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Reevaluation of the post-marketing safety of Xuebijing injection based on real-world and evidence-based evaluations

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ABSTRACT

Aims: To determine the causes of adverse reactions associated with Xuebijing injection and provide medical evidence for its safe and rational post-marketing use in clinical practice.

Materials and methods: We used prospective nested case-control and prescription sequence analysis designs. Using data from the Hospital Information System, patients exhibiting trigger signals after receiving Xuebijing injection were classified as suspected allergic patients. Logistic regression analysis was performed on the risk factors associated with Xuebijing-induced allergic reactions. Randomized controlled and cohort studies on adverse drug reactions to Xuebijing injection were screened from databases and the results were subjected to meta-analysis.

Results: The overall incidence of allergic reactions or anaphylaxis tended to increase with dosage and patient's age. Moreover, compared with Xuebijing alone, co-administration of Xuebijing with other drugs or agents (including Ringer's sodium acetate solution, reduced glutathione, aspirin-*DL*-lysine, and torasemide) increased the risk of adverse reactions. The use of glucose as a vehicle also provoked a greater incidence of allergic reactions than that by the use of 0.9% w/v sodium chloride as a vehicle. Adverse reactions occurred more frequently in patients receiving indicated dosages than in those receiving off-label dosages.

Conclusions: Adverse reactions to Xuebijing injections were correlated with vehicle type, dosage, age, and drug combination. There was no clear association between patient's condition at admission and suspected adverse reactions to Xuebijing injection. Factors influencing the adverse reactions to Xuebijing injection must be fully considered in clinical practice.

1. Introduction

Xuebijing is a Chinese herbal medicine extract composed of safflower, *Salvia miltiorrhiza*, angelica, and other ingredients. Its main component is safflower yellow A. Xuebijing antagonizes endotoxins, inhibits various inflammatory mediators, and improves microcirculation and coagulation dysfunction [1]. Xuebijing is derived from traditional Chinese medicine extracts with highly complex compositions. Certain macromolecular substances, such as proteins, peptides, and polysaccharide complexes, may be present in these formulations and act as antigens. They may directly activate the immune system and trigger allergic reactions in certain patients. In 2004, Xuebijing was approved as a treatment for sepsis, severe pneumonia, and multiple organ dysfunction syndrome. At the clinical level, Xuebijing has been shown to be highly effective in treating sepsis and other diseases [2]. Clinical adverse reactions to Xuebijing injection have not been clearly described. However, an unpredictable allergic reaction associated with Xuebijing injection might have serious consequences and pose a great threat to the life of patients, such as breathing difficulty, dropped blood pressure, anaphylactic shock, and even death. In recent years, reports on adverse reactions to Xuebijing have increased as its clinical application has become more widespread. However, the incidence and influencing factors of these side effects differ among studies [3–6].

A real-world study is a patient-centered approach using broad inclusion criteria and epidemiological research methods in the practical application of diagnosis, treatment, prognosis, and other interventions with minimal bias in a real population. It focuses on individualized diagnosis, and treatments that generate results approximating those found in clinical practice [7].

A real-world study is an observational approach that reflects a

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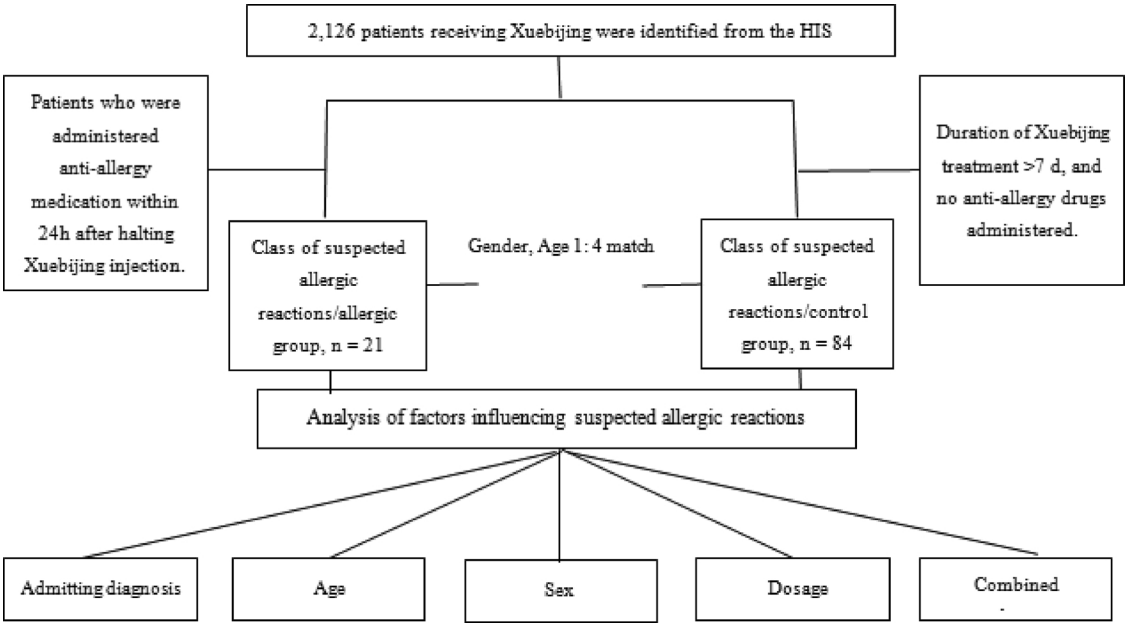

Fig. 1. Flow of case-selection process.

global population using a large "real-world sample" to evaluate intervention safety and external validity [8]. This method captures trigger signals [9–11]. A nested case-control study (NCCS) was combined with a prescription sequence analysis (PSA) in a real-world assessment of Xuebijing. Patients with suspected adverse reactions were screened from cases who received Xuebijing injection. A control group was set up and logistic regression analysis was performed on the factors suspected to cause adverse reactions to Xuebijing. Evidence-based evaluation was combined with reports on adverse reactions to Xuebijing injection collected from several databases, and relevant influencing factors were identified. The incidence of both serious and rare adverse reactions was quantified and recorded to guide the clinical application of Xuebijing, as well as to prevent and control adverse drugs reactions (ADRs). This approach also provides new research and technical methods for re-evaluating the safety of Xuebijing injection (Fig. 1).

