Effect of *Panax notoginseng* in Patients with Multiple Fractured Ribs and Pulmonary Contusions Caused by the 2008 Wenchuan Earthquake

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Keywords

Multiple fractured ribs · Pulmonary contusions · *Panax notoginseng* · Earthquake injury

Summary

Background: The aim of this study was to investigate whether the combination of conventional treatment and *Panax notoginseng* (PN group) is superior to conventional treatment alone (CG group) in reducing the clinical symptoms of patients with multiple fractured ribs and pulmonary contusions. **Patients and Methods:** We retrospectively analyzed the medical records of patients treated for multiple fractured ribs and pulmonary contusions with either conventional treatment (n = 17) or *P. notoginseng* (n = 18). Visual analog scale (VAS) pain scores and arterial oxygen saturation were measured at baseline and at 1 and 2 weeks following treatment. The duration of mechanical ventilation, systemic analgesics, and hospital stay were also recorded. **Results:** VAS scores in the PN group were lower than in the CG group at 1 week (p < 0.01) and at 2 weeks (p < 0.05). Arterial oxygen saturation in both groups was higher after treatment than at baseline (p < 0.05), but there was no statistically significant difference between the 2 groups (p > 0.05). The duration of mechanical ventilation, systemic analgesics administration, and hospital stay in the PN group was remarkably decreased as compared to the CG group (p < 0.05). **Conclusion:** Combining conventional treatment and *P. notoginseng* seems to be an efficient method that can improve the clinical symptoms of multiple fractured ribs and pulmonary contusions.

Schlüsselwörter

Multiple Rippenfrakturen · Lungenprellungen · *Panax notoginseng* · Erdbeben · Verletzung

Zusammenfassung

Hintergrund: Ziel der Studie war zu prüfen, ob die Kombinationsbehandlung aus konventioneller Therapie und *Panax notoginseng* (PN) einer rein konventionellen Behandlung bei der Linderung von klinischen Symptomen bei Patienten mit multiplen Rippenfrakturen und Lungenprellungen überlegen ist. **Patienten und Methoden:** Wir haben retrospektiv Patientenakten von Betroffenen ausgewertet, deren multiple Rippenfrakturen und Lungenprellungen entweder konventionell (n = 17) oder mit PN (n = 18) behandelt wurden. Der Schmerzscore sowie die arterielle Sauerstoffsättigung wurden zur Baseline und eine sowie 2 Wochen nach Behandlung auf der Visuellen Analogskala (VAS) gemessen. Erhoben wurden die Dauer der mechanischen Beatmung, der Verabreichung von Medikamenten und des Krankenhausaufenthalts. **Ergebnisse:** Die VAS-Scores in der PN-Gruppe waren nach einer Woche (p < 0,01) bzw. 2 Wochen (p < 0,05) niedriger als in der Gruppe mit konventioneller Therapie. Die arterielle Sauerstoffsättigung war nach der Behandlung in beiden Gruppen höher als zur Baseline (p < 0,05), jedoch gab es keinen statistisch signifikanten Unterschied zwischen den beiden Gruppen (p > 0,05). Die Dauer der mechanischen Beatmung, der Medikamentenverabreichung sowie des Krankenhausaufenthalts war in der PN-Gruppe bemerkenswert gesunken, im Vergleich zur konventionell behandelten Untersuchungsgruppe (p < 0,05). **Schlussfolgerung:** Die Kombination aus konventioneller Behandlung und PN scheint eine effektive Methode zur Linderung klinischer Symptome bei multiplen Rippenfrakturen und Lungenprellungen zu sein.

Introduction

Blunt thoracic trauma is a serious injury that has a high incidence and morbidity and can be caused by a variety of injuries. Multiple fractured ribs (MFRs) and pulmonary contusions are common in blunt thoracic trauma, with a reported incidence of approximately 10% [1] and 30–75% [2], respectively. MFRs and pulmonary contusions increase morbidity and mortality in patients with underlying pulmonary complications. In the clinic, pain management, fluid management, and ventilatory support have been widely used, which can improve the clearance of pulmonary secretions; this approach enables deep breathing, prevents pulmonary complications, and decreases the requirement for tracheal intubation and assisted ventilation [3–6]. Previous study has shown that pain management is beneficial for MFRs and improves pulmonary function which promotes the clearance of pulmonary secretions to enable deep breathing, prevent pulmonary complications, and decrease the requirement for tracheal intubation and assisted ventilation [7–9]. Nevertheless, different pain control methods have myriad side effects and associated complications [10, 11]. Fluid management and ventilatory support are commonly used in the management of pulmonary contusions; however, these methods do not affect mortality and morbidity, which is attributed to a lack of understanding of the associated pathophysiology [4]. This important issue has not been well studied; efforts are ongoing to identify potential therapeutic interventions in MFRs and pulmonary contusion that have similar efficacy.

