



Perioperative Anticoagulation for Colorectal Cancer Patients

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Abstract

Population ageing has substantially contributed to the rising number of new cancer cases worldwide. Fifty percent of new diagnoses of colorectal cancer are made in patients aged over 70 years and 25% are aged 80 years or over. Older patients present with more co-morbidities and frailty than younger patients.

Here we describe the case of a 78-year-old lady with atrial fibrillation (AF) and previous stroke who had a right hemicolectomy for a cecal adenocarcinoma. Unfortunately, whilst off anticoagulation at day 5 post operatively she suffered a catastrophic stroke.

For patients requiring surgical management of colorectal carcinoma who are on anticoagulation for AF, bespoke perioperative planning is required to assess risks and benefits of bridging anticoagulation.

Introduction

Population ageing has significantly contributed to the growing number of new cancer diagnoses. Nearly six out of every ten new cases are in a patient over the age of 70. Higher level of screening and early detection of cancer has led to increased survival over the last few decades but despite this, older patients with colorectal cancer are more likely to be undertreated [1,2]. Compared to younger patients, elderly patients are operated on less and have a lower rate of curative surgery and more emergency surgery [3]. However, a study by Ng et al. 2016 [4] showed that when patients did have curative treatment for right-sided cancer, they survived longer.

Hence, it is essential to realize that though patients may be older, frailty is a highly individualized process and not solely reflected in chronological age. Assessment for their fitness for surgery must therefore be done in a more holistic manner than the general population and they require bespoke perioperative planning [2].

In this article, we describe the case of a 78-year-old female with a past medical history of atrial fibrillation (AF), type 2 diabetes and stroke, who underwent a right hemicolectomy for adenocarcinoma. We explore her perioperative planning with regards to anticoagulation and look at existing literature on the subject.

Case Presentation

A 78-year-old lady of East Asian origin was referred for a colonoscopy following blood results that revealed incidental iron deficiency anemia. Her Computed Tomography (CT) scan showed a 23 mm mass in her cecum in keeping with a suspected malignancy which was radiologically staged at T2, N0. She underwent a biopsy that confirmed the presence of an invasive moderately-differentiated colorectal adenocarcinoma.

As she had a background of type 2 diabetes, stroke and atrial fibrillation (AF), she had an extensive preoperative review. Following her stroke, she had residual right sided weakness and whilst she was able to mobilize short distances with a tripod stick, she required some assistance with most personal and domestic activities of daily living. At home, she was set up in a micro-environment and her carers visited her four times a day. She was identified as a frail patient at risk of delirium, deconditioning and deterioration in hospital and each of these concerns were addressed in the clinic along with aspects of care related to frailty, nutrition, diabetes and specifically AF and anticoagulation. It was discussed that the period of time off anticoagulation could result in a stroke

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and possibly worsening morbidity and mortality.

The plan with regards to her AF was to stop her rivaroxaban 48 hours pre-operatively without bridging and to restart it as soon as the surgical team were satisfied with Hemostasis. Her P-POSSUM score showed a predicted mortality of 2.9% and morbidity of 50% for a planned elective operation, but on balance it was believed that the benefits outweighed the risks. In addition, the patient was extremely keen to proceed despite her risks. On the day of surgery, there were no intra-operative complications and post-operative she was started on 20 mg enoxaparin (reduced due to her low weight).

Two days post-operatively, patient had an episode of fast AF. The decision was made to continue her prophylactic enoxaparin and hold oral anticoagulation as she was likely to have impaired absorption with her ileus.

Five days post-operatively, the patient had an acute drop in her consciousness prompting a medical and stroke review. On examination, she had a score of 8 on the Glasgow Coma Scale and 28 on the National Institute of Health Stroke Scale. An urgent CT head revealed a large right Middle Cerebral Artery (MCA) territory infarct and associated swelling and effacement of the sulci and ipsilateral ventricle. She also had a CT abdomen and pelvis which showed a persistent ileus.

As her intracranial event occurred on a background of a previous left anterior, middle and posterior circulation infarcts, the new stroke was considered to be a terminal event. The family was aware of possible stroke as a perioperative risk and a joint decision was made to shift the focus of care to comfort and dignity. She passed away shortly after with her family by her side.

Discussion

AF is an arrhythmia that carries a high burden of morbidity and mortality. The incidence and prevalence of AF increases with age, affecting up to 17% of the population over the age of 80. People with AF have a five-fold increase in their risk of stroke and a two-fold increase in all-cause mortality [5]. As thromboembolism is an established risk factor of ischemic stroke with AF, oral anticoagulants are employed to reduce risk [6]. Agents like warfarin can be used to reduce the risk of strokes by 64% but limitations include over- and under-anticoagulation as it requires you to be in a narrow therapeutic range [7]. In comparison, Direct Oral Anticoagulants (DOACs) have demonstrated the potential to improve outcomes in patients with AF whilst reducing the burden of monitoring and the risk of bleeds. This has been demonstrated across several trials, namely RE-LY, ARISTOTLE and ROCKET-AF [8-10]. Most importantly however, it has been shown that regardless of the use of warfarin or a DOAC, the risk of stroke without anticoagulation often outweighs the risk of bleeding, even in frail patients who are at a higher risk of falls [11].

