Original Article

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TANAFFOS

Effects of Morphine and Fentanyl on Patients with COVID-19

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Background: Sustained inflammation has been observed in the majority of severe COVID-19 cases. The impact of choice of opioid on perioperative inflammatory processes has not been assessed in the clinical setting.

Materials and Methods: Patients with novel coronavirus (COVID-19) who referred to Masih Daneshvari and Noor-Afshar Hospitals in Tehran were included in the study after providing full explanations and obtaining written consent. Patients were then randomly divided into three groups: morphine, fentanyl and control. Patients in the morphine group received 3 mg of morphine intravenously every 6 hours for 5 days, whereas in the fentanyl group, 1.5 mcg / kg / h of fentanyl was infused for 2 hours on 5 consecutive days. The results were evaluated based on the design of the questionnaire and its completion using t-test and SPSS25 software.

Results: A total of 127 participants responded to the survey between 20 April and 20 June 2020, of whom 90 (70.86%) with the average age 65.2 years, provided complete data on variables included in the present analyses. 53 (58.33%) of all individuals were men and 37 (41.12%) were women. Accordingly, 22 (24.4%) patients had a history of hypertension. However, diabetes with 16 (17.77%) cases and kidney diseases with 12 (13.33%), were the next most common underlying diseases. Evaluation of patients' clinical, laboratory and inflammatory conditions at different time intervals in both fentanyl and morphine groups did not show significant changes between these groups and the patients in the control one.

Conclusion: The results of this study did not show any significant change in the use of fentanyl and morphine compared to patients with COVID 19. This may be due to the use of these drugs in the viral phase of the disease. The use of morphine and fentanyl in the viral phase of COVID 19 disease do not show significant benefits.

Key words: Opium; Morphine; Fentanyl; COVID19

INTRODUCTION

Cytokine storm has been observed in the majority of severe COVID-19 cases (1,2). High concentrations of cytokines such as IL-2, IL-7, IL-10, G- SCF, IP10, MCP1, MIP1A, and TNF-α were recorded in plasma of critically ill patients infected with SARS-CoV-2, indicating that the cytokine storm could be associated with disease severity (3). Due to the fact that intensive inflammation leads to disease-induced morbidity and mortality, using anti-inflammatory agents may provide a new relevant strategy (4). Infection is

regulated by multiple cytokines that act in concert to proceed inflammatory responses (5,6). Opioid/cannabinoid receptors-based drugs can modulate immune cell migration and cytokine/chemokine secretion, and represent a promising pharmacological platform for developing anti-inflammatory therapeutics (7).

Opium is one of the strongest analgesics used for the treatment and control of pain (8). Numerous studies have examined the relationship between innate and drug-compatible immune cells in vitro, in vivo, and epidemiological and clinical studies in different patient groups (9-12). Laboratory studies in animals have shown that opium suppresses the immune system in the body (13). Also, physicians in the past used anodynes of opium tincture as a treatment of "bronchitis" and other ailments in infants and children, as case reports and experience "demonstrated the efficacy" of the concoction in controlling coughing and facilitating breathing.

Morphine is a member of morphinone-shaped alkaloids found in the poppy plant (14), which is a potent agonist of opioid receptors that acts on three types of receptors, causing effects that are mainly at the supraspinal and spinal level. Research on the antiviral properties and effects of this drug has shown its beneficial effects in the treatment of viruses such as SHV-1 (15). However, some studies have shown evidence of suppression of immunological factors with the use of morphine (16). Fentanyl, also is synthetic opioid used as a pain medication (17). Fentanyl works primarily by activating μ-opioid receptors (18). It is around 100 times stronger than morphine, and some analogues such as carfentanil are around 10,000 times stronger (19).

Opioids interfere with the immune system in a number of ways, including some components involved in the immune response, such as granulocytes and macrophages (20). A large source of endogenous opioids is inflammatory tissues of immune cells. In addition to its analgesic effects, morphine also has some anti-inflammatory effects. Reduction of hyperthermia and leakage of vascular fluids caused by carcinogens and the tendency of opioids to suppress the immune system, suppress edema, changes in leukocyte cytotoxicity and suppression of endothelial damage caused by granulocytes are the anti-inflammatory effects of morphine (21-23).

