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Short term therapeutic dose effects of non steroidal anti inflammatory drugs on serum creatinine levels

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Abstract

Aim: People who take analgesic drugs frequently may be at increased risk for renal disease, but the extent of this risk remain unclear. The aim of this study to find out the short term therapeutic dose effects of non steroidal anti inflammatory drugs on serum creatinine levels.

Methods: In this study, three types of NSAIDs i.e diclofenac sodium (group I), acetaminophen (group II) and mefenamic acid (group III) were used. For each drug 10 patients were selected. As NSAIDs has impact on kidney function. So, to rule out its effect on kidney, we have chosen serum creatinine levels as a marker in our study. First blood sample is taken before dispensing the drug (stage I), second sample 7 days after giving the complete course of drug (stage II) after that third blood sample was taken 10 days after stopping the course of drug (stage III).

Statistical Analysis & Results: When comparing to the baseline levels the serum creatinine in group I and group III were significantly higher as compared to group II with first follow-up. After second follow up, group II serum creatinine level was increased as compared to first follow-up. At the end, group I and group III had significantly higher mean value as compared to baseline with second follow-up.

Conclusion: This study suggested that the even short term regular consumption of analgesics should be considered as a risk factor for kidney function. So, further studies should be done to assess that, whether these changes are transient or long lasting.

Keywords: Non-steroidal anti-inflammatory drugs (NSAIDS), serum creatinine

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for many years but gained popularity only in the late 1970s.[1] Both the number of drugs & the indications for their use have increased substantially since 1971, when their effects on prostaglandin synthesis were discovered.[2] In subcontinent the availability of these drugs in over the counter preparations calls for a better understanding of the benefits and risk of their use.[1]

Non-steroidal anti-inflammatory drugs are used primarily to treat inflammation, mild to moderate pain ,fever and other specific uses which include the treatment of headache , arthritis etc . Now a large number of non-steroidal anti-inflammatory drugs exist , and there is variability in clinical response to NSAIDs among individual patients , concern over the widespread use of non-steroidal anti-inflammatory drugs is largely related to their side effects. These include adverse reactions in the gastrointestinal tract, kidney and central nervous system as well as hematological problems.[2,3] There are many drugs which, without proper clinical trials and without their known side effects gained popularity in the market and also soon they disappeared from the market when they were proved to be hepatotoxic and nephrotoxic.

Non-steroidal anti-inflammatory drugs have been identified as nephrotoxic agents with both acute and chronic effects on kidney function. The long term biological effect of sodium retention, oedema, acute renal failure with non-steroidal anti-inflammatory drugs are well documented.[3,4] There are limited scientific data reporting the safety of these drugs on kidney function when these drugs were taken on short term basis or chronically taken by the patients without pre- existing kidney disease. Existing data regarding short term and long term effects of non-steroidal anti-inflammatory drugs exposure on kidney function is inconsistent.[5]

Non-steroidal anti-inflammatory drugs have been identified as nephrotoxic and also many clinical trials of these drugs have proved this fact. It is not well established that, whether this nephrotoxic effect is transient or long lasting.[3]

Serum creatinine is a useful and inexpensive method of evaluating renal dysfunction. Creatinine is a non protein waste product of creatinine phosphate metabolised by skeletal muscle tissue. Its production is continuous and is proportional to individual's muscle mass. Renal dysfunction diminishes the ability to filter creatinine and the serum creatinine level rises. Thus, they are used to evaluate renal function.[5]

Serum creatinine measurements take in to an account as a useful indicator for diagnosis renal function and also serve as, the early diagnostic tool. Creatinine is detected in both serum and plasma.[5] Serum creatinine level has an important effect on kidney function as well as other major functions of our body. Kidney dysfunction reduces the quality of life. And, also it is one of the leading cause of morbidity and mortality in subcontinent.[4] With the recent over the counter availability and increasing popularity of non-steroidal anti-inflammatory drugs, the possibility of analgesic abuse and also, the incidence of kidney diseases is increasing.[2]

As, dental surgeons frequently prescribe these non-steroidal anti-inflammatory drugs on short term basis to treat mild to moderate pain of odontogenic or non odontogenic cause, along with increasing rate of analgesic abuse , and also increasing the incidence of kidney diseases in the society. So this study has been undertaken to evaluate the short term effects of non-steroidal anti-inflammatory drugs on kidney function, and also to assess that, whether these changes are transient or long lasting.