When it comes to post-operative risk of stroke in patients with AF, after adjustment for age, race, sex, diabetes, heart failure, hypertension, and prior stroke, the adjusted odds ratio is 2.1 (CI, 2.0-2.3). Patients with chronic atrial fibrillation have twice the risk of postoperative stroke within 30 days compared to those without atrial fibrillation [12]. Other risk factors for post-operative stroke include previous cerebrovascular disease, hypertension, increased age and atherosclerosis, all of which our patient had [13]. This is significant because the increase in absolute risk of mortality in a perioperative stroke patient is 21%; this is an 8-fold increase [14]. Therefore, whilst

perioperative management of patients on DOACs can be challenging, it is essential to patient outcome.

In this case, the patient's rivaroxaban was stopped 2 days prior to her right hemicolectomy which was appropriate as supported by the PAUSE-trial [15]. PAUSE found that if a DOAC was held 48 hours pre-operatively, almost all patients had a residual anticoagulant level less than 50 ng/mL. Moreover, 85.4% of the patients on rivaroxaban had a residual anticoagulant level less than 30 ng/mL which is considered an optimal preoperative anticoagulant level. The consensus is that if withheld for 48 hours (with normal renal function), the DOAC is sufficiently out of the system to allow a safe operative procedure due to their short half-life (~12 h).

As there were no intra-operative or immediate post-operative bleeding concerns, patient was started on prophylactic enoxaparin 24 h after surgery and at 72 h her anticoagulation was reviewed. The plan was to initially restart her DOAC however, as she developed an ileus, there were concerns surrounding her gut absorption so no changes were made.

Like in our patient, there are many potential post-operative complications that we must consider. Post-Operative Bleeding (POB) is a common event and has been reported to occur after 12.5% of colorectal resections [16]. Although POB does not often lead to fatality, it is a known risk factor for ileus and anastomotic leaks, both of which have high rates of mortality and morbidity [17]. Those on DOACs have a significantly greater risk ratio (3.04 at 95% CI) of POB than healthy patients. Rivaroxaban specifically has an even higher risk ratio of 4.13 (95% CI) [18]. However, data from the PAUSE-trial [15] demonstrates that forgoing bridging is effective at protecting patients against POB. In addition, overall rates of major bleeding events are comparable between the PAUSE- and BRIDGE-trial [19], suggesting warfarin also follows the same pattern when bridging therapy is not used when patient are on anticoagulants for AF.

The PAUSE-trial [15] initiated patients on a simple standardized perioperative DOAC interruption and resumption strategy without the use of bridging therapy. In addition to omitting DOAC 48 h before a high bleeding risk procedure, they suggested, restarting it 2 to 3 days post-operatively. Following this strategy, the perioperative major bleeding and arterial thromboembolism was found to be less than 2% and 1%, respectively. This finding is in keeping with the BRIDGE-trial [19] which showed that forgoing bridging anticoagulation was non inferior to perioperative bridging with LMWH for the prevention of arterial thromboembolism. However, the PAUSE-trial has some limitations as it is not wholly representative of our patient population. The participants were predominantly male, had mean CHA₂DS₂-VASc scores of 3.3 and less than 10% of the patients had active cancer or a previous stroke. This is not representative of our patient who had a score of 6 as well as a history of stroke and active cancer which suggests more research must be completed, if the same conclusions are to be drawn.

Another common complication of colorectal resections is prolonged post-operative ileus, occurring in 10.3% of cases [20]. One question we must ask is if her operation and subsequent ileus would affect the absorption of DOACs. We know that rivaroxaban's bioavailability is increased when taken with food. Under fasting conditions, the oral bioavailability of 20 mg rivaroxaban is 66% but when taken with food, almost complete absorption is noted [21]. In this instance, the patient was not tolerating any oral intake as a result

of her ileus which would have impacted not just her ability to keep the medication down but also the absorption of the drug. Whilst there are no studies dedicated to post-operative bioavailability of DOACs, a case report by Tomaszuk-Kazberuk et al. 2019 [22] discussed a case where paralytic ileus affected the absorption of dabigatran. In another 45-patient study, Manafi et al. 2007 [23] looked at the absorption of metronidazole in the postoperative ileus state and found that the oral bioavailability was significantly reduced. A further study looking at the absorption of oral paracetamol also found that the peak concentration was approximately half post-operatively compared to the pre-operative phase [24].

These papers [22-24] suggest that absorption of drugs is impaired during the postoperative phase. It could therefore be reasoned that when there is a high risk of postoperative ileus in a patient with an even higher risk of stroke as suggested by their past medical history and CHA₂DS₂-VASc score, bridging with Low Molecular Weight Heparin (LMWH) may be more appropriate. LMWH's subcutaneous formulation means that its bioavailability is unlikely to be affected by recent surgery, however as there is little evidence around this, next steps include investigating this further [25].

Conclusion

An ageing population means that older patients are presenting and being considered for colorectal surgery. These patients are more likely to have multiple medical conditions. One condition that affects nearly 20% of over 80-year-olds is AF. This has implications during the perioperative phase particularly linked with cessation of anticoagulation and increased stroke risk. Individualized perioperative planning is essential for the successful treatment of older patients. Furthermore, counseling and shared decision-making with patients and relatives is fundamental.

Author Contribution

SM and AB involved in writing manuscript. MS involved in revisions. LJK involved in revisions and concept of manuscript.

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