Thought Experiments

Chloroquine is a safe parachute: a COVID-era fairy tale

A cloroquina e o paraquedas: uma fábula da era COVID19

Renato Gorga Bandeira de Mello

Universidade Federal do Rio Grande do Sul (Porto Alegre). Rio Grande do Sul, Brazil. renatogbmello@gmail.com

ABSTRACT | The current scenario of COVID-19 has brought so many anxieties for health service professionals and patients. It is natural for society to demand quick responses. However, knowledge derived from scientific studies requires high financial investment, proper methodology and hard work to get trustful data to be analyzed to provide robust results, therefore, to be translated into evidence based medical actions directed to diseased populations. However important scientific steps have been "skipped" to try to speed up responses required by the current moment. More worryingly, studies of low methodological quality are being published and inappropriate conclusions have been gaining popularity in newspapers and unreasonable posts in the media. Based on heuristics, scientific assumptions and data so far published on chloroquine and hydroxychloroquine, this text presents a narrative, metaphorical and somewhat sarcastic discussion about unreasonable medical prescription during the Sars-Cov2 pandemic, drawing a critical appraisal over hydroxychloroquine recommendations claiming the parachute paradigm or compassive use for viral suppression in COVID-19.

KEYWORDS: Hydroxychloroquine. Chloroquine. Parachute. COVID-19.

RESUMO | O cenário atual da COVID-19 tem gerado muitas angústias. É natural que a sociedade anseie por respostas rápidas. Entretanto, o conhecimento gerado por estudos científicos demanda alto investimento, rigidez metodológica e árduo trabalho para que dados coletados sejam confiáveis e gerem resultados robustos e, assim, possam ser aplicados diretamente à população adoecida. Passos científicos importantes têm sido "pulados" para se tentar dar celeridade às respostas exigidas pelo momento atual. De forma mais preocupante, estudos de baixa qualidade metodológica estão sendo publicados e conclusões inapropriadas têm ganhado as páginas dos jornais e posts pouco racionais nas mídias. Baseado em heurística, preceitos científicos e nos dados até aqui divulgados sobre cloroquina e hidroxicloroquina, este texto trata de forma narrativa, metafórica e algo sarcástica o tema através de uma fábula aplicável ao cenário atual, traçando um paralelo liberal entre o paradigma do paraquedas e as recomendações de hidroxicloroquina para tratamento da COVID-19.

PALAVRAS-CHAVE: Hidroxicloroquina. Cloroquina. Paraquedas. COVID-19.

Submitted 07/01/2020, Accepted 07/19/2020, Published 08/26/2020
J. Évid-Based Healthc., Salvador, 2020 June;2(1):93-96
Doi: 10.17267/2675-021Xevidence.v2i1.3091 | ISSN: 2675-021X

How to cite this article: Mello RGB. Chloroquine is a safe parachute: a COVID-era fairy tale. J Évid-Based Healthc. 2020;2(1):93-96. doi: 10.17267/2675-021Xevidence.v2i1.3091

CC BY

The backpack and the parachute

Is a backpack always a safe parachute? Some may claim it is, because one resembles another as both can be carried in the back.

An airplane goes through flight difficulties, there seems to be mechanical failure. There is panic, insecurity. Until a passenger exclaims:

"Look, there are several backpacks here! They must be parachutes! "

Immediately most passengers understood that there was a parachute there, because someone claimed it was a parachute, because there were some backpacks there.

No one checked or tested whether, in fact, they were parachutes.

Behold, someone says that the plane can crash.

Everyone in panic! As somebody said the plane will crash and there are parachutes available, people run to desperately wear the backpacks.

The pilot didn´t announce at any time that the plane is crashing and never ordered people to seek for parachutes, because he knows the greatest probability is, even after some difficulty, he will be able to either reverse the problem (I´d say 75 to 95% probability depending on the aircraft previous conditions and problem severity).

