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ORIGINAL RESEARCH ARTICLE

Trends in the Use of Sedative-Hypnotics, Opioids, and Neuromuscular Blockers in Hospitalized Patients During the COVID-19 Pandemic: Observational Retrospective Study

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Abstract

Background The coronavirus disease 2019 (COVID-19) pandemic has increased the use of drugs administered for mechanical ventilation, leading to shortages in some countries.

Objective The aim was to identify trends in the consumption of sedatives, hypnotics, neuromuscular blockers, and opioids used for anesthetic induction and deep sedation in hospitals in Colombia.

Method This was a descriptive, longitudinal, and retrospective study with monthly follow-up of sedative, hypnotic, opioid, and neuromuscular blocker dispensing in 20 clinics and hospitals from January to November 2020. The frequencies of use of each drug and variations in the institutions and intensive care units (ICUs) were identified.

Results A total of 1,252,576 units of the analyzed drugs were delivered to 79,094 treated patients, 55.0% of whom were women (n = 43,521). The drugs with the greatest increase in consumption were rocuronium (1058% variation in March–November) and propofol (511%). The consumption of midazolam and vecuronium initially increased, but by the end of the study period, it decreased. Among drugs dispensed only in ICUs, 920,170 units were delivered (73.5% of the drugs dispensed during the study), and the most often dispensed drugs were fentanyl (n = 251,519; 27.3% of the drugs used in the ICU) and midazolam (5 mg/5 mL) solution (n = 188,568; 20.5%). Specifically in the ICU, the drugs with the greatest increase in use were rocuronium (19,709%), propofol (2622%), and ketamine (2591%).

Conclusion Rapid changes in the use of drugs were evident, which demonstrates the need for closer cooperation among treating physicians, service providers, pharmaceutical managers, and state institutions to maintain a sufficient and timely supply of critical drugs in this type of contingency.

Key Points

Correct management of critically ill patients with severe coronavirus disease 2019 (COVID-19) requires mechanical ventilation.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic significantly increased the consumption of sedatives and anesthetics.

The drugs with the greatest increase in consumption were rocuronium (+ 1058%) and propofol (+ 511%).

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1 Introduction

The end of 2019 marked the beginning of the pandemic officially known as coronavirus disease 2019 (COVID-19), caused by the viral pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a high transmission rate and can cause severe acute respiratory syndrome (SARS) [1, 2]. The pandemic led to a 91% increase in the number of beds occupied in intensive care units (ICUs) in cities in Colombia [3], and the number of patients hospitalized in these departments with SARS increased up to 90% [3, 4].

Correct management of critically ill patients with severe COVID-19 and SARS requires the use of mechanical ventilation to improve gas exchange and oxygen transport to the tissues [5], which in turn requires sedation with drugs such as midazolam, propofol, and dexmedetomidine, opioids such as fentanyl, and, with some frequency, neuromuscular blockers to better tolerate the course of the intervention [5, 6].

The increase in the number of ICU beds occupied and in the number of patients requiring mechanical ventilation, some of whom are overweight and require higher drug doses, has led to a shortage of certain drugs in hospitals, as has been reported by health teams in France [7]. Therefore, it is of interest to determine the trends in the consumption of sedative-hypnotics, neuromuscular blockers, and opioids used for anesthetic induction and deep sedation in Colombian hospitals during 2020, which may be useful to improve the planning and supply of these drugs.

2 Materials and Methods

A retrospective, longitudinal, descriptive study was conducted based on hospital drug-dispensing data provided by Audifarma S.A., which included information from 20 clinics and hospitals in 14 cities of Colombia. Audifarma S.A. is the largest drug-dispensing company in Colombia, and provides medications to over 8 million people in the country, both for ambulatory and hospital centers. All study sites were tertiary to quaternary care level of attention and had a mean of 170 beds (range 60–405 beds). Regarding location, four institutions were from Bogotá (20.0%), three from Pereira (15.0%), and the remaining from 12 other cities in Colombia (Armenia, Barranquilla, Bello, Guadalajara de Buga, Cali, Cartagena, Chía, Ibagué, Itagüí, Manizales, Medellín, and Popayán).

