IJPSR (2013), Vol. 4, Issue 10 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 May, 2013; received in revised form, 11 July, 2013; accepted, 26 September, 2013; published 01 October, 2013

THE REAL-WORLD STUDY OF SHENMAI INJECTION AND ITS ADVERSE REACTIONS ASSOCIATED TO PATIENTS IN CHINESE HOSPITALS: A PROSPECTIVE RESEARCH

Qing-ping Shi [1, 2], Xiao-dong Jiang*[1], Jinxiu Zhu[1], Yan Liu [1], Rang Sang [1], Feng Ding [1], Mu-hua Wang [1], Dao-hua Guo[1], Pei-lan Shi [1], Mei-ling Yu [1], Shengtong Wei [3], Zhiming Xin [4], Ru Song [5], Shu-qiang Zhang [6]

Department of Pharmacy [1], The First Affiliated Hospital of Bengbu Medical College, Bengbu 233000, China
Education and Research Center [2], Bengbu Medical College, Bengbu 233000, China
Department of Pharmacy, The Hospital of Traditional Chinese Medicine of Huaiyuan County [3], Bengbu 233000, China
Department of Pharmacy, No. 1 Hospital of Bengbu City [4], Bengbu 233000, China
Department of Pharmacy, No. 2 Hospital of Bengbu City [5], Bengbu 233000, China
Center of Adverse Drug Reaction Monitoring, Bengbu Food & Drug Administration [6], Bengbu 233000, China

Keywords:

Real-world study, Adverse drug reactions, Shenmai injection, drug use

Correspondence to Author:

Xiao-dong Jiang

Department of Pharmacy, the first Affiliated Hospital of Bengbu Medical College, 287 Changhuai Road, Bengbu, 233004, China

E-mail: sir_shi@126.com

ABSTRACT: Shenmai injection (SMI) is the Traditional Chinese Medicine Injection (TCMI) prepared by Red Ginseng and Radix Ophiopogonis extract. The aim of this study is to reveal the real-word of SMI, to evaluate its use and its adverse reactions associated to patients. A prospective, observational combined nested case-control clinical research carried out in two tertiary care teaching hospitals and two secondary hospitals in China. During the study period, 7632 cases were enrolled and 8 cases of ADR / ADE were reported. It was found that 1.05‰ (95% CI: 0.45-2.06‰) of the patients treated with SMI had some of ADEs classically induced by the use of this drug from the data collected and 6 cases were also in accordance with the instructions, the incidence of ADR to SMI was 1.60‰ (95% CI: 0.58-3.44‰). A total of 121 different diagnoses were stated, most of them were off-label use. 3257 cases (42.68%) in the usage of solvent does not meet the requirements of the specification in accordance with the instructions. 65 cases (0.86%) mixed insulin injection and 13 cases (0.17%) mixed vitamin K_1 injection and dexamethasone injection. In conclusion, SMI have excessive use and its clinical application need to further strengthen the supervision, but the safety of SMI is more reliable.

INTRODUCTION: Shenmai injection (SMI) is the Traditional Chinese Medicine Injection (TCMI) prepared by Red Ginseng and Radix Ophiopogonis extract, it's the clear liquid with the color from pale yellow to light brown [1-2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(10).3902-09

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(10).3902-09

Pharmacological studies on SMI [3-5]:

1. It applies to all kinds of shock, can excite adrenal cortex system and increase the scavenging effect to pathological substances of the reticuloendothelial system when the shock occurs.

   It can improve the blood supply to the heart, liver, brain and other vital organs, improve microcirculation and anticoagulant effect.

2. As is applied to angina pectoris, myocardial infarction, viral myocarditis, pulmonary heart disease, heart failure and so on, it can enhance cardiac function and blood pressure, improve coronary blood flow, enhance antianoxia capacity of the body, reduce oxygen consumption of myocardial, and has the effect of protecting, repairing myocardial cells and certain anti-arrhythmic.

3. For various types of cancer patients, there is obvious synergy coordinate with chemotherapy or radiotherapy, can improve general health of cancer patients, protect hematopoietic function of the bone marrow, improve cellular immune function of cancer patients (increase the activity of NK, LAK and TH / TS value), improve the disappear, shrink rate of tumors.

