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Review

Nutritional pharmacological and toxicological characteristics of pitaya (*Hylocereus undatus*): A review of the literature

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Studies on the cacti of the genera, Hylocereus Tropical and Subtropical America are scarce. Cultivation and consumption of different species and varieties of pitaya (*Hylocereus undatus*) may represent a source of diversified agricultural activity since these species contain rich bioactive compounds that add a rustic beauty to the cultivation of the fruit in addition to the benefits they bring to the health of the population. The functional attributes assigned to this fruit, prompt the need to study its physical, chemical, nutritional, pharmacological and toxicological characteristics. The objective of this study was to review the literature on the pitaya, investigating the relationship between post-harvest production, technological and pharmaceutical applications, in addition to nutritional properties, and the chemical components that are beneficial and toxic to health. Hence, a literature search at the PubMed and SciELO Medicine® sites, with descriptors "Hylocereus" and "pitaya" was held. Recent studies on the bioactive compounds in pulp and peel, antioxidant activity and the relationship between use and health were mainly selected, based on *in vivo* studies. Based on the articles studied, observation showed that the intake of bioactive compounds present in pitaya boosts immunity in individuals, thus inducing better health and improving physical and mental performance. However, additional research is necessary to obtain consistent and reliable data to explore unrestricted use by the food, pharmaceutical and cosmetic industry.

Key words: Cactaceous, pitaya, *Hylocereus undatus*.

INTRODUCTION

Brazil is the world's third largest fruit producer, ranked behind China and India (Duarte, 2013). According to Kist (2012), the estimated Brazilian production in 2011 involved 20 species of fruit at 42,101 million tons. However, Brazil's potential for fruit farming is even greater due to a large land area and good weather

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conditions, which favor the planting of species of tropical, subtropical and temperate climate as well as special situations that allow year round production.

Fruit consumption in Brazil, according to the Ministry of Agriculture, was 125 kg per person/year^{-1} in 2009. In some European and North American countries, average fruit consumption ranges between 140 and 150 kg per person/year^{-1}, respectively. Although, Brazilian data are far from desirable, a growing awareness of the health benefits provided by the regular intake of fruits has portrayed an increasing demand for fresh fruits (Brazil, 2011).

Introducing fruits in daily dietary practices has made room for different, even exotic fruit species with distinctive flavor and interesting mineral, fiber and antioxidant contents. Among the various options of exotic fruit species with good prospects for commercialization, is the pitaya (also known as dragon fruit), a native cactaceae fruit from the tropical forests of Central and South America, India and Malaysia, (Canto, 1993; Nerd and Mizrahi, 1997).

Pitaya (*Hylocereus undatus*) is among the lesser-known tropical fruits, but has high economic potential in domestic and foreign markets, which justifies intensifying research aimed primarily at obtaining basic information on farmer cultivation (Lima, 2013). In this context, the purpose of the study was to review literature on pitaya (scientific name), relating the general aspects of post-harvest production, the technological and pharmaceutical applications, in addition to the chemicals that are beneficial and toxic to human health.

MATERIALS AND METHODS

The literature review was conducted at the PubMed, SciELO Medicine® research sites with the descriptors "Hylocereus", "dragon fruit" and *"Hylocereus undatus."* Articles were selected on the cultivation of pitaya, the bioactive compounds in pulp and peel, antioxidant activity, the toxicological, as well as the pharmacological aspects and the relation between the potential use of pitaya, within the health context, through *in vivo* and *in vitro* studies.

The pitaya species

The plant that produces the fruit called pitaya (*Hylocereus undatus*), originates from tropical and Subtropical America and belongs to a group of fruit trees considered promising for farming, which are distributed in Costa Rica, Venezuela, Panama, Uruguay, Brazil, Colombia and Mexico (Canto, 1993). Until recently, this fruit was unknown and, more recently, represents a growing niche market of exotic fruits (Moreira et al., 2012).

Pitaya is a rustic fruit, which belongs to the Cactaceae family, known worldwide as "Dragon Fruit" because it presents a bright red shell with overlapping green scales covering the fruit (Jaafar et al., 2009). Plants of this family are able to tolerate extreme heat and cold in addition to dry periods and low-nutrient soils. The structure of these plants present stem modification for water storage, reduction or the absence of leaves, surfaces coated with natural waxes and nighttime stomata opening to absorb carbon dioxide (CAM metabolism), which allows the plants to tolerate the most difficult conditions (Marenco and Lopes, 2011).

Depending on the species, the fruit may take on diverse characteristics, such as size, the presence of thorns, color of pulp and skin, thus reflecting high genetic variability (Junqueira et al., 2010).

According to Le Bellec et al. (2006), the dragon fruit can be grouped into four botanical genera: *Stonecereus* Briton & Rose, *Cereus* MiLL, *Selenicereus* (A. Beger) Riccob and *Hylocereus* Briton and Rose. The variability of species is related mainly to the size and color of fruit and production time (Marques, 2010). The most common and commercialized species are: *Selenicereus megalanthus*, yellow pitaya with white flesh, known as "Colombian pitaya"; *Hylocereus polyrhzius*, pitaya with red rind and flesh; *H. undatus*, red pitaya with white pulp (Donadio, 2009). The *Selenicereus setaceus* species, also known as bush land pitaya, is commonly found in Brazil, displays thorny small fruits (Junqueira et al., 2010).

