Non-steroidal anti-inflammatory drugs induced acute kidney injury: incidence, clinical presentation, management and outcomes of patients at Tertiary Hospital based longitudinal study in Mymensingh, Bangladesh

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed in primary care for their analgesic and anti-inflammatory effects. Twelve percent of individuals currently report taking a NSAID daily. Renal injury caused by these agents can present in various forms, resulting from either acute or chronic use. Historically approximately five percent of patients initiated on NSAIDs experience a kidney-related adverse event. Drug-induced renal injury accounts for twenty percent of episodes of acute kidney injury (AKI). Patients requiring renal replacement therapy (RRT) have experienced an increased length of stay with associated healthcare costs per incident. The adverse effects of NSAIDs contribute to a significant economic burden, both to the patient and to the healthcare system.This study of NSAIDs induced AKI was carried out to highlight this issue. To find out the incidence, risk factors, diagnostic approach, clinical course, management and outcome of patients, this longitudinal study was carried out at Nephrology Department in Community Based Medical College Hospital Bangladesh from July 2015 to June 2016.Total 65 patients of NSAIDs induced AKI were included in this study. Any patient having pre existing renal pathology or chronic kidney disease was excluded from the study. Mean age of the patient was 36±7.12 yrs. Forty nine patients (74.38%) took NSAIDs at their own and 16 patients (24.61%) were prescribed by physician. Fifty six patients (86.15%) took NSAIDs because of musculoskeletal pain. Dehydration due to physical exertion (29.23%) gastroenteritis (16.92%) and nil per os (NPO) (6.15%)were the common predisposing factors. Common symptoms were swelling of the body (36.9%) headache (26.15%) fatigue (21.53%) and vomiting (13.84%) Oedema was the most common sign (36.9%) Blood urea and serum creatinine were raised in all patients. Treatment includes drug withdrawal (100%), fluid resuscitation (83.07%) fluid restriction (13.85%) short course of steroid (15.38%) and haemodialysis (10.76%) . Fifty one patients (78.46%) had complete recovery within two weeks of therapy whereas ten patients (15.38%) required more than two weeks to one month for complete recovery. Three patients (4.61%) developed chronic kidney disease (CKD). NSAIDs induced AKI carries a good prognosis with early diagnosis and proper management and it can be prevented by limiting the availability of over the counter drugs and creating awareness both in physicians and patients. These medications should be prescribed for the shortest duration, the lowest effective dose, and with careful surveillance to monitor nephrotoxicity precisely. NSAIDs should be used with special caution in elderly patients.

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Key words: Non-steroidal anti-inflammatory drugs (NSAIDs), Acute kidney injury (AKI)

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed in primary care for their analgesic, antipyretic and anti-inflammatory effects. One in fifteen US adults are actively prescribed NSAIDs at any one time.[1] And in many countries low-dose preparations are also available over-

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the-counter (OCT). Partly due to their widespread use, NSAIDs account for 25% of adverse drug events (ADEs) reported in the United Kingdom (UK) and 21% in the United States (US).[2,3]

NSAIDs can cause two different forms of acute kidney injury[14]

1. Haemodynamically mediated (eg, pre-renal injury and/or acute tubular necrosis).
2. Immune mediated (eg, acute interstitial nephritis).

Acute kidney injury represents a continuum of renal injury ranging from clinically asymptomatic changes in renal function to renal failure and death. Acute kidney injury is characterized by a rapid fall in glomerular filtration rate (GFR) over hours to days.

NSAIDs can reduce renal blood flow, cause tubular obstruction through crystal deposition, and induce direct cytotoxicity and cell-mediated immune injury mechanisms leading to the occurrence of acute kidney injury (AKI). Another symptom that is commonly caused by NSAIDs is interstitial nephritis (AIN) which requires specialist review, renal biopsy, high-dose corticosteroid and/or immunosuppressant treatments, and will normally be progression in chronic kidney disease (CKD).[4]

There are no specific signs or symptoms for NSAID induced acute kidney injury. Symptoms of acute kidney injury can be non-specific and may include shortness of breath, fatigue, confusion, nausea, decreased urine output and ankle/leg swelling.[15]

Older age [5,6] and underlying chronic kidney disease are also related to the onset of AKI during NSAID use, with early studies showing that the risk of deterioration in renal function increases 3-4 fold in patients with abnormal baseline renal function compared to those with normal renal function.[7]

