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ADVERSE DRUG REAACTIONS IN INTENSIVE CARE UNIT OF NEWLY ESTABLISHED TERTIARY CARE TEACHING HOSPITAL IN SOUTH RAJASTHAN: A PROSPECTIVE OBSERVATION STUDY

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Abstract: **Background:** Adverse drug reactions reporting in India are inadequate due to lack of awareness in patients and healthcare professionals (HCPs). The main objective of this study to identify and characterize adverse drug reactions (ADRs) in patients admitted in intensive care units (ICU) of a newly established tertiary care teaching hospital in south Rajasthan. **Methods:** This study was a prospective observational study conducted in 910 patients who experienced ADRs in ICU from October 2018-March 2019. ADRs were classified based on Naranjo's probability scale, Modified Hartwig's criteria of severity and Schumock–Thornton preventability scale. Further, ADRs were analyzed in terms of age group, gender, organ system and number of drugs involved. **Results:** Out of 910 study patients, 127 patients (13.95%) developed 152 ADRs. Antimicrobials drugs were suspected to have caused the majority (37.5%) of the ADRs. The most affected organ systems were the gastrointestinal system (42%) and dermatological system (25%). Number of patients with ADRs was significantly more in patients (48.9%) prescribed ≥10 drugs. On the causality scale, 58% ADRs were probably related to suspected medications. About 88% ADRs were probably preventable and 57% ADRs were moderately severe. **Conclusion:** Majority of ADRs are possible in ICU setup. Based on the findings a rigorous study is recommended to determine the burden and identify the risk factors of adverse drug reactions to target interventions. Importance of such studies and need for creating awareness among health professionals about looking for and reporting such reactions.

Keywords: Adverse drug reactions, Intensive care unit, Antibiotics, Prospective study

I . INTRODUCTION

Adverse reactions are recognized as the fourth-leading cause of death in the developed world. Although India is the third largest medicine market of the world, it had documented only 2% of global ADRs until 2013. Pharmacovigilance Programme of India (PvPI) increased the ADRs monitoring centres from 90 to 150 including the private hospitals, which led to increasing in ADR reporting. It has to be made mandatory for all health-care providers such as physicians, dentists, nurses, pharmacists to report ADRs as part of their professional responsibility, even if they are doubtful about the specific relationship with the given medication. One of the most important ways to prevent adverse drug events is to share information since all medication errors are preventable which can be achieved by sensitizing awareness among the healthcare professionals to report and follow-up the events[1].

ADR reporting and monitoring activities are of vital importance for patient safety, which can generate valid data regarding causality association, preventability and severity of ADRs in the human population. It is an inevitable consequence of drug therapy, as no pharmacotherapeutic agent is completely safe and more than 50% of approved drugs are associated with some type of adverse effects that are not detected prior to their approval for clinical use[2-3].

Adverse drug reaction (ADR) reports can indicate the important safety issues on drug treatment. Adverse drug reactions (ADRs) in hospitalized patients can be divided into two broad categories: those that cause admission to hospital, and those that occur in in-patients after hospital admission. In a meta-analysis, using a random-effects model to reduce heterogeneity, Lazarou et al[4] showed that the total incidence of both categories of serious ADRs was 6.7%, of which 4.7% were responsible for admission and 2.1% occurred after admission, with an overall fatality rate of 0.32%. Swedish study has also implicated ADRs as 7th most common cause of death[5].

The prevalence of ADRs has been reported to be 0.3%–17% in pediatric intensive care units (ICUs) and 4.5%–34.1% in adult ICUs**.** The most common drug classes implicated are antimicrobials in medical ICUs, cardiovascular drugs and anticoagulants in coronary care units, and analgesics and sedatives in surgical care units[6]. Further, a systematic review assessing ADRs in

children estimated that anti-infectives and anti-epileptics were the most frequently reported therapeutic class associated with ADRs in hospitalized children[7]. Despite the large number of data, no recent studies on the impact of ADRs on hospitalized patients, particularly in the Intensive Care Units, are available.

