

THROMBOEMBOLISM PREVENTION IN SURGERY OF DIGESTIVE CANCER

Prevenção do tromboembolismo na cirurgia do câncer do aparelho digestivo

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ABSTRACT – Background - The venous thromboembolism is a common complication after surgical treatment in general and, in particular, on the therapeutic management on cancer. Surgery of the digestive tract has been reported to induce this complication. Patients with digestive cancer have substantial increased risk of initial or recurrent thromboembolism. **Aim** - To provide to surgeons working in digestive surgery and general surgery guidance on how to make safe thromboprophylaxis for patients requiring operations in the treatment of their gastrointestinal malignancies. **Methods** - The guideline was based on 15 relevant clinical issues and related to the risk factors, treatment and prognosis of the patient undergoing surgical treatment of cancer on digestive tract. They focused thromboembolic events associated with operations and thromboprophylaxis. The questions were structured using the PICO (Patient, Intervention or Indicator, Comparison and Outcome), allowing strategies to generate evidence on the main primary bases of scientific information (Medline / Pubmed, Embase, Lilacs / Scielo, Cochrane Library, PreMedline via OVID). Evidence manual search was also conducted (BDTD and IBICT). The evidence was recovered from the selected critical evaluation using discriminatory instruments (scores) according to the category of the question: risk, prognosis and therapy (JADAD Randomized Clinical Trials and New Castle Ottawa Scale for studies not randomized). After defining potential studies to support the recommendations, they were selected by the strength of evidence and grade of recommendation according to the classification of Oxford, including the available evidence of greater strength. **Results** - A total of 53,555 papers by title and / or abstract related to issue were found. Of this total were selected (1st selection) 478 studies that were evaluated as full-text. From them to support the recommendations were included in the consensus 132 papers. The 15 questions could be answered with evidence grade of articles with 31 A, 130 B, 1 C and 0 D. **Conclusion** - It was possible to prepare safe recommendations as guidance for thromboembolism prophylaxis in operations on the digestive tract malignancies, addressing the most frequent topics of everyday work of digestive and general surgeons.

HEADINGS - Neoplasms. Venous thrombosis. Heparin. Surgery.

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RESUMO – Racional - Tromboembolismo venoso é complicação frequente após tratamento cirúrgico em geral e, de um modo especial, na condução terapêutica do câncer. A cirurgia do aparelho digestivo tem sido referida como potencialmente indutora desta complicação. Os pacientes com câncer digestivo, têm risco substancialmente aumentado de iniciarem ou de terem recorrência de processo tromboembólico. **Objetivo** - Oferecer aos cirurgiões que atuam na cirurgia digestiva e geral orientação segura sobre como efetuar a tromboprofilaxia dos pacientes que necessitam de operações no tratamento de doenças malignas digestivas. **Métodos** - A Diretriz foi baseada a partir da elaboração de 15 questões clínicas relevantes e relacionadas ao risco, tratamento e prognóstico do paciente submetido ao tratamento cirúrgico do câncer do aparelho digestivo. Elas focaram tanto os eventos tromboembólicos associados às operações quanto os aspectos relacionados à sua profilaxia. As questões foram estruturadas por meio do P.I.C.O. (Paciente, Intervenção ou Indicador, Comparação e Outcome), permitindo gerar estratégias de busca da evidência nas principais bases primárias de informação científica (Medline/Pubmed, Embase, Lilacs/Scielo, Cochrane Library, Premedline via OVID). Também foi realizada busca manual da evidência e de teses (BDTD e IBICT). A evidência recuperada foi selecionada a partir da avaliação crítica utilizando instrumentos (escores) discriminatórios de acordo com a categoria da questão: risco, terapêutica e prognóstico (JADAD para Ensaios Clínicos Randomizados e New Castle Ottawa Scale para estudos não randômicos). Após

definir os estudos potenciais para sustento das recomendações, eles foram selecionados pela força da evidência e grau de recomendação segundo a classificação de Oxford, incluindo a evidência disponível de maior força. **Resultados** - Foram avaliados 53.555 trabalhos pelo título e/ou resumo. Deste total foram selecionados (1ª seleção) 478 trabalhos avaliados pelo texto completo. A partir deles, para sustentar as recomendações, foram incluídos neste consenso 132 trabalhos. As 15 perguntas formuladas puderam ser respondidas com artigos com grau de evidência correspondentes à 31 A, 130 B, 1 C e 0 D. **Conclusão** – Esta revisão possibilitou elaborar orientação segura para a profilaxia do tromboembolismo nas operações sobre o câncer do aparelho digestivo, abordando os tópicos mais frequentes do cotidiano do trabalho dos cirurgiões gerais e do aparelho digestivo.

