Original Article

Oral administration of probiotic *Lactobacillus casei Shirota* relieves pain after single rib fracture: a randomized double-blind, placebo-controlled clinical trial

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Background and Objectives: Probiotic treatment has proven to increase the density of bone mass, prevent against bone loss, and improve bone formation. We aimed to assess the effect of oral administration of the probiotic *Lactobacillus casei Shirota* (LcS) on pain relief in patients with single rib fracture. **Methods and Study Design:** A total of 283 eligible patients who had a single rib fracture were enrolled and randomly assigned to receive skimmed milk containing either a commercial probiotic LcS or placebo every day through oral administration for 1 month after the fracture. The pain relief effect was assessed during activities that elicited pain; meanwhile, sleep quality and sustained maximal inspiration (SMI) lung volumes were monitored. **Results:** Patients in the LcS group had more effective pain relief than those in the placebo group during deep breathing, coughing and turning over the body. Between the two groups of patients, increase in SMI lung volume was larger in LcS group patients than that of patients in the placebo group. Sleep quality did not show significant improvements after 1 month LcS treatment. **Conclusions:** In patients with a single rib fracture, oral administration of the probiotic LcS could exhibit alleviating effects on pain intensity.

Key Words: probiotics, *Lactobacillus casei Shirota*, single rib fracture, pain, sustained maximal inspiration lung volume

INTRODUCTION

Rib fractures, usually resulted from falls or traffic accidents, are one of the most common injuries in blunt thoracic trauma.[1-3] Intense flank pain is the major symptom of rib fractures, and may last for months. The painful sensation impedes the abilities of the patients to deep breath, cough, or turn over in bed,[1,4] and is hence linked to the occurrence of pneumothorax, hemothorax, atelectasis, and pneumonia.[3,5] Further, in patients with a fractured rib, pain often results in prolonged disability and increased mortality in older population.[1,2,6-9]

Practitioners have highly emphasized the importance of acute pain management in patients with rib fractures. However, oral analgesics that are widely used, including nonsteroidal anti-inflammatory drugs (NSAIDs), seemingly provide only limited relief from severe pain.[1, 10] Rib taping as well as other invasive approaches including operative repair and intercostal nerve block have also been employed to alleviate pain induced by rib fractures, but controversies remain over the benefit and their indications.[1,9-12] Therefore, a novel and effective treatment for pain relief in ribs fractures is inevitably needed for both physicians and patients.

Probiotics, which are live microbial food ingredients, have several beneficial effects on health.[13,14] Consumption of probiotics, often in drinks or capsules as dietary supplement, is safe for human as confirmed in a wide range of patients with various diseases,[15-17] including children who were critically ill[18] and professional athletes.[19] Probiotic treatment also exerts beneficial effects in bone-related diseases. For example, valyl-prolyl-proline, a bioactive peptide generated from fermentation of Lactobacillus helveticus, is demonstrated to enhance bone formation *in vitro*.[20] The use of probiotics was consistently reported to increase bone mass density and prevent bone loss in

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different animal models.[21-23] A commercial probiotic *Lactobacillus casei Shirota* (LcS) was also shown to decrease the inflammatory joint damage in collagen-induced arthritis.[24] Our group has recently reported that in elderly patients with a distal radius fracture LcS administration could greatly accelerate the healing process,[25] and in patients with knee osteoarthritis LcS could improve treatment outcome by reducing hs-CRP.[26]

To the best of our knowledge, the role of LcS in pain relief has never been reported. Therefore in this study, we aimed to investigate the effect of LcS in alleviating pain among patients with single rib fracture.

METHODS

Ethical statements

The clinical trial was designed in accordance with the Declaration of Helsinki guidelines, and approved by the Ethical Committee of the Third Hospital of Hebei Medical University (TH2011017). All patients provided signed written consent forms before enrollment, and agreed to the anonymous data utilization policy.

Patient selection

316 patients with single rib fracture as diagnosed with chest X-ray, presenting to the Emergency Department at the Third Hospital of Hebei Medical University during the period from Nov 2011 through Oct 2017, were screened for the study. Inclusion criteria were as follows: (1) age >18 years; (2) presence of single rib fractures diagnosed with chest X-ray; (3) maximal score of rib pain more than 5 on the numerical rating scale (NRS: 0-10)27 obtained after patients took ibuprofen and subsequently preformed any one of three actions including deep breathing, coughing, or turning over; (4) ability to describe the site and evaluate the intensity of pain accurately. Exclusion criteria were as follows: (1) open wound on abdomen and lumbar region; (2) signs of poorly controlled conditions such as atelectasis, pneumonia or other infectious diseases, dysfunction of immune system, tendency to bleed, or psychiatric disorders; (3) could not be examined during deep breathing, coughing and turning over in bed (4) were pregnant; (5) using any medication or food supplements containing any probiotics during the preceding 3 months. After exclusion, a total of 283 patients were eligible to for the rest of the study.

