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Haemorrhoidal Surgery in Patients Under Direct Oral Anticoagulants: A High Risk of Secondary Bleeding. A Prospective Bi-Centric Observational Series

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Keywords:

Haemorrhoids; Surgery; Haemorrhage; Direct oral anticoagulants

1. Abstract

1.1. Purpose: Evaluate post-operative bleeding risk after haemorrhoidal surgery in patients treated by direct oral anticoagulants (DOAs).

1.2. Methods: Prospective study including all consecutive patients under DOAs operated on for haemorrhoids between 2016 and 2019.

1.3. Results: Were included 59 patients (14 women), mean age 71 years (34-85). Were performed resection of one haemorrhoid pile (n=4), of at least two piles (n=26), mucopexy (+/- Doppler guidance and +/- one pile resection) (n=16), haemorrhoidopexy (n=12), submucosal radio frequency destruction (n=1). A secondary haemorrhage requiring hospitalization occurred in 14 patients (24%), one patient bleeding twice. One patient was transfused, and 11 had haemostasis under general anaesthesia. Haemorrhage occurred between day-6 and 16 (median 10). Bleeding frequency when DOAs were resumed before day-15 (33%) was significantly higher than when no treatment was administered until the 15 th postoperative day (8%). Bridge with curative dosage LMWH was associated with a more elevated risk compared to preventive dosage, although not significantly (41% vs 29%). Bleeding frequency was higher after mucopexy 7/16 (44%), compared to other procedures ($p<0.05$).

1.4. Conclusion: Postoperative bleeding rate was elevated in patients where anticoagulation was not discontinued (DOAs resumed before day-15, or bridge with curative LWMH dosage). In selected patients with a low thromboembolic risk, we propose a later than day-15 DOAs reintroduction, or a bridge with preventive LWMH dosage. Therefore, assessing DOAs indication, thrombo-embolic risk, and need for surgery is crucial. As recommendations are lacking, establishment of local protocols is encouraged.

2. Introduction

Haemorrhoidal surgery is not associated with difficult intraoperative bleeding control, but exposes to a risk of delayed postoperative bleeding. This complication is relatively frequent; in a prospective series, 8% of patients operated on for haemorrhoids were re-hospitalized and had severe bleeding, as approximately 2% were re-operated on, or received a transfusion [1-3]. The period of exposure to this risk extended to the twenty-first postoperative day [1-3]. Haemorrhagic risk was not increased by acetyl salicylic acid and was only moderately increased by clopidogrel or newer antiplatelet agents. Antivitamin K (AVK) was associated with a significantly elevated risk of secondary bleeding, but to a lesser extent, when it was not stopped, than during low molecular weight heparin (LMWH) bridge [4,5]. Therefore, French recommendations propose continuing acetyl salicylic acid, antiplatelet agents, and antivitamin K without any bridge after haemorrhoidal surgery [6]. To date, no formal recommendation is available for direct oral anticoagulants (DOAs). As there is a lack of data concerning secondary haemorrhagic events after haemorrhoidal surgery in patients treated with DOAs, we decided that a prospective survey was appropriate.

4. Material and Methods

All patients treated with DOAs who underwent surgery for haemorrhoids from 2016 to 2019 in two tertiary centres were consecutively