Selection Criteria

Inclusion criteria

Patients who are having mild to moderate dental pain are included in the study.

Patients having dental pain but not consuming any non-steroidal anti-inflammatory drugs for past one month are included in the study.

Patients above 20 years of age and below 60 years of age are included.

Exclusion criteria

Patients who are having any systemic diseases which have direct or indirect impact on kidney functions are excluded

Materials and Methods

- In this study, the following medications (i.e diclofenac sodium, acetaminophen, mefenamic acid) is purchased from the pharmacist and opened, then again repacked in tin foil giving importance to sterilization and disinfection.
- Then patient who report to the outpatient department of Kothiwal Dental College and Research Centre with a chief complaint of mild to moderate dental pain will be selected. With proper case history and giving importance to medical history, drug history, and systemic examination. The subjects are randomly selected and divided into 2 groups i.e (20 -40) years of age and (40-60) years of age and then they are subjected to therapeutic dose of NSAIDs.
- Before taking the blood sample, written consent will be taken from every patients. After that the serum creatinine level is estimated in three different stages.
- Ist stage- Before dispensing the drug to the patient.
- 2nd stage- After dispensing 7 days course of the drug to the patient.
- 3rd stage- 1week after stopping the course of the drug..

Inclusion criteria

Patients who are having mild to moderate dental pain are included in the study.

Patients having dental pain but not consuming any non-steroidal anti-inflammatory drugs for past one month are included in the study.

Patients above 20 years of age and below 60 years of age are included.

Exclusion criteria

Patients who are having any systemic diseases which have direct or indirect impact on kidney functions are excluded

Results

A total of 30 patients reporting to the outpatient department of Kothiwal Dental College and Research Centre with a chief complaint of mild to moderate dental pain were selected.

Association of baseline serum creatinine levels with demography, dietary habits and nutritional status of patients.

Mean serum creatinine levels of patients aged 40-60 years, males, non-vegetarians and those in overweight and obese category were higher as compared to those who were aged 20-40 years, females, vegetarians and normal

weight. However, the difference was significant statistically for gender only (p=0.050). (fig.1)

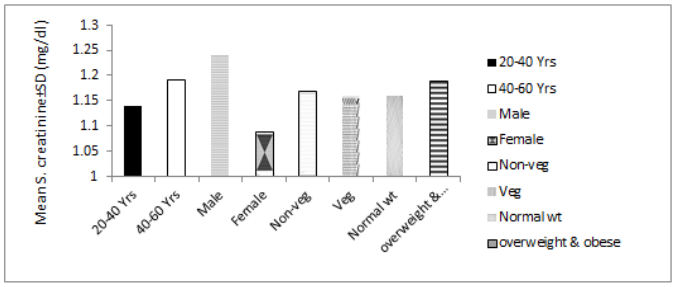

Figure 1: Association of mean baseline Serum creatinine levels with demographic, dietary and nutritional strata of patients

Mean serum creatinine levels of patients aged 40-60 years were higher as compared to others(p=0.050)

Association of baseline serum creatinine levels with demographic, dietary and nutritional strata of patients (according to cut-off <1.2 mg/dl)

As compared to those patients with age 20-40 years, female gender, vegetarian diet and normal weight category, the proportion of patients with serum creatinine levels >1.2 mg/dl was higher among those patients with age 40-60 years, male gender, non-vegetarian diet and overweight/obese weight category. However, the difference was significant statistically only for the comparison between two genders (p=0.025). (fig .2)

