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IMPROVED EFFICIENCY AND REDUCED COSTS DURING INFUSION THERAPY WITH PREMIXED PREPARATIONS COMPARED TO FREEZE-DRYING POWDER

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ABSTRACT

Background: An excessive medical expenditure is becoming a main barrier to good health for several people in China. Hence, there is a need to control this rising medical cost to reduce the financial burden placed on family and society in general.

Objective: Our aim was to understand the expenses incurred during the use of two forms of infusion therapy- the premixed preparations and the freeze-drying powder forms and help select a safe and in-expensive route.

Methods: The study was based on a drug named Metronidazole which comes in both the forms mentioned above and which is being successfully used for years in Chinese hospitals. Various parameters were taken into consideration to determine the costs involved during the treatment such as the actual price of the drug, duration of the treatment, the preparation costs, labor charges, materials involved in the preparation, medical waste disposal, equipment and maintenance expenses, size of the hospital and the energy costs.

Results: Overall, our results revealed that premixed form of Metronidazole is not just a safe intravenous delivery system with negligible error rate but also the most inexpensive method of infusion therapy in small and medium hospital settings, reducing the cost of treatment to 68% over admixed preparation.

Conclusions: Given the considerable cost saving, it might be quite meaningful for the healthcare system to develop and apply premixed systems for intravenous medications, especially for small and medium hospitals.

INTRODUCTION: It is known that China has been suffering from continuous increase in medical cost and the limited medical resources can't meet the increasing public needs on the quality and quantity of medical service [1, 2], this makes pharmacoeconomics play an important role in optimizing the allocation of medical resources and controlling the rapidly growing medical cost. Currently, the conventional reconstituted admixture and the premixed preparation are both widely used as two major injection forms. The premixed system is considered to facilitate efficiency, accuracy and safety and immediate use in emergency situations which could eliminate the need for further manipulations and ensure sterility and potency with a closed system. Compared to those of premixed forms, many intravenous drugs in most Chinese hospitals are available in freeze-drying powder forms, which needs to be reconstituted and diluted for infusion. Actually, the two preparations mentioned above are quite different in many aspects during clinical application especially in the manipulation process, which might bring a significant difference in the overall cost during

the infusion treatment, not only for the patients but also for the hospital and the whole healthcare system as the medical-care payer [3].

Since, there have been no published studies in China to date to evaluate potential economic difference resulting from such two injection forms, this study was conducted in the real context of Chinese hospitals in order to determine the actual cost during infusion therapy with premixed preparations or freeze-drying powder (a form of reconstituted admixture), trying to give some evidence for more economic and rational drug use.

MATERIALS AND METHODS:

Sample collection: This study was performed in a real clinical setting of Peking University Third Hospital in Beijing, China. Defined as an essential drug for anti-anaerobic and anti-amoebic therapy by the World Health Organization (WHO) [4], metronidazole was selected as a sample drug in this study, which has two forms of premixed preparation and freeze-drying powder both used in this hospital: Metronidazole Disodium Phosphate Powder for injection ("A") and Premixed Metronidazole preparation ("B") (**Table 1**).

Both forms of the drug have a history of over 10 years for clinical use with a lot of practical experience. The hypothesis of this study was that, as the efficacy and safety were comparable, so the main objective was to measure potential cost difference associated with the use of each preparation. Therefore, cost-minimization analysis was mainly applied in this article and costs are presented as 2008 values.

TABLE 1: DETAIL OF TWO PREPARATIONS EVALUATED IN THIS STUDY

Manufacture code	Generic name	Dosage form	Specification	Package
A	Metronidazole Disodium Phosphate for Injection	Freeze-drying powder	0.915g per vial	Vial and carton
B	Metronidazole injection	Premix solution	0.5g:100ml	Non-PVC plastic bag

Cost Analysis:

Medication Costs: Medication costs of all drugs used for single intravenous dose given with A or B respectively were determined, including the cost of metronidazole itself and necessary solution for reconstitution. By using the Defined Daily Dose (DDD) recommended by WHO [5], medication cost for one day (cost per DDD) and a whole course were calculated with the data from drug instructions and 2005 Chinese Pharmacopoeia (Ch.P).

Preparation Costs: Pharmacy Intravenous Admixture Service (PIVAS) has played a major role in intravenous admixture preparation in hospitals as a modern aseptic compounding model well accepted by many countries over the world [6]. Based on all regular preparation procedures of a vial of form A in the PIVAS of Peking University Third Hospital, preparation costs were calculated, involving costs of direct labor, medical materials, energy consumption, fixed devices and equipment use and maintenance.

Medical Waste Disposal Costs: The medical waste weight for single intravenous dose given with A or B respectively was measured. The total costs of annual medical waste disposal by using different injection forms were calculated according to the total number of metronidazole injection consumed in 2007 of Peking University Third Hospital.

Cost Analysis from different perspectives: Cost summarization during infusion treatment was performed from different perspectives of the patients, the hospital administration and the social capital.

