RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

Open Access

Pharmacotherapeutic profile of compounded drugs for the treatment of coronavirus in patients admitted to a public hospital

Alessandra Cortes TEOTONIO[1], Cleuber Esteves CHAVES[1], Priscila Faria FRANÇA[1], Vanusa Barbosa PINTO[1]

[1]Hospital das Clínicas da Universidade de São Paulo (HCFMUSP), São Paulo, Brasil;

Corresponding author: Teotonio AC, alessandra.cortes@hc.fm.usp.br/ alessandra.cortes@hotmail.com

Submitted: 01-06-2021 Resubmitted: 17-07-2021 Accepted: 18-07-2021

Peer review: Ana Paula Callejo de Souza e Renata Barbosa

Abstract

Objective: : To characterize the sociodemographic and hospitalization profile of patients, as well as to determine, account for and identify dosages and costs generated with compounded drugs to meet prescriptions for people hospitalized at Hospital das Clínicas of the Medical School at the University of São Paulo (*Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, HCFMUSP*) due to SARS-CoV-2, between April and July 2020. **Methods:** A retrospective cross-sectional study of the use of compounded drugs by patients hospitalized due to coronavirus at the HCFMUSP Central Institute from April to July 2020. Personalized compounded drugs or those produced by the semi-industrial sector of the HCFMUSP Pharmacotechnics Unit were excluded from the study. The variables were presented as mean and standard deviation or proportion. Univariate statistical analysis, one-way ANOVA using Tukey as post-hoc test were applied to compare the manipulated production in the study period and the same period of 2019.3 **Results:** It was shown that a total of 39 standardized compounded drugs were prescribed for a total of 1,557 patients with coronavirus confirmation. Of the total number of prescription drugs, 11 drugs showed a significant increase in production in 2020, namely: furosemide (48.8 ± 17.1, p<0.004); amiodarone (50.0 ± 17.4, p<0.005); amlodipine (70.3 ± 14.4, p<0.003); hydralazine (82.8 ± 22.3, p<0.038); diazepam (95.8 ± 53.4, p<0.037); artificial saliva (146.0 ± 50.6, p<0.004); propantheline gel(155.0 ± 33.9, p<0.042); methadone (174.5 ± 45.2, p<0.002); hydrochlorothiazide (204.5 ± 46.4, p<0.001); omeprazole (537.5 ± 194.8, p<0.031) and quetiapine (597.0 ± 116.3, p<0.000). Omeprazole and quetiapine were the most prescribed products for hospitalized patients. The estimated total cost of meeting prescriptions during the study period was $20,854.01. **Conclusions:** The manipulated drugs provided mechanically ventilated patients with adequate pharmacotherapy and facilitated the process of weaning from sedation. The institution obtained a reduction in cost due to the manipulated product presenting a better cost-effect ratio when compared to injectable forms of medication.

Keywords: SARS-CoV-2; coronavirus; drug costs; pharmaceutical preparations; catheter; pharmacy service, hospital.

Perfil farmacoterapêutico de medicamentos manipulados para tratamento de coronavírus em pacientes internados em hospital público

Resumo

Objetivo: Caracterizar sociodemograficamente e definir perfil de internação dos pacientes, bem como determinar, contabilizar, identificar dosagens e custos gerados com medicamentos manipulados para atender prescrições de internados no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) devido ao SARS-CoV-2, entre abril e julho de 2020. **Métodos:** Estudo seccional retrospectivo da utilização de medicamentos manipulados por pacientes internados por coronavírus no Instituto Central HCFMUSP no período de abril a julho de 2020. Excluiu-se do estudo medicamentos manipulados personalizados ou produzidos pelo setor de semi-industriais da Unidade de Farmacotécnica do HCFMUSP. As variáveis foram apresentadas como média e desvio-padrão ou proporção. Aplicada análise estatística univariada, ANOVA de uma via usando Tukey como teste post-hoc para comprar a produção de manipulados no período de estudo e o mesmo período de 2019. **Resultados:** Demonstraram o total de 39 medicamentos manipulados padronizados que foram prescritos para o total de 1557 pacientes com confirmação de coronavírus. Do total de medicamentos manipulados prescritos, 11 medicamentos apresentaram aumento significativo de produção em 2020: furosemida (48,8 ± 17,1 p <0,004); amiodarona (50,0 ± 17,4 p <0,005); anlodipino (70,3 ± 14,4 p <0,003); hidralazina (82,8 ± 22,3 p <0,038); diazepam (95,8 ± 53,4 p <0,037); saliva artificial (146,0 ± 50,6 p <0,004); propantelina gel (155,0 ± 33,9 p <0,042); metadona (174,5 ± 45,2 p <0,002); hidroclorotiazida (204,5 ± 46,4 p <0,001); omeprazol (537,5 ± 194,8 p <0,031) e quetiapina (597,0 ± 116,3 p <0,000). Os medicamentos omeprazol e quetiapina foram os produtos mais prescrito para os pacientes internados. O custo total estimado para atender às prescrições no período do estudo foi de US$ 20.854,01. **Conclusões:** Os medicamentos manipulados proporcionaram aos pacientes em ventilação mecânica a adequada farmacoterapia e facilitaram o processo de desmame da sedação. A instituição obteve redução no custo devido ao produto manipulado apresentar melhor custo-benefício quando comparado às formas injetáveis dos medicamentos.

