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A PROSPECTIVE INTERVENTIONAL STUDY ON EVIDENCE-BASED MEDICINE APPROACH TO THE MANAGEMENT OF SEPSIS AT A TERTIARY CARE CENTER.

Pharmacology

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ABSTRACT

BACKGROUND: Sepsis is the body's overwhelming and life threatening response in infection that can lead to tissue damage, organ failure and death. Intervention suggested by student clinical pharmacists can be the cornerstone in the prevention of drug related through evidence based medicine approach. These recommendations by clinical pharmacist in health care have a positive influence on clinical outcomes in quality of care. **OBJECTIVES**: The objectives were to reduce drug related problem, improve medication related recommendation & to measure no of accepted recommendation. **METHODOLOGY**: This was a prospective interventional study conducted at a tertiary care hospital. The patient demographic data and medically relevant information were documented using a predefined template. Therapy was closely observed, medication related suggestions if any were given to the treating physician, so as to reduce medication errors & no. of recommendations accepted were measured. **RESULT**: A total of 105 patients were monitored by student clinical pharmacist and were included in the study and 71 recommendations were made by a student clinical pharmacist. Out of which 51 recommendations were accepted by physician caring for the patient (70%). **Conclusion**: Clinical pharmacists made a positive impact on the quality of care for patients. This study helped to identify medication related issues that can be improved to help increase the quality of care for patients.

KEYWORDS

sepsis, intervention, SIRS score, clinical pharmacist, drug related problems.

INTRODUCTION

Sepsis is a clinical condition with a variety of increasingly severe manifestation. The global epidemiological burden of sepsis is difficult to ascertain. It is estimated to affect more than 30 million people worldwide every year, potentially leading to 6 million deaths[1] It is caused by an overwhelming immune response to infection. The body releases immune chemicals into the blood to combat the infection. Those chemicals trigger widespread inflammation, which leads to blood clots and leaky blood vessels. As a result, blood flow is impaired, and that deprives organs of nutrients and oxygen and leads to organ damage.[2] Though data are incomplete, the burden of sepsis is particularly more in resource-limited settings such as low- and middle-income countries (LMICs).[3] It is therefore important to better characterize sepsis in such environments.

Sepsis consequence have been improving in recent years, as it may be due to increased clinical awareness,[4,5] the optimum approach to management remains unclear.[6-9] Early recognition and diagnosis of sepsis is required to prevent the transmission into septic shock. Evidence- based medicine approach has been shown to improve patient care and improved health related outcomes. This practice aims to optimize decision making by use of evidence (national & international guidelines) to answer question in clinical practice in making decisions about the individuals care of patients. This study mainly aimed at integrating individual clinical expertise with best available external clinical evidence in meeting the clinical needs of the patients diagnosed with sepsis and there by optimizing the therapy. Applying guidelines and primary literature to specific patient situation will help reduce the risk of sepsis related progression to multi organ dysfunction and mortality. This study aimed at measuring the impact of clinical pharmacist intervention/recommendations in sepsis management with regard to pharmacotherapy compliance with guidelines and areas of intervention.

AIM: To determine the effect of clinical pharmacist intervention in the management of sepsis at a tertiary care hospital.

METHODOLOGY: This prospective interventional study from 2017-2018 was started after approval from the Institutional Ethics Committee of Bangalore Baptist Hospital, Karnataka. A convenience sampling method utilizing protocols developed at tertiary hospital were used for this study. All the study participants were provided with informed consent before starting the study. Systemic inflammatory response (SIRS) score and patient medical record were reviewed by student clinical pharmacist to identify if a patient was eligible to participate in the study. The student clinical pharmacist used surviving sepsis camping guidelines to help provide evidence -based recommendation for patient to help support patient care. A specially designed data collection form was developed to help the students' document clinical information's. The student clinical pharmacist closely observed the therapeutic plan and patient care; referred various scientific literature and guidelines. Recommendations made to health care providers were documented. The acceptance or non -acceptance recommendation were also mentioned.

INCLUSION /EXCLUSION CRITERIA:

Patients were included in the study if they met the following criteria: >18yrs of age requiring in patient service, with sepsis, severe sepsis (including urosepsis, septic encephalopathy) and septic shock. Patient's visiting the outpatients department of tertiary care facility was excluded from the study. Pediatrics patients and pregnant patients were excluded.

