

Provider-reported Use of Butylscopolamine in Gastrointestinal Endoscopy in Germany



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ABSTRACT

Introduction The anti-cholinergic agent hyoscine-N-butylbromide (HBB) is used in gastrointestinal (GI) endoscopy to decrease motility and facilitate endoscopic procedures. Data from clinical studies to support this practice is limited especially for therapeutic procedures. Likewise, patterns of use among endoscopist are largely unclear. This study sought to assess usage of HBB among German-speaking endoscopists.

Material and Methods We conducted an anonymous on-line survey among endoscopists in German-speaking countries.

Results A total of 207 physicians participated in the survey. The majority (76.9%) were experienced endoscopists and 92.3% of respondents use HBB at least occasionally during procedures. The reported median stated frequency of HBB use varied greatly between different types of procedures and increased with the complexity of the procedure being performed. HBB was rarely used in diagnostic esophagogastroduodenoscopies (EGD) (median stated frequency 1% of procedures), while use frequency was significantly higher in EGD with endoscopic mucosal resection (EMR) (10%; $p=0.002$) and EGD with endoscopic submucosal dissection (ESD) (20%; $p<0.001$). Similarly, use frequency during diagnostic colonoscopy was lower (5%) compared to colonoscopy with EMR (20%, $p=0.005$) or ESD (42.5%, $p<0.001$). The highest use frequency was reported for ERCP (50%). The most frequently stated reason to use HBB was facilitation of the procedure (80.6%) followed by increasing diagnostic yield (58.3%).

Conclusion German-speaking endoscopists commonly use HBB, most frequently to facilitate complex therapeutic procedures. Given there is almost no data supporting HBB use in therapeutic endoscopy, we suggest that more research is needed to evaluate benefits and risks of this practice.

Introduction

While vital to the physiological function of the gastrointestinal tract, intrinsic motility frequently impedes endoscopic examinations and interventions. Motility may obscure the view of parts of the mucosal surface and may make precise interven-

tion more challenging as the target structures keep moving. Anti-muscarinic anti-cholinergic drugs such as hyoscine-N-butylbromide (HBB) lower activity and tone of the smooth muscles, thus reducing the motility of the gastrointestinal tract [1]. Hence, they improve visualization of the mucosa and may facilitate endoscopic interventions including lesion detection

during colonoscopy, cannulation of the ducts during endoscopic retrograde cholangiopancreatography (ERCP) or resection of neoplasms during therapeutic esophago-gastro-duodenoscopy (EGD) and colonoscopy.

HBB is the most widely used anti-muscarinic agent because it is effective, widely available, and cheap. However, HBB is associated with a number of side effects such as tachycardia and hypotension [2]. On rare occasions, these may be life-threatening, especially in patients with underlying heart disease [3]. In rare cases, HBB may trigger acute closed-angle glaucoma, a vision-threatening ophthalmologic emergency [4]. The peptide hormone glucagon acts through a different mechanism of action than HBB but has a similar motility lowering effect on hollow gastrointestinal organs [5]. It is available as an intravenous (IV) preparation and can similarly be employed during endoscopy to reduce gastrointestinal motility and facilitate diagnostic and therapeutic procedures. There is little evidence directly comparing the two agents. In Germany and other countries, HBB is cheaper, more widely available, and much more commonly used. Besides IV spasmolytics, peppermint oil or its main component L-menthol is used as an effective topical antispasmodic in gastrointestinal endoscopy, particularly in Asia [6]. In Germany, it is not commonly employed.

The use of HBB in diagnostic gastrointestinal endoscopy has been investigated and the available evidence has recently been summarized in a position statement by the Canadian Association of Gastroenterology [7]. The majority of studies focus on colonoscopy and evaluate effects of HBB on parameters relevant to colonoscopy quality such as cecal intubation time and rate, withdrawal time, mucosal visualization, and adenoma/polyp detection rate (ADR/PDR). A large retrospective analysis of the English Bowel Cancer Screening Program suggested a 30% higher ADR associated with the use of HBB [8]. However, the majority of individual trials and all available meta-analyses indicate that there is no significant benefit of HBB with regard to ADR, PDR, and cecal intubation rate [7,9,10,11,12].

