



ORIGINALS

Bilingual edition english/spanish

Impact of the implementation of vasoactive drug protocols on costs in the treatment of critically ill patients

Impacto de la protocolización de mezclas intravenosas de fármacos vasoactivos en el coste del tratamiento del paciente crítico

Isabel Cuesta-López¹, Marina Sánchez-Cuervo¹, Ángel Candela-Toha², Juana Benedí-González³, Teresa Bermejo-Vicedo¹

¹Servicio de Farmacia, Hospital Universitario Ramón y Cajal, Madrid, Spain. ²Servicio de Anestesia y Reanimación, Hospital Universitario Ramón y Cajal, Madrid, Spain. ³Departamento de Farmacología, Facultad de Farmacia, Universidad Complutense de Madrid, Madrid, Spain.

Author of correspondence

Isabel Cuesta-López
Servicio de Farmacia,
Hospital Universitario Ramón y Cajal,
Carretera de Colmenar Viejo km 9,1,
28041 Madrid, España.

Correo electrónico:

mariaisabel.cuesta@salud.madrid.org

Recibido el 29 de junio de 2017;
aceptado el 20 de noviembre de 2017.

DOI: 10.7399/fh.10844

Abstract

Objective: To evaluate the efficiency of the protocolization and centralization of the preparation of intravenous vasoactive drug mixtures in the treatment of critically ill patients.

Method: A prospective interventional study (July 2012-December 2014) was conducted to measure the impact of different vasoactive drug protocols on costs in the treatment of critically ill patients. The economic impact was measured by comparing the direct costs (fixed and variable) of the preparation of intravenous vasoactive drug mixtures in the Pharmacy Department with their traditional preparation in hospital care units. The variables time and cost of preparation of an intravenous mixture were measured. Costs included pharmaceutical product, diluent, medical supplies, cost of manpower, and use of laminar flow cabinets in the Pharmacy Department. Costs were measured in Euros.

Results: A statistically significant difference was found between processing times in the Pharmacy Department and those in the hospital care unit (2.10 vs 2.86 minutes). Centralized preparation in the Pharmacy Department was more efficient. The average cost of preparation was €5.24±1.45 in the Pharmacy Department and €5.62±1.55 in the hospital care unit, although this difference did not reach statistical significance. If the analysis had included the cost of intravenous mixtures that had expired prior to their use, the centralized preparation of the mixtures in the Pharmacy Department would have entailed a higher cost (€2174/y).

Conclusions: The centralized preparation of intravenous mixtures in the Pharmacy Department entails significant time savings compared with their preparation in the hospital care unit.

Resumen

Objetivo: Evaluar la eficiencia de la protocolización y centralización de la elaboración de mezclas intravenosas de fármacos vasoactivos en el tratamiento del paciente crítico.

Método: Se realizó un estudio prospectivo, de intervención (julio 2012-diciembre 2014) para medir el impacto de la protocolización de mezclas intravenosas en el coste del tratamiento del paciente crítico. Para realizar el análisis económico se compararon los costes directos (fijos y variables) de la preparación de mezclas intravenosas de fármacos vasoactivos en el Servicio de Farmacia versus preparación en planta. Se midieron las variables tiempo y coste de elaboración de una mezcla intravenosa. Para la determinación del coste final de elaboración se incluyeron medicamento, diluyente, material fungible, personal y utilización de las cabinas de flujo laminar. Los costes se midieron en euros.

Resultados: La diferencia encontrada en los tiempos de elaboración entre el Servicio de Farmacia y la Unidad de Enfermería (2,10 versus 2,86 minutos) fue estadísticamente significativa y favorable a la elaboración centralizada en el Servicio de Farmacia. El coste medio de elaboración por mezcla fue 5,24 ± 1,45 euros en el Servicio de Farmacia y 5,62 ± 1,55 euros en planta, aunque la diferencia encontrada no alcanzó la significación estadística. Al incluir en el análisis el coste de las mezclas intravenosas caducadas antes de su utilización, la preparación centralizada en el Servicio de Farmacia supuso un coste superior (2.174 euros/año).

Conclusiones: La elaboración en el Servicio de Farmacia supone un ahorro significativo de tiempo en comparación con la preparación en planta. La diferencia de coste de esta alternativa, debida principalmente al impacto de las mezclas intravenosas caducadas, se eliminaría al optimizar la producción en la Unidad de Mezclas Intravenosas y al minimizar las pérdidas por caducidad.

