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Original Research Article

Establishment of a failure mode and effects analysis for high-risk breviscapine-based traditional Chinese medicine injection

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Abstract

Purpose: *To assess the failure modes and effects of clinical application of breviscapine-based traditional Chinese medicine injection (TCMI).*
Methods: *229 reports on clinical application errors, medication errors or management measures relating to breviscapine injection were collected by searching various databases. A clinical application and safety evaluation questionnaire was formulated for use in the failure mode and effects analysis (FMEA) of breviscapine injection. The questionnaire survey was then distributed to 100 doctoral, nursing and pharmaceutical personnel in Xinxiang Central Hospital who were randomly chosen to participate.*
Results: *A total of 81 (83.5 %) valid questionnaires were retrieved. A total of 29 potential failure types, failure causes and failure effects were identified. Mean values of all risk priority numbers (RPN) of the 29 failure modes were ranked comprehensively. The failure modes identified as top 10 risk factors include; detailed information regarding the patient's medical, allergy and family disease history not being provided to physicians (75.22); incorrect choice of drug manufacturer and lot number (74.95), drugs not being dispensed on the spot (72.16); inappropriate choice of solvent (71.31); drugs not suitable for combination therapy (70.81); inappropriate choice of solvent dosage (69.14); individual patient differences not taken into consideration (67.07); infusion rate too fast (67.00); off-label drug use (65.32); and age of the patient not taken into consideration (64.96).*
Conclusion: *As a risk management tool, the FMEA conducted in this study reduces potentially dangerous clinical application of high-risk TCMI, standardizes the medication process and significantly reduces occurrence of adverse reactions to TCMI. Future studies are required to validate these claims.*

Keywords: *Breviscapine, High-risk traditional Chinese medicine injection, Failure mode, Adverse reaction, Pharmacology*

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INTRODUCTION

Compared with traditional Chinese medicine (TCM) administered orally, TCM injection (TCMI) has higher bioavailability and onset, and it is widely used in clinical practice [1]. However, due to the complex and diverse components used in TCM, the efficacy of medicinal materials changes based on harvest time and origin. At the same time, with increase in dosage forms and clinical applications, adverse reactions to TCMI are increasing annually. Wang et al [2] revealed that

adverse reaction rate of TCMI was 0.63 % [2]. Adverse reactions to TCMI are not only associated with treatment successes or failures, but also endangers patients' lives [3]. Therefore, clinical application of high-risk TCMI should be monitored and evaluated for safety to detect warning signals early, make judgements based on the circumstances, provide timely treatment and guarantee the safety of drug use. Failure mode and effects analysis (FMEA) is a method used to evaluate failure risk and potential harm to patients in a medical process to identify relevant clinical problems [4]. This method has been successfully applied to many clinical disciplines, such as diagnostic radiology and drug prescription [5]. However, no study has been undertaken on the application of FMEA in clinical evaluation of TCMI. Breviscapine is an active flavonoid component extracted from *Erigeron breviscapus* (Vant.) Hand.-Mazz. of the genus *Feijoa* in the family Asteraceae. It is a mixture of apigenin-7-O-β-D-glucuronide and scutellarin (also known as scutellarein-7-O-β-D-glucuronide), with scutellarin as the main component [6]. It increases blood flow, improves microcirculation, expands blood vessels, reduces blood viscosity, lowers blood lipid levels, and promotes fibrinolysis, antithrombotic activity and antiplatelet aggregation [7,8]. It is widely used in traditional and modern health clinics, and adverse reactions to this active component are increasing yearly [9]. This study focuses on breviscapine injections and intends to establish an FMEA for high-risk TCMI, conduct a hazard analysis and put forward an improvement implementation plan to provide a reference for the establishment of a code of practice in clinical practice of high-risk TCMI.

