Original Article

Low Dose Aspirin Prophylaxis for Cardiovascular Disease in the Elderly Population: Is it safe for the Kidney?

*Mohammad Imtiaz Masroor**
*Abdurahman Hagi Elmi***
*Ghias ud din Butt****
*Sameeh J Khan*****

**Assistant Professor*
***Postgraduate Resident*
****Professor*
*****Professor Emeritus*

Objectives: To evaluate the effects of Low dose Aspirin (LDA) 75mg/day on renal function and uric acid (UA) handling in elderly patients with normal renal function.

Study Design: Case control study.

Place and Duration: This study was conducted at the Cardiology and Medical clinics of Pakistan Institute of Medical Sciences (PIMS), Islamabad over a period of four months.

Materials and Methods: Sixty elderly patients with the Mean age 58.9±6.82 years and range 50-75 years were divided equally in case and control groups. The case group received LDA 75mg/day for two weeks and then discontinued. The control group did not receive aspirin. Patients were excluded if they had serum creatinine (Scr) more than 1.5mg/dl and glomerular filtration rate (GFR) less than 90ml/min determined by MDRD equation or had a contraindication to aspirin use. Blood samples were tested at base line, at 2 weeks of aspirin therapy, and at 4 weeks (i.e. after 2 weeks of cessation of aspirin) for serum levels of urea, creatinine, uric acid and GFR, estimated by both Cockroft-Gault (CG) and MDRD equation.

Results: The base line renal function in aspirin and control group did not differ. After 2 weeks of aspirin therapy only serum UA increased significantly from base line in aspirin group (33.7%) vs. control group (6.14%), mean change 1.607±1.797 vs. 0.28±1.342, respectively (P=0.008), while serum urea , creatinine and GFR remained unchanged in the two groups. After 2 weeks of cessation of aspirin, serum UA returned to base line value in aspirin group and serum urea, creatinine and GFR did not change from base line in two groups.

Conclusion: Short term low dose aspirin 75mg/day does not affect renal function in elderly patients who have normal renal functions at baseline and does not require renal function monitoring.

Key Word: *Low Dose Aspirin Prophylaxis, Elderly, Renal function*

Address for Correspondence:
Dr. Mohammad Imtiaz Masroor
Assistant Professor,
Department of Nephrology,
Pakistan Institute of Medical Sciences (PIMS), Islamabad
Email: imtiazmasroor@hotmail.com

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the world. National organizations have published guidelines recommending the use of aspirin for secondary and primary prevention of cardiovascular events including coronary artery disease, transient ischemic attack, ischemic stroke and peripheral arterial disease and diabetes mellitus over age 40.[1-5]

The optimal dose for CVD prevention remains uncertain between 75-150mg/day and guidelines do not advocate a particular dose. Meta-analysis of aspirin trials have not shown clear additional benefit of aspirin doses greater than 75mg/day for prevention of cardiovascular events, but risk of gastrointestinal toxicity and bleeding increases with escalating dose.[6]

Aspirin being a member of non steroidal anti-inflammatory drugs, shares its nephrotoxic potential due to cycloxygenase (COX) inhibition, whereby vasodilatory prostaglandin PG I2 and E2 production is suppressed, posing risk of increased toxicity in patients with such risk factors as diabetes mellitus, heart failure, renal dysfunction and elderly. The use of low dose aspirin (LDA) is expected to escalate in view of recent guidelines for prevention of CVD, particularly in older population. The renal effects of LDA in elderly patients have not been widely studied and only limited studies have addressed this issue with conflicting results.[7-12] So further studies are warranted to study the renal effects of LDA. The present study aimed to evaluate the effects of LDA 75mg on renal function and uric acid handling in elderly patients with normal renal functions and the

requirement of routine monitoring of renal functions in this population.

Materials and Methods

This study enrolled patients from the Cardiology and Medical clinics of Pakistan Institute of Medical Sciences (PIMS), Islamabad over a period of 4 months. It included 30 patients aged more than 50 years, with the diagnosis of hypertension, coronary artery disease and diabetes mellitus, who were started on low dose aspirin 75mg daily for either primary or secondary prevention of cardiovascular disease forming the aspirin group designated as case group. Another 30 patients of the similar characteristics who did not receive low dose aspirin served as control groups. Patients were excluded if they had baseline serum creatinine more than 1.5mg/dl or calculated GFR less than 90ml/min by MDRD equation, hyperuricemia, history of active peptic ulcer disease, gastrointestinal bleeding, chronic liver disease, congestive heart failure, and hemorrhagic stroke or if they were receiving anticoagulant, aspirin or non steroidal anti-inflammatory drugs (NSAID). Concomitant medications considered necessary during the study were allowed. On entering the study informed consent and medical history were obtained.