4. As a result of the acute toxicity test, LD_{50} is 19.7ml/kg, there is no significant toxicity to the liver and kidney function and organization of the mice, indicating that this product has a large security.

The incidence of adverse reactions and its occurrence type of SMI: Wang Li and *et al.* of XiangYa Hospital Central-south University adopted case retrospective study methods to work out the adverse reaction rate that was of 3.6% [6]. The ADR incidence reported by Wen ZeHuai of the Design Measurement Evaluation (DME) Center of Guangzhou University of Chinese Medicine was 0.82% [7]. This may be due to the latter conducted the study in the Chinese Medicine Hospital.

The TCMI used in the Chinese Medicine Hospital met syndrome differentiation of traditional Chinese medical science, the medicine usage was reasonable, perhaps made it a low incidence of adverse reactions. The adverse reactions of SMI reported in literature [6-9] were allergic reactions, infusion reactions. the adverse reactions could affect multiple organ systems in the body studied by Wang Li, *et al*. Xiangya Hospital of Central South University, The clinical manifestations were also complex and diverse, among which the main types according to the incidence were as follows: Digestive system, such as nausea, vomiting, diarrhea was common; Respiratory system, such as dyspnoea, shortness of breath, hiccups was common; Systemic damage, fever was common, anaphylactic shock was occasional; Nervous system, the dizziness was common; Skin and its appendages damage, dermatitis, itching was common; Cardiovascular system, the main symptom was arrhythmias, chest tightness; To the blood system, it was increase of white blood cells. The adverse reactions described in the SMI product instruction [10-13]:

1. Allergic reactions, infusion reactions were the major, the severe allergic reaction was anaphylactic shock, dyspnoea.

2. Intravenous infusion for15 days (a course of treatment), occasionally the alanine transaminase elevation in some patients. A small number of patients felt dry mouth, thirst, sausarism.

3. It should avoid to be used on patients with a history of drug allergy or atopy.

4. The adverse reactions this product can cause is:

   a. Skin itching, rash, redness of the skin, cyanosis, dermatitis, urticaria, facial flushing, drug fever, anaphylactic shock, phlebitis.

   b. Dyspnoea, shortness of breath, chest tightness, apnea, airway obstruction, shortness of breath, upper respiratory tract infection symptoms.

   c. Tachycardia, angina, heart failure, heart palpitations.

   d. Nausea, vomiting, upper gastrointestinal bleeding, hiccups.

   e. Consciousness, irritability, nervousness, coma, dizziness, headache, chest pain, back pain, abdominal pain, spinal anesthesia, general malaise, tingling.

   f. Liver dysfunction (jaundice), renal dys-function.

According to the formulation of the risk minimization execution programme and the perfect technical guidelines issued by FDA of U.S. in 2005

[14], Pharmaceutical Industry Guide "Pharmaco-vigilance quality management norms and Drug epidemiological assessment" [15] developed jointly by U.S. Department of Health and Human Services, the U.S. Food and Drug Administration (FDA) and the golden rule of International Society for Pharmacoepidemiology (ISPE) Specification Pharmacoepidemiology (GPP) [16], combined with Annex 2 "The TCMI safety re-evaluation of basic technical requirements" of "Notification of working well on re-evaluating the security of TCMI" issued by the State Food and Drug Administration [17], selected three tertiary care teaching hospitals and twp Secondary level hospitals, exerted the methods of non-intervention, observational cohort monitoring, carried out prospective centralized monitoring to SMI.

The research purposes are: 1. The type and incidence of adverse reactions of SMI; 2. Made adverse clinical manifestations of SMI clear, in particular the serious ADR/ ADE, and its disposal and outcome; 3. Observed the main influencing factors of adverse reaction of SMI; 4. Summarized the characteristics of susceptible population that the adverse reactions appeared on who used SMI; 5. Discover the clinical application of off -label use.

