Protocol violations in López-Medina et al.: 38 switched ivermectin (IVM) and placebo doses, failure of blinding, widespread IVM sales OTC in Cali, and nearly identical AEs for the IVM and control groups

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re: López-Medina et al., Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial (*JAMA*, 2021; links to study paper and supplements are below).¹

Abstract

A randomized controlled trial for treatment of mild cases of COVID-19 conducted in Cali, Colombia reported no statistically significant differences in outcomes for its ivermectin (IVM) and placebo arms. A striking anomaly, however, was that certain adverse events (AEs) that are distinctive for the study's high-dose IVM use occurred at nearly identical rates in its IVM and placebo arms. The backdrop for these indicators of IVM use in study controls was widespread sales of IVM for COVID-19 in the Cali area during the study period, with 1.6 IVM doses sold over the counter for each case of COVID-19. The study compounded these risks of contamination of the control arm with critical errors in blinding and segregation of IVM v. placebo doses. A labeling error substituted IVM for placebo doses of 38 patients. Also, 5% dextrose solution was used for the first 64 patients in the placebo group, easily distinguishable from bitter tasting IVM. Given widespread availability and sales of IVM in Cali, lapses in segregation and blinding of IVM and control doses, and IVM-characteristic AEs in controls, the integrity of the study's control arm was violated. Some useful information can nevertheless be salvaged from outcomes of this study's IVM treatment arm, which had 0 deaths and generally mild symptoms, with AEs typical for high-dose IVM (replicated in the control group) that were generally mild and transient.

Introduction

On March 4, 2021, results of a randomized clinical trial by López-Medina et al. were published in *JAMA*, the subjects of which were generally young COVID-19 patients with mild disease.¹ The study was conducted by the *Centro de Estudios en Infectología Pediátrica* (CEIP) in Cali, Colombia. During the study's enrollment period of July 15 through November 30, 2020, Ivermectin (IVM) was administered to 200 subjects, with placebo given to 200 randomized controls. The time to resolution of symptoms was 10 days for the IVM group and 12 days for the controls, not a statistically significant difference, nor was the difference between 0 deaths in the IVM group and 1 in the controls. A striking anomaly, however, was that certain adverse events (AEs) that are distinctive for IVM use, especially at the high dose of this study, occurred at almost identical rates in its IVM and placebo groups. What were in effect these fingerprints of IVM use in the placebo arm will be considered with respect to: 1) extensive interest in and sales of IVM among Cali residents during the study period, and 2) critical errors in blinding and segregation of IVM v. placebo doses, including the substitution of IVM for placebo doses of 38 patients.

Interest, availability and OTC acquisition of IVM in Cali and environs during the study period

On July 9, 2020, a week before the CEIP study began recruiting patients in Cali, in the state of Valle del Cauca in Colombia, its mayor, Jorge Iván Ospina, announced that his city would begin distributing 10,000 doses of IVM to COVID-19 patients the following day.^{2,3} But these government distributions of IVM were far outpaced by OTC sales of IVM to the area's residents. As shown in Table 1, OTC sales of IVM, available without prescription in Colombia during the study period, quintupled in Valle del Cauca from June to July 2020. Sales of IVM during the study period of July through November 2020 totaled 154,919 units (each unit about one dose), 1.6 times the number of COVID-19 cases (95,387, see Table 2) during that period.

This surge in OTC sales of IVM at the start of the study period coincided with a spike in google searches for *ivermectina* to 33 times that for *vacuna covid* (COVID vaccine) in Valle del Cauca during the week of July 5 (Figure 1).⁴ Searches for *ivermectina* in the weeks beginning in July through November 2020 persisted at a

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high level, 2.7 times greater than that number for *vacuna covid*. Interest in IVM treatment of COVID-19 in Colombia was reflective of general attention in Latin America to such results from that region. Outcomes in Peru were of particular interest, with a 14-fold decrease in excess deaths with nationwide treatments of COVID-19 thru November 2020, $p=.002$ for this effect by state, then a 13-fold increase in excess deaths after IVM use was restricted under a new Peruvian president.⁵

Table 1. Sales of Ivermectin in liquid and capsule form in the Colombian state of Valle del Cauca, encompassing the study region, from January 2019 through November 2020.⁶ Units of liquid IVM were bottles each containing 5 ml of 0.6% IVM, and units of capsules were blister packs of 7 pills, 3 mg each.

