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Research progress on vascular clips for minimally invasive surgery

Jiaqi Jiang[1], Haipo Cui[1], Fang Geng[2], Xudong Guo[1]

[1]School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai 200093, China. [2]Medtronic China Research and Development Center, Shanghai 200100, China

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Hightlights

- Material and mechanical structures of absorbable vascular clips affect its hemostatic efficiency.
- The tooth shape, tail end, and closure of vascular clips are the main direction of mechanical structure improvement.
- The coating of the vascular clips can regulate the degradation rate and improve hemostatic efficiency.
- Reasonable mechanical properties and degradation rate are the main development direction for absorbable vas cular clips.

Abstract

Minimally invasive surgeries are widely applied due to the advantages of small surgical wound, short postoperative recovery period, and low surgical infection rate. In minimally invasive surgery, vascular clips play a significant role in hemostasis and managing the direction of blood flow, ensuring the success of surgical procedures. The mechanical structure and manufacturing materials of vascular clips have an important influence on its clinical application effect. In this paper, we classify and summarize the mechanical structure and manufacturing materials of the currently available vascular clips worldwide, and then analyze the hemostatic coating materials of vascular clips. Besides, we also summarize the shortcomings of the existing vascular clips and propose a coat-absorbable vascular clip with future research potential.

Keywords: Vascular clips, mechanical structure, absorbable material, mechanical properties, coating

Introduction

Hemostasis is one of the core techniques in surgical operations. Hemostatic technology has developed from simple instrumental hemostasis measures in the past to a complete technical system, including drugs, materials, equipment, and anesthesia. Finding the bleeding site and treating the bleeding vessels are the key steps of hemostasis. Traditional methods, such as ligation, suture, packing, and heat hemostasis, are still in effect today. Besides, vascular clips, hemostatic gauze, staplers, high-frequency electrosurgical units, ultrasonic scalpels, and ligation bundles for vascular closure systems have been developed and widely used in surgery. Given the increasing preference for minimally invasive surgical procedures, laparoscopes have gained widespread utilization in surgeries, and vascular ligation during various laparoscopic surgeries has always been a challenge in clinical operations. Due to the limited space of laparoscopic surgery and the heat sensitivity of some deep small and medium blood vessels, vascular clips are more convenient and precise than traditional sutures of blood vessels under laparoscope. At present, the materials of tissue vascular

Address correspondence to: Haipo Cui, School of Health Science and Engineering, University of Shanghai for Science and Technology, NO.516, Jungong Road, Shanghai 200093, China. Tel: +86-21-55271290. E-mail: h_b_cui@163.com.

clips are mostly metal or polymer [1]. Common metal clips include silver clips, titanium clips, and tantalum clips. Due to the high price of silver and tantalum, titanium clips are commonly used in clinical practice. Especially, U-shaped titanium clips are widely used clinically, which clamp and close blood vessel by metal plastic deformation. Polymer clips mainly include polyoxymethylene non-absorbable clips, etc. The main products are Hem-o-lok vascular clips and Teleflex products of the same type. Due to its non-absorbability, this type of vascular clips is eventually wrapped by tissue and left as a foreign body in patients, which may cause foreign body reactions or complications, such as inflammation, pain, and stones. Besides, metal vascular clips also affect the conduction of postoperative X-ray, CT, MRI and other examinations.

Absorbable vascular clips can be dissolved through a simple hydrolysis reaction, leading to no foreign body residue in the body, which can effectively avoid the above problems, and at the same time, the distal closure technique can avoid cutting the tissue [2]. The current absorbable metal clips mainly include pure magnesium vascular clips invented by Jorgensen et al. and magnesium alloy vascular clips developed by Ikeo et al. [3, 4]. The marketed absorbable polymer vascular clips mainly include Medtronic's Laproclip and Johnson & Johnson's Absolok vascular clips. At present, the standards for tissue clips are only for metal clips and clip appliers, but there is no standard for absorbable tissue clips. With the gradually increased use of absorbable tissue clips, relevant standards in this field need to be established and strengthened.

In this review, we classify and summarize the mechanical structure and materials of vascular clips in clinical use and analyze the research progress of hydrogel materials used as vascular clip coatings. Besides, we also summarize the shortcomings of existing vascular clips and point out the main research directions of vascular clips in the future.