RESULTS:

Medication Costs: Containing 0.5g of metronidazole, each bag of form B costs 7.07Yuan, which could be infused directly without reconstitution making the total medication costs with form B for one intravenous dose is 7.07Yuan. Each vial of form A, containing 0.915g of freeze-drying powder equal to 0.5g of metronidazole, costs 14.78Yuan, which should be reconstituted in 100mL of 0.9% NaCl or 5% glucose injection before infusion according to the drug instruction approved by the State Food and Drug Administration (China).

As a result, medication costs of form A should cover the cost of necessary carrying solvent. The 0.9% NaCl injection of 100mL capacity in Non-PVC soft bag (Baxter Healthcare, Co., Ltd, Tianjin, China), the same

infusion package as form B, was selected as the solvent and each bag costs 7.38Yuan. Consequently, the total medication costs when using form A for single intravenous dose comes to 22.16 Yuan.

Metronidazole injection should be given 0.5g every eight hours generally for seven days on the basis of drug instructions and 2005 ChP, indicating that the DDD of metronidazole is 1.5g.

Accordingly, medication costs for treatment with A or B for each day (the cost per DDD) and a course of seven days were calculated (**Table 2**).

TABLE 2 MEDICATION COSTS FOR METRONIDAZOLE INFUSION THERAPY (MONETARY UNIT: YUAN)

	A	B
Single Dose	22.16	7.07
Cost per DDD	66.48	21.21
One course	465.36	148.47

Preparation Costs: Dependent on the whole preparation process of all regular procedures of a vial of form A in the PIVAS of Peking University Third Hospital, preparation costs were investigated as follows.

Direct Labor Cost: Average time spent on the preparation process of a vial including several procedures such as orders review, medication-preparation, aseptic compounding and product packing is about 5 minutes, indicative of a direct labor cost of about 1.98Yuan.

Medical Materials Cost: A sterile disposable syringe, a specialized packing bag with label, a pair of sterile disposable gloves and a respirator are included in major medical materials consumption. Besides that, sterilizers such as alcohol, gauze and cotton are also taken into consideration. The medical materials cost per vial comes to about 2.01Yuan.

Cost for Fixed Devices and Equipment use and Maintenance: Apportionment of expenses for the use repairing and maintenance of clothing, clean rooms and workstations and other related “hardware” were involved in this item, amounting to a total of 0.92Yuan per vial.

Energy Cost: Energy cost for, such as water and electricity consumption was also brought into preparation costs, totaling 0.67Yuan per vial. Consequently, all the items listed above should be contained in the total cost for preparing a vial of form A, which accounts to 5.58Yuan and 5 minutes while there was no such cost and time taken with form B since it can be infused directly without preparation process.

Medical Waste Disposal Costs: Besides the same infusion bag as form B, the waste produced from use of form A also included a glass vial, a small carton and related medical materials consumed during preparation as mentioned before, which will not be involved when using form B. That means the medical waste of form A outweigh that of form B by about 38g.

Cost analysis from different perspectives: For the patients, the medication cost is what actually matters to them, which should be partly or all undertaken by themselves. Treatment with metronidazole of form B allows 68% reduction of about 316Yuan for one course in medication cost compared to that of form A. For the hospital, it should bear the cost of preparation and medical waste disposal as most Chinese hospital PIVAS are not legally allowed to get charge for compounding service from patients or medical insurance at present [7].

Based on the total number of 53,688 metronidazole injection consumed in 2007 in our hospital and the average medical waste disposal cost of 3000Yuan per 1000kg in this area, the different annual costs with respective use of two forms of metronidazole injection that should be undertaken by a hospital like ours were extrapolated as below.

Besides that, the preparation time could be saved by 4474hours in the premixed group compared with the reconstituted group according to the hospital record in 2007.

For the healthcare system as a whole, which should pay for all costs actually produced from start to end during infusion treatment, costs of medications, preparation and medical waste disposal should all be taken into consideration, indicating a significant difference between the two forms (**Table 3**).

TABLE 3 COST COMPARISON BETWEEN A AND B FROM DIFFERENT PERSPECTIVES (MONEY UNIT: YUAN)

Different Costs	For the patients			For the Hospital			For the social capital Package		
	A	B	Δ^2	A	B	Δ^2	A	B	Δ^2
Medication	465.36[b]	148.89[b]	316.89[b]	-	-	-	1189726.08[c]	379574.16[c]	810151.92[c]
Preparation	-	-	-	299579.04[c]	0	299579.04[c]	299579.04[c]	0	299579.04[c]
Medical Waste Disposal	-	-	-	7892.14[c]	1771.71[c]	6120.43[c]	7892.14[c]	1771.71[c]	6120.43[c]
Total	465.36[b]	148.89[b]	316.89[b]	307471.18[c]	1771.71[c]	305699.47[c]	1497197.26[c]	381345.87[c]	1115851.39[c]

a Δ^2 = A-B. b- Cost for one course treatment according to DD of metronidazole injection. C- Based on the total number of 53688 metronidazole injection consumed in 2007 of our hospital

DISCUSSION:

Other factors involved in Cost Analysis: The premixed preparation and reconstituted admixture of metronidazole injection were selected to perform economic evaluation of a drug. However, the difference between such two forms of other drugs in those costs mentioned above, especially in medication costs mainly depending on specific drug prices, is probably not the same as that between the two of metronidazole.