Pitaya pulp is delicate, juicy and contains numerous dark edible seeds of approximately 3 mm in diameter (Nerd and Mizrahi, 1997). From a nutritional standpoint, this fruit is considered highly nutritious, with high water content, sugars and minerals, antioxidants and low calories (Molina et al., 2009). However, the red rind pitaya has great potential to be used as natural pigment, due to the presence of betacyanin (Harivaindarn et al., 2008), in addition to the interesting antioxidant activity of this pigment (Kim et al., 2011).

PITAYA PRODUCTION IN BRAZIL

For a long time, the consumption of pitaya fruit was restricted to North American, European and Australian regions. It arrived in Brazil in the 1990s through imports from Colombia, which triggered the interest of Brazilian fruit producers (Lima, 2013).

The farming areas of this fruit in Brazil are small and located mainly in the state of São Paulo, specifically in Catanduva County. However, increased consumption of exotic fruits and their commercial value have sparked the fruit grower's interest in cultivating the fruit. In the Southeast, the fruit production occurs from December to May (Bastos et al., 2006).

According to Junqueira et al. (2010), there is no cultivar released to the market which meets the climate needs for

production. All seedlings sold in recent years do not come from selected matrices and present a large variation in production such as fruit size and shape, as well as the physicochemical characteristics, reflecting the need for cultivars that are appropriate for the bush land region of the Central Plateau.

Pitaya harvest and post-harvest conditions

Pitaya is a perennial plant that commonly grows on trees or rocks, due to abundant fibrous roots and that develops numerous adventitious roots, which assist in setting and obtaining nutrients; the cladodes are triangular, juicy, exhibiting 2 to 4 mm wide spines. The flower is large (measuring about 20 to 30 cm wide) hermaphroditic, white-colored, night-blooming flower (Canto, 1993).

The harvest usually occurs when the fruit has reached full maturity, that is, 30 to 40 days after blooming, in which the shell acquires pink to deep red coloring and a still quite-firm creamy-white pulp texture (Marques, 2010).

Post-harvest surveys show that the dragon fruit, under environmental conditions deteriorates with relative ease. As a result, the post-harvest life for commercialization is short, approximately six to eight days at room temperature (Nerd and Mizrahi, 1997). Studies by Hoa et al. (2006) show that the fruit may have a shelf life of upto ten days without any chemical treatment.

In a study conducted by lim et al. (2010), the authors demonstrated that *Salmonella* spp. could grow on freshly harvested pitaya under inadequate storage conditions, indicating that the harvest of fresh fruit could act as a potential vehicle for salmonellosis. Therefore, the study conducted by the authors suggested that fresh (minimally processed) pitaya harvests should be stored at 4°C to ensure food product safety and to extend the shelf life of recently harvested fruits.

Nutritional and pharmacological aspects of pitaya

Due to its sweet taste, the pitaya fruit, which has emerged with great potential to be used in Brazilian cuisine, can be used in jams, juices, ice cream and candy or be enjoyed *in natura* (Donadio, 2009). Its nutritional properties and pulp color make the fruit to become an attractive raw material for various types of drinks, including fermented drinks or beverages produced using enzymes (Yien Ong et al., 2012).

Further, for nutritional importance and culinary applications, pitaya can be utilized in the pharmaceutical and cosmetic industry (Molina et al., 2009). Ancient Mayas traditionally used the leaves and flowers of *H. undatus* for hypoglycemic purposes, as a diuretic and healing agent (Arquete et al., 1994). The pitaya is also used for medicinal purposes. The flowers can be ingested or used to make tea, the seeds have a laxative effect, the fruit has an effect on gastrites, the stalk and flowers are also used for kidney problems (Donadio et al., 1998). The vegetative parts of the cactus have application in the pharmaceutical industries (Stintzing et al., 2005).

Extracts from some cacti have been associated as central nervous system stimulants and regulators of blood pressure, sleep, hunger and thirst (Franco et al., 2003).

Pitaya seeds contain oil that is a mild laxative (Crane and Balerdi, 2005) capable of reducing total cholesterol and low-density cholesterol (LDL) in humans (Phebe et al., 2009). This oil has a high level of functional lipids and can be used as a new source of essential oil (Lim et al., 2010), which is comparatively superior to linseed (*Linum usitatissimum* L.) and canola oil (*Brassica napus L. var. Oleifera*) (Ariffin et al., 2009), in addition to already being heavily used as a natural colorant in the food industry (Jamilah et al., 2011; Esquivel and Ayara-Quesada, 2012). These characteristics can bring about a significant market demand for fruits considered exotic.

In a recent survey, Luo et al. (2014) identified 24 components in the carbon dioxide extract obtained by gas chromatography-mass spectrometry of the *H. polyrhizus* peel, of which 90.66% were identified; 29.77% were triterpenoids and 16.46% steroids. In the *H. polyrhizus* extract, 92.82% of the chemical compounds were identified, of which 23.39% were triterpenoids and 19.32% steroids. According to the authors, the chemical compounds found in these plants possess anti-cancer and anti-HIV activities (Patocka, 2013).

