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Original Article

Evaluating the effect of montelukast tablets on respiratory complications in patients following blunt chest wall trauma: A double-blind, randomized clinical trial

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ABSTRACT

Purpose: Patients with multiple traumas are at high risk of developing respiratory complications, including pneumonia and acute respiratory distress syndrome. Many pulmonary complications are associated with systemic inflammation and pulmonary neutrophilic infiltration. Leukotriene-receptor antagonists are anti-inflammatory and anti-oxidant drugs subsiding airway inflammation. The present study investigates the effectiveness of montelukast in reducing pulmonary complications among trauma patients.

Methods: This randomized, double-blind, placebo-control trial was conducted in patients with multiple blunt traumas and evidence of lung contusion detected via CT scan. We excluded patients if they met at least one of the following conditions: <16 years old, history of cardiopulmonary diseases or positive history of montelukast-induced hypersensitivity reactions. Patients were allocated to the treatment (10 mg of montelukast) or placebo group using permuted block randomization method. The primary measured outcome was the volume of pulmonary contusion at the end of the trial. The secondary outcomes were intensive care unit and hospital length of stay, ventilation days, multi-organ failure, and the in-hospital mortality rate.

Results: In total, 65 eligible patients (treatment = 31, placebo = 34) were included for the final analysis. The treatment group had more pulmonary contusion volume (mean (SD), mm^3) at the right (68726.97 (93656.54) *vs.* 59730.27 (76551)) and the left side (67501.71 (91514) *vs.* 46502.21 (80604.21)), higher initial C-reactive peptide level (12.16 (10.58) *vs.* 10.85 (17.9)) compared to the placebo group, but the differences were not statistically significant ($p > 0.05$). At the end of the study, the mean (SD) of pulmonary contusion volume (mm^3) (right side = 116748.74 (361705.12), left side = 64522.03 (117266.2)) of the treatment group were comparable to that of the placebo group (right side = 40051.26 (64081.56), left side = 25929.12 (47417.13), $p = 0.228$ and 0.082, respectively). Moreover, both groups have statistically similar hospital (mean (SD), days) (10.87 (9.83) *vs.* 13.05 (10.12)) and intensive care unit length of stays (mean (SD), days) (7.16 (8.15) *vs.* 7.82 (7.48)). Of note, the frequency of the in-hospital complications (treatment *vs.* control group) including acute respiratory distress syndrome (12.9% *vs.* 8.8%, $p = 0.71$), pneumonia (19.4% *vs.* 17.6%, $p = 0.85$), multi-organ failure (12.9% *vs.* 17.6%, $p = 0.58$) and the mortality rate (22.6% *vs.* 14.7%, $p = 0.41$) were comparable between the groups.

Conclusion: Administrating montelukast has no preventive or therapeutic effects on lung contusion or its complications.

1. Introduction

Patients with multiple blunt traumas are at risk for a broad spectrum of respiratory complications mainly caused by extensive

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immune system activation, especially neutrophil infiltrations.[1–3] Pneumonia, respiratory failure, acute lung injury, acute respiratory distress syndrome (ARDS), and pulmonary emboli are among such complications that most often lead to morbidity and mortality during the chronic phase following trauma.[4]

Neutrophil infiltration and recruitment are primarily mediated by leukotrienes (inflammatory molecules produced within the leukocytes) and local mast cells via entering the cell membrane's arachidonic acid and the 5-lipoxygenase pathway.[5,6] These mediators, especially leukotriene B4 (LTB4), are the main chemoattractants involved in recruiting neutrophils to damaged tissues, subsequently leading to a broad range of pathophysiological responses.[7–9] Moreover, patients with pulmonary complications such as ARDS have high levels of leukotrienes (especially LTB4) in the bronchoalveolar lavage fluid and blood, which have pro-inflammatory characteristics and cause neutrophil-induced lung damage.[4,10,11] Other leukotrienes, including leukotriene C4 and D4 (LTC4, LTD4), also constrict the pulmonary bronchi.[12,13]

Neutrophils play an essential role in the inflammatory process by producing and releasing inflammatory mediators.[14] Many pulmonary complications, including ARDS, are associated with systemic inflammation and neutrophil infiltration into the lung.[15] These white blood cells secrete proteolytic enzymes and oxidants, which can cause localized pneumonitis, airway remodeling, microvascular damage, and eventually, lung damage. Moreover, Auner et al.[4] and Störmann et al.[3] declared that the long-term presence of neutrophils within the pulmonary parenchyma is associated with poor prognoses.

