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Incidence of drug-related adverse events related to the use of high-alert drugs: A systematic review of randomized controlled trials

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ABSTRACT

Background: High-alert medication (HAM) is more predictable to cause significant harm to the patient, even when used as intended. The damage related to the HAM lead not only suffering to the patient, but also raise the additional costs associated with care.
Objective: Evaluate the incidence of drug-related adverse events related to the use of high-alert medications.
Methods: It was conducted an active search for information through COCHRANE databases, LILACS, SciELO, SCOPUS, PubMed/MEDLINE and WEB OF SCIENCE. The search strategy included the following terms: "Patient safety", "Medication errors" and "Hospital" and "High Alert Medications" or "Dangerous Drugs" in different combinations. Then two reviewers independently conducted a preliminary evaluation of relevant titles, abstracts and finally full-text. Studies quality was evaluated according to PRISMA declaration.
Results: The systematic review evaluated seven articles, which showed that only 11 HAM identified in the literature could have serious events. The most frequently cited were warfarin (22.2%) which progressed from deep vein thrombosis to gangrene, suggesting lower initial doses, followed by cyclophosphamide (22.2%) and cyclosporine (22.2%) which presented invasive fungal infection and death. In addition to these, morphine was compared with its active metabolite (M6G), with M6G causing fewer serious clinical events related to nausea and vomiting, reducing the need for concomitant use of antiemetics.
Conclusions: The most reported drug classes in the articles included that were related to incidence of drug-related adverse events in use of high-alert medications: morphine, M6G-glucuronide, haloperidol, promethazine, ivabradine, digoxin, warfarin, ximelagatran, cyclophosphamide, cyclosporine, and ATG. The formulate protocols for the use of these medications, with importance placed on evaluating, among the classes, the medication that causes the least harm.

1. Introduction

Adverse drug events (ADE) occur frequency and increase morbimortality of patients, consolidating as a public health problem,[1] what has direct impact on the safety of patients. ADE comprise adverse drug reactions (ADR) and medication errors (ME). The occurrence of a

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ME can increase the risk of experiencing an ADR. It can occur in whatever step of the medication system (prescription, dispensing and/or administration of drugs), and it can be done by any health professional from the multidisciplinary team responsible for actions related to drug therapy such as doctors, pharmacists, and nurses.[2,3,4]

It is estimated that every year 100,000 patients die of ADE in hospitals, in United States of America (USA),[5] and 4% of hospital admissions in this country are due to Adverse Drug Reactions (ADR), and 57% of these reactions are not recognized in the moment of the admission. Adding patients with serious ADR, which hospitalization is required, to patients with ADR that occurred during the hospitalization, >2,2 million of people every year, 6000 patients every day, are victims of this harm. In both situations, from 32% to 69% of these events are preventable[6]. The occurrence of ADR in hospital inpatients can represent a range of 5–9% of hospital costs, and 45% of them are preventable.[7,8]

Nevertheless, even knowing the most drugs have a therapeutic safety range, there are drugs associated to high percentage of errors, and/or sentinel events, and drugs with high risk of adverse outcomes, besides these drugs have an inherent risk to cause harm to patients when there is failure in their utilization process.[9] These drugs are called high-alert medications (HAM) or high-risk medications. Errors that happen to these medications are not the most common, but when they happen, they have high severity and can lead to permanent lesions or be fatal.[10,11]

Thus, HAM are more predictable to cause significant harm to patients, when administered incorrectly, as disclosed by the Institute for Safe Medication Practices (ISMP). The Joint Commission, referring the ISMP study, described high-alert medications as "drugs that carry an increased risk of causing significant harm to individuals when they are used without special care".[12,14]

According to results obtained from the use of IHI Global Trigger tool, and from the experience of hospitals participating in the Institute for Healthcare Improvement Collaboratives study,[12] the selection of drug classes focused on four groups of drugs that require more attention – anticoagulants, analgesic and opiates, insulin and sedatives. The most common types of associated harms to these drugs include hypotension, bleeding, hypoglycemia, delirium, lethargy and excessive sedation.[12]

Other authors are in agreement that harms related to HAM can lead to patient's suffering as well as elevated additional costs associated to patient's care.[11,12] In 2005, ISMP listed 19 classes or categories of drugs and 14 were considered high-alert specific drugs. Although, it is important to improve management of all these drugs, some of them require special attention because they are associated with more frequent harms than others.[13,14]