Case group received oral aspirin 75mg/day for two weeks and then discontinued. Patients were again followed up after two weeks of discontinuing the drug. Serum urea, creatinine and uric acid were measured by standard laboratory methods and glomerular filteration rate (GFR) was estimated by both Cockroft-Gault (CG) formula, Creatinine clearance ml/min = [140-age in year x body weight in kg / Scr, mg/dl x 72] x 0.85 if female and by MDRD equation (abbreviated) GFR (ml/min) = 186 x (Scr, mg/dl) $^{-1.154}$ x (age in years) $^{-0.203}$ x (0.74 if female) x (1.210, if African American) at baseline, after the end of two weeks of aspirin administration and two weeks after discontinuation of aspirin in both case and control groups. Patients, who missed follow up were excluded and new patients enrolled to maintain a total of 30 patients in each group. Patients were advised to report any adverse effect related to aspirin therapy.

Statistical Analysis: All data stored and analyzed with SPSS (version 10). All numerical variables, like serum creatinine, serum albumin, serum urea, serum uric acid and GFR, their mean and standard deviation were determined. Students paired t-test was used to compare the results of the case against the control at 5% level of significance.

Results

The study comprised 60 patients, 30 each in non aspirin and aspirin group designated as control and case groups. Male: female ratio 1:1 in each group. Mean age was 58.9± 6.82 and range was 50-75 years. Demographic and medical data of the patients are presented in Table I.

Table: I Demographics and Baseline Characteristics of the Aspirin treated Patients and the controls

Characteristic	Aspirin 75mg/day (n=30) Number (%) or Mean±S Drange	Controls (n=30)	P Value
Male:Female	1:1	1:1	>0.05
Coronary Artery Disease	9(30)	9(30)	>0.05
Hypertension	9(30)	9(30)	>0.05
Diabetes	8(26.7)	8(26.7)	>0.05
Stroke	4(13.3)	4(13.3)	>0.05
Serum Urea (mg/dl)	22.70±8.03	22.20±6.23	>0.05
Serum Creatinine (mg/dl)	0.73±0.091	0.730±0.099	>0.05
Serum Albumin(G/dl)	3.73±0.18	3.83±0.17	>0.05
Serum Uric Acid(mg/dl)	4.76±0.98	4.56±0.92	>0.05
GFR(MDRD) (ml/min)	95.73±18/40	99.20±16.53	>0.05
GFR(CG ml/min)	83.40±10.75	80.35±14.83	>0.05

The baseline laboratory parameters at inclusion are presented in Table II. There were no significant differences in the two groups at base line regarding serum creatinine, serum urea, serum uric acid and GFR. All patients, who completed the study period, were included for analysis. Aspirin was well tolerated. No adverse effects, such as allergy, asthma, gastrointestinal complaints, bleeding were recorded.

Table III shows the changes in serum urea creatinine, uric acid and GFR by CG formula and MDRD equation. After 2 weeks of aspirin therapy, the mean serum creatinine increased 8.5% (mean 0.062±0.2091, p=0.1171) vs. control 2.7% (mean 0.020±0.1064,P=0.3115) which was not significant, p=0.3642.

Table II: Mean Changes from Baseline in Renal Function and Uric Acid at Week 2 (End of Low Dose Aspirin) Mean ± SD Range

Parameter	Aspirin	Control	P Value
Serum Urea (mg/dl)	-0.03±1.1	-0.23±0.72	0.872
Serum Creatinine (mg/dl)	-0.06±0.20	-0.02±0.10	0.364
GFR (MDRD)(ml/min)	0.70±18.2	2.33±15.71	0.391
GFR (CG) (ml/min)	2.30±6.4	-0.30±0.89	0.894
Serum Uric Acid (mg/dl)	-1.60±1.79	0.28±1.34	0.0008

A significant increase in serum uric acid level was noted in aspirin group vs. control from base line to the end of therapy i.e. 33.7% (mean 1.607±1.7973,p=0.000) vs. 6.14% (mean 0.28±1.3420, p=0.2625) respectively P=0.008. There was no significant change in serum urea and GFR estimation with both CG formula and MDRD equation among the aspirin and control groups.