Panax notoginseng (Burk.) F. H. Chen is a medicinal herb that has been widely used in China for thousands of years. The pharmacology of *P. notoginseng* has been studied and has resulted in its widespread use in the clinical setting [12, 13]. Currently, *P. notoginseng*, as a powerful and beneficial therapeutic management tool, is useful in treating hemorrhoids and reducing inflammation; it is also used as an analgesic. However, the question of whether *P. notoginseng* is useful in increasing the pulmonary function in patients with MFRs and pulmonary contusions via its analgesic effects has not been studied.

We retrospectively analyzed the medical records of patients treated for MFRs and pulmonary contusions caused by the Wenchuan earthquake. We investigated whether the combination of both conventional treatment and a *P. notoginseng* supplement is superior to that of conventional treatment alone in alleviating the clinical symptoms of MFRs and pulmonary contusions.

Patients and Methods

Patients

Both patient care and the retrospective review of medical records were conducted with the approval of the Ethics Committee on Human Research of the People's Republic of China (No. 2008BL-001). The patients were hospitalized at the Chengdu University of Traditional Chinese Medicine Hospital following MFRs and pulmonary contusions caused by

the Wenchuan earthquake. The following inclusion criteria had to be met: i) age > 18 years; ii) anteroposterior and lateral chest radiographs confirming 3 or more unilateral fractured ribs and pulmonary contusions; and iii) normal mental status and ability to answer a verbal rating assessment and adequately perform ventilatory function tests. Exclusion criteria were: i) possible influence of confounding injuries such as severe spinal fractures, acute traumatic brain or spinal cord injuries, unstable pelvic fractures, and an open abdomen; ii) unstable cardiac status including thoracic aortic transection and coagulopathy; iii) prior liver or kidney disease; and iv) existing contraindications to pain management or *P. notoginseng*. According to our retrospectively analyzed medical records, all of patients included in the study met the above criteria.

Conventional Treatment

Patients with pneumothorax or hemothorax underwent drainage procedures, any required surgical procedures were carried out, and aggressive pulmonary hygiene with deep breathing was performed; suctioning of cough secretions was employed as needed. Any other clinically significant abnormalities were corrected. Analgesics were administered during electrocardiographic monitoring and noninvasive monitoring of blood pressure, heart rate, and arterial oxygen saturation electrocardiogram. For this, patients were awake and were either lying in the lateral decubitus position or sitting upright. The location of the administered analgesia depended on the location of each fractured rib. Bupivacaine 0.125% plus fentanyl (2.5 µg/ml) was administered at a dose of 0.1 ml/kg/h, which is the dosing used at the Prince of Wales Hospital, Hong Kong. The epidural catheter was replaced every 4th day to avoid infection. All patients were followed up every 24 h over the next few days. Analgesia were administered until pain could be controlled with oral non-steroidal anti-inflammatory drugs (NSAIDs) (celecoxib 200–400 mg twice daily). Appropriate mechanical ventilation criteria included the following: i) respiratory rate > 40/min or < 8/min; ii) partial pressure of oxygen (PaO_2) < 8 kPa (60 mmHg), fraction of inspired oxygen (FiO_2) > 50%, partial pressure of carbon dioxide (PCO_2) > 6.67 kPa (50 mmHg); iii) chest abbreviated injury scale (AIS) ≥ 4 ; iv) Glasgow coma index ≤ 7 ; v) blood transfusion amount ≥ 3 units; vi) associated with shock; and vii) oxygenation index ($\text{PaO}_2/\text{FiO}_2$) < 300. Positive end-expiratory pressure was employed; patients were on mechanical ventilation until the arterial blood gas analysis returned to normal.