Perez et al. (2005) studied the wound healing properties of aqueous extracts from the leaves, shell, fruit pulp and flowers of *H. undatus*, and observed positive healing process effects in mice from all parts of the fruit. In diabetic animals, healing usually occurs late, and topical applications of *H. undatus* produced a significant increase in hydroxyproline, tensile strength, total protein, DNA collagen content and improved epithelialization, thus facilitating healing. In this study, however, the authors failed to observe hypoglycemic activity of *H. undatus*.

In research carried out by Wu et al. (2006), the authors evaluated the antiproliferative activity of red pitaya in melanoma cells, determining if the fruit could be considered a promising anticancer agent. The results obtained showed antiproliferative activity on B16F10 melanoma cells, revealing that the chemical compounds of pitaya peel are presented as a more potent inhibitor of cancer cell growth of B16F10 melanoma than the chemical components present in the pulp.

Anand et al. (2010) conducted a study that evaluated the *in vivo* vascular properties from the aqueous extract of *H. undatus* in diabetic rats induced by streptozotocin (STZ), and concluded that administration of pitaya extract increased protection of the aorta in these cases.

IN- VITRO AND *VIVO* STUDIES OF ANTIOXIDANT PROPERTIES OF PITAYA

Diverse research has been conducted in order to investigate the presence of compounds with antioxidant activity in pitaya fruit, but available information is scarce (Mahattanatawee et al., 2006). Studies indicate that pitaya is rich in antioxidants and betacyanin (Wybraniec and Mizrahi, 2002) and that species of the Cactaceae family are a source of betaninas, filocactinas, hilocereninas, betacyanins with 5-O-glycosides and 6-O-glycosides (Herbach et al., 2006).

Wu et al. (2006) observed in their studies that the total phenolic content of pitaya pulp and peel are similar, and the contents of flavonoids indicate that the fruit pulp and peel are rich in polyphenols and are valuable sources of antioxidants. However, in a study conducted by Gregoris et al. (2013), the authors found in four different *in vitro* methods and pitaya is an exotic fruit poor in compounds with antioxidant properties.

Kim et al. (2011) investigated the antioxidant activity of total polyphenols and flavonoids against various free radicals of pulps and peels of white pitaya and red pitaya of Korean origin. The authors found that the content of flavonoids and polyphenols in the methanolic extract of both red and white pitaya bark were approximately three to five times higher than the content of these antioxidants in the pulp of red and white pitaya, respectively. The investigators were able to identify the presence of phenolic compounds, the derivatives of hydroxycinnamic acid, glycosides, betacyanin flavonoids and their derivatives, in addition to some unknown compounds.

In a study conducted by Anand et al. (2010), the authors endeavored to evaluate the *in vivo* antioxidant properties of the aqueous extract of the *H. undatus* fruit in diabetic rats induced by streptozotocin (STZ), and concluded that administration of the this extract increased oxidative defense in such cases.

TOXICITY OF PITAYA

Toxicological studies are particularly relevant to help prove the safety of foods and ingredients, since they contribute to the identification of potential adverse effects; definition of exposure conditions required to produce these effects; evaluation of dose-response relationship for adverse effects, including the definition of doses that do not produce such effects and interpretation of experimental data for risk assessment, like information on the mode of action and its relevance to humans, as well as data on metabolism and toxicity, extending the results from animals to humans (ANVISA, 2013).

According to Hor et al. (2012), there is little information on toxicity studies related to the safe exposure of pitaya fruit. In this context, the potential toxicity of the methanolic extract from this fruit was assessed by acute and subchronic administration in rats. In the study on acute toxicity, single doses of fruit extract (1250, 2500 and 5000 mg/kg) were administered for rats by oral gavage, and animals were then monitored for 14 days. In the study of subchronic toxicity, pitaya extract was also administered orally to rats at doses of 1250, 2500 and 5000 mg/kg/day for 28 days. The authors neither observed mortality, nor signs of acute or subchronic toxicity, nor significant difference in body weight, organ weight or hematologic parameters in subchronic study. No abnormalities of internal organs were observed between the treatment and control groups, and the lethal oral extract of pitaya was determined to be higher than 5000 mg/kg, and doses with no observable adverse effects of the extract for male and female rats was considered to be 5000 mg/kg per day for 28 days.

In studies carried out by Luo et al. (2014), the authors used the MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide) to determine the cytotoxic activity of the supercritical carbon dioxide extract obtained by gas chromatography mass spectrometry of the *H. polyrhizus* and *H. undatus* bark in tumor cell line human prostate cancer cell line (PC3), human breast cancer cell line (Bcap-37) and human gastric cancer cell line (MGC-803). The authors used Adriamycin (ADM) as positive control and after 72 h of contact with the pitaya extracts of cells, dose-dependent inhibition of cell proliferation was observed.

FINAL CONSIDERATIONS

Pitaya farming is very important worldwide, and the fruit and its parts need to be further studied from a nutritional and bromatological quality standpoint, to be best utilized by the pharmaceutical and food industry. By offering quick economic return, since production starts in the first year after planting and, also due to its adaptive metabolic conditions where water is a limiting factor, cultivation can be indicated for areas that are not feasible for growing other fruits, which need better climate, as well as an available water supply and irrigation.