METHODS:

Setting: The research is a prospective, observational combined nested case-control study. The "observation table" was filled in by the clinical pharmacists or research nurses of the medical institutions which used SMI. The case group is as following: There were adverse drug events after using SMI, and the adverse events were suspected to be relevant to SMI (the relevance evaluation was positive, most possible, may be relevant). The control group is as following:

(1) There were no ADEs/ADRs during using SMI.

(2) The patients who were in the same period with the case group (±15 days) used the same batch SMI, the patients who were in the same age bracket (±5 years), the same sex, the same principal diagnosis in the same hospital or in the same department.

Case-control study: The case group and the control groups were matched 1:4 in accordance with the nested case- study method. The study was carried out in larger than the secondary level hospitals.

Patients: The inclusion criteria:

(1) The hospitalized patients who were used SMI during the study period;

(2) Taking medicines in different time for the same patient, the interval of the twice administration was less than 15 days (the twice administration was the inpatients in the same hospital) would look as observed object once. If it was more than 15 days, it should take as a new object to complete the observation table.

Exclusion criteria:

(1) The patients whose disease was critically;

(2) The survival expected of hospitalized cancer patients was less 1 month.

The study steps: Figure 1 shows the steps of research and the technical route of the study.

Evaluation of ADRs: According to *the approach "Adverse Drug Reaction Reporting and monitoring management*" (May 24, 2011) [18], we evaluated the relationship between ADE/ADR and Drug. Among them, the "*definitely"*, "*probable*" and "*possible*" was calculated to the ADR and counted the incidence of adverse reactions. The incidence of ADEs =number of ADEs/all number of patients received SMI during the observation period×1000‰. The incidence of ADRs = number of ADRs/all number of patients received SMI during the observation period×1000‰.

Statistical: The measurement data were described using the arithmetic mean and the standard differential if they met the normal distribution, the t-test and paired t-test was adopted in the univariate hypothesis testing. The constituent ratio was applied to describe, the chi-square test, Fisher exact test was used in univariate hypothesis testing; chi-square test was used in the orderly ranked data hypothesis testing.

