Tele-management of home isolated COVID-19 patients via oxygen therapy with non-invasive positive pressure ventilation and physical therapy techniques: A randomized clinical trial

Aya Sedky Adly, Mahmoud Sedky Adly, Afnan Sedky Adly

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Aya Sedky Adly[1, 2] MSc, PhD; Mahmoud Sedky Adly[3, 4] DDS, MSc, HDD; Afnan Sedky Adly[5, 6] MSc

[1]Faculty of Computers and Artificial Intelligence Helwan University Cairo EG
[2]Faculty of Engineering and Technology Badr University in Cairo (BUC) Cairo EG
[3]Faculty of Oral and Dental Medicine Cairo University Cairo EG
[4]Royal College of Surgeons of Edinburgh Scotland GB
[5]Faculty of Physical Therapy Cardiovascular-Respiratory Disorders and Geriatrics, Laser Applications in Physical Medicine Cairo University Cairo EG
[6]Faculty of Physical Therapy Internal Medicine Beni-Suef University Beni-Suef EG

Corresponding Author:
Aya Sedky Adly MSc, PhD
Faculty of Computers and Artificial Intelligence
Helwan University
Cairo, Egypt
Cairo
EG

Abstract

Background: With the enlarging stress on hospitals caused by the novel coronavirus disease 2019 (Covid-19) pandemic, the need for home based solutions has become a necessity to support these overwhelmed hospitals.

Objective: To compare two non-pharmacological treatment methods for home isolated Covid-19 patients using a new developed tele-management healthcare system.

Methods: In this randomized, single-blinded, clinical trial, adults with stage one pneumonia caused by SARS-CoV-2 infection were treated. Group (A) receiving oxygen therapy with Bi-level positive airway pressure ventilation (BiPAP), and group (B) receiving osteopathic manipulative respiratory and physical therapy techniques. Arterial blood gases, potential of hydrogen (pH), vital signs, and chest CT scan, were utilized for follow up and for assessment of the course and duration of recovery.

Results: Analysis of the results showed a significant difference between the two groups ($p<0.05$) with group (A) showing lower recovery period than group (B) (14.9±1.7 days and 23.9±2.3 days respectively). Significant differences were also observed between base line and final readings in all of the outcome measures in both groups ($p<0.05$). The post-treatment patient satisfaction with our proposed tele-management healthcare system showed positive response for most of the patients.

Conclusions: It was found that home oxygen therapy with BiPAP can be an effective prophylactic treatment approach to avoid exacerbation of the early stage COVID-19 pneumonia. Tele-management healthcare systems are promising methods to help pandemic-related shortage of hospital beds as they showed reasonable effectiveness and reliability in monitoring and management of the early stage COVID-19 pneumonia patients. Clinical Trial: ClinicalTrials.gov, identifier:NCT04368923.

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Abstract

Background

With the enlarging stress on hospitals caused by the novel coronavirus disease 2019 (Covid-19) pandemic, the need for home based solutions has become a necessity to support these overwhelmed hospitals.

Objective

To compare two non-pharmacological respiratory treatment methods for home isolated Covid-19 patients using a new developed tele-management healthcare system.

Methods

In this randomized, single-blinded, clinical trial, sixty patients with stage one pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were treated. Group (A) receiving oxygen therapy with Bi-level positive airway pressure ventilation (BiPAP), and group (B) receiving osteopathic manipulative respiratory and physical therapy techniques. Arterial blood gases of partial pressure of oxygen (PaO2) and partial pressure of carbon dioxide (PaCo2), potential of hydrogen (pH), vital signs (temperature, respiratory rate, oxygen saturation, heart rate and blood pressure), and chest CT scan, were utilized for follow up and for assessment of the course and duration of recovery.

Results

Analysis of the results showed a significant difference between the two groups ($p<0.05$) with group (A) showing shorter recovery period than group (B) (14.9±1.7 days and 23.9±2.3 days respectively). Significant differences were also observed between base line and final readings in all of the outcome measures in both groups ($p<0.05$). The post-treatment patient satisfaction with our proposed tele-management healthcare system showed positive response for most of the patients in both groups.

Conclusion

It was found that home oxygen therapy with BiPAP can be a more effective prophylactic treatment approach than osteopathic manipulative respiratory and physical therapy techniques as it can impede exacerbation of the early stage COVID-19 pneumonia. Tele-management healthcare systems are promising methods to help pandemic-related shortage of hospital beds as they showed reasonable effectiveness and reliability in monitoring and management of the early stage COVID-19 pneumonia

patients.

Trial Registry

ClinicalTrials.gov, identifier: NCT04368923.

Keywords: Telemedicine; oxygen therapy; non-invasive positive airway pressure; BiPAP; osteopathic medicine; physical therapy.

