Ann Med Res 2020;27(9):2319-25

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.07.757

Original Article

Effects of Pelargonium sidoides (UMCA ®) on pulmonary contusion from blunt thoracic trauma in rats

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Abstract

Aim: The aim of the present study was to evaluate the effect of Pelargonium sidoides (UMCA ®) which was antibacterial, antiviral, anti-inflammatory and antioxidant, on pulmonary contusion (PC) caused by isolated blunt thoracic trauma (BTT) in an experimental rat model.

Material and Methods: A total of 24 rats were divided into three groups: control group (CG), sham group (SG), and Pelargonium sidoidesgroup (PSG). PC was induced by isolated BTT for all the groups except the control group. Pelargonium sidoidestreatment was performed by gavage for 72 hours to the PSG after truma. Blood and tissue samples were collected from the groups. Malondialdehyde (MDA), superoxide dismutase (SOD),glutathione (GSH) and arterial blood gas parameters were measured. Lung tissue samples were collected for histopathology.

Results: Histopathologically, alveolar congestion, hemorrhage,edema,disruption and neutrophil infiltrationwere significantly higher in SG when compared with CG($p<0.001$, $p=0.007$, $p=0.040$, $p=0.003$, $p=0.001$). Leukocyte infiltration was significantly decreased in PSG when compared with SG ($p=0.025$). Biochemically, MDA level was significantly higher in SG than in CG ($p<0.001$) and GSH level was significantly lower in SG than in CG ($p<0.001$). MDA level was significantly lower in PSG than in SG ($p=0.002$). In blood gas parameters PH and PO2 level was significantly higher in PSG than in SG ($p=0.013$, $p<0.001$) and PCO2 level was significantly lower in PSG than in SG ($p<0.001$).

Conclusion: PS prevents further injury by decreasing leukocyte infiltration,MDAand regulating ventilation -perfusion in lung contusions. PS may have a role in the progression of inflammation but not in preventing the pathologic disruption of pulmonary parenchyma exactly.

Keywords: Pelargonium sidoides; pulmonary contusion; rat

INTRODUCTION

Chest traumas are observed in approximately ¼ of the patients who present to pediatric trauma centers due to blunt and penetrating trauma (1). Thoracic trauma is relatively rare in childhood; however, it is an important cause of mortality (2). The severity of chest traumas varies from minimal conditions such as soft tissue trauma to lung contusion, pneumothorax, hemothorax, and rib fractures, rapidly causing fatality. The most frequent cause of chest injuries in children is blunt trauma (3). In fact, it has been known for some time that lung contusions may occur in children without any broken ribs, as the rib cage is more flexible (4). They may lead to lung pathologies that may particularly require intensive care, have a high mortality rate, and may progress similar to acute respiratory distress syndrome (ARDS) (5). The pathophysiology of pulmonary contusion (PC) includes inflammation, increased alveolocapillary permeability, pulmonary edema, ventilation/perfusion mismatching, increased intrapulmonary shunting, and a loss of compliance (6).

Pelargonium sidoides (UMCA ®) is a South African Geranium (Umkaloabo) (7). This plant, whose homeland is South Africa, has been used there as part of traditional medicine practices for a long time. Pelargonium sidoides (PS) extract has been found to be effective in bronchitis, sinusitis, angina (sore throat), runny nose due to viral infections and pharyngitis (8). PS extract has antiviral properties that strengthen the immune system. Moreover, it has antioxidative properties in addition to its antibacterial effect against some bacteria. Besides, it has been reported that it strengthens the immune system of

Received: 20.07.2020 **Accepted:** 20.08.2020 **Available online:** 18.09.2020
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the organism and has an expectorant effect by increasing the ciliary beat frequency in the respiratory mucosa (8,9). As there is still no widely accepted and standardized pharmacological therapeutic approach to blunt chest trauma-related PC, treatment options are derived from empirical observations and clinical judgments (10). For this reason, there are many experimental studies in the literature about its treatment.

Our assessment of the literature revealed no previous studies of this drug to treat pulmonary contusions. Our hypothesis in this study is that PS, antibacterial, antiviral, anti-inflammatory, antioxidant, has therapeutic effects in experimental pulmonary contusions formed in rats.

MATERIAL and METHODS

All experimental protocols conducted on animals were consistent with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and approved by the Health Sciences University, Ankara Education and Research Hospital Ethics Committee of Animal Care and Usage Rats were kept in separate cages under controlled conditions of 24 ± 1 °C room temperature with 55% ± 5% humidity and 12/12 h light/dark cycle. They were fed with standard pellet and water ad libitum.

