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SYSTEMATIC REVIEW

THE ROLE OF PHARMACISTS IN MINIMIZING MEDICATION ERRORS IN THE NEONATAL INTENSIVE CARE UNIT: A SYSTEMATIC REVIEW

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Abstract

Background: Hospitalized pediatrics, especially neonates, are more prone to excessive medication errors. Implementation of pharmacy services shows a decline in medication errors in hospitals and clinics. In this study, we aimed to demonstrate the role of pharmacists in reducing medication errors in hospitalized neonates;

Methods: The systematic review of the literature was undertaken through the PubMed database from 2002 to 2022. The search MESH terms were multiple combinations of "Medication error", "Clinical pharmacist", "Clinical pharmacy services", "Infant & newborn". Afterward, the results were filtered to include the role of pharmacy services in preventing medication errors for the inpatient neonatal population; Results: a total of 15 articles were eligible to be included in the current review, comprising neonatal or whole pediatric population, including neonates. The primary pharmacy interventions were prescription auditing, identification of medication errors, changing preparation and administration, medication reconciliation, educating healthcare workers, and developing policies;

Conclusions: Our systematic review illustrated that pharmacists' integration with other healthcare teams could help minimize medication errors before reaching neonates.

Introduction:-

Errors are expectable in medical practice due to the nature of humans and the complications of medical management. Some errors may not produce severe consequences, but some may lead to serious conditions and death [1]. Medication errors can happen from diagnosis till discharge. The main steps of patient care are prescribing medicine, dispensing, and administering medications. Prescription error is the most common and important cause of medication error. Moreover, the prescription error causes errors in dispensing and administration [2].

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There are many causes of a medication error, such as inadequate knowledge of medicines, lack of awareness of medication error, and poor adherence to work. A poor working environment and insufficient staff may also lead to medication errors [3, 4]. Therefore, it is recommended that all medical staff, such as physicians, pharmacists, and nurses, be well informed and more aware of medication errors. Many studies showed that about 44,000 to 98,000 patients die yearly from adverse drug events, and about 7000 of those were due to medication errors [5].

Hospitalized neonates and pediatrics are more exposed to medication errors than adults [6].The reason is that neonates and children receive the appropriate dose according to their clinical condition and weight, but adult patients take the standard dose. Additionally, the appropriate dose for children and neonates needs more calculations by physicians, which may increase the possibility of error. Furthermore, most medications were found in a suitable dosage form and concentration for adults, not neonates or children. For this reason, physicians and pharmacists must adjust the dosage form and concentration of drugs to be suitable for neonates and children. That process needs several steps that also increase the likelihood of medication errors [7]. Unfortunately, those medication errors may cause severe injury or death, especially if the medication has a narrow therapeutic window [1].

In the neonatal intensive care unit (NICU), neonates almost suffer from premature absorption, secretion, or metabolism of drugs. Therefore, dilution of drugs is necessary for appropriate dosage that may increase the incidence of medication errors. Additionally, studies showed that the probability of medication error in neonates is eight-time than in adults [8]. Moreover, studies showed that about 13-91% of medication errors might happen in NICU. Many studies also demonstrated that medication errors in developed countries mainly occurred during the prescribing phase [8-10]. The presence of a clinical pharmacist and a predesigned medical order sheet are considered effective practical methods for reducing medication errors in the NICU [11].

Many studies illustrated that pharmacists' review of medication charts is essential in determining medication errors. Therefore, pharmacists play an influential role in improving drug therapy in children [12]. Another three studies were conducted in USA and UK. The two studies showed significantly reduced medication errors due to pharmacist intervention [13]. We conducted a systematic literature review to determine the pharmacist's role in minimizing medication errors in treating neonates in a hospital setting.

Materials and Methods:-

This systemic review of the literature was undertaken on the PubMed, Web of Science, MEDLINE, Scopus, the Saudi Digital Library and Google Scholar database between 2002 and 2022 to assess the role of pharmacists in decreasing medication errors for the neonatal population in a hospital setting.