At the same time, patient's safety related to drugs is the main topic of thousands of published studies in scientific literature, the estimation of prevalence and incidence values of harms caused by drugs is still a challenge due to the large amount of published information, great variability of studies quality, and often conflicting results.[15–17] In May 2004, at the 57° World Health Assembly was established the Global Alliance to patient's safety, and one of its guidelines is the development and widespread of knowledge about policies and best practices in patient's safety.[4]

Given the importance of errors involving HAM, by the point of view of its prevalence or its potential risk to inpatients, the present study has as aim evaluate the safety profile of these drugs through a Systematic Review of randomized clinical trials, and identify strategies to reduce risks and harms caused to patients that are submitted to treatments with these types of drugs in the hospital environment.

2. Methods

This review was carried out in seven steps, adopting recommendations of the Cochrane Handbook. The research question guides the steps of the systematic review, from the direction of the search, data extraction and presentation of the results, as from this it is possible to identify the population included in the RCTs and the outcomes evaluated in the included studies.

In order to guide the research question formulation, the question was structured according to the components of the PICO acronym, where each letter represents a question component, according to the following concepts:

P – population: patients and inpatients who take high-alert medications (HAM).

I – intervention: adverse events described.

C – control: patients who do not take HAM *versus* the ones who take these drugs.

O – outcome: serious adverse events described.

With the following research question:

"Do patients who use HAM have more severe adverse events described when compared to patients who do not use HAM?"

2.1. Location of the studies

It was conducted an active information search through the databases COCHRANE, LILACS, SCIELO, SCOPUS, PUBMED/MEDLINE e WEB OF SCIENCE, with unbounded time.

Thus, the search strategy included the following MeSH/DeCS terms: "Patient safety", "Medication errors" and "Hospital" and other non-MeSH/DeCS terms also used were: "High Alert Medications" or "Dangerous Drugs" in different combinations.

2.2. Selection of the studies

In all stages of selection of this review were applied inclusion criteria previously established such as: (i) all studies must be clinical trials; (ii) the study could be published in Portuguese, Spanish and English; (iii) the study must consider patients who use high-alert medications; (iv) full-text articles available in databases. It is important to note that inclusion criteria including just randomized clinical trials in this review was given through the high level of clinical evidence of this type of study for the effectiveness and safety of the drugs found.

In this systematic review were excluded theoretical articles, case reports, congress summaries, letters to the editor, results and reports awards, studies that focused at evaluation tools as well as those that do not presented available full-text and those that were not possible to search through none of the attempts made (direct contact with the author, and/or attempts to search on international databases through the partnership between the Central Health Library at University Hospital and these databases).

2.3. Data extraction, analysis and presentation

Independently, two reviewers (M.S.M.) and (G.A.A.D.), both pharmacists, extracted the relevant data from the articles to investigate the data considered important to the analysis of this review, at the same year and location of the search. It was obtained information about the study design, place of research performance, number of included participants, inclusion and exclusion criteria as well as main results and described limitations by the authors.

The reviewers conducted the initial evaluation of relevant titles, subsequently abstracts, and finally, full-text. Possible divergences were analyzed and judged by a third evaluator. Articles indexed repeatedly in two or more databases were considered as just one.

2.4. Interpretation of the results

Studies quality was evaluated according to PRISMA declaration. The tool deals with methodological guidelines and elaboration of systematic review and meta-analysis to randomized clinical trials.[18]

The calculation of the degree of agreement between the evaluators at the presented steps was conducted through Bio Estat version 5.3, by

analysis of two related samples.

3. Results

Initial search on databases identified 1717 articles, after exclusion of the repeated studies were identified 427 titles, from which were selected 53 abstracts considered potentially relevant. After evaluation of these ones, 25 articles were selected to full-text reading. Degree of agreement between both evaluators was considered good in the first and second steps, respectively ($k = 0.898$, $p < 0.0001$) e ($k = 0.7115$, $p = 0.0017$).

After reading and evaluation of the selected studies, seven articles meet the eligibility criteria according to PRISMA methodology adapted by the reviewers to this study. Related to articles that did not provide full-text, attempts were made to obtain them through direct contact with the author and by the Brazilian Institute for Information in Science and Technology (IBICT-Comut). Fig. 1 shows the selection process and the number of excluded and included articles at each step of the articles search and selection.

