EDITORIAL

Polypectomy adverse event interpretation: it's complicated

Colonoscopy is a powerful tool in the battle against colorectal cancer, permitting the detection and resection of premalignant polyps. Studies show that this practice significantly reduces the incidence and mortality of colorectal cancer. Nowadays, almost all premalignant lesions can be removed endoscopically, particularly with the advent of advanced therapeutic techniques such as EMR and endoscopic submucosal dissection (ESD). These techniques reduce the need for surgery, with its associated morbidity, mortality, and loss of colonic integrity; thus, colonoscopic polypectomy has saved countless lives by the prevention of colorectal cancer and the avoidance of surgical mortality. However, colonoscopic polypectomy is not risk free. It exposes patients to adverse events such as bleeding or perforation. Perforation is the most feared colonoscopy-related adverse event for endoscopists and patients alike. A review of recent studies calculated an overall therapeutic perforation rate of 0.1% (1 in 1000).[1] Post-polypectomy bleeding (PPB) is the most common polypectomy-related adverse event; PPB rates ranging from 0.26% to 6.1% have been reported.[2,3]

ADVERSE EVENT RISK FACTORS

Although polypectomy-related adverse events are relatively rare, it is important to keep them to an absolute minimum. Although it may never be possible to abolish all polypectomy adverse events, many are undoubtedly preventable. Knowledge of the risk factors for polypectomy adverse events helps to improve polypectomy training and performance, which are key steps in the reduction of adverse events. Identifying risk factors is challenging, however; such events are relatively rare, data are usually retrospective and incomplete, and multiple polypectomies may have been performed during a single procedure, thus making it unclear as to which polypectomy led to the adverse event. Studies consistently show that the size of the resected polyp is the main risk factor for adverse events. Polyp location is also relevant; small studies have shown that proximal location is a risk factor, but they have been too small to enable analysis at a segmental colonic level. Recently, however, a study of 167,208 polypectomies performed within a national screening program was large enough to do this, showing that cecal location of the polyp, but not other locations in the proximal colon, was an independent risk factor both for perforation and for PPB.[4] Recognized patient-related PPB risk factors include cardiovascular disease, chronic renal disease, age, and use of anticoagulant agents. Some studies have also demonstrated, perhaps not unexpectedly, that the endoscopist's experience also plays a role; any endoscopist or endoscopy nurse will tell you instantly who they would, or perhaps more tellingly would not, allow to remove their own polyp.

The study by Niikura et al[6] in this issue of *Gastrointestinal Endoscopy* strengthens our knowledge of postpolypectomy adverse events. The authors should be congratulated for performing the largest published study on this topic. Their retrospective analysis included 345,546 patients undergoing polypectomy (31.5%), EMR (63.6%), or ESD (4.9%) over a 2-year period, using a national inpatient discharge coding database that covers more than 1000 Japanese hospitals and includes data from more than 7 million patients a year. The authors provide adverse event rates (discussed later) and perform a multivariable analysis of risk factors for adverse events. The latter throws up some interesting results. PPB was associated with larger polyp size, comorbidity, male gender, ESD, and many antithrombotic drugs—no real surprises there. Direct oral anticoagulants (DOACS) were part of this list, confirming, as anticipated, that they also increase the risk of PPB. The retrospective study design did not permit any insight into how this excess risk should be managed; indeed, the authors do not describe any antithrombotic management policy. Should the endoscopist accept the increased risk of PPB in favor of

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minimizing the risk of a thromboembolic event? We still do not know—there is no no-risk option, of course, but my hunch is that in many instances we probably should, given the gravity of having a stroke or heart attack, as opposed to the usually benign outcome after PPB. Prospective studies are required in this area. Perforation was also associated with male gender, larger polyp size, and ESD, along with renal disease and drugs including warfarin, steroids, and nonsteroidal anti-inflammation drugs. This drug association with perforation is interesting. The authors offer plausible explanations, including mitochondrial damage, disruption of the mucosal barrier, or intestinal mucosal injury, either exacerbating the injury caused by polypectomy or delaying postresection healing; alternatively, the association may be due to confounding from the comorbidities for which these drugs are prescribed, which in themselves may affect tissue integrity and wound healing. A large, prospective, randomized controlled trial would be required to study this further. Until then, although the absolute effect is small, the pros and cons of continuation or discontinuation of this wider range of drugs should be considered when a patient is being prepared for polypectomy.

