Xuebijing attenuates decompression-induced lung injuries

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Abstract
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Introduction: The lung is among the primary organs involved in decompression sickness (DCS). Xuebijing (XBJ), a traditional Chinese medicine, has been widely used in the treatment of various acute lung diseases. This study aimed to explore potential benefit of XBJ on lung injuries induced by DCS in a rabbit model.
Methods: Twenty-four male New Zealand white rabbits underwent a simulated air dive to 50 meters' sea water for 60 min with 2.5 min decompression, and received an intravenous injection of XBJ (5 ml·kg^{-1}) or an equal volume of saline immediately following decompression. DCS signs were monitored for 24 h, and blood was sampled before simulated diving and at 6 h and 12 h following decompression for determination of inflammatory indices. Lung tissues were sampled after euthanasia for histology analysis and lung water content, as well as tumour necrosis factor-α level. Another six rabbits were used as control.
Results: XBJ significantly ameliorated lung injuries (lung wet/dry ratio and total protein content in bronchoalveolar lavage fluid), and notably inhibited systemic (serum level of interleukin-1β) and local (tumour necrosis factor-α in bronchoalveolar lavage fluid) inflammation responses.
Conclusions: The results strongly suggest the benefits of XBJ on ameliorating DCS lung injuries, which is possibly via inhibiting systemic and local inflammation. XBJ may be a potential candidate for the treatment of decompression-induced lung injuries.

Introduction

Decompression sickness (DCS) is a major concern for scuba divers, compressed air workers and other personnel exposed to hyperbaric environments.[1] It has been well demonstrated that the severity of DCS is related to circulating bubbles induced by decompression, which may lead to mechanical obstruction, venous congestion, endothelial dysfunction, inflammation and coagulation activation.[2,3] The lung is a pivotal organ involved in DCS, in which the pulmonary capillary network bears the brunt of venous bubble formation as a superb filter,[4] and prevents bubbles flowing into the systemic circulation by trapping and excreting venous bubbles.[5] Bubbles could induce inflammation cascades, as well as mechanical injury of the endothelial cells, giving rise to increased permeability of the blood-lung barrier,[6] and leading to interstitial lung oedema as a result.[7] When overloaded with large numbers of bubbles pulmonary vascular obstruction occurs producing symptoms including chest pain, cough, dyspnoea and even death.[8] It has been suggested that the early death following decompression may be associated with pulmonary DCS.[9] Studies have confirmed lung injury, such as pulmonary oedema, induced by decompression.[7,10] Hence, protection from lung injury caused by bubbles may be of great importance for the prognosis of DCS. Although hyperbaric oxygen treatment (HBOT) is the primary intervention for DCS, there is frequently a time delay for DCS patients to receive HBOT, and potential for drugs targeting DCS pathophysiology to improve its prognosis.

Xuebijing (XBJ) is a traditional Chinese medicine, which is composed of *Carthamus tinctorius*, *Radix paeoniae rubra*, *Ligusticum wallichii*, *Radix salviae miltiorrhizae* and *Radix angelicae sinensis*.[11] Properties of inflammation inhibition, immune function enhancement and microcirculation improvement have been confirmed in animal and clinical trials.[11,12] XBJ was approved for the treatment of sepsis and multiple organ dysfunction syndromes (MODS) by the China Food and Drug Administration in 2004. Clinical studies indicate that addition of XBJ to standard treatment for severe community-acquired pneumonia significantly improves prognosis, reduces 28-day mortality and shortens duration of intensive care stay with a low incidence of adverse effects.[13,14] Other experimental and clinical studies suggest significant benefits for treating acute lung

injuries,[13,15,16] and it is also recommended for the treatment of COVID-19 in China.[17] Considering that DCS is a systemic disease accompanied with inflammation, oxidative responses, coagulation and endothelial dysfunction,[1,18,19] we explored potential effects of XBJ on lung injury in a rabbit DCS model.

Methods

ANIMALS

The experimental protocol was approved by the Ethics Committee for Animal Experiments of the Naval Medical University (Approved number: 20180820060), and all the procedures were performed in line with related guidelines and regulations. A total of 30 male New Zealand White rabbits with weights varying from 2.0 to 2.3 kg were obtained from Shanghai Shengwang Laboratory Animal Co. Ltd. The rabbits were housed individually in metal cages with controlled humidity (50–60%), temperature (24–26°C) and a natural light/dark cycle. Food and water were provided *ad libitum*. Prior to experimental procedures, rabbits were acclimatised to the laboratory environment for one week.