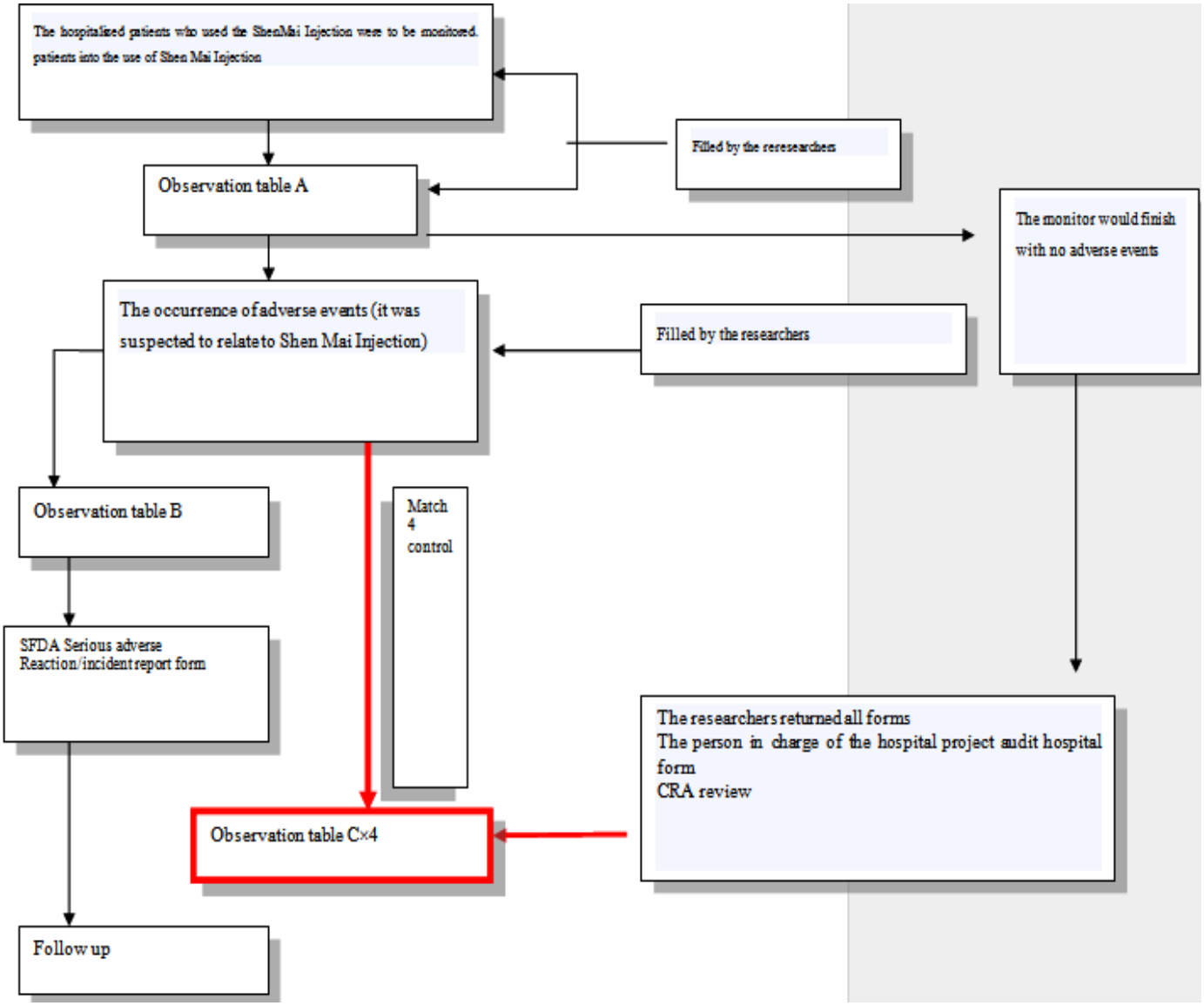

FIGURE 1: THE STEPS OF REAL WORD STUDY IN SMI

Logistic regression was applied in multivariate analysis to analyze the influence factors and degree of ADE/ADR. All statistical tests were two-sided test, it was discriminated as statistical significance when *P* was less than or equal to 0.05. The database was established in Excel. Stata 11.0 software was adopted to analyze.

Ethics: This survey was adhered to secrecy of the information collected, regulations relating to Human Research, and requirements regarding the confidentiality.

RESULTS:

Sample Characteristics: During the study period, 5 hospitals (**Table 1**) were enrolled in the research. Each case number shall not exceed more than 3000 cases, and shall not be less than 300 cases.

A total of 7632 observation tables were collected, 109 tables were unqualified (main reason is the lack of some of the key data), and the pass rate of observation table was 98.60%. 8 cases of ADR/ADE were reported during the study period.

Among 7632 patients, the mean age was 51.39±38.67 years, the minimum age of was 1 years, the maximum age of was 99 years, mainly in the age of 30~70 years old (**Table 2**). The ratio of male and female was 45.56:54.44 (3477/4155). 5 children less than 3 years of age (0.05% in total) were used SMI.

Prevalence of Adverse Reactions for SMI: The prevalence of ADEs to SMI observed in study is presented in **Table 3**. It was found that 1.05‰ (95% CI: 0.45-2.06‰) of the patients treated with

SMI had some of ADEs classically induced by the use of this drug from the data collected. Among 7632 patients, 3818 cases were used in accordance with the instructions of SMI, and 6 ADE cases were also in accordance with the instructions, so the incidence of ADR to SMI was 1.60‰ (95% CI: 0.58-3.44‰). Upon causality assessment of 6 ADRs, 3 ADR reports were rated as possible, followed 2 ADR reports by probable and 1 report by definitely. Mild and moderate reactions accounted for two and three, respectively, and only 1 ADR was deemed to be severe. The ADR of vision abnormal was considered to be a new and rare reaction.

