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RESEARCH ARTICLE

EFFECT OF LOW ENERGY LASER ON INFLAMMATORY MARKERS AND WEANING IN PROLONGED MECHANICALLY VENTILATED PATIENTS

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ABSTRACT

Background: Mechanical ventilation is a life support treatment. Prolonged mechanical ventilation, defined as ventilation for 21 or more consecutive days with medical support.It has been shown to have significant effects on lung levels of inflammatory cells and soluble mediators. Low level laser therapy has become one of the most commonly used protocols in various physical therapy sub-specialties and cases. It has biostimulative and tissue regenerative properties as well as antimicrobial, anti-inflammatory and analgesic effects.

Objective: This study was conducted to investigate the therapeutic effectiveness of non-surgical gallium arsenide laser (905 nm) as an anti-inflammatory agent and its reflection on mechanical ventilator parameters, as well as inflammatory markers, in prolonged mechanically ventilated patients.

Subjects and methods: this randomized control study was conducted on thirty prolonged mechanically ventilated patients. Their age ranges from 50 to 60 years old of both sexes. Patients were randomly assigned into two groups. Group 1 (study group): fifteen patients (9males, 6 females), were enrolled into low energy gallium arsenide laser therapy daily for ten days in addition to the routine ICU physical therapy program, while, Group 2 (control group):fifteen patients (10 males,5 females), received routine ICU physical therapy program only. CRP, ESR, ventilator PEEPand ventilator pressure support were measured in both groups.

Results: There was a statistical significant decrease in the mean values of CRPand ventilator pressure support of the study group compared with that of the control group post treatment and there was no statistical significant difference in the mean values of ESR and PEEP between the study and control groups post treatment.

Conclusion: low energy laser therapy (905 nm) has a significant effect on inflammatory markers and weaning in prolonged mechanically ventilated patients.

INTRODUCTION

Mechanical ventilation use is common and accounts, particularly in urban hospitals and with elderly patients. (Wunsch et al, 2010). Prolonged mechanical ventilation (PMV), defined as ventilation for 21 or more consecutive days with medical support. (Rose et al, 2015). It is estimated that, between 4 and 13% of mechanically ventilated patients require prolonged mechanical ventilation (PMV), resulting in between 7250 and 11,400 patients according to Medicare database in US undergoing prolonged mechanical ventilation (PMV) at any one time.

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This produced much effort directed to create predictors to be used in the selection of patients for transfer to a long-term acute care facility (Lone and Walsh, 2011). Prolonged dependence on mechanical ventilation after critical illness is an emerging public health challenge; however, long-term outcomes are incompletely understood. Quality improvement and cost-reduction strategies targeted at these patients are warranted.(Damuth et al, 2015). Low level laser therapy has become one of the most commonly used protocols in various physical therapy sub-specialties and cases. It is an excellent addition to the rehabilitation professional's therapeutic intervention, when combined with sound examination and treatment skills (Gallo and Wijting, 2006). Laser therapy has bio-stimulative and tissue regenerative properties as well as antimicrobial, anti-inflammatory and analgesic effects.

Studies on its effects in respiratory disease have shown improvement in gas exchange and pulmonary function, as well as enhanced immunity and other health benefits (Rindge, 2005). Inflammation is the body's immune response to harmful stimuli, possibly in response to an infection. Since inflammation is believed to have a role in the pathogenesis of cardiopulmonary events, measurement of markers of inflammation has been proposed as a method to improve the prediction of the risk of these events. The erythrocyte sedimentation rate (ESR) is the time-honoured test used to measure the acute phase response to investigate the presence of infection or inflammation and to monitor the disease activity. Measuring of specific proteins such as C- reactive protein (CRP) are more recent innovations. For general screening purposes and monitoring of inflammatory disorders the erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) is convenient and readily available in the laboratory. (Teixeira et al, 2014). Our study was conducted to investigate the therapeutic effectiveness of non-surgical gallium arsenide laser (905 nm) as an anti-inflammatory agent and its reflection on mechanical ventilator parameters, as well as inflammatory markers, in prolonged mechanically ventilated patients.

