



REVIEW ARTICLE

Adverse drug reactions of Shenmai injection: a systematic review

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Abstract**Objective** To analyze adverse drug reactions (ADRs) associated with Shenmai injection and possible contributing factors.**Methods** We searched all clinical studies and ADR reports of Shenmai injection from the China National Knowledge Infrastructure (CNKI) database, the Data Bank of Chinese Scientific Journals (VIP), and Chinese Biomedical (CBM) database. We collected relevant information such as gender, age, allergic history, and diseases treated in ADR cases; types, occurrence times, and severity of ADRs; and menstruum and compatibility of Shenmai injection.**Results** Of the 1828 clinical studies of Shenmai injection, 146 (7.99%) mentioned 576 ADR cases; 181 ADR reports mentioned 246 ADR cases. The most commonly affected age group was 40 to 69 (57.32%). In 36 (14.63%) cases, patients were described as having an allergic history. The diseases treated in ADR cases were principally heart failure and coronary artery heart disease. Thirty-eight (15.45%) of the 246 ADR cases in ADR reports described anaphylactic shock, while the most common ADR reported in clinical studies was headache/dizziness. Of the 822 total reported ADR cases, 99 (12.04%) were class III, and 637 (77.50%) were class IV, and there were no fatalities. The menstruum of most Shenmai injections was 5% glucose. Incompatible drugs were given in 68 ADR cases. In ADR cases, the most common dosage of Shenmai injection was 40 to 60 ml; 215 (80.90%) ADR cases occurred in first time medication, mainly in the first 30 minutes after injection.**Conclusions** Current evidence shows that Shenmai injection had lower ADR occurrence, but some potential factors such as irrational compatibility, dosages may lead to a high risk of ADR. In future, clinicians should follow indications or functions to promote rational use of Chinese Medicine Injections.

The Shenmai injection, derived from shendong drink described in the *Zheng Yin Mai Zhi* (1) of Qin Changyu in the Ming dynasty, is extracted from ginseng and ophiopogonis. According to traditional Chinese medicine theory, this injection benefits qi, prevents exhaustion, nourishes yin, and replenishes bodily fluids. It is used for clinical treatment of qi-yin deficiency in heart failure, coronary heart disease, chronic pulmonary heart disease, viral myocarditis, cerebral infarction, and malignant diseases (2). Shenmai injection has been on the market since 1995. Because of its effectiveness, the scope of diseases treated with Shenmai injection

has gradually broadened; meanwhile, reports of associated adverse reactions have increased. The number of published literatures ranked Shenmai injection ninth in Adverse Drug Reactions and Adverse Events of 33 Varieties of Traditional Chinese Medicine Injections, on the 2004 edition of National Essential Drugs List (2004 edition) of China (3). To fully understand the manifestations and factors associated with these adverse drug reactions (ADRs), we analyzed reported ADRs since 1995. We hope that our findings can provide guidance for clinicians, and thus help to avoid Shenmai-associated ADRs in the future.

Materials and methods

Study selection

We developed a search strategy using terms including Shenmai, adverse reaction, side reaction, and side effect. We searched the following electronic databases between January 1995 and May 2010: the China National Knowledge Infrastructure (CNKI) database, the Data Bank of Chinese Scientific Journals (VIP), and Chinese Biomedical (CBM) database.

Inclusion and exclusion criteria

Articles in Chinese and English, which reported the ADRs of Shenmai injection were included, and classified into two groups: ADR reports and clinical studies. Clinical studies included randomized controlled trials (RCTs), controlled clinical trials (CCTs), and case reports.

Nonclinical studies, reviews, secondary studies, abstracts, and summaries of ADRs were excluded.

Data extraction

We drew up a standard data extraction form in Microsoft Office Access and extracted the following information: disease treated; syndrome; Shenmai injection dosage, menstruum and coadministered drugs of the Shenmai injection; age, gender, and allergic history of ADR patients; and the types, occurrence times, and severity of the ADRs.

Results

Study selection

A total of 6629 studies were found in our search. We excluded 1441 irrelevant studies, 408 animal experiments, 2306 duplicate articles, and 465 secondary studies, and included the other 2009 articles in our analysis. The 2009 articles included 181 ADR reports and 1828 clinical trials (1105 RCTs, 417 CCTs, and 306 case reports).