Introduction

COVID-19 has become a globally pandemic disease resulting in a gross dramatic impact on hospitals and healthcare systems worldwide [1-3]. Therefore, home isolation may become the only available option for many cases in most of the countries [4-6]. A worldwide shortage of medical devices, protective equipment and pharmacological treatment with an enlarging stress on hospitals resources have led to an obvious drop in the performance of the majority of frontline healthcare workers [7-9]. Therefore, introducing tele-management approaches have become a necessity for coping with the exponential increase in number of cases infected by SARS-CoV-2 virus [10-12].

Home care isolation can be considered for COVID-19 patients with mild illness when inpatient isolation is unavailable. However, advices and precautions regarding respiratory hygiene, environmental ventilation, hand hygiene, shared spaces confinement, and optimal nutritional intake should be followed as a part of the management process [13, 14].

Current evidence suggests that the application of non-invasive Bi-level positive airway pressure can reduce pulmonary complications and raise the pulmonary oxygen pressure by activation of the collapsing alveoli and reduction of the degree of shunt [15]. However, non-invasive positive pressure ventilation is usually considered the last line of treatment in the initial management of hospitalized COVID-19 patients as it is considered an aerosol generating procedure that can increase the risk of infection in a hospital setting [16, 17]. Yet, there is an apparent lack of research on its impact on COVID-19 patients, despite of the evidence from several previous studies that confirm its beneficial effects in different types of pneumonia.

The COVID-19 disease progression and complications was found to be unpredictable. Patients' deterioration was commonly reported to be a result of pulmonary edema due to interstitial fluid accumulation from pulmonary capillaries leakage, cytokines storm, and microvascular thrombosis. Pulmonary edema is characterized by acute-onset and rapid progression [18]. Non-invasive Bi-level positive airway pressure can be capable of preventing this deterioration if applied at an early stage by impeding the consequent pulmonary edema via positive pressure [19].

Recent studies indicate that osteopathic manipulative respiratory and physical therapy techniques can improve the pulmonary functions in both chronic and acute pulmonary conditions [20]. These techniques are directed toward the respiratory musculoskeletal components inducing thoracic

pressure changes, which are essential for effective respiratory process. Additionally, these techniques have enormous potential in alleviation of pulmonary diseases complications through increasing mobility of chest wall muscles and diaphragm [21].

Osteopathic manipulative respiratory and physical therapy techniques have an important advantage of being costless with the ability to be modified for home or self-application which can reduce the risk of infection and overcome the shortage in pharmacological treatment and medical devices [22].

In the presence of COVID-19, Tele-practice has become a transformation in physical therapy as communication-based platforms beyond telerehabilitation, telemedicine, telemanipulation, and telehealth are utilized to advance remote access to therapy [23].

Recent evidence supported the use of self-directed web-based physical therapy over traditional outpatient physical therapy. Moreover, home web-based physical therapy has gained interest owing to its interactive nature which can offer a more formal sense and direction for the patients [24]. Consequently, self-directed web-based physical therapy with remote supervision can be considered as an effective solution to offset the risks associated with infection in COVID-19 patients without compromising the outcomes [24-26].

Non-invasive ventilation (NIV) has been utilized as an adjunct to physical therapy in patients with respiratory diseases. Several studies have demonstrated the positive effects of NIV and supplemental oxygen as adjuncts to physical therapy [27]. NIV was found to unload the ventilatory muscles and reverse the neural drive of fatigue through reducing the number of needed patient efforts as well as reducing the muscle load during an assisted interactive breath [28]. Thus, investigation of these two treatment modalities in COVID-19 patients would be of great challenge.

Evidence has reported that real time telemedicine in patients with acute respiratory infections showed similar rates of clinical management when compared to traditionally treated patients. Furthermore, the frequency of follow-up visits in real time telemedicine was higher than traditional follow-up visits [29].

Preliminary regulations have been issued on controlling infection, diagnosis and monitoring of COVID-19 patients, while there is limited and unclear guidance on the effect of starting management of these patients from the early stage [30-33]. The divergence in the majority of researches in this topic and the need for high quality randomized clinical trials that follow the recommended standards of reporting were the reasons for implementing this study.

Advances in the information and communication technologies (ICTs) have converted the world to a confined village. Remarkable challenges have been addressed by ICTs in various health care sectors [34-36].

Thus, the aim of the study was to assess and compare the oxygen therapy with non-invasive positive pressure ventilation versus osteopathic manipulative respiratory and physical therapy techniques using tele-management healthcare system, which was applied to home isolated COVID-19 patients. In addition to assessment of patient satisfaction with the COVID-19 tele-management

system.

Methods

This single blinded, parallel-group, randomized, clinical trial was approved by the Research Ethics Committee of Cairo University and was registered in Clinicaltrials.gov database with a registration identifier (NCT04368923). The study was performed in accordance with the ethical standards of the Declaration of Helsinki and following CONSORT guidelines for conducting randomized trials (figure 1).