Numerous results have been published on the interaction of opioids and cytokines. The impact of choice of opioid on perioperative inflammatory processes has not been assessed in the clinical setting. We hypothesized that the use of opioid as part of a balanced therapeutic technique would diminish the inflammatory reaction and clinical consequences.

MATERIALS AND METHODS

This study, which is designed as a double-blind clinical trial (with registration number: IRCT20150725023332N4), has been approved by the Ethics Committee in Biomedical Research of Masih Daneshvari Hospital with the code (IR.SBMU.NRITLD.REC.1399.055). Patients with novel coronavirus (COVID-19) who referred to Masih Daneshvari and Noor-Afshar Hospitals in Tehran were included in the study, if they met the inclusion criteria (definitive COVID 19 infection based on clinical and para clinical tests, 18 year <age< 65 year and patients admitted to the ward with mild to moderate symptoms which have been initiated less than 72 hours). They were provided full explanations and written consent was obtained. Exclusion factors were intubation, liver and kidney enzymes> 2 times the normal limit, corticosteroid consumption, opium allergy, opium addiction and alcohol addiction. All patients received similar drugs according to standard protocols. The research physicians were blinded to the patient group and the patients were blinded to the injected drug (double-blind). 90 patients with the new coronavirus infection (COVID-19) were included in the study. Patients were then randomly divided into three groups: morphine, fentanyl and control.

Patients in the morphine group received 3 mg of morphine intravenously every 6 hours for 5 days, whereas in the fentanyl group, 1.5 mcg / kg / h of fentanyl infused for 2 hours on 5 consecutive days. Then variables such as

SaO_2, HR, RR, Temp, WBC, BUN, Cr, ALT, AST, Bilirubin, CRP, ESR and LDH were measured during the study period. The results of questionnaire design and its completion were analyzed using t-test and SPSS version 25 software.

RESULTS

A total of 127 participants responded to the survey between 20 April and 20 June 2020, of whom 90 (70.86%) with the average age 65.2 years, provided complete data on variables and were included in the present analyses. According to the results in Table 1, 53 (58.33%) of all individuals were men and 37 (41.12%) were women. Accordingly, 22 (24.4%) patients had a history of hypertension. However, diabetes with 16 (17.77%) cases and kidney diseases with 12 (13.33%), were the next most common underlying diseases. By comparing and reviewing each of these indicators in the three groups of patients, no significant differences were observed.

Evaluation of patients' clinical conditions (Table 2) at different time intervals in both fentanyl and morphine groups did not show significant changes between the two groups of patients.

Examination of patients' laboratory conditions (Table 3) at different time intervals in the two groups of fentanyl and morphine did not show significant changes between the two groups of patients.

The results in Figure 2 show that the use of morphine and fentanyl could not significantly change the inflammatory parameters of patients.

