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Azul de metileno no tratamento da síndrome vasoplégica em cirurgia cardíaca. Quinze anos de perguntas, respostas, dúvidas e certezas

Methylene blue for vasoplegic syndrome treatment in heart surgery. Fifteen years of questions, answers, doubts and certainties

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Resumo

Objetivo: **Existem fortes evidências de que o azul de metileno (AM), um inibidor da guanilato ciclase, é uma excelente opção terapêutica para o tratamento da síndrome vasoplégica (SV) em cirurgia cardíaca. O objetivo deste artigo é rever o papel terapêutico do AM no tratamento da SV.**

Métodos: **Revisão da literatura em período de 15 anos.**

Resultados: **1) A heparina e inibidores da ECA são fatores de risco; 2) Nas doses preconizadas é droga segura (a dose letal é de 40 mg/kg); 3) O AM não causa disfunção endotelial; 4) O efeito do AM só aparece em caso de supra-regulação de óxido nítrico (NO); 5) O AM não é um vasoconstritor, pelo bloqueio do sistema GMPc ele "libera" o sistema AMPc, facilitando o efeito vasoconstritor da noradrenalina; 6) A dosagem mais utilizada é 2 mg/kg em *bolus* endovenosa, seguida de infusão contínua, pois a concentração plasmática decai acentuadamente nos primeiros 40 minutos; 7) Existe possível "janela de oportunidade" para efetividade do AM.**

Conclusão: **Embora não existam estudos multicêntricos definitivos, a utilização do AM no tratamento da SV em cirurgia cardíaca é, na atualidade, a melhor, mais segura e barata opção, sendo contribuição brasileira.**

Descritores: **Síndrome vasoplégica. Azul de metileno. Procedimentos cirúrgicos cardiovasculares. Circulação extracorpórea. Doenças vasculares. Resistência vascular/efeitos de drogas. Complicações pós-operatórias.**

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Abstract

Objective: **There is strong evidence that methylene blue (MB), an inhibitor of guanylate cyclase, is an excellent therapeutic option for vasoplegic syndrome (VS) treatment in heart surgery. The aim of this article is to review the MB's therapeutic function in the vasoplegic syndrome treatment.**

Methods: **Fifteen years of literature review.**

Results: **1) Heparin and ACE inhibitors are risk factors; 2) In the recommended doses it is safe (the lethal dose is 40 mg/kg); 3) The use of MB does not cause endothelial dysfunction; 4) The MB effect appears in cases of nitric oxide (NO) up-regulation; 5) MB is not a vasoconstrictor, by blocking of the GMPc system it releases the AMPc system, facilitating the norepinephrine vasoconstrictor effect; 6) The most used dosage is 2 mg/kg as IV bolus followed by the same continuous infusion because plasmatic concentrations strongly decays in the first 40 minutes; 7) There is a possible "window of opportunity" for the MB's effectiveness.**

Conclusions: **Although there are no definitive multicentric studies, the MB used to treat heart surgery VS, at the present time, is the best, safest and cheapest option, being a Brazilian contribution for the heart surgery.**

Descriptors: **Methylene blue. Cardiovascular surgical procedures. Extracorporeal circulation. Vascular diseases. Vascular resistance/drug effects. Postoperative complications.**

INTRODUCTION

As a historical review, three facts specifically mark the vasoplegic syndrome (VS) as a Brazilian contribution to cardiac surgery with cardiopulmonary bypass (CPB): a) Its description by Gomes et al. [1-3], in 1994; b) The proposal, also in 1994, that vasoplegia´s phisiopathology was cyclic GMP-dependent and methylene blue (MB) as its treatment [4] and; c) The first documentation of this therapeutic proposal´s efficiency in patients submitted to cardiac surgery presented by Andrade et al. [5], in 1996, at the Brazilian Society of Cardiovascular Surgery Congress.

