MEHES JOURNAL (MEDICAL AND HEALTH SCIENCES JOURNAL) | ISSN:3023-5804
Arrival Date: 03/03/2026 | Published Date: 27/03/2026 | 2026 Vol: 4 Issue: 1 pp: 55-63 |
DOI: https://doi.org/10.5281/zenodo.19238729

ARTICLE TYPE: REVIEW ARTICLE

Non-Adrenergic Approach in Catecholamine-Resıstant Shock: Methylene Blue and Perfusion Safety

Katekolaminlere Dirençli Şokta Non-Adrenerjik Yaklaşım: Metilen Mavisi ve Perfüzyon Güvenliği

Eda G. Katırcıoğlu[1*], Mehmet Burak Coşkun[2], Mahmut Köylü[3], Mihriban Yalçın[4]

[*1]Department of Cardiovascular Surgery, Ordu State Hospital, Ordu, Turkiye, godekmerdan@hotmail.com, 0000-0003-0724-4051

[2]Department of Cardiovascular Surgery, Ordu State Hospital, Ordu, Turkiye, mehmetburakcoskun@yahoo.com, 0000-0001-6748-575X

[3]Department of Medical Pharmacology, Faculty of Medicine, Cukurova University, Adana, Turkiye, mahmut.02085@gmail.com, 0009-0004-2106-983X

[4]Department of Cardiovascular Surgery, Ordu State Hospital, Ordu, Turkiye, kvcmhrbn@hotmail.com 0000-0003-4767-0880

ÖZET

Kardiyopulmoner bypass (KPB) sonrası gelişen vazoplejik sendrom; düşük sistemik vasküler direnç, normal veya artmış kardiyak debi ve yüksek doz katekolaminlere yanıtsızlık ile karakterize, mortalitesi yüksek (%25) bir klinik tablodur. Bu bölüm, vazoplejinin patofizyolojisinde rol oynayan Nitrik Oksit (NO) ve siklik Guanozin Monofosfat (cGMP) yolağının aşırı aktivasyonunu ve bu yolağı hedef alan Metilen Mavisi'nin (MM) terapötik rolünü incelemektedir. MM, çözünür Guanilat Siklaz (sGC) ve indüklenebilir Nitrik Oksit Sentaz (iNOS) enzimlerini inhibe ederek, adrenerjik reseptörlerden bağımsız bir mekanizmayla vasküler tonusu restore eder.

Çalışmada ayrıca, MM kullanımının intraoperatif dönemde yarattığı spesifik monitörizasyon zorlukları detaylandırılmıştır. İlacın optik özellikleri nedeniyle pulse oksimetre (SpO2) ve serebral oksimetre (NIRS) cihazlarında gözlenen "psödo-desatürasyon" (yalancı düşüş) fenomeninin mekanizması ve perfüzyon güvenliği açısından yönetimi tartışılmıştır. Cerrahi açıdan; preoperatif risk faktörleri (ACE inhibitörü kullanımı, endokardit), zamanlama stratejileri (profilaktik vs. kurtarıcı) ve mutlak kontrendikasyonlar (G6PD eksikliği, Serotonin Sendromu riski) güncel literatür ışığında ele alınmıştır. Bu bölüm, kalp damar cerrahı, perfüzyonist ve farmakoloğun ortak perspektifiyle, dirençli vazopleji yönetiminde güvenli ve etkili bir klinik protokol oluşturmayı amaçlamaktadır.

Anahtar Kelimeler: Vazoplejik Sendrom, Metilen Mavisi, Kardiyopulmoner Bypass, Nitrik Oksit, Perfüzyon Yönetimi.

ABSTRACT

Vasoplegic syndrome developing after cardiopulmonary bypass (CPB) is a clinical condition characterized by low systemic vascular resistance, normal or increased cardiac output, and unresponsiveness to high doses of catecholamines, with a high mortality rate (25%). This section examines the excessive activation of the Nitric Oxide (NO) and cyclic Guanosine Monophosphate (cGMP) pathway, which plays a role in the pathophysiology of vasoplegia, and the therapeutic role of Methylene Blue (MB), which targets this pathway. MM restores vascular tone through a mechanism independent of adrenergic receptors by inhibiting soluble guanylate cyclase (sGC) and inducible nitric oxide synthase (iNOS) enzymes.

