Intrinsic and extrinsic factors associated with phlebitis in hospitalized patients: Systematic Review

[Factores intrínsecos y extrínsecos asociados a flebitis en pacientes hospitalizados: Revisión Sistemática]

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Resumen

Los cuidados de enfermería en accesos venoso central y periférico forman parte del trabajo de enfermería, y la calidad de atención se ve afectada por la presencia de flebitis en diversas áreas de hospitalización, por ello se identifica los factores relacionados a la flebitis. Objetivo: Analizar el desarrollo de las evidencias científicas sobre Factores intrínsecos y extrínsecos asociados a flebitis en pacientes hospitalizados. Metodología: Se realizó una búsqueda bibliográfica en las bases de datos en los últimos diez años. No hubo restricción de idioma, se incluyeron estudios en idiomas inglés, español y portugués publicados revistas indexadas de texto completo, llevándose un análisis crítico de cada artículo seleccionado, plasmando una matriz para ordenar y categorizar. Resultados: De un total de 64 artículos se incluyeron 9 de los cuales fueron 2 inglés y 7 en portugués, cuyos resultados fueron que existen factores intrínsecos propios del paciente, los factores extrínsecos que corresponden a los factores que pueden ser evitables por el profesional de enfermería al ser identificados. Conclusiones: Flebitis considerada un indicador de calidad del servicio de enfermería, en el camino de las revisiones de artículos se han identificados múltiples factores relacionados a la flebitis, con los cuales se debe de tomar medidas preventivas, correctivas y educativas en las áreas donde se manipule accesos venosos, evitando futuras complicaciones, asimismo mejorar la calidad de atención reflejados en los indicadores de flebitis con resultado cero como una meta.

Palabras clave: Flebitis y factores, flebitis, revisión sistemática.

Abstract

Nursing care in central and peripheral venous access is part of nursing work, and the quality of care is affected by the presence of phlebitis in various hospitalization areas. Therefore, factors related to phlebitis are identified. Objective: To analyze the development of scientific evidence on intrinsic and extrinsic factors associated with phlebitis in hospitalized patients. Methodology: A literature search was carried out in databases over the last ten years. There was no language restriction, studies in English, Spanish and Portuguese published in full-text indexed journals were included. A critical analysis of each selected article was carried out, creating a matrix for ordering and categorizing. Results: From a total of 64 articles, 9 were included of which 2 were English and 7 in Portuguese, whose results were that there are intrinsic factors specific to the patient, extrinsic factors that correspond to factors that can be avoidable by the nursing professional when identified. Conclusions: Phlebitis is considered an indicator of nursing service quality. In the course of the article reviews, multiple factors related to phlebitis have been identified, with which preventive, corrective and educational measures should be taken in the areas where venous accesses are manipulated, avoiding future complications, as well as improving the quality of care reflected in the indicators of phlebitis with a zero result as a goal.

Keywords: Phlebitis and factors, phlebitis, systematic review

1. Introduction

In the world, phlebitis cases have a very important position as a complication occurring within hospital facilities, where intravenous catheters are used and leading to the patient with phlebitis, a serious infection situation or thrombophlebitis (Johann et al., 2016). There are different factors associated with phlebitis, which need to be identified by nursing professionals, due to the casuistry of cases worldwide. In this sense, in the hospital setting, annual training is carried out to improve the quality of nursing care, which affects the indicator of cases of phlebitis by 50%, so there is a need to strengthen the professional competencies of nurses for the prevention of phlebitis (Woody & Davis, 2013).

Phlebitis is a complication frequently observed in patients receiving peripheral intravenous treatment, classified as a nosocomial infection, phlebitis is a quality indicator, which is the responsibility of the care provided by the nursing professional (Gil, et al., 2017; Colegio de Enfermeros del Perú, 2008). Thus, there are multiple factors associated with phlebitis, including inadequate insertion technique of the peripheral intravenous catheter; clinical condition of the patient; characteristics of the vein; drug incompatibility; tonicity and pH of the solution to be infused; ineffective filtration; caliber, size, width and material of the catheter; and prolonged insertion time (De Souza, 2016; Ray, 2011).