Numerous experimental animal studies have shown the effect of leukotriene-receptor antagonists on lung complications. However, no such study has been conducted on humans so far. Therefore, the current double-blind, randomized control trial aimed to assess the extent to which montelukast decreases pulmonary complications in human subjects.

2. Methods

2.1. Hypothesis generation

The hypothesis of this study is based on the present knowledge of inflammatory-mediated and neutrophil-induced lung complications following blunt trauma and the chemoattractant effect of leukotrienes on neutrophils. Specifically, we hypothesized that leukotriene receptor antagonists decrease neutrophil infiltration and subsequently attenuate lung injuries.

2.2. Study design

This study was conducted as a randomized, double-blind, placebo-controlled, parallel, and unicentric clinical trial investigating the effect of montelukast administration on pulmonary complications among patients with multiple blunt traumas.

2.3. Sample size determination

We could find no evidence that a study of this nature had been performed on human subjects. Therefore, considering type one error (α) = 0.05, power (1-β) = 0.8, and the case-to-control ratio (κ) = 1, the required sample size was 30 for each of the two study groups.

2.4. Study participants

Patients with multiple blunt traumas who were over 16 years of age and had suffered from pulmonary contusion (as diagnosed by CT images) were included in the present study. Exclusion criteria were as follows: patients who did not meet the inclusion criteria, and have a history of heart or lung diseases or previous hypersensitivity reactions to montelukast. Also, any patient (or their next of kin) who did not sign the written informed consent were excluded.

2.5. Randomization method

We used the permuted block randomization method in the current study. Six different block forms were assigned as follows: (1) AABB, (2) ABAB, (3) ABBA, (4) BBAA, (5) BABA, (6) BAAB. Group A included patients from the treatment group, and group B comprised patients in the control group. The block numbers were extracted from random allocation software until 60 blocks of four letters each were obtained.

2.6. Intervention

Well-trained medical staff or nurses recorded patients' demographic and clinical histories. They also took blood samples for hematologic tests and sputum for sputum cultures. The tests were analyzed at the local health service laboratories following their standard practices. Blood samples were taken for routine lab tests (their results are not shown as being irrelevant to our primary objective) and C-reactive peptides. The recorded clinical features consisted of injury severity score, hospital length of stay (HLOS), intensive care unit length of stay (ICULOS), ventilator-dependent days, and the presence of fever.

After the data mentioned above were collected, patients were randomly assigned into the treatment and control groups using the permuted block randomization method. The treatment (intervention) group received Aerocast® tablets (montelukast Tab. 10 mg, manufactured by the Dr. Abidi Pharmaceutical Company) once a day for up to one week. The control group received a placebo (produced by the Faculty of Pharmacy of Shiraz University of Medical Sciences) once a day for up to one week. The placebo tablets were identical to the montelukast tablets in terms of their shape, size, weight, and color.

Thoracic CT images were taken from all patients upon their arrival at the hospital and again one week later, after the intervention. Images were reviewed by a qualified radiologist who was blind to our experiment and the patients' allocation.

2.7. Studies endpoints and outcomes

After five days of the intervention, a radiologist blind reviewed patients' pre- and post-intervention CT images. Our primary outcome was the effect of montelukast administration on the lung contusion volumes (mm^3) following blunt trauma. The secondary measured outcomes were the in-hospital outcome, HLOS and ICULOS and number of ventilator-dependent days. Moreover, in-hospital development of ARDS, ventilator-associated pneumonia, and multi-organ failure were assessed as well.

2.8. Blinding

Placebo tablets (which had the same color, shape, size, weight, and packaging as the montelukast tablets) were designed by the Faculty of Pharmacy of Shiraz University of Medical Sciences. A unique number was engraved on each package regardless of whether it contained a montelukast or placebo tablet). The number and the corresponding contents (montelukast or placebo) were recorded only by the researcher. The nurses, clinical staff, and patients were blind to each package's contents.

A unique number was assigned to each CT scan image, and any patient identifiers were deleted. Therefore, the radiologist was also blind to our aim and patients' allocation.