PROCEDURE AND DESIGN

The rabbits were randomly divided into three groups: 12 each for XBJ and saline groups, and six for the normal control group to acquire normal values, which were in line with animal ethics. Our previous research showed that the simulated diving profile could yield an incidence of DCS in rabbits around 75%, and 12 rabbits in each group would produce approximately nine cases with DCS, which were enough to compare biomedical indices between groups. Rabbits in the former two groups were subjected to simulated diving and rapid decompression to induce DCS. In the XBJ group, rabbits received an intravenous injection of XBJ (Tianjin Chase Sun Pharmaceutical Co., Tianjin, China) 5 ml·kg^{-1} body weight immediately after decompression. Rabbits in the saline group were given the equal volume of saline in the same way. Normal rabbits were sham exposed (normobaric air) in order to acquire normal values of the indices. After rapid decompression, the rabbits were under continuous observation for 24 h by a member of staff blinded to the treatments. Blood was sampled before simulated diving and at 6 and 12 h following decompression for determination of inflammatory indices. Surviving rabbits were euthanised at 24 h after decompression with an intraperitoneal injection of pentobarbital (200 mg·kg^{-1}), and then lung tissues and bronchoalveolar lavage fluid (BALF) were sampled. Normal controls were sham exposed (normobaric air) and sampled similarly.

SIMULATED DIVING

The rabbits were subjected to simulated diving in an animal hyperbaric chamber (DWC150, Yangyuan, Shanghai, China) in pairs, each time with one in the XBJ group and the other one in the saline group. The pressure was increased to 600 kPa (absolute pressure) in 5 min and maintained for 60 min using compressed air. Compression began slowly and was completed in 5 min to minimise any possible discomfort. Thereafter, decompression procedure was conducted linearly to ambient pressure at a rate of 200 kPa·min^{-1}. The chamber underwent continuous ventilation to avoid accumulation of carbon dioxide (CO_2).

DCS SYMPTOM OBSERVATION

After surfacing, rabbits were under continuous observation to evaluate DCS by one observer blinded to the treatments. DCS was diagnosed as individuals with at least one symptom including abnormal biting, respiratory or motor dysfunction, seizure and death. When individuals exhibited paralysis, dyspnoea, seizure or death, then severe DCS was diagnosed. Respiratory function was monitored and scored at 10, 20, 30, 40, 60, 90 and 120 min following decompression using a 0-4 grading scale as follows: 0 = normal breathing; 1 = mild laboured breathing; 2 = restlessness and laboured breathing; 3 = severely laboured breathing, recumbent posture; 4 = collapse, stupor and death.[20] As respiratory changes progressed rapidly and usually recovered within 2 h of decompression, the maximal score observed during the 2 h period was deemed the respiratory score of each rabbit.

DETERMINATION OF SERUM INFLAMMATORY FACTORS

One millilitre of venous blood was sampled and centrifuged at 4°C and 2,500 rpm for 10 min. Serum levels of interleukin-1beta (IL-1β) and macrophage chemokine-1 (MCP-1) were determined by enzyme-linked immunosorbent assay (ELISA) kits (Jiancheng Bioengineering Institute, Nanjing, China). The coefficient of variation of inter-assay and intra-assay was less than 10% and 12%, respectively. The accuracy and precision were ± 1% and ≤ 0.2%, respectively. All assays were conducted according to the manufacturer's instructions.

BALF ANALYSIS

After euthanasia at 24 h following decompression, the right main bronchus was clipped, and 10 ml 0.9% saline was slowly infused in and out three times through a special plastic tube inserted into the trachea. The procedure was repeated for a total of three washes (30 ml), and BALF recovery was approximately 80%. Total BALF protein was measured by bicinchoninic acid (BCA) using enhanced BCA protein assay kits (Beyotime Institute of Biotechology, Nantong, China). Tumour necrosis factor-α (TNF-α) was determined by ELISA kits (Jiancheng Bioengineering Institute, Nanjing, China).

LUNG WET/DRY WEIGHT RATIO ASSAY

Lung water content can reflect the severity of pulmonary oedema, which was assayed by lung wet/dry (W/D) weight

ratio. Right lower lung lobes were taken and weighed as wet weight, and then incubated in an oven at 60°C for 72 h to obtain the dry weight.