All parts of the plant can be eaten, including the cladodes, flowers and fruits, which have large amounts of functional compounds and proven medicinal properties, including hypertension control which has generated the pharmaceutical industry's interest in separating these compounds.

With respect to its antioxidant activity, research indicates a higher concentration of bioactive compounds with antioxidant properties in pitaya bark, making it more interesting from the pharmacological and nutritional standpoint. Regarding *in vivo* studies, no acute and subchronic toxicity studies in rats were observed, and results of cytotoxicity tests indicate the dose-dependent inhibition of cell proliferation through MTT test.

However, toxicological studies on pitaya are scarce,

and further research is paramount until consistent and reliable data to explore its unrestricted use by the food, pharmaceutical and cosmetic industries are available.

According to the research conducted in this study which is related to pitaya, it was observed that the functional properties of fruit help reduce the risk of chronic diseases. And that due to its hardiness, the pitaya is a potentially viable alternative also for the use of stony soils, sandy and rocky massifs which make its promising crop from agronomic and economic point of view. However, the pitaya has desirable features which allow it to be classified as a tropical fruit, still little is known, but with high potential for domestic and foreign markets. Derived food products of pitaya rarely appear on the market and research needs to be done to improve their trading opportunities.

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Full Length Research Paper

Medication incidents related to feeding tube: A cross-sectional study

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The aim is to evaluate the medication incidents relating to incorrect oral medication preparation and administration through enteral feeding tubes in hospitalized patients. A cross-sectional design was used to observe 374 doses of medications at three Brazilian hospitals. The patients consisted mostly of females (48.6%), elderly (65.71%), using polyurethane tubes (82.9%), with jejunal access (82.9%), and circulatory system diseases (45.71%). The most common medication incidents identified were: mixing tablets with other drug(s) (43.5%) and not labelling the prepared medication (60.4%). With regards to incorrect medication administration, not flushing the tube between medications (86.5%) and administering medications together (65.6%) were the most common errors. Tube obstruction was identified in 36.5% of doses administered. There was an association between tube obstruction and mixing tablet with other drug(s); tablet incorrectly reconstituted; tube not flushed prior to medication administration; tube not properly flushed between medications; concurrent administration of a medication and enteral formula; and enteral feeding not interrupted prior to medication administration. The results contribute to the development of knowledge in order to improve hospital nursing practice, especially in developing countries. Future studies should be conducted in order to access patients' outcomes related to incorrect oral medication preparation and administration through feeding tubes.

Key words: Feeding tube, wrong medication preparation, wrong medication administration, incidents.

INTRODUCTION

Oral medication preparation and administration through feeding tubes in hospitals is a major challenge for nurses aiming to provide safe care. Most nurses rely primarily on their own experience and secondarily on the experience

of their coworkers for information and techniques on preparing and administering oral medications through feeding tubes. As a result, a variety of improper techniques are often employed (Grissinger, 2013).

For instance, researchers identified wrong techniques during medication preparation and administration of enteric-coated solid drugs 28.57% of the time (Lisboa et al., 2013). The crushing process destroys the coating film and promotes the immediate release of medication, which can result in toxic effects with potentially severe damages, exposing the patient to unnecessary risks (Institute for Safe Medication Practice-Brazil, 2015).

Evidence also suggested that 91% of nurses often mix solid medications in the same crushing container during medication preparation (Heydrich et al., 2009). This practice is a risk factor for adverse drug interactions, contributing to tube obstruction, especially if the nurse does not flush the tube after each medication administration. In addition, Brazilian hospital pharmacies frequently distribute drugs to be administered via feeding tube in inadequate forms, either due to unavailability in the pharmaceutical market or due to the lack of standardization in the institution. Therefore, tablets and/or capsules that should be administered intact orally are crushed and/or opened and reconstituted in various substances before being administered via feeding tubes (Grissinger, 2013).

Another adverse event related to improper medication administration via feeding tubes is caused by drug interactions in elderly people due to polypharmacy, with a prevalence of 20 to 40%; polypharmacy increases the complexity of clinical management and contributes to adverse medication events (Palleria et al., 2013).

These incorrect medication preparation processes used for administering through feeding tubes disregard the pharmaceutical properties of the drug and its biopharmaceutical characteristics, and they can lead to physical and chemical incompatibilities, resulting in precipitation, flocculation, adsorption, color changes, chelation and drug-nutrient interactions, which causes changes in drug effectiveness or compromises nutritional therapy (Allen, 2014).

According to a study conducted in a Brazilian private hospital, the main reason for the loss of the feeding tube was obstruction (36%) related to wrong medication preparation and administration techniques (Pereira et al., 2013). Estimates of incidence of clogged feeding tubes range widely from 12.5 to 45%, but it is undisputed that they result in increased costs for patients and institutions (Fisher and Blalock, 2014). Health care practitioners, specially nurses, should not assume that a medication intended to be taken by mouth can be safely administered through a feeding tube because this misconception can result in harm to patients and increase medical costs to society (Grissinger, 2013).

Correct medication administration is a nursing responsibility and represents an important target of quality and safety improvement interventions. Thus, it is important that nurses are supported technically and scientifically to carry out safe and effective practices in medication administration via feeding tubes.