Clinical application of vascular clips

Samir et al. used Endoloop sutures, staplers, and Hem-o-lok clips, respectively, to ligate the base of the appendix in patients after laparoscopic appendectomy [5]. Through statistical comparison of the application time, postoperative and intraoperative complications, and related costs of the three medical devices, it was found that the hospital stay of patients using the three devices was not significantly different, but the operation time in those using stapler was significantly shorter than that in those receiving suture, while the operation time was not different statistically between those using ligation clip and suture. The time for ligature in those receiving Endoloop suture was significantly longer than that in those using the stapler and the ligation clip, while the ligature time in those using the stapler was significantly shorter than that in those using the ligation clip. However, in terms of cost, the Endoloop suture costed €57.7, the stapler costed €230.77, while the ligation clip only costed €4.75. These results indicate that Endoloop suture requires more manipulation and is relatively complex for appendix base ligation after laparoscopic appendectomy, hence more time-consuming. The application of staplers or ligature clips is relatively simple compared to sutures, and have lower requirements for manipulation. However, the ligature clip requires accurate application size and ligature position, which is an important reason why it is more time-consuming than the stapler. Chang et al. believed that compared with endoloop sutures, the staplers were simple to operate but expensive, and Hem-o-lok ligature clips were the optimal choice for closing the appendiceal stump after laparoscopic appendectomy [6].

Thereafter, the effectiveness, safety, and limitations of ligature clips were studied. By comparing the clinical data of Endoloop sutures and Hem-o-lok clips, it was found that there was no statistical significance in the incidence of postoperative complications between the two. However, ligation clips were superior to sutures in terms of operation time and cost. Nevertheless, sutures have to be used when the diameter of the appendix stump is greater than 10mm and without inflammation. Therefore, the ligation clips should be designed with a larger clamping range and a more reasonable hinge to meet the stump closure requirements in laparoscopic appendectomy. Colak et al. and Andrea et al. verified the safety and effectiveness of Hem-o-lok clips by comparing the complications, operation time, and hospital stay between Endoloop and Hem-o-lok closure modes for appendectomy remnant after laparoscopic appendectomy [7, 8]. They found that the operation time and cost of the ligature clip group were shorter and lower than those of the suture group. There were no complications or deaths in both groups, and the hospital stay was not significantly different, which proved that the safety and effectiveness of Hem-o-lok were consistent with sutures. Hem-o-lok was also found to be safe for appendiceal stump closure in stump and gangrenous appendicitis. Soll et al. studied the incidence of

Table 1. Classification of laparoscopic nephrectomy types using Hem-o-lok clips

Procedure	Right side	Left side	Total
Simple nephrectomy	2	8	10
Radicel nephrectomy	23	24	47
Nephroureterectomy	3	4	7
Live donor nephrectomy	11	55	66
Total procedures	39	91	130

postoperative abdominal abscess after Hem-o-lok ligation of appendiceal stump after laparoscopic appendectomy, and they reported that the abdominal abscess was mainly affected by three factors: surgical resection technique, histology, and postoperative antibiotic administration [9]. In addition to the short ligature time and low cost, the reverberation sound generated by the ligature clamping can also enable doctors to grasp the ligation situation in time, which greatly reduces the incidence of postoperative abdominal abscess. Therefore, in the design of a ligature clip, the clasp should be retained as much as possible to ensure that the doctor gets feedback from the closing sound. Sadat-Safavi et al. compared the disadvantages of sutures, staplers, and ligation clips in closing the stump of the appendix when performing laparoscopic appendectomy [10]. They concluded that sutures had the potential to break during tension, with the possibility of knot loosening; the ligature clip couldn't be reopened once closed; and the improper design of the ligature clip teeth could result in slipping and detachment. However, it was noted that the procedure was simple and cost-effective. As for the stapler, it couldn't be applied for the appendix stump with large diameter due to its small anastomosis range. Therefore, only suture and clips were compared. Through comparison of clinical data, it was found that there was no significant difference in postoperative complications and recovery time between the two methods, but the ligation time and cost of clips were much lower than that of sutures, and stump suture was highly dependent on the doctor's technique and proficiency in laparoscopic operations. However, enhancements in the design of ligature clips, specifically the tooth shape, are required to prevent slipping and detachment while preserving the integrity of the appendix stump.

Yoshida et al. studied the application of Mg-Zn-Ca metal clips and traditional titanium clips for ligature after cholecystectomy in dogs [11]. By CT scan and analysis of the stained tissue sections 6 months after surgery, it was found that compared with non-degradable titanium clips, magnesium clips produced smaller metal artifacts and less fibrosis of the surrounding tissues. Tissue adhesion was only observed in the titanium clips group, but there was no difference in inflammatory components and interstitium between the two groups. For magnesium alloy clips, the effect of degradation products on the surrounding tissues should be further studied, and the degradation rate should be properly managed to prevent excessive hydrogen resulting in gas cavities, so as to replace the traditional titanium clips in clinical surgery.

A large number of clinical trials have shown that, the use of vascular clips as a means of hemostasis in gastric and colorectal polypectomy can effectively prevent postoperative bleeding and digestive tract perforation [12-17].

In laparoscopic nephrectomy, Herve et al. and Simforoosh et al. studied the effect of traditional staplers and ligation clips on the closure of renal arteries and veins [18, 19]. In living nephrectomy, vascular clip ligation can preserve longer renal veins and renal arteries for transplanted kidneys, thus ensuring faster and better recovery of kidney function after transplantation. Another benefit of using a vascular clip is that the vascular clip can be passed through a smaller port when comparing with a stapler. **Table 1** presents the classification of laparoscopic nephrectomy types using Hem-o-lok clips [18].

