SHORT COMMUNICATION

Evaluation of nephrotoxicity by aspirin-clopidogrel combination therapy in patients with acute coronary syndrome

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Abstract: Although aspirin-clopidogrel combination is more useful for acute coronary syndrome (ACS), the renal safety of this combination had not been established. A total 60 patients with ACS were divided into three groups; receiving aspirin, clopidogrel and aspirin-clopidogrel combination. For determination of renal function, serum BUN, creatinine, uric acid, uric acid clearance and GFR were estimated for four months. The study showed that there were no significant ($p>0.05$) variations in the parameters when used the drugs in combination (aspirin-clopidogrel) compared with the drugs given alone.

Keywords: Aspirin-clopidogrel combination, renal function

INTRODUCTION

Clopidogrel-Aspirin combination is taken as maintenance therapy in patients with acute coronary syndrome (ACS) (Hermosillo *et al*., 2008). Dual combination showed synergistic effect resulting in significantly enriched antithrombotic therapeutic value (Bertrand *et al*., 2000). Clopidogrel and aspirin individually failed to counter spontaneous platelet assembly (SPA) while the dual therapy resulted in decline of SPA events (Jagroop *et al*., 2004). Clopidogrel and aspirin individually affect the renal functions (Clive and Stoff, 1984), and combination of the two might cause synergistic adverse effect leading to sever nephrotoxicity. Although, the combination of aspirin and clopidogrel is more useful for cardiovascular diseases (Liao, 2007), the renal safety of this combination had not been established. Objective of the study was to evaluate the effects of aspirin-clopidogrel combination on renal function in patients with ACS.

MATERIALS AND METHODS

A total 60 patients with ACS from Allied Hospital, Faisalabad, Pakistan were enrolled for the study for four months. The study protocols were approved by Ethical Review Committee. Subjects with a history of active peptic disease, gastrointestinal bleeding, chronic liver diseases, gout, hyperuricemia, or recent use of anticoagulants, aspirin or NSAIDs were not included. During the study a controlled diet consisting of 50-80g protein and 200-300mg purine daily was maintained.

The patients were divided in 3 groups (n=20) and treated for 2 weeks.

Group 1: Patients receiving alone aspirin (75mg/day orally)

Group 2: Patients receiving alone clopidogrel (75mg/day orally)

Group 3: Patients receiving aspirin-clopidogrel (75mg+75mg/day orally)

For determination of renal function, serum BUN, creatinine, uric acid, uric acid clearance and GFR were estimated for four weeks by auto-analyzer using biochemical kits. The values were expressed as mean ±SEM and the statistical difference was determined by Tukey's test.

RESULTS

Renal function parameters of ACS patients given aspirin, clopidogrel and aspirin-clopidogrel combination are shown in table 1.

DISCUSSION

The problem of resistance and tolerance to the existing drugs has created a decreased efficacy of these drugs in use. This problem has been tried to be overcome by increasing the drug delivery to the target site by the use of polymers (Khalid *et al.*, 2009) or through nanotechnology (Naz *et al.*, 2012), synthesis of new drugs, either by the use of proteomics (Qadir, 2011), or synthesis from lactic acid bacteria (Masood *et al.*, 2011), or marine microorganisms (Javed *et al.*, 2011). The other way is to use the existing drugs in combination.

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Table 1: Renal function parameters of ACS patients given aspirin, clopidogrel and aspirin-clopidogrel combination

	BUN (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)	Uric acid clearance (ml/min)	GFR (ml/min)
Aspirin	18.6 ± 0.2^{A}	0.74 ± 0.02^{A}	4.63 ± 0.06^{A}	6.82 ± 0.09^{A}	96.96 ± 2.41^{A}
Clopidogrel	17.8 ± 0.3^{B}	0.77 ± 0.02^{B}	4.94 ± 0.10^{B}	6.89 ± 0.14^{B}	97.65 ± 1.81^{A}
Aspirin-Clopidogrel	18.5 ± 0.2^{AB}	0.76 ± 0.02^{AB}	4.84 ± 0.07^{AB}	6.98 ± 0.10^{AB}	96.35 ± 2.23^{A}

