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Trends of vasopressor use in intensive care units in Colombia

Tendencias de consumo de vasopresores en unidades de cuidados intensivos de Colombia

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What do we know about this issue?

· Circulatory shock is a pathological condition involving acute circulatory failure, characterized by hypotension leading to impaired tissue perfusion, which if not treated promptly, results in multisystem organ failure and potentially death.
· Vasopressors were introduced in the 40's and are one of the most widely used drugs in the ICU. Due to their vasoconstrictive effect, these agents are frequently used in critical care for cardiopulmonary resuscitation, postoperative heart surgery, and the management of hypotension associated with different types of shock, in order to improve the hemodynamic function and restore tissue perfusion, hence improving tissue oxygen delivery.

Which are the new contributions of this study?

· The study evidenced a growing trend in the use of norepinephrine between 2010 and 2017 in the ICUs of eleven hospitals in Colombia; norepinephrine became the most frequently used vasopressor during the study period, followed by adrenaline and dopamine.
· This fact is probably associated with the availability of more extensive scientific evidence supporting the early use of norepinephrine in the vasoplegic patient and its subsequent inclusion in the list of medications in the Benefits Plan of the Colombian Healthcare System.

How to cite this article

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Abstract

Introduction

Vasopressors are essential in the management of various types of shock.

Objective

To establish the trend of vasopressors use in the intensive care units (ICU) in a population of patients affiliated with the Colombian Health System, 2010-2017.

Methods

Observational trial using a population database of patients hospitalized in eleven ICUs in various cities in Colombia. The drugs dispensed to hospitalized patients over 18 years old, from January 2010 until December 2017 were considered. A review and analysis of the vasopressors dispensed per month was conducted, taking into account sociodemographic and pharmacological variables (vasopressor used and daily doses defined per 100/beds/day (DBD).

Results

81,348 dispensations of vasopressors, equivalent to 26,414 treatments in 19,186 patients receiving care in 11 hospitals from 7 cities were reviewed. The mean age of patients was 66.3±18.1 years and 52.6 % were males. Of the total number of treatments recorded, 17,658 (66.8 %) were with just one vasopressor. Norepinephrine was the most frequently prescribed drug (75.9 % of the prescriptions dispensed; 60.5 DBD), followed by adrenaline (26.6 %; 41.6 DBD), dopamine (19.4%), dobutamine (16.0 %), vasopressin (8.5 %) and phenylephrine (0.9 %). The use of norepinephrine increased from 2010 to 2017 (+6.19 DBD), whilst the use of other drugs decreased, particularly the use of adrenaline (-60.6 DBD) and dopamine (-10.8 DBD).

Conclusions

Norepinephrine is the most widely used vasopressor showing a growing trend in terms of its use during the study period, which is supported by evidence in favor of its effectiveness and safety in patients with shock.

Keywords

Vasopressors; Shock; Drug prescription; Norepinephrine; Intensive Care Units; Pharmacoepidemiology.

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Resumen

Introducción
Los fármacos vasopresores son fundamentales en el manejo de los diferentes tipos de choque.

Objetivo
Determinar la tendencia de utilización de fármacos vasopresores en unidades de cuidados intensivos (UCI) en una población de pacientes afiliados al Sistema de Salud de Colombia, 2010-2017.

Métodos
Estudio observacional, a partir de una base de datos poblacional con pacientes hospitalizados en once UCI de diferentes ciudades de Colombia. Se obtuvieron las dispensaciones de pacientes mayores de 18 años hospitalizados desde enero de 2010 hasta diciembre de 2017. Se hizo revisión y análisis de la dispensación mensual de vasopresores. Se consideraron variables sociodemográficas y farmacológicas (medicamento vasopresor usado y dosis diarias definidas por 100 camas/día [DCD]).