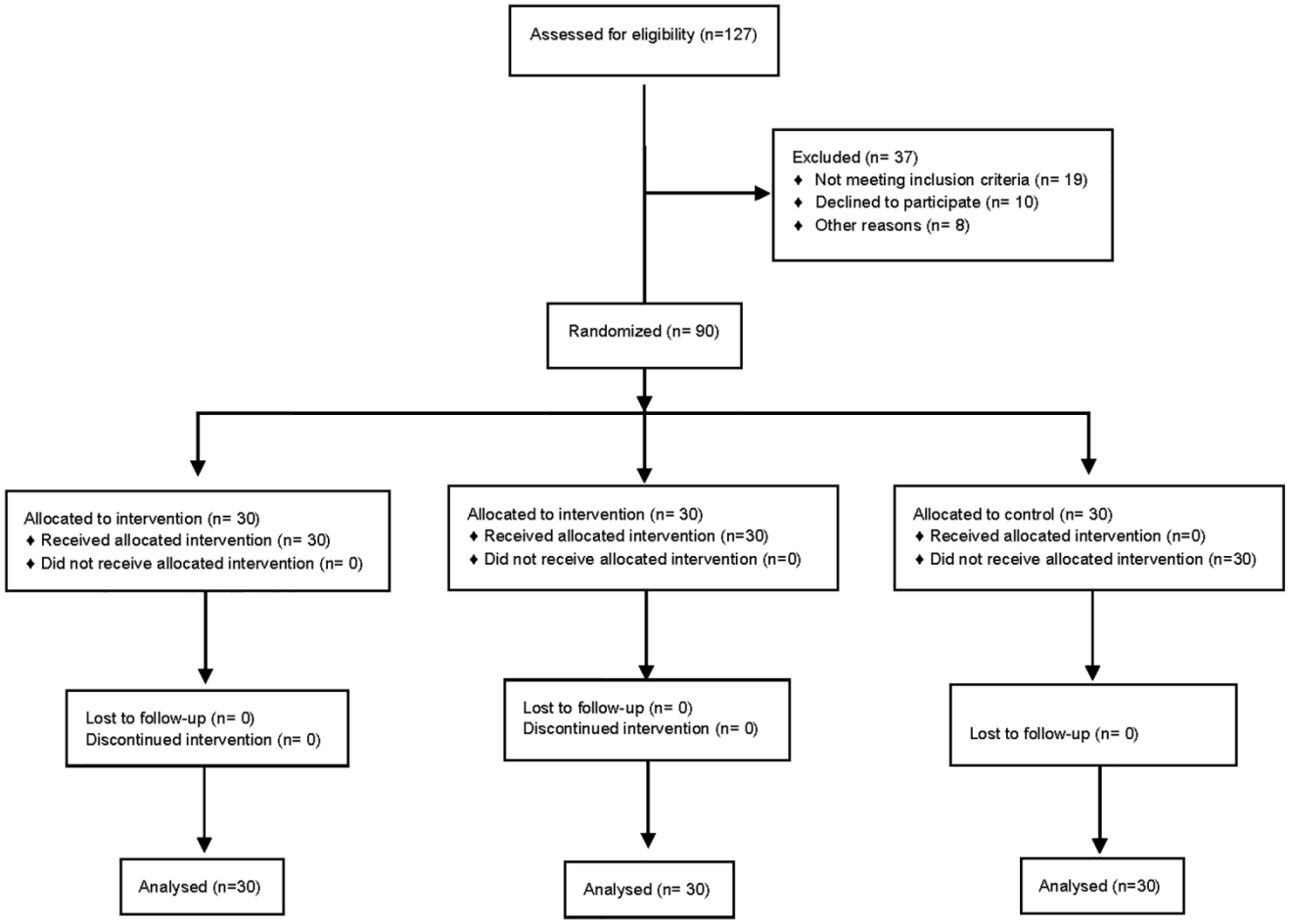

Figure 1. Consort diagram

Table 1. Demographic information and patient records

Indexes	*Total*		*Groups*			
	Mean	N (%)	Morphine	Fentanyl	Control	P-value
Age	65.20	–	63.37	66.01	66.22	0.25
Sex (male)	–	53 (58.33%)	16 (53.33%)	18 (60.00%)	19 (63.33%)	0.42
Diabetes	–	16 (17.77%)	5 (16.66%)	6 (20.00%)	5 (16.66%)	0.13
HTN	–	22 (24.44%)	6 (20.00%)	8 (26.66%)	8 (26.66%)	0.16
MI	–	2 (2.22%)	1 (3.33%)	0 (0.00%)	1 (3.33%)	0.09
CVA	–	2 (2.22%)	0 (0.00%)	1 (3.33%)	1 (3.33%)	0.09
Kidney disorder	–	12 (13.33%)	3 (10.00%)	5 (16.66%)	4 (13.33%)	0.07
Liver disorder	–	2 (2.22%)	1 (3.33%)	1 (3.33%)	0 (0.00%)	0.09
Anemia	–	4 (4.44%)	2 (6.66%)	1 (3.33%)	1 (3.33%)	0.11
Hyperlipidemia	–	15 (16.66%)	6 (20.00%)	4 (13.33%)	5 (16.66%)	0.08
Smoker	–	3 (3.33%)	2 (6.66%)	0 (0.00%)	1 (3.33%)	0.06
Opium	–	0 (0%)	0(0.00%)	0 (0.00%)	0 (0.00%)	0.99

Table 2. Evaluation and comparison of clinical factors of patients in the two intervention groups (morphine group and fentanyl group) compared to control group

