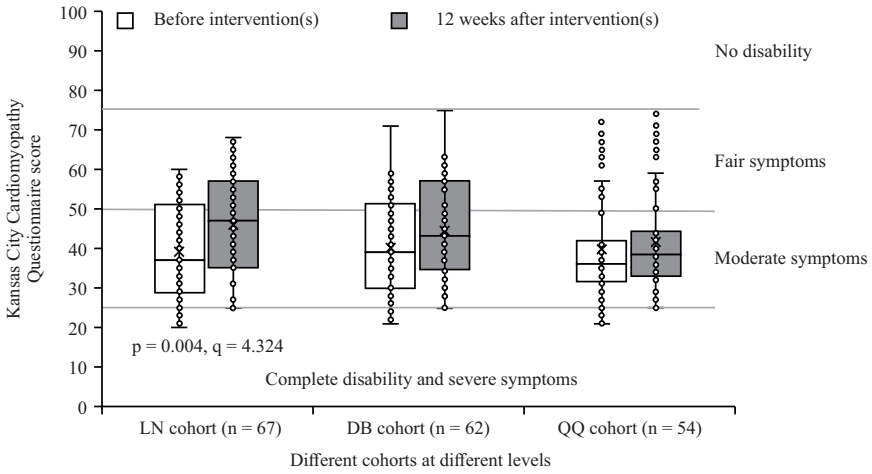

Fig. 5: Kansas City Cardiomyopathy Questionnaire score evaluation

0: Death, 1-25: Complete disability and severe symptoms, 26-50: Moderate symptoms, 51-75: Fair symptoms and 76-100: No disability

hospitalization due to heart failure than Qili Qiangxin capsules alone (p = 0.018, q = 3.814) during 12 weeks from the start of the intervention(s). Intermittent intravenous infusions of levosimendan plus Qili Qiangxin capsules (p<0.0001, q = 7.714) and intermittent intravenous infusions of dobutamine plus Qili Qiangxin capsules (p<0.0001, q = 5.658) were reduced all-cause hospitalization than Qili Qiangxin capsules alone during 12 weeks from the start of the intervention(s). The details of hospitalization due to different causes are reported in Table 3.

Health-related quality of life

EQ-5D-5L score: At EL only patients of the LN cohort (0.40±0.27 vs. 0.52±0.25, p = 0.019, q = 3.872) were improved EQ-5D-5L score as compared to the BL (Fig. 4). At EL, a total of 2 (3%), 4 (6%) and 4 (7%) of patients from the LN, DB and QQ cohorts, respectively had EQ-5D-5L scores less than 0 (the health status worse than death).

KCCQ score: Patients of only the LN cohort (39.21±11.71 vs. 45.81±12.18, p = 0.004, q = 4.324) were an improved KCCQ score at EL (Fig. 5). At EL, 3 (4%), 4 (6%) and 4 (7%) of patients of the LN, DB and QQ cohorts respectively had a complete disability and severe symptoms (KCCQ score: 1-25).

6MWDT value: There were no significant differences for 6MWDT values between BL and EL for patients of all three cohorts. At BL, there were 3 (5%), 3 (5%) and 5 (9%) of the patients with normal 6 MWDT value (> 500 m) into the LN, DB

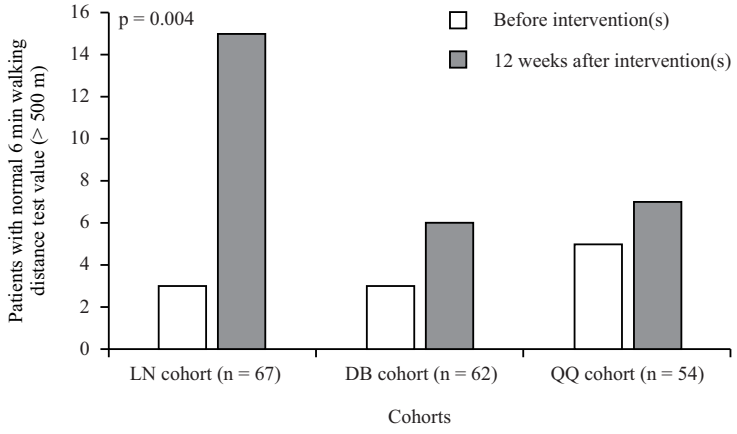

Fig. 6: Patients with the normal 6-min walking distance test value (>500 m)