Resultados
Se revisaron 81.348 dispensaciones de vasopresores, equivalentes a 26.414 terapias en 19.186 pacientes atendidos en 11 hospitales de 7 ciudades, cuya edad promedio fue 66,3±18,1 años y el 52,6 % eran hombres. Del total de terapias registradas, 17.658 (66,8 %) fueron con un solo vasopresor. La norepinefrina fue el más comúnmente prescrito (75,9 % de las dispensaciones; 60,5 DCD), seguido por adrenalina (26,6 %; 41,6 DCD), dopamina (19,4 %), dobutamina (16,0 %), vasopresina (8,5 %) y fenilefrina (0,9 %). El uso de norepinefrina se incrementó de 2010 a 2017 (+6,19 DCD), mientras que el de otros fármacos disminuyó, especialmente adrenalina (-60,6 DCD) y dopamina (-10,8 DCD).

Conclusiones
La norepinefrina es el fármaco vasopresor más utilizado y el que ha demostrado una tendencia de uso incremental durante el periodo de estudio, lo cual está respaldado por evidencia a favor de su efectividad y seguridad en pacientes con choque.

Palabras clave
Vasopresores; Choque; Prescripciones de medicamentos; Norepinefrina; Unidades de cuidados intensivos; Farmacoepidemiología.

INTRODUCTION

Circulatory shock is a pathological condition involving acute circulatory failure, characterized by hypotension, leading to a decrease in tissue perfusion, which if not treated promptly results in multisystem organ failure and potentially death (1,2). Circulatory shock is one of the main causes for admission to the intensive care unit, representing around 33% of ICU patients (3). Among the different types of shock, the most common is distributive septic shock which accounts for 62 % of the ICU patients (4), with mortality rates ranging between 46 and 60 % (5,6). A study conducted in various ICUs in Colombia found that 12 % of the patients were diagnosed with sepsis, with a high overall mortality of 34 % (7).

The ICU stay costs in Colombia are around 400 USD per day (1 USD = 3.281 COP, based on the representative market exchange rate, December 2020. Banco de la República de Colombia), or higher, when considering the medications these patients require (8,9). Vasopressors, introduced in the 1940's are one of the most widely used drugs in the ICU (1). Due to their vasoconstrictive properties, they are often used in critical care for cardiopulmonary resuscitation, postoperative heart surgery care, and the management of hypotension associated with the different types of shock, in order to improve the hemodynamic function and restore tissue perfusion, and hence improving tissue oxygen delivery (1,10,11). The main drugs with vasopressor activity used in the ICU may be classified into two groups: the non-adrenergic agents (vasopressin) and the adrenergic agents (adrenaline, norepinephrine, dopamine, ephedrine, etilefrine and phenylephrine) (12,13).

The choice of a vasopressor and its dose depends on the shock etiology and the clinical context of each patient (1,10). While historically there has been a controversy with regards to the choice of the most appropriate vasopressor for managing septic shock (14), currently, the international guidelines of the Surviving Sepsis Campaign recommend norepinephrine as the first line drug, based on its effectiveness and lower incidence of adverse cardiovascular effects (2-4,11,14-16). Likewise, norepinephrine is used as the last resort for the management of neurogenic and hemorrhagic shock (17,18). With regards to cardiogenic shock, according to the most current European Guidelines, norepinephrine is considered the first choice, usually combined with an inotropic support therapy, and dobutamine is the most widely used drug for this purpose (19). Furthermore, adrenaline is considered the first choice in anaphylactic shock, due to its sympathomimetic and anti-inflammatory properties (20).

Considering that in our region few studies focus on this topic, and due to the significant importance of shock and vasopressor management, the purpose of the study was to establish the trends

in the use of vasopressors in the ICU, in a population of patients affiliated to the Colombian Healthcare System between 2010 and 2017.