The study included all data on monthly deliveries of sedative-hypnotics, opioids, and neuromuscular blockers in each hospital from January 1 to November 30, 2020, to calculate the total of each drug dispensed and the total number of patients to whom the drugs were dispensed for all clinics/hospitals and in ICUs. The dispensing information includes drug name, quantity, date, hospital service, etc. Data from all patients, of any age and sex, who received the study medications were included.

A database was created in Microsoft Excel with the information obtained, which included sociodemographic variables, clinic/hospital name and department, city of care, and the dispensing of the following drugs: (1) sedative-hypnotics: propofol, midazolam, dexmedetomidine, and ketamine; (2) neuromuscular blockers: rocuronium, cisatracurium, vecuronium, and succinylcholine; (3) opioids used for anesthetic induction: fentanyl and remifentanil. The quantity (units, equivalent to each vial of the study medications) and month of delivery were obtained for each drug.

2.1 Statistical Analysis

The data were analyzed using the statistical package SPSS v26.0. Frequencies of use of each drug were determined as well as the variation (percentage change) in monthly consumption as well as changes between the months of March and November because the mandatory quarantine began in Colombia on March 25, 2020 (baseline). Percentage change was calculated as [(final value − initial value)/initial value] × 100.

The total number of COVID-19 cases reported in Colombia during the study period was obtained from the official figures reported by the Colombian Government [8]. This was compared with the number of patients who received the study medications.

The study was classified as risk-free research according to Resolution No. 8430/1993 of the Ministry of Health of Colombia, which indicates that risk-free research does not require informed consent, and abided by the principles of data confidentiality established by the Declaration of Helsinki. Ethical approval was not sought for the present study because data did not contain patient names or any data that may individualize the person. Also, the database is owned by Audifarma S.A., and researchers had the approval to use it considering that no personal data from patients were included. There was no direct contact with any patient. No personal data (such as identifications, names, contact information) were used. Informed consent was not necessary to conduct this study.

3 Results

A total of 1,252,576 units of the drugs included in the analysis were delivered to 79,094 patients. Of these patients, 55.0% were women (n = 43,521).

Table 1 Total number of delivered units of sedative-hypnotics, neuromuscular blockers, and opioids and their monthly variation in 20 clinics and hospitals in Colombia, 2020

Drug	Number (% monthly variation)											% Variation March–November
	January	February	March	April	May	June	July	August	September	October	November	
Sedative-hypnotics												
Dexmedetomidine, 200 mcg/2 mL solution	3191	3354 (5.1)	2851 (− 15.0)	2161 (− 24.2)	2978 (37.8)	4572 (53.5)	7504 (64.1)	9511 (26.7)	8355 (− 12.2)	9717 (16.3)	10970 (12.9)	285%
Ketamine, 50 mg/mL solution	443	519 (17.2)	405 (− 22.0)	356 (− 12.1)	366 (2.8)	389 (6.3)	591 (51.9)	1257 (112.7)	2275 (81.0)	5174 (127.4)	2174 (− 58.0)	437%
Midazolam, 15 mg/3 mL solution	6040	5281 (− 12.6)	5802 (9.9)	5062 (− 12.8)	7678 (51.7)	22354 (191.1)	30363 (35.8)	48540 (59.9)	20392 (− 58.0)	19546 (− 4.1)	4509 (− 76.9)	− 22%
Midazolam, 5 mg/5 mL solution	23529	21088 (− 10.4)	17064 (− 19.1)	12746 (− 25.3)	21657 (69.9)	25029 (15.6)	33346 (33.2)	19705 (− 40.9)	46700 (137.0)	10239 (− 78.1)	5680 (− 44.5)	− 67%
Propofol, 10 mg/mL solution	12047	11313 (− 6.1)	9068 (− 19.8)	4867 (− 46.3)	8866 (82.2)	11076 (24.9)	15225 (37.5)	15634 (2.7)	20848 (33.4)	40535 (94.4)	55398 (36.7)	511%
Neuromuscular blockers												
Cisatracurium, 10 mg/5 mL solution	3628	1969 (− 45.7)	2402 (22.0)	2716 (13.1)	5690 (109.5)	8948 (57.3)	441 (− 95.1)	349 (− 20.9)	2190 (527.5)	9254 (322.6)	8286 (− 10.5)	245%
Rocuronium, 50 mg/5 mL solution	2207	2286 (3.6)	2083 (− 8.9)	1257 (− 39.7)	2150 (71.0)	6998 (225.5)	23024 (229.0)	25319 (10.0)	21251 (− 16.1)	24471 (15.2)	24111 (− 1.5)	1058%
Vecuronium, 10 mg powder for solution	1731	1468 (− 15.2)	1406 (− 4.2)	2762 (96.4)	1307 (− 52.7)	2648 (102.6)	549 (− 79.3)	641 (16.8)	380 (− 40.7)	286 (− 24.7)	233 (− 18.5)	− 83%
Succinylcholine, 1000 mg/10 mL solution	383	387 (1.0)	333 (− 14.0)	187 (− 43.8)	315 (68.4)	344 (9.2)	406 (18.0)	345 (− 15.0)	395 (14.5)	403 (2.0)	381 (− 5.5)	14%
Opioids for anesthetic induction												
Fentanyl, 0.5 mg/10 mL solution	18333	16968 (− 7.4)	14415 (− 15.0)	11712 (− 18.8)	18405 (57.1)	29866 (62.3)	46560 (55.9)	51429 (10.5)	39016 (− 24.1)	26224 (− 32.8)	39342 (50.0)	173%