It should be noted that phlebitis is classified into four types: Mechanical (the cannula causes friction in the vein, causing phlebitis, and the large caliber of the intravenous device also plays a role). Chemical (caused by an infused solution with conditioning factors in the pH and osmolarity of the substances that cause chemical phlebitis). Bacterial (bacteria enter the vein and colonise the local area). Post infusion (occurs 48 to 96 hours after removal of the catheter) (Marquez, 2017). In addition, there is a classification according to: grade 1 (erythema with or without localised pain); grade 2 (erythema and/or oedema); grade 3 (erythema with pain, induration and formation of palpable venous hardening smaller than 6cm); grade 4 (erythema with pain, induration and formation of palpable venous hardening larger than 6 cm plus presence of purulent drainage; Urbanetto et al., 2018).

Pérez (2011), mentions in his update on the use of peripheral venous catheters and its complication post infusion phlebitis, that it is still necessary to extend the research on the correct measures to avoid these complications, however it is the nursing faculty and responsibility to take actions to avoid them or limit their duration (Pérez, 2011). A Scandinavian study on microbiological colonization of peripheral venous catheters in the ports and inner lumen of the catheter found that 11% of the catheters were positive for infection, the port was 8.7%, only the inner lumen 1.7% and the inner lumen and port was 0.7% (Juhlin et al., 2021). According to the Infusion Nurses Society (INS), it has considered that cases of phlebitis should be equal to or less than 5% of patients with peripheral venous catheters (Osti et al., 2019). In Peru, research since the 1990s has shown that morbidity and mortality rates from nosocomial infections have increased from 8% to 30%, and new cases of phlebitis have been as high as 70% (Díaz et al., 2019).

Internationally, in Spain, out of 54.5% of patients with peripheral venous catheters, 23% had cases of phlebitis (González et al, 2013). On the other hand, in China 80% of patients who received parenteral therapy, 20% showed phlebitis (Díaz et al., 2019). Consequently, over the years, national and international research has been carried out on the factors that cause phlebitis. Argues that the risk factor for phlebitis is the caliber or size of the peripheral venous catheter, observing that there are fewer cases of phlebitis in calibers 22 or 24 and the extensions of the catheter are an independent predictor of phlebitis (Arias-Fernández et al., 2017). According to studies at the Secondary Care Hospital in Havana, Cuba. Peripheral venous catheters (CVP) are

the most commonly used devices and these are the active causes of phlebitis, with 80% of patients reporting local reddening and oedema, in addition to not having suitable staff for catheter insertion. In conclusion, it is necessary to identify the quality of catheter indications, insertion, maintenance and other issues related to the risk of phlebitis (González-Valdés et al., 2020).

According to Reyes-Rueda et al., (2021), in his research on the permanence of hospitalized neonates and its relationship with the presence of phlebitis, he concludes that there is an important relationship taking into account some risk factors such as the place of insertion, the number of times it is attempted to cannulate, the length of time spent in hospital and the use of irritant solutions. On the other hand, Gómez-Neva et al., (2015) in their systematic review determined that more research is needed in the population of children regarding the permanence of peripheral catheters and the appearance of phlebitis, the studies were directed to investigate other aspects; unlike adults there is a risk of presenting phlebitis 72 and 96 hours after insertion of the catheter; so it is necessary to perform it in this period and prevent phlebitis (Webster et al., 2013).

In Peru in 2019, new cases of phlebitis were very high in the National Institute of Neoplastic Diseases, identifying mechanical and chemical factors as the main ones (Díaz, 2019). Patient safety will depend on the level of competence of the health team (Martínez et al., 2017), increasing this knowledge in phlebitis, will ensure quality patient care, with nursing interventions in a preventive care plan to phlebitis (Plan Nacional Resistencia de Antibióticos, 2019), (Febré et al., 2018).

Finally, we see the value of this topic to review: What is the scientific evidence on extrinsic and intrinsic factors associated with phlebitis in hospitalized patients? This question was developed through a systematic methodology that sought to highlight the findings, while maintaining a critical stance, of the information obtained.

2. Materials and methods

The design was a systematic, descriptive review where a search was conducted in the SCIELO and LILACS databases, using inclusion criteria with English, Spanish and Portuguese languages, from the period 2011 - 2020. The algorithm "and" was used and the variables were "flebite e fatores" (Portuguese), "phlebitis AND factors" (English), whose central theme was intrinsic and extrinsic factors associated with phlebitis in hospitalized patients. Of the total number of scientific articles found, 64 were evaluated according to full-text relevance and methodological quality of the study. After analyzing and reading the titles and abstracts, 55 articles were excluded, leaving 9 studies that were read in their entirety, which responded to the objective of the study.