Although MB has been used for over 15 years in the treatment of VS, few are the quality clinical studies that permit the treatment to become a protocol. Three studies involving a higher number of patients deserve particular citations: 1) In 2003, Leyh et al. [6,7] reported, in Germany, 54 cases of cardiac surgery patients not carrying bacterial endocarditis who had been treated with MB, with over 90% of the patients responding to the treatment; 2) Levin et al. [8-10], in Argentina, reported the incidence of 8.8% of VS in 638 patients. Among the 56 vasoplegic patients randomly receiving MB or placebo there was no mortality in the group treated with MB and it was possible to discontinue vasoconstrictors in a short period time, with less consequential morbidity and mortality. Whereas, in the placebo group two deaths occurred and the use of amines lasted in average 48 hours, with higher incidence of respiratory and renal problems; 3) From the prevention point of view, Ozal et al. [11], in Turkey, showed in a prospective and randomized study that MB was associated to a minor incidence of vasoplegia and amines use.

As emphasized in the title, the objective of the present paper is to review the MB role in the treatment of VS in cardiac surgery, with emphasis on what we have learned on "fifteen years of questions, answers, doubts and certainties". To help readers, the abbreviations used are: AMPc = cyclic adenosine monophosphate; CPB = cardiopulmonary bypass; ecNOS = endothelial constitutive nitric oxide synthase; GMPc = cyclic guanosine monophosphate; iNOS = inducible nitric oxide synthase; MB = methylene blue; MDA – malondialdyde; NO = nitric oxide; NOS = nitric oxide synthase; VS = vasoplegic syndrome.

METHODS

A wide literature review, and the author´s documented observations through a period of 15 years, was carried out using the data extracted from the two most important databases in the medical area: MEDLINE and SCOPUS. The following combinations of key words were adopted: 1) "Methylene blue and heart surgery"; 2) "Methylene blue and cardiac surgery"; 3) "Methylene blue and cardiopulmonary bypass" and; "Methylene blue and vasoplegic syndrome". This combination of MB with rather generic key words was proposital in the sense of captivating an amplified subject vision.

Beyond the bibliographical data, some capital questions where ellected in the attempt to consolidate the most important aspects of the MB use in VS treatment associated with cardiac surgery: 1) What medications would be listed as VS risk factor in cardiac surgery?; 2) Could the systemic inflammatory reaction be caused by blood exposure to the non-endothelized CPB circuit? 3) Is the *in vivo* MB use safe? 4) What kind of MB use complications are possible? 5) Does the use of MB cause endothelium dysfunction? 6) Does the MB injection cause any hemodynamic effect in non vasoplegic patients? 7) Does MB have proper pressoric effect? 8) Does a therapeutic dosage scheme exist? 9) Why

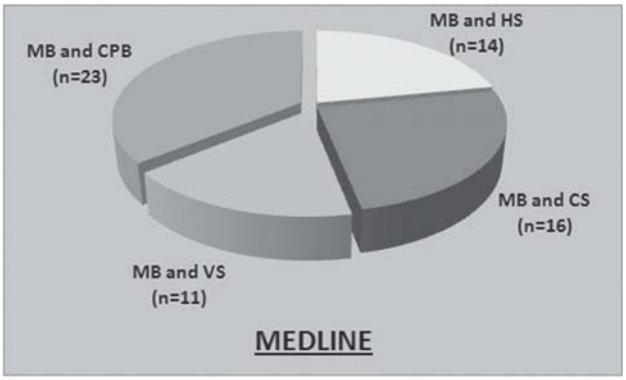
does VS sometimes promptly revert with MB infusion, and sometimes it does not seem to work? 10) Are there any circulatory shock modalities, beyond sepse and VS, that can be benefited by MB? 11) Do worthwhile investigations related to MB use in cardiac surgery exist?

RESULTS

The bibliographical survey on the MB therapeutic use, based on databases MELINE and SCOPUS searches, revealed a total of 58 publications directly related to the VS in cardiac surgery (Figure 1).

Between 40 specific papers on VS and MB, 20 (33.93%) are Brazilian articles; eight (13.33%) are American articles; eight (13.33%) are German articles; three (5%) are Argentinean articles; three (5%) are Spanish articles; three (5%) are Swiss articles; three (5.00%) are Italian articles; three (5%) are Scottish articles; two (3.33%) are Canadian articles; two (3.33%) are Turkish articles and, with one (1.67%) article the French, Belgian and Slovakian papers are included (Figure 2).