ADRs of Shenmai injection in included studies

Number of ADR cases

The 181 ADR reports included 246 ADR cases. Of the 1828 clinical studies, 1090 (59.6%) did not mention ADRs, and most of the others stated that there were no ADRs. A total of 163 (22.1%) mentioned ADRs, but 17 of them did not provide concrete figures; the other 146 clinical studies described a total of 576 ADR cases. A total of 822 ADR

Table 1 Shenmai injection-associated ADR reporting in clinical studies

ADR	No. of studies	No. of patients
Not mentioned	1,090	47,542
Mentioned	738	33,381
ADRs absent	575	25,500
ADRs present	163	7,881
Total	1,828	80,923

cases were mentioned in ADR reports and clinical studies (Table 1).

Gender and age distribution of ADR cases

Clinical studies lacked information on the gender and age distribution of affected patients, so only ADR reports were included in our analysis of these factors. Of the 246 ADR cases, 105 were male and 141 were female, for a male to female ratio of 1:1.34. The youngest case was 12 years old, and the oldest was 77 years old. The most commonly affected age group was 40 to 69 (57.32%). Patient ages were not reported for 38 ADR cases (Table 2).

Patient allergic history

Clinical studies lacked information on the allergic history of affected patients, so only ADR reports were included in our analysis of this factor. Of the 246 ADR cases reported in ADR reports, 36 (14.63%) had an allergic history, and 17 (6.91%) had no allergic history. Most ADR reports did not specify whether there was an allergic history.

Disease treated

In both ADR reports and clinical studies, the most frequently treated diseases for ADR patients were heart failure and coronary heart disease (Table 3).

Table 2 The gender and age distribution of ADR cases in ADR reports

Age (years)	Male	Female	Total	Constituent ratio (%)
<30	5	9	14	5.69
30 to 39	12	18	30	12.19
40 to 49	24	34	58	23.58
50 to 59	15	20	35	14.23
60 to 69	21	27	48	19.51
≥70	10	13	23	9.35
Unclear	18	20	38	15.45
Total	105	141	246	100.00

Table 3 ADR occurrence by disease treated with Shenmai injection

Disease treated	ADR reports		Clinical studies	
	No. of ADR cases	Constituent ratio (%)	No. of ADR cases	Constituent ratio (%)
Circulatory diseases	150	60.98	402	69.79
Coronary heart disease	42	17.07	130	22.56
Heart failure	47	19.11	176	30.56
Pneumocardial disease	27	10.98	36	6.25
Others (including arrhythmia, myocardial ischemia, and viral myocarditis)	34	13.82	60	10.42
Nervous system diseases	26	10.57	53	9.20
Cerebrovascular diseases (including cerebral hemorrhage, ischemic stroke, cerebral thrombosis, etc.)	10	4.07	48	8.33
Vertigo	7	2.84	5	0.87
Headache	9	3.66	0	0
Kidney diseases (including kidney failure, nephrotic syndrome, nephritis, etc.)	12	4.88	5	0.87
Respiratory system diseases (including respiratory tract infection, bronchial asthma, pneumonia, etc.)	12	4.88	10	1.74
Digestive system diseases (peptic ulcer, hepatitis, gastritis, indigestion, etc.)	15	6.09	4	0.69
Cancer (including lung cancer, gastric cancer, breast cancer, etc.)	20	8.13	38	6.60
Others (including cold, injury of waist, diabetes mellitus, hyperthyroidism, rash, anemia, and vasculitis of lower extremity)	11	4.47	64	11.11
Total	246	100.00	576	100.00

ADR types

In ADR reports, ADR cases mainly were systemic reactions (allergic shock), skin lesions (urticaria, pruritus), and local pain. In clinical studies, most ADR cases were nervous system symptoms (headache/dizziness), general reactions (dry mouth/fatigue), and systemic reactions (febrile) (Table 4).

ADR severity

ADR severity for each event as classified according to World Health Organization guidelines (4). Most of the 822 reported ADRs were mild (Table 5).

Other drugs given

In ADR reports, Shenmai injections were diluted with 5% glucose and 10% glucose. Other drugs (often compound Danshen injection) were administered along with Shenmai injection in 17 ADR cases. In clinical studies, Shenmai injections were diluted with 5% glucose. Other drugs were administered along with Shenmai injection in 51 ADR cases,

including Huangqi injection ($n = 13$), dopamine ($n = 10$), and potassium magnesium aspartate ($n = 10$) (Table 6).