Related to studies quality, articles were evaluated according to suitability criteria proposed by Jadad Scale,[19] which were classified six articles with high methodological quality, and just one was evaluated as low quality. Just one article showed failure in the study development process as double-blind trial, other three studies did not explain it. Table 1 shows studies quality distribution and Table 2 describes all the selected studies characterization.

Related to HAM, only 11 drugs were identified in the literature with potential serious events. The most cited were warfarin (22.2%), cyclophosphamide (22.2%), and cyclosporine (22.2%). These results are showed in the Table 3, which illustrates the drug-related events description found in this review.

Two studies evaluated cyclophosphamide use, one in children and other in adults, both with Severe Aplastic Anemia. The second one was compared with cyclosporine, and cyclosporine alone with anti-thymocyte globulin (ATG), which is an immunosuppressant that leads to lymphocyte depletion, recognizing most of the molecules involved in the cascade activation of lymphocytes preventing transplant rejection. In the study conducted with children taking cyclophosphamide was observed that five patients presented uncontrolled infection, six patients confirmed documented fungal infection, and nine patients died.

Patients taking cyclophosphamide+cyclosporine association required more time to recover due to neutropenia besides they needed antibiotic+amphotericin B treatment and red blood cell transfusion. This study demonstrates that the intake of cyclosporine alone can have potentially benefit antifungal effects.

The study comparing cyclophosphamide, cyclosporine, and ATG showed after a median follow-up of 2,2 years that relapse occurred in two patients, and cytogenetic abnormalities (including monosomy 7) occurred in four patients. Four patients from the cyclophosphamide group developed invasive fungal infections (pulmonary aspergillosis in two patients), two other patients from the same group confirmed

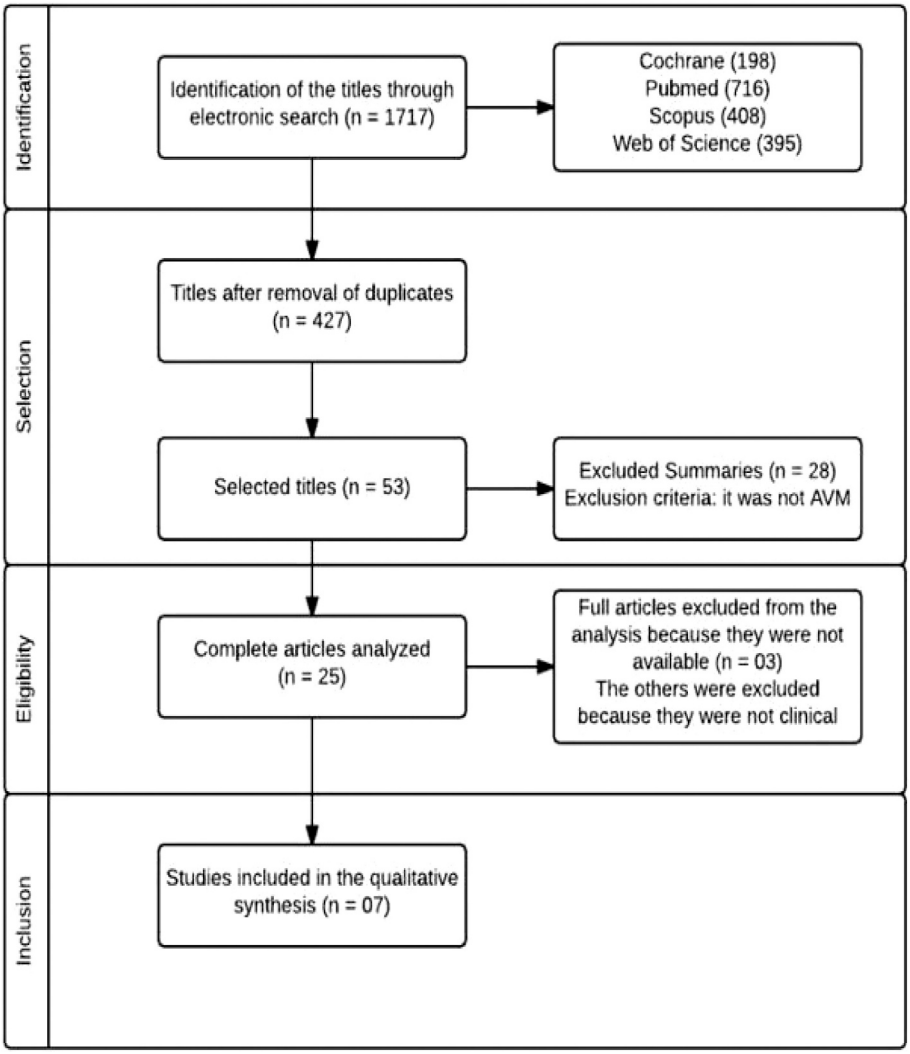

Fig. 1. Flow diagram of study selection.

