**Supplementary File 1: The full version of the Expert Recommendation**

**Rationale, new anus positioning methods, and updated protocols: Expert recommendations on cap-assisted endoscopic sclerotherapy for hemorrhoids from China Gut conference**

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**Abstract**

Cap-assisted endoscopic sclerotherapy (CAES) as an emerging flexible endoscopic therapy has been widely used for internal hemorrhoids and some prolapse in China. However, there does exist some variable understandings on the concept and technique of CAES. Importantly, endoscopists generally do not describe the precise location and direction of the lesions within anus. A panel of experts from China Gut conference aimed to develop expert recommendations for CAES and derive guidelines on the key issues in hemorrhoidal disease research and practice. The modified three-round Delphi method was used to develop the expert opinion on CAES related 7 topics including rationale, new positioning methods for anus, indications, contraindications, techniques, post-procedure management, and core outcome set for evaluation. The panel first time stated the practical endoscopic positioning methods for anal disease. The residual effusion or injected water under endoscopy is the sign for determining the left anus under the left lateral decubitus position. Along the clockwise direction, left anus, posterior anus, right anus and anterior anus (LPRA) is recommended to precisely describe the direction of the anal lesions and endoscopic targeting location. In summary, this expert opinion will guide the research and practice of CAES for hemorrhoidal disease.

**Key words:** Sclerotherapy; endoscopy; hemorrhoids; prolapse; anus; consensus

**Introduction**

Hemorrhoidal disease is one of the most common anorectal disorders that mainly affects adults of any age and sex. It has a genetic component that predisposes to smooth muscle, epithelial and connective tissue dysfunction[1]. Conventional surgical procedures, endoscopic band ligation, injection sclerotherapy and other minimally invasive intervention have been used for internal hemorrhoids[2, 3]. As a crucial component of many non-surgical practices, injection sclerotherapy is most effective for internal hemorrhoids, especially for patients with bleeding. However, traditional sclerotherapy via anoscope may cause iatrogenic risk and complications due to misplaced injections[2]. There were three milestones in the history of flexible endoscopic sclerotherapy. Ponsky et al.[4] in 1991 reported the flexible endoscopic injection of 23.4% saline, with 5-mm retractable needle, and retroflexed position for symptomatic hemorrhoids. Tomiki et al.[5] in 2014 reported the flexible endoscopic injection of aluminum potassium sulfate and tannic acid, with 5-mm retractable needle, retroflexed and anterograde position, and endoscopic cap. Zhang et al.[6] in 2015 reported cap-assisted endoscopic sclerotherapy (CAES) of Lauromacrogol injection, with 10-20 mm retractable needle, normal position, endoscopic cap, and proper air delivery for improving endoscopic exposure. CAES has become a widely used flexible endoscopy technique for hemorrhoidal disease in China in recent years. However, there does exist some variable understandings on the concept and techniques of CAES before the randomized controlled studies and cohort studies were published. Therefore, it is urgent to develop expert opinion for popularization of CAES and driving expert guideline on the key issues in hemorrhoidal disease research and practice.

 The target users of the expert opinion on CAES are endoscopists operating with flexible colonic endoscope, general practitioners, and other medical specialists who treat anorectal diseases.

**Methods** **for expert recommendations development**

A literature review was performed by search terms based on “hemorrhoids (haemorrhoids)” and “sclerotherapy” from PubMed, MEDLINE, Wanfang Data to identify the studies of sclerotherapy for hemorrhoids. The following steps were included: identification of main topics of CAES; invitation of all leading colorectal experts; the modified three-round Delphi-procedure for developing expert opinion[7].

 Individuals (n = 33) with expertise in the field of advanced flexible endoscopy or CAES for hemorrhoids were invited to contribute to the production of this critical expert opinion. The elaborated statements on seven topics (rationale, positioning methods for anus, indications, contraindications, techniques, post-procedure management, and core outcome set for evaluation) were generated based on the literature review analysis. All three rounds of the Delphi survey were administered using online surveys ([www.wjx.cn)](http://www.wjx.cn)) via Email to the experts by the secretaries. Each invited expert did not know who else were invited before the third round. All responses were anonymized. The experts were asked how much they agreed with each statement on a five-point scale 1 = strongly agree; 2 = agree; 3 = neither disagree nor agree; 4 = disagree; and 5 = strongly disagree. The rating of 3-5 was required to briefly describe reasons and related evidence. All experts had the opportunity to adjust their answer when some statements were revised according to comments from experts in the subsequent rounds. Each statement was accepted when ≥ 80% of the experts agreed (a rating of 1, 2). All statements below 80% of the agreement were revised and rated again in a further round of voting. The last round was the face-to-face meeting for discussion and voting.

