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Original Article

Internal Medicine Section

Effect of Silymarin in the Prevention of Cisplatin Nephrotoxicity, a Clinical Trial Study

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ABSTRACT

Background: Reno-protective effect of Silymarin was studied in some studies mainly on rats. In some of these studies, Silymarin was shown to have positive effects on preventing or decreasing severity of Cisplatin nephrotoxicity.

Objective: The aim of this study was to evaluate the protective effect of Silymarin on Cisplatin nephrotoxicity in adult patients with malignancy.

Materials and Methods: In this clinical trial study, 60 patients with malignancy, candidate of Cisplatin treatment were randomly enrolled in two equal groups. In patients of case group, Silymarin tablet 140 mg/bid was administrated seven days before Cisplatin administration together with Cisplatin, and in control group, Cisplatin was prescribed. Blood Urea Nitrogen (BUN) and serum Creatinine (Cr) were checked at the same day and 3 and 7 days after administration of Cisplatin.

Results: Mean age of the patients in case and control groups were 51.1±14.3 y and 51.1±13.7 y respectively (p=0.99). There was no significant difference based on BUN and serum Cr in the beginning of study and three days after administration of Cisplatin in two groups of patients; however, after two weeks, BUN and serum Cr were significantly lower in the case group compared to the control group. Also, in the case group, BUN and serum Cr decreased and in the control group, they increased after two weeks after Cisplatin administration.

Conclusion: This study showed that Silymarin can decrease Cisplatin nephrotoxicity, so because of safety profile and minor adverse effect of Silymarin, we can use it as prophylaxis against Cisplatin nephrotoxicity in various Cisplatin-contained chemotherapy regimens.

Keywords: Malignancy, Prophylaxis, Renal failure

INTRODUCTION

Cisplatin has been used in the treatment of many solid-organ malignancies, including head, neck, lung, breast, testis and ovary cancers [1,2]. Nephrotoxicity is the most important side effects of Cisplatin, but neurotoxicity, myelosupression, ototoxicity and allergic reactions are its other side effects [3]. Renal vasoconstriction, hypomagnesaemia, hypocalcaemia, urinary concentration defect, Fancony-like syndrome and distal RTA, are some common Cisplatin renal side effects [4-7]. In addition, it can cause acute and chronic renal failure. Several days after the prescription of the drug, non-oliguric renal failure may occur. Partial or complete recovery of renal function usually occurs after two to four weeks. Repeated usage of the drug can cause permanent renal failure. High dose and frequent use of this drug increase nephrotoxicity risk. High age, femaleness, baseline renal insufficiency and hypo-Albuminuria are probable risk factors of nephrotoxicity [8,9]. Excretion of the Cisplatin from the body occurs as glomerular filtration and tubular secretion [10]. Cisplatin increased blood level of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha), so damage to kidney occur via its oxidative property and probably with apoptotic pathway [11-13].

Some strategies, such as administration of lower dose of drug, vitamin C, selenium, N-acetylcysteine (NAC) and theophylline have been used for Cisplatin nephrotoxicity prevention [14-17]. Recently, Silymarin have been used in some experimental studies for Cisplatin nephrotoxicity prevention [18,19].

Silybum marianum is a herbal drug containing Silymarin, composed of flavanol lignans silybin (the most biologically active component), Silychristine and Silydianin [20]. Several mechanisms were described for Silymarin effects, including anti-oxidation, inhibition of lipid peroxidation, immunomodulation and anti-inflammatory effects [21-23]. Silymarin 140 mg, two to three times daily, is the recommended dose in adults that has significant anti-inflammatory effect [24].

Both animal and human studies have shown safety profile of Silymarin usage. A few mild adverse effects were reported, including mild allergic reactions or diarrhea in high dose consumption [25]. Because of its safety profile, low cost, and its easy availability, several studies have been performed about the effects of Silymarin on different diseases. For example, Silymarin has been used in a variety of liver diseases, including acute and chronic hepatitis, alcoholic hepatitis, and fatty liver. Hepato-protective property of Silymarin might be due to several mechanism including; inhibition of lipid peroxidation, anti-inflammation, increase of detoxification, anti-oxidation and immmuno-modulatory effects [24].

