Original Paper

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS) Induced Acute Kidney Injury (AKI): Patient Profile and Outcome in Bangladesh Armed Forces

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Abstract

Introduction: In military environment where musculoskeletal injury is more common, NSAIDs abuse and subsequent AKI carries a special risk. This study of NSAIDs induced AKI was carried out to highlight this issue.

Objective: To find out the incidence, risk factors, diagnostic approach, clinical course, management and outcome of patients of Bangladesh Armed Forces.

Methods: This longitudinal study was carried out in nephrology centre, combined military hospital (CMH) Dhaka from July 2010 to Jun 2013. Total 59 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.

Results: Total 59 patients were included in this study. Mean age of the patient was 36±7.12 yrs. Forty five patients (76.27%) took NSAIDs at their own and 14 patients (23.73%) were prescribed by physician. Fifty one patients (86.44%) took NSAIDs because of musculoskeletal pain. Dehydration due to physical exertion (30.50%), gastroenteritis (15.25%) and nil per os (NPO) (5.08%) were the common predisposing factors. Common symptoms were swelling of the body (40.67%), headache (32.20%), fatigue (27.11%) and vomiting (13.55%). Oedema was the most common sign (40.67%). Blood urea and serum creatinine were raised in all patients. Treatment includes drug withdrawl (100%), fluid resuscitation (86.44%), fluid restriction (61.01%), short course of steroid (13.55%) and haemodialysis (10.16%). Forty seven patients (79.66%) had complete recovery within two weeks of therapy whereas nine patients (15.25%) required more than two weeks to one month for complete recovery. Three patients (5.09%) developed chronic kidney disease (CKD).

Conclusion: 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.

Key-words: Nonsteroidal anti-inflammatory drugs (NSAIDs), acute kidney injury (AKI).

Introduction

Non steroidal anti-inflammatory drugs (NSAIDs) represent one of the most common classes of medications used worldwide with an estimated usage of >30 million per day[1]. Some are available over the counter and likely to be abused. NSAIDs exert anti-inflammatory, analgesic and antipyretic effects through the suppression of prostaglandin (PG) synthesis by inhibiting the enzyme cyclo-oxygenase 1and 2 (COX 1 and 2)[1]. Serious gastrointestinal side effects have been minimized with the advent of selective and specific cox-2 inhibitors and misoprostol. However the newer NSAIDs continue to be nephrotoxic much like the conventional ones[1,2]. It can induce two different forms of acute kidney injury (AKI) haemodynamically mediated and acute interstitial nephritis (AIN) which is often accompanied by nephrotic syndrome[2]. 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 withdrawl of NSAIDs, some reports have suggested a persistent residual dysfunction[3].

Patients and Methods

This longitudinal study was carried out in nephrology centre combined military hospital (CMH), Dhaka from Jul 2010 to Jun 2013. Total 59 patients who were

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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 pathology, chronic kidney disease or taking any other nephrotoxic medication concomittently 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

Mean age of the total 59 patients evaluated was 36±7.12 yrs. 48 were male (81.36%) whereas 11 were female (18.64%). 45 patient (76.27%) took NSAIDs at their own and 14 patients (23.73%) were prescribed by physician. 3 of them (5.09%) received NSAIDs in intravenous (IV) or intramuscular (IM) route (Table-I).

Table-I: Patient criteria (n=59).

Variables		Findings
Mean age (Yrs)		36±7.12
Sex (No. & % of M/F)		Male=48 (81.36%) Female=11(18.64%)
Self Medication (OTC) (No. & %)		45(76.27%)
Iatrogenic (No. & %)	Oral	10(16.95%)
	Suppositories	01(1.69%)
	IV or IM	03(5.09%)

Most patients (86.44%) took NSAIDs because of musculoskeletal pain; other causes are non specific pain abdomen, dysmenorrhoea, fever and headache (Table-II).

Table-II: Causes of Taking NSAIDs (n=59).

Cause	Patient (%)
Musculoskeletal pain	51(86.44%)
Pain abdomen (NOS)	04(6.79%)
Dysmenorrhoea	01(1.69%)
Fever	02(3.39%)
Headache	01(1.69%)

Amongst different NSAIDs, diclofenac was the most common (44.07%) drug to cause AKI & mean duration of therapy was 6±2.17 days. Next was naproxen (23.73%) with 4±1.89 days of therapy. Nine patients (15.25%) developed AKI due to indomethacin with 4±1.26 days of therapy. Ketorolac with 3±0.72 days therapy was culpable agent in 08 patients (13.56%) (Table-III).

Table-III: Type of NSAIDs (n=59).