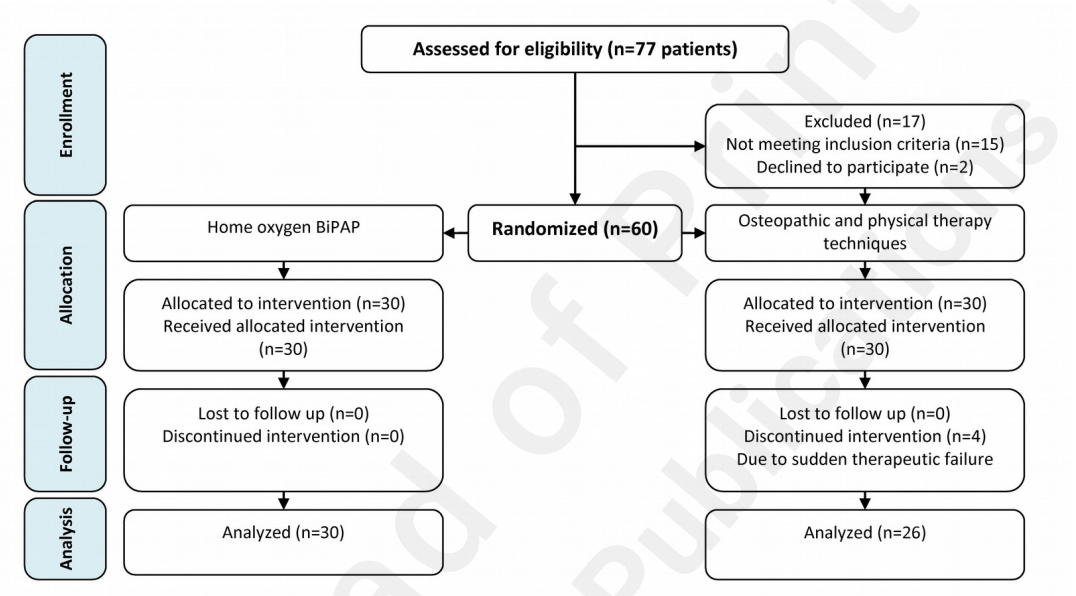

Figure 1: CONSORT flow diagram.

Patients' recruitment was realized through social media using the snowball subject recruitment technique.

Initially the distribution of the invitations were targeted to patients who were meeting the eligibility criteria through the health professionals' social media networks. Then those patients were requested to distribute invitations through their individual social media networks; no restrictions were made on what social media platform they should use. The participants were obligated to send the required data online in order to be assessed for eligibility.

Sixty patients were randomized into two groups in 1:1 allocation ratio using computer generated randomization software (Statsdirect version 2.7.7, StatsDirect Ltd., Cheshire, UK) which was done by a blinded and independent co-worker, to ensure that the randomization process was totally concealed. This study was conducted on a sample of home isolated patients. Informed consent was obtained from all patients who were included in this study.

The inclusion criteria were as follows:

- American Society of Anesthesiologists (ASA) Class I patients before the onset of COVID-19.
- History of close contact to a confirmed positive COVID-19 case as defined by the national guidelines for public health units [37].
- SARS-CoV-2 infection determined by chest CT scan showing typical ground glass abnormalities findings with the onset of two or more clinical symptoms and the patient condition classified as stage one pneumonia according to Feng Pan et al [38].
- Patients indicated for home isolation.

Patients were excluded if they demonstrated characteristics of:

- Not being consistent with home isolation regimen including nutritional supplementation, proper hygiene and room aeration.
- Inability to deal with the tele-management system provided to the patient.
- Therapeutic failure during the study which is characterized by a severe respiratory distress with respiratory rate that is more than or equal thirty breaths per minute, an oxygen saturation (SpO2) less than or equal 93% in room air, and requirement of intubation/mechanical ventilation [39].

Patients were divided equally into two groups with 30 patients in each group. The first received oxygen therapy with Bi-level positive airway pressure ventilation (group A), and the second received osteopathic manipulative respiratory and physical therapy techniques (group B). All patients received the same nutritional supplementation including multivitamins and adequate supportive diet.

Regarding group (A), an oxygen concentrator with BiPAP was given by facemask (AirFit F30 model) with inspiratory positive airway pressure/expiratory positive airway pressure (IPAP/EPAP) 15/3 (cm H_2O) and 5 L/min O2 flow by oxygen flow meter, which was done for 4 hours/day [40]. Procedures of oxygen administration were constant in all patients, clarified in details and accomplished via a supervised teleconference for each patient by an expert respiratory physiotherapist.

On the other hand, group (B) received osteopathic manipulative respiratory and physical therapy techniques in the form of:

- Prone reverse trendlenburg positioning for 4 hours/day [41, 42].
- Cephalic traction with approximate duration of 1 minute/day [43].
- Muscle energy technique for scalene muscles 5 times/day [43].
- Rib raising technique (5 cycles for each rib group with a total of 15 cycles and approximately 5 minutes' duration) [44].
- Sub-occipital area intermittent rhythmic pressure (according to each patient sensitivity) [45].
- Osteopathic lymphatic thoracic pump techniques with respiratory assist for 4 minutes [46].
- Pedal lymphatic pump for 1 minute [47].