KEY WORDS

Protocol; Drug compounding; Vasoactive drug; Critical care; Cost analysis.

PALABRAS CLAVE

Protocolo; Unidad de mezclas intravenosas; Fármacos vasoactivos; Cuidados intensivos; Análisis de costes.



Los artículos publicados en esta revista se distribuyen con la licencia
Articles published in this journal are licensed with a
Creative Commons Attribution 4.0
<https://creativecommons.org/licenses/by-nc-nd/4.0/>
La revista Farmacia no cobra tasas por el envío de trabajos,
ni tampoco por la publicación de sus artículos.

Introduction

High-risk medications (HRM) are medications that incur a high risk of causing severe or even fatal harm to patients when used incorrectly^{1,2}. The Institute for Safe Medication Practices (ISMP) published a list of drugs considered to be high risk in hospitals^{3,4}. This list includes intravenous vasoactive drugs (VAD), such as adrenergic agonists, dopaminergic agents, and organic nitrates. The inclusion of medications in this list does not mean that errors associated with these medications are more frequent, but that if they were to occur, the consequences could be more severe¹. For this reason, HRMs are a priority for professional bodies concerned with patient safety.

No single practice can guarantee complete safety when working with HRMs. Thus, in order to reduce preparation errors, we recommend the implementation of different specific practices, such as the use of detailed and explicit protocols, and the centralization of the preparation of intravenous mixtures of HRMs in the Pharmacy Department (PD)¹.

The concept of the Intravenous Mixtures Unit (IVMU) appeared in the 1960s as a way to guarantee the stability and compatibility of intravenous mixtures (IVM). However, the centralized preparation of IVMs other than parenteral nutrition and chemotherapeutic agents is common in the USA, but not in Europe. In Spain, the preparation of IVMs that require the handler to be protected is widely accepted. Compared to the rest of Europe, the situation is better in Spain^{5,6}, where 9.5% of PDs prepare most of the IVMs.

The preparation of IVMs in hospital care units involves a range of factors that can generate errors. In addition, the preparation of different concentrations increases the risk of error^{7,8,9}. For these reasons, an IVMU is a key asset in the prevention of medication errors^{10,11}. Furthermore, the centralization of the preparation of intravenous mixtures of HRMs enables their standardization¹, as corroborated by the *Guide to Good Practices for the Preparation of Drugs in Hospital Pharmacy Departments*¹².

Although there are still few studies on the costs of preparation of IVMs in the PD compared to their preparation in hospital care units, it has been suggested that the batch preparation of IVMs in an IVMU may be more cost effective than their preparation in hospital care units^{13,14,15}.

The centralization of the preparation of intravenous VADs in our hospital led to improved patient safety¹⁶. Based on this result, we conducted a time-cost analysis to assess the efficiency of the process.

The main objective of this study was to evaluate the efficiency of protocolization and centralization of the preparation of intravenous VADs in the treatment of critically ill patients. The specific aims were:

To analyse the preparation times of vasoactive IVMs with or without protocolization and centralization in the PD.

To assess the economic impact of the protocolization and centralization of the preparation of vasoactive IVMs on costs in the treatment of critically ill patients.

Methods

A prospective interventional study was conducted in a tertiary hospital (July 2012-December 2014) to measure the impact of the implementation of vasoactive IVM protocols on safety, efficacy, and costs in the treatment of critically ill patients¹⁶. Firstly, a working group was set up to select the drugs and preparations to undergo protocolization and standardization. Secondly, the group organized the centralization of the preparation of protocolized IVMs in the PD. The preparation of IVMs in the PD was sequentially implemented in the following Intensive Care Units (ICU): General Medicine (10 beds), General and Digestive Surgery (10 beds), Cardiovascular Surgery (10 beds), and Coronary Care Unit (13 beds).

From these ICU units, we selected patients ≥ 18 years receiving treatment with 1 or more of the protocolized vasoactive IVMs. Patients participating in clinical trials were excluded, as well as patients from the neurosurgical ICU, because of the lack of an electronic prescription system in that unit.

Results on safety and efficacy have already been published¹⁶. To perform the cost analysis, the following variables were measured:

1. *IVM preparation time*: time in minutes of the complete process of the preparation of an IVM in the hospitalization unit or in the PD. The complete process included: time of preparation of materials; and preparation of the IVM and labelling.

To determine the time of preparation of an IVM in the PD and in the hospital care unit, we recorded the time needed to complete all the tasks in the preparation process: verification of the IVM to be prepared; preparation of the materials; preparation of the IVM; disinfection of materials and work surface; and labelling. The pharmaceutical validation of prescriptions was assumed to be similar in both settings.