The search for articles was carried out using concepts and synonyms, as shown in table 1.

Table 1. Concepts and synonyms of the search Intrinsic and extrinsic factors associated with phlebitis in hospitalized patients: Systematic review.

Database	Identification	Selection	Eligibility	Inclusion
Scielo	22	15	7	7
Lilacs	42	40	2	2
Total	64	55	9	9

Each researcher reads the chosen articles in order to analyze, compare and discuss the information obtained, establish results and conclusions.

Concepts	Synonyms
Factors associated with phlebitis.	Patient safety in intravenous access, quality of care in venous access.

Figure 1. Database and phases developed for the collection of information

3. Results

The results obtained from the systematic review are presented below:

Table 2. Countries of origin of the articles

Country	Quantity	Percentage
Brasil	7	77.1%
Portugal	2	22.1%
Total	9	100%

Seven studies were identified from Brazil with 77.1% and two from Portugal with 22.1%.

Table 3. Designs used in the systematic review articles

Design	Number	Percentage
Quantitative	8	88.9 %
Qualitative	1	11.1 %
Total	9	100 %

It was found two designs used eight studies: quantitative with 88.9% and one qualitative study with 11.1%.

Table 4. Systematic review: Intrinsic and extrinsic factors associated with phlebitis in hospitalised patients: Systematic review of indexed journal articles, 2011-2020

Author	Title	Key words	Instruments and/or techniques	Dimensions / categories	Results	Conclusions
Milutinovic, D. et al (2015)	Factores de riesgo de la flebitis: un estudio con cuestionario de la percepción de las enfermeras.	Phlebitis Infusions Intravenous Risk Factors Nurses Questionnaire s.	Modified Lanbeck et al. questionnaire (P et al., 2004)	Perception of risk factors for phlebitis. Phlebitic potentials of some drugs and solutions.	It was found that one third of the nurses consider that it is normal for phlebitis to occur; in addition to cannulation, proper use, short infusions. They identified that lack of knowledge of catheter material and diameter can cause phlebitis. The nurses report that phlebitis increases with a higher level of concentration and pH of the solutions, as well as the presence of comorbidities such as thromboembolic diseases, diabetes mellitus and vascular insufficiency. Vancomycin, benzylpenicillin, calcium gluconate and amiodarone were identified as having greater phlebitic potential.	The nurses identified that some diseases in the patients increased the cases of phlebitis, as well as the phlebitis-causing effects of some medicines and solutions.
Enes, S. , Opitz, S., De Faro, A. , Da C., & Pedreira, M. , Da L. (2016)	Flebitis asociadas con catéteres intravenosos en adultos ingresados en hospital de la Amazonía Occidente Brasileña.	Phlebitis Catheterization Peripheral Intravenous infusions Hospitalized Hospitalized patients Nursing care.	Patient observation and intravenous therapy using the rating scale proposed by the Infusion Nursing Society (INS).	Technique of intravenous catheter insertion. Characteristic s of infusion therapy in children.	They conducted a study with 122 patients, of which those with chronic diseases, infections, use of the catheter for more than 7 days, use of drugs with high pH and vesicant, and with a long time presented phlebitis; the catheter caliber was 20G, located in the forearm and dorsum of the hand with 36.9% of cases and a permanence of 68.4 hours, being responsible for 38 complications in patients with 31.1%.	The most frequent complications in this study were phlebitis present in patients with chronic diseases, infections, continuous infusions, concomitant intermittent, have a significant frequency higher than phlebitis.