RESEARCH DESIGN AND METHODS

Patients

Thirty prolonged mechanically ventilated patients participated in this study; they were selected from the two floors of critical care unit of Cairo University hospitals (Kasr el Einy hospitals), through a period of ten months (from May 2016 to February 2017). They were from 50 to 60 years old of both sexes, all of them were treated by mechanical ventilator more than 21 days for at least 6 hours per day, All of them had mild to moderate survival prediction and their sequential organ failure assessments (SOFA) score from 6 ± 2 points, and all of them were under medical control, continuous intensive care monitoring and receiving their prescribed medications. The exclusion criteria wereuntreated pneumothorax, major cardiovascular problems, recent open heart surgery, rib cage deformity, uncontrolled hypertension or diabetes mellitus, rib cage burns or malignancies, epileptic patients, rheumatoid arthritis, autoimmune diseases, active bleeding conditions, severe acid-base disturbances, dermatitis and very sensitive skin.

This study was a controlled trial with randomization. Patients were randomly assigned into two groups equal in number, A and B. Group A (study group): the first fifteen patients, admitted to the second floor of the critical care unit with all the inclusive criteria, were enrolled into low energy gallium arsenide laser therapy daily for ten days in addition to the routine ICU physical therapy program, while, Group B (control group): the first fifteen patients, admitted to the first floor of the critical care unit with all the inclusive criteria, received routine ICU physical therapy program only.

Procedure

Evaluated parameters

C-reactive protein (CRP) using the Siemens IMMULITE® 1000 system, to interpret the results of the venous blood samples takenfrom each patient in both groups two times: one in day 21 of mechanically ventilation and the other in day 31.

Erythrocyte sedimentation rate (ESR): Using the Westergren method in both groups at day 21 and 31 of starting to mechanically ventilate the patient to detect the changes in ESR. The blood samples was drawn into a Westergren-Katz tube to the 200 mm mark, and then the tube was placed in a rack in a strictly vertical position for 1 hour at room temperature.

The parameters and output of the Engström Pro Carestation ventilator: Were recorded to give us an indication about the readiness for the start of weaning and liberation from the mechanical ventilation. Peak expiratory end pressure (PEEP) and pressure support were recorded for each subject in both groups of this study for the comparison. The study protocol and design was approved by the Ethical Committee for Scientific Researches of Faculty of Physical Therapy, Cairo University, before the study was started. All participants or their relatives were signed a consent form that they agreed and well informed about each step of the study before starting the program.The thirty patients in this study received full assessment, proper medical and ICU physical therapy treatment. Only the fifteen patients included in the study group (G1) were treated with low energy gallium arsenide laser (905 nm) daily for ten consecutive days.

Treatment protocol

Study group (G1): Fifteen patients were subjected to low energy gallium arsenide laser therapy using Phyaction CL apparatus with output of 5–20 mW, wavelength of 905 nm, frequency of 5000 Hz, peak intensity of 13.5 mW, six points application, 3 points each side, and 1 minute duration for each point, delivering a laser dose of $4.86\, J/cm^2$ each session, daily for ten days in addition to routine intensive care physical therapy program, (Mohamed and Shaban, 2014). The application was done using the Mono probe P43 which was put ina direct contact with 90 degrees angle to the skin surface (Stux and Pomeranz, 2012).

Control group (G2): Fifteen patients were treated by routine intensive care physical therapy program only (modified postural drainage, airway clearance associated techniques, lung expansion techniques, breathing exercises combined with upper limbs patterns, circulatory exercises for lower limbs) twice per day, from day twenty one of intubation and mechanical ventilation until day thirty one.