The cardiovascular and cerebrovascular event data are an interesting inclusion, but they are difficult to interpret, given that they are retrospective: were the events unrelated to the therapy and destined to have happened anyway, or were they due to the procedure, perhaps from a degree of dehydration, immobility, or prothrombotic inflammation precipitated by the therapy? As the authors acknowledge, there are several potential risk factors that they could not study because of the limitations of their retrospective data. It would, for example, have been informative to know whether cecal location was a risk factor in their dataset, or to what extent the endoscopist's experience or expertise can reduce the adverse event rate.

ISSUES WITH ADVERSE EVENT RATES

The authors also calculate their adverse event rates: PPB rate 3.25%, perforation rate 0.047%, cardiovascular events rate 0.005%, cerebrovascular events rate 0.088%, and death rate 0.132%. Although the PPB and perforation rates appear similar to those in other published series, they should not be compared, because at present there is no internationally standardized method; every study defines and calculates adverse event rates subtly, or in some cases significantly, differently. For example, this current study counted people with a perforation only if they had surgical treatment; a recent large case series reported that this accounted for only 45.7% of perforations,[5] so the current report may have underestimated the total figure by half. Likewise, the authors do not provide a definition of PPB; although it is likely that the definition will have been internally consistent, it does preclude comparison with other studies. For example, some studies include periprocedural bleeding, and some include only PPB that required subsequent intervention. Another major inconsistency between studies is the postprocedure follow-up period; Niikura's study[6] followed up the patients until postprocedure discharge only; thus, adverse events such as delayed bleeds will not have been identified. The excellent American Society for Gastrointestinal Endoscopy's lexicon for endoscopic adverse events helpfully provided a framework for categorizing event severity (fatal, major, intermediate, or minor), with precise descriptors for each, potentially allowing more objective comparison between studies.[7] It is a shame that 6 years have passed since its publication, with disappointingly little standardization in subsequently published studies. Even when definitions have been standardized, the robustness of case (adverse event) ascertainment in studies is often weak: if you don't look for adverse events, you won't find them, and adverse event rates will appear spuriously low. Indeed, there is a perverse disincentive in looking for adverse events for exactly this reason. A final issue is the lack of a consistent denominator for reporting rate; PPB may be expressed per patient, per colonoscopy, per colonoscopy where polypectomy was performed, or per polypectomy; each will result in a different rate from the same data. Standardization is clearly required.

BIG DATA

It is an exciting time in research now that more and more large databases are being interrogated. With great data comes great responsibility, though; analyses must be carefully constructed, and it is important that the clinical relevance of results is considered, not just the statistical significance. Perhaps we should consider this current study as a definitive piece of work—bigger studies will probably add little because databases have reached the size where clinically meaningful effects should be readily identified on multivariable analysis, provided, of course, that the relevant data are collected. Now is the time for endoscopy research to up its game, developing large prospective trials to answer important questions that cannot be answered by analysis of retrospective data, such as the optimal management of antithrombotic agents in therapeutic endoscopy. Large, well-kept databases also lend themselves to quality assurance processes. Organized cancer screening programs have led the way in this respect, producing automated, real-time performance data. These systems have the potential to become more sophisticated, incorporating risk factors such as those identified in Niikura's multivariable analyses into algorithms so that endoscopists who perform the most complex therapy, with inherent increased risk, are not disadvantaged.[8]

WHERE NEXT?

So where do we go from here? There is clearly a pressing need to standardize definitions and methods for the identification and categorization of endoscopic adverse events. We should carefully harvest the data from large-scale databases to help identify risk factors and for intelligent quality assurance while constructing high-quality prospective trials to resolve key unanswered questions. Let's up our game and drive down adverse events—are you up for the challenge?

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Matthew D. Rutter, MBBS, MD, FRCP
Department of Gastroenterology
University Hospital of North Tees
Stockton-on-Tees
Cleveland, UK
Department of Gastroenterology
Durham University
County Durham, UK

Abbreviations: ESD, endoscopic submucosal dissection; PPB, post-polypectomy bleeding.

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