Panax notoginseng

Patients in the conventional treatment plus *P. notoginseng* (PN) group were concurrently given intravenous drips containing 150 mg *P. notoginseng* extract (Xueshuantong™, Suzhou Pharmaceutical, Guangxi, China) and 250 ml 10% glucose twice daily. The method of extraction included the following steps: i) crushing the *P. notoginseng* roots into a coarse powder (20–30 mesh); ii) adding alcohol to 75%; iii) soaking in the alcohol for approximately 12 h; iv) use of ultrasound waves to emulsify the mixture of coarse powder and alcohol for approximately 30 min; v) filtering and collecting of the mixture, including pressure reduction condensation and vacuum drying. *P. notoginseng* was administered until the patient's pain could be controlled with oral NSAIDs (celecoxib 200–400 mg twice daily).

Pain intensity was assessed using VAS pain scores; oxygen saturation in the arterial blood was measured at baseline and at 1 and 2 weeks following treatment. Patients were evaluated using VAS pain scores in the morning after coughing. The duration of mechanical ventilation, systemic analgesics, and hospital stay was also recorded.

Statistical Analysis

Statistical analysis was conducted using the SPSS 17.0 statistical package (IBM Corp., Armonk, NY, USA). The characteristics and baseline parameters of the CG and PN groups were analyzed and subsequently compared. Data are expressed as the mean $\pm$ standard deviation (SD). To compare differences between the groups, one-way analysis of variance (ANOVA) or multi-way ANOVA were used. *p* values less than 0.05 were considered to be significant.

Results

Demographics and Injury Data

In this retrospective study, 260 patients met the inclusion criteria. In total, 45 refused participation because of unstable pelvic fractures. Additionally, 65 patients suffered severe spinal fractures. 92 patients had unstable cardiac status and other vital organ diseases and were therefore excluded. Furthermore, 23 patients were excluded due to inadequate data regarding the VAS score or other results. In total, 35 patients were included; 17 patients belonged to the CG group and 18 to the PN group. The 2 groups were comparable in terms of mean age, sex, mean number of fractured ribs, AIS, number of flail segments, hemothorax, pneumothorax, and PaO₂. There was no significant difference between the 2 groups (table 1).

Comparison of VAS Pain Score Response to Treatment between Groups

Both the PN group and the CG group showed decreases in VAS score, which were statistically significant ($p < 0.05$). The pain scores of patients in the PN group were lower than those in the CG group at 1 week, which was a statistically significant difference ($p < 0.01$). The difference between the 2 groups at 2 weeks was also statistically significant ($p < 0.05$) (table 2).

Comparison of Arterial Oxygen Saturation Response to Treatment between Groups

The arterial oxygen saturation in both groups was higher after treatment than at baseline ($p < 0.05$), which demonstrated that both treatments were beneficial to pain management. However, there was no statistically significant difference between the 2 groups ($p > 0.05$) (table 3).

Duration of Mechanical Ventilation, Systemic Analgesics, and Hospital Stay

The average duration of mechanical ventilation was 4.5 ± 3.0 days in the PN group and 8.0 ± 6.08 days in the CG group. The average duration of administration of systemic analgesics was 7.0 ± 2.16 days in the PN group and 13.33 ± 5.77 days in the CG group. The duration of hospital stays for the 2 groups was 18.25 ± 5.80 days and 30.00 ± 0.00 days, respectively. There was a remarkably decreased length of hospital stay in the PN group as compared to the CG group.

Discussion

On Monday, May 12, 2008, a deadly earthquake occurred in the Sichuan province of China. According to official statistics, over 68,000 people were killed, and the casualties numbered in the tens of thousands. A previous retrospective investigation reported that of the 256 patients with thoracic trauma, 198 had MFRs and pulmonary contusions [14]. MFRs are common in blunt thoracic trauma; patients may experience significant pain

Table 1. Demographics and injury data

Characteristics	CG group	PN group	p
Age, years	54.59 $\pm$ 12.61	49.56 $\pm$ 14.22	0.277
Sex, n (%)			
Male	10 (58.8%)	8 (44.44)	0.410
Female	7 (41.2%)	10 (55.56)	
Fractured ribs, n	4.80 $\pm$ 1.80	4.80 $\pm$ 1.40	0.912
AIS	3.50 $\pm$ 1.70	3.50 $\pm$ 1.80	1.000
Flail segments, n	3	2	0.500
Hemothorax, n	2	2	1.000
Pneumothorax, n	1	1	1.000

CG = Conventional treatment alone; PN = *Panax notoginseng*;
AIS = Chest abbreviated injury scale.