A. Pharmacy Department:

- Pharmaceutical time necessary to establish Standard Operating Procedures (SOP) relying on the data available in the Product Catalogue and Invoicing of the Spanish Society of Hospital Pharmacy (SEFH)¹⁷ for each new IVM, and time spent in training staff.
- Creation of worksheets and labels. Subsequent verification (pharmacist).
- Preparation of the medication and packaging materials (pharmacy assistant).
- Disinfection of materials and work surface, and preparation of the IVM (Bachelor of Science in Nursing [BSN]).
- Labelling (BSN).
- Final check of the prepared IVM using the worksheet (BSN).

B. Nursing control:

- Using of the nursing checklist to confirm the prescribed IVM and the guidelines to follow in its preparation (BSN).
- Preparation of the medication and packaging material (BSN).
- Disinfection of the work surface and preparation of the IVM (BSN).
- Preparation of the label and labelling of the IVM (BSN).

Some of the preliminary process times (clarification of questions, pharmacy refrigerator checks, calculations needed for scheduling, etc) were not taken into account, because some of these actions were not performed in the hospital care unit. Rest breaks and hospital porter times were also not included, because IVMs were distributed from the PD to the clinical units with other medications while refilling the Automated Dispensing Systems (ADS).

In the PD, the time needed to prepare the batches of IVMs was recorded over 8 working days (405 MIV in total). In the hospital care unit, 2 experienced nurses from 2 different ICUs prepared 3 different IVMs per day for 5 consecutive working days (30 MIV in total). Taking into account the daily batch preparation of the new IVMs in the PD, and individualized preparation per patient in the ICUs according to usual practice, we estimated that the samples would be adequate to perform the analysis⁶. Process times were recorded by the research pharmacist.

- II. *Preparation costs*: final price of an IVM in 2014 Euros (€). Costs included:

Cost of medication and diluent (Average Invoicing Price [AIP]): net cost, including 4% VAT and applicable discounts (€).

Staff costs: gross salary of healthcare staff (€).

Medical supplies costs: net cost, including VAT (10% or 21% according to the article) and applicable discounts (€).

Costs associated with the use of laminar flow cabinets (LFC).

To assess the impact of the protocolization on the cost of treatment, we compared direct costs (fixed and variable) of the preparation of vasoactive IVMs in the PD and in the hospital care unit. The cost of the facilities and the purchase cost of the cabinets were not taken into account because they were already amortized. The cost of maintaining the area was not included in the calculations. To establish the LFC operating, maintenance, and annual filter change costs, we calculated the percentage of the LFC operating time dedicated to the production of IVMs per week.

Net costs of drugs and diluents were obtained from the PD management software database. The cost of medical supplies was obtained from the Supply Service. Staff costs were obtained from the Official Bulletin of the Community of Madrid of January 31, 2014¹⁸, taking into account the total annual salary in the categories BSN and Medical Specialist. Table 1 shows gross staff salaries and net medical materials and supplies costs.

To determine the final cost of preparation of IVMs, we included medication, diluent, medical supplies, staff costs, and use of LFC.

We also calculated the cost of unused and expired IVMs in the PD or in the ADS of the hospital care unit. The cost of disposal of expired IVMs was not included.

Table 1. Unit Costs Used in the Analysis (2014 Euros)

Salary costs	BSN Time	13.35
	PS Time	22.99
Equipment costs (laminar flow cabinet)	Annual filter change	1150
	Annual review/certification	265
	Operation 1 kw/h	0.13
Costs of materials	Syringe 3 mL	0.07
	Syringe 5 mL	0.03
	Syringe 10 mL	0.05
	Syringe 20 mL	0.22
	Syringe 50 mL	0.19
	Needle 16 G	0.08
	Needle 21 G	0.28
	Coat	2.31
	Hat	0.02
	Mask	0.03
	Footwear	0.04
	Sterile surgical glove	0.29
	Vinyl glove	0.02
	Photo-protection bag	0.04

BSN, Bachelor of Science in Nursing; PS, Pharmaceutical Specialist.

Finally, we conducted a univariate deterministic sensitivity analysis to assess whether the results obtained in the baseline analysis were sensitive to changes in the main variables susceptible to uncertainty or with a certain margin of variability. Thus, the following scenarios were considered:

- Exclusion of the cost of expired IVMs. We also estimated to what degree preparation could be optimized to achieve a reduction in the total number of expired IVMs per year.
- Exclusion of the time-cost of the pharmacist required to create new SOPs.

