

The European Medicines Agency (EMA) has advised taking HES off the market.

There are numerous questions arising from this decision:

First, and most importantly, do you agree?

Then: Since 2013, we have already several limitations of HES (in duration, dose and indications), which have been –albeit still questionable– generally accepted. Currently, HES is indicated for surgical and trauma patients with hypovolaemia caused by acute blood loss when crystalloids alone are not considered sufficient. If the “ban” is accepted, (how) can we replace HES in these patients? Gelatins (Less effective), or albumin (money!!!), or can we assume/hope that there is no case where crystalloids are not sufficient? Indeed, don't we need any colloid anymore?

The arguments of EMA are another topic to discuss: a) doctors ignore contraindications, b) it is too difficult to distinguish between patients who might profit or be harmed from HES; c) further measures would be ineffective. Do you agree these arguments? The authority banning from utilizing a drug because of ignoring contraindications, is this not a limiting behavior one considers fit for immature? Furthermore: If you start with “doctors ignore contraindications”, can it be possible we can ban any existing drug? (Or where is the breaking point?)

HES's scientific history is shameful. Can it be possible, that maybe-just maybe- this fact has affected the recommendation of EMA? (A Turkish quote says (liberally translated): “Do not forsake the church, even if you are angry with the priest”). As a matter of fact, we need to be more suspicious about the studies comparing different types of fluids, no matter if the results are “pro” or “con” the use of HES. How do you comment different studies?

Editor

Nüzhet Mert Şentürk

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Hydroxyethyl starch: the Paradigm of Eminence-Based Versus Evidence-Based Medicine-1

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It is an honor and a pleasure to participate into this pro/con debate for the TJAR. The invitation from the Chief Editor of TJAR, Prof. Nuzhet Mert Senturck to participate in a PRO/CON debate on use of Hydroxyethylstarch (HES), has been a nice surprise and I immediately accepted. Interestingly, Prof. Nuzhet Mert Senturck, sent to us-Prof. Abreu De Gama as PRO and to myself as CON-a “debate intro” note to address our contribution, where he reports: “*The European Medicines Agency (EMA) has advised taking HES off the market. (...) HES's scientific history is shameful. Can it be possible, that maybe-just maybe-this fact has affected the recommendation of EMA? (...) How do you comment different studies?*”

In this PRO/CON confrontation we will present HES history (in this document) and HES-related clinical evidence (to be published in a future issue of this journal) along with a reply to possibly divergent positions that might emerge from the Prof Abreu De Gama manuscript.

HES history

HES was introduced in clinical practice in the 1960s, since then concerns on its safety and efficacy have been consistently and extensively raised (1-3). As early as in 1968, it was reported abnormal massive bleeding in patients that received HES and Authors commented: “(...)there is need for further investigation (...)in patients being transfused with this substance” (4). In 1975, Alexander B and coll reported: “(...)the hemostatic defect associated with the use of (HES-like) plasma substitutes is a form of induced von Willebrand-disease or disseminated intravascular clotting, ensuing from precipitation and removal of v. W. factor(s), Factors VIII and I, microcirculatory abnormality, and platelet malfunction” (5). These evidence were further confirmed in 1981 when was reported: “Following massive infusions,(...) a wide variety of laboratory abnormalities were observed, and hemorrhage was documented(...)” (6). In 2002 the Blood Products Advisory Committee, recommended the Food and Drug Administration (FDA) to change the labeling of a 6% HES product because of the increased risk of bleeding during cardiopulmonary bypass in patients whose coagulation status is already impaired; this request was approved by the FDA in 2003 that added a warning statement (7).

Additional concerns, related to renal damage, were reported since 1991 when was found: “(...)acute deterioration of an already existing nephropathy” with development of transient renal failure in patients underwent to hemorheological therapy through hemodilution (8). These evidence were further confirmed in 1993 when renal histological lesions on transplanted kidneys associated with HES use were described (9, 10). In 2008, was reported that:

“fluid resuscitation with(...) HES(...) is harmful in patients with severe sepsis. At recommended doses, it causes renal impairment, and at high doses, it impairs long-term survival. (...)until long-term studies -will be accomplished- (...)HES solutions should be avoided” (11). In 2012, two large clinical trials reported more alarming evidence on HES safety: the 6S trial demonstrated an enhanced risk of death and of renal-replacement therapy in ICU patients treated with HES than in patients treated with Ringer’s Acetate solution; the CHEST study showed that: *“(...)the use of HES resulted in an increased rate of renal-replacement therapy”; “(...)there are no evidences that resuscitation with 6% HES (130/0.4), as compared with saline, in the ICU provides any clinical benefit* (12, 13).