TABLE 1: SHENMAI INJECTION MONITORING IN HOSPITAL DISTRIBUTION

Name of the hospital	Hospital level	Number of cases (n)	Percent (%)
The first Affiliated Hospital of Bengbu Medical College	tertiary care teaching hospital	3000	39.31
No.1 hospital of Bengbu city	tertiary care teaching hospital	989	12.96
No.2 hospital of Bengbu city	secondary level hospital	748	9.80
The Hospital of Traditional Chinese Medicine of Huaiyuan County	secondary level hospital	2895	37.94
Total	Two tertiary care teaching hospitals and two secondary level hospitals	7632	100.00

TABLE 2: THE AGE GROUP OF 9627 PATIENTS RECEIVED SMI

Age group	Number of cases(n)	Percent (%)
<1	0	0
1-2	5	0.07
3-17	107	1.40
18-29	1270	16.64
30-49	1978	25.92
50-69	1996	26.15
>70	2276	29.82
Total	7632	100.00

TABLE 3: PREVALENCE OF ADRs/ADEs TO SMI DURING THE STUDY PERIOD

Adverse symptoms/ reactions	Number of patients	Percentage (‰)	Poisson distribution (‰)
Fever, Palpitation, Hyperpyrexia	3	0.40	0.076-1.15
Dizziness, Dyspnoea	2	0.26	0.025-0.95
Rash, Pruritus	1	0.13	0.003-0.73
Anaphylactoid reaction	1	0.13	0.003-0.73
Vision abnormal	1	0.13	0.003-0.73
Total	8	1.05	0.45-2.06

Primary diagnosis: The primary diagnosis was provided in 57.28% (n=7632) of all samples. Table 3 gives an overview of the top ten diagnoses stated on the request forms. A total of 121 different diagnoses were found, most of them were off-label use. In most of cases (n=7632), more than one diagnosis was stated.

Primary disease was dominated by tumor, circulatory system disease and respiratory system disease. Primary disease of chemotherapy was in 2198 cases, 873 cases of coronary heart disease treatment and 641 cases with chronic pulmonary heart disease (Table 3). The primary diagnosis of 3615 cases (47.37%) was in accordance with indications of SMI for western diagnostic indications (coronary heart disease, viral myocarditis, chronic cor pulmonale, neutropenia, chemotherapy), with SMI instructions TCM diagnosis in 2149 cases, accounting for 28.16%.

Allergic history: Among 7632 patients used SMI, 1.89% patients (n=144) have allergy history, 113 cases have the history of drug and food allergies, 21 cases personal have history of allergic diseases, 10 cases with family history of drug allergy.

Dose: The mean total daily dose of the entire study population (n=7632) was 250mL (median: 40 mL/day; range: 10-100 mL). **Table 4** show that the

shortest duration was 1 day, the longest 109 days and the average duration (M) 4 days. The minimal cumulative length of medication was 1 days, the longest was 109 days, and average day was 5 days.

Combined medication: Most of the combination drugs were antimicrobial drugs, traditional Chinese medicine, electrolyte, acid-base balance and nutritional drugs, accounting for 78.64%. Most of cases (95.43%) were treated with more than two kinds of drugs. The top ten drugs were: ondansetron, magnesium isoglycyrrhizinate, omeprazole, levofloxacin, cefathiamidine, Danshen injection, pantoprazole, Xueshuantong, vitamin, ganglioside (**Table 5**).

Selection of solvent: Among 7632 cases, 3257 cases (42.68%) in the usage of solvent does not meet the requirements of the specification in accordance with the instructions (**Table 6**). 65 cases (0.86%) mixed insulin injection and 13 cases (0.17%) mixed vitamin K_1 injection and dexamethasone injection.

TABLE 4: THE LENGTH OF MEDICATION AND THE TOTAL DAILY DOSE FOR PATIENTS USED SMI

Variable	Median（M）	interquartile range (Q)	Minimum	Maximum
Course of disease（d）	4	4	1	5475d=15years
The cumulative number of days medication（d）	5	5	1	109
Single dose (ml)	40	0	10	100
Total dosage（ml）	250	250	10	22500

TABLE 5: THE TOP TEN COMBINATION DRUGS DURING SMI MEDICATION

Drug	ATC code	Sorting	Number of cases (n)	Percentage (%)
Ondansetron	A04AA01	1	1670	21.88
Magnesium isoglycyrrhizinate	A05BA08	2	1091	14.30
Omeprazole	A02BC01	3	904	11.84
Levofloxacin	J01MA12	4	877	11.49
Cefathiamidine	J01DB	5	729	9.55
Danshen injection	TCMI	6	515	6.75
Pantoprazole	A02BC02	7	394	5.16
Xueshuantong injection	TCMI	8	317	4.15
Vitamin	A11	9	276	3.62
Ganglioside	N07XA	10	276	3.62

