-Λ- **Signa Vitae**

EDITORIAL

Crying wolf in time of Corona: the strange case of ivermectin and hydroxychloroquine. Is the fear of failure withholding potential life-saving treatment from clinical use?

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1. Introduction

Since the beginning of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, over a hundred million people contracted the virus, putting a high pressure over hospitals and healthcare systems.

Hydroxychloroquine, lopinavir/ritonavir and azithromycin have been extensively used attempting to prevent or cure Coronavirus Disease 2019 (COVID-19) during the first wave. However, during the last few months, large clinical trials demonstrated the lack of efficacy of the abovementioned treatments [1–3].

Ivermectin is widely used to treat roundworms and ectoparasites infestation, but also has antiviral effects against RNA viruses. COVID-19 drug repurposing research focused on its possible clinical use. Ivermectin was able to inhibit SARS-CoV-2 replication in monkey kidney cell culture [4]. While its empirical use grew in Latin America, more than 45 trials investigating ivermectin in COVID-19 are ongoing all over the world.

Aim of this research letter was to understand if the administration of ivermectin in COVID-19 patients can reduce mortality.

We performed a meta-analysis of randomized clinical trials (RCTs) investigating the impact of ivermectin on mortality in COVID-19. All randomized studies reporting mortality data – comprising both published and preprints manuscripts –were included in our analysis. Two investigators independently assessed the compliance to selection criteria, selected the studies for the final analysis, and extracted data with divergences finally resolved by consensus. We followed methods previously described in details [5]. Briefly, we used Review Manager (RevMan, Version 5.4. The Cochrane Collaboration, 2020),
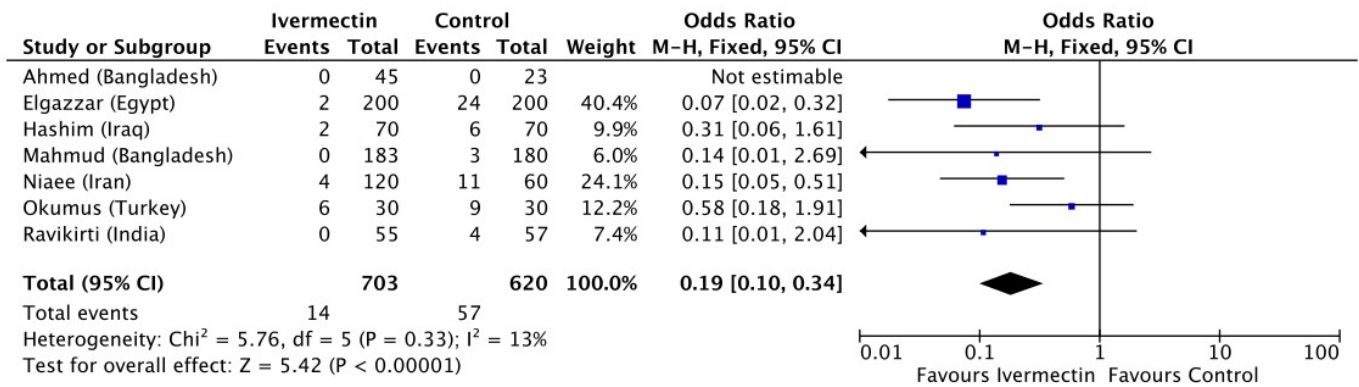
Mantel–Haenszel test and a fixed-effects model. The strength of the association between ivermectin administration and mortality was measured calculating the odds ratio. We focused on survival, as reported at the longest follow up available.

A total of 1323 patients were randomized in 7 RCTs performed in 6 countries. Four trials were multicentric. Ivermectin treatment resulted in a lower mortality when compared to placebo: 14/703 (2%) vs 57/620 (9%), $P < 0.01$, odds ratio 0.19 (0.10, 0.34), $I^2 = 13\%$ (Fig. 1). The funnel plot was symmetrical at visual inspection. Findings were confirmed at the Influence analysis (removing one study at time).

All the mentioned RCTs included only hospitalized patients. Four trials were placebo-controlled. Ivermectin doses ranged between 12-24 mg for an average 60 kilograms subject. Duration of treatment ranged between 1 and 5 days, as reported in Table 1.