and QQ cohorts, respectively. Those were become 15 (22%), 6 (10%) and 7 (13%) into LN, DB and QQ cohorts respectively at EL. Intermittent intravenous infusions of levosimendan plus Qili Qiangxin capsules were increased numbers of patients with a normal 6MWDT value (>500 m) at EL as compared to BL ($p = 0.004$). The numbers of the patients with normal 6 MWDT values of different cohorts at different time intervals are presented in Fig. 6.

Adverse events: Hypotension, atrial and ventricular rhythm were reported in all patients. Patients of the LN cohort were reported infections and infestations, cardiac disorders, gastrointestinal disorders, hypokalemia and skin disorders as the adverse events during 1-year from the start of the intervention(s). While that for patients of DB and QQ cohorts was gastrointestinal disorders. High numbers of death were reported in the LN cohort than the QQ cohort (21 vs. 4, $p = 0.005$, $q = 4.659$) during 1-year of follow-up (Table 4).

DISCUSSION

At EL for intermittent intravenous infusions of levosimendan plus oral Qili Qiangxin capsules, patients were successful for more than 25% % then those who received intermittent intravenous infusions of dobutamine plus Qili Qiangxin capsules or oral Qili Qiangxin capsules only. The results of the NTproBNP of the current study agreed with those of the multicenter LION-HEART trial[1], LevoRep trial[2] and the REVIVE trial[10] on levosimendan and the multicenter trial on Qili Qiangxin capsules[4]. NTproBNP is a biologically inactive fragment of brain natriuretic peptide, which is released by the heart in condition(s) of myocardial tension and in the heart failure condition, the elevated level of NTproBNP is found in blood plasma[4]. Intravenous levosimendan at short time intervals improves the left ventricular performance but does not increase oxygen consumption, which decreases NTproBNP level[1]. The reason for the failure of dobutamine for the management of advanced chronic heart failure is its shorter half-life and no active metabolite[21]. Qili Qiangxin capsules act on the down-regulating ratio of tumour necrosis factor-α/interleukin-10 and improve cardiac functions[22], maintenance anti-inflammatory and pro-inflammatory cytokines balance[4], maintenance signalling pathway of the down-regulating cardiac-chymase and production of β-chymase[23], inhibit angiotensin II type 1 receptor, promote cardiomyocyte proliferation and activate ErbB receptors[24]. Qili Qiangxin capsules as an adjuvant treatment with intermittent intravenous infusions of levosimendan could be preferable for optimal medical management of advanced chronic heart failure patients to improve prognosis.

At EL, intermittent intravenous infusions of levosimendan plus Qili Qiangxin capsules were reduced hospitalization due to heart failure and all-cause hospitalization. The results of the hospitalization of the current study agreed with those of the multicenter LION-HEART trial[1] and randomized trial[16] on levosimendan and the multicenter trial on Qili Qiangxin capsules[4]. Qili Qiangxin capsules as an adjuvant treatment with intermittent intravenous infusions of levosimendan could reduce events and reduces the hospitalization of advanced chronic heart failure patients.

At EL, intermittent intravenous infusions of levosimendan plus Qili Qiangxin capsules were successful in the improvement of the EQ-5D-5L score of patients. The results of health-related quality of life of the current study agreed with those of the multicenter LION-HEART trial[1] on levosimendan and the multicenter trial on Qili Qiangxin capsules[4] but are

not agreed with those of the LevoRep trial[2] on levosimendan. The reason for contradictory results is that patients in the LevoRep trial[2] were received 14 mg per patient levosimendan. While in the current study patients were received 25.12±1.22 mg per patient levosimendan. Also, the sample size in the LevoRep trial[2] was small than that of the current study. Qili Qiangxin capsules as an adjuvant treatment with intermittent intravenous infusions of levosimendan may improve the health-related quality of life of advanced chronic heart failure patients.

