



Guidelines

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Expert consensus guidelines on clinical use of Xiyanping injection for acute infectious diseases

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ABSTRACT

Xiyanping injection, a traditional Chinese medicine injection made of andrographolide sulfonate, consisting of well-defined ingredients with antiviral, antibacterial, anti-inflammatory and antipyretic efficacy, has been widely used for treating infectious diseases of respiratory and digestive systems. However, its wide applications may easily lead to unreasonable clinical medication. In order to guide the precise clinical application and rational use of Xiyanping injection, experts in related fields conducted systematically literature review, evaluated and deliberated the application of Xiyanping injection in treating acute infectious diseases using evidence-based medicine method, and jointly drafted the consensus to summarize types of acute infectious diseases in children and adults that can be treated with Xiyanping injection, and recommend the intervention time, usage and dosage, course of treatment and combined medication of the injection. Besides, the consensus elucidates the safety, precautions and contraindications of the injection, so as to provide guidance for clinical use.

KEYWORDS: Xiyanping injection; Expert consensus; Acute infectious diseases; Evidence-based medicine

1. Introduction

Xiyanping injection is a traditional Chinese medicine injection made of andrographolide sulfonate, consisting of well-defined ingredients with the antiviral, antibacterial, anti-inflammatory and antipyretic efficacy. For over 40 years since Xiyanping injection was sold on the market, the injection has been widely used in the treatment of infectious diseases of respiratory and digestive systems. Research on Xiyanping injection has been rewarded and funded by

the “Twelfth Five-Year” state project for essential drug research and development, the project for applying advances of high and new technologies in production of National Development and Reform Commission, national major infectious disease prevention and control project, and other scientific research projects successively. The injection was listed as a category B drug in the *National drug catalog for basic medical insurance, work-related injury insurance, and maternity insurance*. In several guidelines or expert consensus, Xiyanping injection has been listed as a standard drug and because of its good clinical efficacy and pharmaco-economics benefit^[1–14], it is recommended by National Health Commission,

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National Administration of Traditional Chinese Medicine and different professional institutes for the treatment of more than 10 diseases, including influenza, pneumonia, acute fever and hand-foot-and-mouth disease.

Chinese patent medicines like Xiyanping injection are widely used for clinical treatment of acute infectious diseases. In the treatment of acute infectious diseases of respiratory system and digestive system, clinical or laboratory indications are necessary criteria for the use of antibacterial drugs for bacterial infection, so the choice of antiviral drugs for viral infections is very limited, leaving alone the delayed diagnosis since the viral or bacterial pathogens tests are time-consuming. Therefore, as a drug with antiviral, antibacterial, anti-inflammatory and antipyretic effects, Xiyanping injection can be used complementarily with other drugs or used as the first choice drug. On the other hand, irrational use of the injection is a problem[15–19].

More than 2 300 academic papers studying on the basis and clinical research of Xiyanping injection have been published in recent years (including 359 published in core journals). If these paper findings can be transferred into evidence for clinical use based on evidence-based medicine method, it will provide guidance for recommending indications and principles of using Xiyanping injection, its usage and dosage, as well as combined use of the injection.

Experts from College of Emergency of China Association of Chinese Medicine, Chinese College of Emergency Physicians of Chinese Medical Doctor Association, College of Emergency of World Federation Chinese Medicine Societies, College of Emergency of China Association of Promoting Traditional Medicine, and other associations have made systematically literature review, evaluated and discussed the application of Xiyanping injection for treating acute infectious diseases by evidence-based medicine method, and jointly drafted and formulated the expert consensus on clinical use of Xiyanping injection for treating acute infectious diseases (hereinafter referred to as “consensus”) for the reference of physicians and pharmacists in Emergency Department, Respiratory Department Digestive Department, TCM Internal Medicine Department and Pediatrics Department.