MESH terms included a combination of "Medication error", “Pharmacist", "Clinical pharmacist", "Infant, “Newborn”, “Neonates”, “Pediatrics”, “Intensive care", "Medication error" and "Clinical pharmacy services" using Boolean operator AND or OR. All study titles with the abstracts that appeared from this search were screened systematically. Later, the results were filtered to include all original research articles (comparative and non-comparative) investigating pharmacists' intervention in the neonatal population. Afterward, the selected trials were filtered to include only studies with clinical pharmacists interventions in the neonatal population. Only studies available in English were included, which can be further evaluated in the second step. Then, the subsequent step was determining applying the inclusion criteria to select the studies that will be considered in the review. Abstracts were checked manually to choose the appropriate ones to be included. The inclusion criteria were (1) the presence of sufficient details on the method of analysis, (2) any pharmaceutical intervention aiming to reduce medication error, (3) Newborn from birth to one month, (4) in a hospital setting, (5) assessing the effectiveness of the role of the pharmacist in terms of physician acceptance and change in prescription order or improved health outcome. Moreover, interventions aimed at reducing parenteral nutrition or vaccination errors are excluded. Lastly, the essential data were retrieved from the final record of included studies to be summarized.

The 2020 PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines were used to conduct this systematic review. Data extraction was carried out using the predesigned data extraction form for this systematic review. The following data were extracted from each study: (1) author (s) and year of publication; (2) country; (3) population; (4) sample size; (5) Intervention; (6) Outcomes; (7) Results. The quality of each article was evaluated using a New Castle-Ottawa Scale and Cochrane bias tool.

Results:-

Between 2002 and 2022, a total of 920 articles were retrieved. After applying inclusion and exclusion criteria, only 15 research papers were included in final review as shown in Figure 1. All eligible papers included in the current study are shown in Table 1. Most of the studies were duplicated studies. Four were review articles [14-17]. Other studies were either a comment on medication errors in the NICU [18], a case report on the shortage of pharmacists in the NICU [19] or practice spotlight studies [20, 21]. Few studies did not include newborns [22, 23]. Other studies assessed the pharmacist's impact on vaccination and parenteral nutrition errors [24]. Four studies did not review the pharmacy intervention [25]. The other examined the impact of computerized prescriber orders in reducing medication errors in neonates and pediatrics [26]. Another one evaluated implementing a training program for JCI accreditation [27]. Another study assessed the impact of antibiotic policy on antibiotic consumption [28]. Three were conducted in community pharmacies or clinics [29-31]. Two reported only the incidence, categories, and seriousness of errors without contacting or reflecting on patients [32-34]. One was unable to retrieve complete information [35].

The current systemic review of all the eligible criteria was conducted among neonates or the pediatric population, including neonates. The pharmacists interventions included in this literature were prescription auditing identification of medication errors [30, 34, 36-41], changing preparation and administration, medication reconciliation [42, 43], education to healthcare workers [44, 45] and developing policies and procedures [10, 44, 46]. According to retrieved results, all the studies considered the outcomes assessed were accepted by physicians and applied to the prescription sheet or impacted health outcomes. The summaries of the retrieved studies are discussed in Table 1.

