Safety of traditional Chinese medicine injection based on spontaneous reporting system from 2014 to 2019 in Hubei Province, China

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Traditional Chinese medicine (TCM) injection is widely used in clinical settings, but its adverse drug reactions (ADRs) can be a serious public health concern. The objective is to study the safety of TCM injection and provide suggestions for clinical use. ADR reports collected by the Hubei Adverse Drug Reaction Monitoring Center from 2014 to 2019 were analysed. The safety of TCM injections was described by descriptive analysis and three signal mining methods, including the reporting odd ratio (ROR), proportional reporting ratio (PRR) and comprehensive standard method (MHRA). The findings indicate that the age groups of 0–10 and 41–80 years had the highest rates of reporting ADRs. A total of 96.41% of the ADRs occurred within one week, mostly on the same day that the injection was administered. Among the 60 TCM injections, Shenmai, Xiangdan, Salvia, Shengmai, Astragalus and Xuebijing injection had an above average ratio of severe ADRs (12.63%). A total of 99.24% of the cases improved after treatment. There were 9 deaths whose ADRs were mainly anaphylactic shock, dyspnoea and anaphylactoid reaction. In signal mining, the three methods produced 19 signals that were the same, and 14 of them were off-label ADRs. The frequency of TCM injections in children and elderly patients should be reduced and monitored strictly. Close observation is necessary during the first seven days after receiving the injection. The clinical use of Shenmai, Xiangdan, Salvia, Shengmai, Astragalus and Xuebijing injections should be investigated. Signal mining and more research are needed on TCM injections.

Modern Chinese medicines include almost all modern preparation forms, such as capsules, inhalants, dropping pills, injections and injectable powder1. Among them, injections and injectable powders raise challenges both for pharmacovigilance and drug regulation. Traditional Chinese medicine (TCM) injections, the extension and development of TCM, have a history of more than 70 years of use. Between 2004 and 2007, total sales of TCM injections exceeded $2 billion annually2. In 2017, China approved the sale of 134 kinds of TCM injections from 224 manufacturers3. Only 5 TCM injections are included in Pharmacopoeia of The People's Republic of China (2015), and 10 are included in the National Essential Drugs List (2018).

With the development and widespread use of TCM injections, adverse drug reactions (ADRs) have gradually become a public concern. In China, an ADR is defined as the harmful reaction of qualified drugs under normal usage and dosage, which has nothing to do with the purpose of drug use4. From 2001 to 2016, the National Medical Products Administration (NMPA) issued 15 notifications of ADRs related to TCM injections, involving 20 types5. In 2003, Yuxingcao injection led to 12 cases of anaphylactic shock and 40 cases of dyspnoea, and the use of Yuxingcao injection was finally suspended6. On April 20, 2009, National Adverse Drug Reaction Monitoring Center issued a warning that Qingkailing injection may have serious ADRs, as more than one-quarter of the

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patients who died from the injection were children under 14 years of age. The latest ADR notification related to TCM injection was reported in 2013, showing that there were a total of 3306 cases of safflower injection in the ADR monitoring database in 2012, including 154 severe cases. Recent studies found that ADR reports of TCM injections accounted for more than 50% of the ADR reports of TCMs. Compared with conventional injections, the proportion of severe ADRs in TCM injections was slightly lower (6.02% vs 6.72%), and the proportion of unknown (new) ADRs was much higher (46.74% vs 24.13%).

ADR of TCM injection is a serious public health problem, and there is no strong evidence for their safety, which is mostly based on long-term clinical practice. Special populations, including new-borns, infants, children, the elderly, pregnant women and lactating women, are restricted in the use of TCM injections, and some of them are forbidden. Therefore, it is necessary to evaluate the safety of TCM injections and encourage their re-evaluation. The purpose of this study was to analyse a database of provincial spontaneous reporting systems (SRSs) and study the safety of TCM injections from all aspects of ADRs.