To facilitate the analysis, a spreadsheet was designed using Excel 2007. All estimates were made for a 95% confidence interval (95%CI), and a P value of <.05 was used as a cutoff for statistical significance. Time and cost variables were expressed as mean and standard deviation. The symmetry of the variables was examined using graphic methods and the Shapiro-Wilk normality test. Means were compared using the Student *t* test for independent samples using the Stata software package version 12.0.

Results

IVM preparation time

In the IVMU, 18 batches were prepared (average 23 ± 12 units/batch) with a mean IVM preparation time of 2.10 ± 0.77 minutes (95%CI, 1.33 - 2.87).

In the hospital care units, the mean IVM preparation time was 2.86 ± 1.22 minutes (95%CI, 1.64 - 4.08).

The difference in preparation times (2.10 vs 2.86 minutes) was statistically significant ($P = 0.002$), showing that preparation in the IVMU was more efficient. Preparation time in the IVMU was 26.41% lower than preparation time in the hospital care unit.

In 2014, 8433 IVMs were prepared in the IVMU. The mean time gained by preparation in the IVMU was 0.76 min/IVM (1.26 h/100 IVM [95%CI 0.50 - 2.00] and 106.26 h/y [95%CI, 42.02 - 169.92]).

Preparation time was lower in the IVMU for all types of IVM, except for adrenaline; however, the only difference in preparation time that reached statistical significance was for noradrenaline ($p = 0.007$).

Cost of IVM preparation

Tables 2 and 3 show the cost of medicines, saline solutions, and medical supplies, and the cost of preparation in the hospital care unit and in the PD. The unit cost per IVM was lower in the IVMU for all IVMs.

IVM preparation required 58.82% of the operating time of an LFC working surface, entailing filter change costs (€676.47), annual maintenance costs (€155.88), and operating costs (€34.58). Taking into account the total number of IVMs prepared per year, the additional cost of using the LFC was €0.10 per IVM.

The establishment of protocols for each new IVM prepared in the PD needed 180 minutes of pharmaceutical time (5 new SOPs = 15 hours in total)¹⁷. Taking into account the total number of IVMs prepared per year, the additional cost in pharmacist time was €0.04 per IVM.

Table 4 shows the final cost of each type of IVM by hospital care unit and PD. The average cost per IVM was €5.24 \pm 1.45 in the PD and €5.62 \pm 1.55 in the hospital care unit, entailing a saving of 6.76% in the IVMU. The difference did not reach statistical significance ($P = 0.701$).

Given that 8,433 IVMs were prepared in 2014, the overall **cost of preparation** was €44,188.92 in the PD and €47,393.46 in the hospital care unit. However, the inclusion in the analysis of IVMs that reached their expiry date before use showed that centralized preparation in the PD was more expensive than preparation in the hospital care unit (€2174/y).

Sensitivity analysis

Scenario 1: *Exclusion of the cost of prepared IVMs that reached their expiration date before use.* In this scenario, the centralized preparation of IVMs in the IVMU entails a potential saving of €3165/y.

We also considered the optimization of IVM production, and assessed the impact of *halving the total number of expired IVMs.* In this case, the difference in costs, although lower, would still be favourable to centralized production with savings of €449/y.

Scenario 2: *Exclusion of pharmacy time needed to design the new SOPs.* The average cost of preparation per IVM would be €5.20 \pm 1.44 in the PD and €5.62 \pm 1.55 in the hospital care unit. However, the overall cost difference would not be favourable to centralized preparation in the PD (€1921 more per year).

Combining the 2 scenarios showed that centralized preparation would entail a potential saving of €3511 per year, although this result did not reach statistical significance.

Table 2. Processing Costs in the Hospital Care Unit (2014 Euros)

