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Research Progress on Different Endoscopic Hemostatic Regimens for the Treatment of Acute Non-Varicose Upper Gastrointestinal Bleeding

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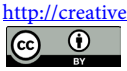

Abstract

Acute upper gastrointestinal hemorrhage is a highly prevalent clinical condition, with the majority of cases representing acute non-variceal upper gastrointestinal hemorrhage. With the advancement of modern medicine, endoscopy has become an indispensable tool in the diagnosis and treatment of various diseases. In order to achieve optimal results in the endoscopic treatment of non-variceal upper gastrointestinal bleeding, it is essential to make an accurate and timely diagnosis and select the most appropriate treatment method. This article introduces the definition of acute non-variceal upper gastrointestinal bleeding (ANVUGIB) and the importance of endoscopic treatment for this disease. It then presents an overview of various assessment systems for ANVUGIB and an overview of endoscopic advances in thermal coagulation, mechanical hemostasis, and topical pharmacological injection hemostasis for three aspects of ANVUGIB-related bleeding. In particular, this article discusses the therapeutic efficacy and safety of different treatment options for non-variceal upper gastrointestinal bleeding, as well as the advantages and limitations of these treatment options in managing this disease.

Keywords

Endoscopy, Non-Variceal, Upper Gastrointestinal Bleeding, Hemostasis

1. Introduction

Acute nonvariceal gastrointestinal bleeding (ANVUGIB) is defined as bleeding caused by nonvariceal disorders of the gastrointestinal tract above the flexor

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ligament. This includes bleeding from the pancreatic or biliary ducts, as well as bleeding caused by disorders near the anastomosis after gastrojejunostomy. ANVUGIB has a high annual morbidity and mortality rate, with approximately 20% of patients experiencing difficulty in hemostasis or recurrent bleeding [1]-[4]. Endoscopic treatment offers distinct advantages over conventional medical treatment in terms of hemostasis, hospitalization duration, and the necessity for blood transfusion [5] [6]. Therefore, it is crucial to select the most appropriate and effective endoscopic hemostatic solution in a timely manner. In order to save the patient's life, improve the patient's prognosis, and shorten the patient's hospitalization time, it is necessary to integrate the endoscopic manifestations, clinical characteristics, conditions of the existing endoscopic equipment, and the operator's skills and experience [5] [7].

2. Risk Assessment

A risk assessment of ANVUGIB patients at the early stage of hospitalization can facilitate the guidance of subsequent patient monitoring. A number of risk assessment systems are available for ANVUGIB. The most commonly used are the Glasgow-549-Blatchford Score (GBS), the Rockall Score, the AIMS65 Score, and the recently proposed ABC Score (2021). The American College of Gastroenterology (ACG) guidelines, the 2019 International Consensus, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, the 2018 Asia-Pacific Consensus, and the 2018 Chinese guidelines all recommend the use of the GBS for ANVUGIB. The ACG guidelines, the 2019 International Consensus, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, the 2018 Asia-Pacific Consensus, and the 2018 Chinese guidelines all recommend the use of the GBS for ANVUGIB. In their 2021 guidelines, the American College of Gastroenterology (ACG) recommends the use of the Glasgow-Blatchford Score (GBS) for risk stratification of ANVUGIB. Similarly, the 2019 International Consensus, the 2021 European Society of Gastrointestinal Endoscopy (ESGE) guidelines, the 2018 Asia-Pacific Consensus, and the 2018 Chinese guidelines all endorse the use of the GBS for this purpose [8]-[12]. The analysis of the studies demonstrated that a GBS score of ≤1 represented the optimal criterion for identifying low-risk patients with ANVUGIB who did not require inpatient hospitalization. Additionally, a GBS score of ≥7 was identified as the most sensitive and specific indicator of the necessity for endoscopic treatment. A GBS score of ≥7 is the most sensitive and specific indicator of the necessity for endoscopic treatment, and a GBS score of ≥10 - 12 is strongly correlated with the requirement for blood transfusion and urgent endoscopic intervention [13]. The most widely validated scores [13] for predicting recurrent bleeding and mortality are the Rockall Risk Scoring System (RS), the Glasgow-Blatchford Risk Scoring System (GBS), and the AIMS65. The GBS score should be used to predict the clinical outcome of all patients with upper gastrointestinal bleeding. The GBS is the most effective predictor of the need for hospitalization, intervention (including endoscopic intervention), and mortality. A GBS score of greater than seven is the most accurate predictor of the necessity for