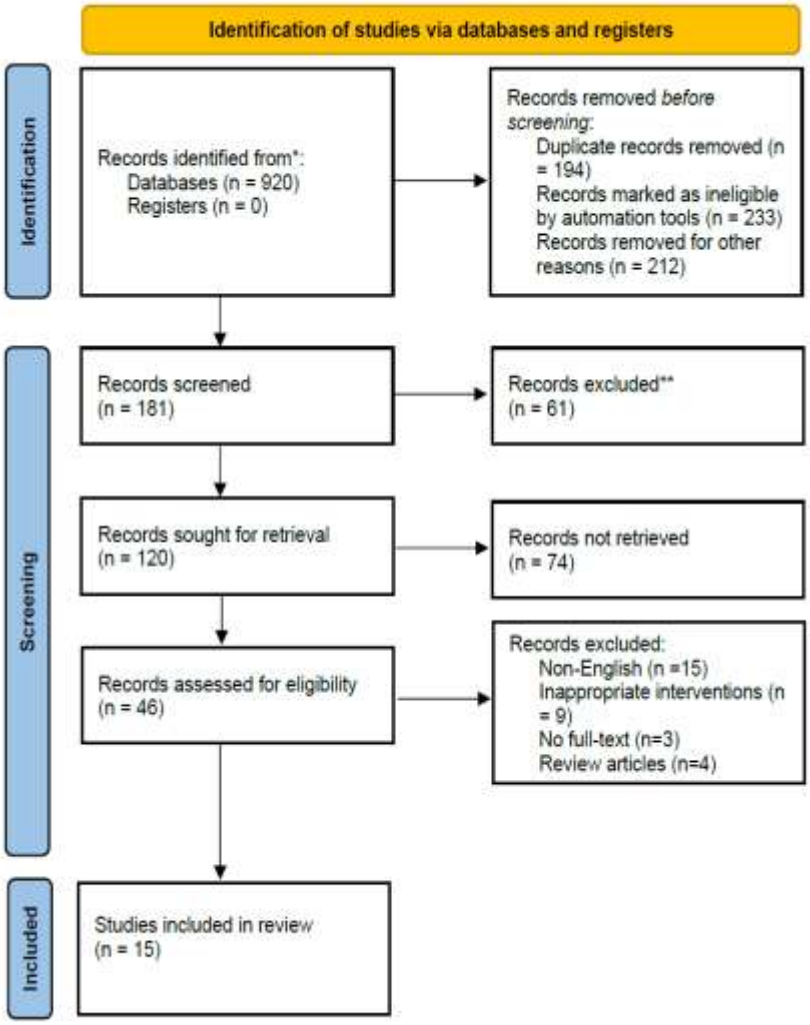

Figure 1:- PRISMA flowsheet.

Table 1:- Summary of included studies:

Author(s)/ Country	Sample size/ population	Intervention	Outcome Assessment	Result
Adil M et al. (2020). (India)	-1149 Pediatrics.	-Prescription audit	-Number of MEs* -Decline in MEs from the first week through weeks of 7,14,20,26.	-A total of 699 errors were detected, with the majority in the prescribing phase (87.1%). -A highly significant decline in MEs per patient from baseline (2.08) to final followup (1.06), and the p-value was <0.0001.
Hamdy R. et al.(2020). (USA)	A 60-bed level IV NICU*.	1) Providing education through developing an interdisciplinary team, including a pharmacist. 2) Initiating 48hour antibiotic time-outs. 3) Standardize empirical antibiotic choices by developing clinical pathways 4) Daily audit with feedback	-Primaryoutcome: vancomycin DOTs* per 1000 patient days. - Secondaryoutcome: acute kidney injury related to vancomycin.	-The use of vancomycin decreased from 112 to 38 DOT* per 1000 patients after the interventions. -The use of vancomycin decreased by 29% after developing the clinical pathway, and the pharmacy initiated 48-hour antibiotic time-outs. - Overall, the use of vancomycin was reduced by 66% from the baseline after the four interventions. The decline in vancomycin use was observed over 12 months. -Acute kidney injury associated with vancomycin decreased from 1.4 at baseline to 0.1 after the four interventions.
Shah C et al (2020). (UK)	-1454 patient discharge summaries and 10 medicines prescribed	-Medicine reconciliation by 43 CC(pharmacists	-Compliance to discharge summary documentatio n -Compliance with medicine prescription standards.	-About half (49%) of discharge summaries were audited by pharmacists. -About 88% of screening summaries included the pharmacist's name. -Most of the medication details were declared according to standards except indication (1.7% compliance), formulation (60.3% compliance), and ongoing use instructions (72.5% compliance).
Leopoldino RD et a (2019). (Brazil)	-600 neonates.	-Prescribing audit	-DRPs* assessment. - Physician acceptance.	-DRPs* affected 59.8% of participants (359/600 newborns) with a rate of 6.8% patients-days. - The most repeated DRPs* were treatment ineffectiveness (54.2%), sub-optimal drug effect (52.8%) and adverse reaction (41.4%). -The acceptance rate of pharmacy interventions was 93.1%.
Al-Jazairi AS et al (2017). (Saudi Arabia)	-374 pediatric (0-18 years old) and 1000 encounters were tracked.	-Medication reconciliation by 11 pharmacy residents.	-Proportion of medication discrepancies. -Number of interventions. - Physician acceptance.	-About 260 medication discrepancies were observed. -Most of the discrepancies were found during admission (69.61%). -Adult patients had more discrepancies than pediatric patients. -About 260 PIs* were detected. -Around 76.92% of PIs* were accepted, and the rest were accepted with modifications. There was no PI