TABLE 6: THE SOLVENT USE OF THE SMI FOR 7632 CASES

Solvent	Number of cases (n)	Percentage (%)
No solvent	1520	19.92
5% Glucose injection	**4375**	**57.32**
0.9% Sodium chloride injection	1360	17.82
Lactated Ringer's solution	107	1.4
5% Glucose and sodium chloride injection	67	0.88
10% Glucose injection	58	0.76
10% Glucose and sodium chloride injection	48	0.63
Invert sugar injection，Invert sugar and electrolytes injection	47	0.61
Fructose injection	37	0.49
Low molecular dextran injection	12	0.16

DISCUSSION: This study is a prospective, observational combined nested case-control research and its real world of usage and adverse drug reactions were reported and evaluated. One case of vision abnormal induced by SMI that is not shown in drug instructions, but also not reported and documented in the literature which belongs to the very rare adverse reactions. The treatment group of SMI included 5 cases of infants under 3 years old and 2276 cases (29.83%) of older patients (>70years). It shows that coverage range of SMI in usage is very wide. Although 6 indications of coronary artery disease, viral myocarditis, chronic cor pulmonale, neutropenia, adjuvant chemotherapy are registered usage of SMI, 121 different diagnoses were found in the research, 116 primary diagnoses were off-label use in the real word.

Females seem to represent the majority of today's SMI users. This gender difference was significant during the study periods, which may reflect that the initial use of SMI was restricted to adjuvant chemotherapy where the gender difference is indeed significant, whereas affective disorders are more common in females. It may also reflect that SMI soon after its launch was particularly recommended for fertile women, mainly due to its lack of induction of the metabolism of hormonal contraception, its lack of endocrine side effects and the notion that it was less teratogenic than other drugs [19].

The mean prescribed dose rose during the observation period. However, the median dose remained unchanged at 40 ml/day. Both the mean and the median doses found in this survey are considerably lower than the defined daily dose (DDD) as suggested by the WHO [20-21], which is 60 ml. This finding confirms the results of a previous study suggesting that, compared to clinical practice; the DDD appears to be too high and should be reviewed. While the mean prescribed doses were essentially identical among cancer and coronary heart disease patients, there was a trend towards higher dose in cancer patients, but there was a trend towards lower dose in other patients. This may be explained by the fact that roughly three-fourth of patients using SMI was non-cancer patients.

Drug combination analysis showed that SMI may be used many kinds of drug compatibility. In this study, SMI was used simultaneously up to twelve drugs in a bottle of infusion in combination. SMI is the TCMI prepared by Red Ginseng and Radix Ophiopogonis extract, the active ingredient is complex and contains saponins, so the SMI are generally required to use alone, not with other drug compatibility. SMI is lack of information of drug interaction that may be the active ingredient is complex. Four hospitals in the study, there is a hospital of traditional Chinese Medicine. 2895 cases received SMI in Hospital of traditional Chinese medicine, 2149 patients treated with SMI instructions TCM diagnosis accounting for 74.23%.

During the period of the study, 8 cases of adverse events were observed, which of these were 6 cases of ADR, 1 cases of ADR belongs to new, no serious adverse reaction cases. Similar to other researches [22-25], the type of ADR reported in the literature. In this study, the most common involved ADR/ADE induced by SMI was chills and fever was, flushing and all kinds of rash (this result is the same as the main components of ginseng). The starting time of ADR/ADE usually occurred in the medication after 30 minutes. Chills, fever and rash were mild damage and impairment, while difficulty breathing, chest tightness and severe allergic reaction were rare (due to the serious damage).