- Thoracic inlet myofascial release for 1 minute [48].
- Diaphragmatic doming for 3 to 5 sequential respiratory cycles [49-52].

A real time videoconference was established between the patient and the physiotherapist for training, directing and supervising the patient during self-application. All techniques were given respectively on a daily basis. The total duration of each therapeutic session was approximately 4 hours and 30 minutes.

In both groups, therapy was ended after the assessment of all the outcome values making sure that all of them are falling within the normal range and continued to be stable for three consecutive outcomes without any clinical symptoms which indicate recovery.

Evaluation procedures included the following:

- Recording of arterial blood gases for both oxygen (PaO2) and carbon dioxide (PaCo2) in addition to potential of hydrogen (pH) for each patient in both groups every 48 hours [53].
- Tele-monitoring of vital signs (temperature, respiratory rate, oxygen saturation, heart rate and blood pressure) for each patient in both groups every 24 hours [54].
- Pre-treatment and 14 days' post-treatment chest CT scan.

All evaluation procedures were recorded, monitored, and analyzed with an application developed by the authors which was used for management of the patients' data and tracking of the therapeutic progress. A continuous online support with comprehensive supervision was done via video conferencing by expert respiratory physiotherapists whenever requested by the patient.

The primary outcome measures for this study included: time to reach normal levels of partial pressure of both PaO2 and PaCo2 in addition to pH which were assessed every 48 hours. Other secondary outcomes were temperature, respiratory rate, oxygen saturation, heart rate and blood pressure which were evaluated every 24 hours.

The participants were provided with wearable devices that have been used for tele-monitoring of the required vital signs. The devices were capable of transmitting the vital signs data via a Bluetooth connection to the authorized gateway (mobile, tablet, or any other gateway).

Collection and reporting of the primary outcome measures were done by three laboratory technicians who were blinded to the groups of study then analyzed via the system. The technicians were assigned to take the samples from patients' homes for analysis. Interrater reliability was assessed using intraclass correlation coefficient which was 0.97 while intra-rater reliability was assessed by utilizing Pearson correlation coefficient and was found to be 0.99.

Secondary outcome measures were collected and reported by the patient himself and the evaluation of these readings were done by a single clinician who was also blinded to the groups under study. All patients were instructed for another 14 days of observation after ending therapy then chest CT scan

was done.

Method for tele-management of the COVID-19 patients

A tele-management system was developed by the authors, which follow the Health level 7 version 3 standard in order to simplify its integration and facilitate receiving and/or retrieving information from other sources/applications as well as enabling the usage of internet of things. This system was able to support live transmissions of the vital signals and allowed for incorporation of different medical sensors through wireless connections. The patient was able to access the system via mobile phone, tablet, or any web platform.

The major components in the platform are included:

- A thorough monitoring plan
- The patient particular interventions
- Alarms and indicators definitions
- The user environment configurations of the therapist's device.
- The user environment configurations of the patient's device.

Additionally, the system was able to provide an efficient flexible scalable integrated solution that adapts artificial intelligence for providing support in planning, predicting, and decision-making. Its platform was specifically designed for managing and providing tele-therapeutic services to home isolated COVID-19 patients. It also covers services of therapists and managing staff while coordinating the work of all the involved professionals. The system was also able to allow the patients to receive an individualized therapeutic program. It also allows the therapists to set up a plan and thresholds that can be personalized in accordance with each patient's profile.

In addition, it has the option for creating combined alerts via several variables. The system provided the patient with a step by step written instructions as well as precautions about each procedure along with a video which explain how to do the procedure. Another advantage of this system was the auto reminder to help with sending the data on time.

After each outcome data was collected for each patient, the results were sent immediately to a server as they would be available for analysis. The system included a decision support option, which provided a tailored feedback for each patient. Depending on the progress of the outcomes variables, the system provided an alerting option when certain outcomes were reached or when a patient performance would require an in-person counseling. After ending therapy, the system enabled each patient to answer post-treatment questions for assessment of patient satisfaction with the quality of this novel tele-management service.

The decision-support engine entailed workflow management routines that are used for coordinating reception of the inputs, managing their interactions, in addition to handling decision-support outputs by means of tasks or actions.

The alert messages were sent to the intended devices with features that can be adjusted as the color-coded displaying, preferred choices for creating alerts, and interface personalization options. The system presented the information on meaningful medical ways where it first presented the alerts then their related information that was gradually presented in a more detailed manner.

With the goal of adapting the designed platform along the certain needs of the COVID-19 patients, we did some consecutive meetings with the patients and the therapists. The platform takes into consideration the normal values of the outcomes according to their follow-up schedule. Furthermore, we incorporated a group of educational elements for improving the patients' knowledge of COVID-19, which is empowered via interactive materials.

Analysis was triggered on the reception of data or periodically scheduled, in accordance with decision support requirements. The input-module functions were dependent on the routines of feature-extraction for the characterization of the data patterns.