Observing the publication's quadrennial evolution graphic, a small tendency of increase was observed (Figure 3).



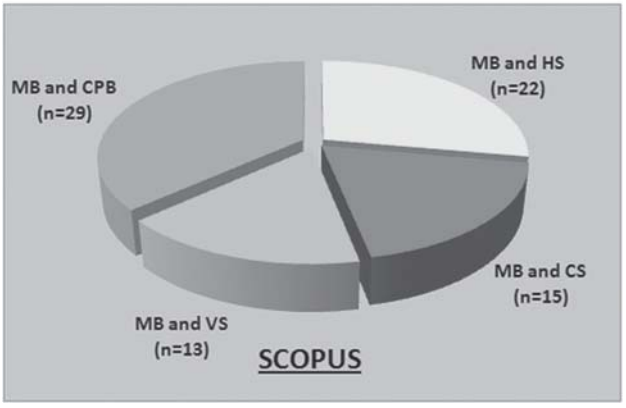


Fig. 1 - Bibliographical research using two databases (MEDLINE and SCOPUS)

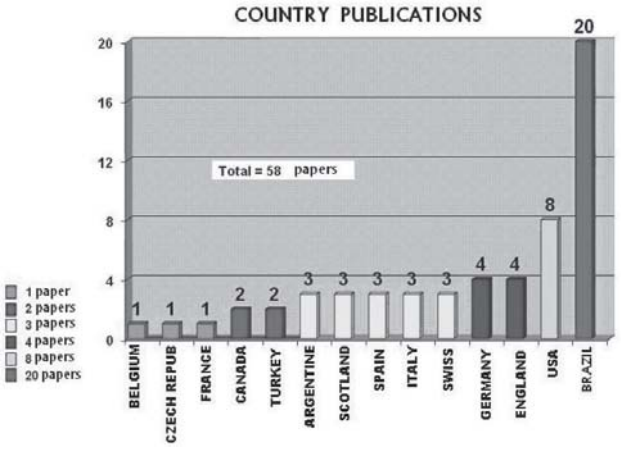


Fig. 2 - Distribution of the papers by country origin

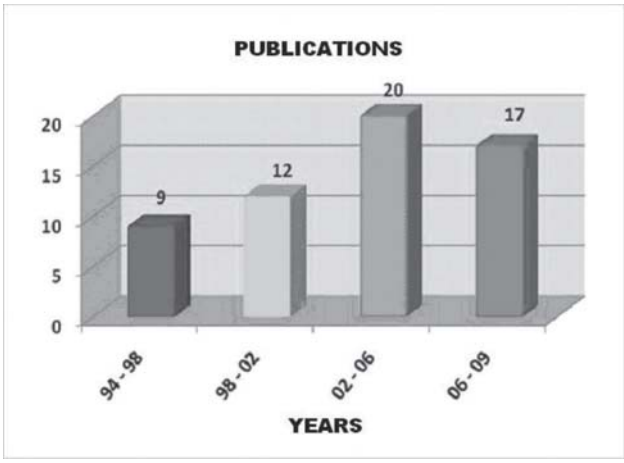


Fig. 3 - Quadrienal distribution of publications

Among the 60 papers that appear in the bibliography of this text, through a laborious and error subjected evaluation, the existence of varied types of publications is evidenced: 1) a first serie (1.67%) of six non-randomized patients [5]; 2) a serie (1.67%) of 60 patients submitted the CPB and randomized to study the inflammatory reaction [12]; 3) a serie (1.67%) of 54 non-randomized patients [6,7]; 4) a serie (1.67%) of 56 randomized patients in which 28 had received MB to treat VS in cardiac surgery´s postoperative [8-10] and; 5) a serie (1.67%) of 100 patients with VS risk factors that had been randomized and 50 patients that received MB before the CPB [11]. Observing the other 55 papers you find: 1) one study (1.67%) based on evidences through methanalysis of literature [13]; 2) seven articles (11.67%) of

revision [4,14-20]; 3) three experimental studies (5%) [21-23]. The other bibliographical citations in number of 44 (73.33%) are distributed as case reports (great majority) [24-36], letters [37-44], technical aspects of the MB use [45-50] and other studies involving risk [51,52], the VS incidence in the "off pump" myocardium surgical revascularization and the possibility of MB use in anaphylaxis and anaphylactic shock [53], also a proposal of the author of this text (Figure 4) [54-58]. The presented numbers, surely, are not totally compatible with the total of publications, but it is possible to assume that this imprecision does not affect the general vision of the problem.