NSAIDs	Mean duration of therapy (days)	Patient (%)
Diclofenac	6±2.17	26 (44.07%)
Naproxen	4±1.89	14 (23.73%)
Indomethacin	4±1.26	09 (15.25%)
Ketorolac	3±0.72	08 (13.56%)
Etocoxib	6±3.26	02 (3.39%)

Regarding predisposing or risk factors, 18 patients (30.51%) were undergone physical exertion in hot & humid environment without adequate hydration. Nine patients (15.25%) had gastroenteritis.Three admitted patients (5.09%) 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 25 patients (42.37%) (Table-IV).

Table-IV: Predisposing factors (n=59).

Predisposing Factors	Patients (%)
Unknown	25 (42.37%)
Physical exertion in hot & humid weather	18 (30.51%)
Gastroenteritis	09 (15.25%)
Nil per os	03 (5.09%)
Old age (>60 yrs)	03 (5.09%)
Liver cirrhosis	01 (1.69%)

Most of the symptoms in NSAIDs induced AKI were vague and mostly revealed on leading question. Oliguria was present in six patients (10.17%). Nineteen patients (32.20%) had headache whereas 16 patients (27.12%) complained of fatigue. Nausea or vomiting was the presenting feature in eight patients (13.56%). Oedema was the most common sign (24 patients). Two patients (3.39%) had haematuria and raised BP was found in six (10.17%) patients. NSAIDs induced AKI was diagnosed incidentally in 17 patients (28.81%) basing on laboratory findings as there was no definitive sign or symptoms (Table-V).

Table-V: Mode of Presentation (n=59).

Symptom/ Sign	Patient (%)
Oedema	24 (40.68%)
Fatigue	16 (27.12%)
Headache	19 (32.20%)
Nausea/Vomiting	08 (13.56%)
Oliguria	06 (10.17%)
Raised Blood Pressure	06 (10.17%)
Confusion	01(1.69%)
Shortness of Breath	01 (1.69%)
Haematuria	02 (3.39%)
Asymptomatic	17 (28.81%)

As usual serum urea & creatinine were raised in all patients. In urine, pyuria (leucocyturia) was found in 18 patients (30.51%). RBC was found in 11 patients (18.64%). 24 hrs urinary total protein was raised (<1 gm) in 20 patients (33.90%). S. potassium (k+) was raised in 21 patients (33.59%). In ultrasonography (USG), six patients (10.17%) had swollen kidney (Table-VI).

Table-VI: Laboratory Findings (n=59).

Investigation		Patient (%)
Urine	↑WBC (leucocyturia)	18 (30.51%)
	+RBC	11 (18.64%)
	↑24 hrs total protein(<1 gm)	20 (33.90%)
Blood	↑Serum urea	59 (100%)
	↑Serum creatinine	59 (100%)
	↑Serum potassium	21 (35.59%)
	↑Uric acid	12 (20.34%)
Others	USG (swollen kidney)	06 (10.17%)
	CT Scan(enlarge kidney)	04 (6.78%)

In all cases, 100% withdrawal of drug was ensured. Fluid resuscitation was given in 51 patients and restriction was carried out in eight patients who had fluid overload. Steroid (prednisolone) was given in eight patients (13.55%) for a short period (2-4 wks).Two of them required IV methyl prednisolone for initial three days due to severe renal failure and unable to take oral medication due to vomiting. Six patients required haemodialysis (Table-VII).

Table-VII: Treatment given (n=59).

Treatment	Patient (%)
Withdrawal of drug	59 (100%)
Fluid resuscitation	51 (86.44%)
Fluid restrictions	08 (13.56%)
Steroid	08 (13.56%)
Haemodialysis	06 (10.17%)

Complete recovery was achieved within two weeks in 47 patients (79.66%) whereas nine patients (15.25%) took more than two weeks to one month for complete recovery. Three patients (5.09%) developed CKD (Table-VIII).

Table -VIII: Patient Outcome (n=59).

Outcome		Patient (%)
Complete Recovery	In two weeks	47 (79.66%)
	In one month	09 (15.25%)
CKD		03(5.09%)

Discussion

Prostaglandins maintain renal blood flow and glomerular filtration rate (GFR) especially in fluid depleted states like hypovolaemia, congestive cardiac failure, liver cirrhosis with ascites, chronic diuretic therapy, glomerulonephritis, urinary tract obstruction, old age, nephrotic syndrome, chronic renal failure, concomitant use of nephrotoxic drugs like calcineurin inhibitor, aminoglycosides etc or direct volume depletion by gastrointestinal or renal salt & water loss[3]. Blockade of either or the isoenzymes (Cox-1 and Cox-2) permits unopposed vasoconstriction by leukotriens, angiotensin II, vasopressin, endothelin and catecholamines leading to decreased glomerular hydraulic pressure and AKI.