Statistical analysis: Descriptive statistics and t-test was conducted for comparison of the mean age, between both groups. T test was conducted for comparison of pre and post treatment mean values of CRP, ESR, ventilator PEEP and ventilator pressure support between study and control groups. Paired t test was conducted for comparison between pre and post treatment mean values of CRP, ESR, ventilator PEEP and ventilator pressure support, in each group. The level of significance for all statistical tests was set at $p < 0.05$. All statistical measures were performed through the statistical package for social studies (SPSS) version 19 for windows.

RESULTS

The study involved thirty patients; the mean ± SD age of the study group was 56.93 ± 2.89 years, while the mean ± SD age was 55.4 ± 2.94 years as shown in table (1).Comparing the general characteristics of the patients of both groups revealed that there was no statistical significance difference between both groups in the mean age ($p = 0.16$).

The sex distribution of the study group revealed that there were 9 males with reported percentage of 60% and 6 females with reported percentage of 40%. The sex distribution of the control group revealed that there were 10 males with reported percentage of 67% and 5 females with reported percentage of 33%. The mean ± SD CRP pre-treatment of the study group was 106.51 ± 16.83 mg/l and that of the control group was 109.32 ± 17.93 mg/l. The mean difference between both groups was -2.81 mg/l. There was no statistical significant difference in the mean values of CRP between the study and control groups pre-treatment (p = 0.66), but there was a statistical significant decrease in the mean values of CRP of the study group compared with that of the control group post treatment (p = 0.03). The mean ± SD CRP post treatment of the study group was 85.66 ± 12.2 mg/l and that of the control group was 95.6 ± 12.4 mg/l. The mean difference between both groups was -9.94 mg/l. (Table 2).

Table 1. Descriptive statistics and t-test for comparing the mean age between study and control groups

	Study group $\overline{X}$ ±SD	Control group $\overline{X}$ ±SD	MD	t- value	p-value	Sig
Age (years)	56.93 ± 2.89	55.4 ± 2.94	1.53	1.43	0.16	NS

Table 2. T test for comparison of pre and post treatment mean values of CRP and ESR between the study and control groups

	Study group $\overline{X}$ ±SD	Control group $\overline{X}$ ±SD	MD	t- value	p-value	Sig
CRP (mg/l): Pre	106.51 ± 16.83	109.32 ± 17.93	-2.81	-0.44	0.66	NS
CRP (mg/l): Post	85.66 ± 12.2	95.6 ± 12.4	-9.94	-2.21	0.03	S
ESR (mm/h): Pre	76.2 ± 12.57	73.86 ± 13.33	2.34	0.49	0.62	NS
ESR (mm/h): Post	79.6 ± 10.32	85.66 ± 14.25	-6.06	-1.33	0.19	NS

Table 3. T test for comparison of pre and post treatment mean values of Ventilator PEEP and ventilator pressure support between the study and control groups

	Study group $\overline{X}$ ±SD	Control group $\overline{X}$ ±SD	MD	t- value	p-value	Sig
Ventilator PEEP (cmH2O): Pre	5.8 ± 1.2	5.26 ± 1.22	0.54	1.2	0.23	NS
Ventilator PEEP (cmH2O): Post	5.06 ± 1.43	5.33 ± 0.72	-0.27	-0.64	0.52	NS
Ventilator pressure support (cmH2O): Pre	23.66 ± 6.98	24 ± 9.33	-0.34	-0.11	0.91	NS
Ventilator pressure support (cmH2O): Post	12.33 ± 6.79	22.2 ± 6.36	-9.87	-4.1	0.0001	S

