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## ORIGINAL RESEARCH

# Low Dose Aspirin Therapy and Renal Function in Elderly Patients: An Institutional Based Study

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## ABSTRACT

**Introduction: The use of aspirin as a pain reliever has been in use for the past 10 years. Its therapeutic use has also been proven to prevent heart attack and other related ailments. Elderly individuals who are at greater risk are mostly prescribed low dose aspirin as an anti-platelet drug to prevent thrombosis.**

**Materials and Methodology: Aspirin drug with a dose of 100 mg/day was administered either through oral route or by a nasogastric tube after having breakfast for a period of 2 weeks and then the drug was stopped, and the investigations were continued for a further 3 weeks. Blood samples and 24hour urine samples were collected every week: before the administration of first dose of aspirin, and at the end of every treatment week, and continued for further 3 consecutive weeks after the discontinuity of aspirin drug. Student's paired t-test is used to check for the weekly changes of all measurements compared to baseline, multivariate analysis of variance with repeated measures (MANOVA) for the overall effect of aspirin drug during the study period.**

**Results: A highly significant association between the variations from baseline to week 2 in both creatinine and Cu acid was recorded ($r = 0.7$, $P < 0.0001$). However, such correlations were not found between changes in values of C-G and Cu acid. The decrease in Ccr was also influenced by low haemoglobin levels ($R2 = 0.075$, $P = 0.006$) and by albumin levels with borderline significance ($R2 = 0.027$, $P = 0.08$).**

**Conclusion: The results of the present study might directly reflect that the low dose aspirin administration in elderly inpatients for a relatively briefer period of time has a significant effect on their renal tubular function; hence a long-term drug intake may have some major harmful effect on renal activity. These findings have received a major necessity to conduct further research in younger and healthier patients and also on long-term usage of aspirin therapy.**

**Keywords: Renal Impairment, Low Dose Aspirin, Geriatric, GFR.**

## INTRODUCTION

Aspirin, also known as acetylsalicylic acid used as pain reliever for more than 10 decades. It is also used to prevent heart attack and stroke and other ailments. In certain conditions when indicated, aspirin is given for a long-term in low dosage.[1] It has been used as an antiplatelet drug to overrule thrombosis and other cardiovascular diseases mostly prescribed for elderly

patients who at greater[2] risk. But the adverse effect of low dose aspirin drug over a period of time lead to renal disturbances. Various studies assessed the effects of low dose aspirin in the elderly and have observed that 1–2 weeks of low dose of aspirin usage of around 75 mg–325 mg/day caused a notable reduction in both creatinine clearance level (CrCl) and uric acid clearance level, along with anincrease in serum creatinine and uric acid levels.[3] It was observed that on withdrawal of usage of aspirin has shown that the uric acid excretion reverts back to normal levels whereas the creatinine clearance levels remain lower. Because of its correlation and findings between the long-term usage of aspirin and renal impairment it requires further research.[4,5] Hence, the present study was conducted to evaluate the effects of long-term low dose of aspirin in a larger population among the elderly patients who are hospitalized in the geriatric ward.

