Potential Adverse Effects of Low Dose Aspirin and Diuretic Drug Combination on Kidney Function.

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Abstract

OBJECTIVE: Low dose aspirin and diuretics are commonly co-utilized in patients with cardiovascular diseases. The objective of this study was to investigate the effects of low dose aspirin and diuretic drug combination on renal function.

METHODS: This is a cross-sectional retrospective study. All patients, excluding those on renal dialysis, admitted to the internal department of Al-Watani hospital were included in the study. Medical data were obtained from patients’ medical files. Estimation of creatinine clearance was carried out using Cockcroft-Gault equation. Patients on the target drug combination were compared with patients who were not on the target drug combination. Independent paired T-test and one way ANOVA were used to test for significance among groups. Statistics were carried out using statistical package for social sciences (SPSS) version 13.

RESULTS: Three hundred and forty patients (54.4% men) were included in the study. There were 90 patients on the target drug combination and designated as study group. There were 250 patients, 114 on zero and 136 on only one target medication, in the control group. There was a significant \( P < 0.001 \) difference in the levels of creatinine clearance between the two groups. Patients on the target drug combination had significantly lower creatinine clearance levels than those in the control group. Men in the study group had lower creatinine clearance than men in the control group. Same was found in women. Patients in study group with \( \geq 2 \) chronic diseases had lower creatinine clearance than patients in the control group with \( \geq 2 \) chronic diseases. Same was found in patients with < 2 chronic diseases.

CONCLUSION: Low dose aspirin and diuretic drug combination was associated with significantly low creatinine clearance levels independent of gender or number of chronic diseases. Monitoring kidney function for patients on this drug combination is required.

Key words: Low dose aspirin, diuretics, drug combination, creatinine clearance, chronic diseases.

Short running title: Drug Combination and Kidney Function.
INTRODUCTION

One important concern about chronic use of medications is their adverse effects on kidney function. Such adverse effects could be induced by different types of medications. For example, kidney damage could be induced by non steroidal anti-inflammatory drugs (NSAIDs) when given alone or in combination (1). The expression “triple whammy” has been used recently to describe the nephrotoxic effects of the combinations of NSAIDs with diuretics and / or angiotensin converting enzyme inhibitors (ACE-I) (2). The mechanism(s) underlying the nephrotoxic effect of NSAIDs is believed to be related to the cyclooxygenase inhibition and alteration in renal hemodynamics (3). The mechanisms of diuretics induced kidney damage are not clear. However, it is believed that diuretics reduce plasma volume, renal blood flow and thus could affect the kidney function. Kidney damage could also be induced by the presence of certain types of chronic diseases, mainly diabetes mellitus and hypertension (4, 5).

Aspirin, as one type of NSAIDs, has been reported to induce kidney damage even when given in mini doses for short periods. Short-term low dose aspirin have been shown to affect renal tubular creatinine in the elderly, which may result in a prolonged or permanent deterioration of the renal function (6). It is also suggested that renal functions be closely monitored among elderly patients using low dose aspirin (6). Low dose aspirin is commonly prescribed among patients with cardiovascular diseases as a preventive therapy of thrombosis. Diuretics are also commonly prescribed for patients with cardiovascular diseases. The co-utilization of low dose aspirin and diuretics raises concerns regarding their potential augmented renal effects.
This cross sectional retrospective study was carried out to investigate the potential adverse effect of low dose aspirin and diuretic drug combination on kidney function. The study was carried out by statistically analyzing the levels of serum creatinine and creatinine clearance of patients who were co-utilizing low dose aspirin and diuretics prior to admission compared with those of a control group who were not on the target combination prior to admission.

METHODOLOGY

Study design and population

A cross sectional retrospective design was applied in this study. Approval of the hospital administration and medical ethics committee was obtained before the start of the study. All patients, excluding those on renal dialysis, admitted to the internal ward of Al-Watani governmental hospital during the period of Feb. 2006 – May, 2006 were included in the study. Al-Watani governmental hospital is a medical referral hospital that serves patients in the north Palestine area. Data obtained for each patient included demographic information (age, gender and place of living), co-morbid chronic conditions, number of diagnosis and medications used in the past year. Co-morbid conditions considered in this study were hypertension, diabetes mellitus, cardiac failure and ischemic heart diseases. Collection of data from patients’ medical files was made by a bedside approach. Weight and serum creatinine level of the patients were obtained at admission. Creatinine clearance was used as a measure of kidney function and was estimated using Cockcroft-Gault equation (7). Patients were categorized based on whether they were on the target drug combination (study group) or not (control group). The target combination investigated was a diuretic with low dose aspirin. In this study, a diuretic medication is
defined as a loop diuretic and/or a thiazide. The low dose aspirin is defined as aspirin in a dose range of 75 – 100 mg/daily. Levels of creatinine clearance were compared between these two groups. The data analysis was made after stratification for gender and number of chronic diseases present in patients. Patients who were not on the target drug combination were further classified based on whether they were on zero or one target drug of the studied combination. Levels of creatinine clearance were further analyzed among patients with zero, one or two medications.