De Lima, K., Ferreira, A., Miranda, A., Gonçalves, M. (2014)	Flebitis asociada a catéteres intravenosos periféricos en niños: un estudio de factores predisponentes.	Peripheral catheterization. Pediatric nursing Patient safety.	Survey where they performed a clinical assessment of ICP four times a day, applying the INS phlebitis rating scale.	Demographic characteristics of the children. Catheter maintenance and permanence. Risk factors for phlebitis in children.	It was found that no demographic characteristic in children was significant to cause phlebitis, they used the catheter for more than 5 days, number of attempts for catheter placement as a risk factor; children who had phlebitis have a history of having presented previously, infusions of medications or solutions of pH and osmolarity are risk factors for phlebitis.	Risk factors were puncture failure, history of phlebitis, drug infusions and high pH and osmolarity solutions.
Rojas-Sánchez, L., Parra, D., Camargo-Figueroa, F. (2015)	Incidencia y factores asociados al desarrollo de flebitis: resultados del estudio piloto de una cohorte.	Phlebitis Incidence Risk Factors Patient safety.	Pilot test	Sample characteristics, cumulative incidence and factors related to phlebitis.	The mean age was 45 years, with a predominance of males, and six risk factors were identified, such as age, length of hospitalization, administration of platelets, number of drugs infused, antibiotics and gastric antisecretory agents.	Contributions are provided with the identification of the factors in the sample, being valuable for nursing professionals when performing nursing interventions with venous access care.
Braga, L., Parreira, P., Oliveira, A. de S., Mónico, L. Dos S., Arreguy-Sena, C., & Henriques, M. (2018)	Flebitis e infiltración: traumas vasculares asociados al catéter venoso periférico.	Nursing Peripheral Catheterization Phlebitis Intravenous infusions Extravasation of materials therapeutic and diagnostic	Survey based on the Portuguese Scales of Phlebitis and Infiltration.	Characterization of patients and medications administered. Characterization of peripheral venous catheter dwell time until removal due to	It was identified that 52.7% were women with an average age of 79 years and a median of 82 years, with comorbidities of arterial hypertension in 6.9% and metabolic diseases in 48.2% were diseases that the patients already had. The disease for which they were hospitalized was infectious. The rate of new cases for phlebitis and infiltration was 43.2 and 59.7 per thousand catheters per day, for the catheter was 11.5 % and 15.8 %, with no evidence of grade 4 phlebitis and infiltration in grades 3 and 4. In the ethereal group with more cases was the elderly, as catheter insertion mostly in the back of the hand, using	There are risk factors related to phlebitis and infiltration, which can be prevented by taking care during implantation.

		Patient safety.		phlebitis and infiltration and respective degrees.	the 22 gauge catheter, followed by catheter number 20, the number of attempts was mostly at the first attempt, what was most used was the sterile transparent film to fix the catheter, the most used drugs were antimicrobials followed by continuous intravenous solutions.	
Buzatto, L. , Massa, G. , Peterlini, M., & Whitaker, I. (2016)	Factores relacionados con la flebitis en ancianos con infusión de amiodarona intravenosa	Amiodarone, Intravenous/ Complicated infusions. Elderly Phlebitis/etiology. Nursing care.	Survey based on the Infusion Nurses Society (INS).	Development of phlebitis in elderly patients with intravenous administration of amiodarone. Relation of phlebitis in the elderly with intravenous peripheral puncture.	The study was carried out with 102 elderly people, the mean age was 70.6 years, 34 of them with 33.3% presented phlebitis and 24 with 70.5% was grade 1, after 72 hours of amiodarone infusion, no phlebitis was observed. Phlebitis was observed mostly in women with 43.6%, in perforated dominant extremity with 36.2% and puncture in basilic or cephalic veins of the forearm with 41.2%. The most commonly used catheter caliber was 20 and 22 with 79.4%. The use of sterile IV Fix dressing was most frequently observed with 39.3%, intima with 34.3%, in the groups there were no significant statistics. Phlebitis was absent in the exclusive rapid infusions, with a marginally significant difference in the occurrence of phlebitis compared to the different types of infusion.	It is concluded that one third of the older adults did present cases of phlebitis due to amiodarone infusions.
De Souza, J., Grassmann, C., & May, T. (2016)	Incidencia de flebitis asociada con el uso de catéter intravenoso periférico y después de la extracción del catéter.	Phlebitis Patient Safety Nursing Intravenous infusions.	Peripheral intravenous catheterization survey.	Characteristics of age, gender, puncture site and medications used. Frequency and occurrence of phlebitis, use and removal of peripheral	The results of the study were able to analyze the complications derived from an intravenous catheter. The predominant gender was male and older than 58 years, the most used catheter was 22 gauge, with a time of permanence of less than 72 hours, the majority had the catheter located in the arm and the most used drugs were sedatives and analgesics followed by antibiotics. Phlebitis during use was 1.25% and post infusion 1.38%.	The presence of post-infusion phlebitis was more important than the time the catheter remained in place. Follow-up after catheter removal is important since in this study there were significantly considerable cases.