HISTOLOGICAL EXAMINATION

Right upper lung lobes were incised and fixed in 10% buffered formalin solution, and embedded in paraffin, which were then sectioned at 5 µm thickness and stained with haematoxylin and eosin (H&E). Sections were examined using a light microscope (DMi8, Leica, Germany) and scanned using an automatic digital slide scanner (Pannoramic MIDI, 3DHISTECH, Hungary). Each section was identified for alveolar congestion, haemorrhage, inflammatory infiltration and thickened alveolar walls, and scored for each item using a histologic scoring system as follows: 0 = normal lungs; 1 = < 25% lung involvement; 2 = 25–50% lung involvement; 3 = 50–75% lung involvement; 4 = > 75% lung involvement. The average score of each section was determined to represent the histopathology score.[21,22]

STATISTICAL ANALYSIS

Where applicable, values were expressed as mean (standard deviation [SD]) or median (interquartile range) except for incidence and death rate of DCS, which were compared between the XBJ and saline group by Chi-square test. Normal distribution of data was determined using the Shapiro-Wilk test. An independent-samples *t*-test was used to compare blood indices between the two groups. Lung W/D weight ratio, BALF TNF-α and protein content were compared using one-way ANOVA followed by Dunnett's test among the XBJ, saline and normal control groups. Respiratory and histological scores were compared between XBJ and saline groups using a Mann-Whitney U test. *P*-values less than 0.05 were considered statistically significant.

Results

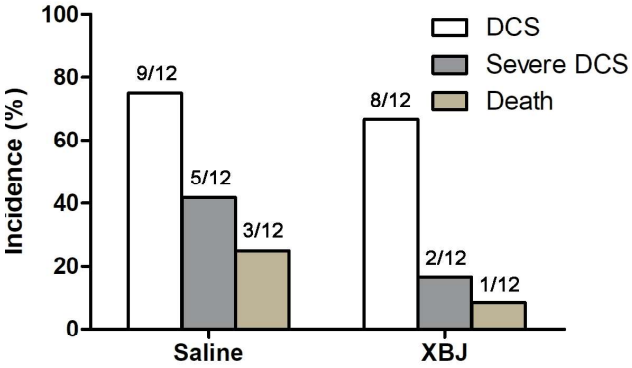
INCIDENCE OF DCS AND DEATH RATE

All DCS cases occurred within 30 min following decompression. Three rabbits died in the saline group within 1 h following decompression after a short period of severe dyspnea and convulsions, and one died in the XBJ group at 6 h following decompression with circulatory dysfunction. There was no significant difference in incidence of severe DCS (2/12 vs. 5/12, χ^2= 0.807, P = 0.369) and death rate (1/12 vs. 3/12, χ^2=0.300, P = 0.584) between XBJ and saline groups respectively (Figure 1).

DECOMPRESSION-INDUCED LUNG INJURIES

After surfacing, 42% of the rabbits exhibited transient tachypnoea. XBJ did not decrease respiratory scores significantly (Z = -1.812, P = 0.070, Figure 2A). Lung water content evaluated by lung W/D weight ratio was significantly decreased by XBJ (4.71 (SD 0.07) vs. 4.81 (0.12), t = 2.335, P = 0.031, Figure 2B). At 24 h following decompression, levels of TNF-α and total BALF protein in the saline group increased significantly (89.2 (10.0) vs. 53.5 (11.5); 0.34 (0.06) vs. 0.21 (0.04), P < 0.05), and were notably inhibited by XBJ (66.6 (19.3) vs. 89.2 (10.0); 0.28 (0.04) vs. 0.34 (0.06), P < 0.05, Figure 2C and 2D).

Figure 1
Effects of XBJ on the incidence and death rate of DCS in rabbits. There were no statistically significant differences between groups in the incidence of severe DCS and deaths



LUNG HISTOPATHOLOGY

Representative histologic examination findings are shown in Figure 3. Rupture of normal alveolar structure, thickened alveoli septum, haemorrhage and infiltration of neutrophils were present in DCS rabbits (Panels B1 and B2) when compared with normal controls (Panels A1 and A2), which were notably ameliorated by XBJ treatment (Panels C1 and C2). Lung injury scores in detail are shown in Panel E, and XBJ significantly decreased histopathology score (1.16 (0.57) vs. 1.89 (0.71), Z = -2.041, P = 0.041, Panel D).

SYSTEMIC INFLAMMATION

Levels of serum IL-1β and MCP-1 significantly increased following decompression, with an average increase of approximately 20% (Panels A and B). XBJ significantly inhibited the increase of IL-1β (0.13 (0.08) vs. 0.21 (0.09), P = 0.040, Panel C). There was no statistical difference in rate of change in MCP-1 between the two groups.