With regard to therapeutic endoscopy, the effect of HBB and glucagon on cannulation rate during ERCP has been the subject of a limited number of studies: a recent randomized controlled trial found that the combination of glucagon plus nitroglycerine compared to HBB plus placebo was superior with regard to cannulation success, need for needle knife papillotomy, and post-ERCP pancreatitis [13]. Conversely, two older trials did not detect a significant difference between glucagon and anti-muscarinic agents while the latter had lower cost [14,15]. To our knowledge, there is no published evidence on the use of HBB during therapeutic EGD and colonoscopy. This is notable because a reduction in motility would seem highly useful to facilitate advanced resection techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).

Furthermore, there is no international consensus on the routine use of antispasmodics. In Germany, endoscopic quality guidelines advocate for the use of HBB during colonoscopies only as needed and not as standard medication. Guidance on its use during EGD and ERCP is not provided [16]. Recently the Canadian Association of Gastroenterology published a state-

ment recommending to use HBB before or during ERCP but not before or during EGD and colonoscopy [7].

Given the lack of international consensus and the conflicting information on the utility of antispasmodics during endoscopy, this study sought to assess usage patterns of HBB among German-speaking endoscopists. We were specifically interested in differences in HBB use depending on the type of procedure being performed. We hypothesized that HBB may be most frequently employed during advanced therapeutic endoscopies i. e. procedures for which very little evidence regarding efficacy and safety exists.

Patients and methods

The methods and presentation of results of this survey are based on the recommendations of the Cherries checklist, which provides methodological advice on reporting web-based surveys in medical research [17].

Study design and distribution

To assess current practices regarding the use of HBB during endoscopic examination, we used a survey-based approach targeting German-speaking physicians performing gastrointestinal endoscopies. The survey was open from January 2021 to July 2021. The software "SurveyMonkey" was used to create and distribute a web-based survey. Eligible endoscopists were invited to participate via various channels including the website of the German professional society for digestive diseases (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)), email, social media and print media directed at endoscopy providers. Furthermore, the survey was highlighted in DGVS's regular newsletter twice.

The survey was designed using an iterative approach by the authors and revised by several subject- and non-subject-specific reviewers. Participation in this research was entirely voluntary, and we offered no monetary or non-monetary incentives for completing the survey. Submission of the questionnaire was considered as consent to participate in this study. The survey was entirely anonymous, and did not include the use of cookies, IP-checks, or any registration of participants.

Survey content

The questionnaire was composed of 35 questions. Questions consisted of both multiple-choice questions and short answers. The survey was designed to be completed in 5 to 10 minutes.

The questions appeared in the same order for all participants. No randomization was integrated into the survey, but adaptive questioning was utilized based on some of the participants' answers. Responses could be reviewed before submitting the survey and only one question was presented per page. To ensure valid results, entries had to comply with predefined formats, and each question had to be answered in order to advance to the next question.

The survey was divided into four sections. The first section of the questionnaire addressed the general use of HBB by participating endoscopy providers, assessing their professional experience practicing endoscopies and asked respondents for

their perspectives regarding the advantages and disadvantages of HBB. The second section included questions on the respective use of HBB in the context of specific interventions. These interventions included a group of EGD and colonoscopy-related interventions as well as ERCP. The third section dealt with side effects, contraindications, and use of other medications during endoscopies. Participants could rate side effects on a 10-point Likert scale ranging from 1 (no relevance) to 10 (very relevant). Responding physicians could record other side effects that were not otherwise listed but were of importance to their practice. Administration of other or additional medicines were queried in five categories from “never” to “mostly/every time” and as fill-in-text. The last section asked for demographic data of participants.

Statistical analysis

Statistical analyses were performed using SPSS version 28.0 (IBM Corporation, Armonk, New York, United States). Results of the descriptive analysis/categorical parameters are presented as frequencies and percentages, while continuous parameters are reported with medians and interquartile ranges (IQRs). For group comparisons, the Mann-Whitney-U test and the Kruskal-Wallis test were used. Pairwise group comparisons were carried out using post-hoc tests. $P < 0.05$ was considered as indicative of statistical significance.