PATIENTS AND METHODS

A descriptive, observational study was conducted on the trends in the use of vasopressors in eleven Colombian ICUs, based on the vasopressors dispensed by the logistics operator of medications at the hospital and outpatient level. The records and various variables are systematically stored in an electronic database. All of the medications dispensed in-hospital in the institutions studied, were administered by this sole operator. The data from patients over 18 years old, both males and females, affiliated with the Colombian Healthcare system who received any vasopressor during their ICU admission from January 2010 through December 2017 were included. Any incomplete records, as well as records associated directly with the ICU instead of a particular patient, were excluded. The study included the dispensing records of vasopressors effectively administered to patients.

Based on the information recorded on the use of medications, a data base was developed to analyze the following variables:

1. Sociodemographic characteristics: age, gender, ICU city. The ICUs included were mixed units with patients with different pathologies.

2. Pharmacological: the vasopressors available for dispensing in Colombia (adrenaline, norepinephrine, dopamine, ephedrine, etilefrine, phenylephrine and vasopressin). Additionally, the use of dobutamine was also analyzed, since it is frequently used in combined therapies with vasopressors (6). When a patient was admitted on several occasions and received vasopressors during the study period, each admission was considered a separate record. Moreover, the continued use for over 48 hours of the study medications was considered a new therapy.

The monthly dispensing with the respective doses to quantify use was analyzed, and the daily defined dose (DDD) was used as the technical unit to quantify use expressed as DDD/100 beds/day (DBD), in accordance with the recommendation of the World Health Organization (WHO), as the standard to conduct pharmaco-epidemiological studies. The DDD value is the average daily dose estimated for the primary indication of the drug, and the WHO Anatomical, Therapeutical, Chemical Classification System index - ATC/DDD - was obtained for each of the study drugs (21). The following formula was used to calculate the DBD (22):

$$DBD = \frac{\left(\begin{array}{c}\text{Daily amount of drug}\\ \text{administered in milligrams}\end{array}\right)}{\left(\begin{array}{c}\text{Number of}\\ \text{occupied beds}\end{array}\right) \times \left(\begin{array}{c}\text{Number}\\ \text{of days}\end{array}\right) \times \left(\begin{array}{c}\text{DDD of}\\ \text{the drug}\end{array}\right)} \times 100$$

Additionally, the vasopressor utilization index (VUI) was estimated as a specific measure used to describe the use of these medications, according to the following formula (1,23):

$$VUI = \frac{\left(\begin{array}{c}\text{total number of days in the}\\ \text{ICU with a vasopressor}\end{array}\right)}{\left(\begin{array}{c}\text{Total number of days in the}\\ \text{ICU with any vasopressor}\end{array}\right)}$$

The database was reviewed and validated by the Pharmacoepidemiology department of the logistics operator. The statistical package SPSS, version 24.0 (IBM, USA) for windows was used for the data analysis. Descriptive statistics was used to estimate averages, standard deviations, minimum and maximum values for continuous variables and percentages for categorical variables. The percentage annual change of variation for each DBD value was estimated, as well as the percentage global change comparing 2017 and 2010 [Change = (final value – initial value) / (initial value)]. The DBD difference was also estimated between the 2017 and 2010 values [Difference = final valor – initial value].

The study was approved by the Bioethics Committee of the Universidad Tecnológica de Pereira in the "no risk category" (approval number: CBE-SYR-162016, August 10, 2017). No personal patient data were used, and the principles enshrined in the Declaration of Helsinki were followed.

RESULTS

Between January 2010 and December 31 2017, a total of 19,186 patients received treatment with vasopressors in the mixed ICUs of eleven hospitals in seven Colombian cities (Table 1). The mean age of patients was 66.3 ± 18.1 years and 52.6 % (n = 10,097) were males. The cities with the largest number of patients cared for were Bogotá (n = 7,054; 36.8 %), Cali (n = 4,735; 24.7 %) and Manizales (n = 3,348; 17.5 %). The ICUs studied had 16.0 ± 7 beds in average.

26,414 treatments were administered in the study population, for a total of 81,348 doses of vasopressors dispensed. The mean treatment duration was 1 day (IQR: 1-3). The vasopressor with the largest proportion of doses dispensed in average during the 8 years of follow-up was norepinephrine (76.0 %), followed by adrenaline (26.6 %), dopamine (19.4 %) and dobutamine (16.0 %). The proportion of use of each of the medications studied over time is shown in Table 1.

