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Telemedicine Strategy for CPAP Titration and Early Follow-up for Sleep Apnea During COVID-19 and Post-Pandemic Future

La estrategia de la telemedicina para la regulación de la CPAP y el seguimiento temprano de la apnea del sueño durante la pandemia de covid-19 y el futuro post-pandémico

Dear Editor,

With the acute first wave of the COVID-19 pandemic over,[1] the long waiting list for sleep tests for OSA management has been further increased.[2,3] The new preventive health measures against Covid-19 imply that patients go to the health centers as little as possible, which is why it is necessary to implement and start up a telematic workflow with home studies to guarantee sleep tests,[4] especially CPAP titration.[5–8] We aimed to test a new telematic workflow to deliver CPAP therapy to OSA patients and to evaluate it in terms of CPAP compliance, costs, residual events, symptoms and satisfaction of patients. The usual titration strategy has the following steps. The patient is scheduled to the daytime-hospital for information, and educational and practical training session with the device (45 min). Then, our CPAP equipment is delivered to him/her for home titration (to be returned the next day), the data is downloaded, and a fixed pressure is prescribed. If the registration is incorrect, the titration is repeated another day. Finally, the patient is scheduled by the service company providing CPAP equipment that informs again how the equipment works, selects a final mask for treatment, and give a short practical session of the CPAP use.

The new telematic titration strategy was developed at 3 university hospitals—Clínic (Barcelona), Clínico Lozano Blesa (Zaragoza) and Bellvitge (L'Hospitalet del Llobregat) in collaboration with a healthcare provider company (Esteve-Teijin). By phone calls from the Sleep Unit, OSA-diagnosed patients waiting for CPAP titration were informed about the telematic process. Patients also received an email with detailed information and links to educational videos made by the group (sleep, hygiene, OSA and a real educational and training session similar as performed at the hospital) as well as written information of all the procedure. Subsequently, patients were addressed to the healthcare provider to pick-up their CPAP device (Dreamstation CPAP Pro, Respironics) with a suitable mask and to attend a CPAP educational as a practical session. CPAP devices were initially set to automatic CPAP mode (range: 6–12 cmH_2O) and equipped with a modem for remote data transmission and titration (EncoreAnywhere platform). The titration procedure was as follows. After the first night with CPAP treatment at home and for the following 2–3 days, a sleep technician telematically analyzed the automatic titration data from the A-trial program in order to set a fixed CPAP pressure value that normalized breathing (AHI < 15 without major leaks). Patients received a phone call if massive leaks occurred based on the device data for > 15% of sleep time or if CPAP use was < 3 h. If leak was moderate no action was performed. If central apneas appeared, CPAP pressure was fixed at 70% of the initial value suppressing obstructive events. If a final decision-making on CPAP pressure was not established until the end of the third day of therapy, it was considered as a re-titration. In addition, at the end of the first week all patients received a brief phone call from the nurse to identify and solve any possible complications with the treatment (nasal congestion and leaks among others). CPAP parameters could also be modified if needed. During the first month of treatment the sleep technician/nurse could call the patient to solve any possible problems. In addition, the patient could contact the Sleep Unit nurse at any time through email or voicemail to solve any problem. At the end of the first month with CPAP, the nurse performed a follow-up visit by phone or videoconference aimed to assess the main outcomes: CPAP compliance, residual events and symptoms such as snoring, restful sleep, witnessed apneas and Epworth sleepiness scale. The nurse could solve any possible problem. Patients also received a phone call from staff who was not involved in patient management to answer a satisfaction questionnaire (9 modified) about the titration procedure.

To analyze the usefulness of the telematic titration two procedures were considered: CPAP compliance and cost–effectiveness. Regarding compliance, two groups were analyzed. Compliance of the telematic titration group (n: 77) was compared with a historical cohort of 193 OSA patients from the year 2019 who were prospectively recruited from the 3 hospitals mentioned. Descriptive statistics were used for basic features of study data. Categorical variables were compared between groups (telematic vs control) using the chi-square test, whereas continuous variables were compared using the t-test or the nonparametric Mann–Whitney U test. Propensity score (PS)[10,11] was used to obtain a 1:1 balance between patients in the telematic group ($n = 55$) and control group ($n = 55$).

Table 1
Comparison of Baseline Data of Both the Hospital (n = 55) and Telematic (n = 55) Groups After PS Matching. Difference in Titration Cost Between the Hospital Clinic Hospital Group (N = 38) and Telematic Group (n = 51).