Experimental groups

In this study, 24 male Wistar Albino rats weighing 200–250 g were used.They were randomly divided into three groups. Control group (CG) (n=8) (no intervention performed), sham group (SG) (n = 8) (no treatment provided following experimental contusion) and Pelargonium sidoidesgroup (PSG) (n = 8) (30 mg/kg/day PS treatment was performed by gavage for 72 hours)(11).All groups were followed for 72 h and then sacrificed.

Experimental protocols

Trauma was done under anesthesia; they were given intramuscular general anesthesia before the blunt thoracic trauma (BTT) by using 40 mg/kg of ketamine hydrochloride (Ketalar®, Pfizer, Turkey) and 10 mg/kg of xylazine (Rompun®, Bayer, Germany) after 6 h of fasting. BTT was induced using the methods defined by Raghavendran et al (12). A pipe system conveying a specified weight to a piston by free fall was mounted on a stand apparatus preventing the impact of the weight to the head and abdominal space. The piston conveys impact force to the isolated thoracic wall without damage to the sternum and heart .In experimental groups; BTT was induced by dropping a cylindrical metal weight (0.5 kg) through a stainless steel tube onto the right hemithorax. The metal weight was dropped from a specified distance (0.4 m), generating an impact energy of 1.96 J (E = m× g× h).

Histopathological examination

After the tissue samples taken from the right lung of the rats included in the study were fixed in 10% buffered formalin, tissues were followed and embedded in paraffin blocks. 5 mm sections were taken from these tissues and stained with Hematoxylin& Eosin (HE). Stained lung tissues were examined under (with digital camera Nikon DS-Ri2, the brand Nikon EclipseNi) the light microscope via the NIS-Elements 4.50 software. In each lung section, each of the alveolar edema, congestion, interalveolarhemorrhage, alveolar disruption, and leukocyte infiltration was evaluated separately and scored. Leukocyte infiltration was performed by counting extravascular leukocytes at the 400-magnification area. Scoring was as follows: in the absence of leukocytes = 0, less than 10 = 1, between 10 and 45 = 2, and higher than 45 = 3. Other histopathological parameters were semiquantitatively scored as none (0) = 0, mild (<10%) = 1, moderate (10-45%) = 2, severe (>45%) = 3 and in the sections (12,13).

Biochemical analysis

The lung tissues were homogenized in tenfold volume of physiological saline solution by using a homogenizer (Ultra-Turrax T25, IKA; Werke 24,000 r.p.m.; Germany). The homogenate was centrifuged at 10,000 ×g for 1 h to remove debris. Clear upper supernatant was taken, and tissue analyses were carried out in this fraction. All procedures were performed at +4°C throughout the experiments.

Malondialdehyde (MDA) (an important indicator of oxidative stress) levels were measured according to the method used by Jain et al. (14). The principle of the method is based on the spectrophotometric measurement of the color that appeared during thiobarbituric acid's reaction with MDA. Concentrations of thiobarbituric acid-reactive substances were calculated by the absorbance coefficient of malondialdehyde-thiobarbituric acid complex and expressed in nmol/mg. The glutathione (GSH) concentration also was measured using a spectrophotometric method and results expressed in nmol/g (15). After lysing samples and removing the precipitate, disodium hydrogen phosphate and DTNB (5,5'-dithiobis-(2- nitrobenzoic acid)) solution were added, and the color formed was read at 412 nm.Superoxide dismutase (SOD) activity was studied on hemolysates using commercial kits (Randox Laboratories, UK) and results expressed in U/mg (16).

Blood gas analysis

After BTT examination, all of the living rats were administered 100% oxygen for 5 min. Then, a mid-line ventral incision was made to expose the descending aorta, from which 0.5 ml arterial blood was drawn into a heparinized syringe, followed by analysis with an ABL5 blood gas analyzer (Radiometer America, Westlake, OH, USA). During dissection, special attention was paid to the possibility of bone fracture and thoracic and peritoneal bleeding.

Statistical analysis

Statistical analyses were carried out with the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) packaged software. Descriptive statistics were presented with mean ± standard deviation (SD) (min-max) in compliance with the data distribution. The normal distribution of the data

was assessed by the Shapiro-Wilk test. The homogeneity of the variances was tested with Levene's test. One-way analysis of variance (ANOVA) with Tukey's multiple comparison test was used for mean comparisons for normally distributed data. Kruskal-Wallis test followed by the Bonferroni correction of the Mann–Whitney U multiple comparison tests was used for non-normally distributed data. P<0.05 was considered statistically significant.