Given that the number of patients with chronic conditions have increased significantly worldwide, as well as in Brazil, it is critical that health care professionals employ a repertoire of evidence-based techniques in order to provide safe and qualified care (Brasil, 2011; World Health Organization, 2011). In addition, errors related to this route of administration happen more often than reported or recognized (Institute for Safe Medication Practice, 2010). The issues raised are pertinent across countries (Phillips and Endacott, 2011), but there is a knowledge gap regarding the safe handling of feeding tubes especially in developing healthcare institutions. Studies that aim to identify evidence-based interventions targeting safe oral medication preparation and administration through feeding tubes can reduce that gap and the risks of complications, and decrease the overall costs of care.

The purpose of this paper is to evaluate the medication incidents related to incorrect oral medication preparation and administration through feeding tubes in hospitalized patients.

METHODOLOGY

This descriptive, cross-sectional study was conducted in three Brazilian general, medium-sized, teaching hospitals located in metropolitan areas: two hospitals in São Paulo State and one hospital in Minas Gerais State. The medical ward was chosen for this study because it provides care for patients in various medical specialties and most of the patients have chronic conditions, thus many require enteral nutrition and medications through feeding tubes.

The unit of analysis was the dose, thus the sample consisted of 374 doses of medications prepared and administered through feeding tubes from February 2014 to May 2014. The sample size calculation was described in a previous study (Lisboa et al., 2013).

Medication incidents were defined as any preventable event that may cause or lead to patient harm while the medication is in the control of the healthcare professional. These may be related to professional practice, drug products, procedures, and include product labelling, compounding, prescribing, administering, and monitoring (Institute for Safe Medication Practice, 2016).

For the purposes of this study, medication incidents categories were: wrong medication preparation and wrong medication administration. Wrong medication preparation was defined as a

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medicine that was incorrectly handled beforeadministration. This included crushing enteric-coated medications; incorrect reconstitution/dilution (incorrect choice or volume of diluents); and medicines mixed in the same container (Tissot et al., 1999). Wrong medication administration was defined as an inappropriate procedure or improper technique used in the administration of a medicine through a feeding tube. This included mixing two or more drugs together; improper flushing of the tube before and after medication administration; improper flushing of the tube between each drug administration; mixing medications with feeding formulas; and failure to test the correct placement of the feeding tube prior to medication administration (Grissinger, 2013; Tissot et al., 1999).

Data were collected through direct observation of oral medication preparation and administration through a feeding tube. According to Flynn et al. (2002), direct observation is a method that requires the data collector to accompany the nurse administering medications and observe the preparation and administration of each dose. The observer records exactly what the nurse does with the medication and witnesses the medication administration to the patient. Data recorded include related procedures, such as giving medications with food. Thus, direct observation is considered more efficient and accurate in detecting medication errors than reviewing charts and incident reports.

Nurses were observed by research assistants, who were subjected to a day of training with a total workload of 4 h, during the processes of preparing and administering medications. The data collection tool used was developed by the research team, assessed for face and content validity by a panel of experts, and tested for three consecutive days.

Observations took place on different days of the week (including weekends and holidays) and at different times of the day and night. The observers were present during a preset series of shifts, to represent the variation of working hours in nursing practice. When a potentially harmful error was identified (that is, dose omission), the observer did not only register the error, but also intervened by talking to the nurse about the case.

Prescriptions were also analyzed in order to identify the presence of enteric-coated tablets prescribed to be administered through feeding tubes. Given the fact that direct observation of medication administration process involved the patient, researchers asked for written authorization from the patients or their legal guardians.

Data were entered in Epi Data version 3.1 and were transferred to the Statistical Package for the Social Program Sciences® (SPSS) version 22.0. The Pearson's Chi-square was used to test associations; a level of significance at 5% ($p<0.05$) was considered in all analyses.

This study was approved by the Research Ethics Committee of the University of São Paulo at Ribeirão Preto College of Nursing (EERP-USP) (CAAE: 17687513.1.0000.5393), according to the Resolution n° 466/2012, of the National Council of ethics in research of the Brazilian Ministry of Health. Nurses and patients were informed of the research and asked to voluntarily sign the consent form. In addition, participants were informed that the results will be used for publication and researchers guaranteed their confidentiality and anonymity.

RESULTS

Patients consisted mostly of males (n = 18; 51.4%), elderly (n = 23; 65.71%), in use of polyurethane tube (n = 29; 82.9%), with jejunal access (n = 29; 82.9%). The most common medical classification included diseases of the circulatory system (n = 16; 45.71%), followed by diseases of the respiratory system (n = 7; 20%) (Table 1).

Feeding tubes were mainly of size 12F (74.2%) and were in place for a mean of 11.66 days (SD = 14.3, 1 - 99). The mean of 6.0 (SD = 2.7, range 1 - 13) medications were prescribed through feeding tube for the same patient/day; and a mean of 2.3 (SD = 1.9, range 1 - 9) medications were scheduled at the same time and for the same patient.

The most prescribed drugs were captopril (n = 38; 10.8%), nimodipine (n = 23; 6.1%), and simvastatin (n = 20; 5.3%). According to the WHO's Anatomical Therapeutic Chemical (ATC) classification, groups C (44.12%), N (11.44%), A (19.1%), and B (10.64%) were the most common drug groups administered through feeding tubes (Table 2).

