Original Article

Use of Indomethacin in COVID-19 Patients — Experience from Two Medical Centres

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Background : Indomethacin is a widely used drug belonging to the class of the non-steroidal anti-inflammatory drug (NSAID), which has also a proven anti-viral effect. This academic study describes our experience in treating hospitalised symptomatic COVID-19 positive patients with it.

Materials and Methods : Patients with COVID-19 (detected by the real-time reverse transcription polymerase chain reaction) admitted to our department were provided the option of receiving Indomethacin 25mg (bid) or 75mg SR (sustained release), (OD) along with proton pump inhibitor, along with the standard care of treatment of the Indian Council of Medical Research (ICMR). Patients who did not agree to the Indomethacin option were offered standard care of treatment which included paracetamol. Development of hypoxia was considered as the endpoint. Time period to become afebrile and resolution of cough and myalgia; was considered as the secondary endpoint. Propensity Score Matching was used for the purpose of comparison between these two arms.

A separate group of patients with COVID-19 having severe disease, who were admitted with hypoxemia were given Indomethacin 75mg SR; admission to the intensive care unit or need for mechanical ventilation were considered as the endpoints.

Results : Twenty-eight of 72 patients in paracetamol arm developed hypoxia and required oxygen; whereas, only one patient out of 72 in the Indomethacin arm, developed hypoxia in the mild-moderate Covid patients. None of the patients in severe disease group treated with indomethacin needed mechanical ventilation. More rapid symptomatic relief was observed in indomethacin group than paracetamol group. Also, no systemic adversity including renal/liver functions observed.

Conclusion : In our experience Indomethacin is very effective and safe for treating COVID-19 patients.

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***Key words* : COVID-19, Indomethacin, Clinical recovery, Inflammation, Cytokine Storm.**

The WHO declared the COVID-19 outbreak as a pandemic on March 11th, 2020. It is caused by the Novel Coronavirus (SARS-CoV 2) and has claimed innumerable lives till date. No drug has been fully proved to be effective against this disease[1,2]. The anti-viral activity of Indomethacin was first reported in 2006[3]. Viral entry into host cells can be inhibited by down regulating the receptors ACE2 and TMPRSS2[4]. The other important factor is inhibiting Cathepsin L for fusion[5]. Ragav *et al*[6] showed that among the group of non-steroidal anti-inflammatory drugs, only Indomethacin has inhibitory property against Cathepsin L.

Editor's Comment :

- Indomethacin, a well-known anti-inflammatory drug; has additional antiviral action
- It produces rapid improvement of symptoms in COVID-19 patients.
- It can effectively substitute paracetamol in these patients, unless there is a contraindication like peptic ulcer or acute kidney injury.

Another important factor Nsp7, which acts as a cofactor of Nsp12 for synthesis of Ribonucleic Acid (RNA), has been discussed in detail by Gordan *et al*[1]. Inhibitory effect on RNA synthesis by this mechanism was also shown by Amici *et al*[3]. Indomethacin reduces IL-6, which is raised in Covid[7,8]. It has been used successfully used to prevent cytokine storm in patients having renal transplant on OKT3 therapy[9,10].

Amici *et al* has proposed effectiveness of Indomethacin in vitro against the Novel Coronavirus[3]. Direct evidence for its anti-viral activity against SARS-

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Cov-2, *in vitro*, *in cellulo* and in Corona-infected canine model are provided by Xu *et al*[11]. In a recent paper, Gordon *et al*[1] showed by retrospective data analysis that Indomethacin markedly decreases hospitalization. Two recent studies[12,13] have shown the effectiveness of Indomethacin in treating a small number of SARS – Cov – 2 patients with severe comorbidities.