In the present meta-analysis of RCTs, administration of ivermectin reduced mortality among patients hospitalized for COVID-19. A possible rationale for these findings, other than a direct activity of ivermectin against SARS-CoV-2, [4] may involve Strongyloides hyperinfection, an uncommon complication of dexamethasone administration, [6] which is overprescribed worldwide in COVID-19 patients.

Ivermectin for the treatment of COVID-19 followed the opposite pathway of hydroxychloroquine: use of hydroxychloroquine was supported at first by medical agencies worldwide, and later proven ineffective by several RCTs including the RECOVERY Trial [1]. On the contrary, ivermectin was mostly neglected so far and only used in a few countries; nevertheless, scientific community is progressively building a body of randomized evidence which points in favor of its use. After the ruinous experience during the first wave, however, physicians became more "skeptical" and less prone to use

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Odds Ratio M–H, Fixed, 95% CI
Ahmed (Bangladesh)	0	45	0	23		Not estimable
Elgazzar (Egypt)	2	200	24	200	40.4%	0.07 [0.02, 0.32]
Hashim (Iraq)	2	70	6	70	9.9%	0.31 [0.06, 1.61]
Mahmud (Bangladesh)	0	183	3	180	6.0%	0.14 [0.01, 2.69]
Niaee (Iran)	4	120	11	60	24.1%	0.15 [0.05, 0.51]
Okumus (Turkey)	6	30	9	30	12.2%	0.58 [0.18, 1.91]
Ravikirti (India)	0	55	4	57	7.4%	0.11 [0.01, 2.04]
Total (95% CI)		**703**		**620**	**100.0%**	**0.19 [0.10, 0.34]**
Total events	14		57			

Heterogeneity: Chi^2 = 5.76, df = 5 (P = 0.33); I^2 = 13%
Test for overall effect: Z = 5.42 (P < 0.00001)

Odds Ratio M–H, Fixed, 95% CI
Favours Ivermectin   Favours Control

FIGURE 1. Forest plot of studies reporting mortality on ivermectin versus control in COVID-19.

TABLE 1. Characteristics of included studies

Author*	Country	Disease severity	Daily ivermectin dose	Treatment duration	Participating centres	Available at
Ahmed S	Bangladesh	Mild	12 mg	5 days	1	Int J Infect Dis. 2020;103:214-216
Elgazzar A	Egypt	Mild to severe	400 mcg/kg (max 24 mg)	4 days	2	Preprint-doi.org/10.21203/rs.3.rs-100956/v1
Hashim HA	Iraq	Mild to severe	200 mcg/kg	2-3 days	2	Preprint-doi.org/10.1101/2020.10.26.20219345
Mahmud R	Bangladesh	Mild to moderate	12 mg	5 days	1	Clinicaltrials.gov - NCT04523831
Niaee MS	Iran	Mild to severe	200-400 mcg/kg	1-5 days	5	Preprint-doi.org/10.21203/rs.3.rs-109670/v1
Okumuş N	Turkey	Severe	200 mcg/kg	5 days	4	Clinicaltrials.gov-NCT04646109
Ravikirti RR	India	Mild to moderate	12 mg	2 days	1	Preprint-doi.org/10.1101/2021.01.05.21249310

* For data available at Clinicaltrials.gov, Responsible Party was indicated as author.

repurposed drugs in COVID-19 patients. Having cried wolf for too long may be preventing the spread of ivermectin use all over the world.

While modern medicine cannot do without ironclad evidence, in an emergency situation the use of a cheap medication without major side effects may be reasonable even if strong verification of its efficacy is still lacking. While there is an urge of large high quality RCTs, results from the reported trials all point in the same direction, and cannot be overlooked.

AUTHOR CONTRIBUTIONS

Pasquale Nardelli, Alberto Zangrillo and Giovanni Landoni designed the study. Gabriele Sanchini, Valery V Likhvantsev, Andrey G Yavorovskiy and Carolina Soledad Romero Garcia collected the data. Pasquale Nardelli and Giovanni Landoni analyzed the results and drafted the manuscript.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interests.

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