The study also details the specific monitoring challenges created by MM use during the intraoperative period. The mechanism of the “pseudo-desaturation” (false drop) phenomenon observed in pulse oximeters (SpO2) and cerebral oximeters (NIRS) due to the drug's optical properties and its management in terms of perfusion safety are discussed. From a surgical perspective, preoperative risk factors (ACE inhibitor use, endocarditis), timing strategies (prophylactic vs. rescue), and absolute contraindications (G6PD deficiency, risk of Serotonin Syndrome) are addressed in light of the current literature. This section aims to establish a safe and effective clinical protocol for the management of refractory vasoplegia from the joint perspective of the cardiac surgeon, perfusionist, and pharmacologist.

Keywords: Vasoplegic Syndrome, Methylene Blue, Cardiopulmonary Bypass, Nitric Oxide, Perfusion Management.

Sorumlu Yazar/Corresponding Author: Eda G. Katırcıoğlu, Department of Cardiovascular Surgery, Ordu State Hospital, Ordu, Turkiye, godekmerdan@hotmail.com, 0000-0003-0724-4051

Atıf /Cite: Katırcıoğlu EG, Coşkun MB, Köylü M, Yalçın M. Non-Adrenergic Approach in Catecholamine-Resıstant Shock: Methylene Blue and Perfusion Safety. Mehes Journal. 27 Mart 2026;4(1):55-63.

The journal is licensed under a Attribution 4.0 International (CC BY 4.0).

INTRODUCTION

Understanding Vasoplegic Syndrome

Hemodynamic Characteristics and Definition Vasoplegic syndrome (VS) represents a particularly demanding hemodynamic complication that often arises following cardiopulmonary bypass (CPB) in cardiovascular surgeries. Frequently termed "post-cardiotomy vasoplegia," it manifests as a type of distributive shock where profound hypotension persists, even when fluid resuscitation is sufficient (1).

The diagnosis relies on distinct hemodynamic parameters, primarily involving three core criteria:

- **Depressed Systemic Vascular Resistance (SVR):** Values usually fall under 800 dyn·s·cm^{-5}. This reflects extensive and unregulated arterial vasodilation.
- **Maintained or Elevated Cardiac Output:** Demonstrating a Cardiac Index (CI) exceeding 2.5 L/min/m^2 is crucial for differentiating VS from cardiogenic (low-output) shock. Although the heart pumps effectively, the lack of vascular resistance prevents the generation of adequate perfusion pressure (2).
- **Refractoriness to Catecholamines:** Mean arterial pressure (MAP) fails to reach adequate targets (typically > 65 mmHg) even with the administration of potent, high-dose vasopressors like norepinephrine (> 0.5 µg/kg/min) (3).

Pharmacologically, systemic inflammation heavily activates the NO-sGC-cGMP signaling cascade, which desensitizes vascular smooth muscle to calcium, culminating in a distributive shock state that ignores adrenergic vasoconstrictive signals.

Prevalence and Associated Risk Factors The reported occurrence rates of VS fluctuate significantly, stemming from varying diagnostic criteria and diverse patient demographics. While standard cardiac procedures observe an incidence between 5% and 25% (4) , this figure can surge to 50% during complex interventions with extended pump durations, including infective endocarditis operations, heart transplants, and ventricular assist device (VAD) implantations (5).

Independent predictors for developing this complication include diabetes, diminished ejection fraction (EF < 35%), and the preoperative use of beta-blockers or angiotensin-converting enzyme (ACE) inhibitors. Intraoperatively, factors like poor myocardial protection, massive blood transfusions, and extended CPB durations promote endothelial damage, further elevating VS risk (6).

Impact on Mortality and Clinical Relevance Rather than just a brief period of low blood pressure, VS acts as a primary driver of postoperative mortality and morbidity. The absence of vascular tension compromises the perfusion of essential organs, notably the gastrointestinal tract and kidneys. Even with a hyperdynamic state, microcirculatory shunting disrupts tissue oxygenation, leading to lactic acidosis (7).