Results

A total of 207 German-speaking physicians participated in the survey. Ten respondents were excluded due to early termination of the survey. An additional two participants stated that they do not perform gastrointestinal endoscopies and were excluded. A total of 195 responses were carried forward for our statistical analysis.

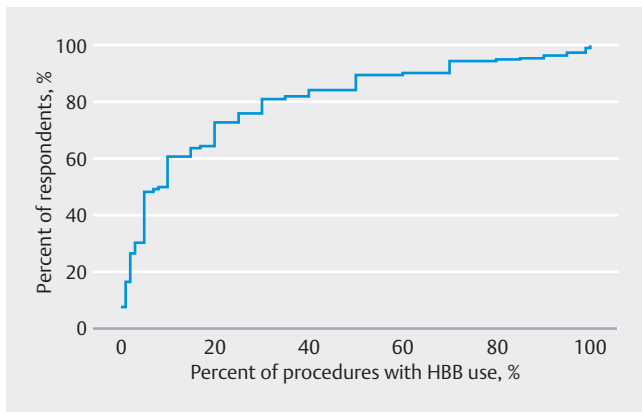
The demographic data showed that only 31 responding endoscopists (15.9%) were female, whereas 149 (76.4%) were male and 15 (7.7%) opted not to disclose their gender (► **Table 1**). The median age of participants was 50 years (R 33–72). The majority ($n = 150$; 76.9%) were experienced endoscopists having performed more than 5,000 procedures in their career. Respondents had practiced endoscopies for a median of 19 years (R 2–45). Most participants ($n = 151$; 77.4%) were specialists in gastroenterology and 90.3% stated that they were based in Germany ($n = 176$), while 7.7% ($n = 15$) opted not to disclose their country of operation or were practicing outside Germany ($n = 4$; 2.0%). The median length of overall clinical experience was 23 years (R 6–48). The respondents had diverse work backgrounds: Most ($n = 101$; 51.8%) of those surveyed worked in non-university hospitals, followed by outpatient care facilities ($n = 69$; 35.4%). A smaller number of endoscopists were employed at university hospitals ($n = 17$, 8.7%). Only eight physicians (4.1%) worked at both hospitals and outpatient care facilities. Forty-six physicians (23.6%) were self-employed and 134 (68.7%) were employed; 15 (7.7%) did not respond to this item.

In the context of gastrointestinal endoscopies 92.3% of respondents ($n = 180$) stated that they use HBB at least occasionally (► **Fig. 1**). However, half of the respondents ($n = 103$; 52.8%)

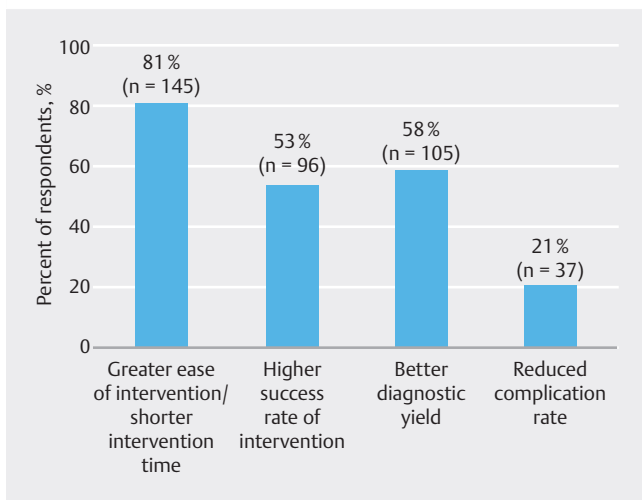
► **Table 1** Characteristics of survey participants (total $n = 195$).