				ultimately rejected. -About 83% of the accepted interventions were of high clinical significance.
Pawluk S. et al. (2017). (Qatar)	-Neonates over a 16months	-Prescribing audit.	-Number and types of MEs*	-About 201 MEs* were detected. -Most MEs* occurred in the prescription phase (98.5%). -The most cause of MEs* recognized by pharmacists was calculation error (58.7%).
Sabry N. et al. (2016). (Egypt)	-About 6 Pediatric patients	-Prescribing audit	-DRPs* -Physician acceptance	-About 313 DRPs* were detected by clinical pharmacists. -The pharmacists detected DRPs* as 45.69% drug-drug interaction, 31.95% prescribing unnecessary medication, 21.09% underdosing, 0.96% inappropriate medication, and 0.32% adverse drug reaction. -Physician acceptance of PIs* were reported as 65%.
Campino A. et al. (2016). (Spain)	-10 NICUs. -522 preparation order.	-Comparison of nurses' bedside preparation error rate in 10 NICUs and one hospital pharmacy service.	-Number of preparation errors	-In NICU, calculation errors were 1.35 %, and accuracy errors were 54.7 %. Conversely, no calculation errors were detected in hospital pharmacy service, and accuracy errors were reported at 38.3 %.
Condren M. et al. (2014). (USA)	-361 Prescriptions in pediatric clinics -40.7% fromclinic 1 (PIs*) and 59.3% from clinic 2 (No PIs*)	-Compare two clinics, one has PIs* in daily prescription review, provider feedback and education, and EMR customization, and the other clinic has no PIs.	-The rate of prescribing errors in both clinics.	-Overall, 14.8% of the prescriptions were written in error. -Clinic 1 had an 11% error rate, significantly less than clinic 2, with a 17.4% error rate (P=0.0012). - Additionally, the rate of error in clinic 1 was 8%, and in clinic 2, it was 17.3%, with $P < 0.001$ in the case of prescriptions performed in a pediatrics-only training program.
Kaestli L. et al. (2014). (Switzerland)	-Pediatric patients discharged with prescriptions for four years.	-Failure modes (FM), effects, and criticality analysis of the pediatric medication discharge process.	-FM*determination afterhospital discharge. -Spontaneous incident reporting by community pharmacists. -CI* (risk priority number) of each FM for each drug in the study.	-About 24 FM* were observed. -Community pharmacists spontaneously reported 48 incidents involving 52 problems. - Additionally, 11 incidents (21%) were reported due to a lack of prescription information. -The multidisciplinary team performed eight strategies, leading to a maximum final reduction in CI (64%).
Prot-Labarthe S. et al. (2013). (Multicenter)	-270 patients with a medianage of 21 months old.	-Prescribing audit	-PIs* and DRPs*. -Physician acceptance.	-About 996 PIs* were reported. -PIs optimized the mode of administration (22 %), dose adjustment (20%), and therapeutic monitoring (16 %). -DRPs were reported as