2.9. Statistical analysis

Gleaned data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described as mean ± SD, while categorical variables were shown as frequencies (numbers and percentages). We used simple and paired *t*-test and Chi-square test for quantitative and qualitative variables. The $p < 0.05$ was considered statistically significant.

2.10. Ethical considerations

The present study was conducted in line with the declaration of Helsinki and approved by the Ethics Committee with the ethics code of IR. BMSU.REC.1398.112 on July 8, 2019. Moreover, all included participants or their next of kin (if the patients had decreased consciousness) signed written informed consent. The consent procedure was undertaken by skilled clinical staff. The study was registered on the Iranian Registry of Clinical Trials available at https://www.irct.ir on November 8, 2019, with the trial identifier code IRCT20190719044270N1.

3. Results

Seventy-two patients were assess for eligibility and considering the recruitment criteria, 65 of them were included for the study (Fig. 1). Of the 65 patients with multiple blunt chest trauma involved in the present study, 31 were assigned into the treatment group, with a mean age of 43.61 (20.54) years and injury severity score of 17.19 (8.57). On average, 1.29 (2.19) and 1.22 (2.09) rib fractures were documented on patients' left and right sides. Of note, no statistically significant differences were detected considering the demographic and baseline clinical characteristics (all $p > 0.05$). In other words, the two groups presented similar baseline characteristics.

The pulmonary contusion volumes were calculated two times; they were first assessed soon after each patient's arrival at the hospital. The mean contusion volumes were 67501.71 (91514) mm^3 (on the left side) and 68726.97 (93656.54) mm^3 (on the right side). Then, these volumes were re-assessed five days after montelukast administration. The mean (SD) contusion volumes were 64522.03 (117266.2) mm^3 on the left side and 68726.96 (93656.54) mm^3 on the right side.

