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RESEARCH ARTICLE

PATHOLOGICAL PROFILE AND RECOVERY RATE IN PATIENTS WITH DRUG-INDUCED ACUTE KIDNEY INJURY: A RETROSPECTIVE STUDY FROM NORTH-EAST INDIA

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Abstract

Introduction : Drug-induced acute kidney injury (DI-AKI) is a common renal event with long-term sequelae. However, pathological profile and recovery rate are scarcely reported from north-east India. Thus, we evaluated the commonly implicated nephrotoxic drugs, pathological findings on renal biopsy, and recovery following treatment in patients with DI-AKI.

Materials and Methods This retrospective, observational study involved the review of Nephrology AKI registry of a tertiary care institute. The review involved data of the adult patients diagnosed with DI-AKI over a period of 24 months (August 2020 to July 2022).

Results : During the study period, a total of 182 patients developed DI-AKI. AKI was predominantly caused by antimicrobials (33.52%), alternative medicine (15.38%), and NSAIDs (11.54%).The younger and elderly patients were involved in significantly higher consumption of NSAIDs and alternative medicine, respectively (p-values<0.05). Biopsy was performed in 79 (43.41%) patients, and findings included mainly acute interstitial nephritis (AIN, 37.97%), allergic interstitial nephritis (ALIN, 18.99%), and acute tubular nephropathy (ATN, 12.66%). Steroid therapy and hemodialysis were required in 66 (36.26%) and 105 (57.69%) patients, respectively. At a mean follow-up of 124.78 ± 30.15 days, complete and partial recovery was observed in 136 (74.73%) and 12 (6.59%) patients, respectively. Recovery rate did not differ significant according to class of drugs (p-value=0.194).

Conclusion : Antimicrobials, alternative medicine, and NSAIDs were predominantly implicated in DI-AKI. AIN, ALIN, and ATN were the most common biopsy findings with absence of any correlation with the offending agents. Around three quarters of the patients recovered completely.

Introduction:-

Acute kidney injury (AKI) is a frequent and critical renal event. Worldwide, it afflicts around 13.3 million persons per year, 5-10% of hospitalized patients, and 60% of those requiring intensive care. However, more than 85% of this

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share belongs to developing world.(1-3) Drug-induced AKI (DI-AKI) is a renal disease or dysfunction that occurs due to either direct drug toxicity or hypersensitivity to a specific drug. With increased usage and easy availability of drugs, its incidence is rising and is reported to affect 14-26% of patients with AKI.(4) Its incidence may be up to 66% in geriatric population due to higher comorbidities necessitating polypharmacy.(5)

Drugs induce a variety of renal injuries, and injury to the tubulointerstitial compartment is most frequently observed. In vulnerable patients, drugs are known to elicit acute tubular injuryby their inherent toxicity and renal excretion. Moreover, in such an event, acute interstitial nephritis (AIN) develops when drugs produce a T cell–mediated immuneresponse that induces tubulointerstitial inflammation. Another mechanism promoting AKI is a result of drug insolubility in urine that leads to intratubular crystal formation with an associated inflammatory response.(6)

In patients with short duration of drug intake, the clinical manifestations of DI-AKIare usually not recognized. Moreover, the real incidence of DI-AKI is underestimated, as only patients with a change in serum creatinine (SCr) are diagnosed.(7)Though usually a reversible event, it may require hospitalization and multiple interventions.(5) In these patients, early follow-up following hospitalization is reported to enhance survival.(8) Thus, early diagnosis, quick discontinuation of offending drugs followed by treatment, and evaluation of recovery rate is critical in patient management. However, recovery of renal function following AKI or DI-AKI, with respect to Indian population, is scarcely reported.(4,9) Thus, we assessed the demographics, pathological characteristics, range of drugs implicated, and recovery rate in patients with DI-AKI.

Materials and Methods:-

This retrospective, observational study involved the review of Nephrology AKI registry of a tertiary care institute. The review involved data of the adult patients diagnosed with DI-AKI over a period of 24 months (August 2020 to July 2022). Data from medical records included age, sex, drug class, SCr(before, during, and after AKI), and renal biopsy findings. The patients with known history of chronic kidney disease (CKD),and AKI ascribed to septic shock due to infection or sepsis, hemodynamic instability due to blood loss following trauma or surgery, obstructive factors (calculi and tumor obstructing the ureter), and other factors (urinary tract infection, lymphoma, or hepatorenal syndrome) were excluded. The study was approved by the Institutional Ethics Committee. Owing to the retrospective nature of the study, informed consent was waived-off.