Baseline data	Hospital	Telematic	*P*-Value
Age, mean ± SD, years	55.7 ± 11.5	56 ± 11.1	.900
Male, n (%)	44 (80)	41 (75)	.495
AHI, mean ± SD, events/hour	49.2 ± 20.9	50.4 ± 19.9	.747
BMI, median (Q1; Q3), kg/m²	31 (27.8; 33.8)	30.1 (26.3; 34.2)	.432
ESS, mean ± SD	10.2 ± 4.6	10.4 ± 5.3	.863
Titration			
COST (€)	231.92	129.91	.000
CPAP compliance, median (Q1; Q3), hours/night	5.8 (4; 6.5)	6.4 (5.3; 7.1)	.071

Linear regression analyses were also used to examine the associations between continuous clinical parameter AHI and telematic and control group. The Wilcoxon signed-rank test was used for comparing two continuous repeated measurements on the telematic sample (baseline vs 30-day), whereas categorical variables were compared using the McNemar test or the McNemar Bowker test.

The cost analysis of the procedure was performed only in patients of the Hospital Clinic (n:51) and compared with a recent hospital group in which cost was obtained with a similar group of study (n:38).[9] Total direct (CPAP devices, material replacements, staff salaries, travel expenses) and indirect costs (patient's lost productivity) were evaluated considering changes in compliance analyzed in terms of costs and time spent by comparing the in-hospital routine vs telematic procedure using an objective Bayesian cost-effectiveness analysis where the effectiveness and the log tranformation of costs are assumed to follow a bivariate normal distribution.[12]

Main results were: 1. *Compliance*. In full cohort, telematic group patients (n = 77) were younger with a lower BMI and ESS than in control group patients (n = 193) (P = .035, P < .001 and P = .042, respectively). However, after PS matching, no significant differences were found in the baseline characteristics (Table 1). CPAP compliance showed similar values in the two groups in both full and PS matching cohort (P = .099 and P = .071, respectively); similar results were obtained using linear regression models, even after adjustment for center, in both full (P = .111 and $p_{adjusted}$ = 0.106) and PS matching cohort (P = .155 and $p_{adjusted}$ = 0.201). In telematic group, there were statistically significant differences between all baseline symptoms scores and 30-day symptoms scores (P < .001). 2. *Cost*: Telematic titration process was analyzed also in terms of costs and time spent by staff. To this end, we compared the in-hospital routine with the patients corresponding to the Hospital Clinic in Barcelona (n = 51) showing that cost-effectiveness of remote titration was better, with similar compliance but lower cost (129.91€) than the hospital (231.92€). 58% of the costs of the telematic titration (75.65€ of 129.91€) are related to the first visit to the healthcare provider (CPAP device, educational session, travel expenses and loss of productivity by patients), and the 34% are related to the follow-up contacts and replacing masks and humidifiers. The costs of the first informative contact and the titration data analysis account for the 8% of the total costs. Bayesian cost-effectiveness analysis concluded that the telematic strategy was cheaper with a probability higher than 99.9% and more effective with a probability of 94.22%. Finally, the patients stated that they were satisfied with the new procedure, 95.8% were satisfied with the initial part of the treatment, 98.6% with the follow-up and the 95.6% with the access to the professionals. Although 18% of subjects would prefer face-to-face visits, most of them (93%) agreed that they would use the telematic procedure again and considered it convenient in the pandemic context. Regarding to the residual events, the median was 3.7 (1.65–6.85). All the clinical symptoms improved significantly after the telematic CPAP treatment (P < .001). Finally, 10 out of the 77 patients included in the study could not be titrated with the telematic procedure.

This new and simple telemedicine strategy proposed in the COVID-19 pandemic is adequate and cost-effective and could contribute to speed up the reduction of waiting lists, with patient satisfaction. We believe that a remote strategy for CPAP titration should be based on (1) the patients should always use their own CPAP, (2) the device should be able to remotely transmit data of CPAP treatment and be able to remote change of parameters which may avoid repetitive appointments for re-titration and (3) a system to hear the patient observations.

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Influence of Cytokine Release Syndrome in Severe COVID-19 Patients Treated With Tocilizumab Over the Quantiferon TB Gold Plus Results

Influencia de la tormenta citoquímica de pacientes COVID-19 graves tratados con tocilizumab sobre los resultados del Quantiferon TB Gold Plus

Dear Editor,

During the first COVID-19 peak and after administering it to approximately 500 patients in Wuhan,[1] the Chinese health authorities included tocilizumab (TCZ), an interleukin 6 receptor antagonist, for the treatment of severe SARS-CoV-2 pneumonia.