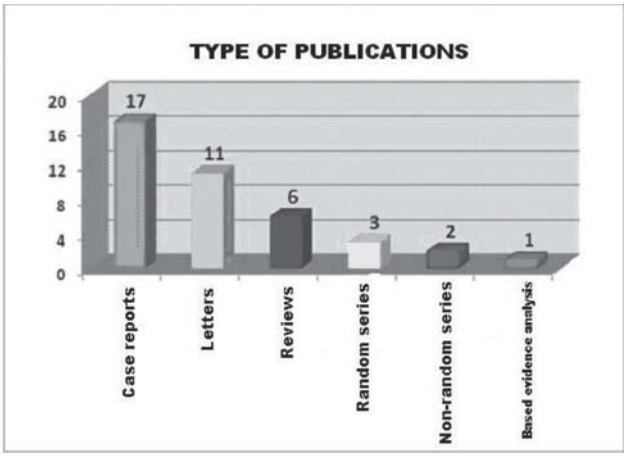


Fig. 4 - Types of publications. Random series = series of randomized patients; series non-radom = series of patients not randomized; Bas study. Eviden. = Based evidenced studies

Regarding the questions presented in methods: 1) Heparin and the ACE inhibitors, until the moment, are the only medications considered as factor of risk for VS [51]; 2) From the verification that the inflammatory reacton can be present in patients operated without CPB, the focus was moved for the concept that, more than the blood contact with the CPB circuit, the contact of the blood with the operatory wound would be the greater responsible to trigger the CPB inflammation phenomenon; 3) In the commonly used doses MB is a safe drug. (the lethal dose is of 40mg/kg). The accumulation of clinical experience has tested the binomium efficiency/security; 4) In contrast to the inhibition of the NO synthesis (L-NAME), *in vivo* MB injections do not cause endothelium dysfunction; 5) The MB injection in non VS patients does not have hemodynamic effects that needs an up-regulated NO state; 6) It is necessary to make it clear that MB, by itself, is not a vasoconstrictor. By blocking the GMPc system it "liberates" the AMPc system, in a kind of "crosstalk" between the two systems and, thus, the noradrenaline one starts to exert its vasoconstrictor effect; 7) A therapeutical protocol does not exist. The dosage used to treat metahemoglobinemia (2 mg/kg in bolus EV) has been used, and as its plasmatic concentration decays strongly in the first 40 minutes, it is logical the maintenance of the same dose in continuous infusion in the next hour after EV bolus. There are personal reports using up to 7 mg/kg without collateral effect; 8) Nowadays a "window of opportunity" is proposed for the MB efficiency to restore systemic vascular the resistance; 9) Beyond sepse and other distributive circulatory shock types, if exist another vasoplegic condition to be benefited by the MB use is speculated; 10) The authors have positive experience in anaphylaxis, anaphylactic shock and to treat protamine reactions and; 11) The authors of this paper, based on isolated clinical comments, have attempted to experimentally investigate two other aspects that are common in cardiac surgery, that could benefit by MB use: cappillary permeability and the blood clotting.

DISCUSSION

One problem in describing the VS is the lack of consistency in its definition. There is no clear definition, not even a single biomarker, including the determination of nitrite / nitrate (NOx), to characterize the syndrome. Actually, the VS is a constellation of signs and symptoms: hypotension, high cardiac index, low systemic vascular resistance, low filling pressures and maintained hypotension despite the use of high doses of vasoconstrictor amines. This problem leads to an indefinition of its incidence ranging from 0.21% to 13% [3,4,10]. The largest series of prospective studies indicate an incidence of 8% to 12% [6,10,11] The mortality is high, ranging from 16 to 27% [6,10,11], and therefore has been the subject of several studies aimed on improving the outcomes of these patients. MB has been used as a therapeutic option in these situations.