	n (%)	Median [range]
Clinical specialty		
Gastroenterologist	151 (77.4)	
Surgeon	3 (1.5)	
Other / Not disclosed	41 (21.0)	
Clinical experience (years)		23 [6–48]
Endoscopy experience (years)		19 [2–45]
Endoscopies performed		
< 5.000	45 (23.1)	
> 5.000	150 (76.9)	
Type of institution		
University hospital	17 (8.7)	
Non-university hospital	101 (51.8)	
Outpatient care	69 (35.4)	
Other/not disclosed	8 (4.1)	
Type of employment		
Self-employed	46 (23.6)	
Employed	134 (68.7)	
Unknown/not disclosed	15 (7.7)	
Sex		
Female	31 (15.9)	
Male	149 (76.4)	
Unknown/not disclosed	15 (7.7)	
Age		50 [33–72]
n, number of responses; %, percentage of responses.]		

reported using it in 10% or fewer of their procedures. Those who never use HBB stated as the main reason for not using HBB a presumably unfavorable relation of benefits and side effects ($n = 11$ of 15; 73.3%). Only 34.4% of respondents ($n = 62$ out of 180) reported using glucagon at least occasionally. None of those interviewed mentioned using peppermint oil or its derivatives. The majority ($n = 163$; 90.6%) of those who use HBB stated that they administer HBB during the procedure as needed. Significantly fewer respondents reported injecting HBB before starting the procedure ($n = 7$; 3.9%) or both before and during the procedure ($n = 8$; 4.4%). Almost all ($n = 179$; 99.4%) administer HBB as an IV bolus. The most frequently stated reason for using HBB was facilitation of the procedure, that is, making the procedure easier and/or faster ($n = 145$; 80.6%), followed by improvement in diagnostic accuracy ($n = 105$; 58.3%) and facilitation of the technical success of the procedures ($n = 96$; 53.3%) (► **Fig. 2**).

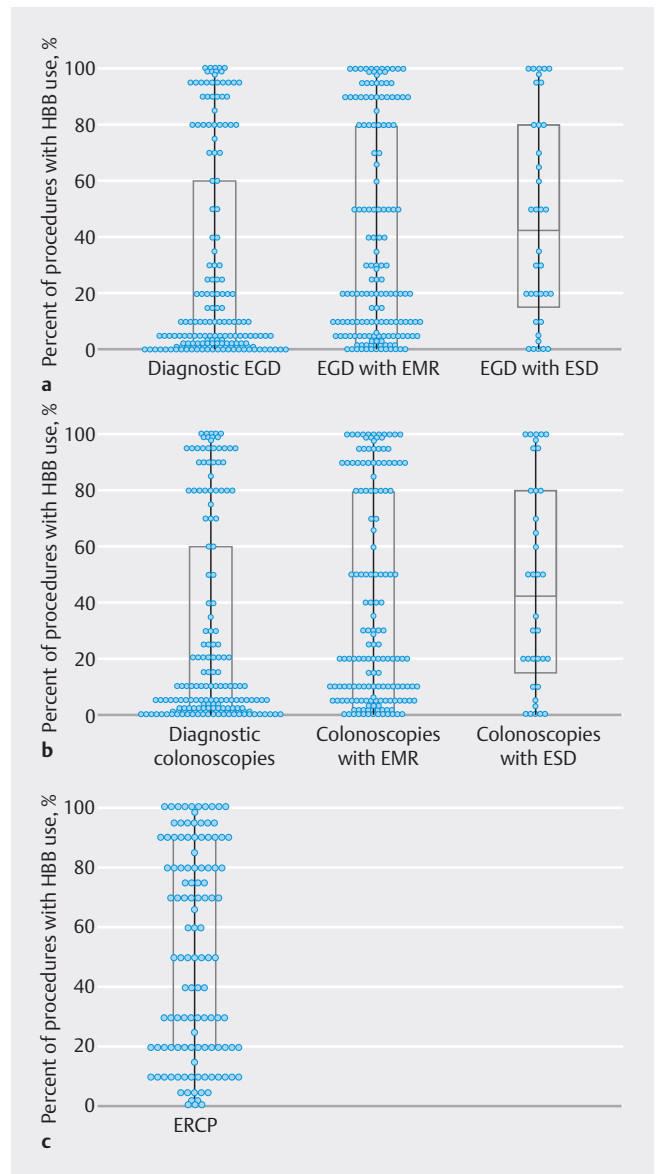


► **Fig. 1 Distribution of the general use of HBB in interventions by endoscopists.** Respondents could indicate their frequency of use of HBB during endoscopies with whole numbers between 0 and 100.