END POINTS:

The studies evaluate several different end points was change in SIRS score before students recommendation and after student recommendation (Day1 & Day2).

In addition, the researcher also evaluated how many recommendation made were accepted by health care professional and what are the major topic areas were for recommendations by student pharmacist.

STATISTICALANALYSIS:

A sample size of 105 patients were enrolled using Cochran formula ($N=Z^2pq/e^2$) from the retrospective data. This sample size was made to resolve the drug related problem (DRP), which were needed to achieve a power of 80% using an alpha error of 0.05.

RESULT

The results have depicted in different headings:

Demographic and general data

A total number of patients taken were 105. In term of gender, male are found to be more incidence of sepsis (70.47%) as compared to female population (29.52%) of total population. The age group of 61-70 has a more incidence of sepsis i.e. 49 (46.67%) and the age group 40-50 &91-100 had less number of sepsis incidence.

Co-morbidities

After analyzing 105 cases, it was found that almost all patient have co-morbidities like 66 case of HTN (62.85%), 74 cases of DM (70.47%) and 61cases have HTN+DM (58%) which was more common compare to other co-morbidities.

Sepsis based on severity

41 out of 105 patients suffered from sepsis and severe sepsis, 23 out of 105 suffered from septic shock.

Total intervention found in sample population

51 intervention were found during the study period, 26 out of 51(50.98%) were adverse drug reactions (Adr), 12 out of 51 (23.52%) were drug interaction, 6 out of 51(11.56%) were doses adjustment and 8 out of 51(15.68%) were potential drug addition**.**

Adverse Drug Effect:

In this study, 26 out of 105 (24.76%) patients were found to have adverse drug reactions (Adr). The incidence of Adr was high in males compared to females. According to the data, piperacilin /tazobactam was the most common medication which caused rashes, constipation & diarrhoea in 5 patients. Other offending drugs were duolin (3.77%), linezolid (3.77%), ivf.dns (1.88%), metronidazole (1.88%), lactulose (3.77%), aminophylline (1.88%), nacetylcystine (1.88%), heparin (1. 88%), ampicilline (1.88%), amiodarone (1.88%), insulin (3.77%), lasix (3.77%), lactulose.

The table number 1 below gives details of the drugs that showed Adr, nature of Adr, and the intervention made by the student pharmacist and post interventional outcomes. The intervention made by the student clinical pharmacist made a positive impact on the health outcome of the patient.

Tabel no.1:- Distribution of Adr in the sample population.

Name Of Drugs	ADR	No. Of Patient	Pre Intervention	Accepted Intervention	Post Intervention
ANTIBIOTICS					
Linezolid	thrombocytopenia	3	*Plts-55000 *115000 *28000	Suggested to discontinue and closely monitor the platelets	1. 88,000 2. 2,50,000 Deceased Improvement in the platelet count.
Piperacilline + Tazobacatm	Rashes	3	1. Redness and swelling. 2. Hypokalemia	1.Suggested to discontinue and advised to start meropenem 2.Suggested to include syp Kcl	1.Redness reduced 2.Potassium levels 3.75
Piperacilline + Tazobactam	Diarrhea	1	Multiple Episodes	Suggested to add Loperamide	No further episodes
Piperacilline + Tazobacatm	Constipation	1	2 days	Suggested to add Syp.Cremaffine	Improved
Metronidazole	Vomiting	1	Two to three Episodes	Suggested to Discontinue And Start Ondansetrone	No further episodes
Ampicillin	Diarrhea	1	5 episodes	Suggested to add Loperamide	No further episodes
OTHER DRUGS					
Furosemide	hypokalemia	3	3.2mEq/l 2.7mEq/l 2.9mEq/l	Suggested to add spironolactone	4.4mEq/l 3.5 mEq/l 3.7mEq/l
IVF.DNS	Hypernatremia	1	160meq/l	Suggested to discontinue and closely monitor Na+ level	150
Aminophylline	Tachycardia	1	102bpm	Suggested to closely monitor heart rate (HR)	58bpm
Duolin	Hypokalemia	2	3mEq/l	Monitor the HR and suggested to start syp. Kcl	3.8mEq/l
Heparin	APPT	1	98sec	Suggested to discontinue and closely monitoring APPT	56sec
contrast dye –crct	Allergic reaction	1	Angioedema	Discontinue and plan for CT scan	No allergic reaction
Heparin	Hematuria	1	RBC found in Urine	Suggested for urine analysis and renal function test	
Lactulose	Hypokalemia	1	3.2mEq/l	Suggested to discontinue And Started Syp.Kcl	4.9mEq/l
Amiodarone	Burning Micturition	1		Suggested to Discontinue And Closely Monitored	No further episodes Noted
Human Actrapid(Insulin)	Hypokalemia	1	3.2 mEq/l	Suggested to Continue With Kcl And Closely Monitor K+ And Blood Sugar Level	4 mEq/l
Human Act Rapid (Insulin)	Hypoglycemia	1	60mg/dl	Suggested to Closely Monitor Blood Sugar Level and IV DNS	Sugar levels are within the range
Heparin	Hematoma	1	In the abdomen following a s/c injection of heparin	Suggested to start thrombophore Ointment	Patient is progressing
N-Acetylcystine	Vomiting	1		Suggested to Discontinue And closely Monitor The Patient	No further episodes