The consensus is formulated mainly based on evidence-based medicine research methods, through a systematical literature review and analysis of published papers on the Xiyanping injection which focused on summarizing experiences of clinical experts Data were mainly retrieved from: (1) Papers on Xiyanping injection indexed in Web of Science and PubMed from the earliest collection date till June 2019; (2) papers on Xiyanping injection included in Wanfang and CNKI databases from the earliest collection date until June 2019; (3) personal experience and opinions of experts.

The criteria for evaluating quality of the evidence based on the GRADE system were summarized in Table 1.

Table 1. Quality of evidence based on GRADE system.

Level of reliability	Criteria
Level A	Evidence from many randomized clinical studies or meta analyses
Level B	Evidence from single randomized study or non-randomized studies
Level C	Evidence from consensus of experts, case reports or documents of diagnosis and treatment

2. Basic information of Xiyanping injection

2.1. Active ingredients

The main components of Xiyanping injection is andrographolide sulfonate. Andrographolide, the effective component of the *Andrographis paniculata* leaves which is insoluble in water, is made into water solution without the help of excipients through the unique sulfonation process (China excellent patent award, patent No.: ZL01131382.X). Xiyanping injection is capable of improving the efficacy of andrographolide while reducing its adverse effects. The pH of Xiyanping injection is 4.5-6.5, and every 1 mL of Xiyanping injection contains at least 0.50 mg andrographolide sulfonate, which is sodium 17-hydro-9-dehydroandrographolide-19-sulfate ($C_{20}H_{29}O_5 \cdot SO_3Na$).

2.2. Pharmacokinetics

Studies on the pharmacokinetics and tissue distribution of active ingredients intravenously injected into the rat tail showed that the distribution of Xiyanping injection in the rat plasma accorded with two-compartment model features. The active ingredients spread rapidly in the plasma and tissues, and are mainly distributed in kidneys, intestinal tracts, liver, lungs, heart, etc., and the drug concentration in the kidney is the highest at the 5th minutes after administration[20,21].

2.3. Pharmacological effects

2.3.1. Antiviral

Xiyanping injection can inhibit influenza A/B virus, parainfluenza virus, respiratory syncytial virus, adenovirus, rhinovirus and Coxsackie virus, showing a dose-effect relationship[22,23]. Xiyanping injection prevents infection of influenza virus by inhibiting the absorption function of hemagglutinin, and reduces virus proliferation by regulating the cellular immune pathways AKT and NF- κ B. It controls the release of progeny virus by inhibiting the expression of Bax protein in the cells infected by adenovirus. The active component XYP-1 blocks the adsorption and proliferation of CVB3 virus, and the active component XYP-2 inhibits the proliferation of CVB-3 virus and directly kills it. Xiyanping injection can also protect a variety of tissues from injury caused by EV71 virus infection through inhibiting ERK and JNK phosphorylation, decreasing the expression of NF- κ B pathway inflammatory factors, and improving the activity of T cells to enhance the immunologic function of the body[24–28].

2.3.2. Antibacterial and anti-*Mycoplasma pneumoniae*

Xiyanping injection shows depressant effects on Gram-positive bacteria such as enteropathogenic *Escherichia coli*, *Bacillus typhii*,

Streptococcus pneumoniae, *Haemophilus influenza*, *Staphylococcus aureus*, *Hemolytic streptococcus*, and proteus and dysentery bacillus[29–31]. Combining with cefoxitin, Xiyanping injection has synergistic antibacterial effects and can damage the biofilm of methicillin-resistant *Staphylococcus aureus*[32].

The minimal inhibitory concentration of Xiyanping injection against *Mycoplasma pneumonia* can reach 0.52-1.05 µg/mL. When the injection is used together with erythromycin, the minimal inhibitory concentration decreased to 1/8-1/2 of dosage versus erythromycin used alone[33].

