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COMMENTARY

Overuse of intravenous infusions in China: focusing on management platform and cultural problems

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Abstract
This article reviews the current status of the overuse of intravenous (IV) infusions in China and implications to patient safety, and analyzes factors associated with the overuse. Although many factors contribute to the overuse of IV infusions in China, we focus on the construction of an IV infusion management system and tackling cultural problems as the first step to address issues of IV therapy in this commentary.

Keywords China · Cultural problems · Infusion management platform · Intravenous infusions · Overuse · Rational use

Over-utilization of intravenous infusions in China and its implications

In China, intravenous (IV) infusions commonly refer to both fluid and medicine-containing infusions such as antibiotics, Traditional Chinese Medicines (TCM), adjuvant medications, and parenteral nutrition. Studies have shown that there is an over- and irrational use of IV infusions in China [1]. An epidemiological survey of IV infusions in hospitalized patients at 156 public hospitals in 30 provinces and municipalities in China shows that 93.1% of patients in 2016 received IV infusions [2]. Among IV medications administered, there were high proportions of TCM injections and broad-spectrum antibiotics. TCM injections accounted to over 40% of IV infusions based on data from six community health centers in Guangdong province in 2015 [3]. Broad-spectrum antibiotics administered by IV infusions for upper respiratory infections in pediatrics were alarmingly high at the county, township and village-level healthcare facilities in rural China based on a 2014 study: 65% (1780/2736), 43% (257/593) and 33% (32/96), respectively [4]. Medications administered intravenously increases nursing workload. A 2014 survey of 287 nurses from 40 hospitals in Sichuan province shows that 78% of nurses spent more than 50% of their daily work administering IV infusions, and this resulted in cutting back their time on other patients' care activities [5].

Over-utilization of IV infusions exposes patients to unnecessary drug-related side effects and brings substantial financial burdens. According to the 2018 Annual Report of China's National Report on Adverse Reaction Monitoring, 14,290,000 adverse drug reactions (ADRs) were reported to China Food and Drug Administration (CFDA) in 2017 [6]. With regards to the administration route, IV administration accounted for 61.0% of the ADRs, exceeding the oral route of 32.0%. Factors contributing to ADRs from IV infusions in China include (1) drug and solution factors such as

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solution pH, osmotic pressure, concentration, and microparticulate contamination; (2) patient's vascular factors such as increased vascular fragility and vascular embolism; and (3) nursing administration techniques such as improper venous puncture, multiple punctures and rate of administration [3, 6].

Use of TCM is unique to the Chinese population, and TCMs accounted for 16.1% of the reported ADRs. With regards to the administration route, TCM IV administration accounted for 54.0% of the reported TCM ADRs, exceeding the oral TCMs of 39.4%. The use of injectable TCMs is the second most common drug-induced anaphylaxis trigger based on a 10-year retrospective analysis of the Beijing Pharmacovigilance Database [7, 8]. Therefore, IV infusions should generally be reserved for patients whose conditions cannot be effectively treated by medications taken orally or by intramuscular or subcutaneous injections.

Factors related to the irrational use of IV infusions

Multiple factors contribute to the irrational use of IV infusions: (1) physician's poor knowledge of IV therapy ("inappropriate prescribing") [9]; (2) lack of criteria on the use of TCM injections especially many TCMs are administered with questionable efficacy; (3) profit-driven behavior related to a higher reimbursements of IV infusions [10]; (4) patient demands of IV infusions based on false therapeutic perceptions of IV infusions ("cultural problems") [11]; and (5) lack of an integrative IV infusion management clinical decision support (CDS) system. Hospital Pharmacy and Therapeutics Committee with relevant sub-committees are vital organs to address all these contributing factors for the rational use of IV infusions.

In this commentary, we are focusing on the IV infusion management system and cultural problems as the first step to address issues with IV therapy.