However, there is a paucity of data on ADRs as the monitoring-reporting and pharmacovigilance related practices are still evolving in India for the figures to be truly reflective of the real burden. Hospital-based intensive monitoring is one of the most effective and applicable methods to identify and assess ADRs[8]. Only a few intensive monitoring studies have been published in India. This study was therefore aimed to understand the incidence of ADRs in ICU patients of a South Rajasthan newly established tertiary care hospital and to characterize them for causality, severity, and preventability. Further, this study explores the observed ADRs in terms of the number of medications, implicated drugs, and organ systems involved.

II. RESEARCH METHODOLOGY

Study design and study population-

This observational prospective study was conducted on Admitted patients in ICU of newly established tertiary care teaching hospital in South Rajasthan. This study was carried out from October 2018-March 2019.

Inclusion criteria-

All Patients of either sex or age >18years admitted in to ICUs (medical and surgical) of the hospital were included in the study.

Exclusion criteria-

- Patients in whom ADRs occurred outside the hospital or in whom ADR was the reason for admission were excluded.
- Patients with overdose, accidental poisoning, drug abuse, Medico-legal cases were excluded from the study.
- Patients referred to higher center, or discharged against medical advice and in whom outcome of ADR was not known were excluded from the study.

Study procedure-

All relevant information was recorded in the patient's case record form. The information that was collected included patient's demographics, admission date, chief complaints, medical history, family history, complete medication history, including known drug allergies.

ADR was identified either subjectively by the appearance of new symptoms, which was not present when therapy was started. Any untoward event was labeled as ADR only after discussing with the treating physician. In the case of any difference of opinion with respect to reaction, treating physician's opinion was considered as final. These ADRs were then recorded in the patient's file for further assessment. In addition, the ADRs spontaneously reported by doctors or nurses were also included. Patients were motivated to report the suspected ADRs to pharmacovigilance cell through regular awareness.

Data analysis-

The identified ADRs were evaluated using Naranjo's ADR probability scale. ADRs were classified into mild, moderate and severe using Modified Hartwig criteria for severity assessment. Schumock and Thornton criteria were used to categorize preventability of ADRs. The drugs that were suspected to have caused the ADR were coded into various drug classes according to anatomical therapeutic chemical (ATC) classification based on the WHO-ATC Index 2019.

Statistical analysis-

All the data were represented as number, average ± standard error mean and percentages. Chi-square test and Proportion *Z*-test was applied for comparing categorical variables. $P < 0.05$ was considered statistically significant. SPSS statistical software was used to generate graphs and tables wherever necessary.

III. RESULTS AND DISCUSSION

A total of **933** patients were admitted in the ICU during study period and 23 patients were excluded as they did not fulfill the inclusion criteria. All patients included in the study were followed up daily. Drug therapy and any changes made in the same were recorded till the patient was discharged. Of those patients used in the study **910**, **127 (13.95%)** experienced at least one ADR. Among those, **108** patients experienced only one ADR whilst **19** patients had more than one ADR: encountered simultaneously or successively, totalling up to **152** ADRs.

Maximum number of ADR (91) occurred in age group 18-50 years [Table 1]. Total number of patients in this group was 546. The incidences of ADR in males and females were 7.69% and 6.26%, respectively [Table 2].

Table 1: Age groups of patients and adverse drug reaction

Age groups	Total number of patients without ADRs	Number of patients who developed ADRs
Group 1 (18-50 years)	546	91
Group 2 (51-65 years)	213	22
Group 3 (>65 years)	151	14
Total	**910**	**127**

Table 2: Sex of patients and adverse drug reaction

Sex	Total number of patients	Number of patients who developed ADRs
Males	508(55.82%)	70 (7.69%)
Females	402(44.18%)	57 (6.26%)
Total	**910**	**127 (13.95%)**

It was found that the number of ADRs significantly (P = 0.019) increased with an increase in the number of medications with maximum ADRs (48.9%) occurring in patients who received ≥10 medications.It was found that 54 (42.5%) patients suffered ADR who received up to 5-9 numbers of drugs, and 11 numbers of patients having ADR received upto 4 drugs [Table 3].