**Results**

A total of three rounds of voting and editing were performed to reach consensus for all statements. In the final round, all statements were presented to 33 of 33 (100%) members on 28 May, 2021, in China Gut conference, Nanjing, China. The panel released 15 statements with comments.

**Rationale**

1. ***Statement:*** The concept and value of CAES for hemorrhoidal disease mainly include: (1) Endoscope with cap and air delivery improves the endoscopic exposure for diagnosis and therapy, which should contribute to avoid iatrogenic injury due to ectopic injection; (2) CAES is an effective therapy for internal hemorrhoids bleeding, and an option for rectal mucosal prolapse; (3) Anorectal lesions differentiation, colon screening and endoscopic therapy can be performed during CAES procedure, for the consideration of better cost-efficacy.

***Comment:*** The demand in quality control of CAES is growing among academic teams involving inexperienced endoscopists, but it is also a matter of concern for all endoscopists, for the following reasons: (1) Patients expect to receive more precise information beforehand to sign a form providing their informed consent to the novel procedure, in accordance with the legal requirements ; (2) Endoscopists and other colleagues concerned in the care of patients require precise positioning description and reliable management; (3) Healthcare providers, whether public health systems or insurance companies, require at least a proof that the procedure has been performed in proper manner, including evidence-based decision, devices, sclerosants, and legal medical records.

**Anus positioning methods**

1. ***Statement:***The residual fluid or injected water within anus under endoscopy is the sign for determining the left anus under the left lateral decubitus position. Along the clockwise direction, left anus, posterior anus, right anus and anterior anus (LPRA) is recommended to replace the typical lithotomy position for the precise direction description on the anal lesions and endoscopic therapy.

***Comment:*** The typical lithotomy position is seldom used for the endoscopists to map the anus directions. The anal canal under flexible endoscopic view needs practical, reliable and simple positioning methods for identification and description. Based on the standard left lateral decubitus position for colonoscopy, the fluid accumulation is located on the left side of the anal canal (Figure 1A). After confirming the position of the left side of the anus by the endoscopic injected water or the residual fluid, along the clockwise direction, the LPRA positioning method is practical, reliable and a simple technique for physicians and patients to have direct and quick understanding. This LPRA four-direction description can be further divided into eight directions: left, left-posterior, posterior, right, right-posterior, anterior, right-anterior, and left-anterior. The LPRA positioning methods for anal lesions and targeting therapy can improve the clinical work-flow, scientific communications and physician-patient communications (Figure 1B).

**Indications**

1. ***Statement:*** Patients with symptomatic Grade I or II internal hemorrhoids are considered for CAES when lifestyle intervention and conservative management are not effective. CAES can be considered for patients with Grade III internal hemorrhoids unsuitable for surgery or those refusing surgery.

***Comment:*** Several studies have shown that flexible endoscopic sclerotherapy is effective minimally invasive therapy for grade I-II internal hemorrhoids, with a relatively low occurrence of post-procedural pain and bleeding[6, 8, 9]. It has also been shown to be a safe and effective treatment for some Grade III hemorrhoids[6, 9].

1. ***Statement:*** CAES is a therapeutic option for symptomatic small rectal mucosal prolapse.

***Comment:*** The most common symptoms of rectal mucosal prolapse is the protrusion itself, such as anal pendant expansion, obstruction feelings, and tenesmus. Several cohort studies suggest that injection sclerotherapy through a fine gauge needle is an effective and minimally invasive primary treatment option for rectal prolapse not responding to conservative management[10-12]. CAES was reported as therapy for small rectal mucosal prolapse[6], however, more solid evidences are necessary.

**Contraindications**

1. ***Statement:*** The contraindications of CAES for hemorrhoids at least include patients with perianal abscess, stricture, fistula, anal malignancies, and pregnancy.

***Comment:*** CAES can be considered as an option for bleeding hemorrhoids during emergency in patients with cerebrovascular accidents, immunodeficiency, or hypercoagulability disorders after balancing potential risk and possible benefits from the interventional procedure. CAES is not recommended to treat thrombosed and strangulated hemorrhoids, grade IV internal hemorrhoids, or external hemorrhoids. Psychiatric consultation should be recommended when a patient with hemorrhoids-like complaints has suspicious mental stability, such as hypochondriasis and somatization of anal symptoms[13].