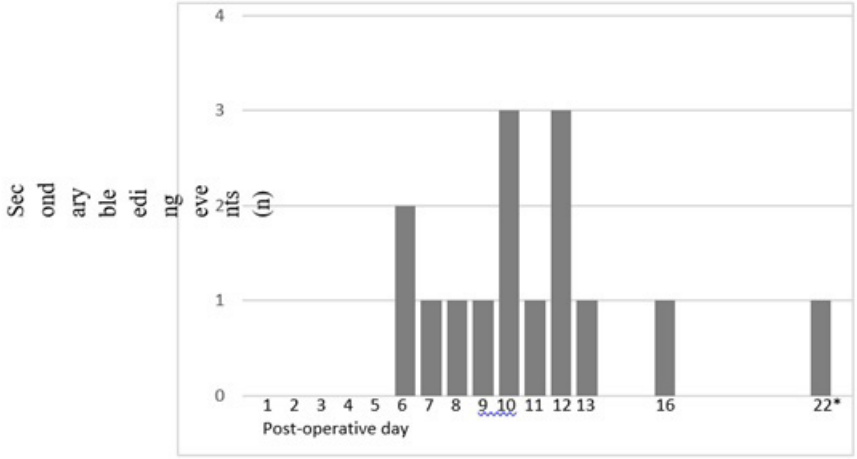
included. Patient follow-up data were recorded prospectively in the computerized files of the two centres. The surgical procedures covered all the techniques used to treat haemorrhoidal disease in these two centres during this period. Photocoagulation, injection sclerotherapy and rubber ligation were excluded. The indication for the type of surgery was decided on a case-by-case basis after discussion with the patient. Senior operators operated all the patients on. No recommendations were available, and the management of haemostatic treatment was left to the expertise of the senior operator. The dates of interruption and resumption of DOAs were noted, as bridge nature and duration. Post-operative haemorrhagic accidents justifying hospitalization were noted. Admission in units other than our two centres was taken into account. The need for reoperation and transfusion were also considered. Quantitative data are reported as the mean (range), and categorical data are reported as the number of patients (percentage). Normally distributed quantitative data were analysed with Student's t test. P was significant when < 0.05.

4.1. Population

Fifty-nine consecutive patients (14 women) with a mean age of 71 years (34-85) were included. All were on DOAs when the surgical procedure was indicated: rivaroxaban 31 times, apixaban 21 times, and dabigatran 7 times.

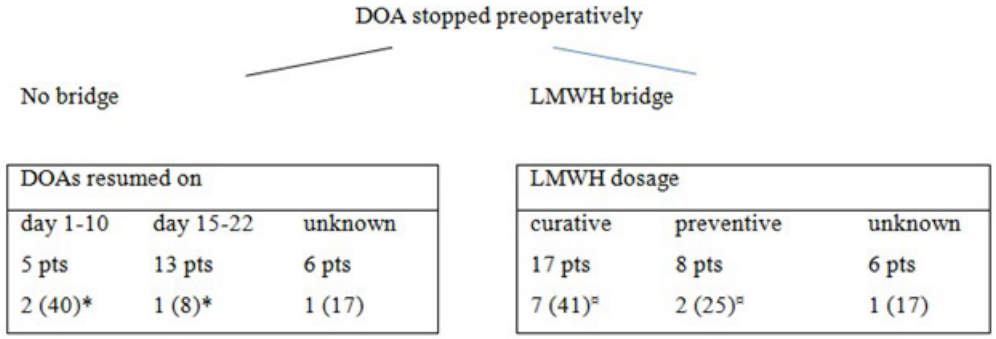
4.2. Overall results

No concerns about intra-operative haemostasis were mentioned. A secondary haemorrhagic accident occurred in 14 patients (24%); one of these patients bled twice. The accidents occurred between day 6 and day 16 (median day 10); one patient bled on days 12 and 22 (Figure 1). All patients were hospitalized, one received a transfusion, and 11 required haemostasis under general anaesthesia. No deaths were noted. Results according to the management of post-operative DOAs use (Figure 2): In all the patients, DOAs were stopped pre-operatively, between preoperative day-2 and day-5 for 54 patients, on day-26 and day-14 for two patients, and on an unknown date for three patients. After surgery, three different strategies were noted: 1 - In 31 patients, a LMWH bridge was established after surgery, until DOAs resumption. The LMWH dosage was curative in 17 (55%), preventive in 8 (26%), and not specified in 6 patients. The median duration of the bridge was 21 days (15-44) (not specified 4 times). Haemorrhagic accidents occurred in 10 of these 31 patients (33%) on median postoperative day-10 (6-16). It occurred during the LMWH bridge period for 8 patients and on an unreported date for 2 patients. It was more frequent, although not significantly, in patients receiving curative dose LMWH (7/17, 41%) than preventive dose (2/8, 29%) (p = 0.226). 2 - In 24 patients, no bridge was established, and DOAs were resumed on median postoperative day-15 (1- 22). Haemorrhagic accidents occurred in 4 out of 24 (17%) patients on median day-10 (6-12). In one patient bleeding occurred before DOAs were reintroduced, and after for the three others. 3 – In two patients, DOAs were stopped before surgery, and were not reintroduced until the last follow-up visit at one month. No bleeding was noted. 4 – In 2 patients, an AVK bridge was established; it started the day after the intervention and continued for more than three weeks, without secondary bleeding complications.