Nurses auxiliaries were responsible for administering 215 (57.5%) doses, followed by nurse technicians (n = 155; 41.4%), and registered nurses (n = 4; 1.1%). In 100% of observations, nurses had experiences with administering oral medications through feeding tubes previously.In relation to the pharmaceutical dosage forms administered, immediate-release tablets were the most common (n = 196; 52.41%), followed by dragée tablets (n = 75; 20.05%), sustained-release tablets (n = 73; 19.52%), effervescent powder (n = 12; 3.20%), liquid (n = 8; 2.13%), and immediate-release capsules (n = 7; 1.87).

Medication incidents occurred during medication preparation and administration through feeding tubes. Mixing tablets with other drugs in a mortar (n = 120; 43.5%) was one of the most common incorrect medication preparation incidents observed. In addition, 21 (5.6%) extended-release tablets were crushed. Incidents related to wrong techniques were also observed with not flushing the tube between medications (n = 147; 86.5%); not testing the correct placement of the feeding tube (n = 253; 67.6%); administering medications together (n = 128; 65.6%); and not flushing the tube prior to medication administration (n = 233; 62.5%) (Table 3).

In addition, in 1.1% of cases/of patients (n = 4), the route of administration did not correspond to the prescribed route (oral route was prescribed for patients in use of feeding tube).

Tube obstruction was another medication incident related to wrong oral medication preparation and administration identified in this study. From 374 observations, there were tube obstructions in 136 (36.5%) cases. Patients using polyurethane feeding tubes (n = 123; 37.3%) had more chances of having an obstruction when compared with patients using Levine tubes (n = 9; 28.1%). However, the result was not statistically significant ($p = 0.305$).

There was an association between tube obstructions and the following variables: mixing tablets with other drug(s) ($p <0.001$); tablet incorrectly reconstituted ($p = 0.006$); tube not flushed prior to medication administration ($p <0.001$); feeding tube improperly or not flushed between medications ($p <0.001$); concurrent administration of medication and enteral formula ($p <0.001$); and enteral feeding not interrupted prior to

Table 1. Patients characteristics (N = 35).

Variable	Frequency	
	n	%
Gender		
Female	17	48.6
Male	18	51.4
Age range		
18-40	4	11.4
41-64	8	22.9
65-74	8	22.9
>75	15	42.8
Type of feeding tube		
Polyurethane	29	82.9
Levin tube	6	17.1
Tube size		
8F	21	5.6
10F	31	8.3
12F	276	74.2
14F	23	6.2
16F	16	4.3
Other	5	1.3
Feeding tube placement site		
Gastric access	6	17.1
Jejunal access	29	82.9
ICD-10		
Certain infectious and parasitic diseases (A00-B99)	1	2.86
Neoplasm (C00-D48)	3	8.57
Endocrine, nutritional and metabolic diseases (E00-E90)	1	2.86
Organic, including symptomatic, mental disorders (F00-F09)	1	2.86
Diseases of the circulatory system (I00-I99)	16	45.71
Diseases of the respiratory system (J00-J99)	7	20
Diseases of the genitourinary system (N00-N99)	3	8.57
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	1	2.86
Injury, poisoning and certain other consequences of external causes (S00-T98)	2	5.71

medication administration ($p < 0.001$) (Table 4). There was also a significant relationship ($p < 0.001$) between tube obstructions and unplanned removal (n = 120; 32.1%).

Although not statistically significant, there were more tube obstructions when patients received tablets (n = 84; 22.6%) than when they received medications in other forms ($p = 0.154$).

The results show that wrong medication preparation and administration techniques contribute to medication incidents. In addition, tube obstruction was a very common incident related with wrong techniques.

DISCUSSION

The aim of this study was to evaluate the medication incidents related to wrong oral medication preparation and administration through feeding tubes in hospitalized patients. A total of 374 doses were observed and the

Table 2. Distribution of oral medications administered through feeding tubes, according to the WHO's Anatomical Therapeutic Chemical Classification Index (ATC).

1st Level-Anatomical groups	Frequency	
	n	%
Group A - Alimentary tract and metabolism	61	16.3
Group B - Blood and blood forming organs	40	10.7
Group C - Cardiovascular system	165	44.1
Group G - Genito urinary system and sex hormones	2	0.5
Group J - Antiinfectives for systemic use	6	1.6
Group M - Musculo-skeletal system	10	2.7
Group N - Nervous system	54	14.4
Group P - Antiparasitic products, inseticides and repelents	18	4.8
Group R - Respiratory system	14	3.7
Group S - Sensory organs	3	1,0
Group V - Various	1	0.2
Total	374	100

Table 3. Medication incidents by category of error (N = 374).

