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RESEARCH ARTICLE

Post-marketing safety surveillance and reevaluation of Motherwort injection: A clinical study of 10 094 cases

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Abstract

OBJECTIVE: To investigate the safety profiles of Motherwort injection (MI).

METHODS: A multi-center, prospective and drug-derived hospital intensive monitoring method was conducted to assess the safety of MI in real world applications. This study was based on a very large population after the injection was approved and marketed in China. All patients using the injection in participating hospitals were monitored to determine the incidence, pattern, severity and outcome of associated adverse events.

RESULTS: The post-marketing surveillance was performed in 10 094 female patients from April to December, 2015. The incidence of adverse drug reactions (ADRs) was 0.79‰ (8/10 094). Among the 8 patients, the reported adverse events mainly included systemic abnormalities, such as fever, chills and eyelid edema; skin and appendages disorders, such as pruritus and rash; gastrointestinal disorders, such as nausea, abdominal distension and pain; heart rate and rhythm disorders, such as palpitation and increased heart rate. All of these ADRs were mild in severity.

CONCLUSION: In this study the ADRs incidence rate of MI is very low, which supports that it is generally safe for use in obstetric and gynecological diseases. However, the total number of 8 ADRs recorded over a relatively short time span seems limited, and the low number of reports could not represent an absolute guarantee of safety.

Keywords: Safty; Product surveillance, postmarketing; Drug-related side effects and adverse reactions; Motherwort injection

INTRODUCTION

Motherwort has been widely used in the treatment of various women's health conditions.[1] Motherwort injection (MI, Zhunzi Z51021448), one of Traditional Chinese Medicine (TCM) Injection (TCMI),[2] is an original exclusive drug marketed in China and has obtained several invention patents. One of the aqueous extracts of Motherwort is alkaloids can be used as an anti-inflammatory medication and also to treat many disorders such as cardiac, obstetric and gynecological abnormalities.[3,4] It has been shown in a preclinical trial that MI could stimulate muscles of mice uteruses and thus

increase the strength and frequency of their contraction.[5] Also, the safety of the aqueous extract has been confirmed in several animal experiments.[6,7]

It has been suggested in a number of clinical studies that MI could prevent postpartum hemorrhage after cesarean section and vaginal delivery, displaying a synergic effect when combined with oxytocin.[8,9] Furthermore, a previous randomized, double-blind, placebo controlled trial has supported its efficacy and safety.[10] Along with the wide application of TCMIs in clinical practice, more and more attention has been paid to their potential ADRs. To date, several studies have been conducted to evaluate the safety of MI[10,11] indicating that the injection is relatively safe. However, due to the limitations of pre-marketing studies, the description about its ADRs is rare and the related precautions for use still remain unclear. It seems that these published studies cannot provide adequate evidence for the clinical use of MI, owing to the lack of data on the efficacy and safety of the drug based on large populations and higher quality studies.

It is reported that hospital intensive monitoring is an appropriate method to be carried out for post-marketing safety evaluation of TCMIs.[12] When supported by a well-trained physician-pharmacist team, such a method could objectively reflect the real world of clinical applications. Hospital-based intensive monitoring consists of routine prospective recordings of drugs administered throughout patients' hospital stay as well as the occurrence of adverse events, no matter whether there is a relationship between drugs and events.[13] This may shed light on the pattern, severity and frequency of occurrence of ADRs in local populations.[14] Therefore, in this study we conducted a large-scale prospective study based on the hospital intensive monitoring method to reevaluate the safety of MI. AND we hope that this study can provide valuable insights for quality improvement of future ADR studies.[15]

MATERIALS AND METHODS

Study design and setting

In order to observe and evaluate the safety of MI, we conducted a large-scale, multi-center, prospective trial using the drug-derived hospital intensive monitoring method. This study was carried out in collaboration with 42 hospitals across China from April 2015 to December 2015.

Ethical approval

The trial protocol was reviewed and approved by the Ethics Committee of Institute of Basic Clinical Chinese Medicine from the Institute of Basic Clinical Medicine in China Academy of Chinese Medical Science and the Approved number of ethic committee was 2015No.5). The study was performed according to the ethical standards stated in the Declaration of Helsinki. All participants received a detailed explanation about the study and provided written informed consent.