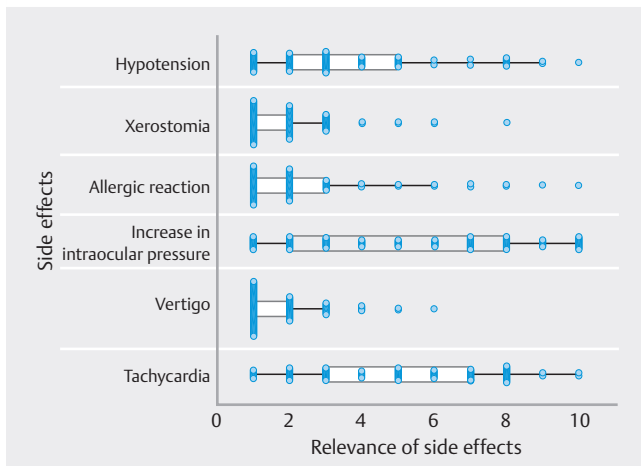
► **Fig. 2 Reasons for HBB use during endoscopic procedures.** Percent of respondents stating possible reasons for HBB use among respondents who use HBB at least occasionally. Multiple answers are allowed.

Next, we evaluated the data for procedure-related factors associated with HBB use. The reported HBB use frequency varied greatly between the different types of procedures with HBB being used more frequently in more complex interventional procedures. For diagnostic esophagogastroduodenoscopies (EGD), the median stated frequency of HBB use was 1% (IQR 0%–5%) compared to 10% (IQR 1%–40%) for EGD with EMR and 20% (IQR 2%–60%) for EGD with ESD (► **Fig. 3a**). Of note, the percentages of respondents who stated that in their clinical practice they regularly perform diagnostic EGD, EGD with EMR and EGD with ESD, were 99.4%, 85.9% and 23.7%, respectively. The percentages for diagnostic colonoscopy, colonoscopy with EMR and colonoscopy with ESD were as follows: 99.4%, 93.1% and 20.8%. Of the respondents, 66.7% reported that they perform ERCP.



► **Fig. 3 Comparison: interventions with regard to the use of HBB.** **a** Comparison EGD procedures and the use of HBB. **b** Comparison colonoscopy procedures and the use of HBB. **c** Comparison ERCP and the use of HBB. Each individual point represents the response of one endoscopist per intervention. Y-axis: Percent of procedures with HBB use (in %). X-axis: Intervention. Horizontal bar = median.

The correlation between frequency of HBB use and type of intervention was assessed by post-hoc analysis and revealed that significantly more HBB use was reported for EGD with EMR ($P=0.002$) or ESD ($P < 0.001$) compared to diagnostic EGD. Similarly, for diagnostic colonoscopies, the median stated frequency of HBB use was 5% (IQR 1%–60%) compared to 20% (IQR 5–80) for colonoscopy with EMR and 42.5% (IQR 18%–80%) for colonoscopy with ESD (► **Fig. 3b**). Post-hoc analysis revealed that significantly more HBB use was reported for colonoscopy with EMR ($P=0.005$) or ESD ($P < 0.001$) compared to diagnostic colonoscopy. Respondents reported the most fre-



► **Fig. 4** Rated relevance of side effects of using HBB during endoscopic interventions. Respondents could choose whole numbers from zero to ten. Zero as being “not relevant” and ten being “very relevant” as side effect. Each individual point represents the response of one endoscopist. Multiple answers are allowed.

quent use of HBB for ERCP procedures (median 50%, IQR 20%–89%); however, there was substantial variability among physicians in their reported frequency of HBB use during ERCP (► **Fig. 3c**).