Drug exposure was defined as a history of drug intake prior to the diagnosis of AKI. The diagnosis of AKI was reached if there was a rise in SCrof 0.3 mg/dL in 2 days, a >50% rise in SCrover 7 days, or a urine output less than 0.5 mL/kg/hour for more than 6 hours. If baseline SCr could not be traced, AKI was diagnosed as SCrhigher than 1.5 folds the age-adjusted reference value.(10,11)

At the end of study, the extent of recovery following AKI was categorized as: complete (SCr 1.4 mg/dL or less), partial (SCr more than 1.4 mg/dL and lower than the highest SCr attained during hospitalization), and none(if the SCr was equal to the highest level noticed during hospitalization or if the patient still required renal replacement therapy).(12)

Statistical Analyses

For the purpose of analysis, patients were categorized into four groups: Group 1, 2, 3, and 4 comprising of patients with AKI induced by antimicrobials, non-steroidal anti-inflammatory drugs (NSAIDs), alternative medicine, and other drugs, respectively. The data was analyzed with SPSS (IBM, Armonk, NY, USA) version 23.0 for Windows. The categorical and continuous variables are represented as frequency (percentage) and mean ± standard deviation (SD), respectively. Between group comparison of categorical and continuous variables was performed with Chi-Square test and one-way ANOVA followed by Bonferroni's multiple comparison test, respectively. A two-tailed probability value of less than 0.05 was considered statistically significant.

Results:-

During the study period, a total of 887 patients were found to have AKI, and 182 (20.52%) of these were diagnosed with drug-induced AKI.AKI was predominantly caused by antimicrobials (Group 1, n = 61) followed by alternative medicine (Group 3, n = 28), and NSAIDs (Group 2, n = 21). However, Group 4 included 72 (39.56%) patients and involved a variety of drug classes implicated in AKI, including multiple drugs (n = 31) the identity of which could not be confirmed, while the remaining included Loop diuretics, Cisplatin, Proton pump inhibitors (PPIs),

Gemcitabine, Calcineurin inhibitors, and Lithium, in decreasing order. Thus, Beta-lactam antibiotics and Clindamycin were the most and least commonly implicated antimicrobial agents, respectively (Table 1).

The patients were predominantly male (63.19%) with a mean age of 55.04 ± 9.70 years (range 28 – 78 years).There was no significant difference between the groups in terms of sex distribution (p-value = 0.126); however, mean age differed significantly (p-value < 0.0001).Post-hoc analysis revealed that the mean age of the patients in the Group 3 was significantly greater than all the patients in the Group 1 (p-value = 0.008), 2 (p-value < 0.0001), and 4 (p-value = 0.026), and the mean age of the patients in the Group 1 (p-value = 0.003) and 4 (p-value = 0.001) was significantly greater compared to the patients in the Group 2(Table 2).

The mean SCr_{max} of the study population was 524.66 ± 216.28 µmol/L (range 154 – 994 µmol/L). On analysis, the mean SCr_{max} differed significantly between the groups (p-value = 0.004). The post-hoc analysis revealed that the mean $SCr_{max}$of the patients in the Group 1 was significantly greater compared to the patients in the Group 2 (p-value = 0.027) and 3 (p-value = 0.013) (Table 2).

Of 182 patients, 79 (43.41%) underwent renal biopsy and demonstrated AIN (n = 30), allergic interstitial nephritis (ALIN, n = 15), acute tubular nephropathy (ATN, n = 10), progressive sclerosing nephritis (n = 9), mild mesangial hyperplasia with glomerulosclerosis (n = 8), crescentic glomerulonephritis (n = 4), IgA nephropathy (n = 3), tubular calcium salt deposition (n = 3), and crescentic IgA nephropathy (n = 2) (Table 2).In Group 1, biopsy revealed AIN (n = 21), ATN (n = 7), ALIN (n = 4), tubular calcium salt deposition (n = 3), and crescentic IgA nephropathy (n = 2). In Group 2, biopsy demonstrated ALIN (n = 6). In Group 3, biopsy suggested progressive sclerosing nephritis (n = 9), AIN(n = 5), and IgA nephropathy (n = 3). Moreover, in Group 4, biopsy revealed mild mesangial hyperplasia with glomerulosclerosis (n = 8), crescentic glomerulonephritis (n = 4), AIN(n = 4), and ATN (n = 3). Immunofluorescence was positive in 56 (70.89%) patients and demonstrated IgA, IgM, andC3, while 23 (29.11%) patients were negative.