Materials & Methods

This open-label study was conducted post ethics committee approval and consent from symptomatic RT-PCR positive Covid patients from two different Medical Colleges located in South and Central India. Effectiveness of Indomethacin (test drug; n=82) along with the SCT which included Hydroxychloroquine, Ivermectin, Azithromycin and vitamins was compared with its control (Paracetamol + SCT; n=109), obtained retrospectively after EC approval. A proton pump inhibitor was also added along with Indomethacin (25 mg bid or 75 mg SR od/5 days). Based on the WHO clinical progression score, hospitalized patients were categorized in to mild/moderate or severe. Mild and moderate patients were treated with Indomethacin (25 mg) in centre 1 and severe cases (n=22) were only treated in centre 2 with 75 mg –SR + SCT + Remdesivir. During admission 21 severe cases were administered supplementary oxygen (O_2); while one case required supplementary-O_2 subsequently. Based on the primary study endpoint (development of hypoxia) or physician discretion, patients were shifted to corticosteroid-regimen. Identical diagnostic tests were done for both the test- and control-drug received groups.

The investigations which were done at the time of admission : CT thorax, Liver Function Test (LFT), Renal Function Test (RFT), C-Reactive Protein (CRP) and D-Dimer. During the treatment or till clinical recovery, all the patients were closely monitored for oxygen saturation, temperature, respiratory symptoms and myalgia along the vitals. Symptomatic improvement was defined as the temperature below 99°F for two successive days and reduction of cough to score 2 on a 1 to 10 scale (1 – no complaint of cough, 2-3 – occasional cough, 4-6 – cough with the ability to do day to day activities, 7-8- persistent cough and 9-10 feeling much discomfort with the cough). Patients were discharged when a consistent oxygen saturation of more than 94% was noted. Except CT scan all other indicated tests were done at the time of patient discharge and their well-being was monitored via phone for additional 14 days.

Rigorous statistical analysis including Propensity Score Matching that mimics randomized controlled trial[14,15], was carried out using open source statistical software package R to match mild and moderate patients received test/control drug (72/arm) and to analyse the efficacy of Indomethacin *versus* Paracetamol.

Results

Propensity score based, on the covariates namely, age, gender, comorbidities (diabetes, hypertension), CT-score and CRP on admission, presence of dyspnea ensures that bias is removed in the recruitment to the two arms. Fig 1 gives the matching of the scores between the two arms and the comparison between the two arms in terms of the covariates. The figure shows that the propensity scores are matched well in

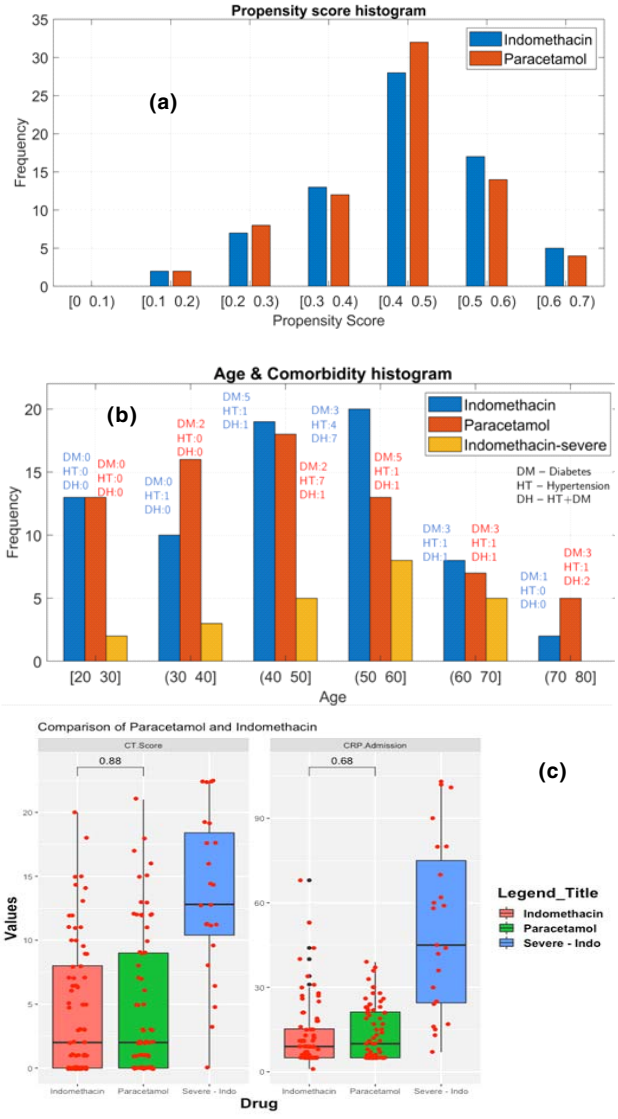

Fig 1 — (a) Propensity Score Matching between the SCT + Indomethacin received arm vs. SCT + Paracetamol received arm; (b) and (c) shows close match of the covariates at the time of admission