Table 1
Methodological quality assessment of the studies based on Jadad Scale.

Authors/Year	Sequence Allocation	Double-Blind Trial	Losses/ Exclusions	Adequation Allocation	Confidentiality	Quality Jadad Scale
Alexander R. Binning e col./ 2010	A	A	A	A	A	HIGH
Giuseppe Cocco, Paul Jerie/ 2013	A	A	A	A	C	HIGH
Gjesdal, J Feyzi, S B Olsson/ 2007	A	A	A	A	A	HIGH
John F Tisdale, e col./ 2000	A	B	A	A	A	HIGH
Phillip Scheinberg e col./ 2014	B	B	A	B	B	LOW
Gisele Huf, et al./ 2007	A	B	A	A	A	HIGH
Jessica Schillig, et al./ 2011	A	B	A	A	A	HIGH

A: adequate description, B: non-described, C = inadequate description.

Table 2
Characterization of the included studies in the Systematic Review (2015).

Authors/Year	Geography Location	Study Design	Type of patients	Study Limitations
Alexander R. Binning e col./ 2010	Czech Republic, France, Germany, Netherlands, Poland and United Kingdom	Multicenter Randomized Double-Blind Clinical Trial	Patients undergoing major abdominal surgery	Not Reported
Giuseppe Cocco, Paul Jerie/ 2013	Non-specific	Crossover Randomized Clinical Trial	Coronary patients	The number of patients does not allow mortality to be assessed. Low statistical guarantee can lead to doubtful results, and endpoint scoring can introduce bias even when the data analysis was blinded.
Gjesdal, J Feyzi, S B Olsson/ 2007	Non-specific	Multinational Randomized Trial	Patients with Atrial Fibrillation at moderate risk	HR prevalence is high, especially among the elderly. The issue about the adverse event severity of digitalis in HR should be addressed by a prospective and randomized study.
John F Tisdale, e col./ 2000	Non-specific	Randomized Clinical Trial	Patients undergoing cyclophosphamide treatment	Not reported
Phillip Scheinberg e col./ 2014	Warren G. Magnuson Clinical Center in Bethesda, MD	Randomized Clinical Trial	Children undergoing cyclophosphamide treatment	Not reported
Gisele Huf, et al./ 2007	Psychiatric Emergency Service, Rio de Janeiro/Brazil	Randomized Clinical Trial	Psychiatric patients	Intervention doses were monitored for differences that could have close results, and no differences were found.
Jessica Schillig, et al./ 2011	Henry Ford Hospital. Detroit, MI 48202, United States of America	Randomized Prospective Clinical Trial of Cluster	Patients using warfarin and admitted to the cardiology unit	Not reported

HR: Heart Rate.

pulmonary fungal infections, and they were treated under the standard protocol, and one of them died. In the total, six patients treated with cyclophosphamide developed invasive fungal disease or died in three months.

Observing Table 3, it is possible to see that at absolute terms, 17% of the patients were quieter or sleeping in 20 min after administration of haloperidol with promethazine comparing to the haloperidol alone administration group. Adverse events were reported in 12 people, which two of them had seizures (one patient taking haloperidol associated to promethazine, and another one taking haloperidol with no association reported). In addition, nine patients presented acute muscle dystonia, what was related to the intake of haloperidol alone, and one patient presented both adverse events (dystonia and seizures) also due to haloperidol alone intake.

Patients with ischemic etiology of heart failure were evaluated to take ivabradine and digoxin related to its more severe clinical events: dyspnea and changes on heart rate, where digoxin demonstrated reduction of 95% in the occurrence of adverse events when compared to ivabradine. Both ivabradine and digoxin demonstrated positive effects on dyspnea, but digoxin was statistically more effective, and its adverse effects were irrelevant. It is important to note the small number of patients from the referred study; therefore, it was not possible to evaluate the mortality.