Palavras-chaves: SARS-CoV-2; coronavírus; custos de medicamentos; preparações farmacêuticas; sonda; serviço de farmácia hospitalar.

RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Introduction

The state of São Paulo was the Brazilian federative unit with the highest number of cases of individuals infected by the SARS-CoV-2 virus in 2020; nearly 14% of the patients affected by the virus develop important complications such as severe dyspnea symptom and 5% of the patients develop respiratory syndrome in its acute severe form. The patients who develop complications resulting from coronavirus are individuals who require hospital care with more invasive treatments such as mechanical ventilation and catheter feeding.[1,2]

On March 30th, 2020, the Hospital das Clinicas of the Medical School at the University of São Paulo (*Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo*, HCFMUSP), located in the capital of the state of São Paulo, started to admit only patients with suspected or confirmed by SARS-CoV-2 who presented a condition considered from moderate to severe.[3] The protocol for the management of patients with coronavirus hospitalized at the HCFMUSP includes the following as drug therapy: antivirals and antimicrobials, in order to rule out the action of other infectious agents; thrombosis prophylaxis, through the administration of anticoagulants; corticotherapy, due to more severe inflammatory processes and, for the intubation process, the use of sedatives, analgesics, neuromuscular blockers and medication for agitation and *delirium*.[4,5]

In the most severe circumstances, it is common for the patients to use catheters for feeding. This material is narrow in diameter and is routinely used to administer solid medications. However, the process of administering solid products can obstruct the catheter, cause discomfort to the patient and increase costs for the institution due to the need for unscheduled changes of hospital material.[1,6-8] The process of changing obstructed catheters is associated with patient safety problems, as the need for exchange increases the chances of errors related to the connection route, such as causing lung abscess, nasal septum injury, pharyngeal perforation and epistitis.[9,10]

Within this context, the pharmacological treatment of hospitalized patients in a moderate to severe state, in which the majority require insertion of catheters and mechanical ventilation to maintain life, becomes a challenge, showing the importance of the compounded drugs process to develop formulations not commercially available, dose adjustments and adequacy of pharmaceutical form, as well as optimization of institutional expenses.[11]

Compounding drugs within the hospital environment makes it possible to meet the aforementioned demands, through the production of personalized medications for the hospitalized patient, with a guarantee of treatment efficacy and safety. The purpose of pharmacotechnics in the hospital environment is not limited to adapting pharmaceutical forms available on the market to the needs of hospitalized patients, but also to enable the development of specific commercially unavailable preparations to meet a specific demand.[12]

In the context of the SARS-CoV-2 virus pandemic and of the changes in the profile of patients hospitalized at the HCFMUSP, the importance of a study aimed at assessing the impact of changing the profile of the medications manipulated by the compounding sector of the Hospital Pharmacotechnics Unit of the Pharmacy Division of the HCFMUSP Central Institute becomes evident.

The objective of this paper was to sociodemographically characterize and define the hospitalization profile of the patients with suspected or confirmed SARS-CoV-2 infection between April and July 2020. The study also determined, counted and identified dosages and costs generated with manipulated medications, produced by the compounding sector of the HCFMUSP Pharmacotechnics Unit.

Methods

A retrospective sectional study carried out with data collected from April to July 2020, in which medical records and prescriptions of patients admitted to the HCFMUSP Central Institute were analyzed, approved under the Certificate of Presentation for Ethical Appreciation (*Certificado de Apresentação para Apreciação Ética*, CAAE) 38573920.4.0000.0068. The Central Institute is the largest institute in the HCFMUSP Complex, with nearly 300 ward beds and 300 Intensive Care Unit (ICU) beds during the pandemic period due to SARS-CoV-2, a large and high-complexity public teaching hospital (tertiary/quaternary care). All the patients hospitalized in the HCFMUSP Central Institute during the study period were included for sociodemographic characterization, as well as the patients with a prescription of at least one manipulated medication for at least 24 hours to analyze the use of compounded drugs produced at the HCFMUSP. Products produced by the semi-industrial sector of the HCFMUSP Pharmacotechnics Unit and patients with prescriptions for non-standardized manipulated medications were excluded.