2.3.3. Anti-inflammatory and antipyretic

Xiyanping injection prevents the over activation of inflammatory cells, promotes the balance between inflammatory factors and anti-inflammatory media, significantly diminishes the inflammatory lesions, and protects the organs through the following mechanisms: inhibiting intracellular MAPK (p38) and STAT3 pathways, nuclear NF-κB (p65) pathway and the release of several inflammatory factors, and inducing mitochondrial autophagy to impede the synthesis of NLRP3 inflammasome. It exerts the antipyretic effects by decreasing the activation of endogenous pyrogenic cells, lessening the release amount of endogenous pyrogenic IL-1 and TNF-α, and reducing the production of centric fever positive regulatory medium PGE2 and 5-HT[34–39].

2.4. Cognition of traditional Chinese medicine

Xiyanping injection is extracted from *Andrographis paniculata*, a traditional Chinese medicine with bitter taste, and it is cold-natured and non-toxic, and its effective components are distributed in heart, lung, large intestine and bladder channels, as recorded in the ancient books and pharmacopoeia. It is also stated in books that *Andrographis paniculata* can clear away heat and detoxify, cool blood and reduce swelling. It is also capable of treating fever and colds, sore throat, sore tongue, cough, diarrhea, dysentery, hot leaching, swollen sore, snake bites, etc.

3. Suggestions on clinical application of Xiyanping injection in treating acute infectious diseases

3.1. Acute upper respiratory infection

Acute upper respiratory infection is a group of diseases including common cold, acute viral pharyngitis, herpangina and bacterial pharyngotonsillitis.

A meta-analysis of 15 randomized controlled trials (RCTs) included 2 457 children suggested that compared with ribavirin, Xiyanping injection showed higher total effective rate in the treatment of children with acute upper respiratory infection, and symptoms of

coughing and pharyngeal congestion vanished in a shorter time[40].

A meta-analysis of Xiyanping injection combined with ribavirin in the treatment of herpangina enrolled 2 796 children in 23 RCTs. The results suggested that the combined use of Xiyanping injection and ribavirin was significantly superior to the use of ribavirin alone or Xiyanping injection alone from aspects of total effective rate, and the recovery of normal body temperature as well as herpes, length of time to restore normal body temperature, length of time for herpes to disappear[41].

A study of 27 RCTs enrolled 3 485 children with acute tonsillitis suggested that compared with using other antibiotics (penicillin/clindamycin/azithromycin/non penicillin β-lactam antibiotics) alone, the combined use of Xiyanping injection and antibiotics could improve the total clinical effective rate, length of time to restore normal body temperature, length of time for the disappearance of fever, sore throat, purulent secretion and tonsil enlargement, as well as length of hospital stay. This may be related to the effectiveness of Xiyanping injection in inhibiting the expression of inflammatory factors IL-6, IL-8 and TNF-α. In addition, three clinical studies on adult patients with acute tonsillitis showed that compared with using antibiotics alone, the combined use of Xiyanping injection and antibiotics could improve the total effective rate, and the recovery of normal body temperatures, as well as sore throat[42–44].

Recommendation: For adults and children with acute upper respiratory infection accompanied by fever (body temperature ≥ 38 °C) or sore throat or severe coughing, Xiyanping injection can be used to improve clinical symptoms according to individual conditions (Level A).

3.2. Influenza

To evaluate the efficacy of Xiyanping injection combined with oseltamivir, a study of 5 RCTs included 316 cases with influenza showed that[45] compared with using oseltamivir alone, the combination of Xiyanping injection and oseltamivir showed higher total effective rate, shorter time to restore normal body temperatures, shorter hospital stay, and a lower incidence of adverse reactions. The results of another study included 9 RCTs which enrolled 997 patients with influenza showed that[46] Xiyanping injection showed shorter antipyretic time than using antiviral Western medicine (ribavirin/oseltamivir) alone, but the difference in the total effective rate and adverse reactions between the two groups was not statistically significant.

Recommendation: Identified patients with influenza are recommended to receive the combined use of Xiyanping injection and antiviral Western medicines like oseltamivir in order to shorten the fever time (Level A). In the case that oseltamivir and other antiviral Western medicines cannot be used, Xiyanping injection is recommended as alternative drug to reduce length of fever time (Level B).

