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Research Article

Effect of Sublingual Piroxicam on Hypoxia in Cytokine Storm Induced Covid 19 Pneumonia - Descriptive Study of Clinicians' Experiences in 2003 Consecutive Cases

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Abstract

Pulmonary compromise and rapidly diminishing serum oxygen levels (SpO_2), affects a significant number of patients suffering from Covid 19, and often necessities hospitalisation and administration of oxygen! Cytokine storm has been identified as one of the principal causes of this diminution of oxygen concentrations. Anti-inflammatory agents are known to assist in control of cytokine storms, and the current study is an observation of 2003 Covid 19 patients, who were administered 20 mg sublingual cuboidal crystals of Piroxicam daily for five days. 134 participating clinicians shared their experience with the molecule. It was observed that Piroxicam was capable of controlling cytokine storm, and rapidly improving oxygen saturation in over 90% of patients and the effect of a single tablet was sustained for over 24 hours.

Keywords: Sublingual Piroxicam; Hypoxia; Cytokine Storm; Covid 19 Pneumonia

Background

Covid 19, a global pandemic, of epic proportions, has taxed the ingenuity and therapeutic skills of the clinician, due to its rapid spread, and many of the patients develop respiratory symptoms, which include dyspnea with fall in oxygen saturation levels.

With no assured or specific proven therapy to this malady, repositioned drugs may hold the key to a breakthrough in both controlling the disease and reducing complications [1].

NSAIDs in general are shown to control Covid 19 immune responses in mouse models [2]. Piroxicam is a long acting non-selective NSAID, widely used as painkiller, anti-inflammatory and antipyretic. Its activity as a Cox 1 and Cox 2 inhibitor is well recognized. Use of NSAID in Covid 19 is also approved by the WHO currently [2].

Sublingual form of cuboidal crystals of Piroxicam is used as a measure to improve faster absorption, and to reduce gastric irritation. Piroxicam was very good in controlling fever in cases not responding to Paracetamol. This drug is in use for decades. It is having a long half-life, so once in a day dose is possible.

Apart from the general anti-inflammatory action, there are other specific protective effects of Piroxicam in lung epithelium [3] and there are anti viral properties of Piroxicam described [4].

Dyspnea and the fall in SPO_2 levels is a common problem seen in late stages of Covid 19 pneumonia. It is generally attributed to cytokine storm involving the lung and lung vasculature. The exact mechanism of this phenomenon is not clear and it generally believed that it is an inflammatory reaction. Steroids are used to control this inflammation and non-steroidal anti-inflammatory drugs might be working in the same pattern.

This inflammation is measurable as fall in SPO_2 levels, changes in chest X ray and Chest CT; and increase in blood inflammatory maker levels. Another, easier way to measure the effect of a drug in this cytokine storm/inflammation is to measure the SPO_2 levels, as the changes are easy to record with a pulse oximeter.

Many Covid Patients with symptoms of fever, myalgia, shortness of breath are receiving Piroxicam as analgesic, anti pyretic and anti-inflammatory agent. Some physicians observed an improved SpO_2 level upon administration of sublingual Piroxicam tablets. The first observation of this effect is traced back to a case in May 2020 by Dr Diwaker [5].

We conducted a survey among clinicians who use this drug, to have a basic understanding about this effect. This may potentially reduce the need of oxygen, in short term and long term. Also, this may have an effect in controlling cytokine storm and eventually the disease outcome [6].

Methods

From April 05 to May 10, 2021, we collected data from clinicians who use sublingual Piroxicam (20 mg Piroxicam once daily, in the sublingual form of cuboidal crystals) in their patients. We collected data through e-mail and smartphone.

Exclusion criteria

We limited our survey to patients who are not in ICU, or ventilator in the beginning of drug treatment. We collected data in two time frames:

1. We asked the report on changes in SpO_2 levels before and after using Piroxicam, in hourly intervals, up to six hours.
2. We also asked for data from long term use, daily once dosage, for next 8 days.

Results

A total of 134 doctors responded, and they have shared observations in 2003 cases. We selected the change in SpO_2 levels as an indicator of clinical improvement, and as a measure of change in cytokine storm. A positive outcome is defined as elevation of more than or equal to 3 % SpO_2 level. Change within 2% or lower is considered as negative or clinically unimportant, as position change and other factors can cause this level of mild fluctuation.

Short term results

After six hours of sublingual dose of Piroxicam 20 mg.

There is a marked level of improvement in oxygen saturation, -3 points to 16 points elevation in 1882 of 2003 patients within one to six hours.

90 patients had elevation of less than 3 points, which we consider as clinically unimportant.

31 patients showed no change in the oxygen saturation levels.

More than or equal to 3% increase in saturation levels were reported in 96% of patients within 6-hour period.

Total number of patients in **SIX Hour** outcome group	Average spO2 before	Average sPO2 after one hour	Average sPO2 after six hour	Average age	% of cases with improvement more than or equal to 3%	% with one or more co morbidities
2003	89%	94%	96%	56	**91.2%**	69%

Total number of patients in **EIGHT DAY** outcome group	Average spO2 before	Average sPO2 after 3 days	Average sPO2 after 8 days	Average age	% Of cases with improvement More than or equal to 3% 8th Day	% with one or more co morbidities	% mortality Or progression into ICU admission
1987	89%	96.4%	97.4%	56	**92.1%**	69%	2.3%

Figure 1

Long term results

Outcome, after 20-milligram cuboidal Piroxicam was given sublingually for five days, with saturation documented for eight days.