METHODS

Search strategies

Search terms included words and phrases such as 'breviscapine', 'apigenin-7-O-β-D-glucuronide', 'scutellarin', 'adverse reactions', 'medication errors' and 'medication error cases'. Searches were performed in PubMed, Embase, Wanfang Data and China National Knowledge Infrastructure to collect data on adverse reactions to breviscapine injections and breviscapine injection–related effect. A total of 229 papers based on reports of clinical medication errors, medication errors or management measures relating to breviscapine injections were collected.

Ethical approval and consent to participate

This study was approved by the Ethics Committee (issued 5 May 2022) of Xinxiang Central Hospital and conducted in accordance with the Declaration of Helsinki [12]. All participants signed an informed consent form for inclusion in the study.

Error analysis

Creating a questionnaire

Referring to the third edition of the Reference Manual for Potential Failure Modes and Effect Analysis and the assessment of Clinical Application and Safety Evaluation of High-Warning Traditional Chinese Medicine Injection—Questionnaire of Failure Modes and Effects Analysis on Breviscapine Injection [10], potential failure modes that had been identified were evaluated for severity, frequency of occurrence and likelihood of detection. These were scored on a 10-point scale from 1 to 10 [11]. Severity scores were as follows; none (1), very mild (2), mild (3), milder (4), average (5), average severe (6), more severe (7), severe (8), very severe (9) and extremely severe (10). Frequency of occurrence scores were classified as very low and unlikely (1), low and relatively infrequent (2–3), moderate and occasional (4-6), high, with the possibility of a repeat occurrence (7-8), and very high, with a repeat occurrence being almost certain (9-10). Likelihood of detection scores was classified as none (1), very mild (2), mild (3), milder (4), average (5), average severe (6), more severe (7), severe (8), very severe (9) and extremely severe (10). After the severity, frequency of occurrence and likelihood of detection scores were obtained, the risk priority number (RPN) was calculated as product of the scores, with a range of 1–1,000.

Risk assessment

A questionnaire survey was conducted randomly among 100 doctoral, nursing and pharmaceutical personnel in Xinxiang Central Hospital, which is a comprehensive Grade 3 A hospital. The RPN of each failure mode was calculated as product of the severity, frequency of occurrence and likelihood of detection scores.

The average RPN value for each failure mode in the questionnaire was taken as the final RPN value and then ranked. In total, 100 questionnaires were distributed, and 97 questionnaires were collected (97 %).

RESULTS

Process mapping

Based on classification and analysis of the literature, brainstorming method was used to create a process map of the four main processes which include; diagnosis and prescription by physicians, dispensing by pharmacists, configuration of the infusion by nurses, and clinical medication of the patient [13]. The study flowchart is presented in Figure 1.

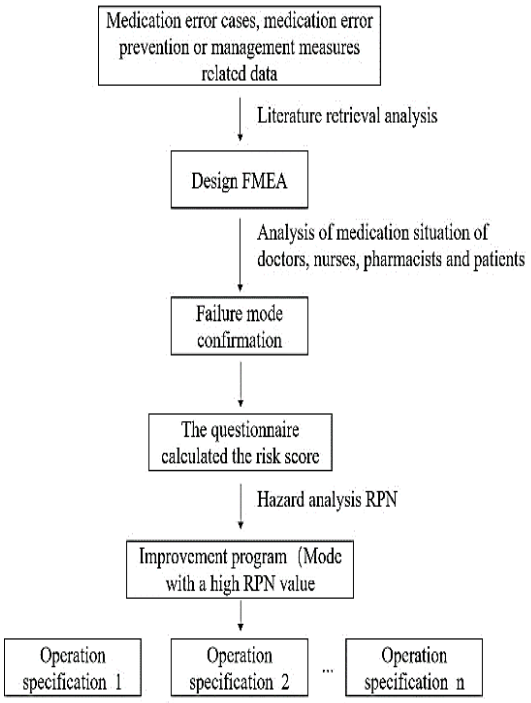

Figure 1: The method framework diagram

Basic information about respondents

Of the 97 questionnaires (97 %) collected, 81 questionnaires (83.50 %) were valid and included in the study. Majority of the respondents 34 (41.98 %) had master's degree, between 21 – 30 (59.26 %), were doctors (49.38 %), and < 5 years (54.32 %) in service (Table 1).