In patients on long term NSAIDs without acute or chronic renal failure, subclinical renal dysfunction such as reduced creatinine clearance and impaired urine concentrating ability has been shown to be present. Although this subclinical dysfunction is reversible on withdrawal of NSAIDs, some reports have suggested a persistent residual dysfunction.[8]

In a prospective community based study, elderly patients over the age of 66 were assessed for correlations between NSAID use and the progression of chronic kidney disease (CKD). Progression to CKD was defined as a greater than 15 mL/min decline in glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) equation formula. The MDRD equation accounts for age, race, sex, and serum creatinine.[9] In this population, 26% of the total cohort developed CKD.[10]

The risk of injury can be observed with the use of either a non-selective cyclooxygenase inhibitor, such as naproxen and ibuprofen, or with a selective cyclooxygenase inhibitor, such as meloxicam or celecoxib.[11] The risk of NSAID-induced AKI in various populations is 3.3%; however, a higher incidence appears to occur in individuals over the age of sixty, as well as in patients previously diagnosed with CKD.[12,13]

Table 1: Risk factors for NSAID induced acute kidney injury(14,15)

Risk Factor	Effect
Increasing age (particularly age >65), chronic hypertension and atherosclerosis	Narrowing of renal arterioles which may reduce their capacity for renal afferent dilatation
Pre-existing glomerular disease or renal insufficiency	Renal afferent dilatation is likely to be required to maintain GFR
Volume depletion True volume depletion (ie, GI or renal salt and water losses, blood loss, diuretic use) Effective volume depletion (ie, cirrhosis or heart failure)	Lowers afferent glomerular arteriolar pressure and stimulates secretion of angiotensin II

Risk Factor	Effect
Use of ACE inhibitors or ARBs	ACE inhibitors and ARBs prevent efferent arteriole vasoconstriction which is also important in maintenance of GFR
Use of the 'triple whammy' (ACE inhibitor or ARB plus diuretic plus NSAID)	Diuretic may cause volume depletion. See above for ACE inhibitor/ARB effects.

ACE= Angiotensin Converting Enzyme;
ARB= Angiotension II Receptor Blocker

Pre-existing chronic kidney disease and increasing age are the most common risk factors for developing acute kidney injury.[16]

There is little evidence about the risk of AKI associated with NSAID use in people with CKD available from randomised trials of NSAIDs because such trials routinely exclude people with CKD and rarely report renal outcomes.[17]

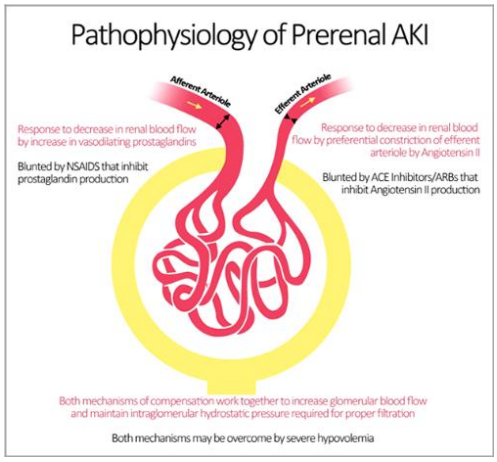

Figure 1: Pathophysiology of NSAIDs induced AKI

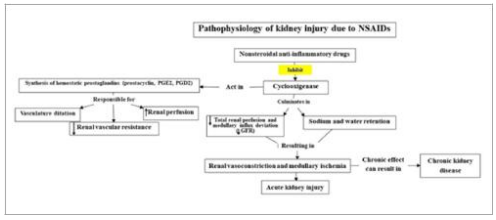

Figure 2: Pathophysiology of kidney injury due to NSAIDs

Prerenal AKI, known as prerenal azotemia, is by far the most common cause of AKI representing 30-50% of all cases. It is provoked by inadequate renal blood flow commonly due to decreased effective circulating blood flow. This causes a decrease in the intraglomerular hydrostatic pressure required to achieve proper glomerular filtration.[18]

The pathophysiology of prerenal azotemia is often a combination of 2 factors, the first being a drop in renal plasma flow and the second being a blunted or inadequate renal compensation leading to further drop in the eGFR.Under physiologic conditions, minor drops in blood flow to the renal circulation are counteracted by changes in the resistances across the afferent and efferent arterioles of individual glomerular capillary beds.[19]