		Fentanyl			Morphine		
		Control group	Fentanyl group	P-value	Control group	Morphine group	P-value
Sao2	Before	89/944 ± 5/359	86± 25/25	0/0383	89/944 ± 5/359	92/3 ± 26/766	0/189
	After 24 h	92/133 ± 34/55	85/50 ± 25/20	0/496	92/133 ± 34/55	92/4 ± 26/842	0/286
	After 72 h	92/625 ±29/194	87/88 ± 34/113	0/203	92/625 ±29/194	94/2 ± 27/253	0/386
	After 120 h	93/857 ± 39/167	87/625 ± 39/192	0/277	93/857 ± 39/167	93/8 ±27/018	0/192
Temp	Before	37/3 ±17/589	37./75 ± 10/85	0/066	37/3 ±17/589	37/045 ± 0/907	0/009
	After 24 h	37/4 ± 18/59	37/22 ± 14/36	0/082	37/4 ± 18/59	37/063 ± 0/467	0/018
	After 72 h	37/011 ±18/506	36/877 ± 14/225	0/047	37/011 ±18/506	37/036 ± 0/499	0/018
	After 120 h	37/01 ± 18/467	37/144 ± 14/328	0/044	37/01 ± 18/467	37/01 ± 0/923	0/005
MAP	Before	106/91 ± 52/461	82/80 ± 43/42	0/048	106/91 ± 52/461	96/555 ±39/852	0/344
	After 24 h	111/61 ± 52/407	83/6 ± 43/465	0/018	111/61 ± 52/407	108/889 ± 45/611	0335
	After 72 h	110/153 ± 51/945	85/6 ± 44/526	0/023	110/153 ± 51/945	95/75 ±45/593	0/309
	After 120 h	103/50± 52/75	91/0 ± 46/632	0/213	103/50± 52/75	97/25 ± 43/484	0/252
HR	Before	88/176 ± 24/055	81/6 ± 26/208	0/182	88/176 ± 24/055	80/454 ±11/179	0/363
	After 24 h	83/533 ± 32/591	88/00 ± 31/573	0/211	83/533 ± 32/591	81/454 ± 13/255	0/136
	After 72 h	81/687 ± 26/983	89/7± 33/570	0/227	81/687 ± 26/983	78/363 ± 11/096	0/260
	After 120 h	87/571 ± 37/106	92/111 ± 41/853	0/321	87/571 ± 37/106	78/818 ±16/089	0/194
RR	Before	22/266 ± 11/096	39/9 ± 46/61	0/072	22/266 ± 11/096	33/363 ±46/421	0/111
	After 24 h	22/692 ± 11/504	39/1 ±46/613	0/060	22/692 ± 11/504	20/00 ± 2/763	0/166
	After 72 h	20/714 ± 9/926	21/3±6/892	0/182	20/714 ± 9/926	19/636 ± 1/822	0/135
	After 120 h	20/454 ± 11/006	25/554 ± 15/721	0/057	20/454 ± 11/006	19/090 ± 1/831	0/034

Table 3. Evaluation and comparison of laboratory indexes of patients in the two intervention groups (morphine group and fentanyl group) compared to control group