Datasets were generated through the acquisitions of the clinical measurements and questionnaires, which were assessed as being a function of time in order to detect sudden deviations, which can indicate health deterioration. The features extraction routines for the distribution analysis and thresholding were implemented as separated modules, then processed data was retrieved, and the notable clinical data patterns were feed-backed into a decision-support engine.

For proper identification of the significant downward or upward values over the analysis window period, an identification analysis routine was utilized. In addition, a threshold analysis routine was used for comparing the values to the adaptive thresholds.

The data in the outer ranges was defined through the confidence intervals and any detected deviation was flagged as being abnormal measurements.

Furthermore, we designed the system with the ability for predicting the probability of a future patient therapeutic failure using deep learning; however, a sufficient training data set is yet to be obtained in order for the system to provide accurate results.

Deep learning was based on a feed-forward multi-layer artificial neural networks that used back-propagation processes for updating the weights among the hidden layers and the output, then a back-propagation of the resulted error was applied. For the predictions, the mean square error, as well as the R-squared error were calculated.

Statistical analysis

The sample size was calculated with a power of 80% and level of significance of 5 % ($\alpha = 0.05$). The analysis was based on the post hoc power analyses utilizing G Power software [55] and accounting for missing data of 15% and was based on the minimal meaningful effect size. This analysis showed that the sample size was adequate. Differences between the two groups were assessed by means and standard deviations. Comparison between the two groups was done using

student t test. Nominal data were summarized in frequencies and percentages. All data were statistically analyzed by an independent statistician who was blinded to the interventions using IBM SPSS statistical software version 20 (IBM, NY, USA).

Results

A total of 60 patients (22 males and 38 females) were included in this study. Their age ranged from 21 to 40 years with a mean age of 31.6 ± 5.8 years. The most presenting characteristics were fever (93.3%) and dyspnea (91.6%) as shown in table 1.

Table 1: Demographics and baseline characteristics of patients.

	Total Mean (SD) / n (%)	Group (A) Mean (SD) / n (%)	Group (B) Mean (SD) / n (%)
Age	31.6 (± 5.8)	32.2 (± 5.4)	30.9 (± 6.2)
Male	22 (36.7)	10 (33.3)	12 (40)
Female	38 (63.3)	13 (43.3)	25 (83.3)
Fever	56 (93.3)	27 (90)	29 (96.6)
Tachypnea	51 (85)	29 (96.6)	22 (73.3)
Tachycardia	29 (48.3)	17 (56.6)	12 (40)
Hypertension	19 (31.6)	11 (36.6)	8 (26.6)
Dyspnea	55 (91.6)	27 (90)	28 (93.3)
Cough	43 (71.6)	17 (56.6)	26 (86.6)
Chest tightness	12 (20)	5 (16.6)	7 (23.3)

Age illustrated as mean and standard deviation (SD). All other variables are illustrated as number (n) and percentage (%). Non-significant difference was found between the 2 groups (ns)

A significant difference was observed between the two groups in the mean number of days needed for recovery ($p<0.05$) with group (A) showing lower recovery period than group (B) (14.9 ± 1.7 days and 23.9 ± 2.3 days respectively), as shown in figure 2 and 3. The unpaired t test value was 16.55 with a mean difference of -9.056 between group (A) and (B) respectively.