Table 2. Visual analog scale (VAS) pain score

	CG group (mean $\pm$ SD)	PN group (mean $\pm$ SD)
Baseline	39.40 $\pm$ 20.14	38.30 $\pm$ 20.12
1 week	22.90 $\pm$ 3.51 ^{a,c}	8.30 $\pm$ 2.18 ^{b,c}
2 weeks	14.70 $\pm$ 2.98 ^{a,d}	1.10 $\pm$ 0.76 ^{b,d}
Patients, n	17	18

^aCompared to PN group ($p = 0.025$).
^bCompared to CG group ($p = 0.011$).
^cCompared to baseline ($p = 0.033$, $p = 0.001$, respectively).
^dCompared to 1 week ($p = 0.029$, $p = 0.001$, respectively).
CG = Conventional treatment alone; PN = *Panax notoginseng*.

Table 3. Arterial oxygen saturation

	CG group (mean $\pm$ SD)	PN group (mean $\pm$ SD)
Baseline, %	82.00 $\pm$ 2.82	81.00 $\pm$ 2.63
1 week, %	87.18 $\pm$ 1.24 ^{a,c}	90.17 $\pm$ 1.29 ^{b,c}
2 weeks, %	93.53 $\pm$ 0.60 ^{a,d}	95.28 $\pm$ 0.67 ^{b,d}
Patients, n	17	18

^aCompared to PN group ($p = 0.259$).
^bCompared to CG group ($p = 0.546$).
^cCompared to baseline ($p = 0.045$, $p = 0.037$, respectively).
^dCompared to 1 week ($p = 0.038$, $p = 0.029$, respectively).
CG = Conventional treatment alone; PN = *Panax notoginseng*.

and pulmonary function deterioration associated with other injuries [15]. Some studies have reported that pulmonary dysfunction is present in up to 38% of patients with rib fractures [16]. The types of MFRs and severe pulmonary contusions vary widely and may lead to pneumonia, acute respiratory distress syndrome, and multiple organ dysfunction/failure [11]. Due to these adverse effects, early administration of pain control, fluid management, and ventilatory support are beneficial to patients. Pain management is important in the treatment of patients with rib fractures, and adequate analgesia alone can improve respiratory parameters. In our study, we chose epidural analgesia because it has been proven by many studies to

be an effective means of managing pain in the clinical setting [17, 18]. Our results showed a decrease in the VAS pain score and a significant improvement in the oxygen saturation in arterial blood in patients treated with conventional therapy. However, there are adverse effects relating to epidural analgesia (including hypotension, epidural infection, and cardiovascular collapse), which have limited the scope of its use [19]. Fluid management and ventilatory support are commonly used in the treatment of pulmonary contusion; however, there are no advantages in terms of mortality and morbidity, which is attributable to a lack of understanding of the associated pathophysiology [4]. Both MFRs and pulmonary contusions have sequelae that are difficult to manage. How can we enhance the treatment modalities of MFRs and pulmonary contusions while decreasing the associated complications?

P. notoginseng is a Chinese medicinal herb commonly used for promoting blood circulation, clearing blood clots, and relieving swelling and pain [20]. Over 50 different saponins have been isolated and categorized, including 20(S)-protopanaxadiol (PPD classification) and aglycone 20(S)-protopanaxatriol (PPT classification) moieties. Currently, *P. notoginseng* extract is being used as a therapeutic agent for treating a wide variety of injuries. Ultrasonic extraction saves time and effort when applied to production. The optimal process includes stably maximizing the retained *P. notoginseng* active ingredient. The active component ginsenoside, Rb1, has been shown in some studies to play a key role in mediating anti-inflammatory, tranquilizing, and vasodilatory effects [21]. Jin et al. [22] demonstrated that the water extract of *P. notoginseng* inhibited neutrophil function, including the production of nitric oxide (NO) and prostaglandin E₂. Lee et al. [23] used lipopolysaccharides (LPS) to induce NO production, which resulted in the increased expression of inducible nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX-2). The authors demonstrated that *P. notoginseng* extract downregulated NO production in response to LPS and the expression of iNOS and COX-2 proteins, which suggested that *P. notoginseng* can inhibit the synthesis of prostaglandin E₂. It is well known that COX-2 induces the production of prostaglandin E₂, which contributes to swelling, inflammation, and pain after injury. We hypothesized that adding *P. notoginseng* to conventional treatment may prevent the aforementioned complications. In our study, the analgesic effect and improvements in pulmonary function in the PN group were significantly superior to the CG group, as reflected by the VAS pain scores, the duration of mechanical ventilation, and the average hospital stay duration. Following the addition of *P. notoginseng*, the duration of systemic analgesics was decreased, and the patients had a reduction in the use of local anesthetic agents, which resulted in a decrease in the adverse effects, including nausea, vomiting, and urinary retention [19]. Because the number of procedures was decreased, the incidence of dural punctures, epidural hematomas, and spinal cord injuries was also decreased.