IVM adrenaline	IVM dobutamine	IVM dopamine	IVM nitroglycerin	IVM noradrenaline					
Medication	0.44	Medication	3.74	Medication	0.37	Medication	0.69	Medication	8.00
GS 100 mL	0.84	GS 250 mL	1.03	GS 100 mL	0.84	GS 250 mL	1.03	GS 250 mL	1.03
Syringe 3 mL	0.07	Syringe 20 mL	0.22	Syringe 5 mL	0.03	Syringe 10 mL	0.05	Syringe 50 mL	0.19
Needle 16 G	0.08	Needle 16 G	0.08	Needle 16 G	0.08	Needle 16 G	0.08	Needle 16 G	0.08
Needle 21 G	0.28	Needle 21 G	0.28	Needle 21 G	0.28	Needle 21 G	0.28	Needle 21 G	0.28
Vinyl glove	0.02	Vinyl glove	0.02	Vinyl glove	0.02	Vinyl glove	0.02	Vinyl glove	0.02
TOTAL IVM adrenaline	1.74	TOTAL IVM dobutamine	5.37	TOTAL IVM dopamine	1.62	TOTAL IVM nitroglycerin	2.15	TOTAL IVM noradrenaline	9.61

GS, 5% glucose solution; IVM, intravenous mixture.

Table 3. Processing Costs in the Pharmacy Service (2014 Euros)

IVM adrenaline		IVM dobutamine		IVM dopamine		IVM nitroglycerin		IVM noradrenaline	
Cost of materials per batch		Cost of materials per batch		Cost of materials per batch		Cost of materials per batch		Cost of materials per batch	
Coat	2.31	Coat	2.31	Coat	2.31	Coat	2.31	Coat	2.31
Hat	0.02	Hat	0.02	Hat	0.02	Hat	0.02	Hat	0.02
Mask	0.03	Mask	0.03	Mask	0.03	Mask	0.03	Mask	0.03
Footwear	0.04	Footwear	0.04	Footwear	0.04	Footwear	0.04	Footwear	0.04
Sterile surgical glove	0.29	Sterile surgical glove	0.29	Sterile surgical glove	0.29	Sterile surgical glove	0.29	Sterile surgical glove	0.29
Syringe 3 mL	0.07	Syringe 20 mL	0.22	Syringe 5 mL	0.03	Syringe 10 mL	0.05	Syringe 50 mL	0.19
Needle 16 G	0.08	Needle 16 G	0.08	Needle 16 G	0.08	Needle 16 G	0.08	Needle 16 G	0.08
Needle 21 G	0.28	Needle 21 G	0.28	Needle 21 G	0.28	Needle 21 G	0.28	Needle 21 G	0.28
Photo-protection bag	0.04	Photo-protection bag	0.04	Photo-protection bag	0.04	Photo-protection bag	0.04	Photo-protection bag	0.04
Total/batch	3.16	Total/batch	3.30	Total/batch	3.11	Total/batch	3.13	Total/batch	3.28
Total/unit	0.32	Total/unit	0.22	Total/unit	0.08	Total/unit	0.21	Total/unit	0.16
IVM Cost		IVM Cost		IVM Cost		IVM Cost		IVM Cost	
Drug	0.44	Drug	3.74	Drug	0.37	Drug	0.69	Drug	8.00
GS 100 mL	0.84	GS 250 mL	1.03	GS 100 mL	0.84	GS 250 mL	1.03	GS 250 mL	1.03
Material	0.32	Material	0.22	Material	0.08	Material	0.21	Material	0.16
TOTAL IVM adrenaline	1.60	TOTAL IVM dobutamine	4.99	TOTAL IVM dopamine	1.29	TOTAL IVM nitroglycerin	1.93	TOTAL IVM noradrenaline	9.19

GS, 5% glucose solution; IVM, intravenous mixture.

Discussion

The difference between preparation time in the PD and preparation time in the hospital care unit was favourable to centralization in the PD. However, in the hospital care unit, the preparation time of adrenaline was shorter, which could be because the new standard dilution (1.6 mg/100 mL) uses only part of the content of 1 ampoule rather than the full unit. The use of part units could increase preparation time in the IVMU, because only the use of whole units would make it possible to systematize the procedure.

The activities included in the measurement of IVM preparation times are not homogeneous in the literature, which makes it difficult to compare results. In this study, the preparation times in the PD and in the hospital care unit were slightly longer than those reported in other studies^{6,19}. However, the times were shorter than those reported in other studies that used a similar methodology^{3,14}, although these studies included preliminary activities not included in the present study (medical order transcription, label printing, double checking by the nursing staff). Nonetheless, our results are supported by the overall similarity between the methodology used in the present study and that used in these other studies (method used to measure time, similar preparation process in the PD and in the hospital care unit, the specific definition of all the activities included in the process).