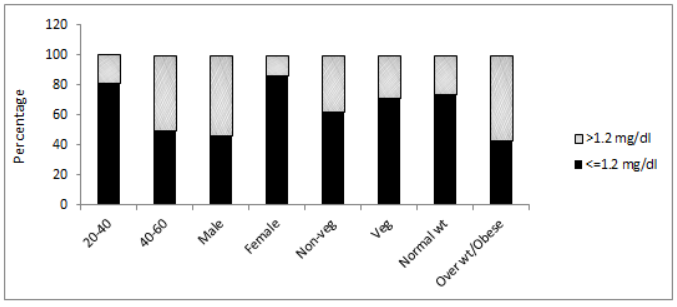

Figure 2: Association of baseline Serum creatinine levels with demographic, dietary and nutritional strata of patients (according to cut-off ≤1.2 mg/dl)

Serum creatinine levels were higher among patients aged 40-60 years, male gender , nonvegetarian and overweight/obese category as compared to other group(p=0.025)

Comparison of three groups according to Serum Creatinine Levels

At baseline, mean serum creatinine levels in three groups ranged from 1.06±0.12 mg/dl (Group III) to 1.24±0.16 mg/dl (Group I). In Group II, mean serum creatinine levels were 1.19±0.25 mg/dl. Overall, mean serum creatinine levels were 1.16±0.19 mg/dl. Minimum S. creatinine level was recorded as 0.9 (in Groups II and III) and maximum S. creatinine level was recorded 1.6 (in Group I). Statistically, there was no significant difference in mean S. creatinine levels of three groups (p=0.079). (fig. 3)

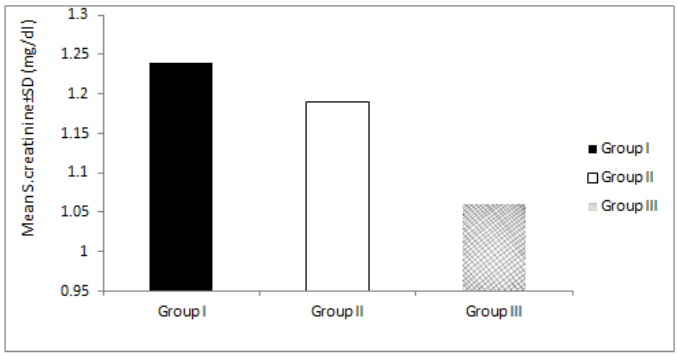

Figure 3: Comparison of three groups according to serum creatinine levels

At baseline maximum serum creatinine level was recorded in group I cases (p= 0.079)

Comparison of baseline and first follow up S. Creatinine levels in three groups as well as combinedly for the three groups

Except for Group II, for all the other groups as well as for overall comparison, there was an increase in mean S. creatinine levels at first follow up as compared to baseline. However, the difference was not significant statistically except in Group I (p=0.011).

Intergroup comparison revealed no statistically significant difference among groups at baseline, however, at first follow up the differences among groups were significant statistically with mean S. creatinine value in Group I being significantly higher as compared to the other two groups (p=0.025) (fig. 4)

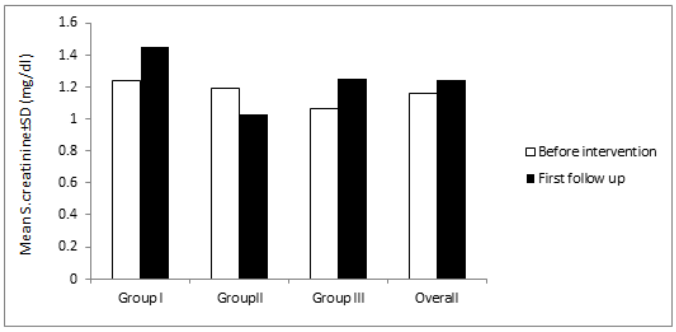

Figure 4: Comparison of baseline and first follow up S. creatinine levels in different groups

After first follow up except for group II and overall groups, an increase in mean S. creatinine levels was observed in other groups compared to baseline (p=0.025)

Comparison of First and Second follow up S. creatinine levels in different groups

Except for Group II, in all the other groups as well as for overall comparison an increase in mean S. creatinine levels was observed, however, for none of the comparisons the change was significant statistically.