Medication incident category	Frequencies	
	n	%
Wrong medication preparation		
No hand washing before medication preparation	151	40.8
Tablets not crushed to fine *powder* mixture	34	12.6
Crushing an enteric-coated tablet	5	1.3
Crushing a sustained release tablet	21	5.6
Mixing tablet with other drug(s) during medication preparation	120	43.5
Liquid medications with a high osmolality incorrectly dilute or not dilute	36	9.6
Prepared medication not labeled	151	60.4
Prepared medication did not correspond to the prescribed drug	1	0.3
Wrong medication administration		
Route of administration did not correspond to the prescribed route	4	1.1
No hand washing before medication administration	180	48.1
Patient not called by name before medication administration	136	36.4
Procedure not explained to the patient prior to medication administration	150	40.3
Gloves not used	136	36.4
No testing of the correct placement of the feeding tube prior to medication administration	253	67.6
Crushing enteric-coated tablets and administered in gastric position	5	1.3
Administering tablet in different position of the optimal site for absorption	96	25.7
No flushing of the tube prior to medication administration	233	62.5
Administering medications together	128	65.6
No flushing of the tube between medications	147	86.5
No flushing of the tube after medication administration	74	20.7
Administering medication that adsorbs or interact with enteral nutrition, without observing the minimum recommended interval between ingestion	114	30.5
Enteral feeding flow not reestablished after medication administration	3	1.9
Patient not monitored after medication administration	78	21.1

Table 4. Tube obstruction, according to medication preparation and administration technique (N = 374).

Medication preparation and administration technique	Tube obstruction				p-value
	Yes		No		
	n	%	n	%	
Medication preparation					
Tablet crushed to fine powder mixture					
Yes	82	35.3	150	64.7	0.179
No	13	48.1	14	51.9	
Mixing tablet with other drug(s)					
Yes	57	50.4	56	49.6	<0.001
No	42	26.9	114	73.1	
Tablet correctly reconstituted					
Yes	70	32.7	144	67.3	0.006
No	30	52.6	27	47.4	
Medication administration					
Tube flushed prior to medication administration					
Yes	11	7.9	129	92.1	<0.001
No	120	54.3	101	45.7	
Administering each drug separately					
Yes	26	40	39	60	0.116
No	62	52.1	57	47.9	
Feeding tube properly flushed between medications					
Yes	3	13	20	87	<0.001
No	76	55.9	60	44.1	
Feeding tube properly flushed after medication administration					
Yes	101	36.6	175	63.4	0.237
No	31	44.3	39	55.7	
Concurrent administration of a medication and enteral formula					
Yes	63	54.8	52	45.2	<0.001
No	35	23	117	77	
Enteral feeding interrupted prior to medication administration					
Yes	28	20	112	80	<0.001
No	63	63	37	37	

WHO's ATC classification evidenced that the most common drug group administered was for the cardiovascular system, and included captopril, nimodipine, and simvastatin. This result is consistent with previous research (Gimenes et al., 2011). Nurses should not assume that all tablets can be safely administered through a feeding tube. For instance, nimodipine is primarily absorbed in the stomach, therefore administering this drug via a jejunal access may reduce the rate of absorption. It is worth noting that, in this study, most patients (82.9%) had jejunal access, thus the bioavailability and efficacy of some drugs may be reduced.

In relation to the pharmaceutical dosage forms, immediate-release tablets were administered in 52.41% of the time, and sustained-release tablets in 19.52%. According to Phillips and Endacott (2011), one third of nurses studied stated that enteric-coated medication

could be administered when no other form was available, revealing that nurses have insufficient knowledge about the safety risks associated with destroying the enteric coating (Lohmann et al., 2015).

In order to achieve adequate clinical outcomes in hospitalized patients, it is essential that medications and enteral nutrition therapy be administered appropriately. However, nursing guidelines on feeding tube care are basically based on traditions, rituals and expert opinions, exposing patients to unnecessary harm (Kalaldeh et al., 2012; Simons and Abdallah, 2012).

Previous research also showed that most nurses had deficient knowledge on the proper administration technique through feeding tubes. Almost 70% have crushed at some time an enteric-coated tablet and 66.2% have crushed a sustained-release tablet (de Amuriza Chicharro et al., 2012). There is a clear need for healthcare institutions to develop strategies to enable practicing nurses to improve their knowledge and skills in oral medication preparation and administration through feeding tubes in hospital settings.

Several medication incidents were identified in this study. In relation to oral medication preparation, mixing tablets with other drugs and crushing extended-release tablets were the most common. Nurses should not mix medications together for administration through feeding tubes because of the possibility of physical and chemical incompatibility, tube obstruction or changes in drug pharmacodynamics (Bankhead et al., 2009; Emami et al., 2012). Modified-release tablets are not suitable for administration via feeding tubes because they are formulated to release the drug slowly over time. Thus, crushing extended-release tablets will affect the pharmacokinetic profile of the drug and may result in excessive peak plasma concentrations and side-effects (White and Bradnam, 2015).

Incidents related to wrong oral medication administration were also common and included: not testing the correct placement of the feeding tube (67.6%); administering medications together (65.6%); not flushing the tube prior to medication administration (62.5%); and not flushing the tube between medications (86.5%). Previous research showed that 74% of nurses had employed wrong medication administration methods to deliver medicines through feeding tubes and according to researchers, those errors could reduce the effects of drugs and lead to unsuccessful treatment (Emami et al., 2012). Special caution must be highlighted for not testing the correct placement of the tip of the tube prior to medication administration.