Integrated "medicine–pharmacy–nursing" intravenous infusion management platform

A lack of common drug information standards and integration of pharmacy database, CDS, and bar code systems can have devastating effects on patient safety [12]. Infusion therapy is the responsibility of any clinician involved in the practice, physicians, pharmacists, and nurses. In Xiangya Hospital, Central South University, an academic tertiary teaching hospital in Chinese Hunan Province, an integrative "medicine–pharmacy–nursing" IV infusion platform was developed to address the rational and safe administration of IV infusions [1, 13]. Figure 1 depicts the components and functions of this Intravenous Prescription Early Warning and Assessment System (IPEWAS). This system integrates continuous but scattered IV infusion processes into one visible digital interface. Through real-time monitoring, the system provides support on all aspects of IV infusions. The massive data accumulated in IPEWAS also allows pharmacists to conduct medication use evaluation and clinical research to improve patients' care [1].

The key to IPEWAS was to establish and incorporate CDS into the system. The construction of the CDS was based on both references of the clinical use of IV medications and the analysis of the hospital IV medication administration data (period January 1, 2016 to December 31, 2016). Major references/guidelines we consulted were: (1) the UK National Institute of Health and Care (NICE) "Intravenous Fluid Therapy in Adults in Hospital" (CG174) [14]; and (2) medication handbooks or drug databases such as ASHP Handbook on Injectable Drugs, the Chinese Pharmacopoeia (Ch.P) and Micromedex®. The following eight categories of inappropriate IV prescriptions were identified through a retrospective analysis of 2016 prescription data in our hospital [1, 15, 16]: (1) contraindicated in patients with hepatic insufficiency (aspartate transaminase AST or alanine transaminase ALT 80–1000 units/L or total bilirubin TBIL 34.2–1000 μmol/L); (2) contraindicated in patients with renal insufficiency (creatinine clearance CrCl < 60 mL/min); (3) contraindicated in pediatrics; (4) overdosing; (5) improper diluent volume; (6) improper diluent choice; (7) improper administration routes; and (8) improper co-administration of drugs resulting in incompatibilities. These references and prescription data ensure the adaptation of international and national references to the local drug utilization pattern.

The CDS for TCM injections presents with unique challenges. TCM injections refer to injections containing extract of traditional Chinese herbs. As of December 31, 2017, 976 items of TCM injections with 134 generic names associated with 224 manufacturers were listed in the CFDA drug registry [17]. However, among the 134 TCM injections, only five meet the requirements to be documented in the present edition of the Ch.P (2015), and the other 129 TCM injections are documented in drug standards other than the Ch.P, i.e., various non-periodical publications issued by drug regulatory agencies. Among the 134 TCM injections, 62 (46.2%) are made from two or more traditional Chinese herbs, and the identity and proportion of the ingredients for many TCM injections remain unclear. A total of 92 (68.7%; 92/134) TCM injections are recommended for only one particular route of administration, and in this group, 30 are exclusively given by IV infusion. Main categories of TCM injections are antipyretic, promotion of blood circulation, anticancer, and pain-alleviating. These characteristics can challenge the safety and efficacy of TCM injections. In building the