With increasing evidence of its effectiveness in severe COVID-19,[2] in Spain the Ministry of Health authorizes TCZ expanded access, prioritizing the inclusion of patients in clinical trials.[3,4] As it is an immunosuppressive agent, it is advisable to screen for latent infections caused by intracellular bacteria, parasites and viruses, such as *M. tuberculosis*, which could be reactivated during treatment with TCZ[5] in patients who may be candidates to receive it for long periods. Additionally, a recent, non-peer-reviewed report indicates that, like pandemic influenza, SARS CoV-2 might increase the number of tuberculosis (TB) cases and related mortality.[6] Moreover, new cases of coinfection TB-COVID-19 have been drescribed.[7] Finally, several original works, reviewed during the first European congress on SARS CoV-2 (ECCVID) held online between September 23 and 25, 2020, coincide in stating that mortality is influenced by SARS CoV-2, as much in patients with a history of TB as in those with active TB.[8]

From March 15 to May 15 2020, an IGRA test, Quantiferon TB Gold Plus (QFN-Qiagen, Venlo, The Netherlands), was requested[9] in our hospital for patients with SARS CoV-2 confirmed by PCR who met clinical (on the COVID-19 severity scales), radiological (new onset or progression of the initial pulmonary infiltrates) and biological (IL-6 > 40 pg/ml) criteria for treatment with TCZ in order to evaluate their immune response to latent tuberculosis infection (LTBI) before starting TCZ. Additional blood tests were done to examine other immune parameters, including CD4+ and CD8+ lymphocyte counts. Patients gave their verbal consent before undergoing treatment and for the use of their clinical data and storage of surplus samples in a biological bank (biobank) for research purposes. Both approval of the Hospital Pharmacy Committee and authorization from the Research Ethics Committee were obtained before treatment began.

Among the 190 patients treated with TCZ, the mean age (±SD) was 59.7(19.6) years and 125 (71%) were male. Seventy-two (38%) required ventilation in Intensive Care (ICU). Twenty-two (30% of those requiring ventilation) and 7 (6% of the non ICU patients) died as a result of refractory distress (ARDS). Valid samples for QFN were obtained in 119 patients (63%). The results were negative in 67 (56.3%), indeterminate in 48 (40.3%) and positive in 4 (3.4%). Upon retesting the patients with indeterminate results after 8 weeks, all but one who tested positive had negative results. The CD4+ and CD8+ counts extracted prior to TCZ administration showed a median of 321 cells/mL (IQR: 49–1356) and 171 (IQR: 16–1083), respectively. There were no differences in these T-lymphocyte counts between patients admitted and not admitted to the ICU (Table 1).

These data illustrate that SARS CoV-2, while producing an exacerbated inflammatory response, may be associated with T-lymphocyte depletion-dysfunction, which may reduce the capability of Quantiferon TB Gold Plus to identify the LTBI response in patients with moderate and severe COVID- 19. In our cohort, severe COVID-19 patients with cytokine release syndrome, showed medians of CD4+ and CD8+ below 350 and 200 cells/mL, respectively, which were probably the cause of the higher-than-expected indeterminate QFN values (40.3%). Similar results have been seen in several IGRA-based LTBI studies in immunosuppressed individuals.[10,11]

Since SARS CoV-2 could influence the dynamics of *M. tuberculosis*, specific follow-up of recovered COVID-19 patients at high risk factors of developing active TB should be considered independently of the results of QFN.

Table 1
Demographic data and results of Quantiferon and CD4+/CD8+ counts in patients receiving TCZ.

	TCZ (*N*)	Mean age (±SD)	Sex (*N*)		T cell (median)*		Quantiferon *N* (%)			Exitus (%)
			M	F	CD4+	CD8+	Pos	Neg	Ind	
ICU admitted	72	59.3 (±22.6)	46	26	293	129	2 (6)	20 (59)	12 (35)	22 (30)
Non ICU	118	60.0 (±10.6)	79	39	347	191	2 (3)	47 (55)	35 (41)	7 (6)
Total	190	59.7 (±19.6)	125	65	321	171	4 (3.4)	67 (56.3)	48 (40.3)	29 (15)

Glossary: ICU = Intensive Care Unit; *N* = cases; M = male; F = female; Pos = Positive; Neg = Negative; Ind = Indeterminate. **P* value non significant between ICU and non ICU (>0.05).