Discussion

Decompression-induced circulating bubbles of >20 µm in diameter are often trapped in the lung capillaries and then dissolve during expiration.[23] Formation of a small number of venous bubbles is common in diving and typically do not cause symptoms because they are usually filtered out by the pulmonary circulation. However, a large number or volume of bubbles might compromise the capability of the lungs to filter them,[24] and cause symptoms including chest pain, cough, dyspnoea and even death.[8] Although HBOT is the most efficient treatment, exploration of potential drugs

Figure 2

XBJ ameliorated DCS induced lung injuries. Numerical values in the bars denote the number of rabbits in each group. # = $P < 0.05$ vs. normal control, * = $P < 0.05$ and ** = $P < 0.01$ vs. saline group

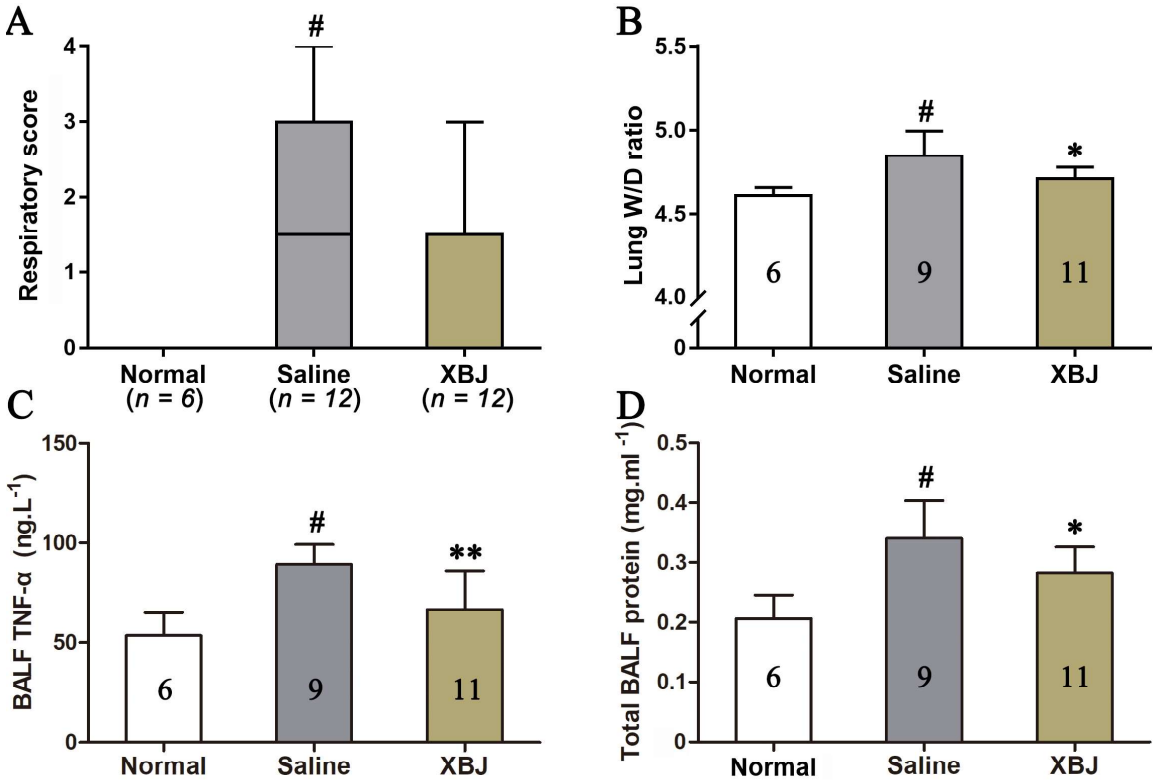
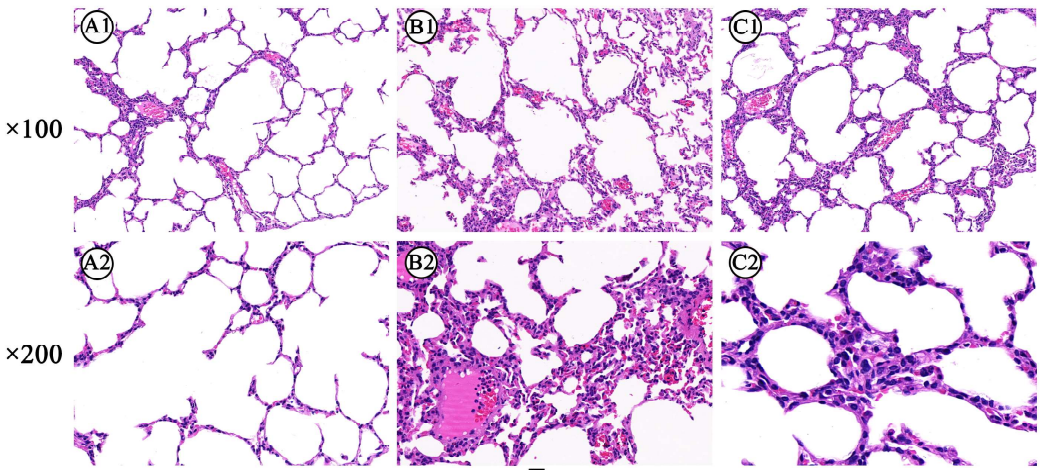
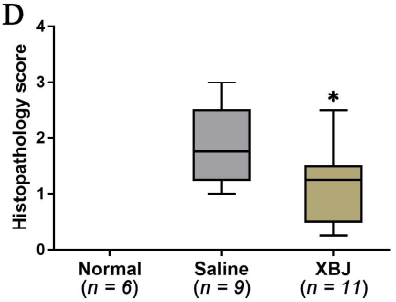