Subjects

According to the aim of the study that was to build a picture of real-world clinical practice in the treatment of MI, investigators were asked to record data from patients using the injection. Patients recruited into the study were those to whom investigators would have prescribed MI as part of their normal clinical practice.

The eligibility criteria for participants were as follows: (a) patients who participated in this study voluntarily; and (b) patients who had the indications of MI and had used MI.

Patients who had the indications of MI but did not agree to participate in the study were excluded.

Sample size

Considering the available data regarding clinical monitoring of drug safety, as well as the low dose and short duration of clinical MI use, a sample size of at least 10 000 patients was required.

Drugs

MI was manufactured by Chengdu No. 1. Pharmaceutical Co., Ltd., (Chengdu, China) Strength: 1 mL/injection.

Implementation

Evaluation Domains: the performance, incidence, severity and outcome of ADRs / adverse drug events (ADEs) were the main evaluation Domains. The severity of ADRs/ADEs referred to the "Adverse drug reaction report and monitoring management approach" (Ministry of Health 81 orders in China).[16]

Length of observation period

The length of observation period was determined according to the specific clinical conditions of each individual patient, and observation would last until the end of MI medication.

Monitoring information

The main monitoring information included general information (e.g. patient visit information, vital signs, demographic characteristics, medical history, allergies, family history of allergies, and history of ADRs); MI indications (e.g. postpartum, abortion, or irregular menstruation); MI medication (e.g. medication days, dosage, and timing of injection); concomitant medications (including drug name, manufacturer, dosage, frequency, and route of administration); as well as safety information (including start date, end date, symptoms, intensity/severity, seriousness, relatedness to study drug, actions taken and outcome of adverse events).

If a serious adverse event (SAE) occurred (i.e. death; carcinogenicity, teratogenicity, or birth defects; life-threatening or resulting in permanent disability; permanent impairment of physical functions), the

monitoring center should collect the blood sample of this patient within 12 h of reporting.

Monitoring method

Two pre-designed case record forms (CRFs) were used to collect necessary information from patients: Form A (CRFA) "Monitoring Form" and Form B (CRFB) "Adverse Events Form". CRFA included the general information, vital signs (temperature, respiration, pulse and blood pressure), medical history, history of ADRs, information about MI medication and other concomitant drugs, as well as the occurrence of ADEs. CRFB included the general descriptions of ADEs, such as symptoms, time of onset, duration, severity, actions taken and outcomes, as well as their relationship to the study drug. According to the specific settings of each participating center, the personnel filling in the forms could be doctors, nurses or pharmacists. If a patient did not experience any adverse events throughout the study, only CRFA should be filled out. If a patient did experience an adverse event, CRFB should be completed within 24 hours.

Causality Judgment for ADRs/ADEs

According to the WHO Collaboration Center for International Drug Monitoring, the causal relationships of adverse events with the administration of a study drug or a study procedure can be judged as certain, probable, possible, unlikely, conditional, and unassessable. The judgment was mainly based on the answers to the five questions listed in Table 1. If the strength of the judgment was certain, probable, or possible, the event should be considered an adverse drug reaction.[17]

In order to make professional judgment on the incidence of ADRs of MI, a Safety Reevaluation Committee (SRC) consisting of clinical and pharmacy experts was set up. These experts, who participated in the interim and concluding meetings, used their expertise to make a final decision on ADRs based on the initial judgments from each center. If necessary, the committee would go to some of the monitoring centers and carry out trainings and supervisions. Therefore, all of these efforts guaranteed the objectivity, openness and impartiality of judgments on ADRs.

Monitoring management

A three-tier quality management was implemented for this study. The first-level quality management required the relevant personnel from participating centers to conduct self-examination and complete the monitoring report. The second-level quality management was organized by Beijing COMPETE Pharmaceutical Research and Clinical Evaluation Center to monitor the performance of participating centers and check the quality of CRFs every half a month. And the third-level quality management was proposed and conducted by the Data Management Center (DMC) and carry out inspection in participating centers.