In one of the studies was used an oral thrombin inhibitor to Atrial Fibrillation studies (AF), where 7329 patients with moderate to high risk of AF were randomized to preventive treatment of thromboembolism, taking warfarin or an oral direct thrombin inhibitor, ximelagatran. In this study, mainly, patient's mortality was evaluated. 255 deaths were registered over 6047 patients/year related to patients who took digitalis drugs, and 141 deaths over 5300 patients/year related to patients who did not take digitalis drugs.

In another prospective and randomized cluster study, all inpatients in two medical units or two cardiology units, that took at least one dose of warfarin during hospital admission, were studied. The referred research designed the evaluation of the impact of care protocols to patients taking anticoagulants (PDAS) improving transition from hospital inpatients to ambulatory care ensuring patient's safety. The study revealed evidences in the reduction of events, and improvement in patient's safety when there is a multidisciplinary team managing the safety of evaluated patients.

Among the selected articles, one of them evaluated morphine use (a non-selective opioid analgesic, usually taken by post-surgical patients, and its use can cause nausea, vomiting, sedation, and possible respiratory depression), comparing to its active metabolite (M6G-Glucoronide), confirming that it causes less severe clinical events.

The key parameter result (nausea/vomiting) showed a difference of 27% between morphine and M6G treatment, what is comparable to reduction of 26% of the relative risk associated to antiemetic administration. M6G has an analgesia beginning slower than morphine, although it requires a smaller amount to produce comfort on the patient compared to morphine. The study suggests that it can be related to the slower M6G shift through the blood-brain barrier.

4. Discussion

This systematic review showed a reduced number of clinical trials

Table 3
Description of the incidence of adverse events evaluated in the articles as well as the number of patients and recommendation.

Drugs	Therapeutic Class (ATC)	Number of patients involved/ Total	Type of patients	Evaluated events	Incidence of Events	Recommendation
ATG + Cyclosporine	Antineoplastic Agent	16/31	Adult patients with Severe Aplastic Anemia	Fungal Infection; Mortality	One death due to refractory pseudomonas sepsis; One patient presented classical chromosomal abnormality attributed to myelodysplastic syndrome; None fungal disease nor early death occurred among the patients. Three patients died due to cyclophosphamide+cyclosporine association; Six patients developed invasive fungal disease in three months; Four patients developed invasive fungal infections (pulmonary aspergillosis in two); Two patients were suspect of pulmonary fungal infections; At the 39° day, one more patient died. Five patients showed uncontrolled infection; Six patients confirmed documented fungal infections; Nine patients died; 41% (nine) of the patients responded the treatment for six months.	Aplastic anemia and clonal hematological disorders overlapping can indicates these disorders represent different expression of common pathology, so they are not related to the treatment. The reason the study ended early was due to high toxicity of cyclophosphamide in patients. The difference in the clinical onset between cyclophosphamide and TGA is the cytotoxic action of cyclophosphamide on patients with normal neutrophil numbers puts them in the category of high risk of severe disease.
Cyclophosphamide + Cyclosporine	Antineoplastic Agent	15/31				
Cyclophosphamide	Antineoplastic Agent	22	Children with Severe Aplastic Anemia	Prolonged neutropenia; Toxicity; Mortality		After a median follow-up of two years, relapse occurred in two patients, and cytogenetic abnormalities (including monosomy 7) were observed in four patients.
Digoxin + Ivabradine	Digitalis/ Cardiovascular system	42	Patients with ischemic etiology of heart failure	Dyspnea; Changes in heart rate; Arrhythmia	Digoxin use for the patients reduced 95% of adverse events occurrence compared to ivabradine.	Ivabradine is not indicated to improve atrial fibrillation, but it is mistakenly used. Digoxin is considered an outdated and high-risk drug, and although it is effective in the mentioned conditions above, but it is rarely used.
Haloperidol	Antipsychotic	156/316				Exclusive use of intramuscular haloperidol is not an acceptable way of use, since it exposures people to violence more than necessary, and it can cause preventable risk of acute dystonia. Commonly, haloperidol+promethazine association is effective and quietly safe; besides it is the treatment to acute aggression due to psychosis (greater evidence).
Haloperidol + Promethazine	Antipsychotic/ Opioid	160/316	Psychiatric patients who needed intramuscular sedation urgently due to agitation and dangerous behavior or both.	Sedation; Tranquilizer; Behavior of perturbation	Nine patients presented acute dystonia; One patient presented seizures; One patient presented dystonia + seizures; 26 patients were more quiet or sleeping after 20 min; One patient presented seizure.	
M6G-Glucoronide	Opioid	223/450	Adult patients undergoing major abdominal surgery	Nausea; Vomiting; Respiratory depression; Sedation	75% of the patients presented sedation; Reduction of 30%–35% in antiemetic use (nausea and vomiting); Only 44 patients presented severe sedation.	There was no significant difference on nausea and vomiting parameter. Due to the relative hydrophilicity of M6G compared to morphine, it is suggested to start M6G administration two hours before the surgery end.
Morphine	Opioid	227/450				
Warfarin	Antithrombotic Agent	500	Patients taking warfarin when were hospitalized or patients who started warfarin use post-hospitalization in a cardiology unit.	Severe hemorrhage; Thromboembolism	From the 227 patients, 199 presented sedation, and 71 presented severe sedation. The protocol did not reduce bleeding and thrombotic events, but it originated a better management of coordination and documentation, and improvement in patients transition from the hospital environment. The impact of the Pharmacist-Directed Anticoagulant Service (PDAS) implementation was greater when the length of stay was longer than five days.	The study suggests when the opportunity of adverse events and communication is large, in other words, long hospitalization periods, it seems to have safety improvement with the PDAS.
Warfarin + Ximelagatran	Antithrombotic Agent	7329	Patients with Atrial Fibrillation at moderate risk	Stroke and systemic embolism	396 patients died, and 3899 from the total number of patients used digitalis. They were into the moderate to high	If digitalis have serious adverse effects, the number of patients can be larger. The issue about the