Methods
Data source and preprocessing. The data of the adverse drug reaction reports collected by Adverse Drug Reaction Monitoring Center of Hubei Province from January 2014 to December 2019 were classified and analysed, and spontaneously reported by medical institutions, enterprises, and the public in Hubei.

The data were cleaned and preprocessed to ensure that they were clean and complete. The ADR database includes all reported adverse reaction reports. Reports of TCM injections with the registered category of Chinese medicine and the drug approval number containing “z” in the NMPA were selected for inclusion. Injections with herbal ingredients but registered under the category of chemicals were excluded. The analysis only included reports with certain, probable, and possible relationships of drugs and ADR evaluated by the reporting unit, and excluded reports that were unlikely or impossible to evaluate. Since there was no unified standard for the entry of drug names and ADRs in the report, the drug names registered in the NMPA were used as the standard to unify the generic names and the ADRs and clinical manifestations were organized according to the World Health Organization Adverse Reaction Terms (WHO-ART).

For the death cases, relevant information was detailed and carefully analysed to find other key points that had contributed.

From January 2014 to December 2019, the ADR Monitoring Center collected a total of 420,114 reports. There were 25,416 reports meeting the inclusion criteria. Since there might be two or more ADRs in a report or case, and the occurrence of an ADR in the use of a certain drug was considered an event, 33,446 events were included in the statistics.

Data analysis. A descriptive analysis of age, sex and occurrence, severity, types and results of ADRs in the reports was carried out.

The amount of each ADR of each TCM injection was sorted for ADR signal mining, which quantifies the qualitative nature of the relationship between drugs and ADRs. In ADR signal mining, the reporting odds ratio (ROR), proportional reporting ratio (PRR) and comprehensive standard method (MHRA) as measures of disproportionality were adopted, which is generally used in this area to detect the imbalance of target events compared with other events in the database. When the frequency of the target drug event combination (DEC) is significantly higher and reaches the threshold compared to the background frequency, a signal is considered to be generated. The strength of the association between drugs and ADRs was expressed as the ROR and PRR with 95% confidence intervals (CIs). The fourfold table used in the measures of disproportionality is shown in Table 1. The calculation formulas and the threshold for generating a signal with these three methods are presented in Table 2. In this study, signal mining of a single drug and a single ADR was conducted without considering the combination of drug use and drug interaction.

Result
Sex and age distributions of ADRs. Among the 25,416 reports related to TCM injections, except for 46 cases in which the sex was unknown, the number of women (13,632) who had ADRs was slightly greater than that of men (11,738), and the male–female ratio was 1:1.16 with a small discrepancy. The sex differences in specific age groups were more significant. Excluding 50 reports of unknown information, the age groups with higher reporting rates were concentrated in 0–10-year-olds (2978) and 41–80-year-olds (17,861) (see Fig. 1). That is, children and middle-aged and elderly patients were the most common.

The occurrence of ADRs. The occurrence of ADRs during medication was counted, and reports with obvious errors of entry and whose ADRs occurred after drug withdrawal were excluded. A total of 24,707 reports

| Category of drugs | Target ADR N | Other ADRs N | Sum |
|-------------------|-------------|-------------|-----|
| Target drug       | a           | b           | a+b |
| Other drugs       | c           | d           | c+d |
| Sum               | a+c         | b+d         | a+b+c+d |

Table 1. The fourfold table used in measures of disproportionality.

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were included. Figure 2 shows the occurrence time of ADRs after starting the medication. The majority of ADRs occurred on the day of injection (18,898, 76.49%).

**Severity of the reported ADRs.** The Administrative Measures on Reporting and Monitoring of ADRs states that according to the severity of ADRs, ADRs were divided into serious and non-serious ADRs. Serious ADRs result in death, life-threatening effects, cancer, a congenital anomaly, birth defects, significant or permanent human disability, damage to organ function, hospitalization or prolonged hospitalization or events that require intervention and treatment to avoid the above results. New and known ADRs are also subdivided according to whether the ADRs are recorded in the drug insert. In addition, ADRs whose types are known but whose severity is greater than that described in the drug insert are also regarded as new ADRs. Serious and new ADRs have always been the focus of ADR research, as they pose a greater threat to the life and health of patients.