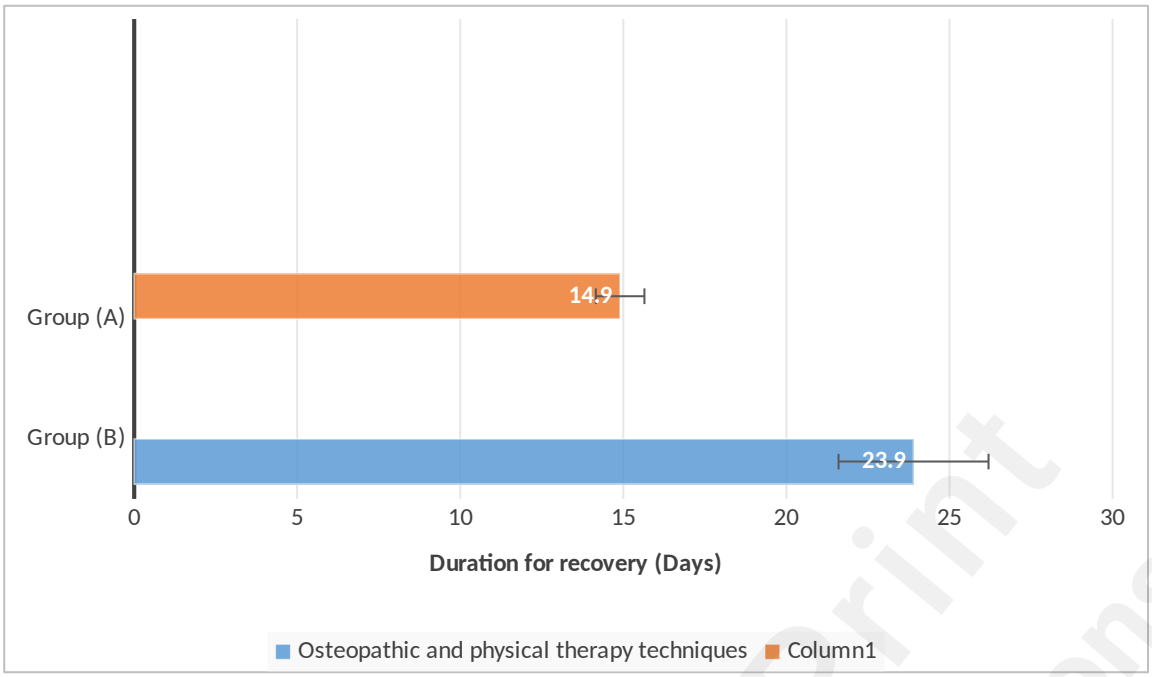

Figure 2: mean of number of days needed for group A and group B to recover.

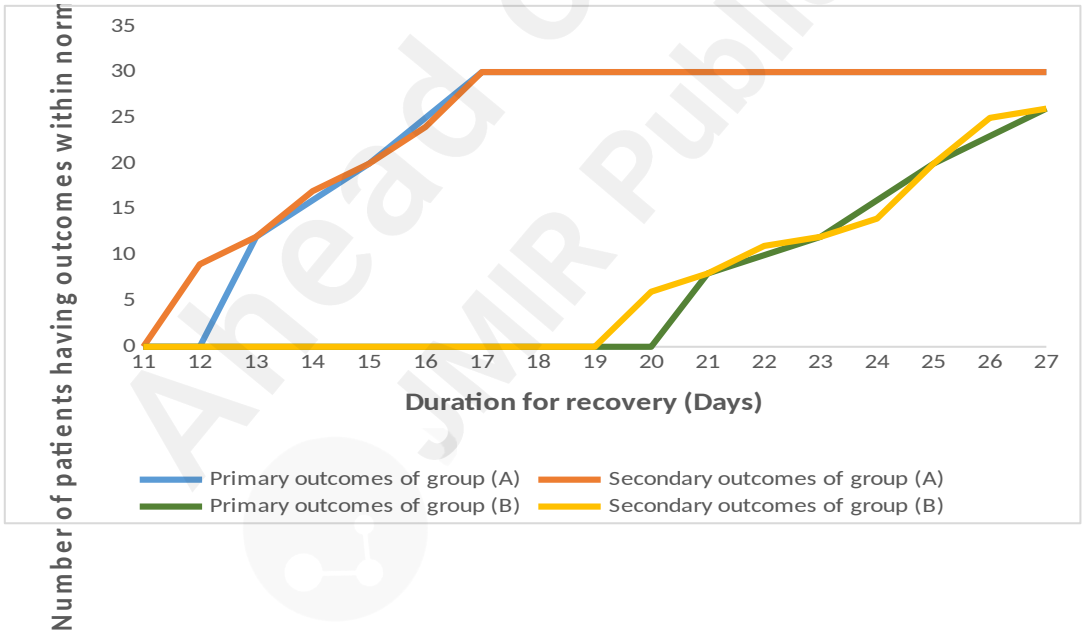

Figure 3: Patients outcomes recovery rates (number of patients having outcomes within normal ranges classified according to number of days needed for recovery).

Four patients from group (B) were excluded because of sudden therapeutic failure during the course of osteopathic manipulative respiratory and physical therapy techniques as these patients required hospitalization and/or intubation.

All the patients that were included in the analysis underwent chest CT scans two times one before

starting therapy and the other after ending the therapy by fourteen days. The early stage COVID-19 pneumonia mainly appeared as minor subpleural, bilateral or less commonly unilateral ground-glass opacities in the lower lobes.

Fifty-one of the sixty patients (85%) were having bilateral lung pneumonia, while, nine of the sixty patients (15%) were having unilateral lung involvement. The unilateral lung involvement cases comprised of six patients having a right lung involvement and three patients having a left lung involvement.

After two weeks of ending therapy, the CT showed complete resolution in group (A) patients, however in patients of group (B) the lesions were mostly absorbed compared with images before therapy in twenty-three patients, while the other three patients showed no worsening than the previous CT results. The four patients who have been excluded from the study due to therapeutic failure were instructed to be admitted to the hospital.

The data sets of the study were based on the daily reports. These reports included arterial blood gases analysis and vital signs. The data sets consisted of 1735 daily records. After filtering of these data sets by removing the records of the excluded patients, the finally analyzed data sets included 1686 records. The submitted records parameters for each attribute are shown in Table 2.

Table 2. Submitted records parameters

Attributes	Duration	Total number of submitted records (Group A)	Total number of submitted records (Group B)
PaO2	Every 48 hours	238	324
PaCo2			
pH			
Temperature	Every 24 hours	476	648
Respiratory rate			
Oxygen saturation			
Heart rate			
Blood pressure			

Our system predictions showed an R-square of 0.965 with a mean square error of 0.27 which means that more than 96% of the variations were in the predictions.