The demographic characterization of the patients was performed using the following variables: age, gender, length of stay, clinical outcome, definite diagnosis and hospitalization unit of the patients from April to July 2020. The demographic data were provided by the Epidemiological Surveillance Center (*Núcleo de Vigilância Epidemiológica*, NUVE) with information from electronic medical records of patients with suspected or confirmed SARS-CoV-2 infection (PEP-MV). The identification of the standardized manipulated medications prescribed, number of prescriptions, as well as the volume of prescribed drugs for subsequent calculation of dosages (prescribed volume x drug concentration) and cost (prescribed volume x value per volume) of the products were obtained from the report contained in the analytical mean cost panel of the SOULMV® (MV Informática Nordeste Ltda.) system, which enables access to the electronic medical prescriptions of patients hospitalized with suspected or confirmed infection by SARS-CoV-2 from April to July 2020; and the relation of values of the manipulated medications present in the study was provided by the compounding sector of the HCFMUSP, the values provided by the compounding sector for each product are based on the number of products produced in a batch added to the amount of raw materials consumed, the quality control analyses most used and the necessary workforce. It is to be noted that the costs were recorded in Brazilian reais and converted to US dollars on June 11th, 2021; in this period, US$ 1 was equal to R$ 5.119.

The counting of the standardized medications that were produced and distributed to the decentralized pharmacies of the HCFMUSP Central Institute in the period from April to July 2020 and 2019 was obtained through the general registration spreadsheet of manipulated medications provided by the compounding sector of the HCFMUSP Pharmacotechnics Unit.

In the descriptive analysis, the continuous variables were presented as mean and standard deviation, and proportions were estimated for the categorical variables. Comparison of the production of manipulated medications from April to July 2020 with those produced and distributed from April to July 2019 was performed by means of univariate analysis, one-way ANOVA using Tukey as a post-hoc test. The results were considered as statistically significant when p<0.05. All the data were analyzed in the IBM® SPSS® Statistics 20 program.

Results

The total number hospitalized patients from June to July 2020 with suspected or clinical confirmation of infection by SARS-CoV-2 was 2,823 individuals. Based on the data informed by the NUVE, 1,537 (54%) were male and 1,286 (46%) were female (Table 1). The mean age of the hospitalized patients was 61 ± 16 years old, while the distribution of the number of patients according to age group, in descending order, was as follows: 60-69 years old (23.7%), followed by patients aged 50-59 (18.4%), 70-79 (18.3%), 40-49 (13.3%), 30-39 (9.6%), 80-89 (9.2%), 20-29 (4.6%), >90 years old (1.7%), and 0-19 years old (1.2%) (Table 1).

Table 1. Sociodemographic and hospitalization characterization of patients admitted for suspected or confirmed coronavirus at the HCFMUSP between April and July 2020.

Hospitalizations in the HCFMUSP	**Total N=2,823**
Sociodemographic information	
Male[1] n (%)	1,537 (54.4)
Age (years old) Mean (SD)	61 (16.0)
Age groups (years old) n (%)	
0-19	35 (1.2)
20-29	129 (4.6)
30-39	270 (9.6)
40-49	376 (13.3)
50-59	520 (18.4)
60-69	670 (23.7)
70-79	518 (18.3)
80-89	260 (9.2)
>90	45 (1.7)
Hospitalization information	
Inpatient unit n (%)	
ICU	1,445 (51.2)
Ward	625 (22.1)
Emergency Room	753 (26.7)
Diagnosis n (%)	
Coronavirus	2,291 (81.1)
Unspecified respiratory failure	490 (17.4)
Other respiratory infections	34 (1.2)
Other diseases	8 (0.3)
Clinical outcome n (%)	
Hospital discharge	1,950 (69.1)
Hospital transfer	30 (1.1)
Death due to coronavirus	743 (26.3)
Death due to other causes	100 (3.5)

[1] Dichotomous variable for which the result of only one of the categories was presented.

Regarding the distribution among the hospital inpatient units (Table 1), most of the patients, 51.2%, remained in ICUs, followed by 26.7% in the emergency room and 22.1% in the ward. In relation to diagnosis, we observed that 2,291 (81.1%) confirmed coronavirus (CID-10 B34.2), while 17.4% were hospitalized for unspecified respiratory failure (CID-10 J96.9); other respiratory infections represented 1.2% and other diseases not related to the respiratory system accounted for 0.3% (Table 1).

In the patients' clinical outcome, Table 1, most of the hospitalized patients were discharged (69%), although 26% of the patients died due to SARS-CoV-2 infection and the rest (4%) due to other diseases not related to coronavirus.

During the research period, a total of 1,925 (68%) patients, regardless of diagnosis, used some manipulated medication; from this group of patients with a prescription for compounded drugs, it was observed that 1,557 (55%) patients confirmed the SARS-CoV-2 diagnosis. A total of 39 manipulated medications that were standardized in the electronic prescription were prescribed to hospitalized patients. Of this total, 6 medications (15.4%) were recommended in the institutional management of patients with coronavirus and 33 (84.6%) were not included in the protocol.

