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Associations between high-alert medications and potential drug-drug interactions in a pediatric intensive therapy unit

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Abstract

Objective: To analyze associations between high-alert medications and potential drug-drug interactions in pediatrics. **Methods:** The medical prescriptions of patients admitted to the pediatric intensive care unit within a period of six months were analyzed. The characterization of pDDI involving the high alert medications (HAM) was performed using the Micromedex® software. To identify factors associated with the incidence of pDDI found, inferential statistical tests were performed using the R software version 4.1.0. The significance level adopted was 5% ($p<0.05$**). Results:** Of the prescribed drugs, 27.9% were HAM. Seventeen of them were involved in some pDDI. Fentanyl, midazolam, methadone and regular insulin were associated with an increased chance of a patient having some pDDI. Fentanyl, midazolam, potassium chloride 10%, phenobarbital, methadone, clobazam, ketamine and morphine were associated with increased the average pDDI per patient. Having at least one HAM in the pDDI increased the severity of the pDDI, and fentanyl, potassium chloride 10%, phenobarbital, methadone, clobazam, ketamine, dexmedetomidine, morphine and tramadol were associated with severity. The amount of HAM involved in pDDI is directly correlated with the severity of pDDI. **Conclusion:** Knowledge of the factors associated with the incidence of pDDI involving HAM enables the reduction of adverse drug events, and consequently the promotion of pediatric patient safety.

Keywords: Patient Safety; High-alert medications; Drug Interactions.

Associações entre medicamentos de alta vigilância e interações medicamentosas potenciais em uma unidade de terapia intensiva pediátrica

Resumo

Objetivo: Analisar as associações entre os medicamentos de alta vigilância e as interações medicamentosas potenciais na pediatria. **Métodos:** Foram analisadas as prescrições médicas de pacientes internados na UTIP no período de janeiro a junho de 2020. A caracterização das IMP envolvendo os MAV foi realizada por meio do *software* Micromedex®. A fim de identificar fatores associados à incidência das IMP encontradas, foram realizados testes estatísticos inferenciais através do software R versão 4.1.0. O nível de significância adotado foi de 5% ($p<0,05$). **Resultados:** Dos medicamentos prescritos, 27,9% eram MAV. Dezessete deles estiveram envolvidos em alguma IMP. Os MAV fentanil, midazolam, metadona e insulina regular foram associados ao aumento da chance de um paciente apresentar alguma IMP. Os MAV fentanil, midazolam, cloreto de potássio 10%, fenobarbital, metadona, clobazam, cetamina e morfina foram associados ao aumento da média de IMP por paciente. Ter pelo menos um MAV na IMP aumentou a gravidade desta, e o fentanil, cloreto de potássio 10%, fenobarbital, metadona, clobazam, cetamina, dexmedetomidina, morfina e tramadol foram associados à gravidade das IMP. A quantidade de MAV envolvida na IMP está diretamente relacionada à gravidade da IMP. **Conclusão:** Esse estudo irá auxiliar o farmacêutico clínico na análise da farmacoterapia do paciente contribuindo, assim, para a segurança do paciente pediátrico.

Palavras-chave: Segurança do Paciente. Medicamentos Potencialmente Perigosos. Interações de Medicamentos.

Introduction

Pediatric patients have physiological factors that undergo changes throughout their development. These physiological modifications alter the pharmacokinetic stages (absorption, distribution, metabolization and excretion) and the pharmacodynamic action stage of the drugs[1]. Due to its peculiar characteristics regarding physiology and morphology, the pediatric population is more susceptible to harms and errors, especially those related to medication[2].

It is estimated that the probability of errors occurring in the hospital environment is approximately three times higher in pediatric patients than in adults with the same conditions[3,4,5].

Some drugs are classified as Potentially Dangerous Medications (PDMs) or also called High-Alert Medications (HAMs) because they have a narrow therapeutic window or because of the risk, inherent to their use, of causing considerable harms to the patient due to errors in their use process[6].

Although medication errors involving HAMs are not the most common, there should be high surveillance throughout their drug chain (prescription, dispensing and administration) due to their risk of causing serious harms to the patient, which can lead to death. In the case of pediatric patients, the prescription of HAMs represents an even greater alert for the professionals involved in the health care process, considering the vulnerability inherent to the age group among other factors[7,8].