3.3. Acute tracheo–bronchitis

Most acute tracheo-bronchitis is caused by respiratory virus infection, such as rhinovirus, coronavirus, influenza virus and respiratory syncytial virus. Only less than 10% cases are caused by bacteria, among which the most common pathogens are *Bordetella pertussis*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*[47–49]. Therefore, supportive treatment, not empirical antibiotic treatment, is recommended for acute tracheo-bronchitis[50–52]. The results of related studies suggested that the combination of Xiyanping injection and conventional supportive treatment could improve the total effective rate, relieve coughing, shorten the fever time, and accelerate the disappearance of lung and asthma symptoms[53].

Recommendation: For patients with acute tracheo-bronchitis, Xiyanping injection is recommended to be used as early as possible in order to relieve symptoms, shorten the fever time and accelerate the disappearance of lung symptoms (Level A).

3.4. Community acquired pneumonia (CAP)

3.4.1. Bacterial pneumonia

A study of 31 RCTs included 2 881 children with *Mycoplasma pneumoniae* showed that compared with using azithromycin alone, the combined use of Xiyanping injection and azithromycin showed better effects in total effective rate, faster recovery from fever, coughing, lung rales, chest film, and shorter hospital stay, etc.[54]. Another study of 18 RCTs showed the combined use of Xiyanping injection and antibiotics in the treatment of 1 924 adult patients with community-acquired pneumonia could improve the clinical treatment efficiency of CAP in adults, relieve coughing, and shorten the time of fever and hospitalization[55]. Additionally, a study including 18 RCTs showed that the combined use of Xiyanping injection and azithromycin in the treatment of 538 elderly patients with community acquired pneumonia could increase the total effective rate, shorten the fever time, relieve coughing, increase the bacterial clearance rate, and shorten the course of disease[56].

Recommendation: For adults and children with CAP caused by bacterial infection or *Mycoplasma pneumoniae* infection, Xiyanping injection and appropriate antibiotics are recommended to be used as soon as possible at the time choosing antibiotics reasonably, which can help regulate airway inflammation, improve clinical symptoms, and shorten fever time and the disease course (Level A).

3.4.2. Viral pneumonia

Viral pneumonia, commonly seen in children, is the inflammation of lung parenchyma caused by respiratory virus infection. A study of 10 RCTs enrolled 861 children with viral pneumonia showed that compared with ribavirin, Xiyanping injection could shorten the fever time, and accelerate the disappearance of asthma symptoms and lung rales[57]. Another study of 20 RCTs included 2 126 children with viral pneumonia showed that compared with ribavirin or other

Chinese patent medicines, Xiyanping injection has more advantages in terms of antipyretic time, disappearance of cough, asthma, lung rales the hospitalization time, etc.

A study of 5 RCTs enrolled 461 adults with viral pneumonia, 3 RCTs evaluated the clinical recovery rate indices, which indicated that Xiyanping injection could improve the recovery rate compared with ribavirin; 2 RCTs evaluated the time of fever, cough and lung rales to disappear, which indicated that Xiyanping injection could shorten the time for cough and lung rales when compared with ribavirin, but the difference in fever time between the two groups was not statistically significant[58].

Recommendation: For adults or children in the early or middle stage of viral pneumonia, Xiyanping injection is recommended to regulate the inflammation reaction, promote the inflammatory absorption in lungs, shorten the hospital stay, prevent disease progressing and decrease the complication rate (Level A).

3.5. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

Most acute exacerbation of chronic obstructive pulmonary disease (COPD) is caused by respiratory infection, and their treatment often includes antibacterial drugs. The results of a study included 1 500 patients in 19 RCTs showed that compared with conventional symptomatic treatment plus antibiotic treatment, conventional symptomatic treatment plus antibiotic plus Xiyanping injection could improve the total effective rate, reduce the leukocyte count and amount of C-reactive protein, shorten the time of cough, expectoration, dyspnea and other symptoms, improve the status of partial pressure of oxygen and carbon dioxide, and the percentage of FEV1 in predict value (%) [59,60].