The most common dosages of Shenmai injection in ADR reports and clinical studies were 40 to 60 ml (accounting for 32.11% and 55.73%, respectively), followed by 20 to 40 ml (accounting for 26.42% and 18.75%) (Table 7).

Occurrence time

Clinical studies lacked information on ADR occurrence time, so only ADR reports were included in our analysis. In 215 (80.90%) of the 246 ADR cases, ADR occurred the first time the medication was given, usually in the first 30 minutes of use. Seventeen ADR cases occurred two minutes to eight days after Shenmai injection treatment ended (Table 8).

Discussion

Our study included 181 ADR reports and 1828 clinical studies. 181 ADR reports included 246 ADR cases. Of the 1828 clinical studies, 146 described a total of 577 ADR cases. A total of 822 ADR cases were mentioned in ADR reports and

Table 4 ADR types in included studies

Reaction	ADR reports		Clinical studies	
	No. of ADR cases	Constituent ratio (%)	No. of ADR cases	Constituent ratio (%)
General	0	0	82	14.24
Systematic	52	21.14	78	13.54
Febrile	14	5.69	78	13.54
Allergic shock	38	15.45	0	0
Nervous system	11	4.47	100	17.36
Digestive system	15	6.10	38	6.60
Respiratory system	21	8.53	30	5.21
Circulatory system	18	7.32	58	10.07
Skin lesion	89	36.18		14.76
Urticaria	42	17.07	5	0.87
Pruritus	28	11.38	19	3.30
Rash	18	7.32	30	5.21
Facial blushing	0	0	31	5.38
Exfoliative dermatitis	1	0.41	0	0
Local pain	21	8.54	34	5.90
Multisystem (nervous, circulatory, and digestive systems)	0	0	53	9.20
Others	19	7.72	18	3.12
Total	246	100.00	576	100.00

clinical studies. We identified several potential contributing factors to ADRs:

Gender and age distribution, allergic history of ADR cases

In ADR reports, the most commonly affected age group was 40 to 69 (57.32%). Females were more commonly affected than males. Due to a decline in kidney function and body resistance, combination therapy, and other reasons, the elderly have a poor tolerance to drugs (5). It is important for doctors to take the special physiology of

older people into consideration and learn a medication's contraindications in order to prevent or reduce adverse reactions (6).

However, due to lack of ADR rate, we cannot know from this research whether people from 40 to 69 are really at greater risk for ADRs, or whether they were simply the most likely group to be treated with Shenmai injection, and thus had the most ADRs.

Of the 246 ADR cases, 36 (14.63%) had an allergic history, while allergic history was not mentioned for the other 193 (78.46%). Doctors should routinely ask about and record allergic history before prescribing medications, since allergic

Table 5 Classification of ADR severity for Shenmai injection

Classification of ADR severity		No. of ADR cases	Constituent ratio (%)
Class I	ADRs are deadly or life-threatening; patients need to be withdrawn from drugs and treated immediately; or ADRs last for more than 1 month.	38	4.62
Class II	Patients have pathologic and physiologic changes and must be withdrawn from drugs and treated; or ADRs last for more than 7 days.	48	5.84
Class III	Patients cannot endure the ADRs and must be given a lower dose or withdrawn from drugs; patients improve after symptomatic treatment.	99	12.04
Class IV	Patients can endure the ADRs, and no lowering of dose or drug withdrawal is necessary. Whether without treatment or through symptomatic treatment, patients improve.	637	77.50
Total	822	100.00	

Table 6 Menstruums and coadministered drugs of Shenmai injection

Menstruum	ADR reports			Clinical studies		
	No. of ADR cases	Constituent ratio (%)	Other drugs administered	No. of ADR cases	Constituent ratio (%)	Other drugs administered
0.9% NaCl	28	11.38	Ciwujia, Huangqi, dopamine, compound Danshen injection	76	13.19	No
5% glucose	98	39.84	Dobutamine, glonoin, Danshen, ligustrazine, Huangqi, Shengmai, compound Danshen injection	217	37.67	Potassium magnesium aspartate, magnesium sulfate injection, Huangqi injection, ligustrazine injection
10% glucose	56	22.76	Vitamin C, dopamine, narcon, glonoin	57	9.90	Dopamine, glonoin
50% glucose	23	9.35	None	5	0.87	No
5% glucose or 0.9% NaCl	-	-	-	152	26.39	Danshen injection, Shuxuetong injection
Unclear	41	16.67	Vitamin C, phentolamine	69	11.98	Huangqi injection, Danshen injection
Total	246	100.00		576	100.00	

reactions often cause ADRs. Doctors should also do a skin test before using Shenmai injection.