The mean ± SD ESR pre-treatment of the study group was 76.2 ± 12.57 mm/h and that of the control group was 73.86 ± 13.33 mm/h. The mean difference between both groups was 2.34 mm/h. There was nostatistical significant difference in the mean values of ESR between the study and control groups pre-treatment (p = 0.62) and post treatment (p = 0.19).The mean ± SD ESR post treatment of the study group was 79.6 ± 10.32 mm/h and that of the control group was 85.66 ± 14.25 mm/h. The mean difference between both groups was -6.06 mm/h. (Table 2). The mean ± SD ventilator PEEP pre-treatment of the study group was 5.8 ± 1.2 cmH2O and that of the control group was 5.26 ± 1.22 cmH2O. The mean difference between both groups was 0.54 cmH2O. There was no statistical significant difference in the mean values of ventilator PEEP between the study and control groups pre-treatment (p = 0.23) and post treatment (p = 0.52).The mean ± SD ventilator PEEP post-treatment of the study group was 5.06 ± 1.43 cmH2O and that of the control group was 5.33 ± 0.72 cmH2O. The mean difference between both groups was -0.27 cmH2O (Table 3). The mean ± SD ventilator pressure support pre-treatment of the study group was 23.66 ± 6.98 cmH2O and that of the control group was 24 ± 9.33 cmH2O.

DISCUSSION

The mean difference between both groups was -0.34 cmH2O. There was nostatistical significant difference in the mean values of ventilator pressure support between the study and control groups pre-treatment (p = 0.91), but there was astatistical significant decrease in the mean values of ventilator pressure support of the study group compared with that of the control group post treatment (p = 0.0001). The mean ± SD ventilator pressure support post-treatment of the study group was 12.33 ± 6.79 cmH2O and that of the control group was 22.2 ± 6.36 cmH2O. The mean difference between both groups was -9.87 cmH2O (Table 3). Low energy laser apparatus became available to use in many intensive care units and physiotherapy clinics for everyday application.However, the mechanisms underlying the anti-inflammatory and analgesic properties of low-level laser remain unknown (Oton-Leite *et al.,* 2015). Our study aimed to investigate the therapeutic effectiveness of non-surgical low energy laser as an anti-inflammatory agent on mechanical ventilator parameters and weaning, as well as inflammatory markers, in prolonged mechanically ventilated patients. It was performed on thirty prolonged mechanically ventilated patients admitted in the critical care unit of Cairo University hospitals, for ten days each patient, through the period from May 2016 to February 2017. Their mean age was 56.17 ± 2.92 and all of them had SOFA score equals 6 ± 2. Measurements were applied to all the patients pre and post study regarding CRP, ESR, ventilator PEEP and pressure support.The result of our study revealed statistical significant improvement in CRP and ventilator pressure support, However, There was no statistical improvement in ESR and ventilator PEEP, and this can be explained as: The low energy laser therapy (LELT) was believed to be a strong anti-inflammatory agent. It helps in the reduction of the local and systemic inflammation through decreasing the levels of pro-inflammatory cytokines' secretion (such as: IL-1beta, IL-6 and TNF-alpha) and collagen deposition, (Oliveira *et al.,* 2014). That's supposed to be the cause of the significant decrease of the levels of CRP released from the liver. The result of the study agreed with the result of Tanzila, (2017), who examined the influence of low level laser therapy (LLLT) on CRP in the recovery process of 20 normal subjects undergo high intensity interval training for 30 minutes. LLLT was found to prevent the occurrence of inflammation due to damage by suppressing the secretion of pro-inflammatory cytokines (especially IL-6 which is the determinant of the concentration of CRP in the circulation) if done before the training session, and then the CRP value was back down. Also the result by Leal *et al.,* (2010), who evaluated the use of LLLT irradiation in preventing the development of skeletal muscle fatigue and biochemical markers of inflammation in nine healthy male volleyball players performing resistive elbow flexion exercises in 75% of their maximum voluntary contraction. Their CRP levels were significantly lower after the exercises when compared to their pre-exercise values, after receiving the LLLT treatment. This was related to the LLLT capability of reducing reactive oxygen species release and creatine phosphokinase activity, in addition to improving the mitochondrial function and reversing the induced dysfunctional state. The erythrocyte sedimentation rate (ESR) is another marker of the acute inflammatory phase reaction. During an inflammatory reaction, the sedimentation rate is affected by increasing concentrations of fibrinogen, the main clotting protein, and alpha globulins. The test mainly measures the plasma viscosity by assessing the tendency for red blood cells to aggregate and fall through the variably viscous plasma.The ESR slow response to the acute inflammatory reaction leads to false negatives early in an inflammatory process. Normalization of an elevated erythrocyte sedimentation rate once an immunoglobulin response has occurred may take weeks to months, (Osei-Bimpong *et al.,* 2007). This can explain the ESR result in our study as there was no significant drop in ESR values in the study group, although the drop happened in the other inflammatory marker tested, the C-reactive protein.