Table 1 (continued)

Drug	Number (% monthly variation)											% Variation March–November
	January	February	March	April	May	June	July	August	September	October	November	
Remifentanil, 2 mg powder for solution	3624	3978 (9.8)	3426 (− 13.9)	1278 (− 62.7)	2298 (79.8)	3242 (41.1)	3188 (− 1.7)	2443 (− 23.4)	3801 (55.6)	13808 (263.3)	4560 (− 67.0)	33%

Of the drugs analyzed, the most commonly used in all hospital departments according to the quantity delivered were fentanyl (0.5 mg/10 mL solution) (n = 312,270; 24.9%), midazolam (5 mg/5 mL solution) (n = 236,783; 18.9%), and propofol (10 mg/mL solution) (n = 204,877; 16.4%). Table 1 shows the quantities delivered, the monthly percentage variation, and a comparison between the months of March and November for each analyzed drug. The drugs with the greatest increase in consumption were rocuronium (% variation March–November 1058%) and propofol (511%). In contrast, the final consumption of midazolam and vecuronium decreased.

Analysis of the subgroup of drugs dispensed only in the ICU showed that 920,170 units were delivered (73.5% of the drugs dispensed during the study), and the most commonly dispensed were fentanyl (0.5 mg/10 mL solution) (n = 251,519; 27.3% of the drugs used in ICUs), midazolam (5 mg/5 mL solution) (n = 188,568; 20.5%), and midazolam (15 mg/3 mL solution) (n = 147,200; 16.0%). The drugs with the greatest increase in consumption were rocuronium (19,709%), propofol (2622%), and ketamine (2591%). Table 2 shows the details of the monthly consumption and its variation throughout the 11 months of follow-up, and Figure 1 shows the number of patients who received any of the five most commonly used drugs compared to the total number of COVID-19 cases reported in Colombia.

Table 3 shows the monthly quantities delivered for the entire institutions, excluding the ICUs. In this setting, the drugs with the greatest increase in consumption were rocuronium (166%) and dexmedetomidine (110%). Finally, in the supplementary figure (see the electronic supplementary material), the number of patients with the most commonly used drugs are also compared to the total number of patients attended in the study hospitals.

4 Discussion

The present study results reveal the changes in the frequency of use of drugs administered for anesthetic induction and sedation and in mechanical ventilation procedures in patients treated in hospital departments in general and specifically in the ICUs of a group of clinics and hospitals in Colombia during the first 9 months of the COVID-19 pandemic. These results show increases of more than 200% for most of the analyzed drugs and up to 19,709% for rocuronium use in ICUs.