At the beginning of the study, all personnel who participated in the study including doctors, nurses, pharmacists, quality control and monitoring staff of each center must receive unified training on safety monitoring. The training content involved the standard operation practice (SOP) about the study procedures and the filling requirements of CRFs.

Data management

In order to assure data quality, the DMC was set up in December 2014 and the expert member was Professor Gao Xuemin from Beijing University of Traditional Chinese Medicine; other committee members were Professor Weng Weiliang from Chinese Academy of

Table 1 Judgment of causal relationships of adverse events with study drug

Questions	Judgment						Assessment
	Certain	Probable	Possible	Unlikely	Conditional	Unassessable	
Is there a reasonable time relationship between medication and AE/AR?	+	+	+	-	Need to add material to evaluate	The necessary information for the evaluation is not available	
Does the reaction meet the known adverse reaction type of the drug?	+	+	-	-			
Does the reaction disappear or diminish after withdrawal or reduction?	+	+	±?	±?			
Is the same reaction / event happening again with the suspected drug?	+	?	?	?			
Whether the reaction / event is available and explained by the effect of the combined drug, the progression of the disease, or the effects of other treatments?	-	-	±?	±?			
Conclusions							

Note: +: denotes affirmation; -: denotes negation; ±: denotes that it is difficult to affirm or deny; ?: denotes unknown.

Sciences Xiyuan Hospital; Director Yang Huixia from Peking University First Hospital; Professor Zhang Li from Beijing Oriental Hospital; Professor Ma Kun from China Academy of Traditional Chinese Medicine Xiyuan Hospital; and Zhang Shichen, deputy director of State Administration of Traditional Chinese Medicine of China.

The DMC developed a detailed monitoring work plan on May 31, 2015. From July 31 to September 1st, 2015, the DMC carried out spot checks on data records, after which they drafted the self-examination requirements and specific verification measures for safety evaluation of MI. Then, Beijing COMPETE Pharmaceutical Research and Clinical Evaluation Center urged all participating centers to check data, ensuring the authenticity, reliability and integrity of the reported data about ADRs/ADEs.

Statistical analysis

Descriptive analysis was performed to examine participant's general characteristics, including age, vital signs, disease diagnosis; the first medication time, dosage, course of treatment, use of other concomitant medications during and before injection; allergies, family history of allergies and the performance. The incidence and characteristics of ADEs/ADRs were also analyzed.

Continuous variables were expressed as mean ($\bar{x}$), standard deviation (S), median (M), minimum (Min) and maximum (Max); and categorical variables were presented as number (n) and constituent ratio (% / ‰) or rate.

Data analysis was performed using the Statistical Analysis System software 9.3 (SAS Institute, Cary, NC, USA). All two-tailed statistical tests were considered to be significant at $P < 0.05$.

RESULTS

The overall flow chart of post-marketing safety surveillance and reevaluation of MI was shown in Figure 1.

Subject characteristics

A total of 10,094 female patients from 42 monitoring hospitals were enrolled in this study. Of the 10,094 patients, the mean age was 29.48 ± 5.33 years (minimum, 14.31 years, maximum, 63.02 years). The main nationality of this patient population was Han nationality (9328, 92.41%). Most patients using MI in this study were hospitalized patients (9,664, 95.74%) and