Failure mode evaluation results

A total of 29 potential types, causes and effects of failure were recorded (Table 2). The mean scores of all RPN values of the 29 failure modes collected from the 81 questionnaires were ranked comprehensively, and the top 10 most dangerous risk factors are recorded (Table 3 and Table 4). Also, considering that different occupations have varying insights, awareness and judgement criteria regarding failure mode severity, frequency of occurrence and likelihood of detection, the mean scores of the RPN values of the failure modes mentioned by respondents with different occupations were also ranked.

Top 10 risk factors in RPN mean value

The results illustrated that detailed information regarding medical, allergy and family disease history not being provided ranked first in the overall RPN mean of the risk of failure mode, eighth in physicians' evaluations, sixth in nurses' evaluations and fourth in pharmacists' evaluations. Several other failure modes were not included in the top 10 based on the RPN average but were among the top 10 most dangerous failure modes. However, pharmacists and nurses thought that a lack of infusion monitoring could lead to the occurrence of adverse reactions to breviscapine and that corresponding improvement measures should be taken based on actual circumstances (Table 8).

Table 1: Basic information of investigators

Item	Classification	Composition (%)
Education background	Junior college	19.75
	Bachelor	38.27
	Master	41.98
Age	21-30	59.26
	31-40	29.63
	41-50	7.41
	More than 50	3.70
Years of working	Less than 5	54.32
	6-10	28.40
	11-15	7.41
	16-20	2.47
	21-25	2.47
	25-30	2.47
	31-35	1.23
	36-40	0.00
	More than 40	1.23
Occupation distribution	Physician	49.38
	Nurse	33.33
	Pharmacist department	17.28
Department distribution	Oncology	34.57
	Pharmacy	17.28
	Arthritis	6.17
	Respiratory medicine	1.23
	Emergency department	2.47
	Urology	1.23
	Endocrinology	7.41
	General Surgery	3.70
	General practice	1.23
	Neurology	6.17
	Nephrology	9.88
	Cardiovascular Medicine	8.64

Table 2: Failure modes, failure cause and failure effect in each link

Activity	Potential failure mode	Potential failure cause	Potential failure effect
Diagnosis and prescription by physicians	Too fast infusion rate	1. Do not understand the impact of drug infusion rate on the incidence of adverse reactions 2. Lack of responsibility did not promptly explain to the nurse to pay attention to the infusion rate	Infusion speed is too fast, and too much liquid is injected in a short time, which leads to a sharp increase in circulating blood volume, cardiac overload and injection site pain, which increases the incidence of adverse reactions
	Excessive dosage	1. Failure to differentiate individual differences 2. Physicians use medication based on experience	May cause excess concentration of drugs in the body, adverse reactions, causing injury to patients
	Not suitable for combination therapy	1. Repeated use of drugs 2. Unfamiliar with the physical and chemical properties of drugs and drug-drug interactions	Increases the incidence of adverse reactions in patients, which may cause harm and prolong hospitalization
	Inappropriate choice of solvent dose	1. Reducing the amount of solvent of breviscapine considering the amount of liquid intake by the patients 2. Lack of responsibility, relatively arbitrary choice of solvent dose 3. Not considering the effect of clinical application, empirical use of drugs	1. Affect the solubility of the drug, increase the insoluble particles of the drug, increase the concentration of the drug, and increase the incidence of adverse reactions. 2. May cause injury to patients, prolong the length of hospital stay
	Failure to consider individual differences of patients	Lack of understanding of individual differences of patients	Increases the incidence of adverse reactions in patients, may cause injury, and prolongs length of hospitalization
	Continuous use, long course of treatment	The doctor failed to discontinue the medicine on time	1. Patients with long-term use may experience varying degrees of reversible thrombocytopenia, resulting in bleeding 2. Increased incidence of adverse reactions
	Failure to carefully ask patients about their allergy history	1. Patients do not know about their allergies 2. Doctors do not ask carefully enough 3. Doctors do not consider the impact of allergies other than the drug on the occurrence of adverse reactions	Increased incidence of adverse reactions in patients, may cause injury to patients
	Contraindications	1. Not carefully studying the instructions 2. Empirical use of medication	Affects the curative effect, makes the patient's condition worse, causes injury
	The choice of drug manufacturer and lot number	Different manufacturers have different production processes and may contain different allergic mediators	High incidence of allergic reactions
	Off-label	Lack of understanding of drugs and failure to treat with evidence	Off-label is one of the main reasons for unsafe clinical use, which may cause harm to patients and prolong hospitalization days
	Inappropriate solvent selection	1. Lack of understanding of the instructions 2. Lack of drug-related knowledge 3. Lack of responsibility of doctors and relatively arbitrary choice of solvents	1. Affects drug stability and solubility 2. Increases incidence of adverse reactions in patients
	Failure to consider the age of patients	Physicians are not aware of the high incidence of adverse reactions to drugs in people ≥ 60 years of age	Increase the incidence of adverse reactions in patients, may cause injury to patients
	Unauthorized changes in the route of drug administration	Not strictly in accordance with the instructions for drug administration	1. Affects efficacy of drugs 2. Increases incidence of adverse reactions