Studies indicate that patients experiencing vasoplegia require notably longer stays in the intensive care unit (ICU-LOS). Crucially, resistant vasoplegia drastically elevates the mortality risk up to 25% when contrasted with uncomplicated recoveries (8). Consequently, when traditional adrenergic drugs fail, the prompt administration of alternative non-adrenergic rescue therapies, like methylene blue, becomes vital.

Pharmacological Mechanisms

The Nitric Oxide (NO) Pathway in Vasoplegia Comprehending the molecular pathology is essential to grasp how methylene blue (MB) treats this syndrome. Ischemia-reperfusion injury and the exposure of blood to artificial surfaces during cardiopulmonary bypass provoke a systemic inflammatory response syndrome (SIRS). The ensuing release of pro-inflammatory cytokines, such as IL-1β and TNF-α, significantly upregulates inducible nitric oxide synthase (iNOS) within smooth muscle and vascular endothelial cells (9).

Under normal conditions, endothelial NOS (eNOS) releases minimal NO to maintain vascular tone; however, during pathological vasoplegia, iNOS generates massive NO volumes, triggering uncontrolled vasodilation. This NO permeates smooth muscle cells to stimulate soluble guanylate cyclase (sGC). The active sGC transforms Guanosine Triphosphate (GTP) into the intracellular messenger cyclic guanosine monophosphate (cGMP). Increased intracellular cGMP levels block calcium channels, hindering cellular contraction (10).

This mechanism explains why external adrenergic agonists like epinephrine and norepinephrine fail; the overwhelming intracellular cGMP cascade prevents the contractile machinery from responding. Literature defines this phenomenon as "catecholamine refractoriness" (11).

Methylene Blue's Unique NO/cGMP Blockade Methylene blue represents a distinct pharmacological category compared to traditional vasopressors. Rather than agonizing receptors, it functions as an enzyme inhibitor. Its dual mechanism involves:

- **Primary Action (sGC Inhibition):** MB binds to the heme group of soluble guanylate cyclase, directly blocking it. Consequently, excess NO cannot trigger cGMP synthesis, effectively halting vasodilation (12).
- **Secondary Action (iNOS Suppression):** It acts as a competitive inhibitor of iNOS, diminishing NO synthesis at the cellular source (13).

Surgical literature often summarizes this effect simply: while noradrenaline attempts to force vessel constriction, methylene blue stops the vessel from relaxing. Thus, MB revitalizes vascular tone and maintains kidney perfusion without sacrificing cardiac output. To summarize, MB is not a standard vasoconstrictor; it neither opens Ca^{2+} channels nor directly triggers adrenergic receptors. Instead, by blunting the NO-sGC-cGMP axis, it indirectly restores the Ca^{2+} sensitivity and contractility of the vascular smooth muscle. In other words, it renders vascular smooth muscle contractile.

Dosing and Pharmacokinetics Intravenous (IV) administration of methylene blue yields a rapid distribution, achieving maximum efficacy within 30 to 60 minutes. Commercially available as BLUMET 100 mg/10 ml I.V., its elimination half-life spans roughly 5 to 6 hours. Although hepatic metabolism occurs, 75% of the dose is cleared unaltered via the kidneys, imparting a distinct blue-green hue to the urine (14).

Standard cardiac surgery protocols include:

- **Rescue Administration:** An IV bolus of 1.5 - 2 mg/kg, infused slowly over 20-30 minutes, is given for refractory vasoplegia in the ICU or while weaning from the pump.
- **Prophylactic Administration:** For elevated-risk scenarios like VAD insertion or endocarditis, 1 - 2 mg/kg is either added to the pump prime or infused right before initiating CPB (15).

Toxicity Risks and Safety Window The therapeutic index for MB is tight; cumulative amounts exceeding 7 mg/kg introduce cytotoxicity, paradoxically elevating oxidative stress and triggering methemoglobinemia. Furthermore, its intrinsic monoamine oxidase (MAO) inhibition necessitates strict vigilance for "serotonin syndrome" among patients on SSRI antidepressants. MB is strictly contraindicated for individuals with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency due to the risk of severe hemolytic events (16).