When avoidable and without benefits for the patient's pharmacotherapy, Drug Interactions (DIs) are considered Adverse Drug Events (ADEs)[9]. DIs can be classified into real (those that can be proven by clinical manifestations of the patient) and into potential, which configure the possibility of these clinical manifestations actually occurring[10].

Due to the difficulty establishing a relationship between the clinical manifestations observed and DIs, the scientific literature has relied on the study of Potential Drug Interactions (PDIs) that are already well known and documented, evidencing the risks to which patients are exposed[11].

DIs can compromise patient safety, leading to prolonged hospitalization times, increased morbidity and mortality risks, and higher hospital costs related to the treatment[12,13].

This study aimed at analyzing associations between high-alert medications and potential drug interactions in Pediatrics.

Methods

Study data and design

A cross-sectional, retrospective and quantitative study was carried out, and the data were collected over 6 months (from January to June 2020) in a pediatric ICU of a university hospital located in Rio de Janeiro, through the analysis of electronic medical prescriptions.

Eligibility criteria

All patients admitted from January 1st to June 30th, 2020, with any outcome and who received at least two concomitant medications during their hospitalization period were included in the research.

Exclusion corresponded to patients that remained hospitalized for less than 24 hours, prescribed medications with dosages at the physician's discretion, sprays, eye drops and mouthwashes, medications administered by inhalation and topical route, and enteral nutrition.

Data collection

The following patient characterization information was collected: gender, date of birth, age at the first hospitalization day, outcome (discharge or death), date of admission to the Pediatric ICU and date of the outcome; as well as data related to the medications prescribed, such as name of the drug and administration route. The medications prescribed were compared to the last bulletin published by the ISMP (2019) in order to be considered HAMs.

Readmissions were considered as new patients. The hospitalization time was calculated based on the first day the patient was admitted to the Pediatric ICU until the day they received any outcome.

The patients were classified into the following age groups: term newborns (from 37 weeks to 27 days old), infants (from 28 days to 23 months old), preschoolers (from 2 to 5 years old), schoolchildren (from 6 to 11 years old) and adolescents (from 12 to 19 years old)[14].

The number of medications prescribed to the patients was stratified into the following categories: Oligopharmacy- less than or equal to 4; Polypharmacy – greater than or equal to 5; and Excessive polypharmacy – greater than or equal to 10[15, 16].

Descriptive analysis

The PDIs were identified and characterized using the *Thomson Micromedex®* database. All the medications prescribed for each patient were individually incorporated into the platform during the hospitalization period, identifying all PDIs within the set of drugs included.

PDIs were those in which the medications involved were prescribed in the same medical prescription. The clinical manifestations of drug interactions were not within the objectives to be evaluated and, therefore, the expression "potential drug interaction" was adopted[10,17].

The PDIs were classified according to the scientific evidence as excellent, good and reasonable, and according to the severity degree as contraindicated, severe, moderate and minor.

Statistical analysis

In order to test the association between variations in the HAMs prescribed and presence of PDIs, chi-square and Fisher's exact independence tests were used. Bivariate tests using the *Mann-Whitney* non-parametric test were also employed to compare the number of PDIs between patients that were prescribed HAMs and those who were not prescribed HAMs during their hospitalization time.

To analyze the impact of HAM prescription on the severity of potential drug interactions, an association test was performed between severity of the PDIs (minor, moderate, major and contraindicated) and presence of HAMs in PDIs using the *Mann-Whitney* non-parametric test. An analysis was also performed

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comparing severity of the PDIs to the number of HAMs involved in the PDIs by means of *Spearman*'s correlation coefficient.

Finally, in order to verify which HAMs are associated with increased severity of the PDIs, an ordinal logistic regression model was adjusted. The magnitude of the associations was estimated by means of the *Odds Ratio* (OR), which in this analysis indicates the chance of increasing (in cases of positive coefficients) or decreasing (in cases of negative coefficients) the severity of a given PDI in the presence of the HAM tested.

All statistical tests were evaluated by means of the p-value that is associated with the hypothesis test. The significance level adopted for the tests was 5% (p<0.05) under the two-tailed hypothesis, and the calculations were performed with the aid of the R software, version 4.1.0 (R Core Team 2014).

Ethical issues

The project was submitted to *Plataforma Brasil* and approved under CAAE: 36514820,6.0000.5264.