Additionally NSAIDs produce hyporeninemia and hypoaldosteronism which causes spectrum of nephrotoxicity like acute tubular necrosis, acute tubulointerstitial nephritis, glomerulonephritis, renal papillary necrosis; CKD, salt and water retention, hypertension and hyperkalemia[4], there are reports of subclinical renal dysfunction due to NSAIDs[5]. But NSAIDs induced CKD remains a debatable issue which may be due to chronic papillary necrosis or chronic interstitial nephritis[6]. ARF (AKI) associated with NSAIDs accounts for 15.5% of all case of drug induced renal failure[7]. Although NSAIDs induced nephropathy is more common in old age, in our study mean age of the patient was 36±7.12 yrs and most (81.38%) were male as our hospital mainly deals with male dominated military population. For the same reason, cause of taking NSAIDs was mostly (86.44%) due to musculoskeletal pain of acute nature.

AKI can occur with any NSAID[9]. 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[8]. 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[9]. We found diclofenac is the most culpable agent causing AKI (44.07%), then naproxen (23.73%). 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[9].

In this study, mean duration of therapy to develop AKI was 6±2.17 days for diclofenac and 4±1.89 days for naproxen. Since typically administered NSAIDs can be systematically absorbed such therapy should also be terminated in suspected cases[10]. NSAIDs increase the risk of AKI particularly in the elderly with multiple co-morbidities and the use of the combination of ACE inhibitors, angiotensin II blockers, diuretics and NSAIDs. Regular use of either aspirin or acetaminophen was associated with 2.5 fold increase in the risk of CKD[11]. We found fluid depleted state like gastroenteritis, vomiting as the common predisposing factor (15.25%) after physical exertion in hot and humid weather (30.51%). Surprisingly patient developed AKI when kept NPO and on IV fluid may be due to inadequate infusion (5.09%). No predisposing factor could be ascertained in most of the cases (42.37%) in this study.

NSAIDs induced AKI is commonly haemo dynamically mediated, diagnosis of which is mostly incidental as found in our study (28.81%) as the symptom like fatigue, headache, polyuria, nausea are subjective and vague. But the clinical presentation of AIN is more specific like acute onset oedema, oliguria and sometimes anuria. Macroscopic haematuria is rare. Urine analysis reveals proteinuria, microscopic haematuria and leucocyturia. Serum creatinine varies from minimal elevation (1.5 mg/dl) to > 10 mg/dl at first presentation. In our study, leucocyturia was found in 18 patients (30.51%) whereas microscopic haematuria was present in 11 patient (18.64%). Urinary total protein was raised (<1 gm) in 20 patients (33.90%).

Raised serum urea and creatinine were found in all patients (100%). Hyperkalaemia was detected in 21 patients (35.59%). USG findings revealed swollen kidney in six patients (10.17%). Ravnaskov[12] studied published case reports of NSAIDs associated nephropathy. Of the 97 cases, AIN was present in 19 patients (19.59%) and rest of the 78 cases (80.41%) had different forms of glomerulonephritis (e.g., minimal change disease, membranous nephropathy, focal segmental glomerulosclerosis and other glomerulonephritis subgroups). Hyper-sensitivity reactions were seen in all groups.

Although haemodynamically mediated AKI can be responsible for acute tubular necrosis when ischaemia is severe and persistent, most cases improve within weeks to a few months after the drug is discontinued whereas resolution of AIN is a relatively more prolonged process. Only when renal function doesn't improve rapidly after the drug is discontinued, one can perform a renal biopsy to distinguish between NSAIDs induced acute tubular necrosis and AIN[13].

Schwartz et al[14] studied the outcome of AIN and the 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. In 59 (85.51%) of these it was drug induced, NSAIDs were responsible for 17 (28.81%) cases (Renal insufficiency was reversible in 69% and permanent in 31% [12% partially reversible and 19% irreversible]). Permanent renal insufficiency for NSAIDs induced cases was 56%. In this study renal biopsy was carried out in one patient & the findings were consistent with AIN.

Steroids have not been proven to be effective in cases caused by NSAIDs. However a course of prednisolone may be considered for the patients whose renal function does not return to normal after 2-3 weeks of withdrawl of the offending NSAIDs. Suchpatient should avoid the subsequent administration of NSAIDs. Relapse may occur with rechallenge[15]. In this study, eight patients (13.56%) were treated with prednisolone where AIN was suspected. Fluid resuscitation [51 patients (86.44%)] & restriction [08 (13.56%) patients] was done where necessary. Six patients required haemodialysis. Complete recovery was achieved in 56 cases (94.92%) of which 47 cases (79.66%) were recovered

within two weeks, nine (15.25%) patients required more than two weeks to one month for complete recovery. Three patients (5.09%) developed CKD.

Conclusion

NSAIDs are associated with all forms of renal injury while acute syndromes generally carry a good prognosis; the same is not true for CKD. Subclinical CKD can be a silent forerunner of CKD. Analgesic toxicity can be prevented by limiting the availability of over the counter NSAIDs. Physicians should always prescribe the lowest effective dose of NSAIDs for the shortest possible time ensuring adequate hydration[16].

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