Table 2: Failure modes, failure cause and failure effect in each link *(contd)*

Activity	Potential failure mode	Potential failure cause	Potential failure effect
Dispensing by pharmacists	Failure to explain precautions	1. Large workload, many patients, few windows, no time to explain overly detailed precautions 2. Lack of drug safety knowledge	Patients may not be able to use drugs correctly, affecting drug efficacy and increasing the incidence of adverse reactions
	Wrongly dispensed drugs	High workload, distracted pharmacists, not checked for errors	Dispensing errors may cause harm to patients and have complaints
	Mixed batches of drugs	1. Confusing drug placement 2. No awareness of giving drugs in the same batch	Different batches of drugs may contain different allergic mediators, increasing the incidence of allergic reactions
Configuration of infusion by nurses	Lack of infusion monitoring	1. Nurses are not responsible enough to perform necessary infusion monitoring 2. Are not aware of the importance of infusion monitoring 3. Do not understand the infusion monitoring process 4. Many patients and few nurses, unable to adequately monitor	Inability to detect symptoms of adverse reactions in a timely manner, delaying the time for patient treatment
	Changing the infusion rate arbitrarily	1. Blur the concept of infusion drip rate control and is not adjusted carefully at work 2. Help patients to adjust the drip rate faster by meeting patients' requests arbitrarily	1. Infusion too fast may lead to the drug accumulating in the body and lead to excessive negative inotropic effect, which causes a drop in blood pressure and T-wave inversion 2. Increased the incidence of adverse reactions in patients
	Failure to ask the patient about allergy history	1. Think that the doctor has inquired, not reconfirmed 2. Lack awareness that history of non-target drug and food allergies could lead to adverse reactions	Increase the incidence of adverse reactions in patients, may cause injury to patients
	Failure to check the quality of the drug solution	1. Lack rigorous work, not carefully checking the drug 2. Lack of knowledge about drug properties	Affect the efficacy of the drug, causing patient harm and complaints
	Failure to flush the tube as required	1. The nurse being in a hurry forgets to flush the tube. 2. Not clear whether to flush the tube before and after the use of drugs.3. The time of flushing the tube is too short	Crystalline particles and flocculent material could be formed in the tube, which could cause harm to the patient and prolong the hospitalization days
	Explanations to patients were not performed	1. The work is not rigorous, forgetting to explain the medication to the patients. 2. Lack of awareness of explanation	1. The patient may change the dropping rate at will. 2. The symptoms of adverse reactions cannot be found and informed on time. 3. Once the symptoms of adverse reactions occur, it is easy to cause panic
	Drugs are not dispensed on the spot	1. Nurses have a large workload and concentrate on bulk configuration of drugs at the same time, without considering the actual time of patients' medication 2. Do not arrange patients' infusion orders reasonably	Affects drug stability and increases the incidence of adverse reactions
	Nurse execution does not match with physician's prescription	1. The nurse does not check the patient's name and medication 2. Wrong medication 3. Missing or giving more medication	Medication administration error occurs, resulting in patient injury and complaints
	Failure to deal with patients' questions in a timely manner	1. Lack of responsibility and patience in listening to the questions raised by patients and accompanying family members 2. Lack of knowledge of countermeasures related to problems in the process of drug use	1. Delay disposal time of adverse reactions 2. Affect the mood of patients and family members