(*continued on next page*)

Table 3 (*continued*)

Drugs	Therapeutic Class (ATC)	Number of patients involved/ Total	Type of patients	Evaluated events	Incidence of Events	Recommendation
					risk of thromboembolism, usually, elderly patients and/or with cardiovascular disease, besides AF. These ones had higher mortality than the patients who did not take digitalis.	potential severity of the adverse events of digitalis in AF should be approached by a randomized and prospective study.

ATG: Anti-thymocyte globulin.

developed with high-alert medications (HAM) on inpatients, what has limited the comparison among the studies. However, the data collected on this study highlighted the need for further discussion about the topic, since from the 19 drug classes and 13 high-alert specific drugs described by the ISMP, in Brazil, for hospital use, were found just 11 drugs distributed in six classes.[20]

The review points out two studies that evaluated cyclophosphamide use, one in children and other in adults, both carriers of Severe Aplastic Anemia (SAA). It was observed in another study that children have more favorable outcomes in comparison to older patients with the same problem treated with immunosuppressive therapy (cyclosporine use). Higher response rates were found, and global survival was great in this age group by the ones who obtained response.[21]

On research performed in 2014 that aimed to evaluate the cyclosporine and ATG treatment on children with Severe Aplastic Anemia demonstrated the general response rate in six months was 34.6%, which three patients responded to treatment between six and 12 months, resulting on a response rate of 46.2% during this time. The cumulative incidence of clonal evolution was 8.3%. Both clonal evolutions occurred in patients with no response that acquired a karyotype with monosomy 7, and who died due to infectious complications. Global survival in five years was 73.6%. There were four deaths due to disease complications (septicemia), and two deaths due to secondary clonal evolution.[22]

Fungal infections are the main cause of death to patients with Severe Aplastic Anemia (SAA), however, hemorrhage, evolution to clonal disease (myelodysplastic syndrome [MDS], leukemia, and paroxysmal nocturnal hemoglobinuria [PNH]), and transfusional iron overload are other causes of severe morbidity and mortality. SAA can affect people of all age, but it is more common in children and young adults. Nevertheless, additional immunosuppressive drugs are added to treatment (ATG/CsA) with the expectancy to reduce the clonal disease relapse, but so far none outcome improvement was observed.[23]

After cyclosporine and ATG therapy, Rosenfeld et al. reported 55% of global survival in seven years; in patients with SAA, 12 from 48 patients died in three months after treatment compared to three from 74 patients showing neutrophil count higher than 109. Only two from 31 participants (6.5%) relapsed, one of them reached a second continuous remission after the second course of therapy. Myelodysplastic Syndrome (MDS)/leukemia is the most feared secondary clonal disease to develop from aplastic anemia with monosomy 7, being the most common chromosomal abnormality to appear in these patients.[24]

Garantino and collaborators research observed 96% of global survival on 24 patients in treatment included in the SAA study, where only one death was reported in 18 months after a high dose of cyclophosphamide. In addition, only one of the 44 patients in treatment died on the first three months after treatment. Thus, myelosuppressive properties of high doses of cyclophosphamide did not influence early mortality. In the same group, two patients developed Myelodysplastic Syndrome: one with normal cytogenetic and other with monosomy 7. Relapses occurred by up to 40% of the treated patients with ATG/CsA. Potential benefit of high doses of cyclophophamide over ATG/CsA is that it shows most of the responses, besides response does not depend of continuous administration of immunosuppressive drug; >40% of all patients in treatment reached complete remission (CR), and none of them relapsed or developed secondary clonal disease.