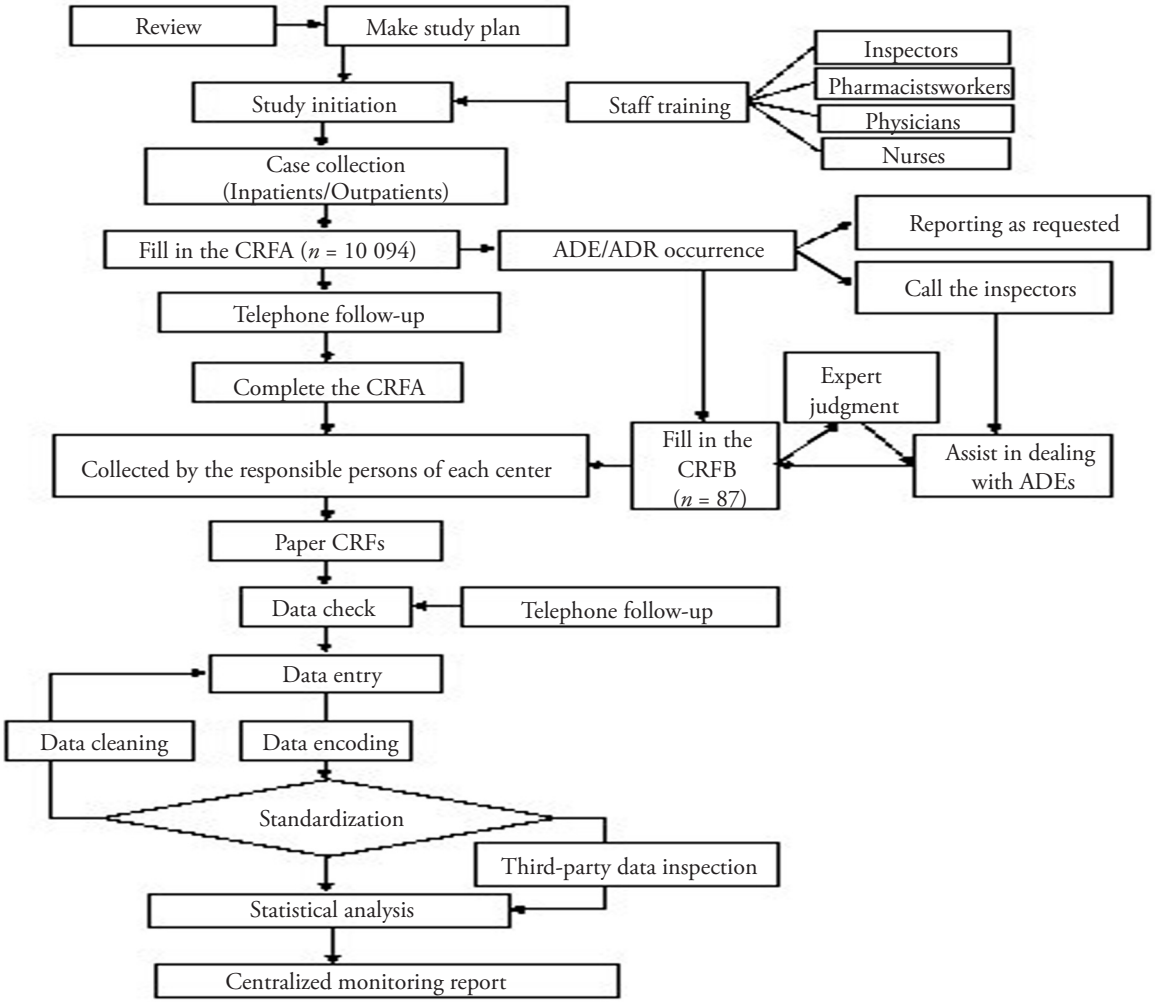

Figure 1 Overall flow chart of post-marketing safety surveillance and reevaluation of MI
CRF: Case Record Form; MI: Motherwort injection.

the others were outpatients (430, 4.26%). Table 2 summarizes the basic characteristics of these patients (Table 2). Table 3 presents the height, weight and vital signs of these subjects (Table 3).

Medication characteristics

Among the 10 094 observed subjects, 9583 (94.94%) were first-time users of MI. The major indication of MI was delivery (9012, 89.52%), followed by abortion (872, 8.93%). For most patients (9456, 93.68%), the initial dose of MI was 2 mL. The mean number of injections was 4 ± 2, the mean cumulative dose was 8 ± 5 (mL) and the mean length of observation period (from starting to stopping using MI) was 38.7 ± 33.4 (h).

In addition to the use of MI, 8340 (82.63%) patients used other concomitant drugs. The most commonly used concomitant drug was oxytocin injection (7422, 35.32%), followed by antibiotics (3553, 16.91%). Table 4 lists medication characteristics.

Primary evaluation of ADRs and distribution in monitoring hospitals

Of the 42 monitoring hospitals, 18 hospitals reported the occurrence of ADEs. Of the 10 094 individuals, 87 patients reported a total of 117 ADEs (Table 5).