Among the 25,416 reports related to TCM injections, there were 3211 reports of serious ADRs, accounting for 12.63% of the total reports, of which 1223 were new and serious reports. There were 22,205 non-serious reports containing 8244 new and non-serious reports, accounting for 87.37% of the total. The severity of ADRs in males and females is presented in Fig. 3. The severity of ADRs was not significantly different by sex. Figure 4 describes serious and non-serious reports in different age groups and the proportion of serious reports in each age group.
In the study, few patients were over 100 years old (8 cases), all of whom had non-serious ADRs. Regardless of patients older than 100 years, it is worth noting that the proportion of serious reports steadily increased with age. Table 3 shows the number and proportion of serious and non-serious reports by TCM injections (top 15 ordered by the number of serious reports). A total of 60 TCM injections were involved in the study. Among them, Shenmai injection, Xiangdan injection and Qingkailing injection had the most severe reports. It is worth mentioning that the proportions of severe reports of Shenmai injection, Xiangdan injection, Danshen injection, Shengmai injection, Huangqi injection, and Xuebijing injection were higher than the overall proportions (12.63%).

**Table 3.** Number and proportion of serious and non-serious reports by TCM injections (top 15).

| TCM injections                              | Serious N (%) | Non-serious N (%) | Total  |
|---------------------------------------------|---------------|-------------------|--------|
| Shenmai injection                           | 541 (15.45)   | 2961 (84.55)      | 3502   |
| Xiangdan injection                          | 465 (16.11)   | 2422 (83.89)      | 2887   |
| Qingkailing injection                       | 368 (12.62)   | 2547 (87.38)      | 2915   |
| Panax notoginseng saponins injection        | 247 (10.86)   | 2028 (89.14)      | 2275   |
| Salvia injection                            | 212 (15.28)   | 1175 (84.72)      | 1387   |
| Tanreqing injection                         | 176 (10.33)   | 1528 (89.67)      | 1704   |
| Safflower injection                         | 142 (11.14)   | 1133 (88.86)      | 1275   |
| Xueshuantong injection                      | 129 (9.56)    | 1220 (90.44)      | 1349   |
| Xiyangping injection                        | 109 (8.27)    | 1209 (91.73)      | 1318   |
| Shengmai injection                          | 108 (15.02)   | 611 (84.98)       | 719    |
| Astragalus injection                        | 93 (18.53)    | 409 (81.47)       | 502    |
| Reduning injection                          | 86 (11.03)    | 694 (88.97)       | 780    |
| Dan hong injection                          | 62 (11.36)    | 484 (88.64)       | 546    |
| Shuanghuanglian injection                   | 54 (9.54)     | 512 (90.46)       | 566    |
| Xuebijing injection                         | 44 (18.49)    | 194 (81.51)       | 238    |

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**Frequently reported ADRs.** A total of 33,446 events involved a total of 28 system-organ damage reports, mainly including skin and appendage damage, body as a whole-general disorders and autonomic nervous system disorders. The detailed number and proportion of events are shown in Table 4.
According to the statistics, a total of 209 ADRs were identified, which were concentrated in skin reactions such as rash and pruritus, anaphylactoid reaction of systemic damage and palpitation related to heart rate and arrhythmia. Table 5 shows the distribution of the number of ADRs in the top 95%. Anaphylactoid reaction and anaphylactic shock were the most concerning ADRs, with proportions of 14.39% and 0.72% respectively.

**Outcome of ADRs.** The vast majority of patients (99.24%) improved or recovered after treatment and intervention after the occurrence of ADRs (see Table 6). Among the 9 deaths, 6 were males and 3 were females. The age distribution was relatively scattered, while there were slightly more elderly patients (> 70 years old, 4). The patients mainly suffered from respiratory,
cardiovascular and cerebrovascular diseases as well as spinal diseases. The main ADRs were anaphylactic shock (5), dyspnoea (3) and anaphylactoid reaction (2) (see Table 7).

