The Protective Effect of Curcumin on Hepatic Function in Cancer Patients Receiving Taxane-Based Chemotherapy: A Randomized Controlled Clinical Trial

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Abstract

Background: Cancer has become a significant health challenge in recent decades. The Taxane family is one of the popular chemotherapeutic agents which can cause hepatic injury. The present study was conducted with the aim of evaluating the hepato-protective effect of Curcumin on cancer patients treated with Taxanes.

Method: This controlled randomized clinical trial (RCT) has been conducted on 80 patients with either breast, ovary, or pancreas cancer randomly allocated to the intervention group (n = 37) treated with daily 47.5 mg Curcumin extract or the control group (n = 34) treated with placebo. Hepatic indices, including alanine transaminase, aspartate transaminase, total bilirubin, and alkaline phosphatase, were measured and compared at baseline within three and six weeks after the intervention initiation.

Results: The assessments revealed a remarkable increase in all of the indices in both groups by the time ($P < 0.05$), while these increases were remarkably less among the patients treated with curcumin in comparison with placebo treatment ($P < 0.05$). The Mean ± standard deviation was 26.3 ± 8.6 and 29.8 ± 10.5 for aspartate transaminase, 25.5 ± 8.3 and 30.2 ± 10.6 for alanine transaminase, 122.9 ± 18.02 and 126.8 ± 16.9 for alkaline phosphatase, 0.88 ± 0.10 and 0.95 ± 0.12 for bilirubin in the intervention and control groups, respectively.

Conclusion: Based on the current study's findings, Curcumin could act relatively as a hepatoprotective agent against Taxane; however, further studies are strongly recommended to determine the dosage and consumption instruction of this agent for patients with cancer.

Keywords: Taxane, Curcumin, Plant extracts, Neoplasms

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Introduction

Cancer is a life threatening severe event for human beings. In developed countries, it is the first leading cause of mortality, while in developing countries, it is the second. According to the World Health Organization, in 2015, one in six deaths was caused by cancer.[1] In addition to the harmful effects of cancer on patients' health, cancer brings severe pain, affects the quality of life, and imposes a great psychological and economic burden on families.[2]

Chemotherapy is one of the basic approaches used in cancer management. Numerous chemotherapeutic agents, such as Paclitaxel, Docetaxel, Etoposide, Doxorubicin, and Cisplatin, are among the most common regimens used to treat various types of malignancies.[3,4]

These agents have been associated with promising results regarding their excellent potential in trials and improved survival of cancer patients.[5] However, chemotherapy agents have significant and even life threatening side-effects
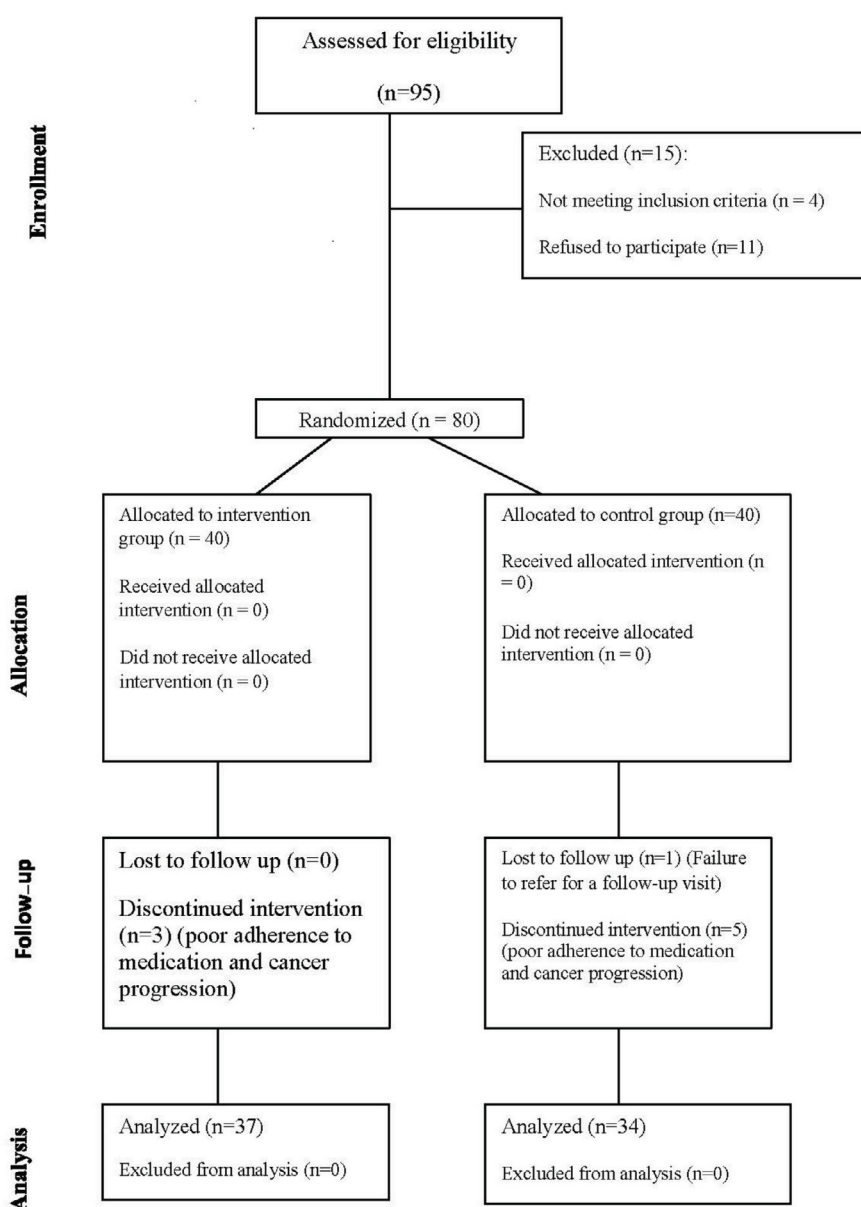