2. Methods

2.1. Data source

Real-world case data were obtained from the medical records of 2126 patients who received Xuebijing injections at the First Affiliated Hospital of Bengbu Medical College between September 1, 2016 and August 31, 2017. The allergic and control groups were selected from this population. The data were unified and standardized before analysis. Ethical approval was given by the Clinical Medicine Research Ethics Committee of the First Affiliated Hospital of Bengbu Medical College, and written informed consent was obtained from the patients. Information from the medical records of patients was maintained as confidential. The data for the evidence-based evaluation were derived from PubMed, EMbase, the Cochrane Library, CNKI, VIP, Wan Fang Data, and other internet databases. Data from each database were retrieved from the construction time until April 30, 2018. The search was conducted by combining subjects and free words. The documents were screened according to the established exclusion criteria. In PubMed, the search strategy was as follows. (1): Xuebijing injection; (2): efficacy; (3): side effects OR safety OR adverse reaction; then (3) (1) AND (2) AND (3).

2.2. Research design

2.2.1. Real-world research design

Real-world studies used a prospective, NCCS-integrated PSA approach to determine whether a trigger signal occurs after Xuebijing injection [13]. According to previous studies [14–16], a signal indicating possible allergic reactions to Xuebijing occurred because patients used anti-allergic drugs, such as dexamethasone, or other drugs during the administration of Xuebijing. Patients were divided into allergic and control groups. Adverse reactions to Xuebijing were divided into late- and rapid-onset allergic reactions. Most of the rapid allergic reactions appeared within 30 min of administration [17,18]. In contrast, most of the late-onset ADRs occurred within 1 day (d) of dosing.

The Hospital Information System (HIS) holds a large amount of real-world clinical data. It records all information on medication during hospitalization. Although the HIS database does not document specifically whether a patient had an allergic reaction, such reactions can be inferred, if, for example, certain medications, such as dexamethasone, were administered subsequently after Xuebijing injection [19]. In addition, the Naranjo ADR Probability Scale was used to evaluate cases of adverse reactions to Xuebijing. The Naranjo ADR Probability Scale emphasizes on evidence-based medical evidence and logic of clinical medication, and it is an authoritative method to evaluate ADRs [20,21]. Objective evaluation using the Naranjo ADR Probability Scale revealed that the score of the selected patients was above 6, which suggested a possible or even definite relation to the evaluation level, indicating that the inevitable connection between the use of Xuebijing and ADRs was relatively strong. In the present study, we used both PSA and NCCS to extract and analyze large-scale real-world data. Patients who used anti-allergic drugs after Xuebijing injection were suspected to have allergic reactions. The control group was set up and data were processed.

Allergy group: This group comprised of patients who discontinued Xuebijing use within the first 24 h and had a record of only one Xuebijing injection. It also included those who used anti-allergic drugs within 24 h after stopping Xuebijing administration because of suspected allergic reaction. This group did not have any records of patients using anti-allergic drugs before and/or during Xuebijing treatment. The allergy group finally consisted of 21 cases.

Case-control: In the present study, the patients in the control group

used no anti-allergic drugs after initiating Xuebijing injections, and they used Xuebijing injection until the time to stop using it after 7 days. The inclusion criteria for the control group were based on the age (± 5-years old) and gender of patients in the allergy group. The allergy and control groups were randomly selected at a ratio of 1:4, in which one patient selected for a group was excluded as a candidate for the other group. In total, 84 cases were included in the control group.

2.2.2. Evidence-based research design

The inclusion criteria included the following. 1) A randomized controlled trial (RCT), case-control study, cohort study, or observational research. The language of communication and recordkeeping were Chinese and English only. 2) Patients who received Xuebijing injection, and included a wide range of age, both sexes, and various disease types. 3) The test drug was Xuebijing administered either intravenously or intramuscularly either alone or in combination with other drugs. 4) The incidence and rate of adverse reactions/events were reported.

The exclusion criteria included the following: 1) interventions involving drugs that could interfere with the determination of adverse reactions attributable to Xuebijing; 2) adverse reactions not previously described; 3) incomplete data; 4) brief reports; 5) reviews; 6) animal models; 7) basic medical research.

The quality of randomized controlled trials methodologies was analyzed with the Cochrane System Evaluator Manual v. 5.1.0 offset risk assessment tool [22], whereas for observational studies (cohort studies and case-control studies), we followed the quality score of MOOSE guidelines [23]. They included several criteria. Each criterion was counted as one point. A total score of ≥ 4 indicated high-quality literature. The rating criteria included the following: 1) the hypothesis or purpose of the study were clearly described; 2) the study object was explicitly included in the exclusion criteria; 3) the treatment program had a detailed description; 4) a definitive diagnosis or definition of the outcome of the measurement was made; 5) sample size was estimated in advance, or patients were recruited consecutively; 6) the description of the main findings was clear, or the end-point evaluation was objective; 7) the statistical analysis was appropriate, or the outcome required stratified analysis and reporting, such as according to the disease stage, abnormal test results, and the characteristics of patients. Two reviewers independently extracted the data according to the inclusion and exclusion criteria, and then cross-checked the results for accuracy. When there was an inconsistency, the research team convened to decide whether to include the articles in the study. The general information extracted included author name, article title, publication date, study type, object of observation, intervention measure, and quality score. Care was taken to avoid offsets and if they were encountered, sensitivity analyses were performed.

2.3. Statistical analyses

2.3.1. Real-world statistical analysis

Data were analyzed by logistic regression using Stata v. 11.0. Univariate and multivariate regression analyses were used to identify the independent risk factors for adverse reactions/events. By regression analyses, we also determined whether the suspected allergic reactions were dependent variables (Y), and the suspected influencing factors, such as age and drug combination, were their respective independent variables (X). The variables were as follows. Y: allergy group, Y = 0; control group, Y = 1. × 1: sex, male = 0, female = 1. × 2: medication indication level, indicated medication = 0, hyper-indicated medication = 1. × 3: age, ≥ 60 y = 0, ≤ 60 y = 1. × 4: administration mode, intravenous drip = 0, pump = 1; X5-X72: drug combinations being administered, drug combination = 0, no combination = 1. The significance level was set to $P < 0.05$.