Just behind came a second plane! Passengers travelling in it experiencing minimal turbulence, see a horde of passengers wearing backpacks jumping from the first aircraft and, alarmed by what they just watched, just in case, they also think they should wear backpacks.

Frightened by what they see, even though their flight is safe, they take the same action as done by passengers in the first airplane and everyone jump wearing backpacks.

Let's imagine some possible scenarios to explain what really happened:

Assuming the airplane makes an emergency landing and the backpack really contains a kind of parachute that had never been tested. Furthermore, there are 200 people on board and 100 parachutes available.

Scenario A

Of the 100 passengers that jumped wearing the parachute, 90 survived. Among those who remained on board, 70 resisted. That is, 20 fewer people died among those who jumped out using the safety device.

Scenario B

Of the 100 that jumped, 70 survived; of the 100 that remained on board, 70 resisted. That is, the same number of deaths in both groups.

Scenario C

Of those who jumped, 70 survived; of those who remained on board, 90! 20 more resisted among those who remained inside the plane.

Then now it is time to think and decide! Without knowing which scenario is the real one, wondering all three are equally probable, would you wear the backpack and jump off the plane?

The same prerogative must be applied when choosing to use or prescribe a medication. It is reasonable to know the odds first and not to "jump" blindly to the clouds. It is imperative to consider "previous airplane technical status" and "flight conditions" and, more than everything, if the "backpack" is a truly effective "parachute" before taking any action.

As described above, in Medicine it is not recommended to "jump" with a "backpack" before knowing if it is an effective "parachute". Primum non nocere is a cornerstone of health care! Except in situations of extreme biological plausibility, it is not assumed that "backpacks" have a "parachute effect" without first testing them in a properly designed experiment. Because sometimes "backpacks" or even "parachutes" can do more harm than good!

When it comes to science, it is assumed that the "Scenario B" (equal effect between active and inert treatment) is the most probable answer and, from that, a properly controlled study is built to test and refute

this hypothesis and then quantify whether something is really effective. Beyond that it is necessary to compare measured effect in the treatment arm with a control group, because it is the only way to make any inference of effect regardless of bias or observational interferences (Hawthorne effect).

It is imperative to run a controlled experiment to address treatment effect to decrease clinical outcomes incidence, since diseases have their own course; a natural history: even when no treatment is given, there are a number of patients who will spontaneously recover over time, another who will survive with sequelae and another who will not survive. These numbers vary significantly depending not only on disease natural course and treatment prescribed; it can be directly influenced by patient´s baseline characteristics as well as by delivered quality of care. That is why there is no absolutely known number that can be used arbitrarily as a comparator in scientific studies.

Recovered patients could have improved in any way due to the clinical course of a given disease. Therefore, in clinical trials it is necessary to have a control group to verify if there is lower clinical outcome incidence in the treatment group compared to the placebo group. Thus, if there is a real difference, we reject null hypothesis and, then, accept the alternative hypothesis: superiority of the drug in relation to the control (Scenario A) or greater harm caused by the intervention (scenario C described above). But, to accept that the difference found is caused by the treatment itself (either benefit or harm), groups must be very similar to allow unbiased comparisons. And the best way to achieve this homogeneous distribution without researcher influence is through intervention random allocation, a method based on chance alone to assign a participant to one of study´s arm. Those are the main assumptions of a so called Randomized Clinical Trial.

Randomization reduces the risk of external interference on treatment assignment and minimizes potential imbalance between groups regarding possible intervenient characteristics - either measured and unmeasured. For example, if treatment is intentionally given to seriously ill patients and healthier individuals are selected as unpaired controls, it is very likely that the number of deaths will be higher among those who took the drug just because they were sicker. Someone could assume that the tested drug increases mortality rates, ignoring that the difference is possibly due to the imbalance between groups. What is called "randomization" allocates patients randomly among groups, generating “the magic of randomization”: all characteristics (age, sex, presence and severity of diseases) will be very similar in the two or more study´s arms, allowing, in an ideal scenario, that the only difference between groups is the intervention itself. Then, and only then, robust interpretations are allowed.