Of interest, since 2010, Joachim Boldt -a German anesthesiologist and worldwide known scientist, an “eminence” in fluid therapy and a strong supporter of HES- was accused of forgery and falsification of study data, indicted into a penal trial, stripped of his professorship and he is currently under criminal investigation (14). After that, >90 studies related to HES have been withdrawn by international anesthesia and critical care journals (15). His case has been included among the biggest medical research scandal and his fraudulent studies caused significant harm to critically ill patients (16). In 2013, a meta-analysis on HES use in ICU patients-that excluded data from Boldt’s studies- showed an increase risk of acute kidney injury and higher mortality (17). In 2013, because of the growing evidence on potential risks associated with HES use, the German Federal Institute for Drugs and Medical Devices required to EMA-PRAC to withdraw HES from the market (18). At an initial evaluation, in June 2013, the EMA-PRAC suggested to suspend HES market authorization (19). In November 2013 -also because of the producers pressures (20, 21)- the PRAC made a step back and delivered restrictive criteria for HES clinical use: *“HES solutions may continue to be used in patients to treat hypovolaemia(...) caused by acute (...)blood loss, where treatment with alternative infusions solutions known as ‘crystalloids’ alone are not considered to be sufficient* (22). Similar criteria were delivered by the by the Food and Drug Administration (FDA) in US (23, 24).

In 2016 the European Society of Anaesthesiologists accepted to act as clinical research organization for the HES producers companies and launched two “safety and efficacy” trials sponsored by the HES producers: Phoenixis (long-lived bird that cyclically regenerates or is otherwise born again) on HES use in the perioperative setting and Thetys (daughter of Uranus and Gaia, sister and wife of Titan-god Oceanus, mother of the Potamoi -the Rivers- and the Oceanids -the Oceans-) on HES use in trauma patients.

On February 2017, a US consumer advocacy organization (“Public Citizen”) sent a petition to FDA to request the immediately remove from the market of HES solutions *“because the solutions’ risks outweigh their limited benefits and there are a number of other, safer alternative solutions for the uses for which HES solutions are approved”* (3).

On October 2017, EMA was called to start a new HES product evaluation following the request of the Swedish Medical Products

Agency that reported data from two drug utilization studies that took place in 11 European countries: HES use is associated with non-adherence to current product information in 67%-77% and non-adherence to HES contraindications in 20% to 34% in an estimate 750.000-1.5 million European patients exposed yearly. *“Consequently, in view of the serious public health impact, Sweden considers suspending the marketing authorizations for the HES containing medicinal products, and requests an urgent review of the matter at the European level”* (25). In January 2018, the PRAC recommended that: *“HES solutions for infusion be taken off the market across Europe because previously announced measures that were put in place to protect patients have not been effective”* (26). The PRAC recommendation was confirmed by EMA’s Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) but before the decision becomes legally binding, an endorsement of the European Commission is required. After that, some anesthesia and re-animation national societies (France, Spain, Czech Republic) have questioned this decision and the plenary meeting of the Standing Committee on Medicinal Products for Human Use on April 2018, decided: *“in light of these new questions, it was agreed that the Commission would suspend the decision making procedure and refer the CMDh position/PRAC recommendation back to the Agency for further consideration”* (27). Final decision will be taken in a future meeting.

Of note, on February 2018, Prof Bernhard Zwißler –the President of the German Society of Anaesthesiology and Intensive Care (DGAI)- wrote a letter to the National Anaesthesiologists Societies Committee (NASC), the World Federation Of Societies of Anaesthesiologists (WFSA) and to the European Society of Anaesthesiology (ESA) where he states: *“(...)DGAI is very concerned about the current pharmacovigilance procedure regarding HES-containing solutions. (...)the PRAC of the EMA recommended the suspension of the marketing authorisation of this - from our point of view - very important and clinically valuable medicinal product”*. He also solicited: *“Thus, we would like to ask you to make an impact through your local authorities on the decision taken by the European commission. Moreover, we would like to suggest publishing an article which critically discusses the decision of the EMA in the EJA(...) . This Artikel will be sent to the European Commission and the EMA”* (28).

In response to this request, a group of British, Australian, Danish and German scientists appealed to the Director General of World Health Organization (WHO) claiming for the need to *“protect patients by banning the use of HES solutions worldwide”* (29). Furthermore, the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) and the national societies of Iceland, Denmark, Finland, Sweden and Norway, published a letter where they fully support the recommendation to suspend the market authorization of HES solutions in the name of the guiding principle of *primum non nocere* (first do no harm) (30).

It is now time for Nemesis (“The Ineludible”)....justice brought by the time) to come for the appropriate retribution against those who succumbed to *hubris* (the excess of self confidence that –according Aristotle definition- turns into: “shaming the victim”).

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