2.3.2. Statistical analysis of evidence-based evaluation

The meta-analysis was performed using R v. 3.2.3 [24]. In the meta-analyses, the confidence interval for each effect was expressed as 95% CI. The data were also subjected to the homogeneity (Q) test at $\alpha = 0.1$. Quantitative I^2 was combined to determine the degree of heterogeneity, where the thresholds were $P \geq 0.1$ or $I^2 \leq 50\%$. When heterogeneity was low, a fixed-effects model was used for the analysis. Otherwise, a random-effects model was used.

3. Real world research results

3.1. Data extraction and analysis process

3.1.1. Basic patient information

In this study, records of 2126 patients receiving Xuebijing were collected from the HIS; these included 1251 males and 875 females. The youngest patient was aged 15 y and the oldest was aged 97 y. Twenty-one patients were suspected of having allergic reactions. In the nested case study, 84 controls were selected according to a 1:4 match ratio. The average age of patients in the allergy and control groups was 63.43 ± 20.07 and 62.18 ± 18.81 y, respectively. The sex-matching ratio was the same for both groups (1:4). There were no significant differences in sex between the two groups ($P = 0.159$). The aforementioned results indicated effective patient-matching in both groups, as well as comparable age and sex distributions between them. These distributions are shown in Table 1. The cumulative medication time of the patients ranged from 1 to 21 d. The dose range of a single patient was 10–100 mL. Total patient dose ranged from 10 to 3000 mL. Patients diagnosed with inflammatory disorders, such as pancreatitis and cholecystitis, received Xuebijing either by intravenous drip or pump. The vehicle of choice was 0.9% sodium chloride (NS) solution.

3.2. Analysis of factors affecting suspected allergic reactions

It has been reported that age, allergy history, single or multiple doses, indicated/off-label use, and single or combination drug therapy are the factors influencing adverse reactions to Xuebijing [18,25,26]. The current study explored the effect of these variables on the occurrence of suspected allergic reactions to Xuebijing. Unconditional univariate logistic analysis was performed on factors possibly associated with adverse reactions to Xuebijing, including sex, age, dosage, days of medication, hyper-indication, and combination of medications. The specific criteria were total medication dosage and combined use of Xuebijing with Ringer's sodium acetate solution, reduced glutathione, safflower, aspirin-*DL*-lysine, midazolam, Honghua, torasemide, and other drugs that could be correlated with adverse reactions to Xuebijing injection ($P < 0.05$). Multivariate logistic analysis was performed using

Table 1
Distribution of patients by age and sex [*n* (%)].

Group	*n*	Age				Sex	
		≤ 40 y	41–60 y	61–80 y	> 80 y	Male	Female
Allergy group	21	2 (9.52%)	7 (33.33%)	6 (28.57%)	6 (28.57%)	13 (61.90%)	8 (38.10%)
Control group	84	9 (10.71%)	26 (30.95%)	34 (40.48%)	15 (17.86%)	50 (59.52%)	34 (40.48%)

Table 2
Multiple logistic regression analysis of the factors associated with adverse drug reactions to Xuebijing injection.

Suspected factor	Multi-factor logistic analysis				
	Regression coefficient	Standard value	*P*	OR	OR 95% CI
Total patient dose	−0.002	0.001	0.018	0.10	0.097–0.101
Ringer's sodium acetate solution	3.165	1.012	0.002	23.69	3.258–172.296
Reduced glutathione	2.143	0.795	0.007	8.52	1.794–40.493
Aspirin-*DL*-lysine	2.148	0.733	0.003	8.57	2.034–36.076
Torasemide	3.276	1.408	0.020	26.48	1.675–418.467
Honghua	−1.009	1.126	0.370	0.36	0.040–3.314
Midazolam	1.246	1.281	0.331	3.48	0.282–42.858

statistically significant candidate variables. The results showed that total patient dose and combinations of Xuebijing with Ringer's sodium acetate solution, reduced glutathione, aspirin-*DL*-lysine, Honghua, or torasemide were statistically independent risk factors (Table 2).

4. Evidence-based evaluation results

4.1. Literature search results

A total of 7394 related reports were retrieved from databases. There were 7267 articles retrieved from Chinese databases, including 2254 articles from the VIP Database for Chinese Technical Periodicals, 2570 articles from the Wan Fang database, and 2443 articles from the China National Knowledge Infrastructure. There were 127 articles retrieved from English databases; one from the Cochrane Library and 126 from PubMed. All articles were screened according to the predetermined inclusion and exclusion criteria. Fifty-two studies, including 49 RCTs, were selected for use in the meta-analysis.

4.2. Basic overview of the included studies

The 52 articles included in this study and the details are listed in Table 3. A total of 4196 patients were enrolled. Among them, 2095 were treated with Xuebijing and 134 had adverse reactions. Most of the reported ADR cases involved middle-aged and elderly patients. The daily dose ranges of adults and children were 30–400 mL d^{-1} and 0.5–1 mL $kg^{-1}d^{-1}$, respectively. The reported adverse effects of Xuebijing injection consisted mainly of allergic reactions, which included 24 cases. Skin and accessory damages were the most commonly reported adverse reactions; they accounted for 41.04% of the cases (55/134). The remaining 36.5% of the cases (49/134) were gastrointestinal reactions.

4.3. Meta-analysis results

A meta-analysis was conducted on vehicle type, course of treatment, drug combination, dosage, and hyper-indication, and the analysis results are shown in Table 4. The results showed relatively high incidence of adverse reactions associated with the use of 5% glucose vehicle, course of treatment for > 14 d, drug combination, off-label use, and age of > 60 y (Table 4). There were statistically significant differences between the 5% glucose injection vehicle, course of treatment for > 14 d, drug combination, and age of > 60 y groups ($P < 0.05$).