It should be noted that in one of these studies¹⁹, a pharmacy technician prepared most of the medications prepared in the IVMU. However, in our IVMU, BSNs prepared the medications, which should be taken into account when comparing staff costs. Increasing the number of technical staff would reduce staff costs in the PD. Nevertheless, the main cause of the reduction in preparation times in the PD was centralized preparation, which permits batch production instead of individual dose production. Every 100 IVMs prepared in the IVMU saves nursing time, which could be used to greater effect in the hospitalization unit to improve patient care. Therefore, centralization is an opportunity to improve efficiency in the use of medication¹² and in the use of human resources, which in itself could be considered a means to contain costs².

Although the overall cost analysis showed that centralized preparation was not more economical than traditional preparation when the cost of expired IVMs was included in the analysis, we consider that the marginal increase in costs is acceptable given the marked improvements in safety, since there was a significant decrease in prescription errors (55.89%), validation

errors (68.05%), and administration record errors (78.75%)¹⁶. Some studies have found an association between reduced costs and avoided errors. In Spain, a study conducted in a tertiary hospital used the calculated cost of an adverse event in the United States, concluding that medication errors caused an average increase of 303 days in hospitalization time, with an annual increase in costs of approximately €76,000²⁰.

We believe that the result "not favourable" to centralization may be due to the low cost of the drugs studied. In fact, other studies conducted with antibiotics, antifungal agents, and drugs with greater economic impact have shown savings following centralization^{6,19,21,22}. Furthermore, the present study did not take into account savings in drug costs that would have been generated by the use of multidose vials⁶. It was not possible to assess this scenario using the specialty pharmaceuticals marketed for the active ingredients studied. If an increase in the number of IVMs prepared in our IVMU was under consideration, we would recommend the use of multidose vials. Savings in the IVMU could be increased by the use of large-volume saline solution for the reconstitution of lyophilized specialty pharmaceuticals. Furthermore, centralization would lead to cost savings in medical supplies. For example, the centralized preparation of a batch of medication uses 1 syringe and needle, whereas the preparation of each IVM in the hospital care unit uses 1 syringe and needle. This study found that the costs of medical supplies were 3.4 times higher in the hospital care unit, which result is in line with those of other studies^{3,14}.

Sensitivity analyses showed that centralization always entails a potential saving if the IVMU optimizes its production by adjusting stock according to need, thus reducing the number of IVMs that unnecessarily expire before use. This aspect particularly applies to the case of noradrenaline, which is the most expensive and less stable IVM⁶. This approach would also avoid stock shortages, which would lead to higher costs in the preparation of IVMs in hospital care units. This point should be confirmed by further studies. Likewise, the implementation of protocols would eliminate pharmacy time costs in the creation of new SOPs, and thus these costs would not affect the average cost of preparation per IVM in subsequent years.

Although the use of multivariate probabilistic sensitivity analysis is generally recommended for this type of study, some aspects, such as the effect of changing some assumptions, can only be assessed using deterministic

Table 4. Final Cost of Preparation in the Pharmacy Department vs the Hospital Care Unit (2014 Euros)

Processing cost by type of IVM			
	Hospital Care Unit	PD	Difference
IVM adrenaline			
Production cost I ^a	1.74	1.60	
LFC use	-	0.10	
BSN Time	0.42	0.71	
PS Time	-	0.04	
TOTAL IVM adrenaline	2.16	2.45	-0.29
IVM dobutamine			
Production cost I	5.37	4.99	
LFC use	-	0.10	
BSN Time	0.71	0.65	
PS Time	-	0.04	
TOTAL IVM dobutamine	6.08	5.78	0.30
IVM dopamine			
Production cost I	1.62	1.29	
LFC use	-	0.10	
BSN Time	0.46	0.38	
PS Time	-	0.04	
TOTAL IVM dopamine	2.08	1.81	0.27
IVM nitroglycerin			
Production cost I	2.15	1.93	
LFC use	-	0.10	
BSN Time	0.77	0.74	
PS Time	-	0.04	
TOTAL IVM nitroglycerin	2.93	2.81	0.11
IVM noradrenaline			
Production cost I	9.61	9.19	
LFC use	-	0.10	
BSN Time	0.81	0.41	
PS Time	-	0.04	
TOTAL IVM noradrenaline	10.42	9.75	0.67

^aProcessing cost I includes medication, saline solution, and materials. BSN, Bachelor of Science in Nursing; CFL, laminar flow cabinet; PS, Pharmaceutical Specialist.