**Statistical analysis:**

The data were entered and analyzed using the Statistical Package for Social Sciences (SPSS) software for windows version 13. We conducted the analysis on two groups of patients: study and control groups. Descriptive statistics were shown as means and frequencies with standard deviation. $P$-values < 0.05 were accepted as statistically significant. A 2-tailed independent paired $T$ test was used to test for significant difference between the two groups. One way ANOVA was used to test for significant differences when comparing more than 2 groups. Multiple discriminate analysis was also used to test for significant differences among the groups with different number of target medications. The graphics were carried out using SPSS.

**RESULTS**

A total of 340 patients, 54.4% men, were included in the study. The average age of the total population was 60.4 ± 14.22 years. There were 90 patients (study group) on the target drug combination and 250 patients (control group) on zero or one medication of the studied target combination. The average weight of the total patients was 77.6 ± 17.1
kg. The average weight for the study group was 81± 17 kg while that of the control group was 76.3 ± 17 kg. A 2-tailed independent sample T test indicated that there was no significant difference between the study and control groups in age, gender, number of chronic medications and number of diagnosis (P= 0.076; P= 0.321; P= 0.224; P= 0.057 respectively). However, a 2-tailed independent sample T test indicated a significant difference in serum creatinine and creatinine clearance levels between the two groups (P=0.028; P= 0.0001). Demographic and clinical characteristics of the two groups are shown in table 1.

Important chronic diseases that have been implicated in renal impairment and could influence the interpretation of the results include diabetes mellitus, hypertension, cardiac failure, ischemic heart disease and atherosclerosis. To further confirm the renal effects of the target drug combination, the study population was subdivided into two groups based on the number of target diseases they were diagnosed with. Group number one included all patients with less than 2 target chronic diseases and group number two included all patients with 2 or more chronic diseases. We compared the creatinine clearance levels for the patients in group number one and two stratified with the number of target diseases. As seen in figure 1, the levels of creatinine clearance decrease as the number of target diseases increases. Also, in each group, patients who were on the target drug combination had significantly lower creatinine clearance levels than patients who were not on the target drug combination. For example, men on the 2 target medication had a creatinine clearance of 67.3 mL/min compared with patients on one or zero target medication (92, and 114 mL/min respectively). In women, similar pattern was obtained.
Further analysis of the study population was carried out by dividing the patients who were not on the target drug combination into two subgroups: those on zero target medication, and those on one target medication, either aspirin or a diuretic. The three groups were compared (table 1). Analysis using one way ANOVA indicated significant differences among the three groups in levels of serum creatinine and creatinine clearance ($P < 0.001$). This difference was also statistically significant when using multiple discriminate analysis, with Wilks Lambda test yielding a $P < 0.001$. Patients with zero target medication had the highest creatinine clearance level followed by those on one target medications (112.5 and 92.9 mL/min respectively). The lowest creatinine clearance level was for patients utilizing the 2 target medications (67.3 mL/min). One way ANOVA indicated no significant differences among the three groups in age or number of chronic medications. To exclude gender as a possible factor for the differences, we compared the levels of creatinine clearance among the three groups stratified with gender. In either gender, as the number of target medications increases the level creatinine clearance decreases, more significantly among men. In both genders, those who were on 2 target medications were having significantly lower creatinine clearance than those who were not on any target medication.

**DISCUSSION**

The incidence of kidney diseases, particularly, end stage renal disease (ESRD) is rising worldwide and thus imposing an economical burden on the health system (8-10). In Palestine, kidney diseases are the seventh leading cause of death among people aged 20-59 years (12). Early detection and prevention of kidney diseases is important to reduce
mortality and morbidity. This may be achieved by identifying patients at risk, assessing their renal function, and applying therapeutic strategies using evidence-based medicine.

In this cross sectional retrospective study, 26.5% of the patients were on target drug combination proven to be harmful to the kidney. Although it is possible to think that patients with more medications might be more diseased and thus at a higher baseline risk of renal damage than others, the study results indicated that this was not the case. Statistical analysis indicated that the low creatinine clearance levels among patients utilizing the target drug combination were not due to differences in age, gender or number of chronic diseases. This suggests that the low dose aspirin with diuretics combination is an independent risk factor for renal dysfunction.