endoscopic therapy, and is comparable to RS and AIMS65 [14]-[16] scores for mortality and endoscopic intervention. AIMS65 scores are the most precise predictors of inpatient mortality, ICU length of stay, and all-cause mortality. GBS is the most accurate predictor of the necessity for endoscopic intervention. The AIMS65 score is the most effective predictor of inpatient mortality, ICU length of stay, and all-cause mortality [17]. Two additional studies [17] [18] also demonstrated that the AIMS65 is more accurate than the GBS in predicting mortality and ICU admission. However, further large-scale prospective studies are necessary to ascertain the precise role of the AIMS65 in classifying patients with ANVUGIB. A study [19] also demonstrated that the GBS was the most effective predictor of the necessity for hemostatic interventions and transfusion requirements. Furthermore, the researchers developed a scoring system (CANUKA) that was comparable to the GBS in predicting 30-day mortality and rebleeding. However, this system more accurately identified low-risk patients with unfavorable outcomes. A review of 16 preendoscopic risk scores (GBS, RS, and AIMS65) [20] demonstrated that the GBS is a reliable predictor of recurrent bleeding, the necessity for intervention, and 30-day mortality. Furthermore, it was identified as the most accurate score for patients who require hospital intervention, blood transfusion, endoscopic treatment, and surgery.

3. Endoscopic Hemostasis

Endoscopic hemostasis represents a novel treatment modality that encompasses the utilization of local drug injection, metal titanium clips for hemostasis, and electrocoagulation for hemostasis. Endoscopic treatment enables the simultaneous diagnosis and treatment of bleeding lesions and cessation of bleeding. A comparison of the various endoscopic treatments and an analysis of the optimal timing of endoscopic treatment may result in an improvement in the cure rate of patients with upper gastrointestinal bleeding (UGIB) and a greater overall benefit to the patient [21]. A variety of drug injections may be utilized, including 10,000-adrenaline saline, hypertonic sodium-adrenaline solution, and others. Injectable thrombin is a relatively simple and straightforward option, yet it is less effective in treating high-risk ulcers and has a higher incidence of rebleeding. Thermal coagulation techniques, including high-frequency electrocoagulation, argon ion coagulation, thermal probes, and microwave, have a reliable hemostatic effect. However, these methods require a certain degree of equipment and technological expertise, and they are not associated with complications such as perforation. The risk of complications such as perforation is considerable. Mechanical hemostasis primarily employs a range of hemostatic clips, a prevalent hemostatic technique, particularly suited to active bleeding. However, it is challenging to operate on specific regions of the lesion.

3.1. Endoscopic Thermal Coagulation Hemostasis Treatment

Additionally, thermo-coagulation hemostatic treatment is classified into two categories: contact thermo-coagulation and non-contact thermo-coagulation. Contact