4.3.1. Meta-analysis on allergic reactions to Xuebijing injection

The present study included a meta-analysis of the incidence of adverse reactions in response to vehicle type, course of treatment, drug combination, dosage, age, and indicated or off-label drug use. The results showed that the incidence of adverse reactions to Xuebijing was 5.62% [95% CI (0.0458–0.0675)] and the incidence of allergic reactions to Xuebijing was 3.16% [95% CI (0.0458–0.0675)]. The incidence of adverse reactions in the glucose or other vehicle groups was 5.96% [95% CI (0.0310–0.0716), which was higher than that of the 0.9% w/v sodium chloride vehicle group [4.52%; 95% CI (0.0432–0.0583)]. The incidence of adverse reactions in the > 7-d course of treatment group was 6.80% [95% CI (0.0508–0.0871)], which was higher than that of the ≤ 7-d course treatment group [4.76%; 95% CI (0.0348–0.0620)]. The incidence of adverse reactions in the drug combination group was 5.87% [95% CI (0.0421–0.0775)], which was higher than that of the single-agent group [5.47%; 95% CI (0.0417–0.0692)]. The incidence of adverse reactions in the < 60 y group was 5.28% [95% CI (0.0401–0.0668)], which was lower than that of the ≥60 y group [5.82%; 95% (0.0415–0.0770)]. The incidence of adverse reactions in the indicated drug use group was 5.59% [95% CI (0.0449–0.0678)], which was lower than that for the off-label drug use group [5.98%; 95% CI (0.0296–0.0979)]. Nevertheless, the differences between groups were not statistically significant ($P > 0.05$).

5. Discussion

5.1. Methodology

In recent years, numerous real-world studies have been conducted to evaluate the effectiveness and post-marketing safety of drugs [27,28]. These studies have been based on large sample datasets and HIS records. Clinical treatment data included all information on patient medication during hospitalization. It can be widely applied in the safety reevaluation of traditional Chinese medicines [29–32]. In the present study, suspected allergic reactions to various Xuebijing injections were analyzed using a combination of PSA and NCCS. PSA is based on complete, existing prescription record in databases. It aligns with good clinical practice and has a high level of external authenticity. When the use of certain drugs indicates ADRs of other drugs, the requirements of PSA are met [33]. The advantage of NCCS is that the data are collected first, thereby reducing human resources and conserving material resources. Moreover, the survey bias is small. Matching lowers the interference of confounding factors to some extent. This way, the allergy and control groups were balanced and comparable. This research method is economical and extrapolates well. By using the HIS data, this study explored the factors influencing adverse reactions to Xuebijing. The data collected in this study avoided the recall bias common to classic case-control studies. The controls were selected among patients receiving Xuebijing who were from the same cohort. The comparability was good and selection bias in the estimation of effects was reduced to a certain degree.

Most evidence-based medical studies in traditional Chinese medicine involve clinical randomized controlled trials. An RCT has several advantages: it prevents selective migration, has good comparability between groups, generates authentic results, and has high evidence level. A meta-analysis of widely used RCT data improves their credibility by enabling a more objective evaluation of the evidence and accurate assessment of effect indicators.

The novelty of this study was that it evaluated the incidence of adverse reactions to Xuebijing on the basis of both literature databases and real-world analyses. It elucidated the factors influencing suspected adverse reactions and the incidence of serious adverse reactions. This approach constructed a methodology for continued and ongoing research in post-marketing drug safety assessments. The data from literature database analysis reported herein helped clarify the real clinical situation of adverse reactions to Xuebijing injection. When combined with the HIS data, it can be used to predict the type and incidence of clinical adverse reactions with reasonable certainty. These two methods can complement and be critically compared with each other.

Evidence-based evaluation and real-world research are the

Table 3
Basic information of clinical studies included in the meta-analysis.

Study	Type of study	Solvent type	Type of disease treatment	Age (y)	Experimental group sample size			Control group sample size		
					Male	Female	Total	Male	Female	Total
Zheng2015	1	3	Organophosphorus pesticide poisoning	29.8 ± 4.6	24	25	49	25	24	49
Zhang2016	1	1	Acute pancreatitis	48.28	27	15	42	24	17	41
Liu2016	1	2	Diabetic nephropathy	64.7 ± 8.2	–	–	67	–	–	65
Hu2016	1	1	Chronic pulmonary obstructive disease	69.3 ± 6.3	37	13	50	37	13	50
Fang2014	1	1	Severe pneumonia	56.3 ± 4.5	–	–	76	–	–	77
Liu2016	1	3	Sepsis	73.6 ± 12.4	17	13	30	16	14	30
Zhu2016	1	1	Sepsis	59.7 ± 11.9	17	12	29	15	14	29
Ou2015	1	1	Ascariasis	51.8 ± 11.2	13	15	28	12	16	28
Yang2016	1	1	Severe pancreatitis	37.9 ± 7.3	13	26	39	15	24	39
Tian2015	1	1	Sepsis	48.6 ± 2.5	11	9	20	12	8	20
Yuan2016	1	1	Severe pneumonia	46.4 ± 8.6	–	–	48	–	–	48
Meng2016	1	–	Severe pneumonia	54.8 ± 10.3	22	13	35	20	15	35
Wu2013	1	–	Acute pancreatitis	–	–	–	16	–	–	13
Gu2008	1	1	Malignant tumor	62.3	15	15	30	16	14	30
Xue2012	1	1	Chronic obstructive pulmonary disease	47.5 ± 8.8	20	13	33	18	9	27
Chen2015	1	1	Severe pneumonia	65.3 ± 6.3	17	13	30	16	14	30
Lin2016	2	2	Sepsis	67.7 ± 11.6	–	–	25	–	–	25
Ying2008	1	3	Postoperative pneumonia	56	21	14	35	19	11	30
Fu2015	1	1	Pediatric appendicitis	62.5 ± 26.3month			32			31
Ding2013	1	1	Bronchitis	6.4 ± 3.2month	29	23	52	27	25	52
Huang2016	1	3	Severe pancreatitis	48.6 ± 5.4	26	19	45	27	18	45
Ding2015	1	1	Sepsis	40.0 ± 3.4	17	17	34	18	16	34
Guo2016	1	1	Pneumonia	70.1 ± 5.5	36	24	60	35	23	58
Li2013	1	3	Appendicitis	36.7 ± 10.2	36	24	60	35	25	60
Tan2014	1	1	Gout arthritis	41.9	37	5	42	35	7	42
Wang2015	1	1	Bacterial peritonitis	37.85 ± 4.52	23	21	44	22	22	44
Wang2013	1	1	Urinary tract infection	44 ± 10.8	19	21	40	18	20	38
Xie2011	1	3	Cancerous fever		20	10	30	22	18	40
Ren2016	1	1	Acute pancreatitis	8.67 ± 2.93	16	11	27	14	13	27
Zhao2013	1	1	Chronic obstructive pulmonary disease	69.2 ± 9.4	22	14	36	20	16	36
Wang2007	1	3	Chronic obstructive pulmonary disease	49–88	43	22	65	42	19	61
Zhang2016	1	3	Severe pneumonia	58. 5 ± 11. 7	26	15	41	24	17	41
Lin2014	1	1	Malignant tumor	58	–	–	42	–	–	41
Deng2010	1	1	Psoriasis	47.8	19	13	32	22	10	32
Lan2016	2	3	Severe pneumonia	35.9 ± 7.3	28	24	52	24	21	45
Gao2014	1	1	Severe pneumonia	50.2 ± 18.9	34	29	63	36	27	63
Wang2013	1	1	Severe pneumonia	47.4 ± 9.1	33	27	60	31	29	60
Feng2015	1	1	Brain infarction	60.28 ± 15.64	30	15	45	29	16	45
Zhang2015	1	1	Severe pneumonia	70.5 ± 6.7	14	10	24	15	9	24
Shao2013	1	3	Pancreatitis	45.5 ± 13.5	18	14	32	20	12	32
Jiang2017	1	1	Sepsis with kidney injury	56.8 ± 12.2	31	21	52	13	13	26
Chen2017	1	1	Brain Injury	48.12 ± 10.98	28	24	52	27	25	52
Li2009	1	1	Sepsis	75 ± 11	20	8	28	19	9	28
Dong2017	1	1	Brain Injury	41.8 ± 4.6	24	15	39	22	17	39
Xu2017	1	1	Chronic obstructive pneumonia	63. 24 ± 10. 33	22	19	41	21	20	41