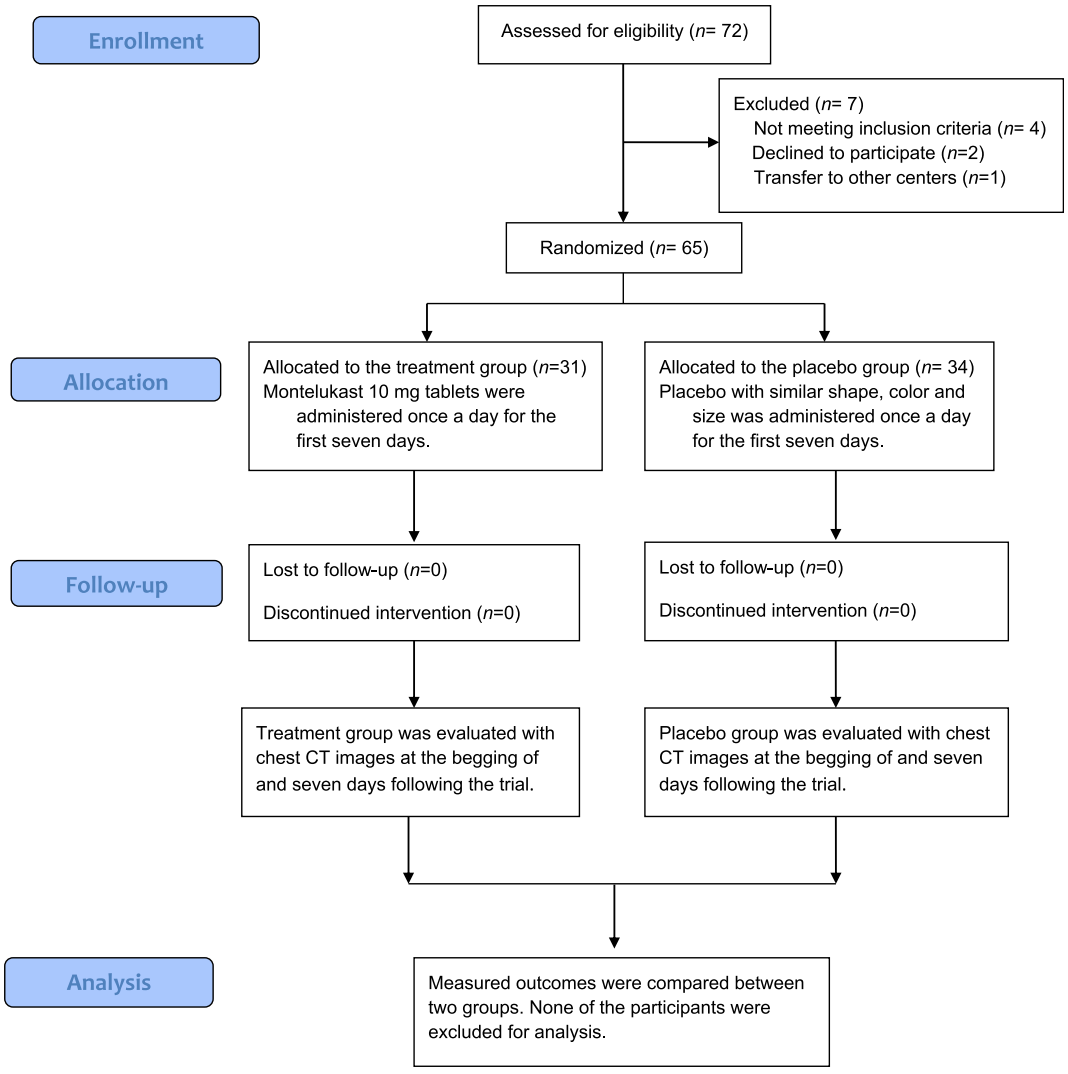

Fig. 1. Consort flow diagram for the monteleukast *vs.* placebo study for mitigating the extend of pulmonary complications.

Table 1
Demographic and clinical characteristics of included patients, mean (SD).

Variables	Treatment group ($n = 31$)	Placebo group ($n = 34$)	p value
Age (years)	43.61 (20.54)	42.06 (17.53)	0.74
ISS	17.19 (8.57)	20.17 (10.27)	0.21
Left rib fracture	1.29 (2.19)	1.74 (2.15)	0.41
Right rib fracture	1.22 (2.09)	1.29 (1.96)	0.89
CRP on arrival	12.16 (10.58)	10.85 (17.87)	0.76
CRP on day 3	25.58 (21.43)	24.61 (21.96)	0.84
HLOS	10.87 (9.83)	13.05 (10.12)	0.38
ICULOS	7.16 (8.15)	7.82 (7.48)	0.734
Ventilator days	3.32 (4.35)	3.62 (5.84)	0.82
Arrival left pulmonary contusion volume (mm^3)	67501.71 (91514.04)	46502.21 (80604.21)	0.32
Arrival right pulmonary contusion volume (mm^3)	68726.97 (93656.54)	59730.27 (76551.74)	0.67
Final left pulmonary contusion volume (mm^3)	64522.03 (117266.17)	25929.12 (47417.13)	0.082
Final right pulmonary contusion volume (mm^3)	116748.74 (361705.12)	40051.26 (64081.56)	0.228

ISS: injury severity score; CRP: C-reactive peptides; HLOS: hospital length of stay; ICULOS: intensive care unit length of stay.

Contrary to our primary hypothesis, there were no statistically significant differences between the treatment and control groups considering pulmonary contusion volume, HLOS, ICULOS, and ventilator days (all $p > 0.05$). The detailed features are summarized in Table 1.

The comparison between the treatment and control groups in terms of ARDS, pneumonia multi-organ failure, fever development, and final outcomes were shown in Table 2. Four (12.9%) patients in the treatment and 3 (8.8%) patients in the control group experienced ARDS complications. Moreover, 13 (41.9%) patients in the treatment group and 15 (44.1%) cases in the control group developed fevers. In contrast with our assumptions, neither complications nor outcomes significantly differed between the treatment and control groups (all $p > 0.05$).

4. Discussion

In the present randomized, double-blind placebo trial, montelukast administration did not affect pulmonary complications and HLOS. This finding is contrary to our primary assumptions and animal studies performed by other researchers.

Pulmonary contusion following trauma increases the HLOS and ICULOS, ventilator days, as well as the incidence of complications such as pneumonia, thus increasing treatment costs. Experimental animal studies suggest that montelukast attenuates pneumonia and acute lung injury, thereby reducing the disease burden and treatment costs. Since montelukast is a safe drug, we investigated its therapeutic effects in pulmonary contusion and its potential to reduce morbidity and mortality among these patients.