DESCRITORES - Neoplasias. Trombose venosa. Heparina. Cirurgia.

INTRODUCTION

Venous thromboembolism is a common complication after surgical treatment in general and, in particular, on management of cancer. Surgery of the digestive tract has been reported to potentially induce this complication. It has greater representation in certain anatomical segments and in the conditions that are associated patients risk factors.

The prevention of thromboembolism (VTE) is a subject of great importance in the daily practice of surgeons. There are several physical forms and drugs that can be used. In recent years new approaches, both with respect to physical maneuvers as in drug dosage have been studied with good methodology. These new approaches are still little known and also are by most surgeons. In cancer the importance of this topic is even greater than in benign diseases.

The Evidence-Based Medicine incorporates data of the most recent systematic reviews available in the literature causing various forms of scientific contributions. The most common are the Guidelines and the consensus.

The first, in Brazil, is made by the associations of specialties affiliated on the Brazilian Medical Association - AMB and the Federal Council of Medicine - CFM, and disclosed by these official entities of the medical profession. They are guides of good care practices answering questions that doctors have in their daily work. They do not replace the experience and expertise of medical care acquired as valid in their medical life. Furthermore, the Guidelines may not be complete or updated recently, since much new publications may not have been incorporated in the latest issue. Users should be encouraged to seek update from the date of publication of the guide till present, the studies that could impact the diagnosis and treatment of their patients in the period of time that separates the official release and the date of service.

The second, is to suggest recommendations to the points where the evidence is not of high degree or do not exist. The best, by its high degree of evidence, are unquestionable and are usually only homologated by the consensus group. The meeting of experienced and renowned experts in the field to discuss the

controversial points is crucial in guiding medical attitudes on topics difficult to approach. Normally these consensuses substantiate the subsequent creation of the Guidelines issued by the official classes. To have to better validity, the papers in witch the consensuses are based on must be printed in journals with good indexation and blindly peer-reviewed. The major indicators of the quality of these journals are the impact factor and international access.

Circumstantial and genetic factors increase the risk of VTE. The recognition of these factors is essential to be able to deal with higher accuracy and efficiency. Several risk classifications have been proposed over time and some based on researches carried out with a high degree of evidence. However, updated guidance is always needed. It should add to the existing evidence the medical possibilities of its application and also the patients conditions. The Brazilian College of Digestive Surgery is collaborating with AMB and CFM in formulating the Guidelines, in which this consensus can be transformed. The theme disclosed herein was motivated by the importance it has in prevention of thromboembolism in pre and post-operative abdominal operations for cancer. In recent years, due to new and interesting features that were added to this theme, medical attitudes are forced in a rethink.

Therefore, the aim of this consensus is to recommend to surgeons who work in cancer of the digestive system (CAD) the latest possibilities in the management and prevention of VTE, based on Evidence-Based Medicine.

METHODS

Description of the method of collecting evidence

The Guideline / consensus was based on 15 relevant clinical issues and their related risk on treatment and prognosis of the patient undergoing surgical treatment for cancer of the digestive system (the statements are described in the results). They focused thromboembolic events associated with operations and thromboprophylaxis. The questions were structured using the PICO (Patient, Intervention or Indicator, Comparison and Outcome), allowing strategies to generate evidence on the main primary

bases of scientific information (Medline / Pubmed, Embase, Lilacs / Scielo, Cochrane Library, Premedline via OVID). Manual search was also conducted looking for evidences on academic theses (BDTD and IBICT).

The evidence was recovered from the selected critical assessment using discriminatory instruments (scores) according to the category of the question: risk, prognosis and therapy (JADAD Randomized Clinical Trials and New Castle Ottawa Scale for not random studies). After defining potential studies to support the recommendations, they were selected by the strength of evidence and grade of recommendation according to the classification of Oxford (available at www.cebm.net), including evidence of greater strength (available at www.cbcd.org.br).