				intravenous catheter.		
Da Silva, E., Barros, A., Celia, R. (2016)	Caracterización de flebitis notificada a la gestión de riesgos en la red centinela hospitalaria.	Nursing Phlebitis Notification	Data collection through questionnaire developed by interview, telephone calls and nursing notes.	Characterization of the degree of phlebitis according to location and cause of phlebitis.	The results of 285 records of phlebitis the main location was the dorsum of the hand 36.5% followed by the forearm 34.4% and arm in 21.4%. In relation to the degree of phlebitis, we have grade I with 63.2%; according to the type of phlebitis, the chemical type 72.6%, followed by mechanical 12.6%, bacterial 12.6% and postinfusion 3.2%, being more in emergency areas followed by clinical wards. Infusions with incorrect dilutions and drug interactions in the lines without washing after the medication are risk factors for phlebitis.	It is essential to create protocols that emphasize the daily monitoring of catheters, training and interdisciplinary measures for the prevention of phlebitis, promoting the safety of hospitalized patients.
Tertuliano, A. C., Borges, J. L. da S., Fortunato, R. A. S., Oliveira, A. L., & Poveda, V. de B. (2014)	Flebitis en accesos venosos periféricos de pacientes de un Hospital Vale do Paraíba.	Phlebitis Peripheral Catheterization Nursing Care	Convenience sample questionnaire of patients from a hospital in Vale do Paraíba - Brazil.	Sociodemographic characteristics and peripheral venipuncture. Description of the cases of phlebitis in the study.	In the study of 76 patients, 24 presented phlebitis, the majority of cases were white males, and the insertion site was 31.6% on the dorsum of the hand. The most commonly used catheter caliber in the study was number 20. Infiltration was the most common reason for catheter change and removal, in addition, the casuistry of Teflon use is higher than polyurethane catheters. The most frequently infused medicines were electrolytes and analgesics with 54.1%, followed by 25% in antibiotics. Regarding the quality of the nurses' notes, 58 with 76.3% were complete and 18 with 23.7% were incomplete.	In the study the cases of phlebitis was high with 31.6%, compared to the 5% expected by the society of Intravenous nurses, with respect to the quality of the nursing records in the majority was incomplete.

4. Discussion

The present research analyzed a total of 9 articles from two databases: 77.7% from Scielo and 22.3% from Lilacs. The countries where most of the articles were published were Brazil and Portugal. In terms of language, the articles were found in Portuguese, Spanish and English. The articles whose methodology was used were: Descriptive with 44.4%, prospective 33.4%, exploratory 11.1% and quantitative in 11.1%. Phlebitis is an adverse event present in different hospital areas, and is under the care of the nursing professional, in the systematic review the factors associated with phlebitis were identified in 9 original articles, being classified into intrinsic and extrinsic, intravenous infusions are provided by different circumstances and times of permanence, making it a high risk of presenting safety accidents in the patient (Reyes-Rueda, et al., 2021); (Fortes, et al., 2019).

Intrinsic factors associated with phlebitis in hospitalized patients.

According to Milutinović D. et al. (2015); Enes et al. (2016); Rojas-Sánchez, et al. (2015); Tertuliano et al. (2014), authors agree that thromboembolic diseases, diabetes mellitus and vascular insufficiency, hypertension and metabolic disease are predisposing factors to a high risk of phlebitis.

On the other hand, Braga, et al. (2018) in his study confirms that patients with hypertension and metabolic diseases present phlebitis. Likewise, Buzatto et al. (2016) states that the older adult population is more likely to present first-degree phlebitis. In this sense, Urbanetto, et al., (2017) indicates that it is more frequent in men. Along the same lines, Tertuliano et al., (2014) mentions that phlebitis occurs mostly in white, black and brown people. It is also important to consider inadequate lifestyle factors such as alcohol consumption, smoking, among others.

The nurse caring for hospitalized patients needs to be knowledgeable about venous access care, maintenance and prevention of phlebitis (Acosta-Gnass, 2021).