1. ***Statement******:*** CAES with conventional dose injection is not recommended for patients with active proctitis, radiation enteritis, immune related ulcer, or unexplained anal ulcer.

***Comment:*** Limited data exist on the management of symptomatic hemorrhoids in radiation enteritis patients. After radiation in the pelvic area, most symptoms are related to radiation therapy and not to hemorrhoids[14]. Thornhill et al. reported that three cases with radiation proctitis developed severe complications due to hemorrhoids treated with rubber band ligation and laser coagulation[15]. D'ugo et al. suggested that the first-line treatment should be medical therapy in IBD patients with hemorrhoids, considering that a spontaneous healing is possible[16].

**CAES techniques**

1. ***Statement:*** Bowel preparation is recommended for meeting the criteria of the required colonoscopic diagnosis and therapy. Anesthesia assistance during CAES is helpful in improving physician–patient satisfaction.

***Comment:*** A complete endoscopic evaluation of the colon should be performed for all patients with symptomatic hemorrhoids and rectal bleeding to make a differential diagnosis among the hemorrhoidal disease, inflammatory bowel disease, colorectal cancer, diverticular disease, radiation colitis, and other colitis. Anesthesia makes the procedure painless, which would improve the satisfaction of patients.

1. ***Statement:*** Both conventional short-straight cap on the endoscope and the proper air insufflationare the key conditions for the effective exposure and fluent therapy during CAES procedure for the hemorrhoids and rectal prolapse.

***Comment:***A conventional short-straight cap is recommended for maximizing visibility of the targeting field for diagnosis and injection (Figure 1C-F). The colonoscope with the cap, instead of the gastroscope with small diameter, is helpful for preventing air leaking from anus during injection of air for improving endoscopic exposure. The anterograde endoscopic injection can avoid the risk of retroflection associated tissue injury and endoscope damage. One colonoscope is recommended to complete the screening of the whole colon and the CAES procedure. The decision on switching the colonoscope to gastroscope during the procedure from colonoscopy to CAES, respectively, will increase the medical cost, wasting procedure time and potential risk of anesthesia. However, gastroscope is suitable for procedure under retroflection.

1. ***Statement:*** The long or short injection needles should be considered according to the condition of hemorrhoidal disease.

***Comment:*** The different techniques using long and short needles are shown in the Table 1. A long injection needle is defined as the length ≥ 10 mm. For the patients only with bleeding hemorrhoids, both long and short needles can be selected for injection[6, 17, 18]. The long needle is recommended for the hemorrhoids combined with prolapse. The sclerosing agent is injected into the submucosal layer for about 5 seconds with 0.5-2.0 mL per site.

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| **Table 1. The different technique using the long and short injection needle during CAES.[17]** |
| **Items** | **Long injection needle** | **Short injection needle** |
| **Endoscope** | Colonoscope; or gastroscope | Colonoscope; or gastroscope |
| **Cap** | Straight and short | Straight and short |
| **Length of the needle** | ≥ 10 mm | < 10 mm, conventional 4-6 mm |
| **Direction of endoscope** | Anterograde | Anterograde, or retroflection |
| **Injection position** | Anterograde | Anterograde, or retroflection |
| **Targeting location** | Longitudinal | One point |
| **Retracting needle** | Retracting the needle during injection | Not retracting the needle during injection |
| **Injection volume** | More in each site than short needle | Less in each site than long needle |
| **Presumed therapeutic role** | Hemostasis and prolapse | Mainly for hemostasis |

1. ***Statemen******t:***The LPRA anus positioning method is helpful for endoscopist to locate the injected and non-injected sites, thus avoiding the use of tracer agent.

***Comment:*** The six o’clock position under endoscopic view is the recommended site for injection. The endoscope should be rotated clockwise to target different injection site[6]. The LPRA four-direction description is helpful for endoscopist to locate the injected and non-injected sites. The methylene blue tracer can be used for tracing by the inexperienced endoscopists. The sclerosing agents for treating the internal hemorrhoids in China mainly include lauromacrogol[6], polidocanol[19], and traditional Chinese medicine (e.g. Xiaozhiling[20], Shaobei[21]). Lauromacrogol is recommended to be injected with original fluid. The foam is preferred for Polidocanol. Aluminum potassium sulfate and tannic acid (ALTA)[5] mainly used in Japan.

**Post-CAES management**

1. ***Statement:*** Patients post-CAES should be advised to remain in supine position for at least 2 hours to prevent prolapse and monitor potential short-term complications.