In order to increase blood flow to the glomerulus, the afferent arteriole vasodilates via 2 mechanisms. The myogenic reflex, leading to medial smooth muscle relaxation in states of decrease perfusion pressure, vasodilates the afferent arteriole leading to increased blood flow. Additionally, intrarenal synthesis of vasodilatory prostaglandins such as prostacyclin and prostaglandin E2 causes further dilation of the afferent arteriole.[1] Hence, the intake of NSAIDs in this context inhibits this autoregulatory mechanism possibly leading to acute kidney injury.[20]

Methods

This longitudinal study was carried out in nephrology ward in Community Based Medical College Hospital Bangladesh from July 2015to June 2016. Total 65 patients who were taking NSAIDs for different reasons within past 15 days were included in this study irrespective of their age, sex and social background. Any patient having pre-existing renal disease, chronic kidney disease or taking any other nephrotoxic medication concomitantly was excluded from this study.

Patients were evaluated in terms of

demography, aetiology, mode of presentation, clinical and laboratory findings, treatment pattern, complications and prognosis including follow-up for at least next six months. Rising of serum creatinine >1.4 mg/dl following taking NSAID was considered as AKI. Management schedule was conventional for all the patients to treat the disease, its complications and follow prognosis.

Results

Total 65 patients were included in this study whereas 53 were male (81.53%) and 12 were female (18.46%). Mean age of the patient evaluated was 36±7.12 year. 49 patients (75.38%) took NSAIDs at their own and 16 patients (24.61%) were prescribed by physicians. 3 of them (4.61%) received NSAIDs in intravenous (IV) or intramuscular (IM) route.

Table 1: Patient criteria (n=65)

Variables		Findings
Mean age (Years)		
Sex (No & % of Male/Female)		Male = 53 (81.53%) Female = 12 (18.46%)
Self-Medication (OTC) (No & %)		49 (75.38%)
Iatrogenic (No & %)		
	Oral	14 (21.53 %)
	Suppository	01 (1.53%)
	IV/ IM	03 (4.61%)

Most patients (86.15%) took NSAIDs because of musculoskeletal pain; other causes are non-specific pain like abnormal pin, dysmenorrhoea, fever and headache (Table 2).

Table 2: Causes of taking NSAIDs (n=65)

Cause	Patients (%)
Musculo Skeletal Pain	56 (86.15%)
Pain Abdomen (NOS)	05 (7.69%)
Dysmenorrhoea	01 (1.53%)
Fever	02 (3.07%)
Headache	01 (1.53%)

Amongst different NSAIDs, diclofenac was the most common (44.61%) drug to cause AKI & mean duration of therapy was 6±2.17 days. Next was Naproxen (24.61%) with 4±1.89 days of therapy. Ten patients (15.58%) developed AKI due to Indomethacine 4±1.26 days of therapy. Ketorolac with 3±0.72 day's therapy was culpable agent in 08 patients (12.30%) Table 3.

Table 3: Type of NSAIDs (n=65)

NSAIDs	Mean duration of therapy (days)	Patients (%)
Diclofenac	6±2.17	29 (44.61%)
Naproxen	4±1.89	16 (24.61%)
Indomethacine	4±1.26	10 (15.38%)
Ketorolac	3±0.72	08 (12.30%)
Etoricoxib	6±3.26	02 (3.07%)

Regarding predisposing or risk factors, 19 patients (29.23%) were undergoes physical exertion in hot and humid environment without adequate hydration. Eleven patients (16.92%) had gastroenteritis. Four admitted patients (6.15%) who were kept nil per OS (NPO) for different reasons and on inadequate IV fluid developed AKI due to NSAIDs. No risk factors could be ascertained in 27 patients (41.53%) Table 4

Table 4: Predisposing factors (N=65)

Predisposing factors	Patients (%)
Unknown	27 (41.53%)
physical exertion in hot and humid weather	19 (29.23%)
Gastroenteritis	11 (16.92%)
Nil per OS (NPO)	04 (6.15%)
Old age	03 (4.61%)
Liver cirrhosis	01 (1.5%)

Most of the symptoms in NSAIDs induced were vague are mostly reveledon leading question. Oliguria was present in eight patients (12.30%). Seventeen patients (26.15%) had headache whereas for less (21.5%) patients complained fatigue. Nausea or vomiting was the presenting feature in Nine (13.84%) patients. Oedema was the most common sign (26 patients). Two patients (3.07%) had haematuria and raised BP was found in seven (10.76%) patients. NSAIDs in during AKI was diagnosed incidentally in 15 patients (23.07%) basing on laboratory finding as there was no different sign or symptoms.