Monitoring Artifacts And Perfusion Management

False Desaturation and Optical Interference The primary intraoperative challenge with MB relates to technical monitoring artifacts rather than hemodynamics. The drug acts as an optical filter in the bloodstream, absorbing the specific wavelengths utilized by oxygen saturation monitors. Standard pulse oximeters measure the ratio of deoxyhemoglobin to oxyhemoglobin using infrared (940 nm) and red (660 nm) light. Because MB strongly absorbs light near 668 nm, it blocks the red wavelength. The oximeter's algorithm falsely reads this light reduction as surging deoxyhemoglobin levels (17).

Consequently, the monitor's SpO2 readings plummet to 65-85% within seconds of the bolus. This phenomenon, known as "pseudo-desaturation," should not alarm the anesthesiologist or perfusionist into raising the FiO2, as co-oximeter arterial blood gas (ABG) analyses will confirm normal PaO2 and SaO2 values (18). This optical illusion generally fades after 20 to 30 minutes as the drug disperses into tissues.

Artificial "Cerebral Ischemia" Warnings Near-Infrared Spectroscopy (NIRS) equipment relies on similar wavelength principles for evaluating cerebral blood flow. After MB injection, regional cerebral oxygen saturation (rSO2) measurements drop precipitously across both brain hemispheres. Reports indicate NIRS values can artificially dive by 15 to 40 points despite no actual ischemic event occurring (19).

The essential response strategy dictates that if ABG values, mean arterial pressure, and pump flow are stable, the perfusionist should treat the NIRS drop as an artifact and refrain from blindly increasing pump output. Nonetheless, during this monitor "blind spot," rigorous adherence to cerebral protection protocols (like maintaining target perfusion pressures and normocapnia) is paramount (20).

Urine Color Changes and Kidney Function As it exits the body, MB colors the urine green or deep blue. Clinicians must distinguish this expected pharmacological effect from the red or brown urine indicative of CPB-induced hemolysis.

- **Differentiation:** If the urine bag shows a green/blue tint, it indicates the expected drug behavior. When uncertainty arises, using a urine dipstick for hemoglobin or centrifuging the sample resolves the ambiguity.
- **Renal Effect:** Crucially, perfusionists should note MB's nephroprotective properties. Evidence suggests that by swiftly ending vasoplegic hypotension, MB helps prevent postoperative acute kidney failure; in fact, re-establishing renal perfusion gradients makes it actively protective (21).

Safety in Application and Chemical Compatibility When flushed through the same IV line as certain medications, such as furosemide, Blumet (methylene blue) can precipitate. Therefore, injecting it straight into the pump's venous reservoir requires confirmation of a fully clear line. Moreover, the drug degrades under light exposure, making it a "Good Clinical Practice" (GCP) standard to shield the infusion bag with an opaque wrapping or aluminum foil to preserve the drug's potency (22).

Clinical Decision-Making And Surgical Strategy

Identifying Candidate Patients Preventing intraoperative crisis starts with the surgical team forecasting the likelihood of vasoplegia. Prophylactic MB is reserved for specific high-risk profiles rather than general hypotensive cases. The most critical predictors include:

- **Medication Background:** The routine intake of calcium channel blockers or ACE inhibitors blunts natural vasoregulation, impeding vascular tone recovery post-bypass.
- **Procedure Type:** Heart transplants, VAD implants, and operations for infective endocarditis (which involves active inflammation).
- **Comorbidities:** Elevated EuroSCOREs (6.8) and depressed left ventricular function (LVEF < 35%).

When these risks are present, the surgeon must preemptively alert the perfusion and anesthesia staff regarding potential vasoplegic complications.

Rescue vs. Prophylactic Administration The literature outlines two primary timing strategies for MB delivery:

- **Rescue Therapy:** The standard approach involves administering MB in the ICU or during CPB weaning when the MAP remains below 60 mmHg despite heavy reliance on norepinephrine (> 0.5 µg/kg/min) and vasopressin (9). Critics of this strategy note that tissue ischemia may already be underway by the time rescue is attempted (23).
- **Prophylactic Intervention:** For patients exhibiting high risk (e.g., endocarditis, ACE inhibitor use), the drug is infused ahead of the surgery, placed into the pump prime, or given at CPB induction. Recent meta-analyses confirm that early prophylaxis effectively dampens the severity and likelihood of VS, secures better vascular resistance, and lowers mortality rates (24).