Dispensing of different pharmaceutical forms of midazolam showed a particular pattern due to the sustained increase in use during the months of May–July and August of 2020 and the subsequent decrease starting in September due to a general shortage of the drug; an increase in the consumption of propofol started this month. In addition,

Table 2 Total number of delivered units of sedative-hypnotics, neuromuscular blockers, and opioids and their monthly variation in 20 intensive care units of 20 clinics and hospitals in Colombia, 2020

Drug	Number (% monthly variation)											% Variation March–November
	January	February	March	April	May	June	July	August	September	October	November	
Sedative-hypnotics												
Dexmedetomidine, 200 mcg/2 mL solution	2518	2752 (9.3)	2414 (− 12.3)	1584 (− 34.4)	2446 (54.4)	3823 (56.3)	6777 (77.3)	8159 (20.4)	7645 (− 6.3)	8706 (13.9)	10053 (15.5)	316%
Ketamine, 50 mg/mL solution	73	89 (21.9)	66 (− 25.8)	83 (25.8)	58 (− 30.1)	75 (29.3)	215 (186.7)	892 (314.9)	1863 (108.9)	4605 (147.2)	1776 (− 61.4)	2591%
Midazolam, 15 mg/3 mL solution	4407	4054 (− 8.0)	4768 (17.6)	4057 (− 14.9)	6391 (57.5)	20424 (219.6)	25004 (22.4)	41662 (66.6)	16910 (− 59.4)	16078 (− 4.9)	3445 (− 78.6)	− 28%
Midazolam, 5 mg/5 mL solution	17960	16060 (− 10.6)	12688 (− 21.0)	9714 (− 23.4)	18534 (90.8)	20183 (8.9)	27539 (36.4)	15180 (− 44.9)	39878 (162.7)	6989 (− 82.5)	3843 (− 45.0)	− 70%
Propofol, 10 mg/mL solution	3268	2168 (− 33.7)	1625 (− 25.0)	1132 (− 30.3)	3584 (216.6)	5087 (41.9)	7672 (50.8)	7409 (− 3.4)	12001 (62.0)	28127 (134.4)	44225 (57.2)	2622%
Neuromuscular blockers												
Cisatracurium, 10 mg/5 mL solution	1712	837 (− 51.1)	829 (− 1.0)	812 (− 2.1)	4540 (459.1)	7649 (68.5)	281 (− 96.3)	290 (3.2)	1952 (573.1)	6917 (254.4)	6748 (− 2.4)	714%
Rocuronium, 50 mg/5 mL solution	114	77 (− 32.5)	95 (23.4)	147 (54.7)	352 (139.5)	4915 (1296.3)	18448 (275.3)	17886 (− 3.0)	16446 (− 8.1)	18460 (12.2)	18819 (1.9)	19709%
Vecuronium, 10 mg powder for solution	1157	956 (− 17.4)	894 (− 6.5)	1938 (116.8)	1052 (− 45.7)	1841 (75.0)	251 (− 86.4)	108 (− 57.0)	145 (34.3)	164 (13.1)	123 (− 25.0)	− 86%
Succinylcholine, 1000 mg/10 mL solution	1	3 (200.0)	1 (− 66.7)	2 (100.0)	5 (150.0)	3 (− 40.0)	10 (233.3)	5 (− 50.0)	1 (− 80.0)	3 (200.0)	5 (66.7)	400%
Opioids for anesthetic induction												
Fentanyl, 0.5 mg/10 mL solution	13300	12127 (− 8.8)	10223 (− 15.7)	8108 (− 20.7)	14788 (82.4)	24757 (67.4)	37474 (51.4)	42604 (13.7)	31723 (− 25.5)	22061 (− 30.5)	34354 (55.7)	236%

Table 2 (continued)

Drug	Number (% monthly variation)											% Variation March–November
	January	February	March	April	May	June	July	August	September	October	November	
Remifentanil, 2 mg powder for solution	73	125 (71.2)	276 (120.8)	1 (− 99.6)	148 (14700)	542 (266.2)	431 (− 20.5)	34 (− 92.1)	746 (2094.1)	9346 (1152.8)	1197 (− 87.2)	334%

dispensing of fentanyl showed a sustained increase starting in April, likely because of rescheduling of various medical-surgical procedures, until September, followed by a marked decrease in October, when remifentanil use significantly increased.