both the arms. Further the matching based on baseline characteristics show that both arms had patients with similar age and comorbidities, and the mean and distribution of CRP and CT-Score are similar between the patients. In other words, Fig 1 comprehensively demonstrates that the patients in both the arms are similar.

Efficacy of Indomethacin :

These results regarding the efficacy of indomethacin in improving fever, cough and myalgia are shown in Fig 2 (Fisher's Exact Test: p = 0.0005 for Afebrile, p = 1.7 x 10^{-13} for Cough and p = 0.0025 for Myalgia). Median (dark line) and interquartile ranges are also shown as a box. The recovery from fever, cough and cold in terms of median values is depicted in Table 1. The results are from a one-sample Wilcoxon test and IQR indicates Interquartile. Range. The Table clearly brings out the recovery in the Indomethacin arm of the study.

(a) No. of days to become Afebrile
(b) Days for Cough Reduction
(c) Days for Myalgia Reduction

Also, the temperature on admission or the CT score on admission had no relation to the patient recovery.

The two key questions in this study are – how many patients developed hypoxia and required steroid therapy? And number of patients stayed more than 14 days in the hospital?

In the paracetamol arm 5 patients with hypoxia and 67 patients without hypoxia were admitted and treated, while in Indomethacin arm 11 with hypoxia and 61 without hypoxia on admission was treated. Number of patients required supplementary oxygen was high in Paracetamol group than Indomethacin group (39% *versus* 1.3%) Table 2.

None in the Indomethacin group required a prolonged stay in the hospital. In the paracetamol arm 23 patients had a prolonged stay.

Twenty-one out of 22 patients in the severe category treated with Indomethacin 75 mg SR were discharged on or before 14 days and one patient, who had acute pancreatitis, was discharged after 17 days.

Safety profile of Indomethacin :

There has been many questions regarding the safety value of indomethacin sice its approval in 1965[16].