(*continued on next page*)

Table 3 (*continued*)

Study	Type of study	Solvent type	Type of disease treatment	Age (y)	Experimental group sample size			Control group sample size		
					Male	Female	Total	Male	Female	Total
Zhou2015	1	1	Acute respiratory distress syndrome	55.93 ± 7.86	–	–	25	–	–	25
Yu2016	1	1	Stroke with pneumonia	46–83	28	16	44	25	19	44
Chai2016	2	1	Myocardial infarction	58.9 ± 10.5	40	25	65	35	27	62
Pan2016	1	1	Severe pneumonia	49.6 ± 11.2	24	15	39	23	16	39
Wu2017	1	1	Pancreatitis	8.53 ± 2.94			30			27
Shen2017	1	1	Pneumonia	45.7 ± 5.9	17	24	41	18	23	41
Qian2017	1	1	Acute appendicitis	36.52 ± 10.36	13	12	25	15	10	25

Study	Total sample size	Dosage	Treatment(d)	Medication	Combined medicine	Medicine used in control group	Document quality evaluation score
Zheng2015	98	100 mL.d^{-1}	5	2	–	Atropine	5
Zhang2016	83	200mL.d^{-1}	7	2	Octreotideinjection	Octreotideinjection	4
Liu2016	132	200 mL.d^{-1}	14	2	PGE1	–	5
Hu2016	100	30mL.d^{-1}	7	1	–	Tanreqinginjection	5
Fang2014	153	100mL.d^{-1}	14	2	Thymopentin	–	4
Liu2016	69	100mL.d^{-1}	7	1	–	–	4
Zhu2016	58	100mL.d^{-1}	7	1	–	–	4
Ou2015	56	50–100 mL.d^{-1}	7	1	–	–	4
Yang2016	78	100mL.d^{-1}	7	1	–	–	4
Tian2015	40	200mL.d^{-1}	7	2	Hydrocortisone	–	4
Yuan2016	96	200mL.d^{-1}	7	1	–	–	4
Meng2016	70	100mL.d^{-1}	10	2	Thymosin α1	–	5
Wu2013	29	100mL.d^{-1}	7	1	–	–	4
Gu2008	60	50mL.d^{-1}	7	1	–	Indomethacin	4
Xue2012	60	100 mL.d^{-1}	7	1	–	–	4
Chen2015	60	200mL.d^{-1}	7	1	–	–	4
Lin2016	50	100mL.d^{-1}	7	1	–	–	3
Ying2008	65	100mL.d^{-1}	10	1	–	–	4
Fu2015	63	1 mL/ kg.d^{-1}	3	1	–	–	4
Ding2013	104	1 mL/ kg.d^{-1}	7	1	–	–	4
Huang2016	90	200mL.d^{-1}	7	1	–	–	4
Ding2015	68	100 mL.d^{-1}	14	2	Shenfu injection	–	5
Guo2016	118	100mL.d^{-1}	3～14	2	Piperacillin and sulbactam sodium	–	4
Li2013	120	–mL.d-1	7	1	–	–	4
Tan2014	84	40mL.d^{-1}	7	2	Anti-inflammatory cream	Colchicine tablets	7
Wang2015	88	50mL.d^{-1}	7	2	Imipenem	–	5
Wang2013	78	100mL.d^{-1}	7	2	Levofloxacin	–	5
Xie2011	70	50mL.d^{-1}	10	1	–	Indomethacin and naproxen	4
Ren2016	54	0.5–1 mL/ kg.d^{-1}	10	1	–	–	4
Zhao2013	72	100mL.d^{-1}	10	1	–	–	4
Wang2007	126	100mL.d^{-1}	10	1	–	–	4
Zhang2016	82	30mL.d^{-1}	10	1	–	–	4
Lin2014	83	50mL.d^{-1}	7	2	Indomethacin tablets	–	4
Deng2010	64	30mL.d^{-1}	28	1	–	–	4
Lan2016	97	200mL.d^{-1}	14	2	Antibiotic	–	4
Gao2014	126	200 mL.d^{-1}	14	1	–	–	4
Wang2013	120	50mL.d^{-1}	12	2	Levofloxacin	–	5

(*continued on next page*)

Table 3 (*continued*)