Figure 3

Representative photomicrographs and scores of the lung histopathology of DCS rabbits. A panels = normal histopathology of lung parenchyma. B panels = saline group showing disruption of alveolar structure, haemorrhage, infiltration of neutrophils and thickened alveoli septa. C panels = XBJ group showing ameliorated histopathology. D and E panels show lung histopathology score distribution and differences. * = $P < 0.05$ vs. saline group





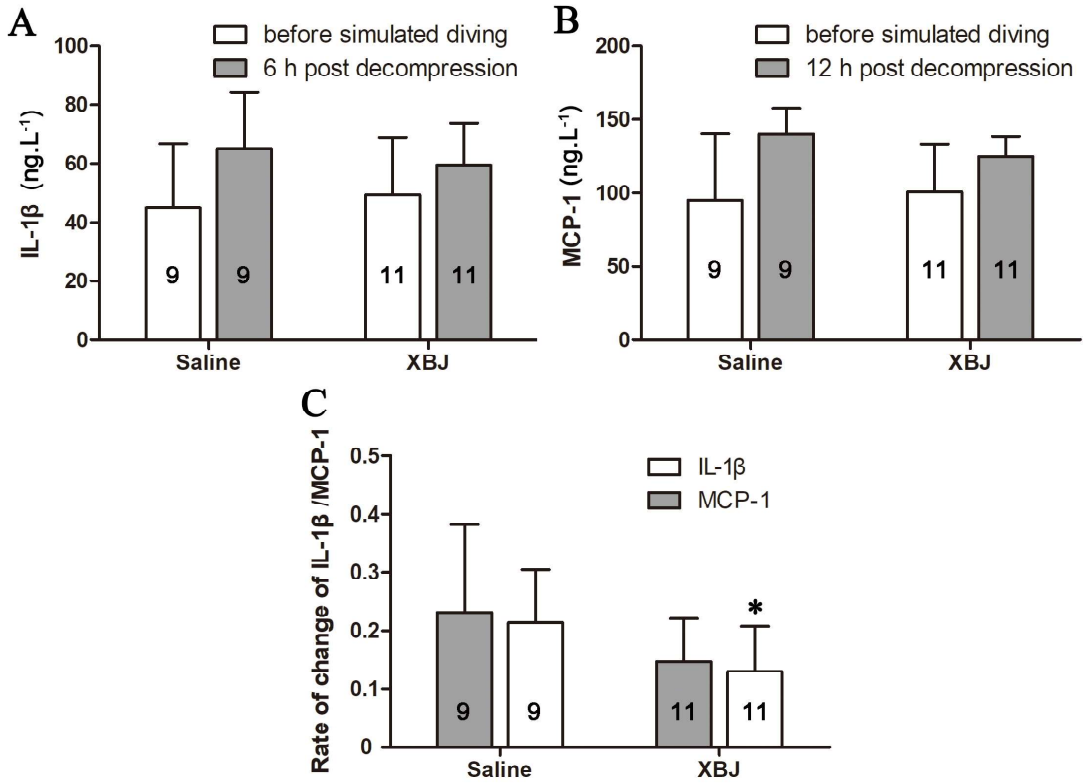
E

Lung histopathology score distribution

Score	Incidence *n* (%)		
	Normal	Saline group	XBJ group
0~1	6 (100)	1 (11.1)	4 (36.4)
1~2	0 (0.0)	4 (44.5)	6 (54.5)
2~3	0 (0.0)	3 (33.3)	1 (9.1)
3~4	0 (0.0)	1 (11.1)	0 (0.0)