Table 3: Total number of drugs administered and adverse drug reaction

Number of drugs	Number of patients without ADRs (n=910)	Number of patients with ADRs(n=127)
1-4	127 (13.9)	11 (8.6%)
5-9	357 (39.3)	54 (42.5%)
≥10	426 (46.8)	62 (48.9%)

Table 4 shows that of the total 152 ADRs reported, 37.5% were suspected to be caused by anti-infective drugs, followed by 12.5% caused by NSAIDS & Opioid analgesics.

Table 4: Drugs involve in adverse drug reactions

Class of drugs causing ADR	Number of ADRs(n=152)
Antibiotics & Anticancer drugs	57
Oral hypoglycemic & Insulin	03
NSAIDS & Opioid analgesics	19
Antiepileptics and Antidepressants	09
Antihypertensives and diuretics	11
Antiretroviral agents	06
Inotropic drugs & Antiarrhythmic Drugs	08
Corticosteroids	06
Bronchodilators	04
Antihistaminics & Anticholinergics	03
Anticoagulant Thrombolytics & Antithrombotics	16
Hypolipidemic agents	05
Antiemetics & Proton pump inhibitors	04
Others#	01

#calcium carbonate

Table 5 shows that the most affected organ systems were the gastrointestinal system (42%) and Dermatological system (25%). Skin rashes were the most frequently identified event followed by vomiting and thrombocytopenia.

Table 5: Organ systems and drugs involved with ADRs

System involved	Reactions (n=152)	Drugs Causing ADRs
Gastrointestinal-**64** (42%)	Vomiting(13),Nausea(7),Constipation(10),Diarrhea (10),Dryness of mouth(5), GI bleeding (3),Gastritis (8), Epigastric pain(8)	Opioids,Antibiotics/anti-parasitics,Laxatives,Aspirin, NSAIDs
Dermatological-**36** (25%)	Urticaria(8),Skin rash(14), Pruritus(7),Swelling around the eye(5),Facial puffiness(2)	Antibiotics,NSAID/paracetamol/ondansetron/allopurinol, NSAID/warfarin,Antiepileptics
Cardiovascular-**8** (5%)	Hypotension (4) Bradycardia(3) Tachycardia(1)	B-blockers,Calcium channel blockers,Diuretics,ACE inhibitors,Amiodarone/hyoscine/terlipressin
Nervous-**14** (9%)	Drowsiness (3), Extrapyramidal symptoms(2), Sedation(2),Restlessness(2),Delirium(2), Intracranial bleeding(1),Tremors(1), Sleep disturbances(1)	Anti-psychotics,Opioids, Systemic corticosteroids,Aspirin + enoxaparin/Salbutamol/metoclopramide,Antiemetics, anticonvulsants
Musculoskeletal-**2** (1%)	Myalgia(2)	Isotretinoin, atorvastatin, rosuvastatin, ofloxacin
Hematological-**19** (13%)	Thrombocytopenia (10),Increased INR(3),Pancytopenia (2), Anemia(3),Leukepenia(1)	Anticoagulants,Antibiotics, Antithrombolytics,NSAID/anti-neoplastics,Zidovudine, Sodium valproate
Respiratory-**4** (2%)	Apnea(2), Respiratory depression(1), Bronchospasm(1)	ACE inhibitors,Polymyxin-B/tramadol/metoprolol, Metronidazole, Lopamide, Zidovudine, Ibuprofen
Metabolics-**5** (3%)	Hypoglycaemia(1),Hyperglycaemia(2),Hypokaliemia(1),Hyperkaliemia(1)	Insulin and sulphonyurea, Corticosteroid,Diuretic,ACE inhibitor and spironolactone