There are many studies that indicate that cellular and sub-cellular injury and inflammatory mechanisms play a funda-

mental role in the pathophysiology of pulmonary contusions [24]. In the progression of a pulmonary contusion, pulmonary injury triggers an inflammatory response; prior studies demonstrated that the activation of Toll-like receptors (TLRs) mediates the innate immune response of a pulmonary contusion [25]. All TLRs, except TLRs-3, induce nuclear transcription factor (NF)- κ B activation via intracellular adapter protein MyD88, which is responsible for the acute inflammatory reaction in the lung and subsequent generation of inflammatory mediators [26]. These inflammatory factors, which are released from the innate immune responses, include cytokines and chemokines, which play an important role in several inflammatory reactions. In the generation of these cytokines, interleukin (IL)-1 and tumor necrosis factor alpha (TNF- α) may upregulate the activity of adhesion molecules on pulmonary vascular endothelium (E-selectin, intercellular adhesion molecule (ICAM-1), and alveolar epithelium ICAM-1). Vascular adhesion molecules improve the adhesiveness of polymorphonuclear neutrophils (PMNs). In addition, they promote the subsequent PMN transmigration into the interstitial and distal lung airways. In addition, alveolar epithelium ICAM-1 increases the ability of alveolar macrophages to adhere to epithelial cells. This action induces the production of cytokines and chemokines. IL-6 increases the production of C5aR on vascular endothelial cells and alveolar epithelial cells. C5a plays a very important role in pulmonary inflammation; an increased production of C5aR causes upregulation of C5a expression, which improves cell function and facilitates the generation of pro-inflammatory mediators [27]. A series of inflammatory responses following the infiltration of PMNs into areas of pulmonary contusion results in the release of inflammatory factors and subsequent pulmonary tissue damage.

Kim et al. [28] found that the active component Rg5, isolated from *P. notoginseng*, could reduce the expression of IL-1 β and TNF- α induced by LPS, as well as COX-2 and iNOS production in the alveolar macrophages. Moreover, Rg5 inhibited the phosphorylation of IL-1 receptor-associated kinases (IRAK)-1 and IKK- β ; it also downregulated the generation of IRAK-1 and IRAK-4. Furthermore, Rg5 influences the activation of NF- κ B by inhibiting the phosphorylation and translocation of p65 into the nucleus. This phenomenon suggests that *P. notoginseng* may inhibit TLR-4 on macrophages and subsequently reduce lung inflammation. Rhule et al. [29] demonstrated that *P. notoginseng* selectively attenuated the production of specific inflammatory molecules (including IL-1 β and TNF- α) and inhibited innate immune responsiveness by modulating TLR ligand-induced activation of cultured DC2.4 cells in vitro. In our studies, the results observed in the PN group, including increased arterial oxygen saturation and reduced length of mechanical ventilation, were better than those of the CG group. These results demonstrate that *P. notoginseng* inhibits TLR activation, decreases the production of specific inflammatory molecules, and improves the innate immune responsiveness.

In China, *P. notoginseng* has been shown to be an effective treatment in patients who have suffered accidents involving fractures, bruises, and muscle and ligament strain. In addition, there have been numerous reports demonstrating that *P. notoginseng* can regulate hemostatic activity. White et al. [30, 31] reported that both the external and internal application of *P. notoginseng* reduced the bleeding time by 52% compared to control-treated rats. Furthermore, some researchers have reported that *P. notoginseng* may promote the proliferation of human umbilical vein endothelial cells in mice by enhancing the mRNA expression of vascular endothelial growth factor and kinase-domain region/fetal liver kinase-1. This finding suggests that *P. notoginseng* promotes angiogenesis and accelerates wound healing [32].

Conclusion

Pain management in patients suffering from MFRs and pulmonary contusions can be significantly improved by using conventional treatment and a *P. notoginseng* supplement. The

use of this therapy improved patients' pulmonary function and reduced the associated morbidities. In addition, *P. notoginseng* eliminates the need for local anesthetic agents and mechanical ventilation, and reduces hospital stay, which results in better outcomes while minimizing complications, side effects, and cost.

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Disclosure Statement

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