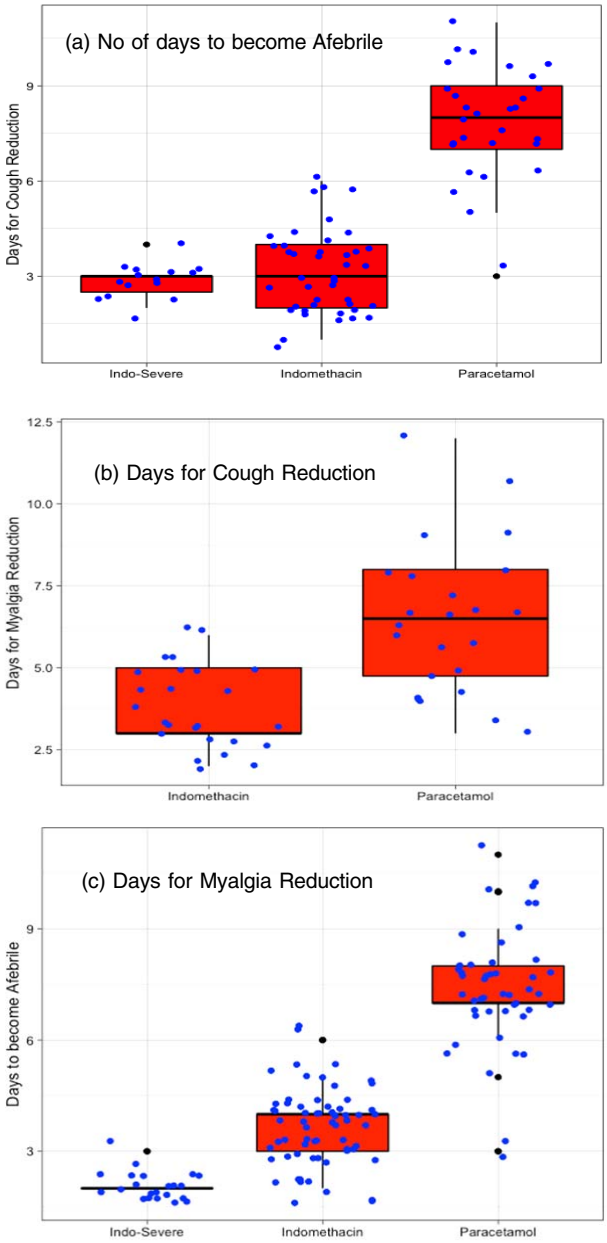

Fig 2 — Symptomatic relief of patients treated with Indomethacin or Paracetamol in combination with the SCT

Patients were tested for Serum Urea and Creatinine, SGOT and SGPT before and after the treatment and the results are given in Fig 3.

Table 1 — *Symptomatic relief due to various treatments*

Treatment	Days to become Afebrile			Days for Cough Reduction			Days for Myalgia Reduction		
	Median	95%CI	IQR	Median	95%CI	IQR	Median	95%CI	IQR
Indomethacin- Mild and Moderate	4	3.5,4.0	1	3	3.0,3.5	2	3	3.0,4.0	2
Paracetamol – Mild and Moderate	7	7.0,8.0	1	8	7.0,8.5	2	6.5	5.5,7.5	3.25
Indomethacin– Severe	2	2.0,2.0	0	3	2.5,3.0	0.5			

Discussion

The major objective of our study was to look whether the patients develop hypoxemia or not; out of total 11 patients who had symptoms of respiratory distress at the time of admission. In the Indomethacin arm, only 1 patient required oxygen, that too was given at low flow (2L/min) only for a couple of days for symptomatic relief. In contrast, all the patients who were in the paracetamol arm, who had symptoms of respiratory distress at the time of admission, needed supplementary oxygen. A significant proportion (34%) of patients, who did not have symptoms of respiratory distress at the time of admission, developed hypoxemia which necessitated administration of oxygen, while no one in the Indomethacin arm had developed hypoxemia. Supplementary oxygen was administered when peripheral oxygen saturation went below 94%. Patients in the paracetamol arm, even after a few days of treatment, deteriorated to hypoxemia. The odds ratio for the development of hypoxia when treated with Indomethacin, compared with Paracetamol was 0.02 (95% confidence interval of 0.003, 0.17).