The VS has multifactorial genesis and in the case of patients undergoing cardiac surgery, is mainly due to exposure of the body to non-physiological materials and the use of heparin/protamine [15], triggering the inflammatory response syndrome (SIRS). During this process occur complement activation, cytokine release, leukocyte activation and expression of adhesion molecules, and various substances production, such as oxygen free radicals, arachidonic acid metabolites, platelet activity factor, nitric oxide and endothelin. The consequences of SIRS can be tragic and may lead to multiple organs and systems dysfunction, as occurs in septic shock. The systemic vascular resistance decrease observed in the VS is associated with excessive production of NO.

In these situations, NO induces loss of vascular sensitivity to catecholamines and myocardial depression that contributes to lethal hipotension. Any process in which there is pro-inflammatory cytokines release can cause excess production of NO, as occurs, possibly in patients undergoing cardiopulmonary bypass. Clinical studies also show increased production of NO in adults and children with various forms of shock, with increased serum nitrate levels if correlated with vasodilation. Vessels isolated from animals in shock show a pronounced hyporeactivity to almost all vasoconstrictor agents tested (epinephrine, norepinephrine, phenylephrine, dopamine, endothelin, angiotensin, thromboxane, etc.). This hyporeactivity can be reversed by NOS inhibitors and specific iNOS inhibitors.

Although endothelial cells can be induced to form NO, it is possible that the major source of production is the vessel´s own smooth muscle. The NO produced by iNOS expression in the vasculature is responsible for the excessive vasodilation and reduced contractile responses to vasopressor agents. In addition to the data showing an increased formation of NO by iNOS in various forms of shock, there are compelling data that demonstrate that the biosynthesis of NO by ecNOS expression in the vascular endothelium in cases of hemorrhagic or endotoxic shock is compromised. This mechanism is sometimes referred to as a functional exchange between the isoforms of NOS with expression of iNOS and down-regulation of ecNOS at the same time. Impaired expression of ecNOS may be detrimental to important organs such as brain, heart, kidneys associating itself to the dysfunction of multiple organs. The reduction in NO production is associated, as well, to the antiplatelet activity and activation of polymorphonuclear leukocytes, contributing, with peroxynitrite dependent mechanisms, to endothelial injury and tissue damage.

These pathophysiology data, presented in a generic sense, may be reviewed by at least three references cited in the text provided [13,14,18]. From these concepts a certainty emanates, that is: the VS is a consequence of systemic inflammatory reaction, being, therefore, an endothelial vasoplegic dysfunction [37].

Regarding the therapeutic principles for endothelial vasoplegic dysfunction treatment associated with heart surgery, some comments are relevant. The first and most important concept concerns the restrictions on the use of nonspecific inhibitors of NO synthesis (L-NMMA, L - NAME, etc.). Another logical approach would be to inhibit NO synthesis with the use of specific inhibitors such as L-NAME and L-NMMA. This approach is prone to criticism for it involves ethical issues related to the use of new therapies, besides blocking, not only iNOS, but also its constitutiveenzyme's (eNOS) physiological form. The use of specific iNOS inhibition, for example, with aminoguanidine, remains in logical and speculative territories. Considering specifically the vasoplegia associated with various states of circulatory shock, some points can be emphasized: 1) the use of steroids to inhibit inflammation and block the action of iNOS, 2) the use of norepinephrine is an amine that does not promote increased heart rate, and may even decrease it, 3) the use of methylene blue (2 mg / kg as intravenous in bolus dose or half the in bolus dose followed by continuous infusion of additional doses), 4) the use of metoprolol injection (5 mg) to reverse the downregulation situation of the beta receptors which is a consequence of tachycardia and the use of amine. Because of this phenomenon a smaller number of beta receptors are available for an effective action of beta-adrenergic drugs, occurring tachyphylaxis. It is extremely important to avoid excessive fluid ressuscitation, the main goal is to reverse the vasoplegia with vasoconstrictors and methylene blue. Because hypotension is refractory to the amine, the use of methylene blue has been a lifesaver. The option of arginine vasopressin use is quite attractive, but there is not enough clinical experience with this drug yet.