*Second bleeding occurred after initial accident on day 12.

Figure 1: Chronology for the 15 bleeding events noted in 14 patients under direct oral anticoagulants after haemorrhoidal surgery.



*p=0.056, ¤p=0.226

Abbreviations: DOAs: direct oral anticoagulants, LMWH: low molecular weight heparin

Figure 2: Flowchart with number of haemorrhages per group of patients (%), according to anticoagulant and low molecular weight heparin management.

4.3. Results by Type of Surgery (Table)

The procedures carried out consisted of single haemorrhoid pile resection (4 patients), at least 2 piles resection (26 patients), sutured mucopexy (+/- Doppler guidance, +/- resection of one haemorrhoid) (16 times), haemorrhoidopexy (including 2 associated with a haemorrhoidectomy) (12 patients), and submucosal internal haemorrhoid radiofrequency coagulation (1 patient). Respective secondary bleeding events are reported in the Table, and the frequency was higher in the mucopexy group than in the other groups ($p<0.05$).

Table 1: Secondary bleeding event frequency after haemorrhoidal surgery in 59 patients, according to surgical technique.

	1 pile	≥2 piles	Mucopexy	Haemorroidopexy	Radio-frequency
N	*4*	*26* ¤*	*16 ¤#*	*12*#*	*1*
Haemorrhage N (%)	*0*	*5 (19)*	*7 (44)*	*1 (8)*	*1*

*p=0.202 ; ¤p=0.046 ; #p=0.021

STROBE Statement—Checklist of items that should be included in reports of *cohort studies.*

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

5. Discussion

Secondary bleeding after haemorrhoidal surgery is relatively frequent, eventually requiring emergency hospitalization and haemostasis surgery and/or transfusion. As it most often occurs after the patients have returned to their home, sometimes far from the centre where they were operated on, the management may be difficult. In a meta-analysis, a haemorrhagic accident was reported in the first 4 post-operative days after haemorrhoidopexy and after haemorrhoidectomy in 9.8% and 6.4% of the patients, respectively, with reoperation in 1/4 and 1/3 of the cases [2]. In their series of 1,294 patients, Yano et al. reported that 1.7% underwent surgery for secondary haemorrhage [3]. In a previous publication, we reported a bleeding rate after haemorrhoidectomy or haemorrhoidopexy of 10%, a hospitalization rate of 7.8% and a reoperation and/or transfusion rate of 2.7% [1]. Accidents occurred at a median time of 6 days after the initial surgery [1]. Haemorrhages frequency is higher in our series, explained by DOAs and LWMH treatments. The management of patients operated on while on acetyl salicylic acid or AVK is roughly codified. According to French recommendations, it is not recommended to interrupt a preventive treatment with acetyl salicylic acid or to bridge AVK with LMWH [6,7]. Regarding DOAs and haemorrhoidal surgery, the message in the literature is less clear. However, DOAs are increasingly prescribed worldwide, particularly in patients at risk of thromboembolic events. In addition, they are recommended as the first-line treatment before AVK in cases of atrial fibrillation [8] and, consequently, the volume of their prescription exceeds that of AVK [9]. Before operating on a patient taking DOAs, it is essential to check that the indication for the treatment is justified. Furthermore, assessing the thromboembolic risk (for example, with the $CHADS_2$ and CHA_2DS_2-VASc scores in patients with atrial fibrillation) can help to select patients whose treatment could be momentarily interrupted [10]. The management of anticoagulant treatments during the perioperative period also depends on the risk of bleeding complications to which the proposed surgery exposes the patient. Concerning AVK and haemorrhoid surgery, the French Working Group on Perioperative Hemostasis (GIHP) recommended not interrupting the treatment if the INR is <2 to 3[11]. We have also shown in a prospective series that the interruption of AVK with LMWH bridging exposed patients to a bleeding frequency higher than that observed if AVK were continued [5]. This finding was similar in the BRIDGE controlled study, which included patients undergoing elective operations or invasive procedures requiring interruption of AVK therapy [4]. Concerning DOAs, they are generally interrupted for a few days in the immediate perioperative period to avoid the risk of an intraoperative or anaesthesia-related haemorrhagic accident. The resumption of treatment is then recommended within 24 to 48 hours after the intervention [11]. In fact, this strategy is suitable for interventions that involve a low risk of secondary bleeding. As haemorrhoidal surgeries expose patients to a delayed haemorrhagic risk, DOAs should be managed differently. The context is comparable to that encountered after otolaryngology surgery, especially after tonsillectomy, where the haemorrhagic risk is moderate peri-operatively but high in the post-operative period [12]. In fact, in a large retrospective series the risk of secondary surgery for haemorrhage after tonsillectomy was 6% and occurred as late as 24 days after the initial surgery [13]. This delayed haemorrhagic risk prompted a German team to propose delay of the resumption of DOAs after such a surgery [12]. For haemorrhoidal surgery in pa-