				inappropriate administration techniques (29 %), untreated indication (25 %), and supra-therapeutic dose (11 %). -About 98 % of PIs were accepted.
Barbara Maat et al. (2013). (Netherlands)	-Patient at age 0-18 years -Patients were admitted to the hospital from March 2004 till January 2008.	-Verificationof electronic medication prescriptions	-Frequency of clinical pharmacy interventions.	-About 81% of PIs* were concerned with correcting a prescription that might have adverse clinical consequences. Additionally, most corrections were related to the wrong dose (45%). -The risk of intervention for patients at age one month -2 years was higher than for patients at age 12 or 18. -The risk of interventions for 'free-text' prescriptions was five times higher than for 'standardized structured template' prescriptions.
Fernández-Llamazares et C. al. (2013). (Spain)	- Pediatrics and neonates	-Prescribing audit.	-The impact of PIs. -MEs* and their severity. -Physician acceptance.	-A total of 646 PIs* were reported. -About 41.2 % of PIs* were concerned with the manual prescribing system, and 58.8 % with electronic prescribing systems. -About 8.2 % of PIs were performed on neonates, 29.7 % on infants, 41.7 % on children, and 20.4 % on adolescents. -The main reasons for PIs were dose errors of 1.5–10 times the recommended dose in drugs with a standard therapeutic range (23.1%), then selecting an inappropriate or unavailable dosage form (15.1%). -MEs* were reported as dosing errors (49.3 %), wrong dosage form (15.1 %), wrong drug (10.7 %), and wrong administration frequency (9.3 %). -Around 51.9 % of prescribing errors were significant, 26.3 % were minor, 19.8% were clinically severe, and 2.0 % were potentially fatal.
Pallás C. et al. (2008). (Spain)	-6,320 prescriptions for neonates.	-A new system included the pharmacists with three informative talks about GPP* and a pocket PCbased automatic calculation system.	-The prevalence ratio of prescriptions with at least one medication errorbefore and after the intervention	-Prescriptions violated from GPP declined from 39.5% to 11.9% after the intervention, with a prevalence ratio of 0.29. -The number of incorrect items in the prescriptions decreased from 11.1% in the first period to 1.3% in the second, with a prevalence ratio of 0.09.

Simpson JH et al. (2004). (UK)	-Neonates over one year (Number not available)	-Incident reporting system. -The educational program.	-The impact of the interventions on MEs*	-About 105 errors were detected. Most of them (75%) were detected by clinical pharmacists. -Poor prescribing was reported for 71% of MEs*. -After four months of interventions, MEs* fell from 24.1 to 5.1 per 1000 neonatal activity days ($p<0.001$).

CI: Critical Index; CCP: Clinical Commissioning Group; DOT: Day of Therapy; DRP: Drug-related Problems; FM: Failure Mode; GPP: Good Prescribing Practice,MEs: Medication Errors; NICU: Neonate Intensive Care Unit; PIs: Pharmacy Interventions.

Discussion:-

Medication errors are accounted for 30% of medical errors in hospitals, which lead to increased morbidity, mortality, and hospital stay [47]. The pharmacist might have a potential role in detecting medication errors of prescribed drugs to neonates. Additionally, pharmacists also can resolve those errors [11, 48, 49]. Previous systematic reviews focused on general interventions regarding preventive medication errors in the neonatal population [50, 51]. In Nguyen MR et al study, the strategies implemented to reduce medication errors were technology, organizational, personnel, or clinical pharmacy intervention[50]. In Santesteban E et al study, the interventions implemented were computerized physician order entry, a barcode management system, an incident reporting system, or a comprehensive educational strategy [51]. In addition, others conducted a few literature assessed impact of pharmacists in all hospital settings [52, 53]. The reviews investigated the role of clinical pharmacists in preventing medication errors, establishing pharmacist-led education, developing pharmacy-related work strategies, and implementing policies for medication error reporting.