RESULTS

The mean values of alveolar hemorrhage, alveolar edema, alveolar congestion, alveolar disruption, and leukocyte infiltration were statistically significantly different between the rat groups (p<0.001, p=0.007, p=0.046, p=0.001, p=0.001, Table 1, Figure 1). According to post-hoc test results, the mean values of alveolar hemorrhage, alveolar edema, alveolar congestion, alveolar disruption,

Table 1. Comparison of the mean values of alveolar hemorrhage, alveolar edema, alveolar congestion, alveolar disruption and leukocyte infiltration by rat groups

	CG (1) Mean ± SD (min-max)	SG(2) Mean ± SD (min-ax)	PSG (3) Mean ± SD (min-ax)	P values	Post hoc P values
Alveolar hemorrhage	0.25±0.46 (0-1)	2.25±0.46 (2-3)	1.38±0.51 (1-2)	**<0.001***	1-2 <0.001 1-3 0.058 2-3 0.175
Alveolar edema	0.50±0.53 (0-1)	1.5±0.53 (1-2)	1.25±0.46 (1-2)	**0.007***	1-2 0.007 1-3 0.076 2-3 1.000
Alveolar congestion	0.75±0.46 (0-1)	1.38±0.51 (1-2)	1.13±0.35 (1-2)	**0.046***	1-2 0.040 1-3 0.444 2-3 0.914
Alveolar distruption	0.25±0.46 (0-1)	1.25±0.46 (1-2)	1.13±0.35 (1-2)	**0.001***	1-2 0.003 1-3 0.009 2-3 1.000
Leukocyte infiltration	1.13±0.35 (1-2)	2.25±0.46 (2-3)	1.38±0.51 (1-2)	**0.001***	1-2 0.001 1-3 1.000 2-3 0.025

*Kruskal-Wallis Test

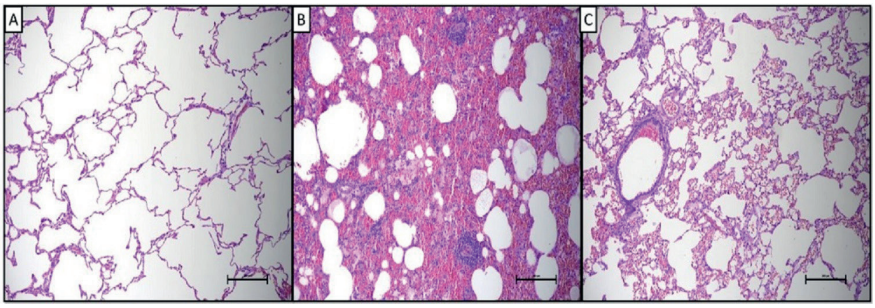

Figure 1. Microscopic images of lung tissues in groups, (A) Normal lung tissue without contusion, (B) The sham group with severe alveolar edema, congestion, intraalveolar hemorrhage, alveolar distruption (alveolar disintegration) and leukocyte infiltration due to contusion (C) The group given Pelargonium Sidoides (UMCA), moderate alveolar edema, congestion, intraalveolar hemorrhage, alveolar distruption (alveolar disruption) and decreased leukocyte infiltration

and leukocyte infiltration were statistically significantly different between CG and SG (p<0.001,p=0.007,p=0.040 ,p=0.003,p=0.001). There was a statistically significant difference between the mean values of alveolar disruption between PSG and CG(p<0.009). The mean values of leukocyte infiltration were statistically significantly different between PSG and SG(p=0.025). There was no statistically significant difference between the other groups (p>0.05).

The mean PO2, PCO2 and PH were statistically significantly different between the rat groups (p<0.001, Table 2, Figure 2). According to post-hoc test results, the mean PO2 of CG was significantly higher than the mean of SG and PSG (p<0.001, p<0.001, respectively). Themean PO2 of PSG was significantly higher than the SG (p<0.001). The meanPCO2 of SG was significantly higher than the CG and PSG (p<0.001, p<0.001, respectively). The mean PCO2 of PSG was significantly higher than the CG (p<0.001, p<0.001, respectively).

The meanPH of CG was significantly higher than the SG and PSG (p<0.001, p<0.001, respectively). The meanPH of PSG was significantly higher than the SG (p=0.013).

Between rat groups, the mean values of MDA and GSH were statistically significantdifferent (p<0.001, p<0.001,Table 3). According to post-hoc test results, the mean MDA of SG was significantly higher than the CG and PSG (p<0.001, p=0.002, respectively). The mean MDA of PSG was significantly higher than CG (p<0.001). The meanGSH of CG was significantly higher than the SG and PSG (p<0.001, p=0.001, respectively). There was no significant difference between the GSH means of PSG and SG (p=0.490). Between the rat groups, there was no significant difference in SOD levels (p=0.269, Table 3, Figure 3).