The post-treatment patient satisfaction questions focused on a group of technical aspects, which are simplicity, effectiveness, acceptability, usability, reliability, and the level of confidence as well as the system ability for assessing a patient’s status remotely. The results of the satisfaction questions were very promising and most of the patients responded positively to the questions as shown in table 3.

Table 3: Post-treatment patient satisfaction questions for the tele-managed system

	Question	Yes	No	No answer
Q1	Were the tele-management procedures simple?	41	12	3
Q2	Were the tele-management treatment procedures useful?	54	0	2
Q3	Were the tele-management procedures well-tolerated?	56	0	0
Q4	Were educational elements and interactive materials useful?	56	0	0
Q5	Did you regret using this tele-management system and preferred admission to the hospital?	1	52	3
Q6	Did the auto-reminder option in this system helped you in sending data in time?	55	0	1
Q7	Do you think that the time spent with you by therapists was adequate?	38	13	5
Q8	Do you think that this tele-management system was consistent?	49	2	5
Q9	Do you think that this tele-management system is an acceptable way to receive treatment services?	56	0	0
Q10	Overall, are you satisfied with the quality of the services provided by this tele-management system?	55	1	0
Q11	Would you recommend this tele-management system to anyone?	51	1	4
Q12	Any comments? * I regret not being admitted to the hospital as I think that I might not have transmitted the infection to my wife. * This tele-management system saved efforts, costs, and time. * I think that the time spent with the therapist need to be more frequently. * The system can be more helpful if it would often send periodical information about my status by informing me if I am getting better or worse.	4	48	4

The tele-management system showed positive response for most of the patients' satisfaction with its simplicity (73%), effectiveness (90%), acceptability (100%), usability (98%), reliability (96%), level of confidence (98%), and ability for remote assessment (68%).

Discussion

Our study explores the feasibility of oxygen therapy with non-invasive positive pressure ventilation therapy versus an osteopathic manipulative respiratory and physical therapy techniques in COVID-

19 patients.

Only fifty-six of the patients have completed the treatment till recovery and achieved all of the required outcomes. The therapeutic procedures were well tolerated, and the clinical symptoms significantly improved over a relatively short time.

The tele-management application addressed variance in the clinical outcomes and increased gain from the specialists' expertise. Tele-management and tele-medicine applications have wide range of implementations, and there have been robust evidences about their clinical benefits, cost-effectiveness, simplicity, and its positive impact on the critical care safety and quality [56].

The tele-management decision support option provided many potential benefits by reducing the specialist's workload caused by regular revision of all the results to only the patients having measurements pattern that indicate health status deteriorations and those who are having higher priorities for revision.

Regardless of the broad usage of the smart devices in health tele-management and collection of data, medical applications of deep learning approaches for predictions are still considered to be challenging [57]. In this study, depending on prevailing health conditions, deep learning was used to assist in defining essential features, predictions, and contextual detections of patterns.

Deep learning was also used as being a recognized candidate to predict the probability of a future patient therapeutic failure, because of its ability of exploiting efficiently the intra-modality correlations that would allow extracting the hierarchical representations of the data, as well as its ability of performing features extractions.

The results obtained from this study clearly demonstrated that non-invasive Bi-level positive airway pressure was able to significantly improve the clinical status of the patients infected with SARS-CoV-2 virus. The PaO2 and oxygen saturation were elevated over a relatively short time. The respiratory frequency and heart rate decreased. Furthermore, 100% of group (A) patients did not require any hospitalization, intubation or experienced any complications.

The results of this study were able to suggest that the application of home oxygen BiPAP therapy could improve respiratory status of patients with COVID-19 pneumonia. It could also significantly improve arterial blood gas analysis status of the patients without any negative influence on haemodynamics.

It was also found that the application of oxygen with BiPAP at the early stage could reduce the need for intubation along with its related complications. The respiratory complications of COVID-19 can be attributed to the rise in the capillary alveolar membrane permeability that can lead to pulmonary edema. Thus, non-invasive Bi-level positive airway pressure may have contributed in preventing deterioration by impeding the consequent pulmonary edema via positive pressure [19].

Nevertheless, some side effects of BiPAP was noticed in this study, such as facial skin and eye irritation, mild oropharyngeal dryness, mild abdominal gaseous distention and stomach pain. Using appropriate face masks with well tissue compatibility along with avoiding mouth respiration and

guiding nasal respiration have been found to be effective in decreasing these side effects.

Regarding the osteopathic manipulative respiratory techniques and physical therapy treated group, the improvement in chest CT scan was not significantly different from the baseline but seemed to be clinically relevant, while there was a significant improvement in rest of the outcomes. The clinical symptoms were also improved over a relatively short time. The osteopathic manipulative respiratory techniques which were used with this group have been reported in several studies to have beneficial effects in treating pneumonia [58]. Our main motives for the use of these techniques were focused on immunity improvement, blood clotting prevention as well as the absence of any noticeable side effect.