Causality judgment of ADRs/ADEs

The causal relationship of ADEs with the administration of the study drug was assessed according to the categories as described by the "adverse reaction causality criteria", which was developed by the Adverse Reaction Monitoring Center of the CFDA. Three rounds of evaluations were performed for causality judgment.

Primary evaluation: According to the initial judgment of monitoring hospitals, a total of 90 CRFBs of ADEs were collected, of which 24 patients experienced more than one ADE.

Secondary evaluation: After the reevaluation by SRC, 3 patients were removed because their ADEs occurred before the use of MI. The total number of ADEs was 87

Table 2 Basic characteristics of subjects [*n* (%)]

Characteristics		*n* (%)	Characteristics		*n* (%)
Age	<20	214 (2.12)	Number of pregnancies	0	1513 (14.99)
	30~	3741 (37.06)		1	3433 (34.01)
	40~	346 (3.43)		2	2481 (24.58)
	50~	26 (0.26)		3	1461 (14.47)
	≥60	1 (0.01)		4	761 (7.54)
Past Medical History	No	8744 (86.63)		5	298 (2.95)
	Yes	1350 (13.37)		6	95 (0.94)
History of ADRs	No	10024 (99.30)		7	30 (0.30)
	Yes	70 (0.69)		8	16 (0.16)
Family history of ADRs	No	9612 (95.22)		9	6 (0.06)
	Yes	6 (0.06)	Number of labors	0	5748 (56.94)
	Not clear	476 (4.72)		1	3654 (36.20)
				2	599 (5.93)
				3	71 (0.70)
				4	21 (0.21)
				6	1 (0.01)

Table 3 Physical characteristics of subjects

Statistics	Physical characteristics						
	Height (cm)	Weight (kg)	Temperature (℃)	Respiration (n/min)	Pulse (n/min)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
$n_{Observe}$ ($n_{missing}$)	10 075 (19)	10 026 (68)	10 093 (1)	10 094 (0)	10 094 (0)	10 094 (0)	10 094 (0)
$\bar{x}$	160.63	68.26	36.62	19.63	85.63	116.24	73.91
SD	4.88	10.93	0.31	1.25	9.93	12.73	9.51
M	160.00	68.00	36.60	20.00	84.00	116.00	72.00
Min	140.00	40.00	35.30	14.00	57.00	80.00	47.00
Max	180.00	108.00	39.30	28.00	130.00	183.00	126.00

Table 4 Medication characteristics

Medication Characteristics		*n* (%)
First-time User	No	511 (5.06)
	Yes	9583 (94.94)
Indications	Delivery	9012 (89.52)
	Vaginal delivery	4440 (44.10)
	Caesarean delivery	4572 (45.42)
	Abortion	872 (8.93)
	Artificial abortion	688 (6.83)
	Drug abortion	157 (1.56)
	Irregular menstruation	11 (0.11)
	Hysteromyomectomy	46 (0.46)
	Vaginal bleeding	40 (0.40)
	Hysteroscopic surgery	37 (0.37)
	Labor induction	28 (0.28)
	Curettage	15 (0.15)
	Vaginal douche	9 (0.09)
	Exploratory surgery	3 (0.03)
	Excision of cervical polyps	2 (0.02)
	Others[a]	15 (0.15)
	Unknown	4 (0.04)
Medication site (initial)	Uterus wall	1888 (18.70)
	Uterus body	47 (0.47)
	Buttock	8146 (80.70)
	Unknown	13 (0.13)
Medication Dose (initial)	1 mL	638 (6.32)
	2 mL	9456 (93.68)
Concomitant Medication	No	1754 (17.38)
	Yes	8340 (82.62)
	Western Medicine	35 (0.35)
	Western and Chinese medicine	8305 (82.28)

Notes: [a]Others included the applying diseases which had only one case or the application was beyound the scope of instructions.

patients (117 cases), 8 of which were considered as ADRs and the remaining 79 were unlikely ADRs. 10 out of the 79 ADEs were considered for reevaluation after additional information was obtained.

Final evaluation: Based on supplementary information, the final judgment of principal investigators indicated that 8 of 87 patients (11 cases of 117ADEs) were considered as ADRs (Table 6). The ADRs incidence rate of MI was 0.79‰ (8/10,094).