At EL, intermittent intravenous infusions of levosimendan plus Qili Qiangxin capsules were successful in the improvement of the KCCQ score of patients. The results of the KCCQ score of patients of the current study agreed with those of the LevoRep trial[2] and the multicenter trial on Qili Qiangxin capsules[4]. Qili Qiangxin capsules as an adjuvant treatment with intermittent intravenous infusions of levosimendan may improve the social quality of life of patients.

At EL, intermittent intravenous infusions of levosimendan plus Qili Qiangxin capsules were increased numbers of patients with a normal 6MWDT value (>500 m). The results of the physical quality of life of patients of the current study agreed with those of the LevoRep trial[2] and the multicenter trial on Qili Qiangxin capsules[4]. Qili Qiangxin capsules as an adjuvant treatment with intermittent intravenous infusions of levosimendan may improve the physical and walking quality of patients.

During 1-year from the start of the intervention(s), patients who received intermittent intravenous infusions of levosimendan plus Qili Qiangxin capsules were reported higher adverse events and mortality. While patients who received Qili Qiangxin capsules only were reported fewer adverse events and mortality. The results of adverse events and morality of the current study agreed with those of the multicenter LION-HEART trial[1], the LevoRep trial[2], randomized trial[16] and REVIVE trial[10] on levosimendan and the multicenter trial on Qili Qiangxin capsules[4]. Intermittent intravenous infusions of levosimendan and dobutamine are responsible for higher adverse events and mortality[10]. Also, the dose of 0.2 μg/kg/min intravenous levosimendan is responsible for mortality[9]. Intermittent intravenous infusions of levosimendan and dobutamine have increased the risk of adverse events and mortality.

Even there are reported adverse effects of hypotension, atrial and ventricular rhythm of intermittent intravenous infusions[10] of levosimendan and dobutamine is preferred in the current study and bolus dose followed by intravenous infusion[3] was not preferred. The bolus dose is caused by trial fibrillation and sudden death[21]. Also, intermittent intravenous infusions are more effective compared to the bolus dose[7]. Therefore, patients were treated with intermittent intravenous infusions of 6-cycles at 15 days intervals.

The limitations of the study, for example, non-randomized retrospective study with small sample size and lack of blinded, adequately controlled compared with placebo or conventional medicine, randomized trial with sufficient statistical power to confidentially and accurately interpret the effect. The small sample size is also responsible for α-error[2]. The randomized trial is not possible in the Chinese population for this study because Chinese people have legal rights for the selection of traditional Chinese medicine for their treatment(s) of disease(s). The study evaluation period is short- and long-term outcomes are not evaluated. The confounders that may affect outcomes are not evaluated. The study lacks characterization of the individual components of Qili Qiangxin capsules.

CONCLUSION

Oral Qili Qiangxin capsules as an adjuvant treatment with intermittent intravenous infusions of levosimendan could be reduced N-terminal pro-B-type natriuretic peptide and hospitalization of advanced chronic heart failure patients. Also, they were successful in the improvement of health-related, social, physical and walking quality of life of advanced chronic heart failure patients. Unlike oral Qili Qiangxin capsules alone and intermittent intravenous infusions of dobutamine plus oral Qili Qiangxin capsules, intermittent intravenous infusions of levosimendan plus oral Qili Qiangxin capsules have increased the risk of adverse events and mortality. The findings of the study provide promising results of significant interest to the international medical community. A large non-randomized trial is required to state the hypothesis clearly.

SIGNIFICANCE STATEMENT

The retrospective study discovers the potential impact of adjuvant treatment of Qili Qiangxin capsules on inotropic agent on N-terminal pro-B-type natriuretic peptide, hospitalization and quality of life of outpatients with advanced chronic heart failure and recommended the Qili Qiangxin capsules as an adjuvant treatment with

intermittent intravenous infusions of levosimendan for optimal medical management of advanced chronic heart failure patients to improve prognosis. The finding will help the cardiologists to uncover the critical issues of advanced chronic heart failure that many physicians were not able to explore. Thus, a new theory on the management of advanced chronic heart failure may be arrived at.

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