Summary of grades of evidence and strength of recommendation

Were classified into the following grades: A - experimental or observational studies with better consistency; B - experimental or observational studies with less consistent; C - case reports (uncontrolled studies); D - opinion without critical evaluation, based on consensus, physiological or animal models studies.

The inclusion criteria used to support the recommendations, regarding PICO, varied with the question, but generally were based on patients with digestive cancer who underwent to curative or palliative operations; and / or evidence extrapolated from populations with cancer; and / or patients undergoing abdominal surgical interventions; pharmacological or non-pharmacological thromboprophylaxis; in the primary prevention of venous thromboembolic events; outcomes related to deep vein thrombosis, pulmonary embolism, bleeding events, mortality and complications in the perioperative period.

Were evaluated 53,555 papers by title and / or abstract. Of this total were selected (1st selection) 478 studies evaluated the full text. From them to support the recommendations were included in the consensus 132 papers. The individual numerical synthesis used is described in parentheses after each recommendation. The full text is available at www.cbcd.org.br

RESULTS

The 15 questions could be answered with articles of levels of evidence corresponding to 31 A, 130 B, 1 C and none D in total. The final recommendations from consensus to each question are described below. In each is mentioned the numerical synthesis of the reviewed papers, and in parentheses are: 1) the total reviewed; 2) the total after first selection; 3) the number of articles included that supported the recommendations.

The abstracts of the articles and their original forms (full text) used as references for

recommendations are available on the website of CBCD: www.cbcd.org.br sector highlighted as "Prevention of thromboembolism in surgery of cancer of the digestive system" (the authors encourage readers to access these supplements in reading this article).

The final recommendations were:

Question 1. The surgical patient with CAD has pre and post-operative increased the risk of VTE?

Recommendation: There is an increased risk of VTE in patients with malignancy of the digestive system in pre and postoperative period, including after discharge. Risk factors (tumor site, stage, chemotherapy, age, etc.) should be considered in decision of making thromboprophylaxis ^{10,19,40,53,67,69,71,75,83,89,107,108,111,118,125,132}.

(Recovered = 6241; first selection = 61, included = 16).

Question 2. There are differences between the locations of CAD and the risk of postoperative VTE (esophagus, stomach, liver, pancreas, colon, rectum)?

Recommendation: After operation for gastrointestinal cancer, the data show that VTE is associated with tumor location, inducing specific postoperative care ^{10,19,40,53,67,69,71,75,83,89,107,108,111,118,125,132}. (Recovered = 6241, first selection = 61; included = 16).

Question 3. The approach by laparotomy or laparoscopy in CAD modifies the risk of VTE?

Recommendation: The laparoscopic operation, as an independent variable, does not modify the risk of thromboembolism (venous and / or pulmonary) in patients with CAD, and the indication for perioperative thromboprophylaxis is similar to open operations ^{17,18, 28,41,61,63,70,73,77,78,80,81,115,121,124}. (Recovered = 23012; first selection = 55; included = 15)

Question 4. Should be employed instruments of risk stratification of VTE in the preoperative evaluation of patients with CAD? Which are the most common? Which are validated?

Recommendation: The instruments for predicting risk of thromboembolic events in hospitalized patients (clinical or surgical) and / or with cancer (curative or palliative) are influenced by many factors (biases). There are no tools to estimate accurately the risk of VTE in these patients. However, there are independent risk factors (clinical and laboratory) that, when present, justify thromboprophylaxis in any of the levels of risk (low, intermediate or high) ^{1,6,7,9,19,23,30,53,54, 55,59,87,96,99,104,109, 110,120,125,131}. (Recovered = 9982; first selection = 117; included = 20)

Question 5. The pharmacologic prophylaxis with heparin, low molecular weight heparin (LMWH) may decrease the risk of VTE in the postoperative patient with CAD?

Recommendation: Prophylaxis with low molecular weight heparin reduces the risk of thromboembolic events in patients with abdominal operation for cancer, compared to those who did not receive thromboprophylaxis. There is no statistically significant difference between the various types of low molecular weight heparins for efficacy ^{1,16,22,29,42,43, 50,53,67,72,86,94,98,100,105,122}. (Recovered = 5806; first selection = 142; included = 16)

Question 6. The pharmacological prophylaxis with unfractionated heparin can decrease the risk of VTE in the postoperative patient with CAD?