Next, we evaluated the data for physician-related factors associated with HBB use. We found that physicians working in outpatient care report significantly more HBB use during diagnostic colonoscopy than physicians in academic ($P=0.003$) or non-academic ($P=0.035$) hospital settings. Likewise, physicians working in any hospital setting reported less frequent HBB use compared to those working in a purely outpatient setting ($P=0.01$). In line with this, self-employed practitioners reported more frequent HBB use compared to employed physicians ($P=0.002$). When only considering diagnostic colonoscopies, there was a significant association between reported higher frequency of HBB use and years of endoscopic experience ($P=0.035$), years of overall clinical experience ($P=0.006$) and physician age ($P=0.011$). Other physician-related factors such as sex or geographic location showed no significant association with any HBB use pattern.

When asked about side effects associated with HBB use, respondents reported that they see the increases in heart rate and intraocular pressure as most relevant (► **Fig. 4**). In response to the question about contraindications to HBB use, glaucoma was selected most frequently ($n=120$ of 170; 70.6% of respondents to this item) followed by cardiac diseases ($n=71$; 41.8%). Thirty-one respondents ($n=31$; 18.2%) consider HBB to have no absolute contraindications.

Discussion

The results of this study indicate that HBB is used frequently in endoscopic procedures with more frequent use in more complex interventional procedures, an area in which only very lim-

ited data on efficacy and safety of spasmolytic use exist. Thus, our data characterize usage patterns, but also suggest an unmet research need. Our survey was conducted among German-speaking endoscopists; however, the results are comparable to a survey among colonoscopy providers in the United Kingdom in which the majority of endoscopists (85%) reported administering HBB at least occasionally, with 11.8% of them using it always and 73.8% sometimes [18].

Procedure-related factors strongly determine HBB use: We observed very infrequent use of HBB in diagnostic EGDs. This may be due to the relatively short duration of the procedure and lower efficacy of HBB in the upper gastrointestinal tract, most notably esophagus and gastric corpus, where expression of muscarinic receptors is more abundant and higher drug serum concentrations are needed to produce a clinically relevant reduction in motility [19]. HBB use was significantly more frequent in therapeutic EGD. In colonoscopy, frequent HBB use was reported, again with significantly higher frequency in therapeutic procedures, most notably ESD. For diagnostic EGD and colonoscopy, there is some evidence regarding antispasmodic use: Omata et al. evaluated whether use of HBB facilitates detection of lesions in EGD and observed no significant increase in detection of gastric cancer [20]. In diagnostic colonoscopy, most studies showed no significant effect of HBB use on relevant quality metrics such as ADR/PDR, cecal intubation rate or procedure time [9, 11, 21, 22, 23], whereas one randomized controlled trial (RCT) and a meta-analysis suggested an increase in ADR/PDR [24, 25]. For therapeutic EGD, there is a single RCT evaluating the anticholinergic agent glycopyrrolate as a premedication before ESD of upper gastrointestinal neoplasia; the investigators found that the examiners reported the procedure to be significantly easier in the glycopyrrolate groups compared to control [26]. To our knowledge, there are no data on HBB use during therapeutic EGD or therapeutic colonoscopy. International guidelines are inconsistent with regard to HBB use: Asian consensus statements recommend the use of spasmolytics to improve lesion detection in diagnostic EGD [27] and during screening colonoscopy [28]. Conversely, the Canadian Association of Gastroenterology advises against the use of HBB during diagnostic EGD and screening colonoscopy [7]. Guideline recommendations addressing interventional procedures in the upper gastrointestinal tract do not exist to our knowledge. Considering the limited evidence and lack of consistent guideline recommendations, the wide variation in terms of HBB use among respondents to our survey is not surprising. However, there is a clear association between procedure complexity and frequency of HBB use while evidence addressing the efficacy and safety of HBB use in therapeutic EGD and colonoscopy is lacking.

Several studies dating back as far as the 1980s have addressed the use of spasmolytic agents during ERCP, specifically to reduce duodenal motility during the initial cannulation of the bile duct [14, 15, 29]. Although firm evidence showing an advantage of HBB is lacking, there is evidence for spasmolytic agent use being helpful and for HBB being comparable to glucagon. Based on this, the Canadian Association of Gastroenterology recommends HBB use during ERCP [7]. In line with this, our

respondents stated that they frequently employ HBB during ERCP – more so than during any other procedure.