Manifestations of ADEs and ADRs

ADEs/ADRs of MI involved several systems, such as skin and its appendages, systemic abnormalities, heart rate and rhythm, and gastrointestinal system. The manifestations of ADRs mainly included skin pruritus or rash; chills, fever, eyelid edema; heart rate disorder; nausea and abdominal pain or distension (Table 7).

Characteristics of patients with ADRs

Among the 8 patients with ADRs, whose nationalities were all Han, all were hospitalized patients and 2 patients had past histories of other diseases (one patient had received laparoscopic stripping for right ovarian chocolate cyst; one patient had experienced artificial abortion), but no history of ADRs was recorded. One patient used MI for treating hysteromyoma, and the other 7 for delivery (3 vaginal deliveries and 4 cesarean deliveries). All of the 8 patients were first-time user of MI. Concomitant medications were used in all of the 8 patients, mainly oxytocin and antibiotics.

Onset time and duration of ADRs

Six patients experienced ADRs within 24 h of MI administration; one patient suffered an ADR on the 4th day and the other patient on the 5th d.

The duration of all ADRs was less than 24 h (range, 6 min to 24 h).

Severity and outcome of ADRs

All of the ADRs were mild in severity. There were no serious adverse reactions or death. For the management of ADRs, two patients stopped using MI and received symptomatic treatment, while the others continued to use the original MI dose. All ADRs were completely resolved. And there were no sequelae or deaths. These ADRs did not affect the treatment of original diseases.

DISCUSSION

Favorable safety

Based on a large sample size of 10 094 patients, our findings confirmed the favorable safety of MI. The ADR incidence rate of MI is 0.79‰. As described by the Council for International Organizations of Medical Sciences (CIOMS), the frequency of ADRs is classified as 'very common (≥ 10.0%)', 'common (1.0-10.0%)', 'not common (0.1-1.0%)', 'rare (0.01-0.1%)', and 'very rare (< 0.01%)'. According to the criteria, the ADR incidence rate of MI is rare. TCMI has been widely used in our daily clinical practice because it not only has the advantages of TCM, but also has a rapid onset of action as western medicine. However, in real

Table 5 The general information and number of ADEs reported by 42 monitoring hospitals