Table 2: Failure modes, failure cause and failure effect in each link *(contd)*

Activity	Potential failure mode	Potential failure cause	Potential failure effect
Patient's clinical medication	Poor infusion monitoring by family members	1. Neglect the infusion education of doctors and nurses. 2. Afraid of disturbing the nurses, early adverse reactions were not reported on time	Further lead to the occurrence of serious adverse reactions, causing injury to patients
	Change the infusion rate at will	1. The patient did not know enough about the danger of the infusion rate and adjusted the rate arbitrarily 2. Do not listen to the nurse's education and adjust the rate without permission in order to finish the infusion	1. Too fast infusion caused the drug to accumulate in the body and resulted in strong negative muscular effect, which caused a drop in blood pressure and T-wave inversion. 2. Increase incidence of adverse reactions
	Poor compliance with medical advice	Do not understand the importance of the frequency of infusion on drug therapy, and ask nurses to infuse at once in order to reduce the number of needle sticks	Too much drug input in a short period of time causes metabolic burden and pain at the injection site, increasing the incidence of adverse reactions in patients
	Lack of detailed explanation of medication history, allergy history, and family diseases to physicians	Lack of awareness that non-target drugs, food allergies, and medication history lead to adverse reactions	Increased incidence of adverse reactions in patients, may cause injury to patients

Table 3: Top 10 risk factors in RPN mean value comprehensive ranking of failure mode

No	Failure mode	RPN mean value
1	Failure to provide detailed information on medication history, allergy history, and family diseases to physicians	75.22
2	Choice of drug manufacturer and lot number	74.95
3	Drugs are not dispensed on the spot	72.16
4	Inappropriate choice of solvents	71.31
5	Not suitable for combination therapy	70.81
6	Inappropriate choice of solvent dose	69.14
7	Failure to consider individual patient differences	67.07
8	Too fast infusion rate	67.00
9	Off-label	65.32
10	Failure to consider the age of patient	64.96

DISCUSSION

Traditional Chinese medicine injection is an innovative dosage form with a high bioavailability and good curative effect, it is widely used in the treatment of acute and severe cases of illness in China [14]. Unlike the single active ingredient of chemical drug injections, TCMI has multiple components [14]. Traditional Chinese medicine pays attention to compatibility, which illustrates those interactions between different TCM components is an important attribute of TCM formulas [15]. The patient's medication or drug allergy history may make TCMI ineffective. This is consistent with two factors identified here in the FMEA which include failure to provide detailed information about patient's medication, allergy and family disease history to physicians and drugs not suitable for combination therapy being used in combination therapies.

Traditional Chinese medicine injection needs to be combined carefully with other drugs [16]. In addition, most TCM exist as concentrated liquid, which must be mixed with an infusion to reach appropriate concentration before being injected into the patient [14]. This may also be the reason why the failure modes of TCMI include incorrect choice of drug manufacturer and lot number, inappropriate choice of solvent and inappropriate choice of solvent dosage as revealed by this study. Doctors should reconfirm whether patients are atopic when diagnosing and prescribing drugs. They should also ask and record whether patients have any history of allergic reactions or diseases, including drug or food allergies, and

explain the risks of not providing information or providing inaccurate information.