Recommendation: Use of unfractionated heparin before abdominal operations (with and without cancer) in a dose of 5000 IU SC and, then, every eight hours for five to eight days, reduces the risk of postoperative thromboembolic events without increasing significantly the risk of bleeding events ^{16,25,27,35,44,50,57,62,90,95,103,114}. (Recovered = 5806; first selection = 142; included = 12)

Question 7. Is there a difference in efficacy between LMWH and unfractionated heparin in the prophylaxis of VTE in patients with CAD?

Recommendation: There is no difference in the occurrence of thromboembolic events (deep venous thrombosis or pulmonary embolism) with the use of low molecular weight heparin or unfractionated heparin in most of the evidence extrapolated to patients undergoing abdominal or general surgery for cancer (35% to 63% of cases). However, in a small part of evidence also extrapolated, when exists difference between the two forms of thromboprophylaxis, it favors the use of low molecular weight heparin, with reduction in bleeding events, in wall hematoma and reoperation for bleeding ^{3,13,15,26,31,34,35,38,45,48,64,74,76,84,101}. (Recovered = 5806; first selection = 142; included = 15)

Question 8. Physical methods are effective in the prophylaxis of VTE? Can replace heparin in the prophylaxis of VTE in patients with CAD?

Recommendation: Physical methods, when properly used, are effective in reducing the risk of thromboembolic event(s). However, they should not replace the pharmacological prophylaxis, and this pharmacological treatment should it be reassume as soon as contraindications cease. The combined use of physical methods, especially graduated compression stockings with low-dose heparin thromboprophylaxis in the perioperative, increases the benefit in reducing the risk of thromboembolic events ^{4,21,51,82,88,92,114,117,126,128,129,130}. (Recovered = 3377; first selection = 52; included = 12)

Question 9. What is the recommended dosage regimen of heparin in the prophylaxis of VTE in surgical patients with CAD?

Recommendation: In the evaluation of prophylaxis for venous thromboembolism in patients undergoing abdominal surgery for cancer, there is no difference between the various treatment regimens with various types of heparin on the occurrence of thromboembolic outcomes. Nonetheless, the available evidence supports the recommendation of 5000 IU every eight hours for unfractionated heparin; for low molecular weight heparins - enoxaparin, dalteparin and nadroparin - the doses are recommended by manufacturers ^{12,22,29,31,34,50,74,86,95,100,105}. (Recovered = 5806; first selection = 142; included = 11)

Question 10. At what moment should be initiated pharmacological VTE prophylaxis?

Recommendation: The beginning of the use of unfractionated heparin before surgery reduces

the risk of thromboembolic event compared to its exclusive use in the postoperative period. The low molecular weight heparin preoperatively may be recommended by extrapolating the comparison with unfractionated heparin preoperatively. The unfractionated heparin can be initiated in one to two hours before surgery. The use of heparin of low molecular weight should preferably be done 12 hours before the procedure; however, two hours before the start appears to be safe since it does not interfere with the anesthesia ^{3,12,29,31,33,42,43,72,74,95,97,98}. (Recovered = 5806; first selection = 142; included = 12)

Question 11. The resumption of deambulation in the postoperative period allows the suspension of pharmacological prophylaxis of VTE or obtaining better results in prophylaxis?

Recommendation: Deambulation (day 1 postoperatively) should be encouraged, but there is no way to estimate the magnitude of their benefit in thromboprophylaxis and, so, is not allowed to replace the latter, even in patients at low risk of thrombosis ^{24,66,85,94,112,116,119,123}. (Recovered = 3576; first selection = 26; included = 8)

Question 12. How long must be maintained at pharmacological prophylaxis of VTE in the postoperative patient with CAD? There is benefit in extended prophylaxis (up to four weeks)?

Recommendation: The pharmacological thromboprophylaxis in postoperative patients with operations for cancer of the digestive system - extrapolating to other abdominal cancers - should be maintained for seven to ten days after surgery. Although still under investigation, the current trend suggests the extent of thromboprophylaxis for up to four weeks after surgery ^{5,11,34,42,46,47,60,72,93,98,99,105,112,132}. (Recovered = 5806; first selection = 142; included = 14)

Question 13. There is a need to adjust the doses of heparin in the prophylaxis of VTE of obese patients with CAD? If yes, from which BMI?