Absolute Contraindications Methylene blue possesses notable pharmacological risks, with G6PD deficiency serving as an absolute hard stop for surgeons. In these patients, the drug acts as an intense oxidant rather than reducing, provoking catastrophic hemolysis, Heinz body generation, and severe anemia.

Additionally, teratogenic risks (like intestinal atresia) make it contraindicated during pregnancy. Due to its MAO-inhibiting behavior, a critical risk/benefit analysis is mandatory for patients on Serotonin Reuptake Inhibitors (SSRIs) , as fatal "Serotonin Syndrome" can occur, presenting as severe agitation, rigidity, and hyperthermia based on the risk/benefit ratio (13).

DISCUSSION AND CONCLUSION

Clinical Implications And Comparative Therapies

Alternative Options While MB serves as the predominant rescue choice for vasoplegic shock, it is not the definitive "gold standard," and newer pharmacological options are emerging.

- **Hydroxocobalamin (High-Dose Vitamin B12):** Functions as a nitric oxide scavenger similar to MB but avoids hemolytic triggers in G6PD deficiency and carries no serotonin risks. However, it turns the blood deep purple/red, potentially setting off false "blood leak" warnings on continuous renal replacement machines.
- **Synthetic Angiotensin II:** Directly activates the Renin-Angiotensin cascade. Approved in 2017 following the ATHOS-3 trial, it powerfully corrects catecholamine-resistant shock, though its adoption is hindered by high costs and thromboembolic risks.

Even with new competitors, MB endures as the premier non-adrenergic drug—especially in cost-conscious settings and developing nations—thanks to its affordability, accessibility, and deeply understood pharmacokinetics.

The Multidisciplinary Requirement Effective vasoplegia resolution demands a synchronized effort from three domains:

- **The Pharmacologist:** Audits the preoperative medication list (SSRIs, ACE inhibitors) for contraindications and risks.
- **The Surgeon:** Triggers the MB request proactively before deep tissue hypoperfusion occurs.
- **The Perfusionist:** Navigates the monitoring artifacts (SpO2 drops) immediately following administration, preventing unwarranted and potentially harmful clinical interventions.

Core Clinical Takeaways

- **Mechanism:** Rather than inducing direct vasoconstriction, MB intercepts the NO/cGMP cascade, stopping vascular relaxation.
- **Clinical Utility:** Acts as a rescue intervention during catecholamine-refractory shock, prominently during long bypass runs and endocarditis.
- **Monitoring:** SpO2 and NIRS metrics will artificially crash post-injection; stable arterial blood gases should preclude panic.
- **Safety Restrictions:** Strictly avoid in G6PD deficiency and exercise extreme caution with SSRI users.
- **Handling:** Infuse slowly and shield the lines/bags from light to maintain potency.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Ethics Approval and Consent

Since this is a review study, ethical approval was not required.

Conflict of Interest

The authors have declared no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

Author Contributions

Eda G. Katırcıoğlu: Literature Review, Writing. Mehmet Burak Coşkun: Conceptualization, Writing. Mahmut Köylü: Data Curation. Mihriban Yalçın: Methodology, Writing.

Financial Support/Funding

None.

