Impact of Antithrombotic Therapy on the Outcome of Patients Undergoing Laparoscopic Colorectal Cancer Surgery: A Systematic Literature Review

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Abstract

In recent years, many operations have been performed as laparoscopic surgeries in the field of gastrointestinal surgery, but the effect of antithrombotic therapy (ATT) on hemorrhagic complications in patients who have undergone laparoscopic colorectal cancer surgery remains unknown. In addition, the efficacy and safety of pharmacotherapy for the prevention of venous thromboembolism (VTE) have not yet been clarified. The purpose of this systematic review study is to clarify the effect of ATT on hemorrhagic complications in patients undergoing laparoscopic colorectal cancer surgery.

Articles published between 2013 and 2020 were searched on Google Scholar and PubMed, and research regarding ATT and laparoscopic colorectal cancer surgery was included after a thorough examination of each study. Each study yielded information on the study’s design, type of surgical procedures, antithrombotic medications used, and surgical outcomes (both thromboembolic and hemorrhagic consequences). This systematic review comprised 20 published papers, including a total of 12,751 patients who received laparoscopic colorectal cancer surgery. Four studies on thrombosis prevention in VTE were randomized clinical trials, and the other 16 were cohort or case-control studies. For the effects of prolonged use of ATT on hemorrhagic complications, most studies demonstrated that laparoscopic colorectal cancer surgery with continued preoperative aspirin could be safely conducted without an increase in the frequency of bleeding complications. On the other hand, most included papers have shown that patients receiving VTE pharmacoprophylaxis may be at an increased risk of bleeding complications, but its effectiveness has not been statistically proven, especially in the Asian patient population.

Laparoscopic colorectal cancer surgery in patients on prolonged ATT can be safely conducted with no increase in the incidence of hemorrhagic or thrombotic complications. The efficacy and safety of VTE pharmacoprophylaxis in laparoscopic colorectal surgery is still an issue. It is necessary to establish available protocols or guidelines by validating reliable studies.

Keywords: thromboembolism complication, bleeding complication, antithrombotic therapy, colorectal cancer surgery, laparoscopic surgery

Introduction And Background

The three leading causes of death in the world are cancer, cerebrovascular disease, and heart disease. With the aging of society in recent years, the risk for patients suffering from cerebrovascular disease and cardiac disease to require non-cardiac surgery are expanding. Most of these patients receive antithrombotic therapy (ATT) to prevent thrombosis, but patients undergoing ATT are at an increased risk of both thromboembolism and bleeding during the perioperative period. Therefore, strict antithrombotic drug management is required [1].

ATT is classified into two types: antiplatelet therapy and anticoagulant therapy. Antiplatelet agents are used for primary and secondary prevention of cerebrovascular and cardiovascular diseases, the mechanism of which is to prevent thrombosis by suppressing platelet aggregation [2,3]. Anticoagulants are primarily used for acute coronary syndrome, deep venous thrombosis, arterial fibrillation, post-cardiac prosthetic replacement, and venous thromboembolism (VTE) pharmacoprophylaxis, the mechanism of which is to prevent blood coagulation by inhibiting the native coagulation cascade [4]. Table 1 summarizes the types of antithrombotics, specific drugs, and durations of action. Antiplatelet agents include thienopyridines (e.g., clopidogrel, ticlopidine, or prasugrel), acetylsalicylic acid (aspirin), type III phosphodiesterase inhibitors (e.g., cilostazol), and other nonsteroidal anti-inflammatory drugs. Anticoagulants include unfractionated heparin, heparin derivatives (e.g., fondaparinux), low-molecular-weight heparin (e.g., dartepalin), vitamin K antagonists (e.g., warfarin), and direct-acting oral anticoagulants (DOACs), also known as non-vitamin K antagonist oral anticoagulants (NOACs). DOACs are further divided into factor Xa inhibitors (e.g., apixaban, rivaroxaban, edoxaban) and direct thrombin inhibitors (dabigatran).
| Agent class               | Type of agent | Specific drugs                  | Duration of action |
|--------------------------|---------------|---------------------------------|--------------------|
| Antiplatelet agent       | Thienopyridines | Clopidogrel                      | 5-7 d              |
|                          | Prasugrel      |                                 | 5-7 d              |
|                          | Ticagrelor     |                                 | 5-7 d              |
|                          | Ticlopidine    |                                 | 10-14 d            |
|                          | Other NSAIDs   | Ibuprofen, loxoprofen, diclofenac etc. | Varies            |
| Anticoagulation agent    | Unfractionated heparin | Heparin                | 1-2 h              |
|                          | LMWH           | Dalteparin (iv)                | 2-4 h              |
|                          |                | Enoxaparin (sc)                | 8-12 h             |
|                          |                | Nadroparin (sc)                | 8-12 h             |
|                          | Vitamin K antagonist | Warfarin               | 5 d                |
|                          | Factor Xa inhibitor (sc) | Fondaparinux           | 1-1.5 d            |
|                          | DOAC: Direct thrombin inhibitor | Dalteparin           | 1-2 d              |
|                          | DOAC: Factor Xa inhibitor | Rivaroxaban         | 1-2 d              |
|                          |                | Apixaban                        | 1-2 d              |
|                          |                | Edoxaban                        | 1-2 d              |

TABLE 1: Types, specific agents, and acting duration of commonly used antithrombotic drugs.

DOAC, direct-acting oral anticoagulant; iv, intravenous; LMWH, low-molecular-weight heparin; NSAID, non-steroidal anti-inflammatory drug; PDE, phosphodiesterase; sc, subcutaneous.