A total of 66 (36.26%) patients received treatment with methylprednisolone pulse followed by steroids. The groups differed significantly in treatment received (p-value = 0.001). Post-hoc analysis suggested that significantly greater proportion of patients in Group 1 and Group 3 received treatment than those in Group 4 (p-value = 0.007), and Group 2 (p-value = 0.026) and 4 (p-value < 0.0001), respectively. Moreover, hemodialysis was required in 105 (57.69%) patients and the groups did not differ significantly among each other. The patients were followed-up for a mean duration of 124.78 ± 30.15 days (range 52 – 187 days), and the mean duration of follow-up did not differ significantly between the groups (p-value = 0.286).At the end of the study, 136 (74.73%) had complete recovery, 12 (6.59%) had partial recovery, 9 (4.95%) did not recover, and 25 (13.74%) were lost to follow-up, though majority had declining creatinine levels at last follow-up visit. On analysis, the groups did not differ significantly in terms of recovery rate (p-value = 0.194) (Table 2).

Discussion:-

The evaluation of patients with DI-AKI suggested that antimicrobials, and alternative medicine were most frequently implicated class of drugs. AIN, ALIN, and ATN, in decreasing order, were the most common biopsy findings. Moreover, at a mean follow-up of 4-months, around three quarter of the patients recovered completely.

In patients with DI-AKI, frequently implicated risk factors include age, pre-existing CKD, causal drug (single and/or cumulative dose), and simultaneous exposure of other nephrotoxins. Of the total drugs evaluated, antimicrobials were predominantly found to induce AKI. Among antimicrobials, beta-lactam antibiotics were most common. In a recently published study from India, Farooqui et al. assessed the utilization of antibiotics at community level, and reported a 22% rise in per capita antibiotic consumption between 2008 and 2012. This rise in antibiotics consumption mainly comprised of carbapenems, lincosamides, glycopeptides, 3rd generation cephalosporins, and beta-lactam antibiotics.(13) In another study from India, Koya et al. found consumption of large amount of broad-spectrum antibiotics, majority of which were unapproved and fixed-dose combinations discouraged by the World Health Organization.(14) These findings support the dominance of antimicrobials-induced AKI observed in the present study.

Among all the global healthcare concerns, fungal infections are usually neglected. Available data suggest gradual rise in consumption of triazoles and terbinafine in middle- and high-income countries.(15) Moreover, liposomal amphotericin B is relatively less nephrotoxic than the conventional preparation, and toxicity ascribed to triazole

antifungals is further lower.(16) Similar to antibiotics and antifungal agents, consumption of antiviral agents has increased and they are known to produce nephrotoxicity. In a recent case report, Chávez-Iñiguez et al. reported a case of oral acyclovir-induced AKI.(17) However, these agents are less frequently used, relative to antibiotics, thereby explaining less proportion of patients with AKI associated with them. Moreover, physician tend to prescribe newer class of antibiotics,(13) thus highlighting low incidence of Vancomycin- and Clindamycin-induced AKI in the present study.

Advancing age is a risk factor for DI-AKI. In a study from north-east India, Sharma et al. observed that the mean age of patients with DI-AKI was 45 ± 12.09 years.(4) Cui et al. from China reported a mean age 51.1±16.4-year, and more than two-third of the patients were aged less 60 years.(18) Likewise, in the present study, the mean age was 55.04 ± 9.70 years, and 72.53% were under 60 years. Contrarily, other studies have reported higher incidence of DI-AKI among elderly.(19,20) This could be attributed to predominance of relatively younger individuals in India and China.