Recommendation: Although the existence of available evidences that the stratification of the heparin dose based on BMI can be safe and effective on thromboprophylaxis in obese patients undergoing bariatric surgery, this evidence should not be extrapolated to patients undergoing cancer operations on digestive tract; in this situation the stratification has not been adequately studied ^{20,32,39,52,59,65,68,91,102,106,127}. (Recovered = 1561; first selection = 25; included = 11)

Question 14. The pharmacological prophylaxis increases the risk of bleeding during and after surgery in patients with CAD operations?

Recommendation: There is also no difference in the occurrence of bleeding and increased risk of intraoperative or postoperative bleeding regarding the use of low molecular weight heparin or unfractionated heparin in most evidence extrapolated to patients undergoing general surgery or by abdominal malignancy. Nevertheless, the use of thromboprophylaxis compared with not using

heparin perioperatively, may increase postoperative bleeding events^{3,13,35,42,43,47,64,72,74,94,95,98,103,105,122}. (Recovered = 5806; first selection = 142; included = 15)

Question 15. There are medical conditions that contraindicate the use of heparin in the prophylaxis of VTE in CAD operations?

Recommendation: The contraindications for thromboprophylaxis in patients that carry digestive tract surgery - extrapolating to elderly with cancer without surgery - may be particularly hypersensitivity to heparin, septic endocarditis, hemorrhagic stroke, documented bleeding diathesis, treatment with anticoagulant or platelet antiaggregant, and renal or hepatic dysfunction^{12,14,15,16,22,31,37,38,42,72,86,95,103}. (Recovered = 5806; first selection = 142; included = 13)

DISCUSSION

Evidence-based research is an arduous task and requires experience. Initially are raised all correlated existent papers in major virtual libraries, crossing appropriated headings. This search generates a very large amount of articles, like what happened here. There were 53,555 papers by title and / or abstract, number impossible to be handled. Through filters, the search technique greatly reduces the amount, looking for uniformity of topics. Then, by reading the full text is obtained the homogeneity among the items. This reduces the total to a much smaller number to be used on the recommendations. Even this way, the final number of articles is large, as in this case: 132.

As expect, the theme of thromboprophylaxis is very broad and difficult to search. This fact can be recognized by the dispersion of selected articles in their degrees of evidence: 31 A, 130 B, 1 C and 0 D. However, the number with the highest grades (A + B) was good (131) and ensures reliability of these recommendations.

The Guideline is characterized by answering practical questions of the day-to-day medical practice. This one now presented, do not intent to be exhaustive. It was focused on the most frequent questions from the daily practice of the digestive surgeon forward to the prevention of thromboembolism, and tried to be objective, quick and easy understanding. Were removed from the text all the details of the exhaustive search (only because there is no editorial space to insert them) and they were placed on the CBCD web site where all studies can be checked and read in its entirety. The authors think that this interactivity easily accessible, can collaborate with continued education in digestive surgery. On CBCD site there is special attention to this consensus, freely available. Like any guideline, it is not intended that the reader faces these recommendations in a dogmatic way, but as a guidance. The clinical expertise is irreplaceable in moments of decision and these recommendations wish to be a safe tool for surgeons to help their decisions.

As can be seen by the low amount of references with higher degrees in relationship to total, is important the community to expand the academic research on thromboembolism. Only in this way and through prospective studies with better methodology, will be possible to increase the security of guidelines for the practice of thromboprophylaxis.

The CBCD will make efforts to transform this consensus in AMB / CFM Guideline, giving even more strength and respectability to it. But even so, due to the constant and uninterrupted publishing articles with new methods of treatment, this theme will continue to be updated by CBCD. The dynamism of research in the area is very large - although with only moderate evidence - requiring constant updating. The intention is that, by reading this article, our surgeons are guaranteed that they are offering the best for their patients by the time of the publication.

Recent estimations, shows that Brazil is aging. Thus, special attention should be given to the research of thromboembolism in the elderly. The recommendations will change? Only time and authors commitment in the theme will provide the answer.

Finally, the main objective of this exhausting paper was focused on the reduction of the morbidity and mortality of surgical procedures on the digestive tract. Proper management on prevention of thromboembolism results in lower costs in the overall patients care, reduces hospital stay and improves quality of life to those who come to us looking for high level of medical assistance.

CONCLUSIONS

This consensus could develop safe guidance for the prophylaxis of thromboembolism in operations of the digestive system cancer, answering the most frequent questions of everyday practice in general and digestive tract surgery.

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