**Signal mining results.** According to the calculation formulas and thresholds, DEC signals that do not meet the criteria were excluded. The ROR generated 19 signals, the PRR generated 19 signals, and the MHRA generated 123 signals. The three signal mining methods produced a total of 19 signals of the same DECs as shown in Table 8. The larger the ROR and PRR values, the stronger is the correlation between the drug and ADR.

**Discussion**

Statistics showed that the reports of TCM injections reported by the spontaneous reporting system in the past 6 years were mostly from children and middle-aged and elderly patients. Wang also found that patients who suffered from ADRs caused by TCM injections were mainly over 50 years old. It was speculated that the occurrence of ADRs might be highly correlated with the patients’ own constitution, metabolism and the maturity and decline of organs\(^1\). Due to the limitations of data collection, it was impossible to know the usage frequency of TCM injections by age group.

In terms of the occurrence time of ADRs, most ADRs were found on the day of injection, and 96.41\% of the ADRs occurred within one week. For patients injected with TCM injections, family members should be reminded to observe the signs of ADRs following injection.

**Table 7.** Detailed information of the 9 deaths. \(^*\)Time means the occurrence time of the ADRs.

| Case | Sex | Age | Suspected drug | Time* | Diseases | Dosage | ADR |
|------|-----|-----|----------------|-------|----------|--------|-----|
| 1    | Male | 37  | Dan hong injection | 1     | Open hand injury | 40 ml  | Palpitation, dyspnoea, opisthotonus, anaphylactic shock |
| 2    | Female | 14  | Xiyaping injection | 2     | Upper respiratory tract infection (URTI) | 80 mg  | Dyspnoea |
| 3    | Male  | 77  | Saflower injection | 0     | Spinal disease | 20 mg  | Anaphylactic shock |
| 4    | Male  | 74  | Shenmai injection | 7     | Chronic obstructive pulmonary disease (COPD), pulmonary heart disease (PHD), heart failure, ambulatory NYHA class IV | 50 ml  | Dyspnoea |
| 5    | Male  | 82  | Shenmai injection | 0     | Coronary heart disease (CHD), cerebral infarction | 40 ml  | Anaphylactic shock |
| 6    | Female| 73  | Salvia injection | 0     | Essential hypertension | 20 ml  | Anaphylactic shock |
| 7    | Male  | 62  | Acanthopanax senticosus injection | 0     | Heart failure, cerebral infarction, pulmonary heart disease (PHD) | 400 mg | Anaphylactoid reaction |
| 8    | Female| 51  | Xiangdan injection | 0     | Spinal disease | 20 ml  | Anaphylactic shock |
| 9    | Male  | 50  | Panax notoginseng saponins injection | 0     | Rheumatoid arthritis, bronchitis | 400 mg | Anaphylactoid reaction |