		Fentanyl			Morphine		
		Control group	Fentanyl group	P-value	Control group	Morphine group	P-value
WBC ×1000	Before	3/721 ±1/38	9/249 ±2/64	0/114	3/721 ±1/38	6/382 ± 3/210	0/198
	After 24 h	4/82 ±2/32	8/14 ±2.73	0/078	4/82 ±2/32	7/288 ± 5/621	0/129
	After 72 h	5/14± 2/24	8/05±2/291	0/051	5/14± 2/24	5/897 ± 2/258	0/224
	After 120 h	6/12 ± 2/15	8/40 ±2/23	0/047	6/12 ± 2/15	5/316 ± 4/051	0/215
Lymph (%)	Before	14/76 ±8/91	14/7 ± 7/702	0/339	14/76 ±8/91	16/4 ± 9/726	0/329
	After 24 h	9/08 ± 5/934	15/94 ± 7/643	0/0006	9/08 ± 5/934	13/70 ± 9/703	0/003
	After 72 h	10/927 ± 7/440	15/06 ± 7/702	0/013	10/927 ± 7/440	16/363 ± 9/392	0/003
	After 120 h	10/918 ±7/334	12/637 ± 8/763	0/214	10/918 ±7/334	15/591 ±10/959	0/021
BUN	Before	48/00 ± 34/058	35/933 ± 23/54	0/333	48/00 ± 34/058	40/109 ± 22/704	0/326
	After 24 h	77/363 ± 75/067	42/788 ± 26/292	0/309	77/363 ± 75/067	36/409 ± 22/441	0/327
	After 72 h	72/090 ± 52/367	72/818 ± 66/184	0/294	72/090 ± 52/367	36/554 ± 24/257	0/334
	After 120 h	72/188 ± 66/184	44/662 ± 31/00	0/294	72/188 ± 66/184	34/721 ± 24/467	0/276
Cr	Before	1/272±0/337	1/488 ± 0/881	0/411	1/272±0/337	2/250 ±2/730	0/079
	After 24 h	1/6 ± 1/188	1/722 ± 1/063	0/174	1/6 ± 1/188	2/027 ± 2/136	0/056
	After 72 h	1/42 ± 0/989	1/733 ± 1/037	0/168	1/42 ± 0/989	1/972 ± 1/942	0/053
	After 120 h	1/4 ± 1/059	1/65 ± 1/088	0/287	1/4 ± 1/059	2/23 ± 2/326	0/053
ALT	Before	92/875 ± 72/69	51/375 ± 31/465	0/456	92/875 ± 72/69	27/001 ± 15/921	0/267
	After 24 h	89/125 ±71/188	55/714 ±34/544	0/431	89/125 ±71/188	34/801 ± 24/065	0/365
	After 72 h	59/777 ± 45/411	58/428 ± 34/279	0/330	59/777 ± 45/411	30/021 ± 17/450	0/295
	After 120 h	49/01 ± 28/369	63/857 ± 36/700	0/049	49/01 ± 28/369	40/501 ± 34/371	0/078
AST	Before	90/181 ± 108/667	70/888 ± 36/406	0/467	90/181 ± 108/667	37/272 ± 24/258	0/271
	After 24 h	50/625 ± 28/427	81/125 ±44/088	0/007	50/625 ± 28/427	32/725 ± 21/021	0/450
	After 72 h	59/75 ± 34/45	86/285 ±49/072	0/044	59/75 ± 34/45	36/725± 21/021	0/450
	After 120 h	61/555 ± 38/021	71/857 ± 44/027	0/179	61/555 ± 38/021	36/791 ± 23/310	0/288
Bili	Before	0/771 ± 0/458	0/58 ± 0/33	0/086	0/771 ± 0/458	2/140 ± 3/771	0/054
	After 24 h	0/966 ± 0/557	0/583 ± 0/280	0/487	0/966 ± 0/557	2/292 ± 3/856	0/078
	After 72 h	0.80 ± 0.458	0/607 ± 0.362	0.222	0.80 ± 0.458	2/595 ± 3/795	0/031
	After 120 h	0.9 ± 0.500	0.641± 0.361	0.374	0.9 ± 0.500	2/524 ± 4/66	0/055