Among the total of 39 manipulated medications, 11 products had a statistically significant increase in production and distribution in the period from April to July 2020 when compared to the same period in 2019 (Table 2), namely: Furosemide (48.8 ± 17.1 vials in 2020, p<0.004); Amiodarone (50.0 ± 17.4 vials in 2020, p<0.005); Amlodipine (70.3 ± 14.4 vials in 2020, p<0.003); Hydralazine (82.8 ± 22.3 vials in 2020, p<0.038); Diazepam (95.8 ± 53.4 vials in 2020, p 0.037); Artificial saliva (146.0 ± 50.6 vials in 2020, p<0.004); Propantheline gel (155.0 ± 33.9 tubes in 2020, p<0.042); Methadone (174.5 ± 45.2 vials in 2020, p<0.002); Hydrochlorothiazide (204.5 ± 46.4 vials in 2020, p<0.001); Omeprazole (537.5 ± 194.8 vials in 2020, p<0.031) and Quetiapine (597.0 ± 116.3 vials in 2020, p<0.000).

Mycophenolate mofetil (3.0 ± 3.8 bottles in 2020, p<0.039) and PEG (polyethylene glycol) (13.3 ± 9.3 bottles in 2020, p<0.004) were products that had a statistically significant reduction in production and distribution in the period from April to July 2020 when compared to the same period in 2019 (Table 2).

The total daily dose of manipulated medications prescribed with higher production and distribution (23% of the drugs), disregarding topical ones, between April and July 2020 can be seen in Table 3. Seven medications had a mean daily dose above the median, the median concentration was higher than the mean only for amiodarone and amlodipine, the latter with no difference between mean and median.

Furosemide, quetiapine, amiodarone and hydrochlorothiazide, respectively, were the manipulated drugs that had the greatest variation between the minimum dose and the maximum dose prescribed. On the other hand, amlodipine was the compound that least varied in relation to the minimum and maximum dose. Regarding the number of prescriptions, it was possible to observe that omeprazole was the most prescribed compounded product, followed by quetiapine, methadone, hydrochlorothiazide, diazepam, amiodarone, amlodipine, hydralazine and furosemide (Table 3).

The total estimated cost (Table 4) to meet the prescriptions with the most produced manipulated drugs in the period from April to July 2020 was US$ 20,854.01. Manipulated quetiapine was the product that most varied between the minimum (US$ 0.02) and maximum (US$ 6.24) daily prescribed total cost, while amlodipine was the

manipulated product that varied the least between the minimum (US$ 0.04) and the maximum (US$ 0.29) (Table 4) daily cost.

The mean daily cost per prescription of the manipulated medications ranged from US$ 0.15 to US$ 1.18, with amlodipine being the product with the lowest mean value and omeprazole the medication with the highest mean value. Omeprazole was the medication with the highest daily cost value prescribed throughout the study period, with US$ 10,667.76; it was also the item that was most prescribed in that period, with 9,055 prescriptions. The second medication with the highest amount in daily prescribed cost was quetiapine (US$ 5,369.36), which was also the second most prescribed drug for hospitalized patients (8,346 prescriptions) (Table 4).

Table 2. List of standardized compounded drugs and the number of drugs produced and distributed in the period from April to July 2020 compared to the same period in 2019.