Randomization and group design

A total of 283 eligible patients were assigned by random into two treatment groups: LcS (141 patients) and placebo (142 patients) using a permuted-block randomization method stratified to their baseline NRS. All patients were then instructed to consume one serving of either skimmed milk containing at least 6×10^9 colony-forming units (CFU) LcS as verified by Food Safety Administration of Hebei, or plain skimmed milk as placebo (both from Mengniu Co. Ltd.) at breakfast every day for 1 month. Skimmed milk was chosen over capsules as the vehicle of LcS in this study due to its optimal preservation of probiotics activity plus higher willingness of patients to consume. Both types of skimmed milk were issued weekly to all patients, with closed labels that masked the contents to both patients and investigators. Patients were instructed not to consume any other food supplements or medication containing any probiotics, other than the skimmed milk provided by the investigators during the 1 month study period. All patients were revisited every week, and 8 patients in the LcS treatment group and 11 patients in the placebo group were dropped out during the study period due to non-compliance to the study protocols or personal reasons. Their data had been subsequently excluded from the analyses.

Treatment outcome

All evaluations of treatment outcomes were performed by investigators blind to group assignment. The primary outcome was effective pain relief, based on maximal pain intensity (NRS: 0-10) assessed by participants themselves during deep breathing, coughing and turning over in bed in sequence. A decline of NRS score up to 3 points was defined as "good pain relief". The duration of pain relief was monitored as well. The secondary outcome was sustained maximal inspiration (SMI) lung volumes evaluated using the incentive breathing spirometer TriFlow. The overnight sleep quality of all patients was evaluated using NRS (0-10), in which a score of 0 indicates perfect sleep quality and 10 indicates totally interrupted sleep by pain. Body mass index (BMI) was calculated as body weight divided by square of body height (kg/m^2). Any complications or side effects throughout the study period were recorded as well.

Statistical analysis

Statistical analysis was performed using the SPSS software (SPSS Inc., USA). Data is presented as mean ± standard deviation (SD). The data distribution normality was determined by Kolmogorov-Smirnov goodness-of-fit test. Then two tailed Student's t-test was used to compare normally distributed data, while Mann-Whitney test was used to analyze non-normally distributed data. p values less than 0.05 were considered as statistically significant.

RESULTS

The design of this clinical trial is illustrated in a flow diagram in Figure 1. After initial exclusion and withdraw during the study, 133 patients in the LcS group, and 131 patients in the placebo group, completed the follow-up per the protocol, and their data was analyzed and presented in the current study. First of all, as listed in Table 1, baseline properties of patients from both groups were compared and analyzed. No significant difference was observed between the two treatment groups with regard to gender, age, BMI and NRS scores of initial pain intensity. In particular, the initial pain intensity under all evaluated conditions before the treatment was not significantly different ($p>0.05$) between the LcS group and the placebo group.

Table 2 demonstrates the pain intensity and the effect of pain relief in patients during deep breathing, coughing and turning over before and after the trial. After the 1-month treatment, pain intensity in both treatment groups exhibited significant improvements (in-group $p<0.05$), indicating steady recovery of all patients from the initial single rib fracture. Importantly, pain intensity was significantly different between the LcS group and the placebo