There is marked level of improvement in oxygen saturation, - 3 points to 14 points elevation in 1863 patients in eight days.

9% patients had elevation of less than 3 points.

29 patients showed no change in the oxygen saturation levels.

More than or equal to 3% increase in saturation levels were reported in 91% of patients within 3 day period.

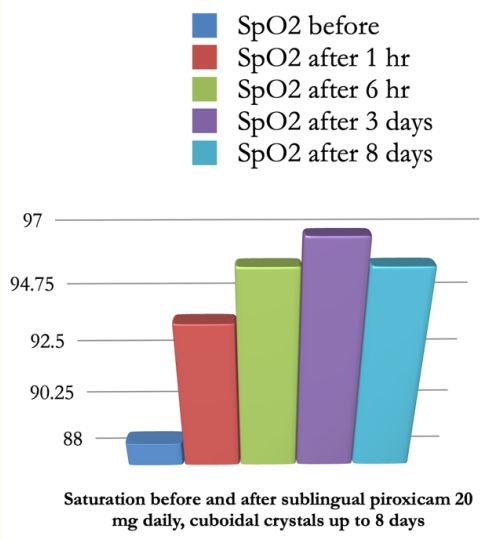

Figure 2

We have not taken other outcomes into considerations, like avoiding hospitalisation, oxygenation, Intensive Care Unit Admissions, mortality benefits, and changes in other parameters, like fever improvement etc.

Discussion

As seen in all cases, Piroxicam was very good in controlling cytokine storm and increasing oxygen saturation. The clinicians providing us with the data began administration of Piroxicam when patient developed the dyspnea as a symptom. Most of the cases were also monitored with CT chest, Blood values etc. and had used multiple drugs along with piroxicam.

In 91% of patients taking Piroxicam sub lingual, non-needle cuboidal form, (Drug molecules except Pfizer Dolonex) showed rapid improvement in oxygen saturation, with or without supplemental oxygen. So, we postulate that, this drug is having a role in management of hypoxia and cytokine storm of Covid 19. There is a possibility of good therapeutic outcome, if the drug is used in the early phase of hypoxia itself, then to wait till it is very late.

In most cases in our series, Piroxicam was taken with other combination drugs such as antivirals, Ivermectin, steroids and antibiotics. Thus, it cannot be concluded presently that diminution of fever and increase in oxygen saturation seen after few days of Piroxicam use, are solely due to Piroxicam alone. This requires further randomized studies. We could however, say that the short term result seen in six hour period could be due to the drug.

Since, COVID 19 infection is taxing the ingenuity and patience of the clinician, repositioned drugs can be critical in saving many lives [7]. Piroxicam can be tried under medical supervision in cases, which are progressing to MODS or increasing in severity.

Therapeutic potential of combination regimens with Piroxicam with low dose steroids or non-steroidal immunosuppressant and immunomodulation drugs may need to be explored further. As steroids are currently the only mainstay treatment for controlling cytokine storm, and usage of steroids often cause complications like mucormycosis, other molecules like Piroxicam to control cytokine storm need to be evaluated.

We assume that this effect on hypoxia is because of the drug effect in controlling cytokine storm. There are other known specific protective effects of Piroxicam in lung epithelium, and there are antiviral properties of Piroxicam described. However, whether these effects are contributing to the clinical outcome is not clear.

Piroxicam having effects on QT interval. This is also a problem with some of the common drugs used in the treatment of Covid19, especially Azithromycin and Hydroxychloroquine. A combination of Azithromycin, Hydroxychloroquine, and Piroxicam can be risky. Concomitant use of Deriphyllin, H_2 blockers etc. can also be problematic.

The limitations of this survey are that this is not a direct observation, (Except for 321 cases personally treated by the authors) and we rely upon data sent to us.

Contraindications and cautions in the use of Piroxicam, especially in Covid 19 scenario

1) History of Sulpha allergy.

2) History of peptic ulcer or severe gastritis under treatment.

3) History of aspirin induced asthma.

4) Not to be used in combination with QT blockers like Azithromycin, Cinchona alkaloids, Deriphyllin, and H2 blockers.

5) Chronic heart failure, cardiac dependent edema, and post cardiac surgery.

6) EGFR less than 50 and patients with stents and on anti platelets.

Figure 3

A randomized double-blinded placebo controlled study is warranted to make definite conclusions.

Conclusion

Preliminary findings show:

- **Short-term effects:** Obvious improvement noted in SpO_2 levels in persons who received Piroxicam sublingually; an average improvement greater than 3% SPO_2 in 91% cases. The results are sustained in six hours. These patients are receiving a multitude of drugs, but the effect observed in a six-hour period following a sublingual dose can be attributed solely to the drug effect.
- **Long-term effects:** Result after five days of daily doses of Piroxicam shows, sustained improvement of SPO_2 levels greater than or equal to 3% in 92% of cases even maintained at 8 days. This is a valuable therapeutic outcome. However, this result may not be solely due to the effect of Piroxicam, as the patient is taking other drugs too, including antivirals, Ivermectin and steroids. Definite answer can be obtained from prospective randomized trials.

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