Information	**Total N=18,037**	**Pharmaceutical preparations-April to July**					**p-value**
		2019			**2020**		
Medications	**Preparations** n (%)	**Preparations** n (%)	**Monthly** Mean (SD)		**Preparations** n (%)	**Monthly** Mean (SD)	
Amiodarone 200 mg/5 mL	247 (1.4)	47 (0.3)	11.7 (3.8)		200 (1.1)	50.0 (17.4)	0.005*
Amlodipine 5 mg/5 mL	396 (2.2)	115 (0.6)	28.8 (9.2)		281 (1.6)	70.3 (14.4)	0.003*
Atenolol 25 mg/5 mL	198 (1.1)	82 (0.5)	20.5 (2.4)		116 (0.6)	29.0 (7.1)	0.063
Atropine sulfate 1%	1,256 (7.0)	500 (2.8)	125.0 (28.0)		756 (4.2)	189.0 (46.8)	0.057
Baclofen 10 mg/5 mL	128 (0.7)	75 (0.4)	18.8 (18.2)		53 (0.3)	13.3 (5.7)	0.585
Captopril 25 mg/mL	119 (0.7)	49 (0.3)	12.3 (5.9)		70 (0.4)	17.5 (3.0)	0.164
Carvedilol 5 mg/5 mL	58 (0.3)	19 (0.1)	4.8 (2.5)		39 (0.2)	9.8 (8.1)	0.281
Diazepam 10 mg/5 mL	468 (2.6)	85 (0.5)	21.3 (16.6)		383 (2.1)	95.8 (53.4)	0.037*
Fluoxetine 20 mg/5 mL	61 (0.3)	26 (0.1)	6.5 (7.2)		35 (0.2)	8.8 (3.9)	0.603
Furosemide 40 mg/5 mL	237 (1.3)	42 (0.2)	10.5 (1.7)		195 (1.1)	48.8 (17.1)	0.004*
Gabapentin 300 mg/5 mL	355 (2.0)	196 (1.1)	49.0 (28.4)		159 (0.9)	39.8 (11.3)	0.567
Hydralazine 25 mg/5 mL	476 (2.6)	145 (0.8)	36.3 (27.3)		331 (1.8)	82.8 (22.3)	0.038*
Hydrochlorothiazide 25 mg/5mL	1,005 (5.6)	187 (1.0)	46.8 (14.7)		818 (4.5)	204.5 (46.4)	0.001*
Hydroxychloroquine 400 mg/5 mL	53 (0.3)	1 (0.0)	0.3 (0.5)		52 (0.3)	13.0 (18.0)	0.208
Hydroxyzine 10 mg/5 mL	305 (1.7)	144 (0.8)	36.0 (10.5)		161 (0.9)	40.3 (34.1)	0.820
Methadone 10 mg/5 mL	878 (4.9)	180 (1.0)	45.0 (24.7)		698 (3.9)	174.5 (45.2)	0.002*
Mycophenolate Mofetil 500 mg/10 mL	84 (0.5)	72 (0.4)	18.0 (10.7)		12 (0.1)	3.0 (3.8)	0.039*
Omeprazole 10 mg/5 mL	3,110 (17.2)	960 (5.3)	240.0 (81.9)		2,150 (11.9)	537.5 (194.8)	0.031*
Oseltamivir 75 mg/5 mL	254 (1.4)	0 (0.0)	0.0 (0.0)		254 (1.4)	63.5 (85.6)	0.188
Prednisone 20 mg/5 mL	292 (1.6)	132 (0.7)	33.0 (14.7)		160 (0.9)	40.0 (26.0)	0.656
Propranolol 40 mg/5 mL	80 (0.4)	42 (0.2)	10.5 (6.3)		38 (0.2)	9.5 (1.0)	0.766
Quetiapine 25 mg/5 mL	2,721 (15.1)	333 (1.8)	83.3 (32.3)		2,388 (13.2)	597.0 (116.3)	0.000*
Artificial saliva	693 (3.8)	109 (0.6)	27.3 (11.3)		584 (3.2)	146.0 (50.6)	0.004*
Sertraline 50 mg/5 mL	27 (0.1)	24 (0.1)	6.0 (5.0)		3 (0.0)	0.8 (1.5)	0.089
Simvastatin 40 mg/5 mL	114 (0.6)	44 (0.2)	11.0 (3.7)		70 (0.4)	17.5 (6.2)	0.122
Mucositis solution	18 (0.1)	8 (0.0)	2.0 (1.6)		10 (0.1)	2.5 (2.4)	0.741
Tacrolimus 1 mg/mL	113 (0.6)	68 (0.4)	17.0 (6.3)		45 (0.2)	11.3 (4.9)	0.199
Zinc sulfate 70 mg/mL	216 (1.2)	57 (0.3)	14.3 (9.8)		159 (0.9)	39.8 (27.2)	0.129
Chamomile 10% gel	23 (0.1)	0 (0.0)	0.0 (0.0)		23 (0.1)	5.8 (5.1)	0.066
Papain 2% gel	168 (0.9)	71 (0.4)	17.8 (11.3)		97 (0.5)	24.3 (6.3)	0.354
Papain 4% gel	158 (0.9)	71 (0.4)	17.8 (15.2)		87 (0.5)	21.8 (3.8)	0.628
Papain 6% gel	290 (1.6)	114 (0.6)	28.5 (10.7)		176 (1.0)	44.0 (20.4)	0.288
Papain 8% gel	329 (1.8)	136 (0.8)	34.0 (17.4)		193 (1.1)	48.3 (11.6)	0.223
Papain 10% gel	1,258 (7.0)	485 (2.7)	121.3 (78.8)		773 (4.3)	193.3 (90.7)	0.276
Propantheline 10 mg/g gel	1,057 (5.9)	437 (2.4)	109.3 (10.8)		620 (3.4)	155.0 (33.9)	0.042*
Activated charcoal	50 (0.3)	32 (0.2)	8.0 (7.5)		18 (0.1)	4.5 (7.1)	0.525
PEG (polyethylene glycol)	429 (2.4)	376 (2.1)	94.0 (33.7)		53 (0.3)	13.3 (9.3)	0.004*
Boricated talc 5%	313 (1.7)	145 (0.8)	36.3 (10.3)		168 (0.9)	42.0 (15.6)	0.561

* Drugs with a statistically significant difference

Table 3. Relation of total daily doses of standardized manipulated drugs, with a significant increase in production, prescribed to patients between April and July 2020.

Pharmaceutical preparations	Total daily dose prescribed (mg)			Number of prescriptions
	Min.	Max.	Mean (SD)	N=29,685
Amiodarone 200 mg/5 mL	100.0	1,200.0	479.0 (164.9)	1,159
Amlodipine 5 mg/5 mL	2.5	20.0	10.0 (4.3)	1,059
Diazepam 10 mg/5 mL	2.5	320.0	32.0 (30.9)	1,427
Furosemide 40 mg/5 mL	20.0	1,920.0	155.0 (179.9)	739
Hydralazine 25 mg/5 mL	10.0	750.0	123.0 (84.2)	947
Hydrochlorothiazide 25 mg/5 mL	12.5	1,000.0	145.0 (109.8)	2604
Methadone 10 mg/5 mL	1.0	80.0	17.0 (9.9)	4349
Omeprazole 10 mg/5 mL	4.0	160.0	31.0 (13.4)	9,055
Quetiapine 25 mg/5 mL	5.0	1,500.0	155.0 (146.0)	8,346

Table 4. Relation of total daily cost and of number of patients with standardized manipulated drugs, with a significant increase in production, prescribed to patients between April and July 2020.