COVID-19, Chloroquine and Science

The current scenario of COVID-19 has brought so many anxieties for healthcare professionals and patients. It is expected society to demand quick responses. However, knowledge derived from scientific studies requires proper methodology, hard work and high budgets and grants to collect trustful data to be analyzed so then it may provides robust results and finally to be translated into evidence based medical actions directed to specific ill populations .

However important scientific steps have been “skipped” to try to speed up responses required by the current pandemic. More worryingly, studies of low methodological quality are being published and inappropriate conclusions have been gaining popularity in unreasonable news and posts in the media.

Based on heuristics, scientific assumptions and data so far published on chloroquine and hydroxychloroquine efficacy, it is most probable that hydroxychloroquine recommendations that claim the parachute paradigm as well as the compassive use as ground stone are flawed! Maybe it is a consequence of several cognitive biases in those who want to find a simple solution for a complex problem. Perhaps a quackery imposed by those who defend it and want to harvest personal or political benefits. For sure it is not derived from appropriate scientific reasoning.

However, another topic has to be considered: even if the results found in a RCT indicate that a specific drug is more effective than placebo, this is not yet enough to conclude its clinical relevance. Then further analysis should be considered to interpret

treatment´s clinical impact. A measure called NNT, or the "number needed to treat" to reduced 1 event, is very useful to allow proper conclusions over treatment effect. For example: NNT equals to 30 means that for each 30 patients treated, 1 death will be prevented. This number is a weighted absolute risk reduction difference between groups. However it is still not sufficient to allow final conclusions about clinical impact as the NNT must be confronted with the NNH - number needed to treat to cause harm. So it is mandatory that the number of patients "saved" by a drug is substantially greater than the number of subjects harmed by a drug.

Below, I present potential scenarios of hydroxychloroquine clinical effectiveness to prevent death in severe COVID-19 patients under intensive care.

If A is the real scenario, the result shown will not be a 10% reduction in mortality - from 80 to 70%. It will be, in a realistic hypothesis, somewhat around 71 patients saved in 100 with chloroquine and 70 saved without chloroquine. That is, an absolute reduction of death around 1% and a NNT of 100 to reduce 1 death.

In an optimistic hypothesis, an astonishing resultwould be (I´d say almost illusory) = 74 saved in the treatment group compared to 70 survivors in the standard of care treatment group. In absolute terms, the difference would be of 4%, that is, 25 people would have to be treated with chloroquine to reduce one death. This number reflects a clinical impact considered excellent in medicine. For note that, even among treated individuals, there will be a portion of these patients who will die despite medical care plus medication!

There are no "parachute" remedies in medicine, I dare to say! Any treatment must be tested in well designed and powered Randomized Clinical Trials. Potential harm associated with medical treatment may never be ignored, thus the so-called “compassionate use” must be seen cautiosly, as there is always a possibility that "scenario C" described above is the real one, that is, more deaths in the intervention group compared to the placebo group.

We are facing an extremely complex situation which, as anticipated, demands complex solutions. Only science can provide trustful answers regarding treatments and vaccines effectiveness. Science must thrive over beliefs and magical exits. Because of the aforementioned reasons, claiming for new drugs or new treatment applications without solid knowledge about biomedical statistics and medical science methodology and medical reasoning is not only wrong, it is dangerous.

Acknowledgments

To medical colleagues who, even in the face of society's anxieties, their patients´ suffering as their own fears and distresses, have not given up on science, ethics and medical rationality. And to Carl Sagan (in memorian) for his scientific legacy and for his endeavor to stand for science and significantly improve science communication to the public.

Competing interests

No financial, legal or political conflicts of interest involving third parties (government, companies and private foundations, etc.) to be declared for any aspect of the submitted paper (including, but not limited to grants and funding, participation in advisory council, study design, manuscript preparation, statistical analysis, etc.).