Diseases for treatment of Shenmai injection

In included studies, Shenmai injection was mainly used for diseases such as heart failure, coronary heart disease, pulmonary heart disease, and malignant tumor. But only 5.6% of included studies concretely described syndrome differentiation and treatment in traditional Chinese medicine terms. Its major functions are to benefit qi and consolidate doffing, nourish yin, and regenerate the body fluids. It is used for treatment of qi-yin deficiency of heart failure, coronary heart disease, chronic pulmonary heart disease, viral myocarditis, cerebral infarction and malignancy, shock, and other diseases. It should be used on the basis of its functions, and be

chosen according to the principle of syndrome differentiation and treatment in the theory of traditional Chinese medicine. We suggest avoiding abuse of Chinese medicine injection and promote rational use.

ADR type

The ADR types reported in ADR reports and clinical studies tended to be different. There is a small sample size and short period, serious ADRs fail to occur in clinical studies. So there is a further need to carry out ADR monitoring after the drugs come into the market (7). In addition, some doctors often ignored mild ADR in clinical application. Once severe ADR

Table 7 Dosage of Shenmai injection

Dosage (ml)	ADR reports		Clinical studies	
	No. of ADR cases	Constituent ratio (%)	No. of ADR cases	Constituent ratio (%)
<20	31	12.60	5	0.87
20 to 39.9	65	26.42	108	18.75
40 to 59.9	79	32.11	321	55.73
60 to 79.9	19	7.73	97	16.84
80 to 99.9	0	0	5	0.87
100	14	5.69	35	6.07
Unclear	38	15.45	5	0.87
Total	246	100.00	576	100.00

Table 8 ADR occurrence time after start of Shenmai injection

	No. of ADR cases	Constituent ratio (%)
First time injection	215	80.90
Less than 5 min after start of administration	18	7.32
5 to 15 min	88	35.77
16 to 30 min	45	18.30
31 min to 1 hour	15	6.10
1 to 3 hours	16	6.50
2 min to 3 hours after treatment ended	11	4.47
1 to 8 days after treatment ended	6	2.44
Not first time injection (exact time unknown)	16	6.50
Unknown	31	12.60
Total	246	100.00

occurred, ADR cases were reported, so there were possible publication bias.

Menstruums and coadministered drugs of Shenmai injection

In included studies, the most commonly used menstruum of Shenmai injection was 5% glucose. Huangqi, potassium magnesium aspartate solution, dopamine solution, and compound Danshen injection were the most common coadministered drugs with Shenmai injection.

pH changes and turbidity or sedimentation can appear when Shenmai injection is combined with other drugs. For example, Xu (8) reports that a white precipitate appears when Shenmai injection is combined with DianSha (pefloxacillin mesylate and glucose injection). Hao (9) found that when Shenmai injection was combined with vitamin C, ATP, and coenzyme A, there were no obvious changes in appearance and clarity, but there were some changes in pH. We suggest that manufacturers should do further research on the compatibility of Shenmai injection with other substances to give evidence support for good clinical practice.

Occurrence time of ADR

Since most ADRs occurred in the first 30 minutes of the first Shenmai injection administration, we suggest that patients should be closely observed during this time period. Meanwhile, for patients who had continuous treatment with Shenmai injection, there is a need to be paid close attention.

Reporting of ADRs in available studies

Of the clinical studies on Shenmai injection, more than half did not mention whether ADRs occurred. Some of those, which mentioned ADRs did not describe the number of patients affected, while others lacked information such as the gender, age, allergic history, occurrence time, and ADR severity. Future ADR reports should follow the "Recommendations for reporting traditional Chinese medicine adverse drug reactions" (10) to provide more complete information; clinical research, especially RCTs, should follow the CONSORT guidelines for adverse reactions (11) to provide enough information on ADR, promote evidence-based use of Chinese medicine injections, and avoid risk.

Limitations

We only searched the national databases, so there was possible publication bias; especially, gray literature and data on ADR monitoring were not searched. Some studies failed to provide detailed information on ADR, which led to inadequate conclusion. Our study did not examine the total number of patients treated with certain conditions.

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