Results

Characterization of the population

Of the 102 pediatric patient hospitalizations, 69 (67.6%) were male. Their age varied from 1 day to 16 years old, with a mean of 3.73 years old (± 4.37) and predominance of infants (45.1%). The hospitalization time ranged from 1 to 47 days, with a mean of 6.26 days (± 7.03) per patient and a median of 3. Seven patients (6.9%) evolved to death.

Most of the patients (40.2%) were on polypharmacy, whereas 39.2% were subjected to excessive polypharmacy during the hospitalization period.

Drug interactions involving high-alert medications

Of the 102 patients, 49 (48.0%) had some Potential Drug Interaction (PDI) involving High-Alert Medications (HAMs) in their medical prescriptions. 97 different PDIs involving HAMs were identified, which were detected 1,100 times in medical prescriptions throughout the study period. Of these 97 PDIs, there was participation of 194 medications that interacted in pairs.

Of the 41 HAMs prescribed, 17 (41.5%) were involved in some PDI. Fentanyl was the most interacting drug, participating in 24 different PDIs. This means that this HAM interacted with 24 different medications. These 24 PDIs were identified 369 times in the medical prescriptions.

The PDIs involving HAMs represented 43.7% of the total PDIs in relation to the different types of PDI identified, and 51.5% in terms of the frequency with which they were recorded. The most prevalent PDI was between fentanyl and midazolam, which was recorded 94 times and affected 32 patients (31.7%).

Of the 1,100 PDIs involving HAMs identified, 789 (71.7%) were of major severity and 284 (25.8%) of moderate severity. Only 8 (0.7%) were considered contraindicated. Regarding documentation, the majority (767 [69.7%]) had a reasonable level of scientific evidence.

High-alert medications associated with the occurrence of drug interactions

When found in medical prescriptions, the fentanyl, midazolam (p<0.001), methadone (p=0.032) and regular insulin (p=0.047) HAMs increased the chances of the pediatric patients presenting some PDI (TABLE 1).

Table 1. High-alert medications predicting the occurrence of potential drug interactions

High-Alert Medications	HAM prescription or not	Number of patients with or without PDIs		p-value
		No	Yes	
Fentanyl	No	28 (42%)	39 (58%)	<0.001a
	Yes	0 (0%)	35 (100%)	
Midazolam	No	28 (41%)	40 (59%)	<0.001a
	Yes	0 (0%)	34 (100%)	
10% potassium chloride	No	9 (36%)	16 (64%)	0.398a
	Yes	19 (25%)	58 (75%)	
Phenobarbital	No	24 (30%)	57 (70%)	0.488a
	Yes	4 (19%)	17 (81%)	
Methadone	No	28 (31%)	63 (69%)	0.032b
	Yes	0 (0%)	11 (100%)	
Clobazam	No	28 (30%)	65 (70%)	0.06b
	Yes	0 (0%)	9 (100%)	
Ketamine	No	28 (28%)	71 (72%)	0.56b
	Yes	0 (0%)	3 (100%)	
Dexmedetomidine	No	27 (28%)	69 (72%)	1b
	Yes	1 (17%)	5 (83%)	
Morphine	No	28 (28%)	71 (72%)	0.56b
	Yes	0 (0%)	3 (100%)	
Diazepam	No	28 (28%)	73 (72%)	1b
	Yes	0 (0%)	1 (100%)	
Epinephrine	No	27 (29%)	66 (71%)	0.438b
	Yes	1 (11%)	8 (89%)	
Cyclophosphamide	No	28 (28%)	73 (72%)	1b
	Yes	0 (0%)	1 (100%)	
Tramadol	No	28 (29%)	67 (71%)	0.185b
	Yes	0 (0%)	7 (100%)	
Vasopressin	No	28 (29%)	69 (71%)	0.319b
	Yes	0 (0%)	5 (100%)	
Enoxaparin	No	28 (28%)	73 (72%)	1b
	Yes	0 (0%)	1 (100%)	
Rocuronium	No	28 (28%)	72 (72%)	1b
	Yes	0 (0%)	2 (100%)	
Regular insulin	No	24 (25%)	72 (75%)	0.047b
	Yes	4 (67%)	2 (33%)	

(a) Chi-square test
(b) Fisher's exact test

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High-alert medications associated with an increased number of potential drug interactions.