The NO actions depends on the cyclic GMP activation, but besides this mechanism of paramount importance, we have also focused our attention on the cyclic AMP system, which is why we are using, almost as a routine, beta-blockers injection (metoprolol), when the patient is very tachycardic [4,20].

Regarding the medications associated with the emergence of VS in cardiac surgery, heparin and angiotensin-converting enzyme (ACE) are, so far, the only ones considered as a risk factor for VS. In our daily practice during the 15 years account for the observations included in this text, we have sought a causal relationship, and various aspects were considered: 1) the majority of cases occurred during or after CPB, 2) in the past, there were several cases associated with curare aloferine use during anesthesia induction, 3) some, more attenuated, cases occurred during anesthetical induction with standardized technique with etomidate, fentanyl, and pavulon diazepine, 4) some cases were clearly associated with the use of protamine, 5) in some cases we had the impression that vasodilation occurred after heparin use, 6) vasoplegic syndrome in non-cardiac surgeries was observed, 7) It seems that the cases occur in outbreaks, suggesting a relationship with drug lots, 8) there is no relation with the type of heart surgery, 9) many patients are diabetics, and 10) many patients had previously used the calcium antagonist diltiazem[19].

There was a change regarding the paradigm that inflammatory reaction associated with VS would be caused by blood exposure to the non-endothelial surface of the ECC, after it was verified that the inflammatory response is present in off-pump patients [54]. A change tendency is observed inthe concept that, more than the contact with the CPB circuit, the contact of the blood with the woundnd

would be the biggest responsible for the inflammation phenomenon in CPB [20].

As to the safety and ethical aspects of MB´s clinical use, it can be affirmed that, in recommended doses it is a safe drug (the lethal dose is 40 mg/kg) [22]. The accumulation of clinical experience has been testing the binomial efficiency / safety. These results show that intravenous infusion of MB seems to be safe. The findings support clinical trials where MB was used to treat VS post-coronary artery bypass grafting with CPB on inflammatory response syndrome patients - SIRS and anaphylaxis. These results are not unexpected, especially when analyzed in healthy animals, in which the hemodynamic presents a fine regulation, but not total, under the control of NO. In these conditions no action is expected when there is inhibition of guanylate cyclase by MB.

MB injection in a non VS carrier individual does not have hemodynamic effects in normal conditions. The MB effect only appears in the case of NO supra-regulation, and thus, spasm occurrence in coronary arterial grafts is unlikely [22]. The vasospasm risk and thrombosis of these grafts require confirmation in vivo. The security perception is fully grounded in data set in studies in healthy animals that received the MB in vivo. Although ischemic events were not evidenced in the ECG monitoring, the normal vascular reactivity, endothelium dependent and independent, was determined by in vitro studies [21]. With a wide safety range, these data support the assumption that, unlike the NO (L-NAME) synthesis inhibition, the injection *in vivo* does not cause endothelial dysfunction.

Regarding to recovery and better control of blood pressure, it must be made clear that MB alone is not a vasoconstrictor. By blocking the cGMP it "releases" the cAMP system in a kind of "crosstalk" between the two systems and, thus, norepinephrine exercises its vasoconstrictor effect.

Regarding to the treatment regimen, it still does not exist a therapeutic dosage protocol scheme. It has been adopted in most publications, the dosage used for the treatment of methemoglobinemia and sepsis (2 mg / kg bolus IV). As its plasma concentration declines sharply during the first 40 minutes of bolus infusion, we have been maintaining the same dose in continuous infusion on the next hour. There are personal reports of its use on up to 7 mg / kg without side effects [8-10]. As the lethal dosage, determined in goats, is 40 mg/kg, we believe that there is, in extreme cases, the total dosage use of up to 10 mg / kg. It should be noted that this is an assumption and can not be considered a therapeutic principle. There is at least one report at the dosage of 10 mg / kg without complications and with clinical improvement of patients [42] and clinical and statistical improvement of systemic vascular resistance, lactate and norepinephrine. The criterion used was: NE µg/kg/min, CI > 2.5 L/m^2/min and SVR <350 dyne * s * cm-5. We should highlight two technical aspects: the MB injection interferes with pulse oximetry, giving the false impression of arterial unsaturation, and this effect is transient.