In our review, we focused only on the role of pharmacists in neonatal settings. Based on our review, we demonstrated the role of pharmacists in identifying errors in prescriptions, medication reconciliation, performing education programs, and being part of a multidisciplinary system to detect or reduce medication errors. Our review showed a number of articles that only investigated the pharmacist's role in decreasing medication errors in the neonatal setting [10, 34, 37, 44, 45, 51]. Several studies demonstrated pharmacists' prescribing audits' effectiveness in identifying medication errors and preventing those errors. Concerning the neonatal population specifically, Pawluk Sh et al, carried out a study to demonstrate the impact of pharmacists in detecting medication errors in the NICU. The study illustrated that pharmacists reported the majority of medication errors. Additionally, all the medication errors reported did not reach patients, so they did not cause any harm [37]. Another study focused on prescription auditing in the NICU. The study showed the high acceptability of pharmacists' interventions by NICU physicians and nurses. The study also demonstrated that nine out of ten drug-related problems were prevented [34]. Cecilia M Fernández-Llamazares and other authors conducted a study with clear mention of pharmacists` intervention in neonates. Indeed, 64.7% of the pharmacists' recommendations significantly impacted the public health of neonates. The study was carried out on both manual and electronic prescriptions. The study also illustrated the severity of medication errors plus the degree of impact of pharmacists` interventions [42].

Meanwhile, the other five studies illustrated the impact of prescribing audits through treating pediatrics, including neonates in the hospitals. For instance, Condren M. and his colleagues demonstrated the significant effect of pharmacists` interventions in decreasing medication errors. The study did not focus on neonates but showed that higher medication errors occurred at ages 0-4. Additionally, the study's results could not be generalizable as the study was carried out over two months [30]. Sabry N et al. conducted a study including pediatrics at ages 0-18. The study was conducted only on drug-related problems in a cardiac care center. The author showed that pharmacists' interventions significantly reduced prescription errors by 35.2% ($P<0.001$). The study also showed that more clinical pharmacists' intervention in the prescribing decisionmaking at an early stage might help resolve drug-related problems [38].

Moreover, Adil MS and his colleagues conducted a study in India. The authors successfully illustrated the impact of clinical pharmacy service in lowering medication errors. The study was conducted on all pediatrics, including neonates [36]. Furthermore, Prot-Labarthe S. and other authors showed the pharmacists' interventions in four pediatric centers in France, Switzerland, Quebec, and Belgium. They illustrated the role of pharmacists in

optimizing the route of administration and dose adjustment.46 Additionally, Maat B. and other colleagues focused on pharmacists' intervention in electronic prescriptions. The study also illustrated the high pharmacists` interventions for children aged one month to 2 years [40].

The medicine reconciliation of pharmacists was assessed in two studies in our review. Both studies were conducted on all populations with no sub-analysis of neonates. Indeed, Shah C. showed the usefulness of medicine reconciliation after discharge from secondary care at hospitals [42]. However, Al-Jazairi A. and his colleagues showed the impact of the medical reconciliation of pharmacists on cardiac surgery patients. The study illustrated the ability of resident pharmacists to solve all observed medication discrepancies. The study also had a large sample size which strengthened the generalizability of the results in this regard [43]. Regarding the impact on medication preparation in the NICU, Campino A. and other colleagues compared the rate of error in intravenous preparation at the NICU bedside and the rate of error in a hospital pharmacy service. The study illustrated that the more accurate preparation was in hospital care service [51]. In our review, two studies highlighted the importance of a pharmacist-led program in declining medication errors in the NICU. Hamdy R. and her colleagues showed the impact of education programs in reducing the use of vancomycin drug and its related acute kidney injury in neonates [44]. Furthermore, Simpson J. and other authors emphasized the other studies on the effectiveness of more awareness and education of clinical pharmacists in reducing medication errors in NICU [45].

Finally, Pallás C. and other colleagues conducted a study focused on the quality of medical prescriptions in the neonatal unit, which led to Prescriptions declining in physicians' violations from 39.5% to 11.9% [10]. Additionally, Kaestli L. conducted a study by a multidisciplinary team to implement eight strategies for pediatrics after their discharge from hospitals. These strategies led to a maximum final reduction in critical scores by 64%. Both studies illustrated the implementation of a new system involving pharmaceutical care. The two studies showed a significant impact of those systems in reducing and solving medication errors. Our systematic review results demonstrated that few studies only address the pharmacist's role in preventing medication errors in the neonatal setting. Also, the impact of these pharmacy interventions was not discussed clearly in the literature.

Conclusions:-

Our systematic review showed promising results for the impact of pharmacy services in the hospital setting, including the NICU. Future studies addressing the health outcomes in neonatal care are required.

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