Figure 1. This figure depicts the consort diagram of the studied population.

that should be considered by physicians.[6]

The Taxane family is one of the popular chemotherapeutic agents prescribed for various types of cancer, such as breast, ovarian, pancreatic, and lung cancer. This drug is mostly metabolized in the liver by cytochrome P450 enzymes.[7] Therefore, an increase in hepatic indices due to Taxol treatment is a usual event occurring in 5%-20% of the patients.[8]

Curcuma longa or turmeric, is a perennial herb and a member of the Zingiberoside (ginger) family. This substance has been used as one of the main types of food, especially in Asia, because of its color and taste.[9] Since long ago, curcumin extract has been used for various pathological diseases such as jaundice, menstrual problems, hematuria, bleeding and colic; however, the basis of this prescription has not been well investigated. Curcumin is a compound made of diferuloyl-methane, desmethoxycurcumin, bisdemet hoxycurcumin, volatile oils (turmerone, atlantone, and zingiberene), sugars, proteins, and resins. This water insoluble agent is a lipophilic polyphenol that is nearly stable against the acidic environment of the stomach.[10,11] O-methoxyphenol and the methylene groups are the two most remarkable structural properties of curcumin that mediate its antioxidant activity. Therefore, various medicinal activities of curcumin are used as an antioxidant, anti-inflammatory, anticancer, antidiabetic, and reprotective agent.[12-14]

Curcumin has received more attention recently for its anti-inflammatory and antioxidative properties. As a result, scientists are designing novel studies to investigate the efficacy of curcumin extract.[15] The present study evaluated the effectiveness of curcumin treatment in preventing and reducing the enzyme increase caused by chemotherapy in cancer patients undergoing chemotherapy with Taxol and its derivatives.

Methods and Materials
Study population

This parallel designed randomized clinical trial (RCT) aimed to investigate curcumin's hepatoprotective effects in hospitals affiliated with universities from January to September 2020. This study met the Helsinki declaration criteria and was primarily approved by the Ethics Committee of Isfahan University of Medical Sciences under the ethical code IR.MUI.MED.REC.1398.579. The study protocol was then registered in the Iranian Registry of Clinical Trials and obtained the code IRCT20190918044815N1. In addition, patients were informed about the study process, assured about the confidentiality of their data, and signed a written consent form. Patients aged 30 to 60 years undergoing chemotherapy with Paclitaxel or Docetaxel with liver biomarkers in the normal range, who could prescribe oral medications, were included in this study. Anticoagulant (heparin or warfarin) or antiplatelet (aspirin, clopidogrel, dipyridamole, or ticlopidine), pregnancy or breastfeeding, previous history of liver disorders, and peptic ulcer disease were determined as exclusion criteria. Also, gastrointestinal bleeding and the occurrence of pregnancy during drug use were defined as exclusion criteria.

The sample size was calculated based on the sample size formula to compare means with a confidence level of 95%, test power of 80%, and an effect size of about 0.7. The sample size was calculated based on these parameters as 32 patients in each group, which was considered to be 40 due to the possibility of falling. Cancer patients undergoing chemotherapy were assigned to the study based on convenience sampling. They were randomly divided into two medication groups with Curcumin (intervention group) or placebo (control group). Each patient was assigned to one of the study groups using Random Allocation software, and a specific number was given to them. Physicians and patients were blinded to the type of treatment because the capsules were similar in shape, color, and size and were coded into groups of one or two. The statistician was the only person who was aware of the group type.