Global Initiative for Chronic Obstructive Lung Disease (GOLD) report points out explicitly that virus is the main trigger of AECOPD[61]. AECOPD accompanied by virus infection may lead to more obvious airway inflammation and systemic inflammation[62]. The early application of Xiyanping injection which has a wide range of the antipyretic, antiviral and anti-inflammatory efficacy in the treatment of AECOPD may help to balance between pro-inflammatory and anti-inflammatory factors, and reduce the airway inflammation and systemic inflammation[63].

Recommendation: For patients with early to moderate AECOPD, at the time of initial targeted antimicrobial treatment, the combination of Xiyanping injection can reduce airway inflammation, improve clinical symptoms, such as cough, expectoration and antipyretic, and shorten the disease course and hospital stay length (Level C).

3.6. Hand–foot–and–mouth Disease (HFMD)

A study of 10 RCTs showed that the addition of Xiyanping injection on the basis of conventional treatment was superior to ribavirin plus conventional treatment in terms of length of recovering time

of overall clinical symptoms, antipyretic rash and oral herpes[64]. Another study of 8 RCTs enrolled 926 children with HFMD showed similar results[65].

Multiple clinical evidence showed that Xiyanning injection plus conventional treatment for patients at the stage of neurological involvement (severe cases) is significantly superior to conventional treatment in reducing incidence of severe complications, shortening the mean antipyretic clearance time, promoting recovery of skin and oral mucosa[66,67]. The results of another two RCTs on the application of interferon and Xiyanning injection in the treatment of severe HFMD complicated by viral encephalitis demonstrated that compared with ribavirin plus Xiyanning injection, the combination of interferon and Xiyanning injection could shorten the time of fever and rash, relieving headache and vomiting, abating the mental symptoms and recovering consciousness[68].

Recommendation 1: For children with HFMD characterized by fever and rash (including herpes), it is recommended to use Xiyanning injection or its combination with other drugs at the early stage (Level A).

Recommendation 2: While receiving symptomatic supportive treatment, children with severe HFMD complicated by viral encephalitis can be treated with Xiyanning injection and interferon, which can coordinate to exert the anti-inflammatory and antiviral effects, thereby reducing the incidence of severe complications of HFMD, relieving headache, vomiting and mental symptoms, and recovering the consciousness more quickly (Level B).

3.7. Acute infectious diarrhea

Diarrhea is one of the five leading causes of children deaths in the world[69–72]. Acute infectious diarrhea in children is often caused by virus infection, among which the most commonly detected ones are rotavirus and norovirus. Bacterial pathogens include *Escherichia coli*, *Campylobacter*, *Salmonella* and *Shigella*. A meta-analysis of 18 RCTs included 3 557 children with rotavirus enteritis showed that Xiyanning injection group showed a higher total effective rate, higher negative conversion rate of rotavirus, shorter antipyretic time and duration of diarrhea than the ribavirin group; 6 of 18 RCTs reported adverse events, and there were no significant difference in the incidence of adverse events between groups[73]. Another meta-analysis of 30 RCTs included 5 320 children with rotavirus enteritis showed that compared with ribavirin, Xiyanning injection could greatly shorten the time of diarrhea, fever and dehydration correction, and had a higher total effective rate for children with rotavirus enteritis, but the adverse events rates between Xiyanning injection and ribavirin were not significantly different[74]. To evaluate the efficacy and safety of Xiyanning injection combined with montmorillonite powder, a meta-analysis of 17 RCTs included 1 841 children with diarrhea, suggested that Xiyanning injection combined with montmorillonite powder had a higher total effective rate, and shorter time for diarrhea to relieve, body temperature to decrease,

and stool property to return to normal[75].