Similar letter in a column are statistically non-significant ($p>0.05$)

The major cause of death worldwide is cardiovascular diseases, which are due to antithrombotic stages (Weisman *et al*., 2002). Antiplatelet therapy has immense importance. Clinical trials have evaluated the benefits of aspirin and clopidogrel combination (Mehta *et al*., 2001). The combined therapy is very useful to cure ACS either due to unstable angina (Gaspoz *et al*., 2002) or MI (Squizzato *et al*., 2007). In the present study, when compared with the parameters for the patients given aspirin and clopidogrel alone, there was significant variation ($p<0.05$) except for GFR. This variation has also been observed by Keltai *et al*., (2007). However, there was non-significant difference on renal function associated with clopidogrel-aspirin combination as compared with aspirin and clopidogrel alone.

CONCLUSION

It was concluded that aspirin-clopidogrel combination was not significantly affecting renal functions compared with the renal functions affected by the drugs given alone.

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REFERENCES

Bertrand ME, Rupprecht HJ, Urban P and Gershlick AH (2000). Clinical investigation and reports-double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin. *Circulation-Hagertown.,* **102**(6): 624-629.

Clive DM and Stoff JS (1984). Renal syndromes associated with nonsteroidal anti-inflammatory drugs. *N. Eng. J. Med.,* **310**: 563-572.

Gaspoz JM, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink MM and Goldman L (2002). Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N. Eng. J. Med.,* **346**(23): 1800-1806.

Hermosillo AJ, Spinler SA. Aspirin, clopidogrel and warfarin: Is the combination appropriate and effective or inappropriate and too dangerous? *Ann. Pharmacother.,* **42**(6): 790-805.

Jagroop IA, Matsagas MI, Geroulakos G, Mikhailidis DP. The effect of clopidogrel, aspirin and both antiplatelet drugs on platelet function in patients with peripheral arterial disease. *Platelets,* **15**(2): 117-125.

Javed F, Qadir MI, Janbaz KH and Ali M (2011). Novel drugs from marine microorganisms. *Critical Rev. Micro.,* **37**: 245-249.

Keltai M, Tonelli M, Mann JF, Sitkei E, Lewis BS, Hawken S and Yusuf S (2007). Renal function and outcomes in acute coronary syndrome: Impact of clopidogrel. *Eur. J. Cardiovas. Preven & Rehab.,* **14**(2): 312-318.

Khalid SH, Qadir MI, Massud A, Ali M and Rasool MH (2009) Effect of degree of cross-linking on swelling and drug release behaviour of poly(methyl methacrylate-co-itaconic acid) [P(MMA/IA)] hydrogels for site specific drug delivery. *J. Drug Delvr. Sci. Tech.,* **19**: 413-418.

Liao JK (2007). Secondary prevention of stroke and transient ischemic attack is more platelet inhibition the answer? *Circulation,* **115**(12): 1615-1621.

Masood MI, Qadir MI, Shirazi JH and Khan IU (2011). Beneficial effects of lactic acid bacteria on human beings. *Critical Rev. Micro.,* **37**: 91-98.

Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK and Fox KA (2001). Clopidogrel in Unstable angina to prevent recurrent events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. *Lancet.,* **358**(9281): 527-533.

Naz S, Qadir MI, Ali M and Janbaz KH (2012). Nanotechnology for imaging and drug delivery in cancer. *J. Chem. Soc. Pak.,* **34**: 107-111.

Qadir MI (2011). Qadirvirtide. *Pak. J. Pharm. Sci.,* **24**: 593-595.

Squizzato A, Keller T and Middeldorp S (2007). Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. The Cochrane Library.

Weisman SM and Graham DY (2002). Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Arch. Intern. Med.,* **162**(19): 2197.