The observed increase in propofol and remifentanil consumption occurred because they were used to a greater extent together with other drugs due to the shortage of other options resulting from the increased number of patients requiring invasive mechanical ventilation due to COVID-19 in ICUs in the country [5]. In addition, it should be noted that remifentanil, within opioid analgesics, is preferred in patients with impaired renal or hepatic function and in obese and older adults [9]. Reports from Germany and Belgium have shown that patients with COVID-19 have required higher doses of sedatives compared to patients without this pathology [10, 11], which could also partly explain the significant increase in their consumption.

The dramatic increase in the consumption of rocuronium was probably due to the difficulty in obtaining the other neuromuscular blockers due to their shortage in Colombia (such as cisatracurium). A high variation in the consumption of this type of medication was also reported in ICUs in France, with changes of more than 100% for rocuronium and atracurium, and greater than 300% for cisatracurium, comparing March 2019 to March 2020 [12]. This study also reported great variations for other molecules, such as propofol (> + 160%) and midazolam (> + 200%) [12]. Of note, these comparative values change according to the study periods and the baseline chosen for comparison.

This analysis highlights the changes in drug use that in some cases occurred quickly and emphasizes the need for closer and more coordinated work among treating physicians, service providers, pharmaceutical managers, and state institutions. Such coordination is necessary to maintain a sufficient and timely supply of critical drugs in these types of contingencies, which can often exceed the forecasts and supplies of high-complexity care providers [13]. This situation even led the Colombian Ministry of Health to recommend the use of single doses of sedatives, anesthetics, and other drugs at risk of shortages, in services other than ICUs [14]. Likewise, the Colombian Association of Intensive Care Medicine and the Colombian Society of Anesthesiology generated specific documents with recommendations for the sedation and analgesia approach in the context of the pandemic and drug shortages [15], which included the use of inhaled sedatives (a suggestion also reviewed by other authors [16, 17]). The call for the rational use of pharmaceutical resources was widely described in the world, taking

Table 3 Total number of delivered units of sedative-hypnotics, neuromuscular blockers, and opioids and their monthly variation in 20 clinics and hospitals in Colombia, excluding Intensive Care Units, 2020

Drug	Number (% monthly variation)											% Variation March–November
	January	February	March	April	May	June	July	August	September	October	November	
Sedative-hypnotics												
Dexmedetomidine, 200 mcg/2 mL solution	673	602 (− 10.5)	437 (− 27.4)	577 (32)	532 (− 7.8)	749 (40.8)	727 (− 2.9)	1352 (86)	710 (− 47.5)	1011 (42.4)	917 (− 9.3)	110%
Ketamine, 50 mg/mL solution	370	430 (16.2)	339 (− 21.2)	273 (− 19.5)	308 (12.8)	314 (1.9)	376 (19.7)	365 (− 2.9)	412 (12.9)	569 (38.1)	398 (− 30.1)	17%
Midazolam, 15 mg/3 mL solution	1633	1227 (− 24.9)	1034 (− 15.7)	1005 (− 2.8)	1287 (28.1)	1930 (50)	5359 (177.7)	6878 (28.3)	3482 (− 49.4)	3468 (− 0.4)	1064 (− 69.3)	3%
Midazolam, 5 mg/5 mL solution	5569	5028 (− 9.7)	4376 (− 13)	3032 (− 30.7)	3123 (3)	4846 (55.2)	5807 (19.8)	4525 (− 22.1)	6822 (50.8)	3250 (− 52.4)	1837 (− 43.5)	− 58%
Propofol, 10 mg/mL solution	8779	9145 (4.2)	7443 (− 18.6)	3735 (− 49.8)	5282 (41.4)	5989 (13.4)	7553 (26.1)	8225 (8.9)	8847 (7.6)	12408 (40.3)	11173 (− 10)	50%
Neuromuscular blockers												
Cisatracurium, 10 mg/5 mL solution	1916	1132 (− 40.9)	1573 (39)	1904 (21)	1150 (− 39.6)	1299 (13)	160 (− 87.7)	59 (− 63.1)	238 (303.4)	2337 (881.9)	1538 (− 34.2)	− 2%
Rocuronium, 50 mg/5 mL solution	2093	2209 (5.5)	1988 (− 10)	1110 (− 44.2)	1798 (62)	2083 (15.9)	4576 (119.7)	7433 (62.4)	4805 (− 35.4)	6011 (25.1)	5292 (− 12)	166%
Vecuronium, 10 mg powder for solution	574	512 (− 10.8)	512 (0)	824 (60.9)	255 (− 69.1)	807 (216.5)	298 (− 63.1)	533 (78.9)	235 (− 55.9)	122 (− 48.1)	110 (− 9.8)	− 79%
Succinylcholine, 1000 mg/10 mL solution	382	384 (0.5)	332 (− 13.5)	185 (− 44.3)	310 (67.6)	341 (10)	396 (16.1)	340 (− 14.1)	394 (15.9)	400 (1.5)	376 (− 6)	13%
Opioids for anesthetic induction												
Fentanyl, 0.5 mg/10 mL solution	5033	4841 (− 3.8)	4192 (− 13.4)	3604 (− 14)	3617 (0.4)	5109 (41.2)	9086 (77.8)	8825 (− 2.9)	7293 (− 17.4)	4163 (− 42.9)	4988 (19.8)	19%