Intergroup comparison revealed mean value of Group I to be significantly higher as compared to the other two groups at first follow up (p=0.025). At second follow up too, Group I had significantly higher mean value as compared to other two groups (p=0.009). (Table 5, fig 5)

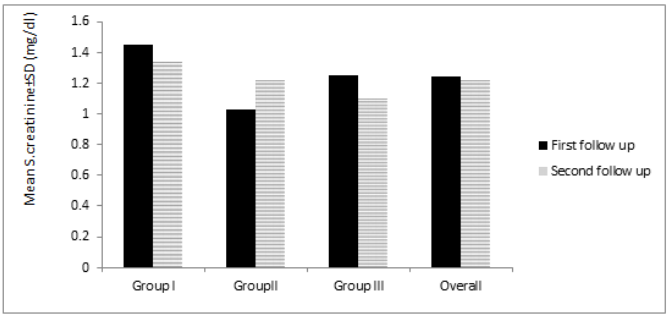

Figure 5: Comparison of first and second follow up S. creatinine levels in different groups

Comparing first follow up with second follow up, group I had higher mean creatinine value as compared to other groups (p=0.009)

Comparison of Baseline and Second follow up S. creatinine levels in different groups

In all the groups an increase in mean serum creatinine levels was observed between baseline and second follow up. However, none of the changes were found to be significant statistically (p>0.05).

Intergroup comparison did not reveal a significant difference among groups at baseline (p=0.079). However, at second follow up, Group I had significantly higher mean value as compared to other two groups (p=0.009). (fig. 6)

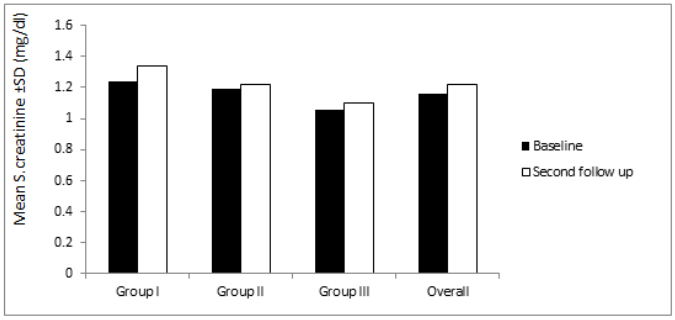

Figure 6: Comparison of baseline and second follow up S. creatinine levels in different groups

Comparison of baseline and second follow up group I had significantly higher mean values as compared to other two groups (p=0.009)

Discussion

Creatinine is a small freely filtered solute whose production varies little from day to day since it is derived from the metabolism of muscle creatine. Creatinine can be secreted by the proximal tubule through an organic cation pathway. The secreted creatinine component confounds GFR measurements because it can vary within individuals over time; moreover the proportion of secreted creatinine increases as the GFR decreases.[5]

Creatinine production is primarily a function of muscle mass and the amount produced is fairly constant. Creatinine is removed from plasma by glomerular filteration and is then excreted in urine. Therefore, creatinine clearance is a measure of glomeular filteration rate (GFR) and its measurement is useful in assessing renal function.[5-7]

Serum creatinine is a more specific and sensitive indicator of renal function. The concentration of SCr rises when there is impaired formation or excretion of urine, irrespective of whether the causes are pre-renal, renal or post renal in origin. In clinical investigations, it is essential to utilize more accurate and sensitive measures of renal function to estimate GFR and progression. [5,6,8]

The concentration of creatinine in serum has long been the most widely used and commonly accepted measure of renal function in clinical medicine. However, the use of SCr as an indirect marker of GFR has been criticized because it is also affected by age, sex, race, diet, body mass. It was recently suggested that a more precise estimation of GFR can be obtained using specific equations that take into account the influence of many other factors that potentially affect serum creatinine concentrations. The common reference range used for creatinine in the general population is 0.7-1.3 mg/dl for male adults, determined using Jaffe reaction in automated systems. In a recent report based on a wide population, the range was 0.68-1.13mg/dl for male adults, narrower than the one above.[6]

In the present study, the observed mean serum creatinine level for below 40 years age group is 1.14 whereas for above 40 years age group it is 1.19mg/dL. This result is in accordance with the study conducted by Mascha verma et al in their study they observed that serum creatinine level ranges from 0.4-1.3mg/dL for age group 21-40 years and 0.6-1.3mg/dL for 41-60 years age group and they also suggested that, the standard range as per recommended guidelines is 0.6-1.3 mg/dl.