The trends over time of the DBD for the vasopressor used are shown in Table 2. For 2017, the most frequently used drugs based on the DBD were norepinephrine (59.9 DBD), adrenaline (32.0 DBD) and dobutamine (1.5 DBD). During the time under observation, only norepinephrine experienced a rise in its use (+6.19 DBD); on the other hand, adrenaline and dopamine were the drugs with the highest reduction in use (-60.6 and -10.8 DBD, respectively) (Table 2). Changes in DBD are shown in Figure 1. Additionally, Table 3 depicts the annual evolution of the VUI for each molecule used.

Table 1. Trends of vasopressor dispensing in patients cared for at eleven Colombian ICUs (2010-2017).

Variable	2010	2011	2012	2013	2014	2015	2016	2017	Total
Patients -n	1,973	1,959	2,153	2,245	2,413	2,775	3,202	3,048	19,186
Number of therapies -n*	2,695	2,542	2,882	3,006	3,261	3,729	4,288	4,103	26,414
Doses dispensed -n	9,374	8,314	9,672	9,461	10,569	10,836	12,176	10,946	81,348
Beds -n	108	126	137	170	170	190	195	220	NA
Medication	% use per treatment								% average
Norepinephrine	52.65	52.12	77.06	84.17	85.86	85.25	85	85.62	75.97
Adrenaline	33.25	24.78	24.18	23.89	27.08	26.92	26.38	26.40	26.61
Dopamine	47.50	44.06	22.59	13.81	11.01	7.78	5.06	3.29	19.39
Dobutamine	13.43	21.6	22.45	16.1	14.26	13.73	13.83	12.84	16.03
Vasopressin	12.24	14.79	7.91	6.39	7.36	6.76	6.72	5.87	8.51
Phenylephrine	2.71	0.08	-	-	-	0.03	-	-	0.94
Ephedrine	0.04	0.12	0.14	-	-	-	-	-	0.10
Etilefrine	0.04	0.04	0.24	0.07	-	-	0.07	-	0.09

*Therapy: continuous use (or with interruptions < 48 horas) of the study drugs. **Source:** Authors.

Table 2. Annual evolution of the daily doses defined per 100 beds/day for each vasopressor in patients admitted to eleven ICUs (2010-2017).

Drug – DBD (% annual change)	2010	2011	2012	2013	2014	2015	2016	2017	Change 2017-2010 (%)	DBD Average	Difference in DBD 2017-2010
Norepinephrine	53.7	42.3 (-21.2)	56.8 (34.3)	54.6 (-3.9)	68.0 (24.5)	66.8 (-1.8)	81.3 (21.7)	59.9 (-26.3)	11.5	60.5	6.19
Adrenaline	92.6	25.6 (-72.4)	28.0 (9.4)	33.7 (20.4)	39.3 (16.6)	38.8 (-1.3)	33.6 (-13.4)	32.0 (-4.8)	-65.4	41.6	-60.6
Dopamine	11.3	7.5 (-33.6)	4.6 (-38.7)	2.2 (-52.2)	2.0 (-9.1)	1.3 (-35.0)	0.8 (-38.5)	0.5 (-37.5)	-95.7	4.2	-10.8
Dobutamine	2.2	3.1 (40.9)	3.3 (6.5)	2.0 (-39.4)	1.8 (-10.0)	1.8 (0.0)	2.1 (16.7)	1.5 (-28.6)	-33.5	2.3	-0.74
Vasopressin	3.2	2.5 (-21.9)	1.5 (-40.0)	1.1 (-26.7)	1.2 (9.1)	1.3 (8.3)	1.7 (30.8)	1.3 (-23.5)	-60.1	1.8	-1.91
Phenylephrine	5.2	0.0 (-100.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.8	-
Ephedrine	0.0	0.01	0.01 (0.0)	0.0 (-100.0)	0.0	0.0	0.0	0.0	0.0	0.01	-
Etilefrine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-