tients taking DOAs, no recommendation of this type has ever been made. The results of our study showed that the risk of bleeding was high in patients exposed to active treatment in the early post-operative period, either early DOA resumption (33%) or LMWH curative dosage bridge (41%). The risk of bleeding was significantly higher in patients resuming DOAs before postoperative day-15 than in those resuming them after day-15. We also noted that LMWH administered at a curative dosage exposed the patient to an elevated bleeding risk, although the risk was not significantly different from that with a preventive dosage. Last, the risk was lowest if the DOAs were interrupted without administration of any additional drugs during at least the first 15 postoperative days. As recommended in the literature [14], we have established recommendations in our hospital instituting. For patients on curative anticoagulant therapy that cannot be interrupted, we propose LMWH bridging at a curative dose for at least the first 15 days post-operatively. Although the risk seems comparable between DOAs continuation and curative LMWH bridge, we prefer to recommend LMWH bridge because the long-lasting effect of DOAs and the absence of an antidote could make management of haemorrhagic complications difficult. For patients with a low thromboembolic risk, on a case-by-case basis, a 15-day interruption of DOAs or LMWH preventive dose bridging will be offered, as haemorrhagic complications may be less frequent.

The first bleeding event observed in our series occurred on day 6, and as such, we do not recommend prolonging the hospitalization of these patients, who can as other patients, be treated on an outpatient basis. This reinforces the need to give clear preoperative information to the patient. In particular, information about the elevated risk of secondary bleeding, which could justify rehospitalization, should be provided. There is a need for specific information for patients living far from the hospital where the procedure took place, as emergency post-operative care will take place at their neighbourhood hospital. The assurance of effective continuity of care is crucial for these patients. Without any explanation, we found that the frequency of haemorrhagic accidents was higher after mucopexy. In the literature, mucopexy is not specifically associated with an elevated haemorrhagic risk. For example, readmission for acute bleeding was similar after either Doppler guided artery ligation or haemorrhoidopexy in the Ligalongo randomized trial [15]. It should also be noted that in the event of continued anticoagulant use, the patient cannot benefit from spinal anaesthesia, and no recommendation is made concerning the risk of complications after a pudendal block, which is generally avoided. In addition, antibioprophylaxis with metronidazole should not be combined with AVK, as it would increase this last effect. Non-steroidal anti-inflammatory drugs should also not be used.

6. Conclusion

Even if our data are based on a small number of patients, they showed an overall high risk of secondary haemorrhage in patients taking DOAs who were operated on for haemorrhoidal disease. Globally, the risk of secondary bleeding requiring hospitalization was approximately one in four, and it persisted until day 16. This frequency was highest when DOAs were not stopped, or during therapeutic dosage LMWH bridge. We propose properly assessing the indications for haemorrhoidal surgery in patients taking DOAs, and always question the possibility of temporary interruption of curative anticoagulant treatment. If there is an indication for maintaining effective anticoagulant treatment, we suggest LMWH bridging for at least the first 15 postoperative days to facilitate the management of a possible haemorrhagic accident. In some patients, in whom the thromboembolic risk is low, other options offer a lower haemorrhagic complication rate.

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