Tsai et al.[16] indicated that montelukast, as a cysteinyl leukotriene receptor antagonist, protects asthma patients against lung cancer by showing that montelukast inhibited the growth of the tumor cells in mice. In 2017, Störmann et al.[3] declared that LTB4 overproduction increases pulmonary complications, including pneumonia and ARDS, following blunt trauma. Moreover, patients with lung injuries had significantly higher serum levels of LTB4 than individuals without lung injuries. They also showed that inflammation and changes in the lungs develop three days after the traumatic incident occurs. Their results confirm that LTB4 acts as a biomarker in pulmonary complications and post-traumatic lung contusion.

Table 2
Frequency and prevalence of the complications following blunt trauma between two groups, n (%).

Parameters	Treatment group	Placebo group	p value[a]
ARDS	4 (12.9)	3 (8.8)	0.71
Pneumonia	6 (19.4)	6 (17.6)	0.85
MOF	4 (12.9)	6 (17.6)	0.58
Fever	13 (41.9)	15 (44.1)	0.85
Sputum culture	4 (12.9)	5 (14.7)	0.83
Final outcome			0.41
Alive	24 (77.4)	29 (85.3)	
Dead	7 (22.6)	5 (14.7)	

ARDS: acute respiratory distress syndrome; MOF: multi-organ failure.
[a] The Chi-square test.

However, the treatment and placebo groups in our study did not differ significantly in terms of ARDS or pneumonia frequencies. These findings were inconsistent with those reported in previous studies. Of note, in a survey conducted by Dutton et al.[17], the development of ARDS and pneumonia and the overproduction of LTB4 were attenuated by montelukast administration. In another study, the same researchers found that montelukast did not significantly alleviate fevers in patients in either the experimental or control group. This finding is inconsistent with the other study conducted by Dorreh et al.[18] in which they concluded that montelukast administration could decrease fever and pulmonary infections among children.

In the present study, the volume of damaged lungs measured by CT scan and C-reactive peptides on day 0 and day 3 did not change significantly in either group. This finding contrasts the results reported by Allayee et al.,[15] who showed that montelukast significantly decreased patients' serum C-reactive peptides levels. Rupprecht et al.[19] concluded that montelukast decreases ventilator days and the HLOS. Conversely, we did not detect any statistically significant differences between the two groups—although the mean HLOS was lower in the treatment group than in the placebo group, this difference was not statistically significant.

Montelukast administration did not significantly affect the assessed clinical, radiological outcomes among patients with multiple blunt traumas. Therefore, montelukast does not appear to have a preventive or therapeutic effect on lung contusion or subsequent complications in humans.

Several limitations should be acknowledged. First, our sample size was not large enough; therefore, other studies with larger sample sizes may be needed to confirm or criticize our findings. Second, at the beginning of the study, we decided to assess the serum level of procalcitonin and the serum level of inflammatory cytokines such as interleukin-1, -6, and -8. However, this part is removed due to sanctions, financial burdens, and the kits' unavailability. Third, we could not assess the effect of montelukast administration on the extent of neutrophil infiltration within the alveolar cavity. However, our study has shown that physicians should not generally use montelukast for reducing lung contusions among patients following blunt trauma.

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Ethical statement

The present study was conducted in line with the declaration of Helsinki and approved by the Ethics Committee with the ethics code of IR. BMSU.REC.1398.112 on July 8, 2019. Moreover, all included participants or their next of kin (if the patients had decreased consciousness) signed written informed consent. The consent procedure was undertaken by skilled clinical staff. The study was registered on the Iranian Registry of Clinical Trials available at https://www.irct.ir on November 8, 2019, with the trial identifier code IRCT20190719044270N1.

Author contributions

Soleyman Heydari: Conceptualization, Study Design, contributed data gathering, writing original draft, contributed to the editing the final version of the manuscript. Hadi Khoshmohabat: writing original draft, data analysis, contributed to the editing the final version of the manuscript. Fathollah Ahmadpour: Conceptualization, writing original draft, design data analysis, contributed to the editing the final version of the manuscript. Shahram Paydar: Conceptualization, Study Design, Supervised the study process, data gathering, edit the final version of the manuscript. Ali Taheri Akerdi: Conceptualization, Study Design, Supervised the study process, data gathering, edit the final version of the manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

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