Interventions

Patients assigned to the intervention group were treated with capsules containing 47.5 mg of Curcumin once a day (company, country). In

the other group, placebo capsules of similar shape, size, and color produced by the Pharmacy Faculty of Isfahan University of Medical Sciences were administered daily. Patients took the drugs for 60 days, while receiving their chemotherapy regimen and daily routine medications.

Outcomes

The primary result of this intervention was to evaluate the effectiveness of curcumin in preventing the increase of enzymes caused by chemotherapy. Changes in liver indices, including alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (Bili), and alkaline phosphatase (ALP) levels were measured at the beginning and then during three and six weeks after the end of the intervention. The study checklist also included information about age (years), height (cm), weight (kg), body mass index (BMI) (kg/m^2), gender, and grade of cancer (I and II).

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS) software (version 22, IBM Corporation, Armonk, NY, USA) for statistical evaluations. Descriptive data were presented in the form of mean, standard deviation, absolute numbers and percentage. Analyses were performed using a Chi-square or Mann-Whitney test for categorical variables, and a T-test for quantitative variables. Repeated measure ANOVA test was used to evaluate the effect of time and group on primary outcomes. A P value of less than 0.05 was considered as a significant level.

Results

80 cancer patients undergoing Paclitaxel or Docetaxel chemotherapy were included in the present study, of whom four were excluded because they were ineligible, and one refused to participate.

The remaining ones were randomly allocated into either the intervention group (n = 40) or the control group (n = 40). Three patients in the intervention group (one due to inappropriate adherence to the medication and two because of exacerbation of their cancer) and six (one because

of failure to refer for follow-up visits, three because of poor adherence to the medication, and one due to exacerbation of their cancer stage) in the control group withdrew from the study; therefore, 37 patients under Curcumin treatment and 34 patients under placebo treatment fulfilled the study protocol (Figure 1).

Table 1 shows the demographic information of the intervention and the control groups. The two assessed groups were similar in terms of age ($P = 0.231$), gender distribution ($P = 0.530$), cancer stage ($P = 0.173$) and type ($P = 0.620$), marital status ($P = 0.452$), height ($P = 0.620$), weight ($P = 0.720$) and BMI ($P = 0.933$). Changes in liver indices, including AST, ALT, ALP, and bilirubin, are shown in table 2. Assessments showed significant increases in all hepatic indices in both groups ($P < 0.05$), while these increases were significantly lower among patients treated with Curcumin compared with placebo ($P < 0.05$). Hepatic indices increased in three patients of the intervention group and the control group within three weeks after the intervention ($P = 0.910$). Sixth week assessment showed chemotherapy induced enzyme elevation in four Curcumin treated patients (10.81%) versus six patients (17.61%) in the control group ($P = 0.401$). Assessing the increase in the number of patients with arisen hepatic indices revealed significant alteration in the control group ($P = 0.037$) but not in the intervention group ($P = 0.138$).

Discussion

In the current trial, the study patients were similar in terms of demographic and clinical characteristics, which eliminated the potential confounding role of these factors in the obtained results. The results showed that the increase of hepatic indices among the patients who were treated with Curcumin was significantly slower than the control group. Furthermore, Curcumin treatment reduced the rate of enzyme elevation induced by chemotherapy, suggesting that curcumin could be a valuable treatment option for cancer patients treated with Taxanes. It can be concluded from these results that Curcumin's anti-inflammatory and antioxidant properties may

Table 1. Demographic and clinical characteristics of the studied population

Variables	Intervention group (n = 37)	Control group (n = 34)	*P*-value
Age (year)	43.3 ± 9	45.7 ± 7.7	0.231*
Height (cm)	166.8 ± 7.1	165.9 ± 8.5	0.620*
Weight (kg)	63.6 ± 11.9	62.7 ± 9.4	0.720*
Body mass index (kg/m^2)	22.8 ± 3.7	22.7 ± 2.6	0.933*
Cumulative dose of taxane (mg)	859.38 ± 55.45	874.70 ±76.69	0.340**
Female n (%)	35 (94.6)	33 (97.05)	0.530$
Married n (%)	23 (62.2)	24 (70.6)	0.452$
Cancer stage n (%)			
I	28 (75.7)	30 (88.2)	0.173**
II	9 (24.3)	4 (11.8)	
Cancer type n (%)			
Breast	21 (56.75)	23 (67.64)	0.620$
Ovary	13 (35.13)	10 (29.41)	
Pancreas	3 (8.10)	1 (2.94)	

*: Independent T-test; $: Chi-square;**: Mann-Whitney

be responsible for the promising results for use as an adjuvant in chemotherapy.