Table 5: Mode of Presentation (n=65)

Symptoms/ Signs	Patients (%)
Oedema	26 (36.9%)
Fatigue	14 (21.53%)
Headache	17 (26.15%)
Nausea / Vomiting	09 (13.84%)
Oliguria	08 (12.30%)
Raised B.P	07 (10.76%)
Confusion	01 (1.53%)
Shortness of breath	01 (1.53%)
Hematuria	02 (3.07%)
Asymptomatic	15 (23.07%)

As usual serum urea & creatinine were raised in all patients. In urine, pyuria (leucocyturia) was found in 19 patients (29.23%). RBC was found in 14 (21.5%) patients. 24hr UTP was raised (<1gm) in 22 patients (33.84%). Serum K+ raised in 24 patients (36.92%). In USG, 8 patients (12.30%) hadswollen kidney (Table 6).

Table 6: Laboratory finding (N=65)

Investigation		Patients (%)
Urine	↑ WBC (Leucocyturia)	19 (29.23%)
	+ RBC	14 (21.53%)
	↑ 24hrs Total protein (<1gm)	22 (33.84%)
Blood	↑Serum urea	65 (100%)
	↑Serum creatinine	65 (100%)
	↑K+	24 (36.92%)
	↑Uric Acid	14 (21.53%)
Others	USG (Swollen Kidney)	08 (12.30%)
	CT Scan (Enlarged Kidney)	03 (4.61%)

In all cases, 100% withdrawal of drug was ensured. Fluid resuscitation was given in 54 patients and restriction was carried out in nine patients who had fluid overload. Steroid (Prednisolone) was given in ten patients (15.38%) for a short period (2-4 wks). Two of them required IV methyl prednisolone for initial 3 days to severe AKI and unable to take oral medication due to vomiting. Seven patients required hemodialysis (Table 7).

Table 7: Treatment given (n=65)

Treatment	Patients (%)
Withdrawal of drug	65 (100%)
Fluid resuscitation	54 (83.07%)
Fluid restriction	09 (12.84%)
Steroid	10 (15.38%)
Hemodialysis	07 (10.76%)

Complete recovery was achieved within two weeks in 51 patients (78.46%) where as ten patients (15.38%) took more than two weeks to one months for complete recovery. Three patients (4.61%) developed CKD (Table 8)

Table 8: Patient outcome (n=65)

Outcome		Patients (%)
Complete	In two weeks	51 (78.46%)
	In one month	10 (15.38%)
CKD		03 (4.61%)

Discussion

Older people who were prescribed NSAIDs had a somewhat higher (2-fold) risk of developing AKI, but there was no strong evidence that greater COX-2 selectivity was associated with lower AKI risk. NSAIDs with high COX-2 selectivity (>5-fold) had a lower association with AKI than NSAIDs with COX-2 selectivity <5-fold, and heterogeneity in the subgroups was reduced compared to the overall results consistent with some of the heterogeneity being due to differences in the age of the population studies and the type of NSAIDs examined. Five studies included individual NSAID usage in their analyses in which only Lafrance and Schneider compared dose effect in Rofecoxib, Celecoxib, Naproxen and Meloxicam (Lafrance only).[11,21,22]

In our study mean age of the patient was 36+7.12 yrs and most (81.53%) were male. Most patients (86.15%) took NSAIDS due to musculoskeletal pain. Other causes are non-specific pain like fever, headache, dysmenorrhea and abdominal pain.

AKI can occur with any NSAID. The selective cox-2 inhibitors also may precipitate AKI in certain patients. The

relative frequency with which this occurs compared to the nonselective NSAIDs is not known.[11] There is suggestive evidence that some non-selective NSAIDs (low dose aspirin, ibuprofen and sulindac have a lower nephrotoxic potential than others because of their relative sparing of renal prostaglandin (PG) synthesis.[23] We found diclofenac is the most culpable agent causing AKI (44.61%) then naproxen (24.61%). The rise in the plasma creatinine concentration is seen within 3-7 days of therapy, the time required for attainment of steady state drug levels and therefore maximum inhibition of PG synthesis.