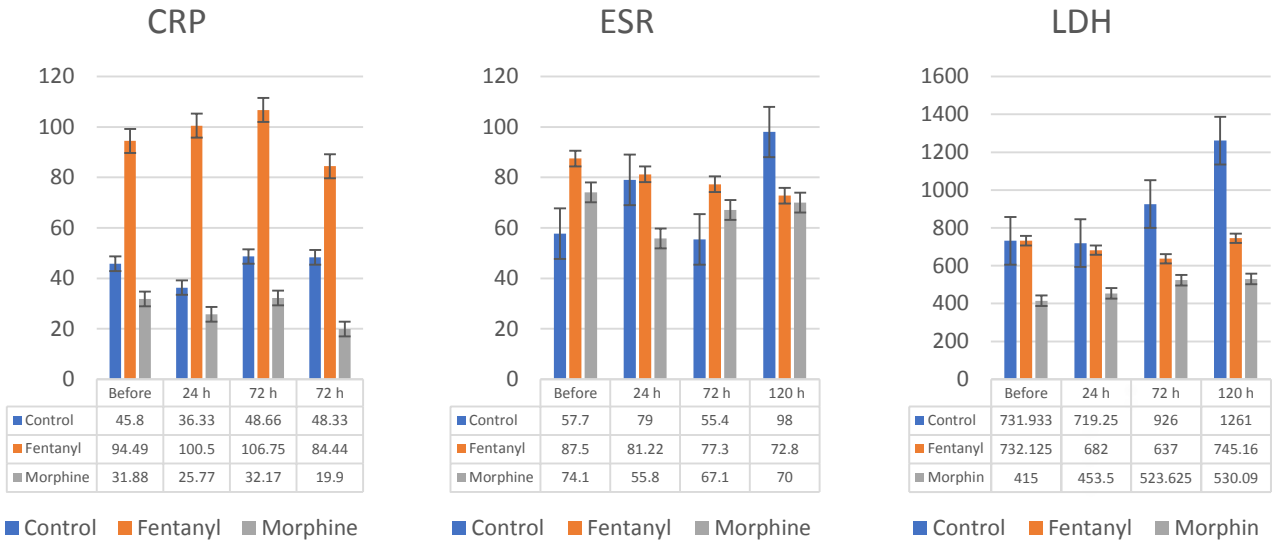

Figure 2. Comparison of the level of changes in inflammatory factors in patients in the two intervention groups (morphine group and fentanyl group) compared to control group patients at different times

DISCUSSION

In COVID-19 infection, an exacerbated pulmonary and systemic inflammatory response occurs, with increased serum levels of inflammatory markers, such as C-reactive protein (CRP), lactic dehydrogenase (LDH), ferritin, D-dimer, and IL-6 (24, 25), all of which may result in cytokine storm (26), similar to Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (27,28).

Experimental data, suggest that morphine has potent immunoregulatory properties, and may attenuate inflammatory processes (29). The pretreatment of activated granulocytes and macrophages with morphine results in a significant reduction in phagocytosis, cytokine production (interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) and the expression of adhesion molecules (30-32). The results in some researches have shown that consumption of opium reduces the level of HbA1C, CRP, factor VII, fibrinogen, apo B, Lpa, SGOT and SGPT, regardless of the period and route of consumption (33-34).

Despite all these details, the results of our study did not show any significant benefit in the use of fentanyl and morphine compared to standard therapy regarding inflammatory markers (CRP, LDH and ESR) in patients suffering from COVID 19. This may be due to the use of these drugs in the viral phase of the disease when the inflammatory reaction does not initiate (35). Studies have signified that patients with this type of infection enter the inflammatory phase in the second 5-7 days of the disease. Another thing is that the lack of different doses of drugs in our study may have caused the present results. Based on previous research, positive effect of opium on the level of inflammatory markers can be dose-dependent (36) and the more the dose, the more the effects. Besides the mentioned reasons, fentanyl unlike morphine does not bind to the μ3 receptor (37-39), so it may not be as effective as morphine in reducing inflammatory factor levels. Hence, our results for fentanyl are not far-fetched.

According to the observation by Radke et al., opioid use improved respiratory symptoms (40). However, we found that use of morphine and fentanyl had no significant effect on these symptoms (such as respiratory rate and SaO_2). This difference in results can be related to the different pathologic mechanism of new coronavirus on the pulmonary tract.

In this study the effect of morphine and fentanyl on the renal or hepatic functional parameters was not considerable. However, some studies have shown that the use of opioids can lead to remarkable changes in the level of these factors (41,42). According to our knowledge, patients with COVID-19 have an inflammatory attack that is known to be the main cause of damage to these organs (not hemodynamic problems and underlying diseases), and because the studied drugs could not justify the inflammatory response, the results seems to be logical.

Because of some restrictions, assessment of cytokines, interleukins, and other biomarkers involved in inflammation and viral infections was not possible, so measuring these factors can lead to more favorable results. Also, conducting a study with the approach of examining patients in the inflammatory phase and using different doses of opium (with emphasis on the increasing dose) may achieve different results.

CONCLUSION

The use of morphine and fentanyl in the viral phase of COVID 19 disease is not associated with significant changes in the clinical, laboratory and inflammatory factors in patients with mild-moderate symptoms.

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