Another study demonstrated evaluation of patients with ischemic etiology of heart failure that were evaluated to ivabradine and digoxin use related to their most severe clinical events. Gheorghiade and collaborators (2013) conducted research about patients' mortality with Atrial Fibrillation with previous or initial use of digoxin that showed the causes of mortality occurred in 14% and 13% of the patients receiving combined treatment and do not taking digoxin as initial therapy, respectively. Association of digoxin with total mortality remained unchanged, and the referred drug did not have association with mortality in all months of follow-up.[25]

In the same study, digoxin did not have association with the mortality related to cardiovascular effects among the evaluated patients. Among the 1780 patients that got propensity score matching, digoxin use was not related to total mortality. It is worth mentioning, the use of this drug does not have association with total mortality when used as monotherapy or combined to other drugs.[25]

There was no evidence of benefit on survival due to digoxin use. AF control rate and higher mortality in the cardiac rhythm control group were predictable due to the adverse effects caused by some aspects of the rhythm control, such as interruption of anticoagulation or antiarrhythmic drug adverse effects. Currently, there are no data concerning digoxin effectiveness in AF, and it was found no evidence that digoxin use to long-term control rate was associated to higher mortality in patients with paroxysmal and persistent AF.[26]

A pragmatic project from a randomized study in psychiatric emergency is viable and informative. Combined to other data from other studies, intramuscular haloperidol and promethazine have been studied, and they have become a safe and effectiveness benchmark treatment against aggression/violence due to psychosis, as shown in the study included in this review.

Research, conducted by Oliveira, evaluated the clinical use of antipsychotic drugs, concluding there were more early treatment interruptions due to the lack of effectiveness among the patients treated with haloperidol than by those treated with other drugs from the same class. Besides this, the early treatment interruption due to adverse effects was more frequent in patients treated with haloperidol than by those treated with other antipsychotic drugs. The use of anticholinergic drugs was necessary only in 15% of the patients treated with olanzapine compared to 49% of the patients treated with haloperidol.[27]

Another study that compared intramuscular olanzapine, ziprasidone, haloperidol and promethazine effectiveness, used to treat patients with agitation and aggressiveness behavior, it was noticed that all drugs had produced a calming effect in one hour of administration. However, only olanzapine and haloperidol reduced agitation for <10 points, and only olanzapine reduced aggression for less than four points at the first hour. Ziprasidone, olanzapine and haloperidol alone produced more stable outcomes to agitation control while ziprasidone, haloperidol and promethazine produced stable outcomes to aggression control.[28]

Deaths related to opiate drugs, such as morphine, are the main cause of accidental death, and most of them occurred in patients receiving chronic pain therapy. Respiratory arrest is the common reason of death, but how the mechanisms increase with the high risk of treatment duration is still obscure. Repeated administration of the drug leads to

tolerance of the analgesic opioid effect leading to dosage increase, but respiratory depression cannot obtain tolerance with the same intensity.[29]

By contrast, *in vitro* studies, showed some potential opiate neurotoxicity. Although sufentanil and morphine did not increase cell death induced by lidocaine in human neuroblastoma cells, morphine increased apoptosis by lidocaine in mice's astrocytes while sufentanil did not present this effect.[30]

A study that evaluated mice receiving morphine chronically showed significant tolerance to morphine effects, sedation and analgesia (five-fold greater ED40). When sedation was reached for all animals in a low dosage group (effective doses: opioid-tolerant, 15 mg/Kg; opioid- naïve, 3 mg/Kg), opioid-tolerant showed similar magnitude of decreased ventilation (−41,4 ± 7,0%, average ± DP), and hypercapnic response (−80,9 ± 15,7%) as found to morphine-naïve (−35,5 ± 16,9% e − 67,7 ± 15,1%, respectively). Recovered ventilation due to current volume without respiratory rate recovery or slower hypercapnic sensibility was present in morphine-tolerant ones.[29]