Fei Pan, *et al* [26] conducted the safety analysis of Shenmai injection via literature, the results shown that use of traditional Chinese medicine injections in hospital of traditional Chinese medicine is based on theory of traditional Chinese medicine and prescription is reasonable, so that the ADR/ADE of the drug is with a low incidence. That is the same as this research. The incidence of ADR in female was higher than male, which may be related to women's physiological characteristics and allergen sensitivity [27].

Significant differences was noted in the incidence of ADR in female and male (3/3477versus 5/4155, $P<0.01$) by χ^2 test in this study. In elderly patients with ADR cases more rate, this may be because the elderly susceptible to cardiovascular and cerebrovascular disease, and thus the use of the drug to increase, coupled with a variety of physiological function decline, on a variety of drug metabolism, excretion function decrease [28]. In this study, the age of all ADR cases was above 50 years that is the same as the literatures.

In order to reduce and control the incidence of serious ADR induced by SMI, we should detailed knowledge of the patient's three history, that are the food and drug allergy history, smoking and drinking history, history of disease and medication history. In addition, we also need to strengthen the drug monitoring especially for patients with allergic constitution. This would greatly reduce the associated costs, and the economic burden on the individual patient, the health-care sector, and medical institutions.

At the same time, we can avoid and control ADR cost induced by SMI by identifying which of the ADR-related costs are relatively greater. This would be the topic of a future research. When the former was greater than the latter, excessive costs

was invested only to prevent some possible occurrence of ADR induced by SMI, it will result in an increase of the total social costs, Therefore, how to optimize ADR induced by SMI social costs is the most important issue. In conclusion, SMI have excessive use and its clinical application need to further strengthen the supervision, but the safety of SMI is more reliable.

ACKNOWLEDGEMENTS: We thank the anonymous reviewers for their reviewing of this manuscript.

COMPETING INTERESTS: The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS: QPS and XDJ: Study design and conception, data/statistical analyses, drafting the manuscript; FD: Study design, data/statistical analyses, Critical revision of the article; RS, YL and HYY: data collection and statistical analyses. All authors contributed to writing of the final manuscript; all authors read and approved the final manuscript.