Study	Total sample size	Dosage	Treatment(d)	Medication	Combined medicine	Medicine used in control group	Document quality evaluation score
Feng2015	90	100mL.d^{-1}	14	2	Edaravone injection	Edaravone injection	6
Zhang2015	48	200mL.d^{-1}	14	2	Thymopentin injection	–	5
Shao2013	64	100mL.d^{-1}	7	1	–	–	4
Jiang2017	78	400 mL.d^{-1}	7	1	–	–	4
		200 mL.d^{-1}					
Chen2017	104	40mL.d^{-1}	14	1	–	–	4
Li2009	56	200mL.d^{-1}	7	1	–	Saline	4
Dong2017	78	200mL.d^{-1}	7	1	–	–	4
Xu2017	82	100mL.d^{-1}	7	1	–	Ulinastatin injection	5
Zhou2015	50	200mL.d^{-1}	7	2	Ulinastatin injection	–	4
Yu2016	88	100mL.d^{-1}	7	1	–	–	4
Chai2016	127	50ml.d^{-1}	7	1	–	–	4
Pan2016	78	200mL.d^{-1}	14	1	–	–	4
Wu2017	57	0.5–1 mL/ kg.d^{-1}	7	2	–	–	4
Shen2017	82	100mL.d^{-1}	10	1	–	Imipenem + cilastatin sodium	5
Qian2017	50	100 mL.d^{-1}	3–10	2	Ornidazole + ceftizoxime sodium	Ornidazole + ceftizoxime sodium	6

Notes. Study type: 1, RCT; 2, non-randomized controlled studies; 3, other observational studies. –; unclear literature. Mode of administration: 1, single use; 2, combination. Quality score includes seven items, with each item counted as 1 point; a total score of ≥ 4 is classified as high-quality literature. Solvent type: 1, 5% glucose solution; 2, 0.9% sodium chloride solution; 3, the solvent used in the literature was unclear.

foundations of prospective clinical research. The results of these two methods can be used to innovatively and comprehensively assess the relative safety of Xuebijing injection. Moreover, the reliable evidence they provide can serve as a reference for the clinical use of Xuebijing.

5.2. Risk factor analysis

The factors affecting adverse reactions to Xuebijing injection have been previously reported [33–37]. These include age, drug combination, drug vehicle type, drug dosage, and disease type. Results of logistic regression analysis of the case data in this study showed that drug dosage significantly influenced adverse reactions to Xuebijing. It was also of a high priority to determine which drugs might induce allergic reactions in combination with Xuebijing. Suspected allergic reaction was related to the drug combination used, especially when Xuebijing is combined with Ringer's sodium acetate solution, reduced glutathione, aspirin-*DL*-lysine, midazolam, Honghua, or torasemide. Results of the meta-analysis of evidence-based medicine showed that the factors influencing adverse reactions to Xuebijing included type of vehicle, course of treatment, age of > 60 y, and drug combination.

It has been reported that Xuebijing can induce ADRs when combined with other traditional Chinese medicines, antibacterial drugs, and immunity enhancers. Drug interactions may occur in the body and induce adverse or allergic reactions. Therefore, injections of Xuebijing and other drug should be separated by a 50-mL injection of 0.9% w/v NS. Hua et al. [5] recommended that 0.9% w/v NS should be used as a vehicle for Xuebijing. A stability study of external compatibility [38] showed that when Xuebijing injection was combined with 5% glucose injection, the number of particles in the solution after 1 h increased significantly; and the number of particles exceeded standard when Xuebijing injection was combined with 10% glucose injection, increasing the risk of adverse reactions in patients. Therefore, it is recommended to use 0.9% NS as a vehicle for Xuebijing injection. When Xuebijing was co-administered with other drugs, the two doses should be separated by a 50-mL NS injection to avoid drug interaction. The only vehicle used in the cases collected from the hospital HIS system was 0.9% w/v NS solution. Therefore, it was not possible to correlate vehicle type with adverse reactions in this real-world study. However, a meta-analysis of the data in the compiled literature indicated many cases where glucose solution was continued to be used as a vehicle for Xuebijing. The meta-analysis also showed that the incidence of adverse reactions with glucose vehicle (5.96%) was higher than that with 0.9% w/v NS vehicle (4.52%), and the difference between the two groups was statistically significant ($P < 0.05$). Therefore, the type of vehicle used was suspected as a factor affecting the occurrence of adverse reactions to Xuebijing, and this drug should be administered in combination with 0.9% w/v NS solution.

Results of the logistic regression analysis of the dosage data for patients in the HIS system showed that patient dose was a factor affecting allergic reactions to Xuebijing injection. In contrast, the meta-analysis results showed that drug dosage had no significant effect on adverse reactions ($P > 0.05$). This discrepancy can be explained by the differences between the two methods in terms of data sources and analytical procedures used.

Earlier studies indicated that the type of adverse reactions associated with Xuebijing may be influenced by patient's age. Nannan et al. [34,35,39] reported that the incidence of infectious diseases is relatively higher in middle-aged and elderly individuals than in younger individuals. In these cases, Xuebijing injection was used mainly to treat systemic inflammatory response syndrome caused by infection. The meta-analysis results showed that the incidence of adverse reactions in the > 60-y age group (5.82%) was greater than that in the < 60-y age group (5.28%). Xuebijing injections may be administered more frequently in elderly patients than in younger patients. Furthermore, drug metabolism and tolerance are lower in elderly patients, and they are also more likely to have several diseases and more susceptible to ADRs

Table 4
Meta-analysis results of the total incidence rate and various factors influencing adverse drug reactions to Xuebijing.