thermo-coagulation methods include monopolar electrocoagulation, bipolar electrocoagulation, multi-stage electrocoagulation, thermal probe, and so forth. In the initial stage of the contact thermo-coagulation method, the electrode at the tip of the probe is used to compress the blood vessel. In the contact thermal coagulation method, the electrode at the tip of the probe initially compresses the blood vessel. Subsequently, a high-frequency current is connected between the two electrodes, which generates heat at the bleeding point, thereby facilitating coagulation and cessation of bleeding. Bipolar and multipolar coagulation are considered to be safer than monopolar coagulation. Furthermore, it is imperative that the endoscopist accurately identify the source of bleeding in order to minimize the risk of delayed perforation due to excessive coagulation [22]. The most prevalent application of non-contact thermal coagulation is argon plasma coagulation (APC), also referred to as argon knife. This is a secure procedure whereby a high-frequency electric current is transmitted to the lesion through argon gas, thereby achieving hemostasis. Endoscopic argon ion coagulation is performed by connecting a high-frequency generator and a high-frequency electrode to ionize argon gas into conductive argon ions, which can form high-frequency currents in the probe and generate thermal effects by forming electric sparks in the target tissues, thereby achieving the objective of hemostasis [23] [24]. In a study conducted by Shang Ruilian and colleagues [25], APC technology was employed in the treatment of 94 cases of non-varicose vein gastrointestinal bleeding. The success rate of hemostasis was 94.6%. However, five cases experienced recurrent bleeding following treatment and were subsequently transferred for surgical intervention or embolization of the abdominal vasculature. Endoscopic argon ion coagulation is a widely recognized clinical application due to its uniform depth, superficial electrocoagulation, lack of carbonization, and automatic identification of diseased tissues. Endoscopic argon ion coagulation is a non-contact treatment that can reach areas that are difficult to reach with other techniques, such as titanium clips, microwave, electrocoagulation, and laser. It does not cause adhesion and has a good hemostasis effect. Some studies have demonstrated that endoscopic argon ion coagulation is a safe and reliable method for treating gastric hemorrhage in elderly patients, with the potential to improve hemostatic efficacy while reducing the incidence of complications [26]. However, thermal coagulation hemostasis requires sophisticated equipment and expertise, and improper execution can result in significant complications.

3.2. Endoscopic Mechanical Hemostatic Therapy

Endoscopic mechanical hemostasis for patients with ANVUGIB is primarily performed using endoscopic titanium clips, which are the most commonly utilized devices. The underlying principle is analogous to that of surgical ligation, which involves the mechanical cessation of bleeding through the mechanical clamping of the severed ends of blood vessels. Titanium clips are a widely used device for a variety of lesions that bleed, including arterial exposure to blood spray, mucosal

tears, fistulas, perforation, and injection. However, their efficacy is limited for active, jet-small arterial hemorrhage (diameter <3 mm), such as deformity of small arterial hemorrhage, Dieulafoy disease, and patients taking anticoagulant or antiplatelet drugs. In such cases, titanium clips are the optimal choice [1]. In cases of acute blood loss in the upper gastrointestinal tract and hemorrhagic shock, as well as in instances where the patient is simultaneously suffering from more serious cardiac and pulmonary diseases, the use of hemostatic drugs is ineffective. In such cases, surgical conditions are also absent, and titanium clamps can be considered an effective indication for hemostatic treatment [27] [28]. In a comparative study, Yi Xin *et al.* [29] evaluated the efficacy of titanium clip hemostasis and endoscopic injection of epinephrine saline in the management of peptic ulcer bleeding. The titanium clip group demonstrated a 97.56% success rate in hemostasis, which was higher than that observed in the control group. Additionally, the recurrence rate of bleeding and the time to symptomatic relief were lower in the titanium clip group compared to the control group. Titanium clips are delivered through the endoscopic orifice with the objective of stopping bleeding lesions, blood vessels, and surrounding tissues by means of physical compression, as observed under the microscope. The principle of hemostasis is analogous to that of surgical suturing, and does not result in coagulation, denaturation, or necrosis of mucosal tissue. However, for chronic fibrous ulcer lesions, the closing force of hemostatic clips is often insufficient to achieve effective hemostasis with adequate compression. In the event that the width of the laceration exceeds the maximum angle of the titanium clip, it is not possible to clamp it. Furthermore, if the surrounding tissue is brittle, the titanium clip will fall off, resulting in re-bleeding. In the event that the lesion is situated in the tangential line of the digestive tract or within the reversed field of view, the titanium clip may prove challenging to operate and difficult to clamp correctly. This is particularly the case in the esophageal cardia, the gastric fundus, the distal part of the stomach, and the posterior part of the duodenal bulb, among other locations. Accordingly, the operator must exercise caution when utilizing the titanium clip to prevent inadvertent damage to the lesion. Consequently, the efficacy of titanium clip treatment is contingent upon the proficiency of the operator and the necessity for close postoperative observation, with the objective of improving the rate of permanent hemostasis [21]-[31]. The majority of metal titanium clips are dislodged automatically within a period of between one and three weeks, with excretion through the feces occurring as a result. An over-the-scope-clip (OTSC) is a further iteration of the titanium clip. It is distinguished by its considerable dimensions, robust closing force, and exceptional controllability, enabling the direct clamping of bleeding vessels to achieve hemostasis. The device is affixed to the exterior of the endoscope and is of a larger size than traditional endoscopic scope clips, enabling the delivery of a more robust closure force. In the treatment of high-risk anastomotic venous graft (ANVUGIB) or rebleeding ANVUGIB, OTSC anastomotic clip hemostasis has been demonstrated to have a higher success rate and lower rebleeding rate than standard