They concluded that serum creatinine levels may vary in the healthy population to different extent or in other words serum creatinine concentration is affected by factors other than glomerular filteration rate (GFR),such as creatinine secretion and generation and extrarenal excretion.[5]

Mascha verma et al, Kathryn M Rexrode et al suggested that an impaired renal function may be expected in older age and thus the normal serum creatinine levels may be expected to vary as the age increases.[3,5]

Low creatinine may result from inadequate dietary protein a well as reduce muscle mass. An increased serum creatinine levels may occur from non creatinine substances including meat ingestion, glucose, pyruvate, uric acid, fructose guanidine, acetoacetate and ascorbic acid. Falsely high serum creatinine concentration is also associated with severe menthanol intoxication.[5-8]

In present study, for 16 non-vegetarian patients the mean serum creatinine level is.1.17mg/dL and for 14 vegetarian patients serum creatinine is 1.10 which is slightly lower than non vegetarian patients. This result in accordance of Mascha et al, Alessandra Calabria baxeman and Perrone Ronald D et al where they suggested that the food

contributes with three distinct components that can alter the urinary excretion of creatinine.

1. Protein that have arginine and glycerin precursors of creatinine and guanidoacetate production.
2. Creatinine itself which leads to a direct increase of muscular creatinine "pool" thereby raising the urinary excretion of creatinine.
3. Dietary creatinine which is excreted readily as soon a absorbed. [7,9]

Individuals with moderate or intense physical activity presented with higher urinary creatinine probably as a result of muscular mass and the higher mean protein and meat intake consumed by these individuals.[8-13]

Body mass index is calculated by weight is kilograms divided by height in meter squared. According to National Heart Lung and Blood Institute Guidelines, over weight is defined as BMI of 23-29.9 kg/m^2, class I obesity as BMI of 30-34.9 kg/m^2 and class III or extreme obesity as 40 kg/m^2 or above. Underweight is defined as BMI is less than 18.5 kg/m^2.[9-11]

A correlation between creatinine and BMI and a positive association between creatinine and physical exercise have been reported in the general population. The origin of creatinine from creatine may explain this correlation and also the higher concentrations in men than women. The correlation between creatinine and BMI is not necessarily only connected with muscle mass. Lean mass is not crucial for defining creatinine concentration as reported in broad population. In our study also male, overweight category persons have higher serum creatinine levels as compared to female, normal weight persons.[6]

In present study, 23 normal weight patients had mean serum creatinine 1.16 whereas7 overweight and obese patients had mean serum creatinine level (1.19). This result shows a high serum creatinine level among overweight patients, which follows the study done by Alessandra calabri Baxmann et al, Mascha et al, Chi yuan Hsu et al, where they suggested that not only higher protein intake but also the lipid and carbohydrate intake can affect the body mass index and thus the excretion of Serum creatinine level.[5,8,9]

Overweight or obesity have been identified as a strong and potentially modifiable risk factors for the development of end stage renal disease. Conversely, kidney failure should be added to the list of adverse consequences of obesity.[9]

Non-steroidal anti-inflammatory drugs are widely used in the treatment of both odontogenic and non odontogenic causes. They inhibit cyclooxygenase, the enzyme that transforms arachidonic acid to prostaglandins. This action is responsible for both the therapeutic as well as the side-effects of these drugs.[14-18]

These drugs have been identified as nephrotoxic agents with both acute and chronic effects on kidney function (7,14). The acute reversible effect of non-steroidal anti-inflammatory drugs on renal function is because of inhibition of renal prostaglandins.[15-20]