Monitoring Hospital	Region	Patient *n* (%)	ADEs *n* (‰)
Beijing Obstetrics and Gynecology Hospital, Capital Medical University	Beijing	292 (2.90)	5 (5.75)
Mentougou Maternal and Child Health Care Hospital	Beijing	200 (1.98)	0 (0.00)
Gansu Provincial Hospital	Gansu	268 (2.66)	4 (4.60)
Yue Bei People's Hospital	Guangdong	200 (1.98)	1 (1.15)
The People's Hospital of Guangxi Zhuang Autonomous Region	Guangxi	300 (2.97)	0 (0.00)
The First Affiliated Hospital of Guangxi University of Chinese Medicine	Guangxi	400 (3.96)	3 (3.44)
Maternal and Child Health Hospital of Liuzhou	Guangxi	300 (2.97)	1 (1.15)
Fourth Hospital of Hebei Medical University	Hebei	100 (0.99)	1 (1.15)
Maternal and Child Health Hospital of Qinhuangdao City	Hebei	203 (2.01)	1 (1.15)
Tang Shan City Maternal and Child Health Hospital of Tangshan	Hebei	200 (1.98)	0 (0.00)
Maternal and Child Health Hospital of Henan Province	Henan	193 (1.91)	2 (2.30)
Nanyang the First People's Hospital	Henan	350 (3.47)	0 (0.00)
Maternal and Child Health Hospital of Pingdingshan City	Henan	241 (2.39)	0 (0.00)
The Fourth Hospital of Harbin Medical University	Heilongjiang	249 (2.47)	0 (0.00)
Shiyan Maternal and Child Health Hospital	Hubei	200 (1.98)	0 (0.00)
Maternal and Child Health Hospital of Xiangyang	Hubei	200 (1.98)	0 (0.00)
The Second Hospital of Jilin University	Jilin	210 (2.08)	0 (0.00)
Changchun Obstetrics-Gynecology Hospital	Jilin	341 (3.38)	0 (0.00)
The First People's Hospital Of Lianyungang	Jiangsu	302 (2.99)	2 (2.30)
Lianyungang Maternal and Child Health Hospital	Jiangsu	302 (2.99)	7 (8.05)
Ganzhou People's Hospital	Jiangxi	203 (2.01)	3 (3.44)
The Second Affiliated Hospital of Nan Chang University	Jiangxi	199 (1.97)	0 (0.00)
Nanchang People's Hospital	Jiangxi	212 (2.10)	3 (3.44)
Ningxia People's Hospital	Ningxia	203 (2.01)	7 (8.05)
Qinghai University Affiliated Hospital	Qinghai	147 (1.46)	7 (8.05)
Qilu Hospital of Shandong University	Shandong	288 (2.85)	8 (9.19)
Yantaishan Hospital	Shandong	205 (2.03)	1 (1.15)
Maternal and Child Health Hospital of Taiyuan	Shanxi	293 (2.90)	0 (0.00)
Shanghai First Maternity and Infant Hospital	Shanghai	201 (1.99)	0 (0.00)
Shanghai Jiading Maternal and Child Health Hospital	Shanghai	200 (1.98)	2 (2.30)
Shanghai Changning Central Hospital	Shanghai	221 (2.19)	0 (0.00)
Chenghua People's Hospital	Sichuan	226 (2.24)	5 (5.75)
People's Hospital of Deyang City	Sichuan	186 (1.84)	2 (2.30)
West China Second University Hospital	Sichuan	294 (2.92)	9 (10.34)
Chengdu Jinniu District Traditional Chinese Medicine Hospital	Sichuan	193 (1.91)	2 (2.30)
East Ward of Sichuan Provincial People 's Hospital	Sichuan	199 (1.97)	4 (4.60)
Maternal and Child Health Hospital of Xinjiang	Xinjiang	298 (2.95)	0 (0.00)
Dali Bai Autonomous Prefecture Maternal and Child Health Hospital	Yunnan	250 (2.48)	0 (0.00)
The People's Hospital of Xiangyun	Yunnan	350 (3.47)	1 (1.15)
Kunming City Maternal and Child Health Hospital	Yunnan	313 (3.10)	0 (0.00)
Qujing NO.1 Hospital	Yunnan	200 (1.98)	0 (0.00)
Women's Hospital School of Medicine Zhejiang University	Zhejiang	162 (1.61)	6 (6.90)
Total		10 094 (100.00)	87 (100.00)

world applications, adverse reactions may occur. The common adverse reactions of TCMIs include allergic reactions, respiratory disorders, digestive disorders, cardiovascular disorders, nervous system disorders, urinary disorders, hematological disorders, motor system disorders and local abnormalities.[19] Some of them are serious or even life-threatening. As a result, more and more attention has been paid to the safety of TCMIs and several large-scale studies have been conducted, such as the safety studies on Shenmai injection, Shenqi-

Table 6 Results of causality judgment for ADEs

Grade	Results	Number of ADEs [*n* (%)]		
		Primary evaluation	Secondary evaluation	Final evaluation
Ⅰ	Certain	0 (0.00)	0 (0.00)	0 (0.00)
Ⅱ	Probable	1 (1.11)	0 (0.00)	2 (1.71)
Ⅲ	Possible	15 (16.67)	8 (9.20)	9 (7.69)
Ⅳ	Unlikely	70 (77.78)	79 (90.80)[a]	99 (84.62)
Ⅴ	Conditional	3 (3.33)	0 (0.00)	2 (1.71)
Ⅵ	Unassessable	1 (1.11)	0 (0.00)	5 (4.27)
Total		90 (100.00)	87 (100.00)	117 (100.00)

Notes: [a]10 out of the 79 ADEs were considered for reevaluation after additional information was obtained. ADEs: adverse drug events.