Analysis type	Number of studies included	Total sample size	ADR cases	Heterogeneity test result	Effect model	Meta-analysis results	
						Consolidation rate (%)	95% CI
Total incidence	52	2095	134	I^2 = 19.4%, P = 0.1159	Fixed	0.0562	[0.0458–0.0675]
Light ADR incidence	48	1948	127	I^2 = 23.9%, P = 0.0731	Fixed	0.0571	[0.0462–0.0689]
Allergic reaction rate	4	147	5	I^2 = 0%, P = 0.7710	Fixed	0.0316	[0.0059–0.0710]
5% glucose injection or other vehicle	12	531	32	I^2 = 53.3%, P = 0.0148	Fixed	0.0596	[0.0310–0.0716]
0.9% sodium chloride injection	38	1539	94	I^2 = 0.0%, P = 0.5786	Fixed	0.0452	[0.0432–0.0583]
Treatment ≤ 7 d	31	1182	62	I^2 = 0.0%, P = 0.9135	Fixed	0.0476	[0.0348–0.0620]
Treatment > 7 d	19	854	67	I^2 = 52.4%, P = 0.0041	Fixed	0.0680	[0.0508–0.0871]
Single medication	33	1283	79	I^2 = 5.6%, P = 0.3763	Fixed	0.0547	[0.0417–0.0692]
Combined medication	19	812	55	I^2 = 38.6%, P = 0.0447	Fixed	0.0587	[0.0421–0.0775]
Dose ≤ 100 mL d^{-1}	37	1487	102	I^2 = 18.4%, P = 0.1655	Fixed	0.0612	[0.0484–0.0751]
Dose > 100 mL d^{-1}	14	574	31	I^2 = 14.4%, P = 0.2962	Fixed	0.0468	[0.0291–0.0677]
Age < 60 y	32	1314	78	I^2 = 6.3%, P = 0.3654	Fixed	0.0528	[0.0401–0.0668]
Age ≥ 60 y	20	807	54	I^2 = 32.5%, P = 0.0470	Fixed	0.0582	[0.0415–0.0770]
Indicated use	47	1877	119	I^2 = 15.6%, P = 0 .1689	Fixed	0.0559	[0.0449–0.0678]
Off-label use	5	218	15	I^2 = 51.2%, P = 0 .0849	Fixed	0.0598	[0.0296–0.0979]

than younger patients.

6. Conclusions

The present real-world study and meta-analysis results suggested that the factors suspected to affect adverse reactions associated with Xuebijing injection included vehicle type, dosage, patient's age, and drug combination. There was no clear correlation between the patient's disease at the time of hospitalization and the suspected allergic reaction to Xuebijing. When Xuebijing is administered clinically, particular attention should be paid to the indications for medication application, dosage, and combination with other drugs. When Xuebijing is co-administered with other drugs, 50 mL NS should be injected between treatments. It is recommended that clinicians heed the recommended dosage of Xuebijing and avoid combining it with other drugs where possible. Extra caution must be taken when administering Xuebijing to the elderly, children, and those with pre-existing allergies in order to avoid ADRs. Xuebijing injection should be prescribed in strict accordance with the indicated instructions to avoid abuse.

The present study combined real-world study with evidence-based evaluation and provided a scientific and intuitive reference for the clinical application of Xuebijing, and the prevention and control of ADRs associated with it. This study also provided novel research and technical methods to for reevaluating the safety of Xuebijing injection. Furthermore, this model can be applied in the post-marketing risk and safety assessments of other traditional Chinese medicines. Although this study analyzed data from the HIS database, its real-world research component also extracted single-center sample data. The limited amount of data necessitated comprehensive judgment of the specific condition and clinical manifestations observed in patients. Therefore, in the present study, we could only analyze currently available data and identify certain tendencies. In the future, larger sample sizes are required to corroborate and substantiate the findings of the present study.

Conflict of interest

The authors declare no conflict of interest with respect to the research, authorship, and/or publication of this article.

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References

[1] S.Q. Feng, Therapeutic effect of Xuebijing injection on systemic inflammatory response syndrome, Prac. Clin. J. Integr. Trad. Chin. Western Med. 17 (02) (2017) 13–15, https://doi.org/10.13638/j.issn.1671-4040.2017.02.007.
[2] Y.L. Dai, J.Y. Li, H.Y. Bai, et al., Xuebijing Injection ( ) increases early survival rate by alleviating pulmonary vasopermeability in rats subjected to severe burns, Chin. J. Integr. Med. 23 (2017) 703–708, https://doi.org/10.1007/s11655-017-2407-y.
[3] F. He, H.J. Chen, X. Zhang, et al., Study on ADR Centralized Monitoring of Xuebijing Injection in Our Hospital, China Pharm. 28 (29) (2017) 4089–4092.
[4] W.H. Sun, Z.T. Ma, Q. Chen, et al., Meta-analysis of adverse reactions and events in Xuebijing Injection, J. Ningxia Med. Univ. 37 (11) (2015) 1296–1299, https://doi.org/10.16050/j.cnki.issn1674-6309.2015.11.013.
[5] H. Guo, P.L. Ren, P. Wang, et al., Literature Analysis of Adverse Reactions in Xuebijing Injection, Anhui Med. Pharm. J. 21 (08) (2017) 1548–1551.
[6] F. Liu, Y.L. Pan, J.H. Lin, et al., Analysis of adverse reactions and influencing factors of Xuebijing injection, Strait Pharm. J. 28 (07) (2016) 276–278.
[7] X.C. Li, G.H. Dai, X.C. Li, Real world study methods and its application in clinical efficacy evaluation of traditional Chinese medicine based on HIS, J. Shandong Univ. Trad. Chin. Med. 40 (05) (2016) 415–418, https://doi.org/10.16294/j.cnki.1007-659x.2016.05.006.
[8] Z.S. Huang, Y.T. Luo, J.L. Liu, Methods and practices of real world study, J. Evid. Med. 14 (6) (2014) 364–368.
[9] R.K. Resar, J.D. Rozich, T. Simmonds, A trigger tool to identify adverse events in the intensive care unit, Comm. J. Qual. Patient Saf. 32 (2006) 585–590.
[10] J.D. Rozich, C.R. Haraden, Adverse drug event trigger tool: a practical methodology for measuring medication related harm, Qual. Saf. Health Care 12 (2003) 194–200.
[11] D.C. Classen, R. Resar, F. Griffin, et al., 'Global trigger tool' shows that adverse events in hospitals may be ten times greater than previously measured, Health Aff. (Millwood) 30 (2011) 581–589, https://doi.org/10.1377/hlthaff.2011.0190.
[13] L. Wang, X.D. Liu, M. Yang, et al., Study on centralized monitoring technology of the adverse drug reactions(ADRs) of XiangDan Injection based on the hospital information system (HIS), Chin. J. Hosp. Pharm. 34 (02) (2014) 159–162, https://doi.org/10.13286/j.cnki.chinhosppharmacyj.2014.02.23.
[14] Y.N. Huang, Literature analysis of 40 cases of xuebijing adverse reactions, Chin. J. Urban Rural Enterp. Hyg. (4) (2012) 18–19, https://doi.org/10.16286/j.1003-5052.2012.04.026.
[15] Y.Q. Zhao, Analysis of 34 cases of adverse drug reactions in xuebijing injection, Chin. J. Clin. Ration. Drug Use 8 (11) (2015) 86–87, https://doi.org/10.15887/j.cnki.13-1389/r.2015.11.056.
[16] Zhang FQ. Literature Analysis of 40 Cases of Xuebijing Adverse Reactions [J], 2014, 41(08):1701-1702. https://doi.org/10.13192/j.issn.1000-1719.2014.08.061.
[17] F.F. Kong, J. Shen, X.Q. Tan, et al., Literature analysis of 14 cases of adverse drug reactions induced by Xuebijing injection, Chin. J. New Drugs 21 (01) (2012) 100–103.
[18] R.J. Chen, Literature analysis of 119 cases of adverse reactions of Xuebijing Injection, Strait Pharm. J. 28 (12) (2016) 290–291.
[19] W. Yang, L. You, Y.M. Xie, et al., Discussion on influencing factors of suspected allergic reaction caused by Shuxuening Injection based on combination with