Bibliography

- Instituto para el Uso Seguro de los Medicamentos (ISMP-España). En colaboración con Ministerio de Sanidad y Consumo y Universidad de Salamanca. Prácticas para mejorar la seguridad de los medicamentos de alto riesgo [Monografía en internet]. 2007 [Consultado 23/04/2014]. Disponible en: <http://www.ismp-espana.org/ficheros/Practicas%20para%20mejorar%20la%20seguridad%20de%20los%20medicamentos%20de%20alto%20riesgo.pdf>
- Cohen MR, Smetzer JL, Tuohy NR, Kilo CM. High-alert medications: safeguarding against errors. En: Cohen MR, editor. Medication Errors. 2nd ed. Washington (DC): American Pharmaceutical Association; 2007. p. 317-411.
- Institute for Safe Medication Practices. ISMP's list of high-alert medications [Monografía en internet]. Huntingdon Valley (PA): ISMP; 2012 [Consultado 20/03/2014]. Disponible en: <http://www.ismp.org/Tools/highalertmedications.pdf>
- Instituto para el Uso Seguro de los Medicamentos (ISMP-España). Lista de medicamentos de alto riesgo [Monografía en internet]. ISMP-España; 2012 [Consultado 23/04/2014]. Disponible en: <http://www.ismp-espana.org/ficheros/Medicamentos%20alto%20riesgo%202012.pdf>
- Tamés M, Echarri E. La Farmacia de Hospital en Europa [Monografía en internet]. 1ª ed. Madrid 2002 [Consultado 27/07/2017]. Disponible en: <https://www.sefh.es/bibliotecavirtual/Monografias/farmacia.pdf>
- Martínez-Tutor MJ. Evaluación económica de la centralización de mezclas intravenosas. Farm Hosp. 2006;30(6):351-8.
- Lesar TS. Tenfold medication dose prescribing errors. Ann Pharmacother. 2002; 36(12):1833-9.

sensitivity analysis. Despite its limitations, we consider that the univariate deterministic sensitivity analysis used in this study was adequate to meet its objectives^{23,24}.

Another limitation is that the measurement of preparation time was not blinded, which could have influenced the results. However, the Hawthorne effect (i.e., improvement in the activity of a worker when monitored), gradually disappears over time^{25,26}. Moreover, this effect would have equally affected measurements in both scenarios in the present study.

In conclusion, the analysis showed that there was a significant reduction in the preparation time of vasoactive IVMs used in the treatment of critically ill adult patients when they are prepared in the PD in comparison with their preparation in hospital care units. The difference in costs of preparation in the PD, mainly caused by expired IVMs, would be eliminated by optimizing production in the IVMU and minimizing losses due to expired IVMs.

Funding

No funding

Acknowledgments

To the multidisciplinary working group composed of: Alcaide López de Lerma JM (Supervisor de Unidad. Servicio de Anestesia y Reanimación. Hospital Universitario Ramón y Cajal. Madrid), Arias Rodríguez CM (Supervisor de Unidad. Servicio de Anestesia y Reanimación. Hospital Universitario Ramón y Cajal. Madrid), Camino López A (Servicio de Cardiología. Hospital Universitario Ramón y Cajal. Madrid), Joga Herranz JA (Supervisor de Farmacia. Hospital Universitario Ramón y Cajal. Madrid), Lieten Villajos A (Servicio de Medicina Intensiva. Hospital Universitario Ramón y Cajal. Madrid), López Fernández M (Supervisor de Unidad. Medicina Intensiva. Hospital Universitario Ramón y Cajal. Madrid), Martínez Castro N (Servicio de Anestesia y Reanimación. Hospital Universitario Ramón y Cajal. Madrid), Pestaña Lagunas D (Servicio de Anestesia y Reanimación. Hospital Universitario Ramón y Cajal. Madrid), Vázquez Martínez JL (Servicio de Pediatría. Hospital Universitario Ramón y Cajal. Madrid).

Conflict of interests

No conflict of interests.

Contribution to the scientific literature

This article presents an economic analysis of a previous study conducted in the setting of Hospital Pharmacy to assess the impact of the protocolization and centralization of the preparation of intravenous vasoactive drug mixtures in critical care patients. Specifically, we assessed the efficiency (time and cost) of the centralized preparation of different intravenous vasoactive drug mixtures (IVM) in the Intravenous Mixing Unit (IVMU) of the Pharmacy Department.

Given the importance of the centralized preparation of drugs, as corroborated by the *Guide to Good Practices for the Preparation of Drugs in Hospital Pharmacy Departments*, we consider the topic of this article to be of interest to our fellow professionals. It should also be taken into account that there has been an increase in the workload of IVMUs due to this task, and thus this study is also motivated by the need to support this activity by providing time-cost analyses.