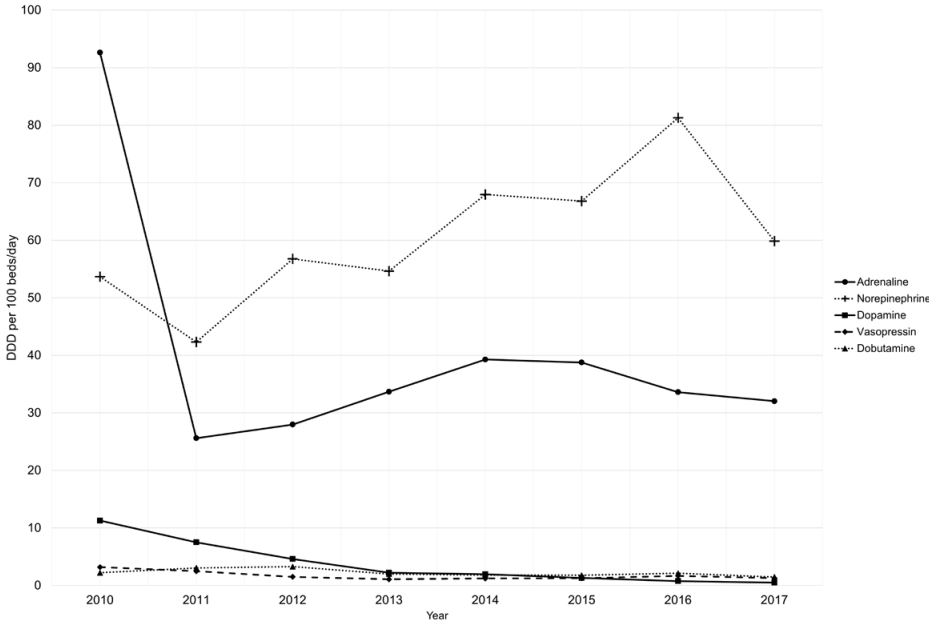
DBD: Daily doses defined per 100 beds/day. **Source:** Authors.

Table 3. Annual evolution of the vasopressor utilization index in patients admitted to eleven ICUs in Colombia (2010-2017).

Drug	2010	2011	2012	2013	2014	2015	2016	2017	General average
Norepinephrine	0.50	0.51	0.71	0.81	0.84	0.84	0.84	0.85	0.75
Adrenaline	0.23	0.12	0.11	0.12	0.13	0.14	0.13	0.15	0.14
Dopamine	0.37	0.33	0.19	0.10	0.08	0.06	0.03	0.03	0.13
Dobutamine	0.11	0.21	0.19	0.15	0.11	0.11	0.12	0.12	0.13
Vasopressin	0.07	0.09	0.04	0.04	0.04	0.04	0.04	0.04	0.05
Phenylephrine	0.03	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ephedrine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Etilefrine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