Pharmaceutical preparations	Total daily cost prescribed (US$)				Number of prescriptions N=29,685
	Total cost calculation (mean x number of prescriptions) Total = 20,854.01	Mean (SD)	Min.	Max.	
Amiodarone 200 mg/5 mL	602.68	0.52 (0.91)	0.11	1.30	1,159
Amlodipine 5 mg/5 mL	158.85	0.15 (0.32)	0.04	0.29	1,059
Diazepam 10 mg/5 mL	385.29	0.27 (1.32)	0.02	2.67	1,427
Furosemide 40 mg/5 mL	266.04	0.36 (2.12)	0.05	4.43	739
Hydralazine 25 mg/5 mL	625.02	0.66 (2.32)	0.05	4.04	947
Hydrochlorothiazide 25 mg/5 mL	1,093.68	0.42 (1.63)	0.04	2.90	2,604
Methadone 10 mg/5 mL	1,696.11	0.39 (1.17)	0.02	1.84	4,349
Omeprazole 10 mg/5 mL	10,684.90	1.18 (2.60)	0.15	6.06	9,055
Quetiapine 25 mg/5 mL	5,341.44	0.64 (3.11)	0.02	6.24	8,346

Discussion

According to data from special epidemiological bulletin N25 published by the Ministry of Health (*Ministério da Saúde*, MS), with epidemiological data issued until August 1st, 2020, 59.9% of patients infected with SARS-CoV-2 were recorded in Brazil and 63.7% in São Paulo; with unspecified respiratory failure, 38.7% in Brazil and 33.6% in São Paulo; and other respiratory infections add up to 1.4% in Brazil and 2.7% in São Paulo. It is to be noted that, still with data from the same epidemiological bulletin, Brazil hospitalized 56.7% of male patients and 43.3% female patients.[2]

Comparing the information issued by the MS with that found in the admission of patients to the HCFMUSP, we can observe that the hospital had a higher rate of hospitalized patients due to coronavirus (81%) in relation to the national level and to the state of São Paulo.[2] Regarding other respiratory infections (1.4%), the rate remained similar to that recorded in the state of São Paulo, while patients with unspecified respiratory failure (17%) had a lower rate when compared to the state of São Paulo and at the national level, showing a higher rate of defined diagnosis of patients admitted to the HSFMUSP.[2]

The distribution rate between the genders of those hospitalized at the HCFMUSP remained similar to that recorded at the national level, since the institution registered 54% of male patients and 46% female patients. Although close, the rates show that the male gender was slightly more affected than the female.

In special epidemiological bulletin N25 published by the MS, the most affected age group was that from 60 to 69 years old with 20.3%, followed by 50 to 59 years old (18.4%), 70 to 79 years old (17.2%), 40 to 49 years old (14.4%), 80 to 89 years old (10.7%), 30 to 39 years old (10.2%), 20 to 29 years old (3.9%), more than 90 years old (2.6%) and from 0 to 19 years old (2.3%).[2]

Comparing the information found with data from the patients hospitalized at the HCFMUSP, it was possible to observe that the number of hospitalized patients by age group was identical to that recorded at the national level, with the most affected age group being between 60 and 69 years old. The sequence of the ranking issued by the ministry was similar to that observed in the hospital, differing only in the age group from 80 to 89 years old with an inverted position with the age group from 30 to 39 years old, and the age group over 90 years old with an inverted position with that from 0 to 19 years old.

Considering the fact that 51.2% of the hospitalized patients are in the ICU and according to data published by Miethke-Morais *et al*., who observed that 41% of the patients in the study were under mechanical ventilation, the high rate of hospitalized patients in serious condition is demonstrated.[13] Noting the need to use the 39 manipulated medications produced to adapt the pharmaceutical form(s) unavailable in the market or medications marketed not standardized by the institution.

According to the updated list of the Medication Market Regulation

Chamber (*Câmara de Regulação do Mercado de Medicamentos*, CMED) of the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA), 28 (71.8%) medications produced by the compounding sector do not commercially present the pharmaceutical form of solution, oral suspension or injectable.[14] Of the 39 medications manipulated, only five products (12.8%) exist in the injectable version standardized at the HCFMUSP, namely: amiodarone, diazepam, furosemide, hydralazine, omeprazole, and tacrolim.