endoscopic treatment [32] [33]. Jensen *et al.* [34] proposed that OTSC anastomotic clip hemostasis, when initiated at an early stage of treatment for severe bleeding associated with peptic ulcer and Dieulafoy's disease, can effectively reduce the 30-day rebleeding rate in patients. The incidence of rebleeding was markedly diminished. Manta *et al.* [35] reported 286 cases in which OTSC anastomotic clips were used for first-line hemostasis. The success rate of hemostasis for ANVUGIB was 97.2%, and OTSC clips were used as the sole treatment for successful hemostasis in 97.1% of cases. As endoscopic technology continues to evolve, titanium clips have been extensively evaluated in the management of acute non-variceal hemorrhage. This has led to the development of novel therapeutic modalities with the aim of further enhancing the efficacy of titanium clips for hemostasis. A typical example is the nylon rope combined with a titanium clip purse-string suture. By tightening the nylon rope, the wound forms a purse-like structure, which is beneficial for patients with a narrow duodenal bulb or ball lumen, elderly patients, or those who have used non-steroidal anti-inflammatory drugs or other drugs that cause gastrointestinal mucosal tissue to become more brittle. The nylon rope can also be adjusted to provide a more solid therapeutic effect by pulling the nylon rope to adjust the strength of the rope [36]. A more efficacious suture is required to encase the vascular stump and ulcer surface. This will prevent further erosion of gastric acid and digestive enzymes on the defect site, thereby providing an optimal environment for ulcer surface healing [4]. Previous research has demonstrated that H. pylori infection is linked to complications such as bleeding and perforation of ulcers, and is a significant risk factor for rebleeding. The purse-string suture can prevent HP from coming into contact with the ulcer surface, thereby reducing the unfavorable damage caused by HP to the ulcer surface and preventing the occurrence of rebleeding [37].

3.3. Local Drug Injection

Thrombin, an enzyme utilized in the process of blood coagulation, has been extracted from the venom of the Brazilian spearhead pit viper. This thrombin has demonstrated the capacity to facilitate the synthesis of fibrin and the release of platelets, enhance platelet aggregation, markedly reduce the duration of bleeding, accelerate the rate of blood coagulation, and promote the hemostasis of lesions [38]. Additionally, thrombin has been observed to stimulate the growth of vascular epithelial cells and facilitate the healing of wounds. The endoscopic local submucosal injection of 1:10,000 epinephrine has been demonstrated to rapidly constrict submucosal blood vessels and promote intravascular platelet aggregation and thrombosis. Furthermore, the local injection can compress microvessels through the swelling of submucosal tissues, which can slow down or stop bleeding [39]. In order to achieve optimal hemostatic efficacy, it is essential to perform hemostasis at the root of the blood vessel to the greatest extent possible. The method is free from the risk of ulcer enlargement and perforation due to injection of a sclerosing agent, and thus suitable for all kinds of vascular bleeding. It has a good

hemostatic effect on small-diameter blood vessels and also has a good hemostatic effect on bleeding from Dieulafoy's disease and anastomotic ulcers. However, it is not suitable for bleeding from the bottom of penetrating ulcers. Local injection of epinephrine alone is a feasible method of hemostasis that does not require excessive cooperation between endoscopists and assistants. However, its efficacy is inferior to that of combined treatments, such as epinephrine combined with electrocoagulation for hemostasis or combined with metal clips [40].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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