Table 4: Top 10 risk factors in RPN mean value of occupational failure mode

Occupation	Rank	Failure mode	RPN mean value
Physician	1	Inappropriate choice of solvents	81.90
	2	Not suitable for combination therapy	75.20
	3	Inappropriate choice of solvent dose	73.53
	4	Off-label	70.48
	5	Unauthorized changes in the route of drug administration	70.18
	6	Failure to consider the age of patient	69.03
	7	Too fast infusion rate	66.48
	8	Failure to provide detailed information on medication history, allergy history, and family diseases to physicians	65.60
	9	Contraindication	64.35
	10	The choice of drug manufacturer and lot number	61.25
Pharmacist	1	Change the infusion rate arbitrarily	88.00
	2	Overdose	82.64
	3	Failure to ask the patient's allergy history carefully	78.43
	4	Failure to provide detailed information on medication history, allergy history, and family diseases to physicians	77.79
	5	Inappropriate choice of solvent dose	77.43
	6	Failure to check the quality of the drug solution before infusion	77.07
	7	Failure to ask the patient about allergy history	76.00
	8	Not suitable for combination therapy	74.14
	9	Poor compliance with medical advice	73.79
	10	Lack of infusion monitoring	70.57
Nurse	1	Drugs are not dispensed on the spot	117.33
	2	The choice of drug manufacturer and lot number	106.22
	3	Patient explanations were not performed	98.30
	4	Wrong medication dispensed	96.78
	5	Failure to flush tubes as required	92.22
	6	Failure to provide detailed information on medication history, allergy history, and family diseases to physicians	88.11
	7	Failure to deal with patients' questions in a timely manner	86.04
	8	Poor infusion monitoring by family member	84.90
	9	Failure to consider individualized patient differences	82.70
	10	Lack of infusion monitoring	77.78

Nurses should confirm patient's allergy and medication history before infusion and educate the patient on prescription drug safety to improve awareness of allergies or other conditions. Patients should be treated according to the principles of dialectical treatment in Chinese medicine. Medical professionals should strictly follow the medications' instructions, correctly understand indications, dosages and courses of treatment, adjust drug regimen according to the condition in a timely manner, and strictly prohibit overdoses, high concentrations and long-term continuous drug use.

It is also pertinent to strictly prohibit the mixing and combining of drugs. If it is necessary to use drugs in combination, drug interactions should be carefully considered, and nurses should endeavour to clean the infusion container. Injection rates and volumes have been proven to be important risk factors in targeted drug delivery [17]. Regular training should be organized for nurses on intravenous infusion procedures and related knowledge to ensure accuracy of drip rate control. Patients' requirements should not be blindly followed; rather, they should be educated about infusion and strictly prohibited from changing the drip rate by themselves. It is recommended that the drip rate be < 40 drops/min and generally controlled at 15–30 drops/min. For the first dose, it is advisable to choose a small dose and reduce drip rate. Senior nursing staff with strong communication skills and rich experience should be selected to be responsible for infusion rounds and to deal with adverse drug reactions promptly once they occur.

For patients who are being given a type of medication for the first time, medication monitoring should be strengthened (especially within one hour of the medication being administered and during continuous medication administration). As regarding the pharmacy department, training of dispensing pharmacists should be strengthened, and attention should be given to the management of high-risk TCMI in pharmacies. Pharmacists should ensure all drugs

are neatly organised, with compounds that have the same batch number stored together. They should also ensure that the compounds are dispensed according to the batch number so that batch numbers are not mixed.

Limitations of the study

The sample size used is small, and there is lack of empirical data to quantify the probability of specific failure modes. There is also a lack of similar study with which to compare the results of this study. In addition, the technical limitations of FMEA itself have not yet been overcome.

CONCLUSION

This study successfully establishes FMEA for high-risk breviscapine-based TCMI which improves clinical application of high-risk TCM in a targeted manner, standardizes medication process, effectively reduces the occurrence of adverse reactions, and improves drug safety although further studies are required to validate these claims.

DECLARATIONS

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None provided.

Ethical approval

This study was approved by the Ethics Committee of Xinxiang Central Hospital, China (approval date: 5 May 2022)).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. MYY and ZTD conceived the study; ZX participated in its design and coordination and BZY helped to draft the manuscript. All authors read and approved the final manuscript for publication.

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