It was observed patients with alternative medicine-induced AKI (Group 3) had significantly higher mean age than other groups. Alternative medicines comprise of undisclosed drugs, including vasoconstrictors, hormones, heavy metals, and other unknown agents.(21) Moreover, Chinese herb is known to contain aristocholic acid, a nephrotoxic compound.(22) As per a national survey in India (2017–2018), individuals aged 60 years or more were 1.2 times more likely to consume alternative medicine.(23) In another study, Sharma et al. reported high prevalence of alternative medicine consumption among elderly.(24)This could be mainly attributed to higher comorbidities, including painful conditions in this age group, and a belief that alternative medicines are harmless. It was further observed that mean age of patients with NSAIDs-induced AKI (Group 2) was significantly less than other groups. This could be ascribed to the global, including India, rise in the consumption of non-prescribed pain relievers among younger age group, majority of which are NSAIDs.(25,26)

Moreover, the use of multiple drugs resulting in AKI is a common occurrence and their identification is difficult in Indian scenario, owing largely to low educational level of patients visiting government-run hospitals. In the present study, Group 4 mainly included patients with multiple drugs-induced AKI, and comprised of males and had a mean age of 55.50 ± 9.64years. Thus, middle aged patients have multiple comorbidities requiring polypharmacy. Other studies have reported similar findings.(4,18) These findings suggest that polypharmacy should be avoided, and patients should be should be closely watched with serial monitoring of SCr levels, thereby mitigating the occurrence of DI-AKI.

Renal biopsy is required to confirm the diagnosis of DI-AKI and the principal findings of DI-AKI can be categorized as injuries involving the vasculature, glomerulus, renal tubules, and renal interstitium.(27)Vascular injury is generally inflicted by anti-angiogenesis drugs, mitomycin C, gemcitabine, calcineurin inhibitors, interferon, and others.(28) Glomerular injury, including the membranous type, is generally attributed to NSAIDs, gold, and penicillamine, while lupus-like glomerulonephritis is linked to hydralazine, methyldopa, quinidine, and procainamide.(29)Tubular injury, including ATN, is generally related to antibiotics, antifungals, antivirals, chemotherapeutic agents, NSAIDs, radiocontrast, and others. Acute crystalline nephropathy is frequently linked to antibacterials (sulfonamides, ciprofloxacin), antivirals (acyclovir, indinavir, atazanavir), ascorbic acid, and methotrexate. Interstitial disease, including AIN, is generally inflicted by antimicrobial agents, NSAIDs, PPIs, Antiangiogenesis drugs, Diuretics, and several others.(6) Minimal change disease and focal segmental glomerulosclerosis are often attributed to NSAIDs, interferon, lithium, and pamidronate.(27,30)

AIN is frequently implicated in AKI, and observed in 15-27% renal biopsies. Moreover, drugs are implicated in majority of patients with AIN.(31) Baker and Pusey demonstrated that AIN was the most frequent DI-AKI biopsy finding, observed in 71.09% patients.(32) In the present study, the most common biopsy finding wasAIN (37.97%), while others included ALIN (18.99%), and ATN (12.66%). However, there was absence of correlation between the pathological findings and the drug implicated. Likewise, Cui et al. observed that AIN (37.25%), ALIN (23.53%), and ATN (15.69%) were the most frequent findings. Moreover, the pathological findings did not correlate with the drugs inducing AKI.(18)

AKI results in prolonged hospitalization and higher mortality.(33)Irrespective ofAKI severity, all patients are vulnerable tocomplications; acute pathological changes may lead to irreversible damage, with transformation to CKD, and greater chances of recurrence. Following an AKI event, renal function is said to have recovered

completely if SCr levels return to baseline.(34) However, as high as 70% of geriatric patients develop de novo CKD within 2 years of an AKI event.(35) Thus, prompt diagnosis and treatment are necessary.

In the present study, 36.26% patients received steroid treatment, and 57.69% underwent hemodialysis. Moreover, 74.73% and 6.59% patients had complete and partial recovery. Sharma et al. reported that 87.6%, and 57.7% patients required steroid therapy, and hemodialysis, respectively. This led to a complete recovery rate of 38% and partial recovery rate of 29.9%.(4) Cui et al. demonstrated a complete and partial recovery rate of 72.4% and 1.8%, respectively.(18) Higher recovery rate, observed in the present study, could be attributed to younger age, quick diagnosis, and subsequent treatment. However, the role of coronavirus disease 2019 pandemic resulting in self-prescribed antimicrobials and NSAIDs, for cold, fever, and pain, leading to AKI could not be ignored. In these patients, the exposure of the offending drugs was of short duration.