Table 3 (continued)

Drug	Number (% monthly variation)											% Variation March–November
	January	February	March	April	May	June	July	August	September	October	November	
Remifentanil, 2 mg powder for solution	3551	3853 (8.5)	3150 (− 18.2)	1277 (− 59.5)	2150 (68.4)	2700 (25.6)	2757 (2.1)	2409 (− 12.6)	3055 (26.8)	4462 (46.1)	3363 (− 24.6)	7%

as example some publications in Singapore [18], the United States [19, 20], India [21], and Italy [22].

Some limitations of this type of analysis are recognized, including that it did not consider variables related to drug consumption such as patient age, weight, and diagnosis, or the production and importation conditions according to the global demand for sedatives, opioids, and neuromuscular blockers. The use of inhaled anesthetics was also not taken into account, which has been promoted during the pandemic as an alternative treatment, because of the shortage of first-line drugs, due to their practicality and cost-effectiveness in low- and high-income countries [9, 23]. Data were only available for the study period, and other information previous to the pandemic or during further waves was not included.

It is evident that during the health emergency due to COVID-19, the health systems of Colombia and the world have faced difficulties [24]. Therefore, a priority for governments, drug regulatory agencies, manufacturing laboratories, and logistics companies should be to identify these challenges. Doing so may help to transform the manufacturing, import, export, and distribution systems that can affect the provision of services and maintain supply chains to both hospital and outpatient pharmacies. In addition to recognizing the increased needs of healthcare personnel for the correct prescription and application of these medications, it is important to strengthen risk assessment and management plans to include the increasing need for these and other health technologies based on integrated information systems, epidemiological control of demand by geographic levels, cooperation within the supply chain with other stakeholders in permanent round-table discussions, and monitoring and control of adequate resource use based on the recommendations of scientific societies using specific decision trees. The recognition of these risks and methods to manage them are vital for any health system [25].

5 Conclusion

The study data revealed trends in the use of sedative-hypnotics, opioids, and neuromuscular blockers. The results showed large and rapid variations resulting from the impact of the pandemic in Colombia during 2020. These findings emphasized the recommendation for closer work among treating physicians, state institutions, service providers, and pharmaceutical managers to maintain a sufficient and timely supply of critical drugs in this type of contingency.