In the MB adverse effects are included: cardiac arrhythmias (nodal rhythm and transient isolated ventricular extrasystoles, angina and coronary vasoconstriction, decreased cardiac output and renal blood flow and mesenteric resistance, increased pulmonary artery pressure with deterioration of gas exchange. Cardiac arrhythmias and angina are transient and have not been reported with a dose of 2 mg / kg. The vast majority of studies reported unchanged lung and kidney function. Other side effects include confusion, headache, vomiting and abdominal pain.

MB is reduced to blue leukomethylene in the erythrocyte and is excreted in the urine at that form and as MB itself, explaining the greenish color of urine. Hemolytic anemia and hyperbilirubinemia have been rarely reported with the use of high doses of MB. Some changes in liver enzymes have been reported in some studies that speculate that these changes are due to combined use of MB and adrenaline [49]. The only drug interaction described concerns hemolytic anemia exacerbation caused by the dapsone by the active hydroxylamine formation, which oxidizes hemoglobin. In our laboratory we have systematically observed increases in tissue levels of malondialdehyde acid (MDA) measured as a free radicals biomarker [22]. The MB antioxidant effects are well known, what presents itself as a contradiction and leads us to speculate that MB may be interfering with the MDA measurement. This fact occurs in relation to lactate. Its sharp decrease can not be considered since MB reacts directly with lactate, giving the false impression of immediate improvement in tissue exchange. In sufficiently vasodilated patients skin color is blue-gray, as well as the rare skin lesions quickly revert themselves [18].

Regarding ethical aspects, it can be affirmed that MB can be used in clinical practice because it has been used since late 19th century for the treatment of malaria, which granted Paul Ehrlich the Medicine Nobel Prize in 1908. MB is the precursory molecule of: chemotherapy, antibiotics and neuroleptics (chlorpromazine), with long use as a urinary antiseptic, Schizophrenia treatment and as an additive to stored blood bags, in order to neutralize microorganisms involved, for example, with AIDS and Chagas Disease. A curiosity, which indirectly relates to its security, is its use in fish tanks, where MB combats algae and microorganisms.

This text could not fail to comment on a question of fundamental importance, related to the use of MB: Why vasoplegic state sometimes promptly reverts and, sometimes, nothing seems to help. Recently, a well established doctoral thesis was defended at the Federal University of Florianopolis. This thesis has been published and brings some extremely important data to try to answer

that question [22]. A sepsis model used in mice allowed the authors to demonstrate, in a period of 24 hours divided into three periods of eight hours, that there is a dynamic guanylate cyclase action in such a way as to create a "window of opportunity" for methylene blue efficiency to help restore systemic vascular resistance. Vasoreactivity no longer occurs in the first eight hours, not only by amines action, but also by the nitric oxide donor drugs. This phase coincides with increased iNOS expression. Between eight and sixteen hours the guanylate cyclase expression is absent, probably by excessive nitric oxide production, and thus, in this phase methylene blue would not act. Later, between sixteen and twenty-four hours there would be a guanylate cyclase synthesis "again", and methylene blue would again be effective (Figure 5).