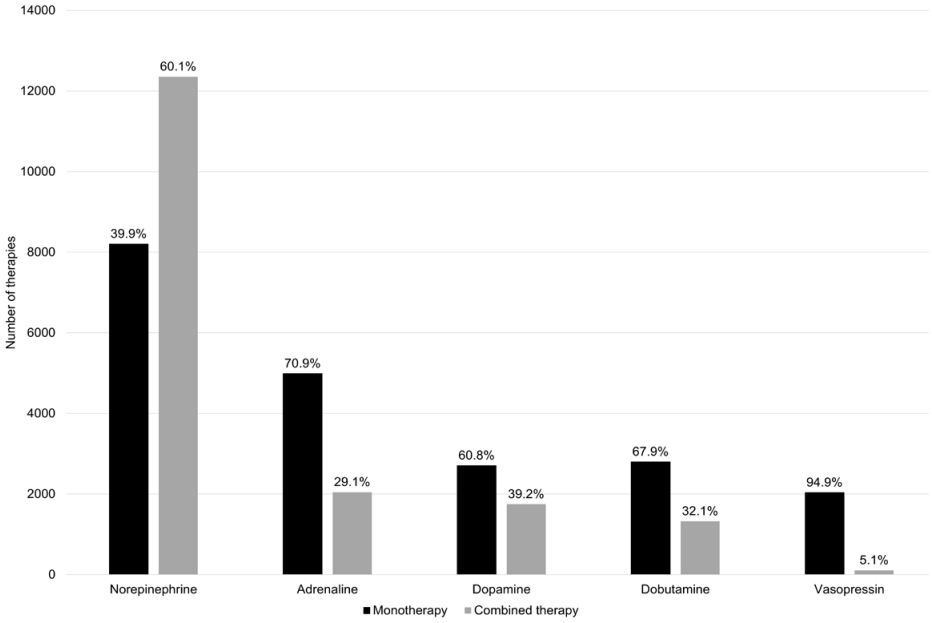
Source: Authors.

FIGURE 1. Trend of the daily doses defined per 100 beds/day of each drug between 2010 and 2017 in patients admitted to ICUs in Colombia.



SOURCE: Authors.

FIGURE 2. Therapies with the main study vasopressors used and their distribution based on administration as monotherapy or combined therapy in the study, in eleven ICUs in Colombia (2010-2017).



SOURCE: Authors.

Monotherapy versus combined therapy

Of the total number of treatments recorded in the trial, 17,658 (66.8 %) were with just one vasopressor and 8,756 (33.2 %) with a combination of vasopressors. Of these latter treatments, 6,117 (23.1 %) treatments included two drugs; 2,090 (7.9 %) included three drugs; and 549 (2.1 %) received between four to six vasopressors. Norepinephrine was used mostly in combined therapy (60.1 %), while adrenaline, dopamine, dobutamine and vasopressin were mainly administered as monotherapy (Figure 2). The most frequently used combinations were adrenaline with norepinephrine (n = 4,535; 51.8 % of the combined therapies), norepinephrine with dobutamine (n = 2,575; 29.4 %), norepinephrine with dopamine (n = 2,256; 25.8 %) and vasopressin with norepinephrine (n = 1,949; 22.3 %).

DISCUSSION

This study evidenced an incremental trend in the use of norepinephrine between 2010 and 2017 in the mixed ICUs in eleven hospitals in Colombia, making it the most frequently used vasopressor during the study period, followed by adrenaline and dopamine. This is probably due to the development of further scientific evidence supporting the early use of norepinephrine in the vasoplegic patient (3,4,11,18,19,24) and its subsequent inclusion in the list of medications in the Colombian Healthcare System Benefit Plan.

Vasoactive drugs, and in general those with a vasopressor effect, are essential as first line therapies for the management of distributive shock conditions, such as septic shock, considered one of the most severe public health problems, representing in average a mortality rate of 25.8 % in the ICU worldwide (25). A multicenter epidemiological study in Colombia reported a 28-day mortality rate of 45.6 % for patients admitted with septic shock (26); this data emphasize the relevance of learning about the trends in the use of vasopressors and a comparison with the rest of the world.

Norepinephrine seems to be the most frequently used vasopressor in the ICU worldwide (1-4,11). This is consistent with a study conducted by Thongprayoon et al., which established the trend in the use of vasopressors in the ICU of a reference medical center in the United States between 2007 and 2013, evidencing that the trend

in the use of norepinephrine showed the highest increase in the period studied and became the most widely used vasopressor for the management of septic shock (1). Jentzer et al. described similar patterns, with an increase of norepinephrine use in ICU patients with heart conditions in the United States, with a decrease in the use of dopamine, during the period from 2007-2015 (27).