Table 7 Manifestations of ADEs and ADRs

Systems/Organs		Number of ADEs [*n* (%)]	Number of ADRs [*n* (%)]
Skin and its appendages	Pruritus, rash	12 (10.26)	2 (18.18)
	Nonspecific tenderness or incision pain	6 (5.13)	
Central and peripheral nervous systems	Headache or dizziness	3 (2.56)	
Visual function	Blurred vision with tears	1 (0.85)	
Gastrointestinal system	Diarrhea	5 (4.27)	
	Nausea	5 (4.27)	1 (9.09)
	Vomiting	2 (1.71)	
	Poor appetite	1 (0.85)	
	Abdominal pain or distension	10 (8.55)	2 (18.18)
Cardiovascular System	Blood elevating	1 (0.85)	
Heart rate and rhythm	Palpitation and increased heart rate	2 (1.71)	1 (9.09)
Respiratory system	Chest tightness	3 (2.56)	
	Cough and expectoration	9 (7.69)	
	Nasal congestion	1 (0.85)	
Blood system	Bleeding or coagulation abnormalities	3 (2.56)	
Female reproductive system	Contraction pain	8 (6.84)	
Systemic abnormalities	Fever	20 (17.09)	2 (18.18)
	Eyelid edema	2 (1.71)	1 (9.09)
	Chills	4 (3.42)	2 (18.18)
	Infection	2 (1.71)	
Immune system	Lymph node swelling and pain	3 (2.56)	
	Blood routine test abnormalities	5 (4.27)	
	Urine routine test abnormalities	5 (4.27)	
	Liver function test abnormalities	2 (1.71)	
Others	Sleep quality decreased	2 (1.71)	
Total		117[a] (100.00)	11[a] (100.00)

Notes: [a]The number of ADEs/ADRs was larger than the number of patients because more than one ADE/ADR might occur in one patient. ADES: adverse drug events; ADRs: adverse drug reactions.

fuzheng Injection and Danhong injection.[18,20-21] Our study showed that although some adverse reactions occurred in association with the use of MI, all of these ADRs were mild in severity and resolved after drug withdrawal or symptomatic treatment. Compared with other TCMIs, MI has a relatively favorable safety profile.

Risk management

The present study provides information about the safety of MI for obstetric and gynecological doctors in their clinical practice; meanwhile, our findings add to the growing body of evidence on the safety of TCMIs.

The ADRs of MI mainly manifest as skin and its appendage abnormalities, systemic abnormalities and gastrointestinal disorders, suggesting that more attention should be paid to these systems in order to prevent or cope with ADRs in a timely manner.

All of the 8 patients with ADRs in this study used other concomitant medications, mainly oxytocin and cephalosporin antibiotics. It is reported that the ADRs of oxytocin include systemic abnormalities and respirato-

ry disorders, such as anaphylactic shock, chest tightness, dyspnea and chills.[22] And the ADRs of cephalosporins mainly include rash, fever, asthma and diarrhea.[23] Therefore, we may need to keep an eye on the concomitant drugs to prevent potential drug-drug interactions.

In addition, since the action mechanism of TCMIs is based on TCM theories, we should follow the principle of "syndrome differentiation and treatment"; otherwise the risk of adverse reactions would increase.[24]

Differences from the previous studies

Prior to the previous studies, of which the incidence rate of ADRs/ADEs are greater or equal to 3%[24-26] and higher than this study. There are some reasons might explain the differences between the results of present and previous studies:

Both the objective and subjects are different from the previous studies. This study aimed to observe the MI safety, the previous studies aimed to observe the MI clinical effect. The mentioned references focus on pregnant women or Lying-in women while this study devote to the patients who had the indications of MI not only include pregnant women or Lying-in women. The pregnant women or Lying-in women are prone to display adverse drug reactions due to their physical conditions.

Besides, the sample size of this study is 10 094, which is significantly larger than the previous studies. This might have some impacts on the statistical results.

Limitations

Because of the short observation period and limited amount of funding, it is difficult to capture all adverse reactions in real word applications, especially when the adverse reactions are rare. Hence, other assessment methods such as spontaneous reporting should be considered, which may help to detect rare adverse reactions. Based on our findings, further studies should be conducted to identify the specific risk factors for the occurrence of ADRs and offer more valuable insights for clinicians.

In conclusion, in this study no sequelae or serious reactions were observed. MI has a favorable safety profile in real world clinical practice, which deserves an even wider clinical application.

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