Of the 6 products that are established in the management protocols for patients infected with SARS-CoV-2, only drugs diazepam, methadone and quetiapine had an increase in prescription and production. The situation of increase in the 3 medications is due to the fact that there is no commercial product, as in the case of quetiapine, to serve patients hospitalized in ICUs who are in a more serious situation and are often intubated (41%), according to Miethke-Morais *et al*.[13] In the case of diazepam and methadone, despite the existence of injectable versions, many clinicians opt for suspension, as enteral medications facilitate the process of weaning from sedation and agitation of the patient on mechanical ventilation.[15,16]

Oseltamivir, hydroxychloroquine and prednisone, despite being established in the management protocol for patients infected with SARS-CoV-2, had no increase in production due to the following situations: oseltamivir was established in the management due to the seasonal risk of concomitant H1N1 infection, but laboratory test results showed that the infection was by SARS-CoV-2 (81%). Hydroxychloroquine was included as an optional therapy due to the great scientific discussion of its efficacy against the new coronavirus but, due to lack of consensus, the product was not prescribed in June and July.[17] Prednisone did not present any increase due to the existence of other options such as injectable methylprednisolone and hydrocortisone.

According to Miethke-Morais *et al*., 48.1% of the patients hospitalized at the HCFMUSP from May to June 2020 were hypertensive and 16.5% presented some cardiovascular disease, which justifies the increase in the use of furosemide, amiodarone, amlodipine, hydralazine and hydrochlorothiazide.[13] The use of mechanical ventilation in 41% of the cases increased the prescription of artificial saliva and propantheline gel, aiming to reduce patient discomfort and the possibility of pneumonia associated with ventilation due to excess salivation.[13]

The significant decrease in the production of mycophenolate mofetil and PEG is due to the following circumstances: the need to transform the operating room into an ICU bed to meet the patient care demand resulted in the cancellation of transplants at the HCFMUSP Central Institute, resulting in a reduction in use and prescription of immunosuppressants such as mycophenolate mofetil.[18] The decrease in PEG production is due to replacement by other laxative substances.

Of the 11 manipulated medications standardized at the HCFMUSP, which had a significant increase in prescription and production, five of them, amlodipine, artificial saliva, propantheline gel, hydrochlorothiazide and quetiapine, do not exist commercially as shown in the CMED list.[14] Furosemide, amiodarone, hydralazine, diazepam, methadone and omeprazole had injectable versions available for prescription and, when added together, would cost at least US$ 23,019.35 (minimum values included in the CMED list) to meet the mean dose of the prescriptions made in study period; however, with the suspension or solution versions produced at the HCFMUSP, the hospital saved US$ 8,759.31.[14]

According to a study by Moraes (2013), nearly 19.8% of the patients who use a tube during hospitalization have a problem with obstruction of the material and the real mean cost of a new catheter is around US$ 5.03.[19] Considering the study by Miethke-Morais, in which 41% of the patients were intubated due to coronavirus and extrapolating to the reality of this study, we could estimate losses around US$ 1,152.79 per obstruction in cases of solid drug administration.[13] However, other studies indicate that hospital materials can demand up to 49% of the institutional budgets, and this estimate may be even higher.[20,21]

Conclusion

Based on this study, it can be said that the HCFMUSP treated a large number of individuals with coronavirus, and most of these people had a defined diagnosis, serious condition and satisfactory outcome (hospital discharge) when compared to the national and state mean values.

The importance of the compounding sector to assist hospitalized patients possibly corroborated with the satisfactory results obtained with the hospitalized patients in the institution, given the importance of adapting medications that are commercially available only in solid or injectable form, especially for intubated patients. Patients on mechanical ventilation benefited from the production of manipulated medications since, in addition to the adaptation of drugs in solid pharmaceutical forms to liquid forms, minimizing the possibility of catheter obstruction, suspension drugs facilitate the process of weaning from sedation and agitation.[15,16]

The institution benefited from the use of manipulated medications, as it managed to reduce costs generated by problems such as unscheduled replacement of tubes and because the manipulated product presents a better cost-benefit ratio when compared to the use of injectable pharmaceutical forms of the drugs in question.

Collaborators

ACT was responsible for the conception of the project, study design, literature review, data collection, statistical analysis, interpretation of the paper's data and writing of the article; CEC, PFF and VBP were responsible for the conception of the project, study design, statistical analysis and critical review of the text and the data.

Financing source

The research did not receive funding for its completion.

Acknowledgments

To the Hospital and Clinical Pharmaceutical Assistance Residency Program of the HCFMUSP and to the Pharmacy Division and compounding sector of the HCFMUSP, which made this research possible.

Conflict of interest statement

The authors declare no conflict of interests regarding this article.