With regards to the VUI values, similar trends and values to those described in medical and mixed ICUs were identified in the United States. For example, norepinephrine during the last few years studied, reached VIU values above 0.8, whilst adrenaline fell below 0.2 (1.23). These changes are not found in other types of ICUs, such as those focused in managing patients with surgical cardiac pathology in whom the main vasopressor according to the VUI was adrenaline (1).

Moreover, the data obtained in this analysis indicate the clear impact of scientific evidence over the last few years, in the management of vasopressors; it is clear that the ICU practitioners have followed the recommendations of the international guidelines of the Surviving Sepsis Campaign, encouraging the use of norepinephrine as a first line vasopressor for the management of septic shock (11,16,28); as well as the information derived from recent studies evidencing the increasing effectiveness in terms of reduced mortality and higher safety offered by this medication as compared against dopamine or adrenaline (3,4,24,27). In this paper it was not possible to establish the diagnosis of the patients that required a vasopressor; however, norepinephrine, besides being the drug of choice in septic shock, is also widely recommended for other types of shock such as cardiogenic, neurogenic and even hypovolemic shock and this fact may also account for its increased used over the years (11,18,19).

Dopamine was the vasopressor with the most significant reduction in use in the ICUs, probably as a result of the SOAP-II trial (4) and a meta-analysis by De Backer et al. in 2012, in which dopamine was compared against norepinephrine for the management of septic shock; they found that the use of dopamine was associated with a higher mortality and incidence of arrhythmia (29).

Vasopressin as monotherapy was relatively stable in the series studied and currently its use focuses on reducing the doses of noradrenaline and as a pharmacological adjuvant in case of failure to achieve the mean arterial pressure goals (11). The studies with vasopressin recommend using the drug mostly in cases of septic shock, with less evidence in other types of shock (2,18-20,30).

With regards to combined therapy, adrenaline which was most frequently associated with norepinephrine in this series (52 % of the combined therapies) could be the result of the recommendations of the guidelines of the Surviving Sepsis Campaign, considering it an option for use in combination with norepinephrine to increase the mean arterial pressure (11). However, this association may change in the future because of new evidence in favor of the combination of norepinephrine with vasopressin (11).

This study presents some limitations because the information was taken from a database of drug dispensation directly to hospital institutions, and the patients' medical records were not reviewed, neither was it possible to establish the diagnosis for which the patient received the medication. The clinical outcomes data, or the effectiveness of various therapies were also missing. Some of the aspects to be highlighted include a detailed report of the use of the medications over time for a specific healthcare service, and on an individualized basis for each patient. The results are only applicable to patients with similar healthcare and insurance characteristics.

CONCLUSION

Based on the previous findings it may then be concluded, that the most frequently used vasopressor in the ICUs of the participating institutions was norepinephrine, a fact that is supported by the evidence in favor of its effectiveness and safety in patients with shock. It is important to conduct further studies considering these aspects to ensure the best possible quality of care for patients in critical conditions.

ETHICAL RESPONSIBILITIES

Endorsement of the ethics committee

This study was approved by the Bioethics Committee of the Universidad Tecnológica de Pereira, at a meeting held on august 10, 2017, as reported in minutes CBE-SYR-162016.

Protection of persons and animals

The authors declare that no experiments in human beings or animals were conducted for this research and that the procedures followed were consistent with the ethical standards of the human experimentation committee and with the World Medical Association and the Declaration of Helsinki.

Confidentiality of the data

The authors declare that they have followed the protocols of their work institution on the publication of patient data.

Right to privacy and informed consent

The authors declare that this article does not disclose any patient data.

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Authors' contributions

AGM: study planning, data collection, interpretation of the results and initial drafting of the article.

JEMA: study planning, interpretation of the results, critical review of the manuscript.
JFBM, SCR and JSRL: interpretation of the results and initial drafting of the article.
PAMG: Data collection, interpretation of the results.
JFGG: interpretation of the results and final revision of the manuscript.

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Conflict of interests

AGM and JEMA have a work relationship with Audifarma S. A., and have no further disclosures to make.

Presentations

None declared.

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