## MATERIALS AND METHODOLOGY

Long-term hospitalized elderly patients with a variety of health conditions, who are in a stable clinical health condition, were recruited for this study after an informed consent and details of the study was explained to both the patients or their guardians. After getting approval from hospital ethical committee individuals with a history of chronic liver/kidney disease, gastrointestinal disorder,peptic disease, gout, hyperuricemia, serum creatinine > 1.5 mg/dl, habit of alcohol consumption, or with the history of use of anticoagulants, aspirin or Non-Steroidal Anti-Inflammatory Drugs were not included in the study. Before the start of the study a controlled healthy diet of about 50–80 g protein and 200 to 300 mg purine daily were started before a week and continued for over a period of 6 weeks. Other medications and their dosage which is taken by the patients such as diuretics remain unchanged. Those patients whose medical condition declined or those who were in a condition to change the medications or diet during the study period were observed and been included in the study until their withdrawal. Aspirin drug with a dose of 100 mg/day was administered either through oral route or by a nasogastric tube after having breakfast for a period of 2 weeks and then the drug was stopped, and the investigate was continued for a further 3 weeks. Blood samples and 24hour urine samples were collected every week: before the administration of first dose of aspirin, and at the end of every treatment week, and continued for further 3 consecutive weeks after the discontinuity of aspirin drug. Most of the patients around 90%had indwelled with bladder catheters or a Penrose device, which allows for accurate urine sample collections, and special attention was given to rest of 10% for accurate urine sample collection. A proper standard method is used to study the serum creatinine, blood urea nitrogen, uric acid and albumin levels. Creatinine levels and uric acid levels in urine were observed by 24hour urine collection for creatininelevel and uric acid clearances (Ccr and Cu acid). Glomerular Filtration Rate (GFR) was calculated using the C-G formula: for example, with the formula (140 years of age) x body weight / serum creatinine (mg/dl) x 72, corrected by x 0.85 for women. [6] Patients were also classified according to their renal failure staging [5,6] before and after aspirin drugadministration.

## STATISTICAL ANALYSIS

Student’s paired t-test is used to check for the weekly changes of all measurements compared to baseline, multivariate analysis of variance with repeated measures (MANOVA) for the overall effect of aspirin drug during the study period, chi-square for measuring the deteriorations in renal failure stages, and Pearson’s correlation coefficient for all data – clinical, laboratory, basal or induced by aspirin. Multivariate regression analyses (forward stepwise) were used to identify demographic, clinical, pharmacological and laboratory data as potentially predisposing factors related to the aspirininduced renal function deterioration (Ccr or C-G, estimated GFR) in the second week of treatment. The basal Ccr and basal estimated

GFR were introduced only at the second step of analysis, after all other background variables. The explained variance percentage is expressed by R2. Significance was considered as $P < 0.05$, two-tailed t test.

## RESULTS

The study group comprised 120 geriatric patients (100 women, 20 men, mean age 85 ± 7 years). Demographic and medical data of the study are presented in Table 1. The distribution of patients according to the severity grade of renal failureis shown in Table 2. Most of the patients were in stages 2-3 (mild-moderate renal failure). Ninety-five patients completed the 5 weeks study, while 25 patients dropped out for a variety of reasons independent to aspirin treatment. Aspirin drug and its dosage is well tolerated by most of the patients. It was recorded that no adverse effects to low dose aspirin drug, such as allergy, asthma, gastrointestinal comp plaints, bleeding, hypertension or acute gout, were observed. The therapeutic effects of aspirin on Ccr and on Cu acid were found to be associated. A highly significant association between the variations from baseline to week 2 in both creatinine and Cu acid was recorded ($r = 0.7$, $P < 0.0001$). However, such correlations were not found between changes in values of C-G and Cu acid.

There are certain factors that may have affected aspirin-induced renal function deterioration were well established by linear multivariate regression analysis. We found that Ccr changes at week 2 were influenced most probably by the basal Ccr. As an inverse proportion, higher the basal Ccr values the deeper is its decrease, both in absolute and relative terms ($R2 = 0.26$, $P < 0.0001$). The decrease in Ccr was also influenced by low haemoglobin levels ($R2 = 0.075$, $P = 0.006$) and by albumin levels with borderline significance ($R2 = 0.027$, $P = 0.08$). These three variables together might explain about the 36% of the changes in Ccr following 2 weeks of aspirin usage. The change in the estimated renal function by C-G was not significantly influenced by any relevant cofactor.