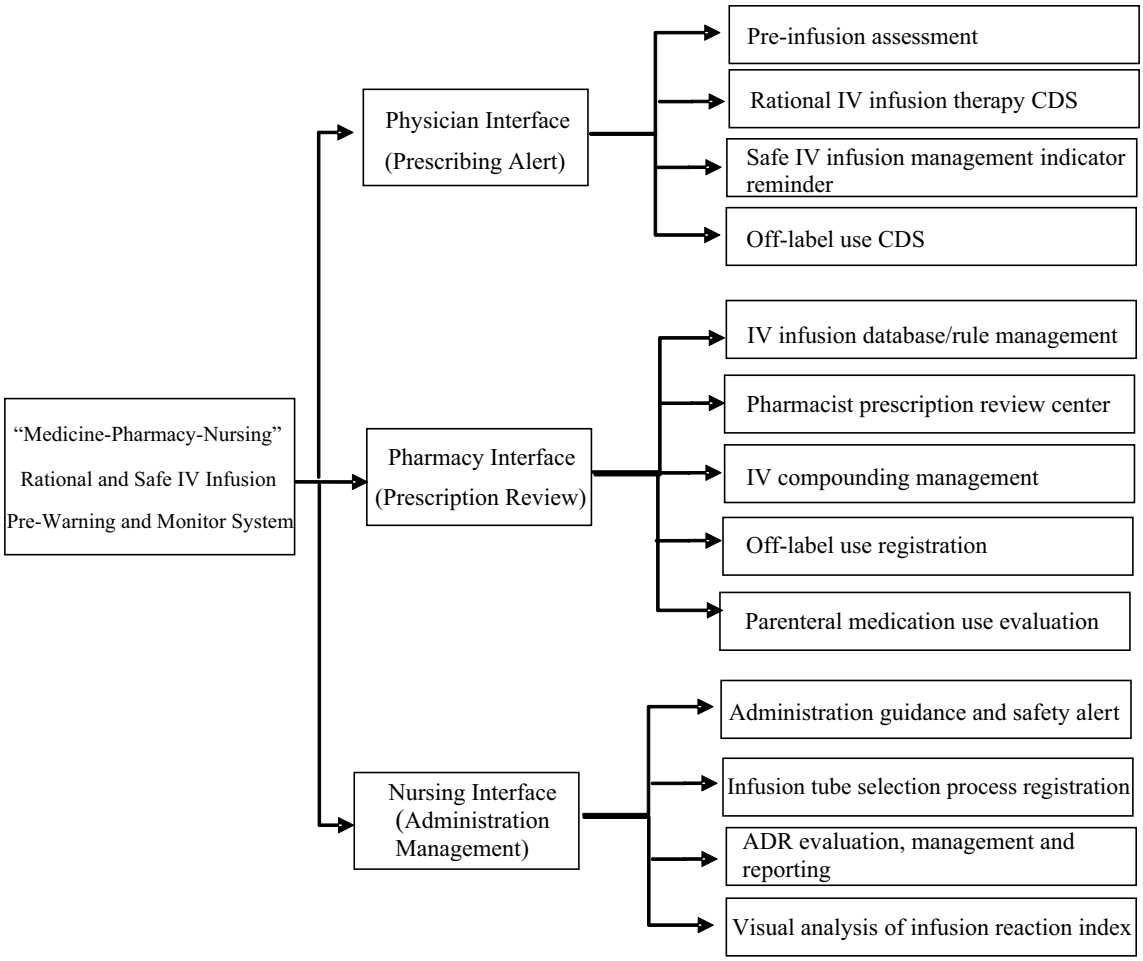

Fig. 1 Integrative parenteral prescription early warning and assessment system. *CDS* clinical decision support, *IV* intravenous

CDS for IPEWAS for TCM injections, we referred to the Ch.P, Basic Principles for Clinical Use for TCM Injections jointly issued by the China Ministry of Health, the CFDA and the State Administration of Traditional Chinese Medicine [18], and CFDA Annual Reports of China's National Adverse Reaction Monitoring and Adverse Drug Reaction Information Bulletins. However, more specific and detailed guidance is still needed on the appropriate clinical use of TCM injections.

The IPEWAS has separate interfaces for physicians, pharmacists and nurses, and a management interface serving as a central repository for IV infusion therapy. The IPEWAS medicine interface provides CDS to physicians to avoid inappropriate prescribing at computerized order entry through pre-built medication orders/order-sets, and medication alert messages (MAM) such as drug dosing, contraindications, and drug–drug interactions. The IPEWAS pharmacy interface provides CDS to pharmacists to conduct prospective medication order review. The IPEWAS flags potential inappropriate medication orders with MAM at the time of order verification and provides an interactive window to initiate discussions with physicians on specific orders. The pharmacy interface allows pharmacists to select appropriate diluent and diluent volume for an IV medication for compounding. The IPEWAS nursing interface guides nurses on the proper administration of IV medications. The interface provides instructions to nurses on the rate and route of administration, and whether special administration precautions are needed, such as light-protection and extravasation management. Take the issue of extravasation as an example. The rates of accidental extravasation have been estimated to occur in 0.01–7% of all patients receiving chemotherapy [19]. Extravasated drugs are classified in IPEWAS according to their potential for causing damage as 'vesicant,' 'irritant' and 'non-vesicant' [19]. In IPEWAS, the management of extravasation is built into all three interfaces of the platform. In medicine and pharmacy interfaces, IPEWAS provides alerts on drug potential to cause extravasations, and treatment options should extravasation occurs. In the nursing interface, it provides nurses with clinical signs and