The fentanyl (p<0.001), midazolam (p<0.001), 10% potassium chloride (p=0.016), phenobarbital (p=0.007), methadone (p<0.001), clobazam (p=0.002), ketamine (p=0.021) and morphine (p=0.047) HAMs appear as more likely to increase the mean number of PDIs per patient (TABLE 2).

For example, the presence of fentanyl in the prescriptions of pediatric patients increased the mean number of PDIs per patient from 10.7 to 41.23.

High-alert medications associated with increased severity of the drug interactions

Through the *Mann-Whitney* test we see that there is an association (p<0.001) between both variables tested (severity and presence of a high-alert medication); in other words, the presence of at least one high-alert medication in the PDI increases severity of this interaction (TABLE 3).

Table 2. Comparison between the number of potential drug interactions in patients who received HAMs in their prescriptions and those who did not

High-Alert Medications	HAM prescription or not	Patients	Potential Drug Interactions							p-value
			Min	Max	1st Quartile	3rd Quartile	Mean	Median	Standard Deviation	
Fentanyl	No	67 (65.7%)	0	136	0	7.5	10.7	2	25.260	<0.001d
	Yes	35 (34.3%)	3	165	13	34	41.23	39	31.197	
Midazolam	No	68 (66.7%)	0	136	0	8.5	10.57	0	24.574	<0.001d
	Yes	34 (33.3%)	3	165	20.25	53.25	42.38	40	31.735	
10% potassium chloride	No	25 (24.5%)	0	75	0	10	9.88	2	19.376	0.016d
	Yes	77 (75.5%)	0	165	1	41	24.65	10	32.887	
Phenobarbital	No	81 (79.4%)	0	136	0	19	16.58	4	26.560	0.007d
	Yes	21 (20.6%)	0	165	6	56	38.9	36	39.926	
Methadone	No	91 (89.2%)	0	136	0	19	16.91	4	26.849	<0.001d
	Yes	11 (10.8%)	12	165	32.5	62.5	56.45	51	40.503	
Clobazam	No	93 (91.2%)	0	165	0	25	19.28	5	31.279	0.002d
	Yes	9 (8.8%)	12	65	29	56	40.78	38	18.793	
Ketamine	No	99 (97.1%)	0	136	0	30	19.17	6	27.283	0.021d
	Yes	3 (2.9%)	25	165	48.5	118.5	87.33	72	71.248	
Dexmedetomidine	Não	96 (94.1%)	0	165	0	29.5	20.01	6	30.540	0.101d
	Yes	6 (5.9%)	0	101	26	46	39.83	31.5	34.057	
Morphine	No	99 (97.1%)	0	136	0	30	19.42	6	27.469	0.047d
	Yes	3 (2.9%)	11	165	36	113	79	61	78.562	
Diazepam	No	101 (99%)	0	165	0	34	21.35	6	31.037	0.784d
	Yes	1 (1%)	4	4	4	4	4	4	NA	
Epinephrine	No	93 (91.2%)	0	165	0	27	20.03	6	31.278	0.09d
	Yes	9 (8.8%)	0	72	4	50	33	41	25.593	
Cyclophosphamide	No	101 (99%)	0	165	0	34	21.14	6	31.082	0.492d
	Yes	1 (1%)	25	25	25	25	25	25	NA	
Tramadol	No	95 (93.1%)	0	165	0	37	22.11	7	31.805	1.00d
	Yes	7 (6.9%)	3	25	5	8	8.57	6	7.569	
Vasopressin	No	97 (95.1%)	0	165	0	31	20.65	6	31.152	0.127d
	Yes	5 (4.9%)	4	72	11	41	31.4	29	26.987	
Enoxaparin	No	101 (99%)	0	165	0	34	21.29	6	31.065	0.85d
	Yes	1 (1%)	10	10	10	10	10	10	NA	
Rocuronium	No	100 (98%)	0	165	0	29.5	20.75	6	31.068	0.133d
	Yes	2 (2%)	34	51	38.25	46.75	42.5	42.5	12.021	
Regular insulin	No	96 (94.1%)	0	165	0.75	34.5	21.45	6.5	31.150	0.25d
	Yes	6 (5.9%)	0	72	0	21.75	16.83	0	29.410	