Table 2. Comparison of PO2, PCO2 and PH means by rat groups

	CG (1) Mean ± SD (min-max)	SG(2) Mean ± SD (min-ax)	PSG (3) Mean ± SD (min-ax)	P values	Post hoc P values
					1-2 <0.001
	81.75±2.65 (79-86)	50.63±2.32 (48-55)	59.75±2.49 (55-63)	**<0.001***	1-3 <0.001
					2-3 <0.001
					1-2 <0.001
	35.25±2.81 (32-39)	59.00±2.44 (56-63)	50.13±2.16 (47-53)	**<0.001***	1-3 <0.001
					2-3 <0.001
					1-2 <0.001
	734.00±2.13 (731-737)	711.75±1.48 (710-714)	714.75±2.05 (711-717)	**<0.001***	1-3 <0.001
					2-3 0.013

*ANOVA with Tukey post hoc test

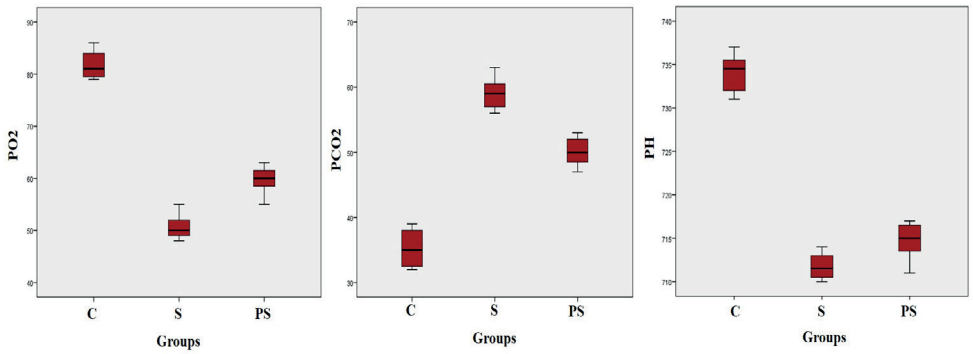

Figure 2. Comparison of PO2, PCO2 and PH means by rat groups on the boxplot graph

Table 3. Comparison of MDA, SOD and GSH means by rat groups

	CG (1) Mean ± SD (min-max)	SG(2) Mean ± SD (min-ax)	PSG (3) Mean ± SD (min-ax)	P values	Post hoc P values
					1-2 <0.001
MDA	18.50±1.19 (17-20)	27.75±1.58 (25-30)	24.25±2.31 (20-27)	**<0.001***	1-3 <0.001
					2-3 0.002
SOD	218.63±17.56 (195-242)	203.50±19.61 (180-238)	212.00±17.14 (188-239)	0.269	-
					1-2 <0.001
GSH	290.75±3.53 (285-296)	274.25±7.38 (260-282)	277.88±7.10 (265-285)	**<0.001***	1-3 0.001
					2-3 0.490

* ANOVA withTukey post hoc test

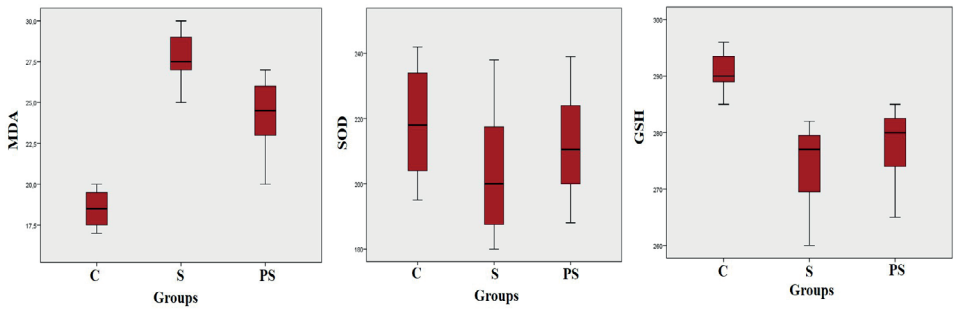

Figure 3. Comparison of MDA, SOD and GSH means by rat groups on the boxplot graph

DISCUSSION

Pulmonary contusion resulting from thoracic injuries is a serious cause of morbidity and mortality (17). Acute respiratory failure or acute respiratory failure syndrome observed in patients as a result of pulmonary contusion is a serious problem. Today, there is no treatment method specified and used other than the symptomatic treatments of clinical pictures such as pneumonia, acute respiratory failure syndrome, and prolonged mechanical ventilation, which arise from pulmonary contusion. This increases the patients' length of stay in the hospital and intensive care units and leads to high hospital costs. Experimental and clinical studies are carried out on pulmonary contusion due to high morbidity and mortality rates and the availability of no obvious treatment methods.We believe the use of medication for lung contusions may prevent major complications and will reduce the need for invasive practices like mechanical ventilation in the intensive care unit. For this purpose, we designed an experimental thoracic trauma model to study traumatic pulmonary contusion. We used a modified model that was defined by Raghavendran et al. (12). We evaluated the effect of trauma on the lung tissue both biochemically and histopathologically.