References

1. Brasil. Ministério da Saúde. Secretaria de Atenção Especializada à Saúde. Departamento de Atenção Hospitalar, Domiciliar e de Urgência. Protocolo de manejo clínico da Covid-19 na Atenção Especializada. 1. ed. Brasília: Ministério da Saúde, 2020.
2. Brasil. Ministério da Saúde. Boletim Epidemiológico Especial doença pelo coronavírus Covid-19 N25. Available in: http://antigo.saude.gov.br/images/pdf/2020/August/12/Boletim-epidemiologico-COVID-25-final--1-.pdf. Accessed on: 06 ago 2020.
3. Superintendência HCFMUSP. Enfrentamento da emergência de saúde pública de importância internacional decorrente do coronavírus (COVID-19). Available in: https://sites.google.com/hc.fm.usp.br/o-hcfmusp-e-o-covid-19/informes-ao-colaborador?authuser=0. Accessed on: 05 mai 2020.
4. Comitê de crise HCFMUSP. Diretriz Institucional Manejo de Tratamento para Pacientes com Covid-19 em Ambiente Hospitalar. Available in: https://sites.google.com/hc.fm.usp.br/o-hcfmusp-e-o-covid-19/informes-t%C3%A9cnicos?authuser=0. Accessed on: 07 mai 2020.
5. Comitê de crise HCFMUSP. Protocolo de Sedação em Pacientes com suspeita ou Confirmação de Covid-19. Available in: https://sites.google.com/hc.fm.usp.br/o-hcfmusp-e-o-covid-19/informes-t%C3%A9cnicos?authuser=0. Accessed on: 09 mai 2020.
6. Brunner & Suddarth. Enfermagem Médico-Cirúrgica,12. Rio de Janeiro: Guanabara Koogan; 2014.
7. Godoi KEPD, Penteado STDS, Mendes AEM, *et al*. Medication administration through feeding tube: practical profile in a tertiary teaching hospital. Rev Bras Farm Hosp Serv Saude. 2019;7(3). Available in: https://www.rbfhss.org.br/sbrafh/article/view/257. Accessed on: 07 jul 2020.
8. Gimenes FRE, Anacleto TA. Preparo e administração de medicamentos via sonda enteral ou ostomias. Instituto para Práticas Seguras no Uso dos Medicamentos (ISMP), 2015; 4 (4).
9. Silva AST, Pinto RLG, Rocha LR. Prevenção de eventos adversos relacionados à sonda nasogástrica e nasoenteral: uma revisão integrativa. J. nurs. health. 2020; 10 (5). DOI: 10.15210/JONAH.V10I4.16947.
10. Motta APG. Eventos adversos relacionados à sonda nasográstrica/ nasoentérica em pacientes adultos: revisão integrativa da literatura [Tese (doutorado)]. Universidade de São Paulo (USP), Ribeirão Preto, 2018.
11. Alonso-Herreros JM, Berisa-Prado S, Cañete-Ramírez C, *et al*. Hospital Pharmacy Compounding against COVID-19 pandemic. Farmacia hospitalaria: organo oficial de expresion cientifica de la Sociedad Espanola de Farmacia Hospitalaria. 2020;44(7):49-52. DOI: 10.7399/fh.11492.
12. Magarinos-Torres R, Osorio-de-Castro CGS, Pepe VLE. Atividades da farmácia hospitalar brasileira para com pacientes hospitalizados: uma revisão da literatura. Ciência & Saúde Coletiva, 2007;12:973-84. DOI: 10.1590/S1413-81232007000400019.
13. Miethke-Morais A, Cassenote A, Piva H, *et al*. Unraveling COVID-19-related hospital costs: The impact of clinical and demographic conditions. medRxiv. 2020. DOI: 10.1101/2020.12.24.20248633.
14. Agência Nacional de Vigilância Sanitária (Brasil). Resolução CMED nº 02, de 05 de março de 2004. definição de preços de produtos novos e novas apresentações. Available in: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/precos. Accessed on: 11 mar 2020.
15. Girard TD, Kress JP, Fuchs BD, *et al*. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. The Lancet. 2008;371(9607):126-34. DOI: 10.1016/S0140-6736(08)60105-1.
16. Wanzuita R, Poli-de-Figueiredo LF, Pfuetzenreiter F, *et al*. Replacement of fentanyl infusion by enteral methadone decreases the weaning time from mechanical ventilation: a randomized controlled trial. Critical Care. 2012;16(2). DOI: 10.1186/cc11250.
17. Lecronier M, Beurton A, Burrel S, *et al*. Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis. Critical Care. 2020;24(1):418. DOI: 10.1186/s13054-020-03117-9.
18. Carmona MJC, Quintão VC, Melo BFD, *et al*. Transforming operating rooms into intensive care units and the versatility of the physician anesthesiologist during the COVID-19 crisis. Clinics. 2020;75. DOI: 10.6061/clinics/2020/e2023.
19. Moura VA. Análise dos Fatores que Contribuem para o Aumento do Custo e do Desperdício Relacionado ao Repasse de Sonda Enteral em Unidades de Internação de Um Hospital De Médio Porte de Minas Gerais [dissertação (mestrado)]. Centro Federal de Educação Tecnológica (CEFET), Minas Gerais, 2013.
20. Paschoal MLH. Estudo do consumo de materiais de um centro cirúrgico após a implementação de um sistema de gestão informatizado [Tese (doutorado)]. Escola de Enfermagem, Universidade de São Paulo (USP), São Paulo, 2009.
21. Vecina Neto G, Reinhardt Filho W. Gestão de recursos materiais e de medicamentos. São Paulo, Editora Fundação Peirópolis Faculdade de Saúde Pública da Universidade de São Paulo; 1998.