Characterization of adverse drug reactions-

Among all the reported ADRs with respect to WHO causality assessment, 56% were considered probable in causality, 42% were possible, and 2% were evaluated as being certain in causality (Figure 1). According to Naranjo's probability scale, 58% of ADR were evaluated as being probable, 38% as being possible, and 4% of ADRs belonged to the certain category. Assessment based on Modified Hartwig scale showed that 57% ADRs were categorized as moderately severe, 40% were of mild severity and 3% of cases were evaluated as severe (Figure 2). No fatalities due to ADR were recorded in the study. Evaluation based on modified Schumock and Thornton criteria on the preventability of suspected ADR revealed that 88% of ADRs were probably preventable, 10% were preventable, and only 2% of reported ADRs were not preventable.

Figure 1: WHO causality assessment

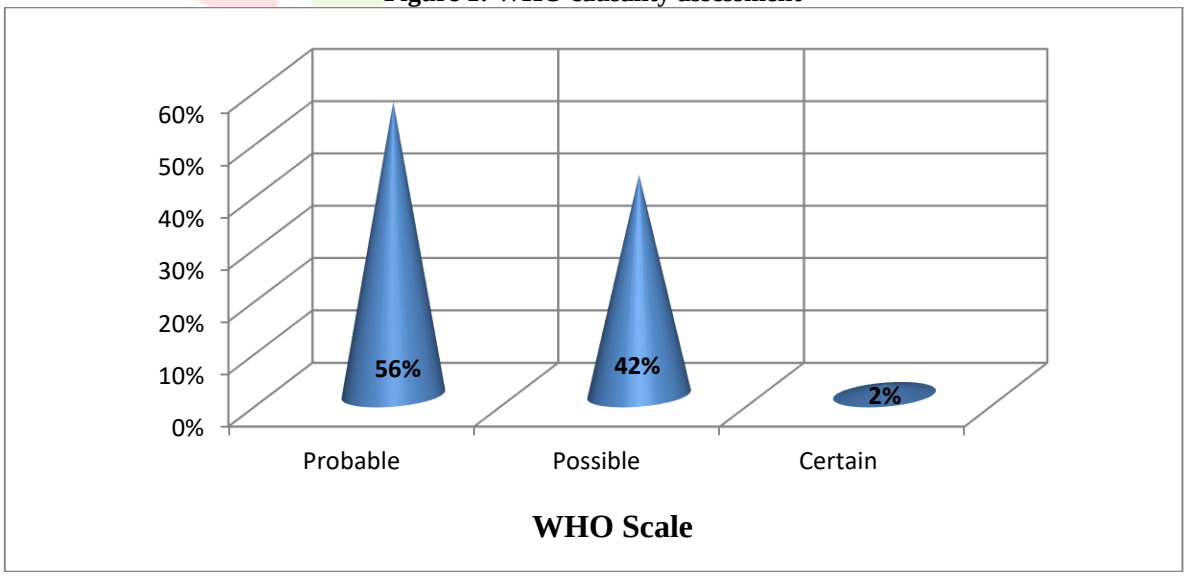
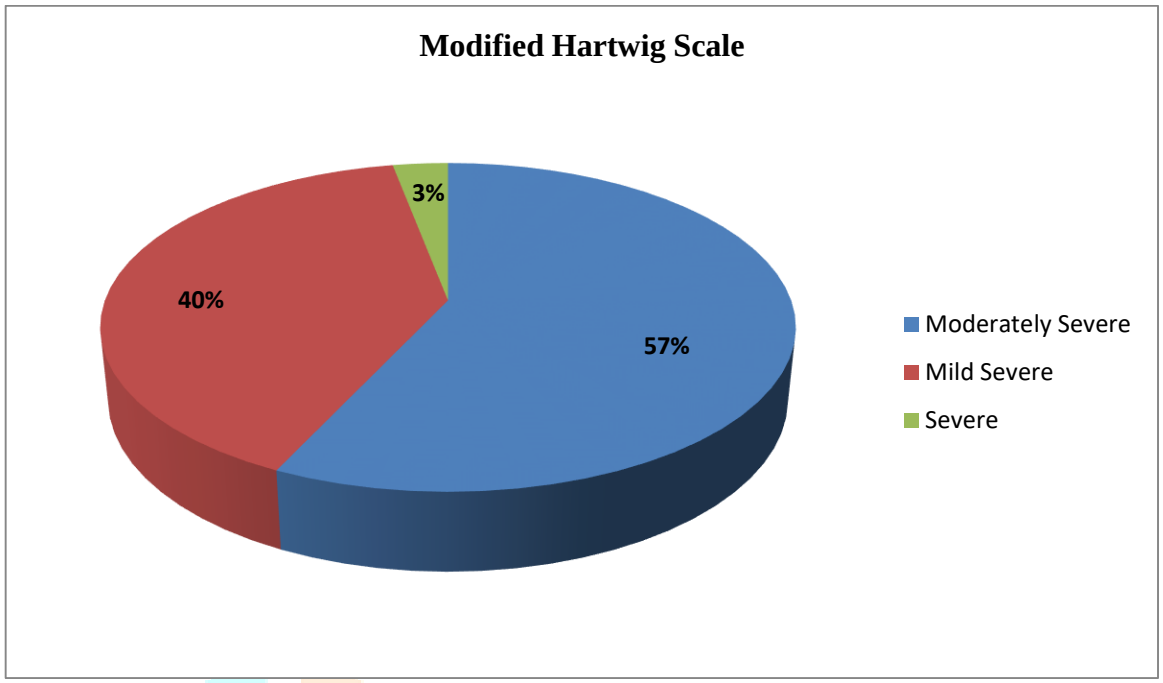