***Comment:*** Given the scarce literature, the supine position in bed for at least 2 hours post-procedure is helpful for monitoring and managing the potential CAES related complications in clinical practice[6]. Diets that might cause defecation during 6-12 hours post-CAES should be avoided for patients.

1. ***Statement:*** Patients with chronic constipation or diarrhea should be treated with etiological treatment after CAES for preventing the recurrence of hemorrhoids.

***Comment:*** Both chronic constipation and diarrhea should be treated post-CAES. Attention should be paid to the health education of patients’ lifestyle for hemorrhoids, especially the diet and training for defecation habits [22, 23].

1. ***Statement:*** Bothantibiotics and hemostatics are not regularly required during and after CAES procedure.

***Comment:*** No evidence supports the necessity of conventional use of antibiotics during or post-CAES. CAES has advantages in preventing iatrogenic risk from misplaced injections by traditional sclerotherapy, which might be related to the potential postoperative infections due to mucosal ulceration or necrosis, prostatic abscess and others[6, 18]. Early recognition and immediate antibiotic usage are fundamental for patients with infection after CAES[19]. Patients at high risk of postoperative infection should be given prophylactic antibiotics. There is no need for using additional hemostatics post-CAES.

1. ***Statement:*** CAES-associated complications mainlyinclude difficulty in passing gas, bleeding, infection, ulcer, and chronic anal pain.

***Comment:*** The CAES procedure-associated complications were mainly reported from physicians who were in the early stage of CAES training, such as difficulty in passing gas, bleeding, infection, and chronic pain[17]. Enema is the way to solve the difficulty in passing gas and defecation, and lower intestinal obstruction[17]. Blood test, ultrasonography/magnetic resonance imaging should be used to assess the extent and location of infection. Early diagnosis and antibiotic treatment are critical for sclerotherapy associated infection. Bleeding post-sclerotherapy should be managed accordingly after the differential diagnosis of the bleeding, such as missing injection in the bleeding sides[17], and sclerotherapy-induced artificial ulcer[24], defecation-induced bleeding[25]. For continuous unexplained post-CAES bleeding, endoscopic examination should be considered for differential diagnosis and corresponding treatment[17]. The sclerotherapy-induced anus pain is mainly related to injection beyond dentate-line area[9]. Other rare complications induced by sclerotherapy were reported in some clinical studies[24, 26], including hematuria, urinary retention, urethral stricture, impotence, septicemia and others.

**Core outcome set for evaluation**

1. ***Statement:***The patient’s self-report based on both hemorrhoids-specific symptoms (pain, prolapse, blood loss, itching and soiling) and quality of life can be applied for efficacy evaluation of CAES in clinical practice and research.

***Comment:*** The patient reported outcome measure based on both hemorrhoids-specific symptoms and patient quality of life has been widely applied to clinical practice and research of hemorrhoids[27]. The primary outcome measurement, which included the core outcome, were sets of ‘pain’, ‘prolapse’, ‘blood loss’, ‘itching’ and ‘soiling’[28]. Other additional domains, such as complications, recurrence, patient satisfaction and others were common sets of the secondary outcomes [17, 28, 29]. Colonoscopy should be used for differential diagnosis of patients with poor outcome, unexplained bleeding or severe pain post-CAES. The methodology of endoscopic efficacy evaluation remains to be established.

In conclusion, this expert opinion on the new anus positioning methods, and the updated protocols of CAES will guide the research and practice of hemorrhoidal disease management.

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**Conflicts of interest**

None.

**Contributors:** Fa-Ming Zhang conceived CAES and LPRA, organized, and developed the project. Quan Wen, Xia Wu, Yun Wang and Bo-Ta Cui joined the panel secretaries and contributed the draft. Ya-Fei Liu drew the conceptual graph. All panel members joined the three-round Delphi-procedure and manuscript revision, and approved the final manuscript.

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Figure Legend:



Figure 1. Cap-assisted endoscopic sclerotherapy (CAES) for internal hemorrhoids. A: Colonoscopy in left lateral position. B: Anus positioning methods under flexible endoscopy: along the clockwise direction, left anus (with residual fluid or injected water), posterior anus, right anus and anterior anus (LPRA). C: The concept sketch of CAES. D: The internal hemorrhoids under colonoscope, anterograde view, proper insufflated air. E: The small internal mucosal prolapse located in left-anterior anus. F: Submucosal injection for internal hemorrhoids complicated with prolapse in anterior anus.