**Table 1: Demographic, clinical and basal laboratory data**

| | |
|---|---|
| **Mean age (yrs)** | 85 ± 7 |
| **Age in range** | 57 – 99 |
| **Females** | 100 |
| **Males** | 20 |
| **Previous cardiac history** | 48 (40%) |
| **Hypertension** | 51 (43%) |
| **Stroke** | 53 (44%) |
| **Diabetes** | 13 (11%) |
| **Diuretic use** | 24 (20%) |
| **Body weight** | 59 ± 12 |
| **Haemoglobin** | 12.8 ± 1.6 |

**Table 2: Distribution of patients according to the stages of renal failure class based on their basal renal function, as determined by measured Ccr or calculated GFR (C-G)**

| Stage (ml/min of GFR) | Ccr (%) | C-G (%) |
|---|---|---|
| **>90** | 25 | 26 |
| **60 – 89** | 42 | 41 |
| **30 – 59** | 41 | 39 |
| **15 – 29** | 12 | 14 |
| **<14** | 0 | 0 |

## DISCUSSION

The present study proves that 2 weeks of low dose aspirin therapy in elderly patients might resulted in a significant decrease in creatinine and uric acid clearances. And this decrease in Ccr and Cu acid affected the majority of patients. In almost about 50% of the decrease in Ccr values is observed in 20% of the study participants. The major finding inthis study was only a very mild decrease in the C-G estimated values. These differences between the measured Ccr and C-G values is indicative of a direct tubular effect of the drug. This ideology is further supported by the small changes in serum uric acid levels when compared with the unexpected higher changes in Cu acid. A relatively marked increase in BUN was found in the second week of aspirin treatment (as compared to the modest changes in serum creatinine and uric acid). A relatable explanation may be a true decrease in BUN clearance or alternatively a variation associated in its tubular handling. Another hypothetical mechanism may be attributed that the aspirin-induced hypovolemia and extracellular volume changes reflected by the significant changes associated with BUN. Therefore, urine output as well as the haemoglobin levels remained stable throughout the study. Although we have not measured the intravascular or extracellular volumes, the large changes associated in both BUN and uric acid which can be better explained by a tubular transport effect than a haemodynamic effect. While changes in Ccr and Cu acid associated well during the aspirin treatment. No correlation was found between them after the drug withdrawal.

The changes associated with the uric acid clearance were attributedto the result of transport of uric acid in the proximal tubuledue to aspirin usage. There are some potentiating factors which are responsible for the harmful effects of low dose aspirin treatment on Ccr (week 2) were found to be lower serum albumin and lower haemoglobin. Hypoalbuminemia may be directly related to increased bioavailability and hence a stronger effect of aspirin on the renal tubules has been documented.[2,5] Hypoalbuminemia and anaemia could also be considered as the non-specific indicators in some of the seriously ill patients[8] within this study participants but we failed to document the straight association of these renal effects of aspirin with co-morbid states or elder age. Interestingly, higher pre-treatment Ccr was associated with a more pronounced decrease in Ccr and there is no satisfactory hypothesis behind this factor which showed a clean contrast with the well-established effects of NSAIDs and anti-inflammatory doses of aspirin.[9]

When there is reported impaired basal renal function, this very low dose aspirin could possibly affect the renal thromboxane/prostacycline which thereby improves glomerular circulation.[10]There is a study on conducted rats following subtotal nephrectomy, where inhibition of thromboxane synthesis decreased the progression of renal impairment which is in support of this hypothesis.,[11] as well as a study that demonstrateda better renal allograft survival in patients treated with low dose aspirin.[12]There are two more studies documented on the effects of low dose aspirin in patients with renal disease[13] and diabetic nephropathy[14]where it was found no significant deleterious effects induced by aspirin on their existing condition.

No study is free from any limitations hence the limitations observed in this study are directly related to its GFR estimations. Based on the American National Kidney Foundation guidelines, the estimates of glomerular function by C-G and MDRD equations are the best overall indices of the level of kidney function. The estimation of GFR by the MDRD formula and the results were almost identical to the results obtained from C-G formula. However, in older patients these methods may usually under or overestimate the GFR values.[15-17]

## CONCLUSION

The results of the present study might directly reflect that the low dose aspirin administration in elderly inpatients for a relatively briefer periodof time has a significant effect on their renal

tubular function; hence a long-term drug intake may have somemajorharmful effect on renalactivity. These findings have received a major necessity to conduct further researchesin younger and healthier patients and also on long-term usage of aspirin therapy.

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