REFERENCES

1. WANG Pan, ZHU Wen-tao. Investigation on the Establishment of Relief System of Traditional Chinese Medicine (TCM) Injection Adverse Reactions. Chinese Journal of Pharmacovigilance 2012; 9 (2): 81-84.
2. BI Feng-lan, ZHANG Li. Discussion on the Safety of Traditional Chinese Medicine Injection. Chinese Journal of Pharmacovigilance 2012; 9 (2): 89-92.
3. Nairu Yun. Development and clinical study of Shenmai injection in pharmacology. Hebei Journal of Traditional Chinese Medicine 2012; 33(8): 1253-1255.
4. Yanping Duan, Chenglong Meng, Ping Li. Pharmacological action and clinical application of Shenmai Injection. Chinese Medical Abstracts 2002; 23(5):698-699.
5. Yonggang Feng, Chuanghai Zhang, Yucai Liu. Progress in pharmacological research of Shenmai Injection. Li Shi Zhen Medicine and Materia Medica Research. 2002; 13(7): 430-431.
6. Wang L, Yin T, Zhu MW. Retrospective study of adverse drug reactions of Shenmai injection. Central South Pharmacy. 2007, 5, 275-279.
7. Wen ZeHuai, Yu Hui, Wu Yaoheng, et al. A report on adverse reactions of injection of Chinese Herbal Medicines. Traditional Chinese medicine and clinical pharmacology 2003; 14(4): 278-281.
8. Wang L, Wang W, Zhao X, Jin L, Bai Y, Yao H, *et al.* Effect of Shenmai injection, a traditional Chinese medicine, on pulmonary dysfunction after tourniquet-induced limb ischemia-reperfusion. J Trauma. 2011, 71, 893-897.
9. Du Y, Jia L. Therapeutic effect of shenmai injection for ad. J Zhangjiakou Med Coll. 1998, 15, 16-17.
10. Guo SP, Zhang YZ. [Study on effect of Shenmai injection in protecting myocardium against ischemia-reperfusion injury in thrombolytic therapy with urokinase for acute myocardial infarction patients evaluated by 99mTc-MIBI myocardial imaging]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2001, 21, 108-110.
11. Li Bin; Wang Zishou; Gao Tian, et al. Analysis of adverse drug reaction and rational use of Shenmai injection. Guangzhou Medical Journal 2012; 43(1): 58-60.
12. LEI Zhao-bao. Literature Analysis of 23 Cases of Shenmai Injection-induced Anaphylactic Shock. China Pharmacy 2012; 23 (12): 1133-1135.
13. Yaohui Zhou, Liping Zhu. Literature analysis and prevention of adverse reactions of Shenmai injection. Clinical Journal of Chinese Medicine. 2012; 4 (10): 31-32.
14. The development of execute programs of minimization Risk and the perfect technology guiding principles. FDA. U.S. 2005. http://www.fda.gov/
15. Pharmaceutical Industry Guide" Pharmacovigilance quality management norms and Drug epidemiological assessment" developed jointly by U.S. Department of Health and Human Services, the U.S. Food and Drug Administration (FDA) and Center of Drug Evaluation Research (CDER) and Center of Biologics Evaluation Research. http://www.fda.gov/
16. Ren Jingtian, Wang bo, Li Liming. "Guide principles of Standardizing drug epidemiological studies "of International Society of Pharmacoepidemiology Chinese Journal of Pharmacovigilance 2011; 8 (4): 252-256.
17. SFDA. Annex 2 "Notification of working well on re-evaluating the security of traditional Chinese medicine injection" of "The traditional Chinese medicine injection safety re-evaluation of basic technical requirements" (State Food and Drug Administration's Office [2009] No. 359) http:// www.sfda.gov.cn/WS01/CL0844/39880.html
18. Ministry of health of the people's Republic of China. People's Republic of China Ministry of Health. Provisions for Adverse Drug Reaction Monitoring and reporting. 2010. http://www.sda.gov.cn/WS01/CL0053/62621.html.
19. Liu Z, Cheng X, Zhang C. [Observation on effect of shenmai injection in treating patients of congestive heart failure]. Zhongguo Zhong Xi Yi Jie He Za Zhi.1998, 18, 212-213.
20. WHO Collaborating Centre for Drug Statistics Methodology. Completed ATC Index 2005. http://www.whocc.no/atcddd/.
21. National Adverse Drug Reaction Monitoring Center. WHO Adverse Reaction Terminology. Peking: China Medicine and Technology Press, 2003.
22. Pan wen, Li Yu, Lei Yu, et al. Literature analysis on adverse reaction of Shenmai Injection. Guiding Journal of Traditional Chinese Medicine and Pharmacy 2012; 18(1): 70-71.
23. Qu Yanhong. Analysis of 26 cases of adverse reactions induced by Shenmai Injection. Chin J of Clinical Rational Drug Use 2012; 5(6): 12.
24. Wu Qi, Qu tao. Analysis of 36 cases of adverse reactions induced by Shenmai Injection. Clin J Med Offic 2012; 40(4): 802.
25. Wang Lianxin, Xie Yanming. Clinical evaluation of the safety of Shenmai injection based on Bibliometric Analysis. China Journal of Chinese Materia Medica 2012; 37(18): 2779-2781.
26. 26 Fei pan, Quanhong Tang, Fang He, et al. the safety analysis of Shenmai injection via literature. China Medica Herald 2011; 8 (6): 106-108.
27. Xin'an Wu. Establishment of Database and Study on Epidemiological Characteristics of ADR Caused by Shenmai Injection. China Pharmacy 2010; 21(20): 1878-1880.
28. Yu Zhang. Investigation and analysis of adverse drug reactions induced by Shenmai Injection. Seek Medical And Ask The Medicine 2012; 10(7): 531-532.

How to cite this article:
Shi Q, 2, Jiang X, ZhuJ, Liu Y, Sang R, Ding F, Wang M, Guo D, Shi P, Yu M, Wei S, Xin Z, Song R, Zhang S: The real-world study of Shenmai injection and its adverse reactions associated to patients in Chinese hospitals: A Prospective Research. *Int J Pharm Sci Res* 2013: 4(10); 3902-09. doi: 10.13040/IJPSR. 0975-8232.4(10).3902-09