Figure 2: Modified Hartwig Scale



DISCUSSION:-

ADRs are an emergent cause of morbidity and mortality worldwide and represent a serious clinical issue[4]. India holds the second place in the global population and the third place in drug marketing but only 2% ADRs are reported. It is, therefore, important to monitor and report ADRs to the vigilance regularities. There are various methods of monitoring ADRs. Hospital-based intensive care monitoring is one of the most effective methods to identify and assess ADRs[8].

The present study revealed the pattern of ADRs reported in Intensive Care Unit. The causality, severity, and preventability of the ADRs were assessed and compared. All patients satisfied the inclusion and exclusion criteria.

In this study, the prevalence of ADRs among ICUs'patients was found to be 13.95%,which is consistent with the range of results from recent prospective studies[4,9,10]. However, the figure in this study is higher than 3.7% and 6.9% incidences which were observed in a prospective study by Ramesh *et al*. (2003)[11] and Patel *et al*. (2007)[12], carried out in a tertiary referral centre in South India and Mumbai, respectively. However, a European review reported incidence of 10%, possibly owing to their efficient ADR reporting systems[13].

The largest frequency of ADRs was very common in the females and has been described in various reports. Wiffen *et al.* (2002) in their review identified gender to be a risk factor for development of ADR[14]. Edwards *et al.* (2000) also reported that women were more susceptible to ADRs than men possibly by an association of factors such as greater concentration of adipose tissue and hormonal determinants that can affect metabolism, leading to the development of ADR[15].

Although studies have shown that females have a higher incidence of developing ADRs than males, our study showed no significant difference in various categories of gender**.** Males have greater risk of ADR (7.69%) than females (6.26%).This could be because the female patients (44.18%) included in the study was lesser than the male patients (55.82%).

Majority of the ADR occurred in the age group of 18–50 year (Group 1). However, maximum number of admissions occurred in this group of patients but this was in accordance with the number of patients enrolled in each group. This report thus slightly differs from other studies[16-17].