Drug Interaction

In this study, 12 interactions were found. 5 out of 12(41.67%) were major drug interactions and 5 out of 12 (41.67%) drug interaction were moderate. 2 out of 12 (1.88%) cases had contraindicated combinations. Fluconazole–Amiodarone is contraindicated which increases the risk of QT prolongation.

Tabel no 2 : Table Showing no. of Distribution Of Drug Interaction with Intervention In Patient

Name of drugs	Sevierty	Effect	Pre-intervention	No.	Intervention/recommend ation	Post-intervention
Insulin –Metformin	Moderate	Hypoglycemia	GRBS;60,58mg/ dl	1	Continue insulin according to sliding scale and reduce dose of Metformin to half of initial dose [500 mg to 250mg]	105mg/d l
Azithromycin-Amidarone	Major	QT-prolongatio n	No follow up of monitoring parameters	1	Recommended to monitor ECG and cardiac parameters	Obtained ECG and closely monitored
Furosemide-Hydrocortisone	Moderate	Hypokalemi a	3	1	Suggested to include syp.kcl 15ml	4.2
Fluconazol-Amiodarone	Contraind icati on	QT-prolongatio n	No follow up of monitoring parameters	2	Suggested to monitor ECG and cardiac parameters	Obtained ECG and closely monitored
Hydroxyzine – Metoclopramide	Major	Increase risk of CNS depression	GCS - 12/15	1	Suggested to monitor GCS	GCS - 14/15
Linezolid – Metoclopramide	Major	Increase risk of hypertensive crisis	BP 170/110	1	Suggested to discontinue Metoclopramide and started Ondansetrone	BP 130/90
Piperacilline + Tazobactam-Vancomycin	Major	Increase risk of acute kidney injury	Patient is diagnosed with multi organ dysfunction	1	Recommended to monitor serum creatinine	2
Pantoprazole-Levothyroxine	Moderate	Decreased effect of Levothyroxi ne	TSH-1.5	3	Recommended to monitor TSH level & suggested to change the timing of Levothyroxine	3.2
Tab.amiodar one – tab.diltiazem	Severe	Increased the effect of Amiodarone.	Headache and decreased HR	1	Suggested for dose reduction and monitoring of BP	Resolution of headache and HR improved

The table number 2 below gives details of the drugs that showed no of distribution of drug interaction with intervention in patient

Potential Drug Addition :

In this Study, 8 Pottential Drug Additions were found out of 51 intervention (15.68%).

Clinical pharmacist recommendation on dosage adjustment:

In this study,6 out of 51 intervention(11.76%) were made and the maximum number of dosage adjustment was done for piperacilline/tazobactam.

Table no.3: table showing no. of distribution of potential drug addition with intervention in patient registered in study

Area of intervention	Pre intervention	Intervention	Post intervention
Untreated indication	Patient complaint on abdominal pain	Suggested to add paracetamol	No fresh complaints
Hypokalemia	Potassium level was low 3.4 mEq/l	Syp.kcl	4.5mEq/l
Hyperkalemia	Potassium level was high 5.96,5.33	k-bind	3.6,3 mEq/l
Hypomagnesemia	1.4 mEq/l 1.2mEq/l	Inj.Mgso4 (2 cases)	2.8mEq/l
Hyperlipidemia	Triglyceride - 356 mg/dl	Atorvastatin	252mg/dl
Hyperammonemia	Ammonia - 125mcg/dl	Syp.lactulose 15ml	60mcg/dl
Hyperkalemia	5.37mEq/l	K-bind	4mEq/l