The frequency of non-steroidal anti-inflammatory drug used, including non selective conventional NSAIDs and selective cyclooxygenase 2 inhibitors has increased in the last several years. Potential factors responsible for this increase include over the counter availability and aging population with concomitant musculoskeletal disorders and perceived superior gastrointestinal safety profiles associated with COX-2 inhibitors.[7,16-20] The acute reversible effects of NSAIDs on renal function due to inhibition of renal prostaglandins are well understood and have been repeatedly demonstrated in randomized controlled trials. These effects appear to be common to all NSAIDs, and are likely to be observed with cyclo-

oxygenase-2inhibitors as well, because cyclo-oxygenase-2 and cyclooxygenase-1 have been identified in adult and foetal human kidneys, suggesting a role for both enzymes in normal renal physiology. Although clinical consensus exists regarding predisposing risk factors for acute renal failure (ARF) following NSAID use (stimulated rennin and angiotensin system due to liver failure, heart failure, nephrotic syndrome or low circulating plasma volume), little is known about the incidence of this event or the magnitude of risk elevation (interaction) associated with these predisposing factors. These important questions can only be addressed by epidemiological studies. Acute effects may become irreversible in some patients, and chronic use seems to be one of the predisposing factors for such a transition. Despite the inherent difficulty in distinguishing acute from chronic effects in many epidemiological studies, some epidemiological evidence regarding chronic effects of NSAIDs on renal function, including end-stage renal failure (ESRF), is available. NSAIDs are potent analgesics, and are largely used for this purpose. With regard to analgesics and nephrotoxicity, analgesic nephropathy caused by analgesics that contain phenacetin (or its metabolite acetaminophen) or by other compound analgesics should be mentioned. [20-23]

Henry et al recently recruited 110 consecutive patients who had a serum creatinine of greater than150 mmol/l on admission that declined at least 20% within the next 14 days, and compared these individuals with 189 hospitalized patients who had a serum creatinine below 120 mmol/l. NSAIDs use (including aspirin) during the month before hospitalization was associated with a (statistically non significant) increase in the risk of acute renal impairment [adjusted odds ratio 1.8, 95% confidence interval (CI) 1.0±3.4]. When NSAIDs were grouped according to pharmaco dynamic half-life, a statistically significant trend for NSAIDs with long half-lives and risk of acute renal impairment was observed. The main limitation of this case-control study is its small size. Murray et al.[13] also used a large database (Indianapolis, USA) to define a cohort of 1908 individuals starting NSAIDs (ibuprofen) and 3933 starting acetaminophen therapy, and repeated serum creatinine measurements to define decline in renal function (rise from normal to abnormal or 10% or more if already abnormal) within 12 months after the start of therapy. The incidence of decline in renal function as defined was 18% in NSAID users. Within NSAID users, age, preexisting renal insufficiency, male sex, systolic blood pressure and diuretic use were associated with a higher probability of decline. Compared with acetaminophen use, NSAID use was a risk factor for decline in renal function in those aged 65 years or more and in those with coronary artery disease. Although this paper is often cited as evidence for predisposing factors for acute decline, the case definition and analysis of the study have several limitations, which are reflected, for example, in the very high incidence (18%) of acute decline. [14]

In 1950 an increasing incidence of chronic interstitial nephritis of unknown aetiology was observed in autopsies carried out in Zurich. Some of the patients had a history of long-term consumption of large amounts of analgesic mixtures. The authors were unable to establish whether abuse preceded or followed the onset of renal disease (Spuhler & Zollinger, 1953).There is sample experimental and clinical evidence linking analgesic abuse with chronic renal disease, but the large majority of reports have incriminated analgesics-and phenacetin in particular-solely on the basis of association and