It was observed that the number of ADRs increased with an increase in the number of medications taken by the patient. Majority of the ADRs (48.9%) occurred in patients taking ≥10 medications, thereby indicating polypharmacy as an important risk factor. This was in concordance with studies by Davies *et al*. and Thiesen[10,18]. In a similar study conducted by Rehan *et al*., it was concluded that more the number of medications more is the risk of developing ADRs[19]. The possible reasons for this fact could be the prescription of multiple drugs which increase the risk of drug-drug interactions and additive or overlapping effects of multiple medications.

Our study conducted on ICU patients reported Antimicrobials & Anticancer drugs are most frequently linked to ADRs. Anti-infective were implicated to cause 37.5% of total ADRs in concordance with other studies reporting 47.3%, 35.7%, and 40.62% antibiotics associated events[19-21]. This could also be related to the fact that antimicrobials are the most commonly and irrationally prescribed class of medications. This suggests the need to increase the awareness with regard to prescription of antimicrobials. The other classes of drugs causing ADRs included NSAIDs-opioids (12.5%), and drugs acting on blood and blood-forming organs like anticoagulants (10.5%). A study conducted by Davies *et al*. also observed opioid analgesics and anticoagulants to be the most commonly implicated class of drugs in causing ADRs[10].

In the present study gastrointestinal ADRs were the most frequently manifested cases accounting for 42% of all ADRs in contrast with the results of other studies which detected gastrointestinal ADRs up to a proportion of 31.3%[22] and 17.9%[23]. The majority of these ADRs were moderate symptoms like vomiting and constipation. There were three cases of GI bleeding induced by aspirin. NSAIDs were responsible for ADRs like gastritis and epigastric pain.

In our present study, cutaneous and hematological reactions were the second and third most frequently manifested ADRs accounting for 25% and 13% of all ADRs, respectively. This observation is consistent with the study conducted in India by Jose

et al. (2006)[24] who reported cutaneous reactions as the most frequent ones. A study conducted in a teaching hospital in Taiwan also reported cutaneous and hematological reactions as the most frequently manifested ADRs[25].

According to the WHO causality scale, the majority (81.39%) ADRs were probably related to the suspected drug. In the study done by Davies *et al.*, majority (66.5%) of the ADRs were probably related to the suspected drug[10]. Naranjo's probability scale also showed that most of the (52%) ADRs were probable, which is consistent with past studies[26-28]. On modified Hartwig's Severity Scale, 58% ADRs were moderately severe, as also observed by Ramesh *et al*[11]. The preventability of suspected ADRs assessed by modified Schumock and Thornton criteria showed that 90% of ADRs were probably preventable, which is in accordance with previous study[29].

IV. CONCLUSION:-

Medication use is significantly associated with the occurrence of ADRs in ICU patients. Poly-pharmacy is important risk factors for the occurrence of ADRs due to drug interaction. The clinical spectrum of ADRs reported from the more common mild reactions such as skin rashes, itching, nausea, and vomiting to moderately severe reactions prolonging the ICU stay of the patients. In this study, antimicrobials contributed to the majority of the ADRs, highlighting the importance of prudent antimicrobial prescription. The most affected organ systems were the gastrointestinal system (42%) and dermatological system (25%).That was a signal for a need for intervention and increased prevention level in ADR related health problems. It is important to note that better knowledge of preventable ADRs could help to design preventive strategies to protect patients from being affected by these reactions unnecessarily. The majority of ADRs were probable in causality assessment, moderate in severity and probably preventable. This study is useful as a preliminary in initiating a culture of ADR reporting among the health care professionals in hospital. Therefore, we recommend further studies by health care professionals to accurately quantify the burden and to identify the risk factors of ADRs in patients and to plan focused preventive strategies to minimize these drug-induced harms and improve the quality of patient care.

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VI. CONFLICTS OF INTEREST

There are no conflicts of interest.

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