**Table 8.** The signals of ADRs (3 methods). \(^*\)Off-label ADR.

| TCM injection | ADR          | ROR  | 95% CI lower limit | PRR  | 95% CI lower limit | \(\chi^2\) |
|---------------|--------------|------|-------------------|------|-------------------|-----------|
| Shuxuening injection | Phlebitisa  | 27.28 | 2.95              | 24.79 | 2.88              | 743.14    |
| Shenmai injection | Back pain\(^a\) | 7.18  | 1.71              | 7.02  | 1.69              | 293.35    |
| Ginkgolide injection | Phlebitisa  | 67.59 | 3.34              | 50.94 | 3.27              | 283.96    |
| Kang-lai-te injection | Phlebitis  | 26.72 | 2.53              | 23.74 | 2.5               | 145.85    |
| Qingkailing injection | Upper respiratory tract infection | 61.06 | 2.64              | 60.81 | 2.63              | 96.11     |
| Cimobutacin injection | Pain        | 28.91 | 2.38              | 23.54 | 2.36              | 85.7      |
| Astragalus injection | Asthma      | 18.67 | 2.06              | 18.47 | 2.06              | 73.06     |
| Salvianolate injection | Headache    | 6.66  | 1.37              | 6.08  | 1.33              | 62.27     |
| Erigeron injection | Asthenia    | 5.09  | 1.03              | 5     | 1.03              | 32.02     |
| Acanthopanax senticosus injection | Injection site pain | 12.84 | 1.53              | 12.53 | 1.53              | 29.98     |
| Aidi injection | Phlebitis\(^a\) | 5.78  | 1.04              | 5.65  | 1.03              | 25.02     |
| Reduning injection | Injection site reaction\(^a\) | 7.25  | 1.09              | 7.21  | 1.09              | 21.3      |
| Shuxuening injection | Dry mouth\(^a\) | 7.78  | 1.12              | 7.71  | 1.12              | 20.55     |
| Java brucea fruit oil emulsion injection | Increased sweating | 6.86  | 1.02              | 6.55  | 1.02              | 18.1      |
| Xiyaping injection | Skin disorder | 10.32 | 1.1               | 10.29 | 1.1               | 15.58     |
| Xingnaojing injection | Allergic reaction | 7.56  | 1                 | 7.48  | 1                 | 15.31     |
| Salvia injection | Phlebitis superficial\(^a\) | 9.06  | 1                 | 9.05  | 1                 | 13.85     |
| Shenmai injection | Renal pain\(^a\) | 25.09 | 1.03              | 25.06 | 1.03              | 13.33     |
| Mailuoning injection | Vision abnormal\(^a\) | 8.9   | 1.01              | 8.81  | 1.01              | 12.78     |
to observe them closely on the day of injection and continue to observe them for a week so that most of the ADRs can be detected as early as possible and treated in time.

Combined with the severity of ADRs, the results showed that the severity distribution was not significantly different by sex. Some recent studies of children’s ADR reports from Chinese hospitals showed that the number of ADR reports of traditional Chinese medicine preparations (mostly TCM injections) is second only to antimicrobials. In addition, Li also indicated that TCM injections posed greater risks to children than adults, and in the paediatric population, TCM injections were significantly associated with anaphylactic shock13. It is important to note that although there are many reports of ADRs in children, the proportion of serious reports was the lowest. The possible reason was that doctors were more cautious in prescribing TCM injections when treating children. The rate of serious reports increased steadily with age, which may be associated with disease severity. The study suggested that the usage frequency of TCM injections in children and elderly patients should be reduced until the safety evaluation of TCM injections is improved.

The ADRs mainly involved skin and appendage damage, the body as a whole-general disorders and autonomic nervous system disorders, including rash, pruritus, anaphylactoid reaction and palpitation. Anaphylactic shock and anaphylactoid reaction were the most common serious ADRs of TCM injections, and posed a greater threat to patient safety or even death8,14.

Although the ADRs of most patients were improved or cured after treatment and intervention, there were still several cases of death and sequelae. Gender and age were not significantly different in death reports, and anaphylactoid reaction and anaphylactic shock accounted for the majority, consistent with previously reported results.

Under the background of TCM injections, some common ADRs of TCM injections such as nausea and vomiting do not generate signals in data mining, while certain ADRs of certain TCM injections may generate signals, which means that the ADR and TCM injection were probably related. Combined with drug instructions, off-label ADRs were found including Shuxuening injection-phlebitis, Shexun injection-back pain, Shenmai injection-renal pain, Ginkgolide injection-phlebitis, Aidi injection-phlebitis, Reduning injection-injection site reaction, Salvia injection-phlebitis superficial and Mailuoning injection-abnormal vision.