A study was done by Pasternak *et al.,* (2014) who evaluated the influence of low level laser radiation from an multi-wave locked system (MLS) of two near infra-red wavelengths (wavelength: 808 nm in continuous emission and 905 nm in pulsed emission, power density: 195 mWcm(-2) and 230 mW cm(-2)) on the erythrocyte membrane of two human blood samples and the post-irradiation ESR. Dose-dependent changes in erythrocyte membrane fluidity were induced by near-infrared laser radiation. Slight changes in the ESR were noted with the 905 nm laser (similar to the one used in our study).
They concluded that the 808 nm laser radiation in continuous emission influenced the structure and function of the human erythrocyte membrane more than the 905 nm laser in pulsed emission resulting in a change in erythrocytes membrane fluidity. This can support the results of our study as the 905 nm was proved to make slight changes on the erythrocyte membrane if done directly to the blood in a test tube, so laser will have a weaker effect on the membrane if applied over the skin of the chest as in our study. There are several remarkable influences that have been observed with low energy photo-modulative lasers, one of them was observed by (Saleh, 2014), who stated that low level laser stimulation (wavelength: 635 nm for 30 seconds each point/ 2 sessions per day) of two acupuncture points bilaterally decreases but does not prevent hemodynamic stress-response (heart rate and blood pressure) to endo-tracheal intubation, and also have a significant effect on decreasing the time of initial ventilation on maximum mechanical ventilation parameters (100% FiO2 and high pressure support), encouraging early start for weaning and discontinuation of the ventilatory support, just the same as the results of our study. This effect can be explained as the low level laser contributes to the body in the same way as acupuncture point stimulation. Regarding traditional Chinese medicine, illness arises as a block or imbalance in energy flow along one or more meridians occurs. Acupuncture restores energy flow well-being and balance.Vital energy is claimed to modify spiritual, emotional, mental, as well as physical health (Benor, 2002). During pressure support ventilation, the value of pressure support is set at a level of 15 to 20 cm H2O above PEEP and then adjusted to maintain a respiratory rate of fewer than 25 to 35 breaths per minute. To wean the patient from high pressure ventilatory support, the level of pressure support is reduced twice daily in steps of 2 to 4 cm H2O and is increased only if the patient develops respiratory distress (Buckley and Gillham, 2007).

Only one study (other than our study) discussed the effect of low energy laser on ventilator PEEP in mechanically ventilated patients. No previous studies worked on the effect of low energy laser on prolonged mechanically ventilated patients Szabari *et al.,* (2016) found that low energy laser (810 nm, 5 J/cm2, during the first 30 min of the MV) had a significant effect on decreasing the need for high ventilator PEEP and improved the outcomes in patients requiring mechanical ventilation in the operating room or in the intensive care unit. This observation contrasted with the result of our study as there was no significant difference in ventilator PEEP in prolonged mechanical ventilator patients. This could be due to the excellent positive effect of chest physiotherapy done to both control and study group on improving compliance of the respiratory system and oxygenation of patients under prolonged mechanical ventilation, as stated by Santos *et al.,* (2009), or due to using different wave length and treatment dose of low energy laser which can affect thechanges in the ventilator parameters.

Conclusion

Low energy laser therapy (905 nm) can significantly decrease the C-reactive proteinand improve weaning outcomes in prolonged mechanically ventilated patients.

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