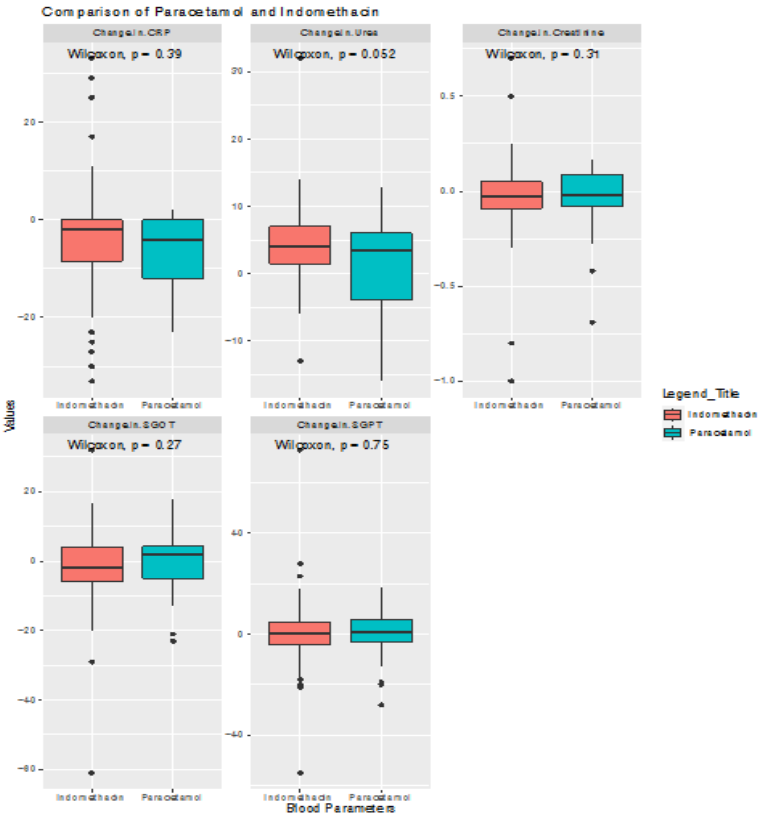

Fig 3 — Change of various blood parameters of the two set pf patients

Table 2 — *Patient requiring supplementary oxygen during treatment*

Outcome	Patients admitted with hypoxia		Patients admitted with no hypoxia	
Patient data	Paracetamol	Indomethacin	Paracetamol	Indomethacin
Patients admitted	5	11	67	61
Patients requiring supplementary oxygen during treatment	5	1	23	0

Our results showed that Indomethacin use is associated with a marked reduction in the duration and severity of symptoms. As depicted in Fig 2, a significant number of patients had symptomatic improvement even after two doses. Complete symptomatic recovery happens within 3-4 days in the Indomethacin arm, in contrast to 7-8 days in the paracetamol arm. Even in severe cases, the improvement in symptoms was rapid.

No study subjects had developed nausea or vomiting after administration of indomethacin, or gastro-intestinal bleeding in the form of hematemesis or melena. One patient who was admitted with acute gastroenteritis like symptoms (vomiting and loose motions) had persistent symptoms during the course of treatment. Though she developed mild hypoxia for a brief period of time, supplementary oxygen was not required.

There was no deterioration of renal- or liver-functions in the Indomethacin arm except in one patient with chronic kidney disease, whose creatinine went up by 0.5 mg% from 1.2 mg%.

Indomethacin use in 22 patients falling into the severe category was analysed separately. They received Indomethacin 75mg SR for a period of five days with Remdesivir. Though the patients had hypoxia at the time of admission, they had evidence of rapid relief of symptoms. However, there was a longer latency of recovery from hypoxia and all of them could be discharged by 14 days except the only patient who had pancreatitis, was discharged after 17 days. It is quite unlikely that Indomethacin caused the pancreatitis as it is under trial for the management of acute pancreatitis[17,18].

The anti-inflammatory efffect of Indomethacin is very

well-established[19]. SARS-Cov-2 is not a cytopahic virus, rather most of the complications of this disease is secondary to inflammation[19]. Indomethacin has both anti-viral and anti-inflammatory properties. It is quite unfortunate that early reports on this aspect cautioned the use of NSAIDs for COVID-19, insted of encouraging its use[20].

Conclusion

The administration of Indomethacin, along with the existing the standard protocol given by ICMR for the treatment of hospitalised patients with COVID-19, was significantly associated with decrease in the severity and duration of illness, without any significant adverse drug reaction. Further study is required to determine the benefit of Indomethacinalone for treatment of COVID-19.

Conflict of interest : The authors have no conflicts of interest to report.

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Data Statement : This study has been conducted with the following approval. Data can be accessed with the consent of the Ethics Committee

(1) Approved 03/08/2020, Institutional Ethics Committee, Narayana Medical College (Nellore 524003, India; +91 (0)8008086119; dean{at}narayanamedicalcollege.com), ref: NMC/ Ethics/Project/006/2020 and Ref. XXXVI/ Ethics/001/ 11/2020

(2) Approved 10/10/2020, Institutional Ethics Committee, Datta Meghe Institute of Medical Sciences (Sawangi (Meghe), Wardha - 442004, Maharashtra, India; +91 (0)7152 287701; icc.dmims{at}gmail.com), ref: DMIMS(DU)/IEC/2020-21/9034

(3) The trial has a registration number: ISRCTN 11970082

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