(d) Mann-Whitney test

Table 3. Statistical analysis according to classification of the PDIs in the Pediatric ICU

Severity	Presence of high-alert medications in potential drug interactions		
	No (n=1,036)	Yes (n=1,100)	
Minor	110 (85.3%)	19 (14.7%)	
Moderate	476 (62.6%)	284 (37.4%)	
Major	448 (36.2%)	789 (63.8%)	p<0.001
Contraindicated	2 (20.0%)	8 (80.0%)	
	1,036	795	

Spearman's test, with p<0.001, allowed us to infer that the number of high-alert medications involved in the interaction is directly correlated with severity of the PDI (p=0.366) (TABLE 4). In other words, the more HAMs involved in the PDI, the greater its severity.

Fentanyl (p<0.001), 10% potassium chloride (p<0.001), phenobarbital (p=0.023), methadone (p<0.001), clobazam (p<0.001), ketamine (p<0.001), dexmedetomidine (p=0.002), morphine (p<0.001) and tramadol seem more likely to exert impacts on severity of the PDI (TABLE 5).

We draw the attention to phenobarbital, whose presence represents a decrease in severity (Coefficient=-0.31), whereas the others exert an impact on increased severity.

Table 4. Number of HAMs involved in each PDI (n=2,136)

Severity	Number of high-alert medications involved in potential drug interactions			
	Zero n(%)	One n (%)	Two n (%)	
Minor	110 (85.3%)	19 (14.7%)	0 (0%)	
Moderate	476 (62.6%)	284 (37.4%)	0 (0%)	
Major	448 (36.2%)	484 (39.1%)	305 (24.7%)	p<0.001
Contraindicated	2 (20.0%)	8 (80.0%)	0 (0%)	
	1,036	795	305	

Table 5. Statistical analysis of the impact of the HAMs on severity of the PDIs

High-Alert Medications	Coefficient	Odds Ratio	Standard Error	t-value	p-value
Fentanyl	4.42	83.29	0.37	12.03	<0.001
Midazolam	-0.10	0.90	0.14	-0.70	0.482
10% potassium chloride	5.78	323.35	1.74	3.33	<0.001
Phenobarbital	-0.31	0.73	0.14	-2.28	0.023
Methadone	6.90	989.08	0.90	7.66	<0.001
Clobazam	3.18	23.98	0.54	5.84	<0.001
Ketamine	3.70	40.57	1.12	3.32	<0.001
Dexmedetomidine	2.62	13.80	0.84	3.13	0.002
Morphine	2.44	11.43	0.50	4.83	<0.001
Diazepam	5.78	323.44	5.26	1.10	0.272
Epinephrine	5.90	365.88	6.05	0.98	0.329
Cyclophosphamide	-1.00	0.37	1.26	-0.80	0.423
Tramadol	5.48	239.00	2.36	2.32	0.020
Vasopressin	5.72	306.40	3.98	1.44	0.151
Enoxaparin	5.72	306.32	4.30	1.33	0.183
Regular insulin	-1.00	0.37	1.77	-0.56	0.574
Minor|Moderate	-2.39		0.10	-24.22	<0.001
Moderate|Major	0.39		0.06	6.28	<0.001
Major|Contraindicated	11.16		0.87	12.78	<0.001

Discussion

This study made it possible to identify the HAMs that negatively impact the occurrence of PDIs by interfering with their severity, the chance of the patients presenting some PDI and the increase in their mean number per patient. In addition to that, the presence and number of HAMs involved in PDIs was also a factor that negatively impacted the results found.

From the characterization of the hospitalized patients, it can be seen that the profile of the institution's Pediatric ICU is similar to those of most ICUs in other pediatric hospitals. Predominance of males (67.6%) was also found in other similar studies[18,19,20,21,22,23,24].

The higher prevalence of infants (45.1%) also converges with other studies conducted in Pediatric ICUs[25,26,27,28]. This result can be explained by the immune system immaturity, which renders them more susceptible to infections and systemic complications[29,30], with the possible need for intensive care to solve the condition.

Regarding hospitalization time, the mean found (6.26 days per patient) was close to the one detected in similar studies, which varied from 5 to 7.5 days per patient[24,31,32,33]. Hospitalization time is a risk factor for in-hospital infections and adverse events[34].