Aspirin, even in low doses, can irreversibly inhibit cyclooxygenase, which is the rate-limiting enzyme in the biosynthetic cascade of prostaglandin (PG). Inhibition of PG synthesis is associated with adverse changes in renal function, particularly in electrolyte homeostasis and impaired renal perfusion. The consumption of low dose aspirin, as an antiplatelet, is a very common practice among elderly patients who are already at high risk of developing renal dysfunction due to advanced age and presence of co-morbid condition (12-14). Therefore, in older patients, especial attention should be made to low dose aspirin when diuretics are present as part of the regimen.

Diuretics are also very commonly prescribed for treatment of hypertension and cardiac failure. Patients with such diseases are usually elderly and have multiple co-morbid diseases with polypharmacy. Several reports about augmented drug induced kidney damage by diuretics when given in combination with other agents have been
published \(^{(2, 15)}\). The expression “triple whammy” has been recently used to describe the renal adverse effects of the three medications, diuretics, NSAIDs and ACE-I when given together. The authors concluded that taking two or more of the identified drugs is associated with significant renal impairment and did not correlate with heart failure or other diseases for which the drugs might have been prescribed. Thus, prescribers need to be to balance the demonstrated advantages of these medications against the risk of inducing renal failure when given together. Diuretics seem to induce renal hypofiltration and subsequently increasing the risk of kidney damage when given with cyclo-oxygenase inhibitors, like aspirin.

The results presented here are in agreement with those reported by other investigators \(^{(2, 6, 15)}\). The finding of this study should raise concerns among physicians regarding co-prescribing these drugs. Patients with hypertension and/or cardiac failure who are on low dose aspirin and diuretics need to have their renal functional activity be monitored regularly. Patients receiving a combination of low dose aspirin and a diuretic need to have their kidney function regularly monitored.

**LIMITATION**

This cross sectional retrospective study has several laminations, most importantly is that such type of studies is useful for descriptive purposes, and to identify associations, but not to determine or proof causation. Although multiple logistic regression and multivariate discriminant analysis showed significance among groups, such tests would not prove the hypothesis that low-dose aspirin combined with a diuretic does harm to the kidneys is absolutely true. It is very difficult to confirm that the renal damage was caused by the drug combination and was not present before the utilization of this combination.
We cannot totally exclude the probability that the part of the results was a consequence of sample selection or a normal physiological response. Renal impairment causes fluid retention which necessitates the use of diuretics. The second important limitation is the relatively smaller sample size of patients on the target drug combination. The third limitation is the hospital settings of the project which could interfere with the outcome since hospitalized patients have many variables that affect their health status.

CONCLUSION & RECOMMENDATIONS

The results of this study need to be taken into consideration in reviewing medications for elderly patients with chronic diseases requiring such drug combination. We strongly recommend similar future studies with different design and different renal marker. The use of GFR is highly recommended in such studies since creatinine tubular secretion and thus creatinine clearance is affected by the drug combination. Finally, a randomized prospective study using GFR as a marker will more confidently prove the negative effects of the drug combination on the kidney function.

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Table 1: Demographic and clinical data in patients utilizing zero, one or two target medications. Significant difference among the three groups in serum creatinine and creatinine clearance exist among the three groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of target medication</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Sample</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Number</td>
<td>340</td>
<td>136</td>
<td>114</td>
<td>90</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>60.4± 14.2</td>
<td>58.7± 15.6</td>
<td>61± 14.7</td>
<td>62.3±10.9</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>185 (54.4)</td>
<td>59 (31.9)</td>
<td>73 (39.5)</td>
<td>53 (28.6)</td>
</tr>
<tr>
<td>Serum Cr.(mean ± SD)</td>
<td>1.3± 1.4</td>
<td>0.94± 0.8</td>
<td>1.5± 1.7</td>
<td>1.7± 1.6</td>
</tr>
<tr>
<td>Cr. Clearance(mean ± SD)</td>
<td>94.4± 64.5</td>
<td>114± 81.5</td>
<td>92.9± 50.4</td>
<td>67.3± 36</td>
</tr>
<tr>
<td>Number of diagnosis</td>
<td>2.3± 0.9</td>
<td>2± 0.86</td>
<td>2.4± 0.90</td>
<td>2.4± 0.85</td>
</tr>
<tr>
<td>Number of chronic medications</td>
<td>4.2± 1.5</td>
<td>4.1± 1.4</td>
<td>4.1± 1.7</td>
<td>4.4± 1.5</td>
</tr>
</tbody>
</table>

* Significant difference exists.
Figure 1: Creatinine clearance levels for patients with different number of chronic diseases versus number of target medications. In patients with < 2 chronic diseases, creatinine clearance levels were significantly lower in those who were on the target drug combination. Similar results were found among patients with ≥ chronic disease. In both cases, patients with higher number of chronic diseases have lower creatinine clearance value.
REFERENCES