Renoprotective effect of Silymarin was studied mainly in rats. In some of these studies, Silymarin was shown to have positive effects on preventing or decreasing severity of Cisplatin nephrotoxicity [18,19]. Therefore, the aim of this study was to evaluate the protective effect of Silymarin on Cisplatin nephrotoxicity in adults with malignancy.

MATERIALS AND METHODS

In a clinical trial study, 60 patients with malignancy, candidate of Cisplatin administration were randomly enrolled in two equal groups.

Inclusion criteria were: age more than 18-year-old, normal liver function tests, GFR>60ml/min or serum Cr<2mg/dl.

Exclusion criteria were: use of nephrotoxic drugs as aminoglycoside or intravenous contrast media, new use of angiotensin converting enzyme inhibitors or angiotensin receptors blockers, significant impair cardiac function (dyspnea on exertion> NYHA class two), acute renal failure need to dialysis during the study, uncoopration of patients).

Case group patients, was received Silymarin tablet 140 mg/bid 7 days before Cisplatin administration together with Cisplatin, and in control group, Cisplatin was prescribed. Two groups of patients were matched based on Cisplatin total dose and duration of

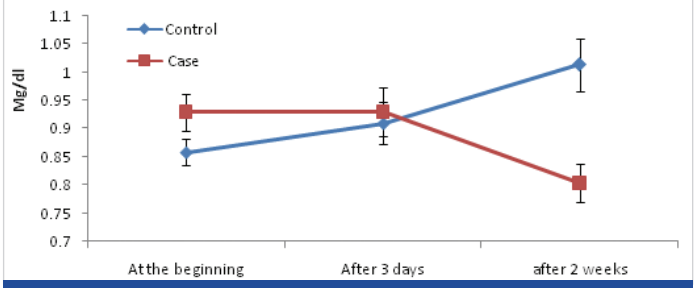
chemotherapy. Blood Urea Nitrogen (BUN), serum Creatinine (Cr), Alanine transaminase (ALT), Aspartate transaminase (AST), Complete Blood Count (CBC) were checked at the same day and 3 and 7 days after administration of Cisplatin. It has been explained to the patients that all information will remain confidential. Besides, written consent forms were filled in by all cases. The results were expressed as mean ± standard deviation (SD) and the analysis was done by SPSS using Chi-square and independent t-test.

RESULTS

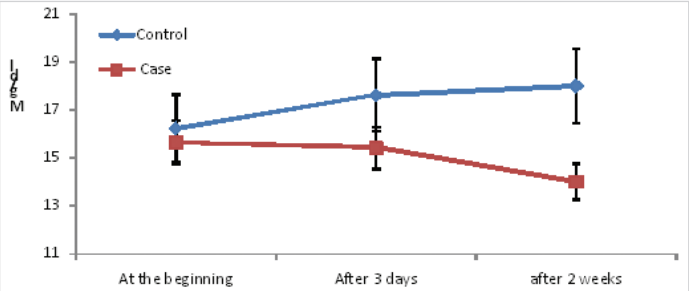
In this study, 60 patients were enrolled in two equal case and control groups. There were 6 (20%) males and 24 (80%) females in case group, whereas there were 11 (37%) and 19 (63%) in control group, respectively. Mean age of the patients in case and control groups were 51.1±14.3 y and 51.1±13.7 y, respectively (p=0.99). As mentioned in [Table/Fig-1], there was no significant difference based on BUN and serum Cr in the beginning of the study and three days after administration of Cisplatin in two groups of patients; however, after two weeks, BUN and serum Cr were significantly lower in the case group compared to the control group. Serum Cr was 0.93±0.18 mg at the beginning of the study and increased up to 0.80±0.19 mg after two weeks in case group (p<0.001), but in the control group, it was 0.86±0.13 mg at the beginning and increased up to 1±0.26 mg after two weeks (p=0.003) [Table/Fig-2]. In addition, in the case group, serum BUN was 15.6±5 mg at the beginning of the study, and decreased to 14±4.2 mg after two weeks (p=0.003), but in the control group, they were 16.2±7.9 mg and 18±8.8 mg at the beginning and two weeks later, respectively (p=0.037) [Table/Fig-3].In summary, in case group, BUN and serum Cr were decreased; however they were increased in control group two weeks after Cisplatin administration.