Month	2019		2020	
	Capsules	Liquid	Capsules	Liquid
Jan	0	2,745	0	4,131
Feb	0	2,980	0	4,541
Mar	0	3,406	0	2,910
Apr	0	4,387	0	9,850
May	0	4,076	0	8,293
Jun	0	4,109	0	10,503
Jul	0	4,727	935	48,943
Aug	0	3,938	3,463	34,228
Sep	0	3,548	821	15,887
Oct	0	3,915	757	21,093
Nov	0	4,225	949	27,843
Dec	0	3,206	—	—

Table 2. COVID-19 cases in the Colombian state of Valle del Cauca, encompassing the study region, from June through December 2020, by month.⁷

Month	June 2020	Jul 2020	Aug 2020	Sept 2020	Oct 2020	Nov 2020	Dec 2020
Number of cases	6,365	14,432	21,785	15,172	20,072	23,926	28,165

The CEIP study’s exclusion of patients who had previously taken IVM within 5 days of first IVM or placebo dosage, allowing patients who had used IVM 6 or more days prior, was unusually permissive and may have reflected difficulty in finding subjects in the Cali region who had not used IVM for prophylaxis or treatment. A much longer exclusion period for IVM use would be expected given that most randomized clinical trials for IVM treatment of COVID-19 monitored effects 10 days or more after last IVM dose.⁸ Also, although the elimination half-life of IVM is 18 hours after oral dosing in human subjects,⁹⁻¹³ this half-life is four-fold greater for the major metabolites of IVM,⁹ and significant biological effects have been manifested in humans^{9,14,15} and rabbits¹⁶ up to one month after a single IVM dose.

Failure to blind and segregate IVM and placebo doses

The study reported that “on October 20, 2020, the lead pharmacist observed that a labeling error had occurred” beginning September 29 such that 38 intended placebo doses were actually IVM (study paper, p. 3; study protocol, p. 43). Dr. Lopez-Medina commented in a rebuttal to this criticism in posted comments for this paper that this mistaken substitution of IVM for placebo solution for 75 patients was not of concern due to adjustments subsequently made in the study protocol and analysis. Indeed, 75 new patients were recruited and randomized, and the 75 patients who all received IVM Sept 29 thru Oct 15 were excluded in the primary analysis (eTable2, eTable5, eFigure 3) but included in the other analyses (eTables 1, 3, 4, 6, 7; eFigures 1, 2).

The key point is that this lapse in quality control in the most basic of study procedures raises questions as to the study's credibility.

Another problem was the specification and use for the first 64 patients in the control group (supplement 2, eFigure 1) of 5% dextrose solution as the placebo, easily distinguishable compared with the bitter taste of the IVM. In recognition of this blinding breakdown, “because blinding could be jeopardized due to the different taste and smell of ivermectin” and sugar water (study paper, p. 2), during these six weeks, the study limited study participants to 1 patient per household. Yet IVM’s bitter taste was easily ascertainable from an internet search, family or friends.

Figure 1. Google trends for *ivermectina* v. *vacuna covid* in the Colombian state of Valle del Cauca, encompassing the study region, during and prior to the CEIP study enrollment period of July 15 through November 30, 2020. The number of google searches for *ivermectina* (Spanish for ivermectin) spiked from 2 times to 33 times that for COVID vaccine (*vacuna covid*) from the last week in June to the first week of July 2020. The total number of searches for *ivermectina* in the weeks beginning July through November 2020 was 2.7 times greater than that number for *vacuna covid*.⁴

Protocol amendment 2 reported that the study’s provider of IVM solution, Tecnoquímicas, could not initially confirm that it could produce a like tasting placebo solution, but did provide that on August 26 (study protocol, p. 43). This solution was described as having “similar organoleptic properties to ivermectin,” with no specifics of composition or report of taste testing provided (study paper, p. 2). But a UN report of 2011 described Tecnoquímicas as having an uneven technical capability and as lacking necessary capability for performing bioequivalence studies¹⁷ and was fined for participation in a price-fixing scheme in 2013.¹⁸ This deficiency plus the study’s decision to begin using dextrose solution, which tastes nothing like IVM, calls taste matching of the new placebo solution to IVM into question. The study’s lead author was asked repeatedly beginning on March 22, 2021 to specify the composition of this new placebo and has refused to do so, even though he has provided detailed deidentified patient data in response to other queries. He again refused to provide any information about the content of this placebo when asked about this in an email of August 26, 2021 as part of a discussion on another topic.¹⁹ So all that is known is that a technologically challenged company that at first could not provide a placebo has now provided one purported to have “similar organoleptic properties to ivermectin,” the composition of which is not specified.

Almost identical rates of IVM-distinctive AEs that occurred for IVM also occurred in the placebo group

The study protocol specified tracking of several adverse events (AEs) which it called “security parameters” (study protocol, pp. 13-14) for its high IVM dose of 1,500 µg/kg over five days, 7.5x the IVM typical dose of 200 µg/kg. It described those AEs as having “historically been reported in subjects receiving ivermectin” (study protocol, pp. 13-14). Those AEs which commonly occur for IVM, especially at high doses, that were tracked included dizziness, blurred vision, nausea and diarrhea. Although IVM’s side effects are transient and rarely serious, its biochemistry is such that its most characteristic AEs are neurological.^{12,20,21} While a transient reduction in visual acuity lasting a few days, including blurred vision, is an AE characteristic for ivermectin when given at 400-800 µg /kg and above,^{22,23} such disturbances in vision are rare in COVID-19 cases.²⁴