REFERENCES

1. Byrne JG, Leacche M, Paul S, Mihaljevic T, Rawn JD, Shernan SK, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. *European journal of cardio-thoracic surgery*. 2004;25(3):327–32.
2. Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. *Seminars in thoracic and cardiovascular surgery*. 2010;22(2):140–44.
3. Shaefi S, Mittel A, Klick J, Evans A, Ivascu NS, Gutsche J, et al. Vasoplegia After Cardiovascular Procedures-Pathophysiology and Targeted Therapy. *Journal of cardiothoracic and vascular Anesthesia*. 2018;32(2):1013–22.
4. Castagna F, Mehra MR, Nabzdyk CGS, Givertz MM. Vasoplegia Syndrome After Cardiac Surgery: Insights Into Mechanisms and Treatment. *JACC. Heart failure*. 2025;13(7):102482.
5. Byrne JG, Leacche M, Paul S, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. *Eur J Cardiothorac Surg*. 2004;25(3): 327-32.
6. Mekontso-Dessap A, Houël R, Soustelle C, Kirsch M, Thébert D, Loisance DY. Risk factors for post-cardiopulmonary bypass vasoplegia in patients with preserved left ventricular function. *The Annals of thoracic surgery*. 2001;*71*(5):1428–32.
7. Landry DW and Oliver JA. The pathogenesis of vasodilatory shock. *The New England journal of medicine*. 2001;345(8):588–95.
8. Busse LW, Barker N, Petersen C. Vasoplegic syndrome following cardiothoracic surgery-review of pathophysiology and update of treatment options. *Critical care*. 2020; 24(1): 36.
9. Evora PR, Alves Junior L, Ferreira CA, Menardi AC, Bassetto S, Rodrigues AJ, et al. Twenty years of vasoplegic syndrome treatment in heart surgery. Methylene blue revised. *Revista brasileira de cirurgia cardiovascular*. 2015;*30*(1):84–92.
10. Habib AM, Elsherbeny AG, Almehizia RA. Methylene Blue for Vasoplegic Syndrome Postcardiac Surgery. *Indian J Crit Care Med*. 2018; 22(3):168–73.
11. Weiner MM, Lin HM, Danforth D, Rao S, Hosseinian L, Fischer GW. Methylene blue is associated with poor outcomes in vasoplegic shock. *Journal of cardiothoracic and vascular Anesthesia*. 2013; 27(6):1233–38.
12. Viaro F, Dalio MB, Evora PR. Catastrophic cardiovascular adverse reactions to protamine are nitric oxide/cyclic guanosine monophosphate dependent and endothelium mediated: should methylene blue be the treatment of choice? *Chest*. 2002;122(3):1061–66.

13. Stawicki SP, Sims C, Sarani B, Grossman MD, Gracias VH. Methylene blue and vasoplegia: who, when, and how? *Mini reviews in medicinal chemistry*. 2008; 8(5):472–90.
14. Peter C, Hongwan D, Küpfer A, Lauterburg BH. Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *European journal of clinical pharmacology*. 2000;56(3):247–50.
15. Paciullo CA, McMahon Horner D, Hatton KW, Flynn JD. Methylene blue for the treatment of septic shock. *Pharmacotherapy*. 2010;30(7):702–15.
16. Hencken L, To L, Ly N, Morgan JA. Serotonin Syndrome Following Methylene Blue Administration for Vasoplegic Syndrome. *Journal of cardiac surgery*. 2016;31(4):208–10.
17. Kessler MR, Eide T, Humayun B, Poppers PJ. Spurious pulse oximeter desaturation with methylene blue injection. *Anesthesiology*. 1986; 65(4): 435–36.
18. Sidi A, Paulus DA, Rush W, Gravenstein N, Davis RF. Methylene blue and indocyanine green artifactually lower pulse oximetry readings of oxygen saturation. Studies in dogs. *Journal of clinical monitoring*. 1987;3(4):249–56.
19. Mittnacht AJ, Fischer GW, Reich DL. Methylene blue administration is associated with decreased cerebral oximetry values. *Anesthesia and analgesia*. 2007;105(2):549–50.
20. Meekin GK. Intraoperative use of methylene blue to localize parathyroid adenoma.*The Laryngoscope*. 1998;108(5):772–73.
21. Hosseinian L, Weiner M, Levin MA, Fischer GW. Methylene Blue: Magic Bullet for Vasoplegia? *Anesthesia and analgesia*. 2016;122(1): 194–201.
22. Booth AT, Melmer PD, Tribble B, Mehaffey JH, Tribble C. Methylene blue for vasoplegic syndrome. *The Heart Surgery Forum*. 2017;20(5):234–38.
23. Taylor K, Holtby H. Methylene blue revisited: management of hypotension in a pediatric patient with bacterial endocarditis. *J Thorac Cardiovasc Surg*. 2005;130(2):566.
24. Ozal E, Kuralay E, Yildirim V, Kilic S, Bolcal C, Kücükarslan N, et al. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. *Ann Thorac Surg*. 2005;79(5):1615–19.