Variable	Time	Case Group	Control Group	p
Serum Cr(mean±SD)	Before study	0.93±0.18	0.86±0.13	0.086
	After 3 days	0.93±0.24	0.90±0.20	0.74
	After 14 days	0.80±0.19	1±0.26	0.001
BUN(mean±SD)	Before study	15.6±5	16.2±7.9	0.73
	After 3 days	15.4±4.9	17.6±8.4	0.21
	After 14 days	14±4.2	18±8.8	0.027

[Table/Fig-1]: Mean±Standard deviation of Serum Cr and BUN of the patients during the study



[Table/Fig-2]: The mean of serum creatinine during the intervention



[Table/Fig-3]: The mean of blood urea nitrogen during the intervention

DISCUSSION

This study showed that use of low dose and short duration of Silymarin can decrease Cisplatin nephrotoxicity. By our knowledge, no study has been carried out about the effect of Silymarin on Cisplatin nephrotoxicity in human and just a few studies were done on animals on laboratory media. For example Turgut F et al., found that Silymarin can reduce reperfusion injury of kidney by decreasing serum enzymatic activities of superoxide dismutase and glutathione peroxidase and increasing serum and tissue anti-oxidant [18]. Mansour et al., in an animal study concluded that, administration of Silymarin has a protective effect against Cisplatin hepatotoxicity. Possible mechanism of protective effect is its antioxidant property, glutathione levels preservation and lipid peroxidation inhibitor [19]. Karimi et al., also showed a protective effect of Silymarin against Cisplatin nephrotoxicity in a rat model [26]. Posttreatment by Silymarin 2 h after Cisplatin however, significantly increase the body weight returning it to the normal value, yet it is failed in complete protection against the pathological alteration caused by Cisplatin. Pre-treatment with Silymarin 2 h before Cisplatin significantly decreased the histological and ultrastructural changes induced by Cisplatin and appear highly protective [27]. Bokemeyer et al., found also a cytoprotective effect of Silymarin in the rat animal model without a significant inhibition of the anti-tumor activity of Cisplatin [28].

Most of other studies on Silymarin are about its protective effect on liver cells, such as fatty liver disease, cirrhosis, viral or autoimmune hepatitis. For example Féher in a review on experimental and clinical studies concluded that, Silymarin reduce tumor cell proliferation, angiogenesis and insulin resistance. In addition, it has an anti-atherosclerotic effect, and can suppress protein production by tumor necrosis factor-alpha [29]. Zarban in an in vitro study found that powerful antioxidant effect can protect cells against oxidative stress [30]. Pradeep et al., in their study on rats showed that Silymarin exhibits significant hepatoprotective and antioxidant effect against diethylnitrosamine induced hepatocellular damage [31].

Present study has some limitations such as lack of placebo prescription in the control group, small sample size, short term follow-up and fixed dose of Silymarin; so, we offer to do double-blind studies with larger sample size, longer duration of follow-up, and to compare different doses and different durations of Silymarin administration.

CONCLUSION

By our knowledge, this is the first study that showed protective prophylaxis effect of Silymarin on Cisplatin nephrotoxicity in human. Based on the obtained results i.e. safety profile and minor adverse effect of Silymarin, we can use it as prophylaxis and probably for the treatment of Cisplatin nephrotoxicity in various Cisplatin- contained chemotherapy regimen.

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