Table III: Mean Changes from Baseline in Renal Function and uric Acid at week 4 (2 weeks after stopping Aspirin) Mean ± SD Range

Parameter	Aspirin	Control	P Value
Serum Urea (mg/dl)	-0.67±0.25	0.43±1.85	0.585
Serum Creatinine (mg/dl)	0.00±0.02	0.007±0.03	0.796
GFR (MDRD)(ml/min)	1.43±17.06	3.00±18.53	0.548
GFR (CG) (ml/min)	0.13±1.85	-0.29±1.07	0.446
Serum Uric Acid (mg/dl)	0.70±0.23	0.11±1.02	0.196

Two weeks following the cessation of aspirin therapy serum uric acid level returned almost to base line values (mean 0.700±0.2246, p=0.099) vs. controls (mean 0.43±1.0258, p=0.5498), P=0.196. Likewise serum urea, creatinine and GFR estimation remained unchanged at the end of aspirin therapy, from the base line among the aspirin and control groups and were not statistically significant.

Discussion

Cardiovascular disease is the leading cause of death in developed countries and the World health organization (WHO) report suggests that the burden of CVD is increasing in developing countries, as well.[13] Low Dose aspirin is widely recommended for prevention of CVD. Because these diseases are more prevalent with increasing age, elderly patients are the major consumers of LDA. Healthy adults have a decline of GFR at an estimated rate of 4.6ml/min/decade in men and by 7.1ml/min/decade in women and the renal blood flow also declines by 10% each decade after 40 years.[14] Age related changes in cardiovascular hemodynamics may also predispose to renal dysfunction in situations like hypovolemia, sepsis, diuretics and NSAID use and congestive heart failure.

Our results indicate that LDA 75mg/day has the potential to cause substantial uric acid retention which was completely reversible after aspirin was discontinued. This finding is in accordance with the previous study in the elderly population, reporting a +4% increase in serum uric acid level and 17% decrease in uric acid clearance, which returned to base line following cessation of the drug.[7] We did not report any change in serum urea level compared to 17% increase in that study which was not explained on basis of hypovolemia. The same authors reported the similar observations in a case control study with use of 100mg aspirin.[8] A similar result of uric acid retention with a 75mg dose of aspirin was noted in the study of Caspi et al.[9] In another study it was found that addition of low dose aspirin to non selective COX2 inhibitor resulted in elevation of serum uric acid level after two weeks of therapy (P=0.01).[15] However in another study with a further smaller dose of 60mg aspirin did not observe decrease in the uric acid clearance after two weeks of therapy, compared to 300mg dose. but the population studied was young healthy adults.[16] Low dose aspirin blocks urate secretion with resultant hyperuricemia, while the high dose aspirin 3-4G/day also blocks reabsorption resulting in a net increase in urate excretion and decrease in serum uric acid.[17] This explains the uric acid retention found in our study and others.

Regarding the renal functions our study showed an 8.5% increase in serum creatinine level at the end of two weeks from base line in aspirin group which was not significant. Similarly the GFR estimation by CG and MDRD equations in both control and aspirin groups at two weeks and four weeks were not different from base line and did not differ in two groups at any level. This is in contradiction to the previous studies reporting deterioration of serum creatinine and creatinine clearance in aspirin treated group (P=0.001 – 0.009) and an increase of serum creatinine by 4% (P=0.05) and a mean decrease in serum creatinine clearance of 19% in 70% of patients, respectively[7]. In this study it was reported that 67% of the patients had some impairment of creatinine clearance even after three weeks of withdrawal of aspirin[7]. These differences with our observations may be due to relative younger age (58.9± 6.82, range 50-75) in our group compared to these studies (81±9, range 56-98). Moreover, more than

two third's of the patients in study of Segal et al were already in stage 2 and 3 kidney disease according to base line values of measured creatinine clearance and GFR estimation by CG formula,[7] while our patients had baseline GFR by CG formula 80.3m;/min and 99.2ml/min and by MDRD formula 83.4ml/min and 95.7 ml/min in control and study groups respectively. Our patients have a mean serum albumin of 3.8±0.1 G/dl compared to 3.0±0.5 G/dl in above noted studies. Hypoalbuminemia may be linked to increase bioavailability, hence a stronger effect of aspirin on the kidney.[18]

Interestingly few other studies support our findings of preservation of renal functions with LDA. It was reported that use of LDA 60mg/day but not 300mg was associated with a stable serum creatinine and creatinine clearance remained unchanged after two weeks of aspirin therapy in healthy young adults and such a dose was recommended for long term use.[16] Two other studies testing impact of low dose aspirin on kidney function in Type 2 Diabetic nephropathy with doses of 1000mg/day and 150mg/day for a period of two months and four weeks respectively, observed no change in GFR from the baseline values.[10,11] The mean age of study population in these two studies was 56±7 years, similar to our patients. In a further study in healthy elderly volunteers with an activated renin angiotensin system from pretreatment with diuretics, who were also being treated with ACE inhibitors, 80mg dose of aspirin did not cause any deterioration in urine flow and GFR compared to placebo.[12]

We did not measure the creatinine clearance and uric acid clearance based on 24 hour urine collection because our patients were outpatients and under or over collection of urine at home could have influenced the results. Based on the American National Kidney Foundation Guidelines the estimates of glomerular function by CG and MDRD equations are the best overall indices of the level of kidney function compared to 24 hour urine collection results for creatinine clearance.[19] We applied both CG and MDRD in our patients at all levels of the study and the results in both equations always correlated.