Although non-invasive ventilation was found to be more effective, combining between the reverse trendelenburg and prone positioning can be beneficial as well. In our study it was reported to be tolerable and comfortable by the patients. When considering studies that investigated the effects of each position [41] [42]. One of those studies demonstrated that prone positioning contributed in improvement of the ventilation perfusion mismatch in COVID-19 patients by inducing dorsal lung regions recruitment, alveolar shunt reduction, tidal volume and end-expiratory lung volume improvement [41]. However, we found that prone positioning can induce abdominal push on the diaphragm especially with patients that have belly abdomen, which can limit diaphragmatic excursion. In another study reverse trendelenburg positioning by tilting-up the patient's head 25 degree showed a decrease in abdominal push on the diaphragm, and therefore, an increase in functional residual capacity and Lung compliance were observed [42]. Thus, we combined the two positions to avoid any limitations in diaphragmatic movement.

While physical therapy treated group have shown less significant results, most of the patients in our study reported relaxation effects immediately after application of cephalic traction and muscle energy techniques for scalene muscles. Similarly, a study demonstrated that these techniques have an effective role in improving vital capacity, increasing respiratory muscle efficiency, cervical flexibility and decreasing fatigability levels [43]. This study also revealed that the more the lengths of the scalene changed per unit volume, the lower alveolar pressure is obtained. Thus, the ventilation volume through thoracic expansion increases when the scalene maintain reasonable lengths. Likewise, rib raising technique was reported to be relaxing to the patients, which is consistent with another study that found this technique to have an immediate reduction in the activity of the sympathetic nervous system without causing any alteration in the parasympathetic activity or the hypothalamic-pituitary-adrenal axis [44].

The patients' arousal feelings that were reported after having intermittent pressure to the suboccipital area can be attributed to the ability of this technique to cause arterial vasomotion at rates usually associated with the cranial rhythmic impulse as being demonstrated in another study [45].

In our study, osteopathic lymphatic thoracic pump techniques with respiratory assist, myofascial release to the thoracic inlet, and pedal lymphatic pump also indicated a good tolerability and were reported in another study to be advantageous for treating pneumonia by targeting the lymphatic flow, activating autonomic-mediated intrinsic lymphatic contractility, improving respiratory function, and improving circulation. In addition, the thoracic lymphatic pump techniques and thoracic inlet release

have been shown to increase chemokines and cytokines in the thoracic as well as the intestinal lymph vessels, while pedal lymphatic pump improves flow into the lymphatic systems [59]. The outcomes of lymphatic pump techniques including improvement of serum interferon levels [46] were carefully directed to the sample of our study as we have taken into consideration that COVID-19 induces hyperactivation of the immune system in the severe stages, while it usually induces impairment of the immune system on the early stages. Therefore, suppressing the immune responses may be targeted in the severe stages, while in the early stages which was our case, focusing on reducing the viral load by stimulating type-I interferon should be targeted [60].

It was also observed that in the first group, non-invasive ventilation promoted a significant increase in chest wall volumes directly after application which can be due to passive expansion. On the other hand, manual diaphragmatic releasing techniques in the second group contributed to the positive outcomes of our study by improving the mobility of chest wall immediately after the intervention, which was in accordance with several studies [49-52].

Compared to physical therapy techniques, BiPAP therapy outcomes were confirmed by this study to be much more effective and promising. Even though physical therapy techniques do not require equipment, those techniques need to be investigated further in order to be considered promising.

Overall, the post-treatment patient satisfaction with our proposed tele-management healthcare system showed positive response for most of the patients even in the physical therapy treated group despite longer recovery periods. This was attributed to their advantage of being costless.

Limitations of the study:

- The study was limited to a relatively small number of patients. Thus, further large randomized controlled trials with larger sample size are recommended.
- Osteopathic manipulative respiratory and physical therapy techniques may have a role in elevating recovery rates and improving outcomes of patients with COVID-19. Therefore, further randomized controlled trials with larger sample sizes would be required to know its therapeutic extent.

Conclusion

From this study, it was found that in the early stage of SARS-CoV-2 virus pneumonia, home oxygen BiPAP ventilation can reduce the need for endotracheal intubation. It can also be an effective prophylactic treatment approach to avoid exacerbation of this disease and the need for hospitalization. Home oxygen BiPAP ventilation was more effective than osteopathic manipulative respiratory and physical therapy techniques as it was associated with shorter recovery periods. Home based COVID-19 tele-management systems with decision support services showed satisfying outcomes and may be recommended in certain cases as an effective solution for the extreme shortage in hospital beds caused by this pandemic. Further investigations are still required for determining the effectiveness of the osteopathic manipulative respiratory and physical therapy techniques in the management of COVID-19 patients in early stages.

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Supplementary Files

CONSORT (or other) checklists