symptoms of extravasation, proper nursing care measures, and ADR reporting. In all three interfaces, relevant IV infusion clinical policies/protocols are linked to specific medications for ease of access for all providers. The IPEWAS has a centralized interface for the hospital IV infusion management team. Here, monthly reports detailing IV medication utilization practices could be generated for all providers to provide feedback to improve prescribing, order verification, and medication administration.

The following principles of clinical use of TCM injections are incorporated into IPEWAS platform at appropriate interfaces given the unique characteristics of TCM injections: (1) carefully inquire about the patient's history of allergies and use with caution in patients with a history of allergies; (2) avoid use in frail elderly patients, pediatric patients and patients who have poor cardiopulmonary functions; (3) only compound in specified diluents with proper diluent volume; (4) avoid mixing with other medications, and separate administration times when given with other medications; (5) prescribe according to the recommended dosage to avoid overdosing; (6) start infusion at a lower rate and gradually increase infusion rate; and (7) carefully monitor patients for ADRs during the entire time of IV infusions [18].

The IPEWAS was first piloted hospital-wide on September 1, 2017. To assess the impact of IPEWAS on overuse and rational administration of IV medications, we first retrospectively analyzed IV infusions at our hospital to identify issues of IV infusions [1]. IV medication orders between the fourth quarter of 2016 (pre-IPEWAS) and the fourth quarter of 2017 (post-IPEWAS) were compared [15]. Compared to pre-IPEWAS, statistical significant differences were observed in the proportion of hospitalized patients who received IV medications, decreased from 88.13% (28,293/32,105) to 87.43% (29,318/33,532), and the proportion of inappropriate IV medication orders prescribed, decreased from 10.90% (88,437/811,563) to 7.23% (55,781/771,441). Statistical significant differences were also noted in the percentages of antibiotics and injectable TCMs administration: from 44.65 to 42.16% for antibiotics and from 18.20 to 12.86% for TCM injections [15]. The decreased use of IV infusions in all categories demonstrates the impact of the management platform in reducing the overuse.

Based on the success of the pilot implementation, IPEWAS has now been fully implemented at the hospital. The next step is to construct a provincial-level IPEWAS through collaborations with area hospitals based on the current hospital model. It is anticipated that information technology can play an essential role in reducing the over-utilization of IV medications.

Although an integrated "medicine–pharmacy–nursing" management platform may improve IV use in China, overcoming the large cultural problems of IV infusions requires our immediate actions as well. There is still a popular belief in China that IV infusions are more convenient and effective than oral medications [11]. A 2017 patient survey (N = 3792) on IV infusions in China reveals that only 1540 respondents (40.6%) knew about the pernicious consequences of IV infusions [16]. Therefore, patients often demand IV infusions seeking quicker recovery from sickness. Meanwhile, from the physicians' perspective, IV infusions are not only making their patients satisfied, but also producing more revenues for institutions due to a higher reimbursement for IV medications [3, 5]. Education to patients can promote public knowledge on the potential dangers of irrational use of IV infusions. This campaign, along with a reimbursement change for IV medications, may work together to improve the cultural problems of IV infusions in China.

In summary, the construction of an integrated 'medicine–pharmacy–nursing' IV infusion management system and overcoming cultural problems can be the first step to solve the overuse of IV infusions in China.

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