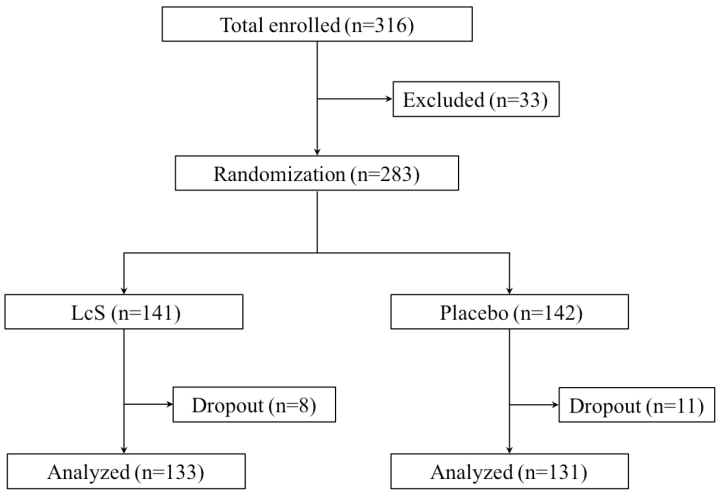

Figure 1. Flow chart of the current trial

Table 1. Baseline characteristics of eligible patients†

	LcS (n=133)	Placebo (n=131)	*p* value
Gender (male/female)	72/61	74/57	>0.05
Age (years)	42.1±5.4	44.8±5.9	>0.05
BMI (kg/m^2)	26.1±3.2	25.7±2.4	>0.05
NRS of initial pain intensity			
Deep breath	4.3±0.6	4.6±0.9	>0.05
Cough	6.2±2.1	6.5±1.7	>0.05
Turnover	6.9±2.4	7.1±2.2	>0.05

BMI: body mass index; NRS: numerical rating scale for pain measurement.
†Values are mean±SD.

Table 2. Pain intensity before and after treatment and change with NRS†

Action of evaluation	LcS (n=133)			Placebo (n=131)			Inter-group *p* value after treatment
	Before	After	In-group *p* value	Before	After	In-group *p* value	
Deep breath	4.3±0.6	2.3±2.0	<0.05	4.6±0.9	3.2±1.3	<0.05	<0.05
Cough	6.2±2.1	2.9±1.6	<0.05	6.5±1.7	4.7±1.8	<0.05	<0.05
Turnover	6.9±2.4	3.8±1.7	<0.05	7.1±2.2	5.8±2.4	<0.05	<0.05

NRS: numerical rating scale for pain measurement.
†Values are mean ± SD.

group under all conditions examined (inter-group $p<0.05$). As for the pain relief after treatment, the pain intensity in the LcS group declined more remarkably under all conditions than the placebo group.

The "good pain relief" was assessed after the treatment as shown in Table 3. 41/131 patient in the placebo group achieved "good pain relief" during deep breathing after the 1-month treatment, while 63/133 patients in the LcS group reported "good pain relief" under the same conditions. Similarly, for the coughing and turning over assessments, 62 and 34 patients out of 131 in the placebo group achieved "good pain relief", respectively. In comparison, 82 and 56 patients out of 133 patients in the LcS group achieved "good pain relief" in the same two assessments. There was statistically significant difference between the two groups during each evaluation condition ($p<0.05$).

Table 4 summarized the SMI lung volumes of patients before and after the treatment. The results suggested that there was a significant improvement in the SMI lung volumes in both groups of patients (in-group $p<0.05$), showing steady recovery. Comparing between the two groups, the LcS group showed significantly higher SMI lung volume than the placebo group after the treatment (inter-group $p<0.05$).

At last, sleep quality was also evaluated (Table 5). Although after the treatment, sleep quality of both groups was significantly improved (in-group $p<0.05$), it was not significantly different between the two groups (inter-group $p>0.05$).

DISCUSSION

In this double-blind, placebo-controlled randomized clinical trial, a total of 316 patients with single rib fracture were enrolled, 283 of whom met the inclusion criteria. The eligible patients had maximal pain intensity of more than 5 using the NRS and responded poorly to pain management by ibuprofen. We aimed to evaluate the efficacy and efficiency of 1-month daily oral administration of the probiotic LcS in reducing pain in these patients. The

Table 3. Number of patients with good pain relief after treatment

	LcS (n=133)	Placebo (n=131)	*p* value
Deep breath	63	41	<0.05
Cough	82	62	<0.05
Turnover	56	34	<0.05

patients were randomly assigned to receive daily treatment of either LcS or placebo since the day after the fracture for a period of 1 month. The general parameters of patients in both treatment groups were compared after randomization, and characteristics including gender, age, height, body weight and injured side were found to be similar. Therefore our randomized group assignment has provided a comparable starting point for the rest of the study.

Overall results demonstrated that patients receiving LcS treatment experience more effective pain relief than the placebo group during movements of deep breathing, coughing and turning over in bed. The pain intensity declined up to 2 points after 1 month of continuous oral LcS administration. Although patients in the placebo group did exhibit a tendency of slight pain relief, LcS treatment still presented a significantly higher efficacy for pain relief through subjective pain assessment. Besides, the influence of natural recovery from rib reunion on pain in both groups should also be considered. Further, it is noteworthy that fearlessness in taking deep breath could reduce the incidence of pulmonary complications and boost the desire for ventilation training.[3] Moreover, some patients in the LcS group mentioned better sputum expectoration, while others indicated the enhanced motivation to get up and move around when LcS alleviated the pain, implying that the LcS treatment lessened the inconvenience caused by trauma and improved the life quality of the patients.