Most cases of adult acute diarrhea are caused by viruses infection, which has a short disease duration and can be cured by symptomatic treatment, so many patients do not seek medical help. For adults with severe diarrhea, the majority of cases are caused by bacterial etiology, which requires antibiotic treatment. The results of 3 RCTs on the application of Xiyanning injection combined with levofloxacin in the treatment of adult acute bacillary dysentery showed that compared with using levofloxacin alone, the combined drugs could improve the total effective rate, and shorten the time for fever and diarrhea to relieve and the blood cell counts to restore normal levels[76–78]. Another control study on the treatment of adult bacillary dysentery by Xiyanning injection-combined lomefloxacin aspartate showed that the effective rate of combined drugs group is higher than that of Lomefloxacin aspartate alone group, and the antipyretic, antidiarrheal time were also faster than that of the control group[79].

Recommendation 1: As most cases of children with acute infectious diarrhea are caused by virus infection, it is recommended to use Xiyanning injection at the early stage to help relieve fever and shorten the duration of diarrhea (Level A).

Recommendation 2: For adults with severe acute infectious diarrhea, Xiyanning injection combined therapy is recommended on the basis of empirical and specific antibiotic treatment to exert the synergistically anti-inflammatory and anti-pyretic effects (Level B).

4. Rational usage of Xiyanning injection

4.1. Route and Dose of Administration

Xiyanning injection is commonly given by intravenous drip, or intramuscular injection.

For adult patients: intravenous drip, once a day, daily dose: 500 mg or less, dripping speed: 30-60 drops/min (recommended by the consensus); intramuscular injection, 2-3 times a day, 50-100 mg once.

For children patients: intravenous drip, once a day, daily dose calculated by body weight (5-10 mg/kg or 0.2-0.4 mL/kg), adjusted within that range according to the disease progressing and severity, 250 mg a day or less, dripping speed: 30-40 drops/min; intramuscular injection, twice a day, daily dose: 200 mg or less.

4.2. Administration method

Intravenous drip: Xiyanning injection is recommended to be diluted with 0.9% sodium chloride injection or 5% glucose injection before intravenous drip. The stability experiments with 0.9% sodium chloride injection and 5% glucose injection showed that when the dosage ratio of Xiyanning injection and 5% glucose injection exceeds 750 mg: 250 mL, the insoluble particles increased

significantly, and 4 h after Xiyanping injection was mixed with 0.9% sodium chloride injection or 5% glucose injection, significant increase in the insoluble particles was observed. Therefore, the concentration of Xiyanping injection for intravenous drip is recommended to be 3 mg/mL, and Xiyanping injection in 0.9% sodium chloride injection or 5% glucose injection should be used up within 4 h[80].

Intramuscular injection: there is no need to dilute Xiyanping injection when injected by intramuscular; the injection is recommended to be given to children over 3 years old through gluteus maximus, gluteus medius, gluteus minimus, vastus lateralis or deltoid muscle; for 1-2years-old children, the medicine should not be injected through gluteus maximus, but gluteus medius or gluteus minimus.

4.3. Course of treatment

(1) For both children and adult patients, Xiyanping injection alone or Xiyanping injection-combined drugs should be used at the early stage of acute infection. The course of treatment, which is generally 3-7 days, depends on the disease severity and patients' response to the treatment.

(2) Xiyanping injection is not recommended for the infection at chronic phase or use for a long-term (≥ 28 days).

4.4. Combined administration

(1) The active component of Xiyanping injection is andrographolide sulfonate, which has the efficacy of reducing heat and detoxifying. It is not recommended to be used in combination with other traditional Chinese medicine injections of similar efficacy.

(2) Previous studies on drug compatibility showed that when Xiyanping injection and drugs including vitamin C injection, cefazolin sodium pentahydrate for injection, ambroxol for injection and dexamethasone sodium phosphate injection were mixed at a high concentration, The mixture is turbid or particles appear. Therefore, the dosage and the above mentioned drugs should be carefully decided. If combination medication is needed, it is recommended to flush the infusion tube with 5% glucose injection or 0.9% sodium chloride injection; when a new drug is applied, use a new infusion ware to avoid the occurrence of adverse reactions caused by drug interactions.