8. Bates DW, Vanderveen T, Seger D, Yamaga C, Rothschild J. Variability in intravenous medication practices: implications for medication safety. *Jt Comm J Qual Patient Saf.* 2005;31(4):203-10.
9. Crimlisk JT, Johnstone DJ, Sanchez GM. Evidence-based practice, clinical simulations workshop, and intravenous medications: moving toward safer practice. *Med-surg Nurs.* 2009;18(3):153-60.
10. Fernández-Esteban I, Baldominos-Utrilla G, López-Muñoz MJ, Durán-García E, Santolaya-Perrín R, Sanjurjo-Sáez M. Selección de aditivos para la implantación de una Unidad de Mezclas Intravenosas. *Farm Hosp.* 1995;19(2):87-90.
11. Jiménez V, Ordovás JP. Unidad centralizada de terapia intravenosa y errores de medicación. En: Lacasa C, Cot R, Humet C, eds. *Errores de medicación. Prevención, diagnóstico y tratamiento.* Barcelona: EASO; 2001. p. 225-40.
12. Guía de buenas prácticas de preparación de medicamentos en servicios de Farmacia Hospitalaria. [Monografía en internet]. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2014 [Consultado 29/07/2017]. Disponible en: https://www.sefh.es/sefhpdfs/GuiaBPP_JUNIO_2014_VF.pdf
13. Plumridge RJ, Maher M. Justification of a pharmacy intravenous admixture service in an Australian hospital. *Am J Hosp Pharm.* 1993;50(3):463-6.
14. Armour DJ, Cairns ChJ, Costello I, Riley SJ, Davies G. The economics of a pharmacy-based central intravenous additive service for paediatric patients. *Pharmacoeconomics.* 1996;10(4):386-94.
15. Paoletti RD, Casey EV. Reducing costs through centralization and standardization of an i.v. admixture program. *Am J Health-Syst Pharm.* 2000;57(12):1147-9.
16. Cuesta López I, Sánchez Cuervo M, Candela Toha A, Benedí González J, Bermejo Vicedo T. Impact of the implementation of vasoactive drug protocols on safety and efficacy in the treatment of critically ill patients. *J Clin Pharm Ther.* 2016;41(6):703-10.
17. Grupo TECNO. Servicio de Farmacia Hospitalaria. Actualización del Catálogo de Productos y Facturación [Monografía en internet]. 2ªed. Madrid; 2009 [Consultado 10/09/2014]. Disponible en: http://www.sefh.es/bibliotecavirtual/urvs/ACSFH2009_2.pdf
18. Boletín Oficial de la Comunidad de Madrid (BOCM núm. 26, de 31 de enero de 2014). [Consultado 20/03/2014]. Disponible en: http://www.bocm.es/boletin/CM_Orden_BOCM/2014/01/31/BOCM-20140131-14,0.PDF
19. Zamora MA, Cabeza J, Moreno T, García MA. Rentabilidad de una unidad de mezclas intravenosas de nueva creación, aspectos prácticos y relación coste-beneficio. *Farm Hosp.* 2000; 24(1):38-42.
20. Pinilla J, Murillo C, Carrasco G, Humet C. Case-control analysis of the financial cost of medication errors in hospitalized patients. *Eur J Health Econ.* 2006;7(1):66-71.
21. van Zanten AR, Engelfriet PM, van Dillen K, van Veen M, Nuijten MJ, Polderman KH. Importance of nondrug costs of intravenous antibiotic therapy. *Crit Care.* 2003;7(6):R184-90.
22. Alonso F, Fernández GP, Garrido MA, Jiménez S, Gimeno MJ, Hierro C. Elaboración en farmacia de los medicamentos intravenosos. *Rev ROL Enf.* 2004;27(5):55-8.
23. Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. *Health Technol Assess.* 1999;3(2):1-134.
24. Rubio-Terrés C1, Cobo E, Sacristán JA, Prieto L, del Llano J, Badia X; Grupo ECO-MED. Analysis of uncertainty in the economic assessment of health interventions. *Med Clin.* 2004;122(17):668-74.
25. Kurtz SL. Measuring and accounting for the Hawthorne effect during a direct overt observational study of intensive care unit nurses. *Am J Infect Control.* 2017 (article in press).
26. Paradis E, Sutkin G. Beyond a good story: from Hawthorne Effect to reactivity in health professions education research. *Med Educ.* 2017;51(1):31-9.