The present study had certain limitations, including retrospective study design, thus causal association between drugs implicated and pathological findings could not be ascertained. Moreover, the study had limited sample size and duration of follow-up was small, thus long-term sequalae of AKI could not be evaluated. Other factors affecting DI-AKI, including dose and duration of exposure of the offending agents, needs to be evaluated in further prospective studies.

Table 1:- Drugs implicated in AKI.

Drugs implicated	**N (=182)**	**%**
Group 1	61	33.52
Beta-lactam antibiotics	24	13.19
Aminoglycosides	11	6.04
Rifampicin	7	3.85
Fluoroquinolones	4	2.19
Liposomal amphotericin B	4	2.19
Vancomycin	3	1.65
Acyclovir	3	1.65
Fluconazole	3	1.65
Clindamycin	2	1.09
Group 2	21	11.54
Diclofenac	15	8.24
Acetaminophen + Ibuprofen	6	3.29
Group 3	28	15.38
Alternative medicine	28	15.38
Group 4	72	39.56
Multiple drugs	31	17.03
Loop diuretics	18	9.89
Cisplatin	11	6.04
Proton pump inhibitors	4	2.19
Gemcitabine	3	1.65
Calcineurin inhibitors	3	1.65
Lithium	2	1.09

Table 2:- Characteristics of enrolled patients.

Characteristics	**Group 1 (n=61)**	**Group 2 (n=21)**	**Group 3 (n=28)**	**Group 4 (n=72)**
Male, n (%)	37 (60.66)	9 (42.86)	18 (64.29)	51 (70.83)
Age, years, mean ± SD	54.57 ± 7.18	46.52 ± 10.46	61.29 ± 9.65	55.50 ± 9.64
SCr_{max}, µmol/L, mean ± SD	588.66 ± 224.40	435.90 ± 198.14	439.46 ± 191.86	529.46 ± 207.12
Biopsy findings				
Acute interstitial nephritis, n (%)	21 (34.43)	0 (0)	5 (17.86)	4 (5.56)
Allergic interstitial nephritis, n (%)	4 (6.56)	6 (28.57)	5 (17.86)	0 (0)

Acute tubular nephropathy, n (%)	7 (11.48)	0 (0)	0 (0)	3 (4.17)
Others, n (%)	5 (8.19)	0 (0)	12 (42.86)	12 (16.67)
Steroid treatment, n (%)	27 (44.26)	6 (28.57)	17 (60.71)	16 (22.22)
RRT, n (%)	41 (67.21)	10 (47.62)	12 (42.86)	42 (58.33)
Follow-up, days, mean ± SD	122.87 ± 29.99	115.71 ± 30.60	131.64 ± 32.58	126.38 ± 29.01
Recovery				
Complete, n (%)	49 (80.33)	12 (57.14)	22 (78.57)	53 (73.61)
Partial, n (%)	3 (4.92)	2 (9.52)	2 (7.14)	5 (6.94)
No, n (%)	2 (3.28)	2 (9.52)	1 (3.57)	4 (5.56)
Loss to follow-up, n (%)	7 (11.48)	5 (23.81)	3 (10.71)	10 (13.89)

RRT, Renal replacement therapy; SCr_{max}, Maximum serum creatinine; SD, Standard deviation

Conclusion:-

Antimicrobials, alternative medicine, and NSAIDs were predominantly implicated in DI-AKI. Beta-lactam antibiotics, and Aminoglycosides were most the frequently implicated antimicrobials, while Vancomycin and Clindamycin were least, thereby highlighting the change in the pattern of consumption of antimicrobial agents. The younger and elderly age groups were involved in significantly higher consumption of NSAIDs and alternative medicine, respectively. AIN, ALIN, and ATNwere the most common biopsy findings with absence of any correlation with the offending agents. Moreover, at end of the study,around three quarters of the patients recovered completely.

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