Yamamoto et al. conducted a prospective study in which peppermint oil was used primarily as an antispasmodic during ERCP and was found to be effective for successful intervention [30]. To our knowledge, the agent is not commonly used in Germany.

Besides procedure-related factors, there are also provider-related factors that determine HBB use: Our data suggest that physicians working in outpatient care and self-employed physicians more commonly employ HBB. This seems in keeping with a survey of colonoscopy practices done in the UK in which private hospitals were found to administer HBB three times more frequently compared to teaching hospitals and district general hospitals [31]. In our data, HBB use during colonoscopy was associated with years of clinical experience. Thus, it could be that more experienced providers are more likely to use HBB. Alternatively, it may be that inpatients are more often considered to have significant comorbidities or to be less stable, and thus, there is more concern about possible side effects of HBB resulting in less frequent use.

In our study, glaucoma was rated as the main contraindication to the use of HBB. However, closed-angle glaucoma with a completed iridectomy is not a contraindication, nor is open-angle glaucoma [32]. Acute closed-angle glaucoma following HBB administration is probably a very rare event and patients with a history of glaucoma are not the ones most at risk. It is likely that cardiac side effects of HBB administration are of greater de facto clinical relevance in practice. Accordingly, the Medicines and Healthcare products Regulatory Agency of the UK advises caution in HBB use, especially in patients with cardiac morbidity [3]. While tachycardia was viewed as a relevant HBB side effect by our respondents, only a minority view cardiac comorbidities as a contraindication. Gastrointestinal endoscopy training programs should address this misconception and educate junior physicians that cardiac side effects are the most relevant clinical risk associated with HBB use. Moreover, information about the use of HBB could also be included in guidelines and curricula of training courses. In patients at risk for acute closed-angle glaucoma and those with cardiac comorbidities, glucagon is a reasonable alternative [15,33]. However, 65.5% of our respondents never use glucagon and the remainder utilize it rarely. Likewise, Bedford et al. reported that even if HBB is contraindicated, the use of glucagon is marginal [18], possibly due to higher costs and storage requirements [14,34]. Another cheap antispasmodic is peppermint oil. This survey revealed no use of this agent by German-speaking endoscopists. However, data from Asia suggest that it may be clinically useful, specifically when conventional antispasmodics such as glucagon and HBB are contraindicated or unavailable [6,30,35].

Our study had several limitations: There is a likely selection bias because of the limited sample size and the voluntary nature of the survey. Due to the use of various different channels including email newsletters, print media, and social media postings to alert the gastroenterological community to the survey and it being open to all comers, we were unable to determine the response rate. If all recipients of any communication

mentioning the survey were considered the denominator, the response rate would very likely be well below 10%. Moreover, the sample is unlikely to be representative of all German-speaking endoscopists, because the vast majority of survey respondents are mainly represented by older, male doctors working at non-university hospitals. Therefore, generalization of the endoscopic procedures resulting from our study to other endoscopists around the world cannot be made with confidence. Moreover, only a portion of our respondents perform advanced therapeutic endoscopies.

Nonetheless, there is a clear trend toward HBB being used more frequently in complex therapeutic endoscopies while most data on HBB use stem from studies that address diagnostic procedures. Thus, our data suggest an unmet need for research into the use of spasmolytic agents, and particularly HBB, in therapeutic endoscopy. To address the need for research, a prospective, randomized trial in the field of interventional endoscopy comparing HBB with placebo, including endpoints such as procedure time, complication rate, and perceived ease of procedure, would be desirable.

Conclusions

Use of HBB is widespread among German-speaking endoscopists in the context of gastrointestinal endoscopies and comparable to use among UK providers. Providers use HBB most commonly to simplify procedures with interventions. The frequency of HBB use increases with the complexity of the interventions. There is a lack of evidence about the efficacy, benefits and risks of HBB used in therapeutics – the area where it is most commonly employed. Providers tend to overestimate the risk of glaucoma and underestimate the risk of cardiac adverse events associated with HBB use.

Conflict of Interest

The authors declare that they have no conflict of interest.

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