Yang once analysed the 8-year ADR case reports of Shuxuening injection in the China SRS, indicating that phlebitis was a common symptom, and the warning signal of phlebitis was also obtained by Bayesian confidence propagation neural network, which was consistent with the ADR signal obtained in this study5,16. No studies have been found suggesting that dry mouth occurred with the use of Shuxuening injection. However, in view of the description of the reported data and the positive signal, more research could be done.

Wang conducted passive versus multicentre active surveillance, ADR case analysis, literature review and comprehensive safety research on Shenmai injection. Back pain was a common ADR and a warning signal of shenmai injection, which also supported the results of this study15,16. In addition, their research also suggested that there was no damage to renal function from Shenmai injection use at a dosage and a treatment course outside the recommended dosage and treatment course4. However, due to several cases with renal pain in the study who recovered after stopping the drug and the positive signal, the study implies that Shenmai injection may have an impact on renal pain, and more studies are needed.

There have been few studies on the ADRs of Ginkgolide injections. Liu analysed 120 related cases in a hospital for one year and found no ADRs18. Zhao found that 55 cases of Ginkgolide injection combined with atorvastatin calcium tablets had 1 case of dizziness and 1 case of nausea20. Perhaps due to the low incidence of ADRs and insufficient observed cases, the occurrence of ADRs cannot be observed. This study found a total of 8 cases of Ginkgolide injection-phlebitis and a positive signal, but the injections they used all came from the same manufacturer. The possibility of product quality as a cause of ADRs cannot be ruled out.

Phlebitis seemed to be an uncommon ADR of Aidi injection, but a few cases have been found in related studies21. This finding may be caused by insufficient solvent leading to poor dissolution and increased insoluble particles or the highly toxic cantharidin contained in the injection, which may cause phlebitis if the concentration is too high at the injection site22,23.

There were many reports of injection site reactions when Reduning injection was used, which supported the results of this study. Reduning injection contains three ingredients namely Artemisia annua, honeysuckle and gardenia. Artemisinin and its derivatives may cause injection site reactions, such as pain and swelling24,25. However, the specific mechanism is unclear.

No report of superficial phlebitis caused by Salvia injection was found, but there were some reports of phlebitis, which seemed to be related to rapid infusion26. The signal mining results had small ROR and PRR values, and the lower limit of the 95% CI was very close to 1, indicating a weak signal. Therefore, the association of superficial phlebitis or phlebitis with the drug could be suspected.

A number of studies and literature reviews on the ADRs of Mailuoning injection found several patients with conjunctival congestion or haemorrhage, which may indicate that eye damage was possible but rare26–31. A positive signal suggested that Mailuoning injection may be associated with vision abnormalities. In-depth research could be performed to uncover rare ADRs and their mechanisms of damage to the eyes.

In the instructions for TCM injections, ADRs are generally listed by items without detailed experimental or clinical data support, even though some of the instructions only record that ADRs are unknown. In the process of examining the instructions, it was found that the ADR items were approximately the same as the statistics for the number of ADRs of each TCM injection. Nevertheless, it was not completely clear whether the ADR was caused by the drug and whether there was a reasonable explanation of the mechanism. The data mining method can be used to obtain ADR signals of TCM injections with complex ingredients, which can be regarded as data support for ADRs in the instructions and is beneficial to the marketization and internationalization of TCM injections.

The statistical results and ADR signals obtained in this study are helpful in guiding the safe use of TCM injections in the clinic, and might be clues for ADR mechanism research, even providing advice for modifying drug labels based on the detection of off-label ADRs. In addition, this study has potential limitations. The effect
estimated in the study is based on the data of a single province. Although the data are considerable, the external validity of the conclusion still needs to be improved. Due to the limitation of the selected signal mining method, the combination of drugs is not considered, and the conclusions may be biased.

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R.H., B.G. and S.T. obtained and collected the data; R.H. conceived and conducted the study; L. Y. and X.S cleaned and pre-processed the data; R.H. and Y.C. analysed the results; R.H., Y.C. and L.Y. wrote the manuscript. All authors reviewed the manuscript.

Competing interests
The authors declare no competing interests.

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