In this study, mean duration of therapy to develop AKI was 6±2.17 days for diclofenac and 4±1.89 days for naproxen. AKI is manifested by rising serum creatinine and the majority of NSAID induced AKI cases are mild and non-oliguric, i.e., urine output of >1 mL/kg/hour [24,25] unless serial serum creatinine values are obtained, AKI can be missed. Prompt diagnosis of NSAID induced AKI with prompt discontinuation of the offending agent will usually reverse the condition within one week, typically within 72 to 96 hours.[26] If for any reason there is a delay in linking use of NSAIDs to AKI, nonwithdrawal of NSAIDs will continue ongoing damage leading to substantial loss of renal function up to the point of requiring dialysis support.[27]

We found fluid depleted state like gastroenteritis, vomiting as the common predisposing factor (16.92%) after physical exertion in hot and humid weather (29.23%). Surprisingly patient developed AKI when kept NPO and on IV fluid may be due to inadequate infusion (6.15%). No predisposing factor could be ascertained in most of the cases (41.53%) in this study.

Raised serum urea and creatinine were found in all patients (100%). Hyperkalemia was detected in 21 patients (36.92%). USG findings revealed swollen kidney in eight patients (12.30%). AKI is manifested by rising serum creatinine and the majority of NSAID induced AKI cases are mild and non-oliguric, i.e., urine output of >1 mL/kg/hour. Unless serial serum creatinine values are obtained, AKI can be missed.[24,25] Prompt diagnosis of NSAID induced AKI with prompt discontinuation of the offending agent will usually reverse the condition within one week, typically within 72 to 96 hours.[27]

Tubulointerstitial nephritis is an inflammatory pathology of renal interstitium and tubules with acute damage, edema, and can potentially heal with interstitial fibrosis. Clinically, AIN resembles ATN though sometimes signs such as rash, eosinophilia, andeosinophiluria can be present.[28,29,30] Over 2/3 of AIN is drug induced .It is important to recognize when AIN may be due to a drug because prolonged injury may cause permanent scarring, and withdrawal of offending agent is obligatory.[25,28,30]

Schwartz et al[29] risk factors of transition from acute to chronic interstitial nephritis in a retrospective study of 1068 renal biopsies. AIN was found in 69(6.46%) of all biopsies. Complete recovery was achieved within two weeks (78.46%) whereas 15.38% patients took more than two weeks to one month for complete recovery. Three patients (4.61%) developed irreversible kidney damage. In this study renal biopsy was carried out in one patient & the findings were consistent with acute interstitial nephritis (AKI).

The role of steroids in the treatment of NSAIDs induced AIN remains controversial. Despite the importance of this entity as a frequent cause of AKI.[30] Some studies have suggested a positive influence, by showing a quicker and complete recovery of renal function in those patients who received steroids.[31,32] However a course of prednisolone may be considered for the patients whose renal function does not return to normal after 2-3 weeks of withdrawal of the offending NSAIDs. Such patient should avoid the subsequent administration of NSAIDs. Relapse may occur with 15 rechallenge.[33] In this study,

ten patients (15.38%) were treated with prednisolone where AIN was suspected. Fluid resuscitation [54 patients (83.07%)] & fluid restriction [09 patients (13.84%)] was done where necessary. Seven patients required hemodialysis. Complete recovery was achieved in 61 cases (93.84%) of which 51 cases (78.46%) were recovered within two weeks, ten (15.38%) patients required more than two weeks to one month for complete recovery. Three patients (4.61%) developed CKD.

Conclusion

In conclusion, NSAIDs pose significant risk of renal damage and the development of AKI due to NSAIDs is under recognized. As OTC products are usually regarded safe and inadequate monitoring of side effects in adult consuming NSAIDs suffering from intravascular volume contraction is a real danger. Physicians need to use caution when treating pain with NSAIDs in patient with abnormal creatinine. Physicians should discuss the risks of administering OTC NSAIDs. Awareness of the dangers of using NSAIDs could reduce the episodes of nephrotoxicity.

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