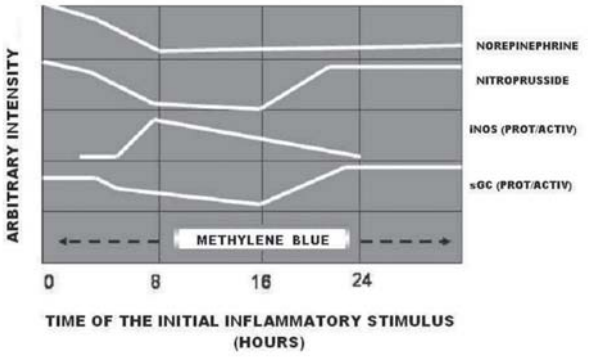


Fig. 5 - "Window of opportunity" for methylene bule use depending on activity of soluble guanylate cyclase (sGC); iNOS = inducible nitric oxide synthase. Prot = protein. Adaptation of Fernandes, 2001 (Reference 23)

Considering these findings, we started to use MB infusion even with no apparent effectiveness, waiting for the "window of opportunity", that is, for the guanylate cyclase synthesis "again". In one patient with diabetes that underwent an aortic valve replacement, we used this principle and the theory of Fernandes seemed to be confirmed. The patient presented excellent response in the cardiopulmonary bypass, then stopped responding, but still we kept a continuous infusion of methylene blue in addition to high doses of adrenaline and noradrenaline. On the fourth day after surgery we repeated new intravenous bolus of methylene blue, the response was very satisfactory and in the fifth day, the infusion of amines to maintain blood pressure and vascular resistance stability in normal values was no longer needed.

Regarding the MB use in other forms of vasoplegia treatment, the author recommended its use in circulatory collapse associated with anaphylaxis and anaphylactic shock. MB can save lives, as demonstrated by the experience that has been recognized nationally and internationally [58]. The same can be said for the therapeutic effect of MB on the catastrophic reactions induced by protamine sulfate [15].

The literature review, illustrated in Figures 2, 3 and 4 shows that 1) the vast majority of publications (33.33%) are Brazilian, 2) only two studies reported large randomized series and 3) there are seven complete revisions on the subject. These data reinforce the VS description in cardiac surgery and its treatment with MB, is a major contribution of Brazilian heart surgery. It is clear that the option is valid respecting the already mentioned "therapeutic window" and that the study we performed, based on evidence [13], confirms the need for multicenter studies.

At least two original and practical lines of research deserve further investigation on MB´s possible effect on capillary blood, and its possible effects on coagulation. Isolated observations in patients with bacterial endocarditis undergoing emergency valve surgery suggest that this group of patients could have pulmonary circulation improvements. On the other hand, MB has been used as an option for heparin neutralization in patients with intolerance protamine use, this option being surrounded by controversy.

Finally, MB is an option for VS treatment in cases of first-line treatment failure (blood volume adjustment and amines judicious use). Early use of MB can block the systemic vascular resistance progression´s decrease in patients responsive to norepinephrine and mitigate the need for prolonged vasoconstrictor use. However, schemes and protocols need to be clearly defined for its routine use. It is a matter of debate whether MB can be a first-line treatment in patients with vasoplegia, and there is still no evidence to support this fact. Studies based on evidence points to the need for more scientific evidence to define the MB role in the treatment of VS refractory to the use of amines [13,18]. One of these studies, from our authorship, using the evidence-based technique, showed lack of experimental evidence , requiring further large multicenter studies, adopting Levin´s (Argentina) [7-9] and Ozal (Turkey) [11] studies principles.

By the historical analysis, it is clear that the use specifically in VS associated with cardiac surgery is a Brazilian contribution. Its use in sepsis is already provided without the use of large multicenter studies confirming the inflammatory process as the main mechanism involved. To assign a possible role of "vasopressin deficiency" as most important VS mechanism is at least reckless. Although no definitive multicentric studies, and despite all the obstacles,

MB use in the VS treatment in cardiac surgery is, nowadays, the best, safestest and cheapest option, and, as already mentioned, a Brazilian contribution for cardiac surgery.

CONCLUSIONS

The data from this extended review leaves the impression that the number and quality of publications do not reflect the frequency at which MB is used in clinical practice. Therefore, it is implied the difficulty of conducting multicenter studies. The disclosure and possible consecration of this therapy will be passed on as verbal information and, depending on the increase of publications, in studies based on evidence. In the literature data and medical practice set remains the certainty that the soluble guanylate cyclase blockage in distributive shock control remains underestimated [59,60].

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