In recent years, many operations in the field of gastrointestinal surgery have been performed as laparoscopic surgeries. Benefits of laparoscopic surgery have been shown to include a decrease in postoperative complications, reduced postoperative pain, and a quick return to social life [4,5], although it is still under debate whether these benefits can minimize the risk of thromboembolism during laparoscopic surgery [2]. Laparoscopic surgery has been reported to significantly reduce intraoperative bleeding [4,5].

Maintaining a bleeding-free surgical field is very important in laparoscopic surgery, and with improvements in various surgical techniques and the introduction of new surgical devices such as soft coagulation systems or ultrasonic coagulating devices, various sorts of advanced laparoscopic surgery, including colorectal cancer resection, can currently be performed. On the other hand, optimal perioperative management of patients undergoing ATT for laparoscopic colorectal cancer surgery is still under discussion.

The aim of this systematic review is to clarify the effect of ATT on thromboembolism and bleeding complications (BCs) in laparoscopic colorectal cancer surgery.

Review

Methods

English-written articles published between 2013 and 2020 were searched by Google Scholar and PubMed. The relevant keywords, including aspirin, clopidogrel, warfarin, anticoagulant, antiplatelet, hemorrhage, bleeding, laparoscopic surgery, and colorectal cancer surgery, were used in the search. We have selected research articles that were published in peer-reviewed journals. Randomized clinical trials, case-control studies, or prospective or retrospective cohort studies were all considered eligible; guidelines, review papers, and case series/reports were not.

After duplicates were removed, each study was carefully reviewed and papers were methodically discarded. Depending on the study design, the quality of each study was evaluated, and relevant papers were identified. Each study yielded information on the study’s design, type of surgical procedures, antithrombotic medications used, and surgical outcomes (both thromboembolic and hemorrhagic consequences). Increased surgical blood loss (SBL) and postoperative BCs were the two types of hemorrhagic consequences.

Results

Features of the Included Studies

Research screening and collection were conducted from December 2020 to January 2021. In total, we analyzed 20 published articles, with a total of 12,751 patients undergoing laparoscopic colorectal cancer surgery. The eligible articles consisted of 11 studies regarding the management of patients with prolonged ATT (Table 2) [6-15] and nine studies regarding pharmacological thromboprophylaxis for VTE (Table 3) [16-24]. Four studies concerning thromboprophylaxis for VTE were randomized clinical trials, and the other 16 were cohort studies or case-control studies. Ten were observational cohort studies, all of which were retrospective in nature. Concerning the research on the management of patients with prolonged ATT, one study was a multivariate retrospective cohort analysis [7] and three were analyses using the propensity score matching method [6,9,11].
Of 11 studies concerning the management of patients undergoing prolonged ATT, seven assessed the safety of preoperative continuation of aspirin during laparoscopic colorectal surgery. In nine studies concerning pharmacological thromboprophylaxis for VTE, patients were generally managed by LMWH. Three studies published in the USA or Italy focused on post-discharge VTE.

Safety of Laparoscopic Colorectal Cancer Surgery in Patients Undergoing Prolonged ATT (Table 3)

In all 11 studies regarding the management of patients with prolonged ATT, the safety and feasibility of laparoscopic colorectal surgery in ATT-received patients were generally reported.

Seven papers centered on the feasibility of preoperative continuation of aspirin during laparoscopic colorectal resection [2,6-10,15]. One large-scale retrospective cohort study reviewed more than 3,000 patients receiving major gastrointestinal malignancy surgery, including 1,450 colorectal cancer resections, and found that the most major risk factor for thrombembolism was the interruption of preoperative aspirin treatment [7]. This study also demonstrated that the preoperative continuation of aspirin monotherapy significantly reduced the rate of postoperative thromboembolism, although it was not associated with increased SBL or postoperative BCs. Other six studies, including three retrospective cohort studies and two case-control studies using the propensity score-matching method, also showed that preoperative continuation of aspirin is not related to increased rates of BC or SBL in patients with prolonged antiplatelet prescriptions during laparoscopic colorectal cancer surgery [2,6-10,15]. These articles suggest that when performing laparoscopic colorectal surgery in patients with prolonged antiplatelet therapy, preoperative continuation of aspirin is safe and should be considered preferable.

Safety of Pharmacological Thromboprophylaxis for VTE (Table 3)

Among nine articles on pharmacological thromboprophylaxis for VTE, seven were multicenter studies, including four randomized clinical trials and three retrospective cohort studies. These four randomized clinical trials were from Japan [19-21], and it was shown that the occurrence of overall and major BCs under pharmacological prophylaxis during laparoscopic colorectal cancer surgery was relatively higher (1.8-13.1% in overall and 0.7-1.7% in major BCs) compared to those without medical prophylaxis, although its efficacy for VTE is not statistically relevant. Three studies from the United States and Italy demonstrated the relevant rate of post-discharge VTE after laparoscopic colorectal surgery (0.7%). These studies suggest the significance of extended chemical prophylaxis in this patient population.

Assessment of these studies has suggested a potentially high risk of bleeding in patients receiving pharmacological thromboprophylaxis. On the other hand, the effectiveness of pharmacological thromboprophylaxis after laparoscopic colorectal surgery is not statistically shown, particularly in the Asian population.

Discussion

To our knowledge, the present review is the first systematic review that analyzes the efficacy of ATT on thromboembolisms and hemorrhagic complications in laparoscopic colorectal surgery. The current review outlines 20 articles, including a total of 12,132 patients who underwent laparoscopic colorectal surgery.
Conclusions

Laparoscopic colorectal cancer surgery in patients receiving prolonged ATT can be safely performed without increasing thromboembolic or hemorrhagic complications. Pharmacological VTE prophylaxis after laparoscopic colorectal cancer surgery is still controversial in terms of efficacy and safety. Establishing a clear guideline or protocol necessitates more research based on credible design research.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors declare that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships relevant to the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to influence the submitted work.