More significant increase in SMI was also observed in patients after LcS treatment, than those after placebo treatment. In line with previous reports using continuous intercostal nerve blocker,[11,28] where increased SMI correlated with decreased pain, data in our current study demonstrated that a better pain relief was achieved via oral LcS treatment. In addition, compared with implement of continuous nerve blocker provider, oral LcS administration was non-invasive and did not interrupt the respiratory functions.

The sleep quality was not significantly improved after 1 month of LcS treatment. However, this does not necessarily mean that the treatments did not have an effect on sleep quality of the patients. All the participants were administered oral LcS in the morning, therefore the effect might be attenuated by the long time before sleeping hours. Moreover, this study cannot distinguish the causes of sleep disturbances, whether being caused by pain or other preexisting factors.

One useful feature of this trial was the active evaluation, which was advocated in a prior study.[29] In contrast with the static assessment in earlier pain-related studies, evaluation of pain intensity during pain-inducing activities was performed. It is known that less pain is felt when patients stay inactive. Therefore, evaluation of pain intensity was more accurate as patients were performing specific motions, which healthy people could perform with ease in daily life. When the goal of treatment is to lessen the disability of these patients, pain is what hinders their recovery, therefore should first be relieved.

The intolerable pain of patients with rib fractures usually rises to a peak and then is alleviated in 2-4 weeks after trauma under the use of analgesics medication.[1,30] While acute pain management during hospitalization has been well studied, there remains room for improvement, and better treatments other than nerve blocker injection and conventional oral analgesics are needed.[1,5,10,28] On the other hand, administration of opioids or systemic injections of nonsteroidal anti-inflammatory drugs are simple and effective means to relieve the pain. However, such medications exhibit serious side effects. Oral analgesic drugs are commonly used, but for patients with fractured rib, particularly in the acute phase of injury, the relieving effects are usually adjuvant. Regional analgesia for rib fractures is currently the most effective method of pain relief.[31,32] It can also reduce the impairment of the immune response that is resulted from pain. However, this method requires administration by a specialist and carries

Table 4. SMI lung volumes†

	LcS (n=133)			Placebo (n=131)			Inter-group *p* value after treatment
	Before	After	In-group *p* value	Before	After	In-group *p* value	
SMI lung volumes (mL)	814±176	1127±193	<0.05	783±181	924±152	<0.05	<0.05

SMI: sustained maximal inspiration.
†Values are mean±SD.

Table 5. Overnight sleep disturbance by pain †

	LcS (n=133)			Placebo (n=131)			Inter-group *p* value after treatment
	Before	After	In-group *p* value	Before	After	In-group *p* value	
NRS of sleep disturbance	4.1±1.2	2.4±0.7	<0.05	4.3±1.6	2.3±1.1	<0.05	>0.05

NRS, numerical rating scale for pain measurement.
†Values are mean±SD.

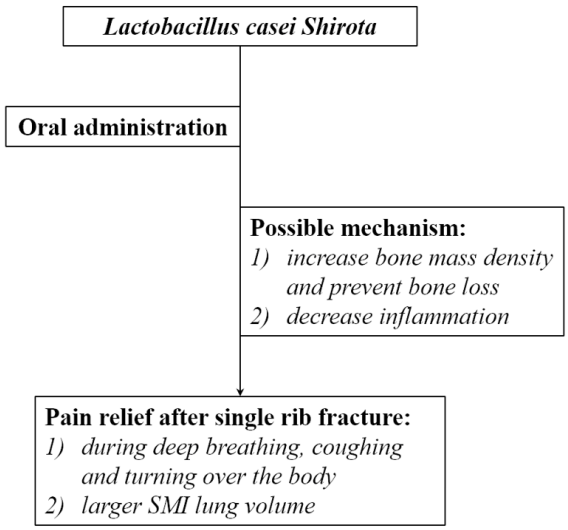

Figure 2. Conceptual diagram of the trial.

high risks, therefore is usually not recommended for patients with a single rib fracture. In this context, oral administration of LcS serves as an ideal prescription as it carries no risk, as shown in this study, and could be administered by the patients themselves after discharge.

Conclusion

In summary, this novel treatment of oral LcS possesses the potential to be a safe and viable therapy for patients with a single rib fracture. Oral administration of LcS produced significant relief of acute pain, when evaluated during deep breathing, coughing and turning over the body (Figure 2). Further studies are needed to uncover the underlying mechanism responsible for the alleviating effect of LcS on pain intensity.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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