The use of adjuvants to minimize the adverse effects of chemotherapy agents has become a research topic for scientists working on the survival and rehabilitation of cancer patients. Adjuvant therapy should be readily available and preferably administered orally rather than administered orally, with minimal side-effects and insignificant interactions with chemotherapy agents. Scientists have been faced with a significant challenge in finding an appropriate adjuvant due to the factors mentioned above.[16-18] We assume that curcumin's antioxidant characteristic is related to its hepatoprotection, which has been investigated against the compound, such as carbon tetrachloride (CCl4), galactosamine acetaminophen, alcohol intoxication, and Aspergillus parasiticus. In addition to its antioxidant effects, Curcumin has shown the ability to reduce pro-inflammatory cytokines, which significantly limits liver damage.[15,19] Inhibition of lipid peroxidation was a way to detoxify liver damage associated with acetaminophen. Soni and colleagues stated that the phenolic group in curcumin was responsible for this antioxidant activity.[20] A study of Aspergillus parasiticus showed 90% reductions in aflatoxin production and full reversion of biliary hyperplasia, fatty changes, and necrosis that

developed after aflatoxin exposure.[20] Another characteristic of Curcumin is its ability to increase the excretion of bile salts, bilirubin, and cholesterol. In addition, Curcumin salts can improve the solubility of bile. In agreement with the previous studies, García-Niño has represented that curcumin leads to a decrease in structural alterations of the liver and total bilirubin, which is accompanied by a decrease in ALT, AST, ALP, and an increase in total protein levels as one of the most important manifestations of hepatic activity.[21] On the other hand, the anti-inflammatory capability of Curcumin should not be underestimated. This feature acts in five dimensions; the first is to modulate arachidonic acid metabolism, including cyclooxygenase and lipoxygenase pathways; the second is to increase glutathione levels indirectly, hepatic detoxification from mutagens, and inhibition from nitrosamine formation. Another characteristic of the liver is related to its ability to down regulate proinflammatory cytokines such as interleukin-6 and transforming necrosis factor-alpha. This last one has been demonstrated through limiting the activation of transcription factors that are activated by free radicals as well as scavenging free radicals.[10,22,23] Free radicals are generally produced by the reduction of molecular oxygen, which in turn leads to the formation of superoxide and peroxide. These products can react with metal

Table 2. The hepatic indices change in the studied population (mean ± standard deviation)

Timing	Intervention group (n = 37)	Control group (n = 34)	*P*-value*	*P*-value**
Aspartate transaminase (IU/lit)				
Baseline	23.5 ± 4.5	25.1 ± 4	< 0.001	0.039
3 weeks	25.1 ± 7.5	26.7 ± 6.3		
6 weeks	26.3 ± 8.6	29.8 ± 10.5		
Alanine transaminase (IU/lit)				
Baseline	24.7 ± 4.5	25.7 ± 4.7	< 0.001	0.020
3 weeks	26.4 ± 7.4	26.7 ± 5.9		
6 weeks	25.5 ± 8.3	30.2 ± 10.6		
Alkaline phosphatase (IU/lit)				
Baseline	121.5 ± 17.1	121.52 ± 12.1	0.002	0.031
3 weeks	122.9 ± 18.2	123.9 ± 13.4		
6 weeks	122.9 ± 18.02	126.8 ± 16.9		
Bilirubin (IU/lit)				
Baseline	0.77 ± 0.10	0.75 ± 0.07	< 0.001	0.028
3 weeks	0.87 ± 0.11	0.89 ± 0.10		
6 weeks	0.88 ± 0.10	0.95 ± 0.12		

* Time effect, repeated measure ANOVA test; ** Group effect, repeated measure ANOVA test

ions and generate hydroxyl radicals and, eventually, main cell components, such as proteins and DNA. Polyphenolic compound in Curcumin has the potential to reduce and inhibit this chain activity.[24]

In summary, limited studies have evaluated the hepatoprotection of Curcumin against anticancer agents, particularly Taxane. Most of the literature studies align with present the study; however, Costa and colleagues introduced the first case with Taxol-related toxicity only after Curcumin use as adjuvant therapy. It may have occurred due to Curcumin administration in high doses, which is hepatotoxic in above 8 g/day dose due to inhibition of cytochrome P450 (CYP) 1A2, 2C9, and 3A4 enzymes.[25] In a similar pattern, other studies have shown the antioxidant and anti-inflammatory properties of curcumin as the main basis for this agent's hepatoprotection against hepatotoxic drugs, especially chemotherapy regimens.[26-28]

The small sample population and short follow-up period were the most important limitations of the present study. In addition, further studies considering confounding variables such as lifestyle, dietary, medication adherence, and psychometric indices, which affect the outcomes of chemotherapy and supplemental agents, are strongly recommended.

Conclusion

Based on the findings of the present study, Curcumin could relatively act as a hepatoprotective agent against Taxane; however, further studies are strongly recommended to determine the dosage and consumption instruction of this agent for patients with cancer.

Conflict of Interest

None declared.

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