Nevertheless, to do a whole economic analysis of the expenditure, costs of preparation and medical waste disposal, of less variability with drug category, might be placed more emphasis on for reference. It is reported that the error rate during intravenous admixture preparation has a range of 9%~13%, of which about 2%~5% would result in serious drug adverse events [8, 9].

Studies have indicated that the hospitalization gets prolonged for another 4.6 days on average with an extra cost of about 4700~8000 US dollars when an adverse event occurs [10, 11]. Often, many compounding operations are performed not in the PIVAS under strict quality control of both operators and environment but in the general preparation rooms present in various wards by nurses themselves without pharmacists' participation. This could lead to an increased error rate up to 21% with the dangers of wrong doses, incompatible drugs mixed and wrong drug or solution used [12-15].

On the contrary, premix products can be used directly without further preparation, which has prevents potential manual errors and consequent extra cost. It would be quite meaningful for reducing medical errors especially in many small hospitals that are unable to have their own PIVAS. It is reported that there is a gradual decline in pH value of the reconstituted metronidazole solution during storage from 8.74 to 8.06 within 24hours [16], showing an advisable delivery life-time of no more than 24hours. Considering frequent changes of clinical orders especially for some critically ill patients, there will be wastage of the drug, indicating unnecessary expense, as the unused portion of the prepared drug solution is often discarded.

On the other hand, premixed solution can be stored for up to 2 years as a final ready-to-use product, which provides more flexibility and adjustability for clinical use in complicated situations. Punctured wound is a kind of unexpected injury of the skin deep enough to cause bleeding. It is demonstrated that the injuries during preparation account for 14% of total punctured wounds while those from syringe management after use account for up to 63% [17]. The danger of punctured wounds always remains during the preparation of a drug which is another reason why the premixed system may be welcomed by medical staff for its potential for prevention occupational injures of handling and preparation.

Development of Intravenous Drug Delivery Systems: A pharmacy-based admixture system allows for maximum flexibility because any dose can be prepared based on patient need, which is thought to be a safe and effective model for preparation of intravenous doses especially applicable for hospitals. Besides, properly labeled products with patient-specific information and instructions on important items such as final volume of admixture, total sodium and potassium content, a pharmacist double check that is less likely to be bypassed resulting in an extra safety step is also built into this system. A full pharmacy-based intravenous admixture system may be more practical in large hospitals, which makes it very common.

However, nurses prepare intravenous medications in general preparation rooms in real clinical settings especially in smaller hospitals, indicating much higher error rates as mentioned above. In addition, the manufactured premixed product is considered to be one of the safest intravenous delivery systems as a ready-to-use dose with an error rate of less than 1% because of reliable quality assurance built into the preparation process [9, 18].

This system lends itself to more rapid availability of the drug without being calculated or manipulated further by pharmacists or nurses and may free the staff to devote more time to other clinical activities and patient-care. There used to be a concern for increasing acquisition costs while it was confirmed in this study, that this system enables the overall cost saving by simplifying preparation steps, eliminating admixing labor, assembly and supplies and reducing medical waste. This preparation lends itself for use especially in smaller hospitals without the human resources or facilities to make their own PIVAS, although disadvantages cited included space considerations for storage, availability of information about the products.

Considering that not all medications or doses are available with premixed system, especially when some drugs need to have strict individualization or required at short notice or are unstable in solutions. This suggests that the admixture preparation work should be shared between PIVAS and manufactures under specific clinical conditions.

Reducing Medical Errors: Even in USA, with highly developed health care system, there are at least 44,000 people and perhaps, as many as 98,000 people, who die in hospitals each year as a result of medical errors many of which could have been prevented. Extra expense caused by medical errors, including cost for related treatment and consequent economic losses, could reach 29 billion dollars each year [11].

As for China, about 73.35% of inpatients in Chinese hospitals undergo intravenous therapy [19]. The error rate of preparation and administration of intravenous medications are up to 13%~84% [20-22]. Actually, during intravenous transfusion what the patients most worry about being given wrong drugs and (or) wrong dose [23], which might be resulted from multi-step preparation and administration [8, 9]. It is demonstrated the simplification and standardization of preparation process helps to reduce the side effects of man-made factors and other procedures [24] which may have effect on the infusion quality, to ensure safe intravenous drug use.

Consequently, the premixed system with appropriate medications without further manipulation is considered as a safe and effective complementary model to PIVAS, which may be quite applicable and economic for small and medium hospitals.

CONCLUSION: The premixed forms of Metronidazole can significantly reduce the medical expenses by avoiding unnecessary manual errors, eliminating admixing labor, decreasing medical waste, preventing occupational injuries and even reducing additional equipment costs. Thus, a premixed form of Metronidazole like drug turns out to be the simplest, safest and the most economic method of infusion therapy.

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