prescription sequence analysis and nested case-control design, China J. Trad. Chin. Med. Pharm. 05 (2015) 1417–1420.
[20] T.B. Agbabiaka, J. Savović, Methods for causality assessment of adverse drug reactions: a systematic review, Drug Saf. 31 (1) (2008) 21–37.
[21] C.A. Naranjo, U. Busto, E.M. Sellers, et al., A method for estimating the probability of adverse drug reactions, Clin. Pharmacol. Ther. 30 (2) (1981) 239–245.
[22] J.P.T. Higgins, D.G. Altman, J.A.C. Sterne, Chapter8:Assessing Risk of Bias in Includsd Studies, Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[EB/OL]. [2013-10-10], http://handbook.cochrane.Org.
[23] D.F. Stroup, J.A. Berlin, S.C. Morton, et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting, Jama 283 (15) (2000) 2008.
[24] M.L. Luo, H.Z. Tan, Q. Zhou, et al., Realizing the Meta-Analysis of Single Rate in R Software, J. Evid. Med. 13 (03) (2013) 181-184+188.
[25] X.F. Hong, Q. Lin, X.X. Chen, et al., Logistic regression analysis on influential factors of Xuebijing Injection - induced adverse drug Reactions, Eval. Anal. Drug-Use Hosp. China 13 (10) (2013) 941–943, https://doi.org/10.14009/j.issn.1672-2124.2013.10.007.
[26] J. Fang, Analysis of Adverse Drug Reactions in Xuebijing Injection, Strait Pharm. J. 24 (05) (2012) 277–278.
[27] A.S. Barritt, N. Gitlin, S. Klein, et al., Design and rationale for a real-world observational cohort of patients with nonalcoholic fatty liver disease: the TARGET-NASH study, Contemp. Clin. Trials 61 (2017) 33–38, https://doi.org/10.1016/j.cct.2017.07.015.
[28] S. Srinivas, D. Stein, D.Y. Teltsch, et al., Real-world chart review study of adverse events management in patients taking tyrosine kinase inhibitors to treat metastatic renal cell carcinoma, J. Oncol. Pharm. Pract. (2017) 1078155217719583, , https://doi.org/10.1177/1078155217719583.
[29] W. Yang, Y.M. Xie, Y.Y. Xiang, Apply association rules to analysis adverse drug reactions of Shuxuening injection based on spontaneous reporting system data, China J. Chin. Matera Med. 39 (September (18)) (2014) 3616–3620.
[30] J. Chen, Y.M. Xie, W. Yang, Analysis of clinical effects of Shuxuening injection on renal function based on hospital information system data, China J. Chin. Matera Med. 39 (September (18)) (2014) 3599–3605.
[31] F. Tian, Y.M. Xie, Real-world study: a potential new approach to effectiveness evaluation of traditional Chinese medicine interventions, J. Integr. Med. 8 (April (4)) (2010) 301–306.
[32] X.C. Li, G.H. Dai, X.C. Liu, Real world study methods and its application in clinical efficacy evaluation of traditional Chinese medicine based on HIS, J. Shandong Univ. Trad. Chin. Med. (5) (2016) 415–418, https://doi.org/10.16294/j.cnki.1007-659x.2016.05.006.
[33] Q.M. Tao, S.Y. Zhan, Application of prescription sequence analysis and prescription sequence symmetry analysis in drug epidemiology, Chin. J. Pharmacoepidemiol. 10 (2012) 517–519.
[34] N.N. Wang, 21 cases of adverse drug reactions in Xuebijing injection, Chin. J. Hosp. Pharm. 33 (9) (2013) 751–754, https://doi.org/10.13286/j.cnki.chinhosppharmacyj.2013.09.011.
[35] F. Cao, F.J. Wu, Study on the clinical application of drugs in traditional Chinese medicine injections by adverse drug reaction/event, Chin. J. Pharmacoepidemiol. 25 (12) (2016) 777–781.
[36] S.G. Wang, Clinical analysis and adverse reaction analysis of Xuebijing injection, China Health Ind. 11 (04) (2014), https://doi.org/10.16659/j.cnki.1672-5654.2014.04.015 67+69.
[37] L. Zhang, 4 cases of adverse reactions of Xuebijing injection, Chin. J. Hosp. Pharm. 35 (05) (2015) 471–472, https://doi.org/10.13286/j.cnki.chinhosppharmacyj.2015.05.26.
[38] D.P. Mu, C.G. Wang, X.W. Ren, et al., Stability of Xuebijing Injection combined with various solvents, Drugs Clinic 28 (6) (2013) 995–999.
[39] H.R. Lu, L.Q. Fan, Evidence-based application, adverse drug reactions and precaution of Xuebijing injection, Chin. J. New Drugs 22 (20) (2013) 2449–2452.