The caregiver needs to recognize the factors to reduce the risk of phlebitis, improve the quality of care and professional warmth, and preventive care programs are valuable, because knowledge and identification of the factors will be taken into account to reduce the risk of phlebitis incidence and avoid extending the patient's hospital stay and patient safety (Parra et al., 2012).

Intrinsic factors are unavoidable, but identifying them will maintain a more continuous observation of peripheral catheters and careful care at peripheral catheter insertion.

Extrinsic factors associated with phlebitis in hospitalised patients.

According to researchers Milutinović et al., (2015); De Lima, et al., (2014); Oliveira et al., (2016), they coincide in the predisposition to phlebitis due to drugs with pH and osmolarity outside the acceptable range and also infusions with vesicant solutions would cause irritation of the veins.

In an intervention programme regarding the association of phlebitis in relation to infectious events and irritants due to the use of peripheral catheters, the results showed that it can be prevented with this type of programme to a limited extent, as those of an infectious nature occurred in smaller quantities, managing to reduce the infectious and mortality rates, those caused by irritant solutions require more specific measures in the ways of administering chemical agents (Vergara et al., 2017).

The authors agree on the use of large diameter catheters Vergara et al., (2017). predispose the hospitalized patient to phlebitis. According to Milutinović et al., (2015) the risk factors in this article were inadequate catheter insertion, lack of nursing staff knowledge of catheter materials and diameter. The nurses' perceptions regarding the prevention of phlebitis occurrence mention

adequate time for drug administration, in situ catheter placement and the importance of the insertion site. Likewise Enes et al. (2016) in this study the factors influencing the presence of phlebitis was the use of the intravenous device for a period longer than 7 days.

In another article De Lima et al., (2014) mentioned that the permanence of the catheter and the administration of drugs and. In addition, Díaz et al., (2019) mention that the length of hospital stay, platelet administration, amounts of drugs administered, catheter location, use of buretrol, use of infusion pump, among others. On the other hand, Braga, et al., (2018) mention that the insertion of a catheter located on the back of the hand was the most common case for the presence of phlebitis.

Furthermore, Urbanetto et al., (2017) in their study, with a length of stay of less than 72 hours, most patients had the catheter placed in the arm and the most commonly used drugs were sedatives and analgesics followed by antibiotics. Furthermore, De Souza et al., (2016) indicated that the cases of phlebitis reported were on the dorsum of the hand. Tertuliano et al (2014) mention that they developed phlebitis with a catheter dwell time of between 3 and 120 hours, with an average of 49 hours.

It is important to know the extrinsic factors, including catheter insertion and peripheral intravenous catheter care, which is the responsibility of nursing, with its permanent monitoring and evaluation of the quality of care in venous access, avoiding adverse events such as phlebitis (Pérez, 2011). In addition, monitoring, improvement and research projects on phlebitis quality indicators on an annual basis, as well as continued surveillance of factors related to phlebitis (Lara et al., 2017), comparative studies on phlebitis prevention measures and performance of nursing care related to the subject are suggested, as well as feedback whenever necessary in order to have adequate levels of information on phlebitis in nursing professionals.

Annual training on nursing care in peripheral catheter insertion and maintenance of intravenous devices is suggested, as well as pre- and post-testing of the training and verification of learning in writing or online, depending on the emergency situation by the COVID19.

5. Conclusions

Phlebitis is considered an indicator of quality of care and its risk factors are multiple, we have those that are specific to the patient (comorbidities, history, age, sex, lifestyles) and modifiable external (catheter location and insertion, peripheral venous catheter caliber, irritant solutions, infusion time, number of drugs to be infused, catheter fixator, catheter dwell time). In addition, the intrinsic factors were agreed by the authors, the elderly population and comorbidities were very important to take into account, but further studies are suggested for the future, and the extrinsic factors could be avoided with nursing professionals who are aware of and trained in preventive measures for phlebitis, and a study is suggested to continue with the revision of articles as the devices change over time, and it should be ascertained whether they are really a quality of care or a risk factor for phlebitis of the mechanical type. Finally, phlebitis is an adverse event considered as a hospital complication, where nurses need to decide, apply and execute taking preventive actions on extrinsic factors to reduce the incidence of phlebitis in hospitalized patients and avoid the risk of death and prolonged hospital stay. Our working group had no information limitations, but did have to learn the article design and the use of the MENDELEY bibliographic manager to manage and share the information required for the systematic review.

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