Anticoagulants have been used in the clinical practice for >60 years. The most commonly prescribed oral anticoagulant is warfarin or coumarin preparations or indanedione derivatives of more prolonged action. Warfarin is an effective anticoagulant, but it shows a narrow therapeutic index, presenting high hemorrhage risk at therapeutic concentrations of the drug. This variable and unpredictable pharmacological response requires frequent prothrombin time monitoring, International Normalized Ratio (INR) reports, and dosage adjustment.[31]

Thrombin has been known as having a major role on coagulation pathways, then this is the importance on its specific inhibition. Ximelagatran is a melagatran oral prodrug, a synthetic small peptide direct inhibitor of thrombin with anticoagulant activity. Ximelagatran-melagatran has a variety of properties that makes it an attractive alternative to warfarin. It suffers a rapid enzymatic conversion to melagatran through two intermediates, ethylmelagatran (melagatran ethyl ester made by hydroxyl group reduction) and hydroxy-melagatran (melagatran hydroxylamine made by hydrolysis of acetate group).[32]

Ximelagatran clinical studies confirmed it is an effective antithrombotic agent preventing stroke in patients with non-vascular atrial fibrillation, venous thromboembolism prevention and therapy, and possibly, in the prevention of recurrent ischemia after acute myocardial infarction. In most clinical indications, studies conclude that ximelagatran is not inferior to well-controlled warfarin therapy related to effectiveness, with no increase in bleeding risk. In comparison to warfarin, ximelagatran has various desirable properties in terms of administration, dosage, and monitoring. Furthermore, diet minimal impact and apparent lack of significant drug interactions makes it a therapeutic significantly option more desirable than warfarin.[31]

Warfarin therapy in patients with thrombocytopenia induced by heparin can cause progression of deep vein thrombosis to limbs gangrene and cutaneous necrosis induced by warfarin.[33] It is usually associated to administration of high doses of the drug, and it developed in 110 days, after introduction of therapy, and the most occurred on a range of 3–6 days. The most susceptible patients to this complication are the ones who present lupus anticoagulant, hypersensitivity to heparin, protein C and S deficiency, and deficiency of antithrombin and factor VII.[34,35]

Pathogenesis is explained through pro-coagulant effects that warfarin presents in the first days of use. This phenomenon occurred because protein C, a natural vitamin K- dependent anticoagulant, has shorter half-life (5 h) than the most pro-coagulant factors (factor II, IX, and X), and it declines rapidly after warfarin starts to act. This pro-coagulant/anticoagulant transient imbalance is exacerbated in protein C deficiency leading to hypercoagulability status with microcirculation thrombotic occlusion. Clinically, the first patients' complaints are: paresthesia, erythematous eruption or just distress at lesion site. Lesions are well-defined, painful, erythematous or hemorrhagic, initially, with formation of hemorrhagic bullae, cutaneous necrosis and bedsores.[36,37]

It is therefore believed the use of lower doses of warfarin reduce the risk of hypercoagulability status development caused by the reduction levels of protein C during the first 36 h of the anticoagulant therapy. It is suggested therapeutic schemes to maintain the protein C levels during the critical period of the beginning of warfarin use with initial low dose (1 to 2 mg/day), and daily increments of 1 to 2 mg/day until it reaches the desirable INR within 10 days.[38] Also, it is described that warfarin treatment interruption or continuity does not change the cure or bedsores progression.[38]

5. Conclusion

The findings of this review show that adverse events related to the use of HAM occur even when used as intended, therefore it is important to promote strategies to improve the safety of hospitalized patients using these medications. The most reported drug classes were: morphine, M6G-glucuronide, haloperidol, promethazine, ivabradine, digoxin, warfarin, ximelagatran, cyclophosphamide, cyclosporine, and ATG. The most reported safety strategy in the articles was to formulate protocols for the use of these medications, with importance placed on evaluating, among the classes, the medication that causes the least harm.

CRediT authorship contribution statement

Michelle Santos Menezes: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Grace Anne Azevedo Doria:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fernanda Valença-Feitosa:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis. **Sylmara Nayara Pereira:** Writing – review & editing, Visualization. **Carina Carvalho Silvestre:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Alfredo Dias de Oliveira Filho:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation. **Iza Maria Fraga Lobo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **LucindoJosé Quintans:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision.

Declaration of competing interest

None.

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