Our study shows that the use of low dose aspirin 75mg/day in elderly patients with normal renal function, for primary and secondary prevention of cardiovascular disease, on short term basis does not have any significant deleterious effects on renal tubular function. We recommend its use without routine renal function monitoring. Further larger studies in future may resolve these issues for long term use of low dose aspirin in patients with cardiovascular risks.

Conclusion

Short term low dose aspirin 75mg/day does not affect renal function in elderly patients who have normal renal functions at baseline and does not require renal function monitoring.

References

1. Smith SC; AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. Circulation. 2006;113:2363-2372
2. Bassand JP; The task force for the diagnosis and treatment of Non-ST-Segment elevation acute coronary syndromes of the European Society of Cardiology. Guidelines for the diagnosis and treatment of Non-ST-Segment elevation acute coronary syndromes. Eur Heart. 2007;28:1598-1660
3. Coull BM, Williams LS, Goldstein LB et al; Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association. Stroke. 2002;33:1934-1942
4. Ryden L; The task force on diabetes and cardiovascular diseases of the European Society of Cardiology (ESE) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007;28:88-136
5. American Diabetes Association; Aspirin therapy in diabetes. Diabetes Care 2001;23[Suppl 1]:S62-S63
6. Kong DF; Aspirin in cardiovascular disorders- what is the optimum dose? Am J Cardiovasc Drugs. 2004; Vol 4:151-2158
7. Seagal R, Lubart E, Leibovitz A, et al; Early and late renal effects of mini-aspirin in elderly patients. Am J Med 2004; 115:462-6
8. Segal R, Lubart E, Leibovtiz A, Iaina A, Caspi D; Renal effects of low dose aspirin in elderly patients. Isr Med Assoc J 2006;8:670-82
9. Caspi D, Lubart E, Graff E, Habot B, Yaron M Segal R; The effect of mini-dose aspirin on renal function and uric acid handling in elderly patients. Arthiritis Rheum 2000;43:103-8
10. Khajehdehi P, Roozbeh J, Mostafavi H; A Comparative Randomized and Placebo-controlled Short-term Trial of Aspirin and Dipyridamole for Overt Type-2 Diabetic Nephropathy. Scan J Urol Nephrol 2002; 36:145-148
11. Gaede P, Hansen HP, Parving HH, Pedersen O; Impact of low dose acetylsalicylic acid on kidney function in type 2 diabetic patients with elevated urinary albumin excretion rate. Neprhol Dial Transplant 2003; 18:539-42
12. Juhlin T, Jonsson BA, Hoglund P; Renal effects of aspirin are clearly dose-dependent and are of clinical importance from a dose of 160 mg. Eur J Heart Fail 2008; 10:892-8
13. Murray CTC, Loptz AD; Mortality by cause for eight regions of the world: Global burden of disease study. Lancet 1997;349:1269-76
14. Choudhury D, Levi M: Renal function and disease in the aging kidney. In Schrier RW (ed): Diseases of the Kidney, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 2387-2420
15. Pamuk ON, Cakir N; The renal effects of the addition of low dose aspirin to COX-2 selective and no selective anti inflammatory drugs. Clin Rheumatol 2005;25:123-25
16. Worawit L, Nuntana K, Ramjai W, Waraporn S; Effect of Minidose Aspirin on Renal Function and Renal Uric Acid Handling in Healthy Young Adults. JCR 2002;8:299-304
17. Yu TF, Dayton PG, Gutman AB; Mutual suppression of the uricosuric effects of sulfinpyrazone and salicylate: a study in interactions between drugs. J Clin Invest 1963;42:1330-9
18. Silagy CA, McNeil IJ. Donnan GA, Tonkin AM, Worsam B, Clampion K; Adverse effects of low dose aspirin in a healthy elderly population. Clin Pharmacol Ther 1993;54:84-9
19. Levey AS, Coresh J, Balk E, et al; National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Ann Intern Med. 2003;139:137-147