Figure 4

Comparison of XBJ and saline groups in respect of plasma inflammatory markers: panel A = IL-1β; panel B = MCP-1; panel C = rate of change in markers. * = $P < 0.05$ vs. saline group



targeting lung injuries induced by DCS are still areas of research focus.

In this study, potential benefits of XBJ were investigated in a rabbit DCS model. Among the indices studied, increased lung W/D weight ratio and BALF protein content following decompression were inhibited by XBJ, indicating amelioration of pulmonary oedema. As DCS is also an inflammatory process, TNF-α, IL-1β and MCP-1 were selected as indices for determining severity of inflammatory responses. In a previous study, IL-1β and MCP-1 peaked at 6 and 12 h following decompression, respectively.[25] XBJ notably decreased the elevated serum levels of IL-1β following decompression. IL-1β is an important pro-inflammatory cytokine mediating other cytokine production and vascular injuries related to decompression.[26] Though no statistical difference existed in rate of change in MCP-1 between groups, XBJ treatment showed a trend toward decreased MCP-1 levels. XBJ significantly decreased TNF-α level in BALF. The alleviated systemic and local lung inflammatory responses may in turn reduce lung injury induced by circulating bubbles.

It is reported that pulmonary pathophysiologic changes caused by DCS include pulmonary hypertension, which is due to either vascular obstruction by bubbles or inflammatory cell accumulation.[27] Accompanied pulmonary hypertension, the permeability of pulmonary micro-vascular and epithelial membranes induces interstitial and alveolar oedema.[28] Although clinical symptoms are typically not present in divers, there is ultrasonic evidence showing subclinical pulmonary oedema following decompression.[7] XBJ has been shown to be effective in attenuating acute lung injury via inhibition of the activity of Toll-like receptor 4 (TLR4) and nuclear factor kappa B (NF-κB) and decreasing lung permeability.[29] As confirmed in the present study, increased levels of BALF protein and lung W/D ratio were significantly inhibited by XBJ when compared with the saline group. XBJ treatment significantly ameliorated pulmonary oedema and showed a tendency to improve respiratory function following decompression. These findings are consistent with other studies of XBJ on acute lung injury caused by dichlorvos poisoning and sepsis.[15,30]

The presence of bubbles is also accompanied by activation of inflammatory cascades, capillary leakage and haemconcentration,[31] which make it more difficult to treat DCS by HBOT alone.[23] As an extraction from many herbs, XBJ exerts powerful anti-inflammatory properties via many pathways including NF-κB inhibition and IκB kinase enzyme activation,[32,33] and it has been found efficient in suppressing uncontrolled release of inflammatory factors.[34] The present results suggest that XBJ ameliorated systemic and local inflammation responses following decompression, and notably attenuated lung injuries as a result, which is in accord with previous studies.[15] XBJ is also reported to reduce lung injuries via ameliorating apoptosis.[16] This alleviation of biochemical indices provides support for the

use of XBJ in treating lung injuries caused by decompression bubbles.

XBJ consists of five Chinese herbs. Though it is unclear which component(s) contribute to its (their) anti-inflammatory effects, XBJ exhibits good batch-to-batch quality consistency (with lot-to-lot variability of 9.6% for the level I pathalide),[33] and no serious side effects were found in 31,913 participants in a clinical study.[35] It has been widely adopted for the treatment of sepsis and MODS, as well as COVID-19 in China.[17,36] The present study explored potential benefits of XBJ in DCS for the first time, and confirmed its potential in treating decompression-induced lung injuries. However, this study has limitations. The current sample size may be too small to detect differences in DCS incidence and death rate, and it was calculated that a sample size of 40 for the two groups would be required to provide 80% power to reach statistical significance. Although XBJ has been adopted clinically in treating various diseases, more animal studies are still needed before using XBJ on divers.

Conclusions

XBJ significantly attenuated decompression-induced lung injuries in this animal model; an effect mainly attributed to its anti-inflammatory properties. XBJ has been widely used clinically with few side effects, and it may be a promising candidate for DCS treatment.

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