5. Safety of Xiyanping injection

5.1. Adverse reaction (ADR)

Adverse reaction incidence: According to literature review, spontaneously reported data (SRS), and large-scale prospective active monitoring data, although the incidence of ADR varies in

different data sources, the overall incidence of adverse reactions is between 0.075% and 2.110%[81]. According to the grading standard of ADR rate recommended by Council for International Organizations of Medical Sciences (CIOMS), Xiyanping injection seldom or rarely induce adverse reactions. However, a large-scale prospective active monitoring study showed that the ADR rate of children under 4 years old injected with Xiyanping injection was 0.073% (12/16 501). For children between 4 and 14 years old injected with Xiyanping injection the ADR rate was 0.079% (3/3 792). No significant differences in ADR rates were observed between these two age groups and that of the young and the middle-aged patients injected with Xiyanping injection, which was 0.066% (5/7 582)[82]. However, the ADR rate of the elderly and patients with hepatorenal insufficiency is not clear.

Adverse reactions of Xiyanping injection mainly occur on skin and its appendages (48.92%) or all over the body (17.97%)[83]. Symptoms such as skin rash, pruritus, shiver and antipyretic are common ADR and can be cured by drug withdrawal or symptomatic treatment. No significant differences in the type and severity of ADR were observed between children and adult patients.

5.2. Severe adverse reaction

Severe adverse reactions of Xiyanping injection account for about 3.72% of the total adverse reactions, and the main clinical manifestations are anaphylactic shock, shiver, expiratory dyspnea, etc[83]. Literature and research analysis showed that there was a higher risk for patients with a history of drug allergy to use Xiyanping injection. It is recommended to inquiry whether a patient had a history of drug allergy before using Xiyanping injection, close attention should be paid to observe and monitor the medication response in patients who are given the injection for the first time.

Severe anaphylactic reactions should be handled with reference to the Proposal of the Emergency Management Guideline (2014)[84] and Guideline for Emergency Management of Anaphylaxis[85] issued by European Academy of Allergy and Clinical Immunology (EAACI).

5.3. Precautions and contraindications

(1) If patients have allergic reactions or other serious adverse reactions after using Xiyanping injection, the treatment must be stopped immediately and proper therapy should be applied in time.

(2) Xiyanping injection and its mixture combined with other drugs should be checked carefully before use, after preparation and during the medication. If the drug solution changes such as turbidity, precipitation, discoloration, crystallization, etc., or there are air leakage and cracks on the bottle, the solution shall not be used. The diluted mixture should be used within 4 hours after its preparation.

(3) It is strictly prohibited to mix and match Xiyanping injection together with other drugs and use them with caution if combined medication is needed, flush the infusion tube with a 5% glucose

injection or a 0.9% sodium chloride injection; please use a new infusion set when a new drug is applied to avoid adverse reactions caused by drug interactions.

(4) It is recommended to inquiry whether a patient had a history of being allergic to Xiyanping injection or other drugs, and whether they had allergic constitution or a family allergic history. If the answer is yes, Xiyanping injection mustnot be used. In addition, for patients with liver and kidney dysfunction, the elderly aged 75 or above, breastfeeding women and children (1-2 years old), the injection should be used cautiously, and surveillance should be strengthened when the injection was given to a patient for the first time.

5.4. Population under special conditions

Pregnant woman: Since there is no study conducted on the application of Xiyanping injection in pregnant women, effects and adverse reactions remain unknown and the injection is not recommended for pregnant women.

Children: It is not recommended to use Xiyanping injection in Children. Ssince the safety of Xiyanping injection for children under 12 months has not been proven, it must not be used in this age group of children;. Xiyanping injection used in children between 1-2 years old should be monitored with caution.

The elderly: The elderly patients over 75 years old are advised to use Xiyanping injection with caution because this treatment often impairs kidney function.

Appendix: List of consensus members

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Cordinator: Yuntao Liu.

Conflict of interest statement

We declare that we have no conflict of interest.

Authors' contributions

The corresponding authors organized and drafted the consensus. Other members made comments and suggestions on the final version of this consensus.

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