According to the National Patient Safety Agency (NPSA), there were 21 deaths and 79 cases of harm related to feeding through misplaced nasogastric tubes, as reported to the National Reporting and Learning System (NRLS), between September 2005 and March 2010 (National Patient Safety Agency, 2011). It is recommended that feeding tubes are checked for placement at least every 24 h, as tubes may be dislodged after vomiting or coughing; before administering each feed; and before giving medication. In addition, the method of testing must be documented (National Patient Safety Agency, 2011; White and Bradnam, 2015).

In this study, administering medications that adsorbs or interacts with enteral nutrition were also observed (30.5%). The consequence of this practice is the increased risk of physical-chemical incompatibilities and potential drug-nutrient interactions (Fisher and Blalock, 2014). This concomitant administration of medications and enteral formulas could derive potential benefits in regards to time and cost; however, uncertainty exists regarding potential drug and nutrient interactions and the influence this may have on both safety and efficacy (Kurien et al., 2015).

The lack of information on the impact of compounding by mixing medications with enteral formula and/or administering through feeding tubes on the drug product safety and efficacy is problematic (Stegemann, 2015). This incident can increase adverse effects and lead to tube obstructions.

The overall occurrence of tube obstruction identified in this study was significantly higher (36.5%) than that reported in other studies (ranging from 2 to 12.5%) (Phillips and Nay, 2008) and it may be attributed to the use of solid form medications. Clogged feeding tubes are responsible for significant loss of delivery of enteral feeding (Fisher and Blalock, 2014) and it is worth noting that, in this study, there was a significant relationship between tube obstruction and unplanned removal ($p < 0.001$). This result is in accordance with a previous study that has shown that the main cause for unplanned removal of the feeding tube was related to obstruction (Pereira et al., 2013).

There was also a statistically significant association ($p = 0.006$) between tube obstruction and incorrect reconstitution of drugs, and it may be attributable to a lack of adequate knowledge related to pharmaceutical formulations. This finding may also be explained by the deficiency in the training process of nurses, specifically for medicines, which does not include items related to pharmaceutical technology.

In addition, in this study feeding tubes were mainly of size 12F (74.2%). The size of feeding tubes used in adults should be between 6F to 12F (National Nurses Nutrition Group, 2016). Narrow tubes and long tubes are more likely to become blocked, thus special precautions should be taken by nurses to prevent tube obstructions, which includes stopping enteral feeding before a drug is administered; flushing the tube before and after each intermittent feed, every four to six hours during continuous feeding, and before and after each drug administration. However, in patients with renal or cardiac disease, the flush volumes will need to be revised to meet the patient's prescribed fluid restrictions (White and Bradnam, 2015).

Another incident observed was the dose of medication administered in a different route to that prescribed (1.1%). In this study, physicians prescribed solid formulations via the oral route, representing a prescription error. However, if the dose was intended to be given orally but the nurse administered it through a feeding tube, this practice could be classified as an administration error (White and Bradnam, 2015). It is important to consider that the route prescribed should match the placement of the tube in the gastrointestinal tract.

The practice of administering medications through feeding tubes has become complex, thus health care institutions must ensure that patients receive safe and competent care (Walsh and Brophy, 2011) through well-trained and qualified nurses. In this study, most medications were administered by nurses' auxiliaries, thus education and training programs should be used and valued as a vital tool for addressing the challenges of improving patient safety (World Health Organization & WHO Patient Safety, 2011).

Despite abundant evidence regarding safe oral medication preparation and administration through feeding tubes, nurses still employ improper techniques in hospitals around the world including those in developing countries, exposing patients to unnecessary risks. The results of this study show that training and education of nurses have not kept pace with advances in patient safety, nor with workforce requirements. In addition, we may conclude that many nurses are not using research conducted in nursing and related disciplines as a foundation for safe medication practices. Nurses and other healthcare professionals should be adequately prepared to provide the best care possible, and education and training should be the foundation of safe, high quality health care.

Our study presented limitations. Observation methods for studying medication preparation and administration errors can influence the results because the presence of an observer may affect nurses' behavior. In addition, prudence is called for when generalizing the results to other departments or other hospitals. This study involved medical wards of general medium-sized hospitals, thus the incidence of errors relating to oral medication preparation and administration may be lower when compared to an intensive care unit or the medical ward of a large university hospital.

Conclusion

Medication incidents were identified during oral medication preparation and administration through enteral feeding tubes in Brazilian hospitals and they were associated with tube obstructions. Mixing tablets with other drugs, not flushing the tube between medications, and not testing the correct placement of the enteral feeding tube prior to medication administration were the most common incidents observed in this study.

The results contribute to the development of knowledge in the field of patient safety and quality in oral medication preparation and administration through feeding tube, in order to improve hospital nursing practice, especially in developing countries. In addition, this study contributes to the body of evidence that may influence the development of national policies focused on the risks associated with these practices.

Our results also reinforce the argument that continuous training and updating knowledge will allow nurses to rethink and to change their current practices. In conclusion, we believe that promoting continuing education programs configures as an important aspect for nursing professionals to acquire skills to correctly prepare and administer oral medications through feeding tubes.

This study did not evaluate clinical outcomes (death and severe harm) caused by medication incidents. Future studies should be conducted in order to assess patients' outcomes related to those incidents.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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