As for PDIs, fentanyl was the most interacting HAM. This result was also found by Cortes and Silvino (2019), where fentanyl was found in 36 of the 54 DI pairs[35].

The most frequent PDI (fentanyl and midazolam) was also the most frequent PDI observed in an integrative review that aimed at evaluating the characteristics associated with potential drug interactions in patients admitted to ICUs in Brazil. This study verified that the most common pair of medications found in three studies corresponded to the fentanyl-midazolam combination[36]. This potential drug interaction has greater severity, reasonable documentation and pharmacodynamic mechanism. This interaction can result in an increased risk of Central Nervous System (CNS) depression, which may cause respiratory depression, hypotension and excessive sedation[37].

Regarding the classification in relation to severity, the high prevalence of severe PDIs (71.7%) is worrying, as children with severe or contraindicated PDIs presented a 9.38-day increase in their hospitalization times, according to Lima *et al.* (2020)[38].

In addition, a study conducted at a Pediatric ICU in Porto Alegre found that hospitalization time exerts a significant effect on the morbidity of critically-ill patients[39].

In turn, regarding documentation, high prevalence of PDIs with reasonable documentation was also found in other studies – 67% and 61.54% – which reasserts the need for further studies regarding the PMIs found[40,41.]

Fentanyl, midazolam, methadone and regular insulin were strongly associated with the occurrence of PDIs; in other words, when found in medical prescriptions, they proved to increase the chances of pediatric patients presenting some PDI. This result was similar to the one found by Cortes (2016), who verified that regular insulin, midazolam and amiodarone were the three drugs that increased the possibility of PDIs[9]. Amiodarone was not found in the medical prescriptions analyzed: therefore, it was not tested. In fact, in our study, fentanyl and midazolam were the most interacting HAMs, interacting with 24 and 21 medications respectively, out of the 147 drugs prescribed. The association of methadone with the occurrence of PDIs can also be explained by its interacting profile, as it was the fourth most interacting medication in our study.

Fentanyl, midazolam, 10% potassium chloride, phenobarbital, methadone, clobazam, ketamine, and morphine were associated with greater propensity to increasing the mean number of PDIs per patient. Nearly 80% of the patients were classified as polymedicated or as excessively polymedicated. Several studies have already evidenced that polypharmacy has a positive correlation with the number of drug interactions[42,43,44,45], being the factor most associated with the occurrence of PDIs[36]

Regarding severity of the PDIs, there was an association between presence of a HAM in the PDI/number of HAMs involved in the PDIs and increased severity of the PDIs. This result was expected due to the narrow therapeutic window or to the inherent risk of HAMs causing significant harms to the patient[46,47,48]. Consequently, the more HAMs involved in a PDI, the greater the severity.

Fentanyl, 10% potassium chloride, methadone, clobazam, ketamine, dexmedetomidine, morphine and tramadol were associated with a greater tendency to increase severity of the PDIs. In our study, all PDIs involving fentanyl, 10% potassium chloride, ketamine, dexmedetomidine and tramadol were classified as of major severity. Nearly 85.7% of the PDIs involving clobazam and morphine were of major severity, 92.9% of the PDIs involving methadone were also of major severity, and 7.1% were contraindicated.

Regarding the study limitations, it is important to note that it was conducted in a single pediatric hospital, requiring similar studies that corroborate the results found. Seasonality may have influenced the medications prescribed due to the brief study period and, consequently, the PDIs observed. The analyses were based on potential drug interactions, without actually verifying the clinical outcome of the DIs; therefore, it would be interesting for future studies to analyze their clinical manifestations.

Conclusion

Identifying the factors associated with the incidence of potential drug interactions will contribute to directing the clinical pharmacists' gaze towards HAMs that negatively impacted the occurrence of important PDIs, the increase in PDIs and their severity during the pharmacotherapy analysis.

Studies like this make it possible to optimize the analysis of pediatric patients' pharmacotherapy and may contribute to their safety in the hospital environment.

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Collaborators

BDC, MAB and RCC were responsible for conception and design of the study. BDC and BCS were in charge of data collection. BCC was responsible for the methodological design. BDC and MAB were in charge of data analysis and interpretation. All authors were responsible for the relevant critical review of the intellectual content and approved the final version of the article.

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Declaration of conflict of interest

The authors declare that there are no conflicts of interest in relation to the article.

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