Table no. 4: table showing Clinical pharmacist recommendation on dosage adjustment:

Drug	Dosage adjustment	Pre intervention	Post intervention
Piperaclline + Tazobactam	Suggested to adjust the dose of piptaz 4.5gm to 2.25gm Suggestion was accepted by doctor and made adjustment	Serum .creatinine - 3.0mg/dl	Sr.cr-2.2mg/dl
		3.8mg/dl	2.2 to 2.4mg/dl
		2.21mg/dl	2.1mg/dl
		4.2mg/dl	2mg/dl
		3.2mg/dl	1.8mg/dl
Meropenem	Suggested to adjust the dose of meropenem 1gm to 500mg	3.83mg/dl	2.65mg/dl

DISCUSSION

With evidence based guidelines, student clinical pharmacists can help formulate recommendations that can aid in improving patient care. This study showcases the ability of the student pharmacists to be a valuable member of the healthcare team through improved sepsis outcomes from evidenced based recommendations generated by the student's clinical pharmacists. The rate of acceptance of interventions or the no of interventions in the current study is better than other research studies that have had used the same research design and methodology. This shows the continued development of inter professional teams and how health care has moved to a more team based approach to support patients and ensure they receive high quality care.

Emanuel rivers et al (2001) in a prospective study on early goal directed therapy in the treatment of severe sepsis and septic shock on a sample population of 133 showed that the incidence of septic shock (56.8%) was higher than severe sepsis (40%). In our study, the incidence of septic shock was 21% where as 39% of the sample population suffered from severe sepsis.[10]

Lima Cassiani SHB et al (2009) in a prospective study on Potential drug interactions in patients with sepsis admitted to the intensive care unit reported that 80% had potential drug interactions, with a mean of 1.84 ± 1.09 interaction per patient. He also reported that 64.2% had a pharmacodynamic drug interaction, 60% were of major severity and 53.3% had a rapid onset of action. In our study, 12 interactions were documented. 5 out of 12(41.67%) were major drug interactions and 5 out of 12 (%) drug interaction were moderate. 2 out of 12 (1.88%) cases had contraindicated combinations.[11]

I. Jesse et al (2016) in a study on clinical pharmacists interventions in the management of sepsis in a tertiary care hospital reported 6% ADR, 12.3% drug interactions, 21.73% interventions on drug additions, followed by 10.86% interventions on dosage adjustments.[12] We have reported 51 interventions out of 105 samples, 50.98% were ADR, 23.52% were drug interaction, 11.56% were dose adjustment and 15.68% were potential drug addition. In the current study, 24.76% patients reported to have ADR. As per the data from our study piperaciline/tazobactam induced rashes, constipation & diarrhea in 3.1% of the sample population. Followed by linezolid induced thrombocytopenia. Other offending drugs includes duolin (3.77%), linezolid (3.77%), ivf. Dns (1.88%), metronidazole (1.88%), lactulose (3.77%), aminophylline (1.88%), nacetylcystine (1. 88%), heparine (1.88%), ampicilline (1.88%), amiodarone (1.88%), insulin (3.77%), lasix (3.77%). In 2.88% of the sample population, concurrent administration of pantoprazole with levothyroxine led to elevated TSH levels. Concurrent administration of contraindicated combination of fluconazole and amiodarone resulted in QT prolongation in 2.88% of the sample population.

LIMITATIONS

In our study the major limitation was, there were barriers to the practice of evidence based medicine. The gap between the demand for health care and resources available to meet that demand is growing and results in clinicians having to care for more patients in less time. There

were shortages of scientific evidence in some cases and even when evidence did exist; there were challenges in applying evidence to the care of specific individual patients. Additionally, this study was performed in one hospital in India and therefore the external validity of the study is low. This is a pilot study and has laid solid groundwork for additional studies that could be performed in multiple hospitals in India. Since patients could not be randomized in the study there are potential confounding variables that could exist based on patients past medication use.

CONCLUSION

A common finding of this study is that, a greater involvement of pharmacists in activities directed to the patients and collaboration with other healthcare professionals within a team environment may improve patient health outcomes and may ultimately affect public health. Clinical Pharmacist interventions were effective in management of sepsis and drug related problem.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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