But blurred vision was reported for 11.6% of the study’s control group, almost identical to the 11.3% for the IVM group (Table 3). Photophobia, the most common ocular symptom of COVID-19,²⁴ which is not a common IVM AE, was only exhibited at 2.0% and 3.3% for the control and IVM groups. Dizziness, another neurological symptom associated with IVM,²⁵ especially at higher doses, occurred in 34.3% of controls, almost the same as the 35.6% incidence for the IVM group. But dizziness was reported in COVID-19 meta-studies at incidences of only 8.7%²⁶ and 6.8%.²⁷ Although nausea and diarrhea occur regularly with COVID-19,^{26,28} these are also common AEs for IVM,²⁵ and incidences of these due to IVM and COVID-19 would be expected to be additive. Yet for the control and IVM groups, respectively, the percentages of AEs for diarrhea were 32.8% and 30.2%, and for nausea, 23.7% and 24.0%. Thus, the tracking parameters that the CEIP study investigators described as “security parameters” for the high dose IVM used, historically reported in subjects taking IVM, showed up almost identically in the control and IVM study arms.

Table 3. Summary of adverse effects, any grade commonly associate with IVM as reported in eTable 7 of López-Medina et al.²⁹

Adverse event	Ivermectin (n=275)	Placebo (n=198)
Dizziness (number, %)	98 (35.6%)	68 (34.3%)
Diarrhea (#, %)	83 (30.2%)	65 (32.8%)
Nausea #, %)	66 (24.0%)	47 (23.7%)
Disturbances of vision, any (#, %)	44 (16.0%)	28 (14.1%)
Photophobia (#, %)	9 (3.3%)	4 (2.0%)
Blurry vision (#, %)	31 (11.3%)	23 (11.6%)

Change in the study’s primary outcome in its third protocol amendment. During the study’s first five days, when all of its IVM doses were administered, 21.5% of the IVM treated patients who had previously been in mild, symptomatic condition became totally free of symptoms, while only two patients (1%) deteriorated to require ICU hospital care (the control group had similar trends). In general, a low percentage of patients in the study experienced a deterioration in disease status (study paper, p. 3). So in the third protocol amendment (study protocol, p. 43), the originally stipulated primary outcome, time until worsening by 2 or more points in a 7-point scale, was changed to time to resolution of symptoms. The new primary outcome measured the status of patients through day 21, more than two weeks after the last dose of IVM in the treatment group.

Given widespread IVM availability OTC in Cali, lapses in segregation and blinding of IVM and control doses, and IVM-characteristic AEs in controls, the integrity of the study’s control arm, was violated

Given serious lapses in study procedures—mix-up of 38 placebo doses with IVM doses and failure to reliably blind IVM from placebo doses—and the almost identical matches in rates of various characteristic AEs for high-dose IVM, the following scenario cannot be excluded with confidence. Study participants who could taste that their placebo dose was not ivermectin and felt sicker purchased and used IVM in the same 0.6% liquid

solution available OTC at a pharmacy. The result was almost identical rates of characteristic IVM AEs as well as similar clinical outcomes (0 IVM deaths, 1 control death) in two study arms.

Conflicts of Interest among the study's investigators.

While it is common for studies to receive funding from various pharmaceutical manufacturers, the declared funding of both this study and fees to investigators by companies with directly competing interests to successful treatment of IVM, in conjunction with these lapses, raises additional concerns (study paper, p. 6). Three of the study investigators reported receiving grants and personal fees from companies that manufacture COVID-19 therapeutics, collectively including Sanofi Pasteur, a vaccine manufacturer; Janssen, a J&J vaccine partner; and GlaxoSmithKline, Merck, and Gilead, which manufacture COVID-19 drugs. Although IVM has been proposed for use complementary to, not in place of vaccinations for COVID-19, cascading national successes with IVM treatments could curtail future sales of other COVID-19 therapeutics.

The exact wording of the “Conflicts of Interest Disclosures” section of this paper (p. 6) is the following: “Dr López-Medina [lead author] reported receiving grants from Sanofi Pasteur, GlaxoSmithKline, and Janssen and personal fees from Sanofi Pasteur during the conduct of the study. Dr López reported receiving grants from Sanofi Pasteur, GlaxoSmithKline, and Janssen and personal fees from Sanofi Pasteur during the conduct of the study. Dr Oñate reported receiving grants from Janssen and personal fees from Merck Sharp & Dohme and Gilead outside the submitted work. Dr Torres reported receiving nonfinancial support from Tecnoquímicas unrelated to this project during the conduct of the study. No other disclosures were reported.

Conclusion

Given AEs distinctive for IVM use in study controls and failures of blinding and boundaries between IVM and placebo arms, results for study controls are unreliable. Some useful information can nevertheless be salvaged from outcomes for this study's IVM treatment arm, in which no deaths and generally mild symptoms occurred, with AEs typical for high-dose IVM (replicated in the control group) that were generally mild and transient.

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Conflicts of Interest: The authors declare no conflict of interest

Links for López-Medina et al.

Study paper: <https://jamanetwork.com/journals/jama/fullarticle/2777389>.

Supplement 1, [study protocol](#). Supplement 2, [Tables and Figures](#).

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