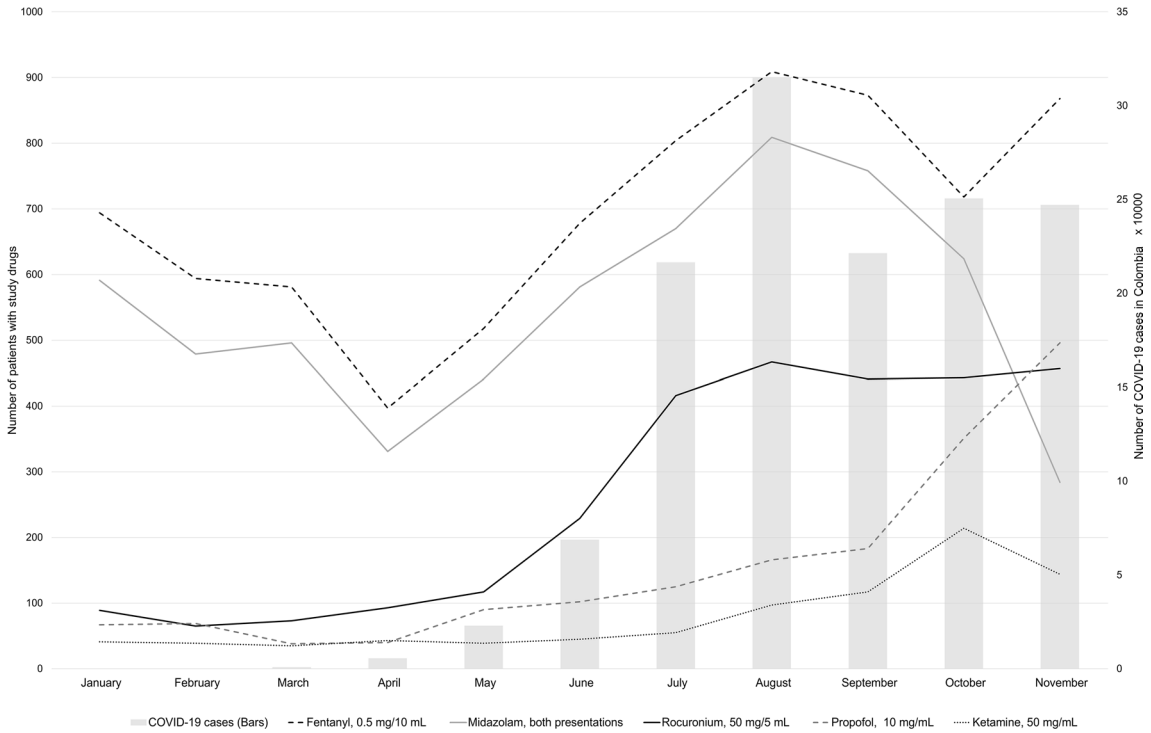

Fig. 1 Variation in the total number of patients treated with the five most commonly used sedative-hypnotics, opioids, and neuromuscular blockers in the intensive care units of 20 clinics and hospitals in Colombia, compared to the total number of patients with COVID-19*; 2020. *COVID-19* coronavirus disease 2019. *Total number of patients with COVID-19 in Colombia during the study period was obtained from official data (Ministry of Health of Colombia, available at: https://www.datos.gov.co/Salud-y-Protecci-n-Social/Casos-positivos-de-COVID-19-en-Colombia/gt2j-8ykr/data—cited 22/11/2021)

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Declarations

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Conflict of interest The authors declare no conflicts of interest.

Ethics approval The study was classified as risk-free research according to Resolution No. 8430/1993 of the Ministry of Health of Colombia, which indicates that risk-free research does not require informed consent, and abided by the principles of data confidentiality established by the Declaration of Helsinki. Ethical approval was not sought for the present study because data did not contain patient names or any data that may individualize the person.

Availability of data and material See http://protocols.io.

Code availability See https://doi.org/10.17504/protocols.io.bx65prg6.

Author contributions MEMD participated in the conceptualization, data curation, formal analysis, and original draft. JEMA participated in investigation, supervision, writing review, and editing. LFVR participated in the data curation, formal analysis, and methodology. AGM participated in the data curation, formal analysis, methodology, and original draft. JPAB participated in validation, writing review, and editing. All authors read and approved the final version.

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