Therefore, in this study, we researched whether the PS treatment had a protective effect on the pulmonary damage through histopathological and biochemical methods by creating a pulmonary contusion model in rats.

PS has been demonstrated to dispose of among others of antibacterial, antiviral, immunomodulatory, antioxidant, and tissue-protective activity (18). It is an approved medicinal product in more than 50 countries for the treatment of airway infections such as acute bronchitis, common cold, and sinusitis (19,20). However, there are no studies on pulmonary contusion in the literature.

The effects of PC depend on the size of the injury. Trauma leads to injury in the pulmonary vasculature, alveolar hemorrhage develops, then inflammation and interstitial edema develop in the surrounding tissue, and the gas transfer in bronchioles and alveoli is impaired. Thus, hypoxemia and hypercarbia develop (21). In a study conducted by Turut et al., when trauma groups and the control group were compared, PO2 and PH values decreased and PCO2 levels increased. (10) Our study is also compatible with the literature; PaO2 and PH decreased and PCO2 increased in SG. While an increase was observed in PaO2 and PH values in PSG compared to SG, there was a decrease in PCO2. Since quick clinical worsening may happen in these patients, all the patients should be monitored closely in the early period.

After BTT, cytokines, reactive oxygen species (ROS), and proteolytic enzymes are released by activated macrophages and leukocytes. As a result, pulmonary alveolar-capillary membrane permeability and microvascular leakage increases, and apoptosis is inevitable (22). Various and numerous free oxygen radicals and proteolyticandlipolytic enzymes cause cellular breakdown (23). Enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) come into action to prevent the destruction caused by these free oxygen radicals. GSH is a tripeptide found in high concentrations both in the cytosol and in alveolar in the lung (24). It is also one of the most significant antioxidant molecules (25). The lung contusion models in rats demonstrated that MDA levels increase in lung tissue as a final product of cellular membrane lipids' peroxidation (10). Başaran et al. found that the MDA levels were significantly higher and SOD, GSH levels were significantly lower in the contusion group than other groups (24). In the study conducted by Turut et al., when the trauma group and the control group were compared, the MDA level increased while the SOD level decreased in the trauma group (10). In our study, the MDA level in SG increased compared to CG, and no statistically significant difference was detected between the groups in terms of the SOD levels, unlike the literature. On the other hand, SOD levels were lower numerically in SG than CG and PSG, but this difference was not found statistically significant. We think that this situation may be due to the sample size. It can be said as a limitation of our study. The GSH level decreased significantly in SG compared to CG. In PSG, when compared to SG, the MDA levels decreased significantly whereas no statistically significant difference was found in the SOD and GSH levels. Therefore, it has been observed that PS has some healing effect on the oxidative damage in the lung tissue by reducing MDA.

When PC was evaluated histopathologically, alveolar hemorrhage, interstitial edema, leukocyte infiltration, alveolar disruption, and alveolar congestion were found in many studies in the literature (10,26,27). Our study is compatible with the literature, and the parameters mentioned in the contusion group increased (Figure 1B). In the PSG, a statistically significant decrease was observed in the leukocyte infiltration. A numerical decrease was observed in alveolar hemorrhage, interstitial edema, alveolar disruption, and alveolar congestion; however, no statistically significant difference was detected (Figure 1C).

CONCLUSION

It was observed in our study that PS regulated ventilation perfusion and reduced leukocyte infiltration and MDA. In most of the experimental studies, antioxidant drugs significantly decreases the oxidave markers but not impact on histopathologic findings.In this case, from a biochemical and histopathological point of view, we can say that it does not heal the damaged lung tissue completely; however, it helps to recover. PS may be considered as an option in organizing ventilation perfusion in pulmonary contusion after thoracic trauma and in helping parenchymal healing. Doubtlessly, there is a need for many more studies to be able to mention about the efficiency of PS.

Acknowledgements: We thanks to Dr. YasinKenesarı, Department of Biochemistry (Sungurlu Training and Research Hospital,Corum,Turkey.) for his assistance with biochemically analysis.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Health Sciences University, Ankara Training and Research Hospital (0061).

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