circumstantial evidence (Prescott, 1982). Several aspects of this disease are still illdefined. Firstly, generally agreed diagnostic criteria include a history of heavy use of analgesics, which may in it bias any causal association (International Committee for Nomenclature and Nosology of Renal Disease, 1975). Secondly, its real incidence is a matter of controversy, and striking geographic differences as a cause of end-stage renal disease (ESRD) have been recorded (Brunner et al., 1989; Brynger et al., 1980; Gault & Wilson, 1978; Gonwa et al.,1981; Murray & Goldberg,1978; Vanherweghem & Even-Adin, 1982), Spain showing the lowest figure in Europe(Anonymous, 1981). Thirdly, the few epidemiological studies published to date have yielded conflicting results. A cohort study carried out in Basel, in which heavy users of analgesics were selected because of phenacetin metabolites in their urine, has shown a higher incidence of both abnormal kidney function and kidney-related mortality in this group compared with occasional users and nonusers after a 10-year follow-up (Dubach et al., 1983). On the other hand, a case-control study, conducted among patients on haemodialysis because of ESRD, was unable to demonstrate an increased risk of ESRD associated with past analgesic use (Murray et al., 1983). These results contrast with those of two recent case control studies. In one of them, conducted in the USA and including patients with newly diagnosed kidney disease, an excess risk of renal disease in daily users of analgesic mixtures was shown (Sandler et al., 1989). Another study from West Germany, including patients with ESRD, has shown a dose-dependent increase in risk with the cumulative use of more than 1 kg of analgesic mixtures (Pommer et al., 1989a,b). Fourthly, the possible aetiological role of analgesics other than phenacetin-and particularly aspirin and the pyrazolones-has not been clearly established. Finally, there is little information on the association between analgesic use and the risk for specific types of renal disease other than interstitial disease (Bennett & DeBroe, 1989; Sandler, 1985). [21, 22,24-28]

In present study before intervention mean serum creatinine levels for diclofenac sodium(group1) users were (1.24) for acetaminophen users were (1.19) and for mefenamic acid drug users were (1.06), 7 days after intervention serum creatinine level was increased in group 1 (1.45) and in group III (1.25) whereas in group 2 it was decreased(1.03). There was lack of data regarding short term dose effects of non-steroidal anti-inflammatory drugs on serum creatinine levels. [22,23]

But there was one study on short term use of NAIDs on renal function during fasting in ramandan conducted by Hussain F Arfaz et al and they concluded that serum creatinine level, blood urea, sodium potassium levels are increased 10 days after giving NSAIDs.[15] There was another case control study done by Dale P Sandler et al, where they suggested that regular use of NSAIDs may increase the risk of chronic renal disease and thus may also increases the mean serum creatinine levels.[1,17]

In present study, after first intervention mean serum creatinine level was increased in group 1 and group 3 and decreased in group 2 but after second intervention mean serum creatinine was increased in group 2 and decreased in group 1 and group 3. Acetaminophen is used in group 2 and another study conducted by Thomas V Pregner et al on risk of kidney failure associated with regular use of acetaminophen, aspirin and other nonsteroidal anti-inflammatory drugs and they concluded that the people who often take acetaminophen or other NSAIDs have an increased risk for end stage renal disease but not those who often take aspirin.[2,4,18,19]

C. Michael fored et al conducted a study on acetaminophen , aspirin and chronic renal failure in their study they concluded that regular use of either acetaminophen, aspirin or both was associated in a dose dependent manner with an increased risk of renal failure. [16,20,21] These all above mentioned studies suggested that, the acetaminophen has an increased risk of altered renal function which supports our result also. In present study also, including all 3 groups an increase in mean serum creatinine level was observed between baseline and second follow-up.

As this study is on short term effects of nonsteroidal anti-inflammatory drugs on serum creatinine levels. So, further study should be done to assess whether, these changes are transient or long lasting.

Conclusion

With regard to acute effects, studies that describe the real magnitude of the problem (incidence) in clinical as well as ambulatory settings are urgently needed, and may be conducted in databases that contain information on routinely measured serum creatinine values.

Further epidemiologic studies are urgently needed not only to assess the role of NSAIDs on renal function, but also to study impaired renal function and ESRF as a multifactorial disease, with several independent or interacting risk factors, leaving behind the monocausal concept of renal impairment. As there is lack of data regarding the short term effects of NSAIDs on creatinine levels in order to rule out renal function. So further studies should be done to come in conclusion that these short term effects were transient or long lasting.

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