Ai et al. compared the effect of ultrasonic scalpel and traditional metal clips on closing the gallbladder duct during laparoscopic cholecystectomy [20]. They found that although ultrasonic scalpel shortened the surgical time of vascular and gallbladder duct closure and the length of hospital stay, there was no difference in the incidence of postoperative complications between patients undergoing the two procedures, and additional ligation was required if the gallbladder had benign disease or the diameter of the cystic duct was greater than 6mm. For small blood vessels with narrow cavities and high heat sensitivity, ultrasonic scalpel is obviously superior to traditional metal clips.

Material and mechanical structures of vascular

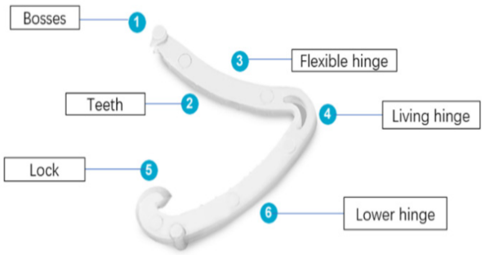


Figure 1. Schematic diagram of Hem-o-lok clip structure. This figure is cited from [23].

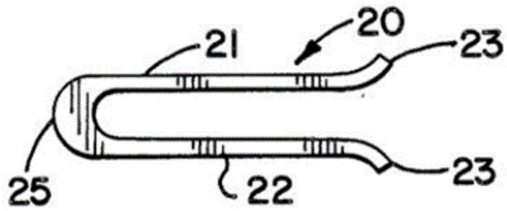


Figure 2. Schematic diagram of the degradable pure magnesium vascular clip.

clips

In terms of structural design, vascular clips require to have clamping stability, clamping durability, and user-friendliness. That is, vascular clips should be stable and firm in clamping the tissue, not easy to slip and loosen, and work well with clip appliers. Under a certain water pressure, the clamped tissue should be free of leakage.

Non-absorbable vascular clips

Titanium clips are the earliest vascular clips that were mass-produced and used on a large scale in modern laparoscopic surgery. They are widely used in the treatment of gastroduodenal hemorrhage and the clamping of lymphatic stumps after lung cancer surgeries. However, due to the inherent properties of the metal material, titanium clips can damage the tissue through an electric current when it touches an electrode during the operation. As a result, it loosens and falls off prematurely due to tissue inflammation after the operation, leading to bile leakage or bleeding. It can also interfere with diagnostic accuracy.

Hem-o-lok vascular clips are disposable and non-absorbable polymer vascular clips made of acetal diethyl alcohol. The overall arc design of the clip makes the ligation range larger and increases the external tension. The clamped blood vessel is also evenly stressed due to the curved design that reduces the risk of rupture. The buckle design at the front end of the clip not only provides a secure closure mechanism when clamping blood vessels, but also gives tactile feedback to doctors. The crescent-shaped air cavity design at the end of the clip can disperse the stress on the tail when the clip is closed, preventing fatigue fracture at the end of the clip. The anti-slip teeth on the upper and lower arms of the clip can effectively prevent blood vessels from slipping [21]. **Figure 1** shows the structure of the Hem-o-lok clip. Since the material of the vascular clip is inert, the clip is non-conductive and will not affect CT, MRI, and X-ray examinations. However, before the clip closes the blood vessel, the vessels can easily slip from the gap between the upper and lower arms of the clip. Since it is not absorbable, it can remain permanently in the body, causing potential harm and bringing psychological burden to the patient [22]. If the material of the Hem-o-lok vascular clips is simply replaced by absorbable polymer without modifying the structure, the tail end with crescent-shaped design will easily degrade before the vascular wound heals due to the thinner inner wall. This in turn sabotages the effect of clamp and leads to bleeding.

Absorbable vascular clips

Richard et al. designed the first absorbable metal hemostatic clip using pure magnesium with high toughness but high brittleness [3]. As shown in **Figure 2**, the hemostatic clamp is designed to enable bending of the clamp by combining the outward bending of part 23 with the clamp structure. This design allows the parts 21 and 22 to remain straight and provides better clamping paths for the blood vessels. This, in turn, facilitates better alignment with the gaps in the unclosed blood vessel clamp [3]. By increasing the thickness of the tail end (25), it can prevent the tail end from breaking and failing when the vascular clamp is closed.

Naoko et al. adjusted the composition of different elements in Mg-Zn-Ca alloy and processed it into bars using hot extrusion technology [4]. The extruded bars were annealed at different temperatures and times, and finally manually bent into U-shaped clamps. The U-shaped clamps underwent dynamic recovery during deformation, resulting in a high compressive fracture strain of 0.40, which is greater than the maximum fracture strain of the vascular clamp. This proves that annealing can reduce strain hardening rate and improve material ductility by weakening the substrate texture. After 12 weeks of degradation, the vascular clamps

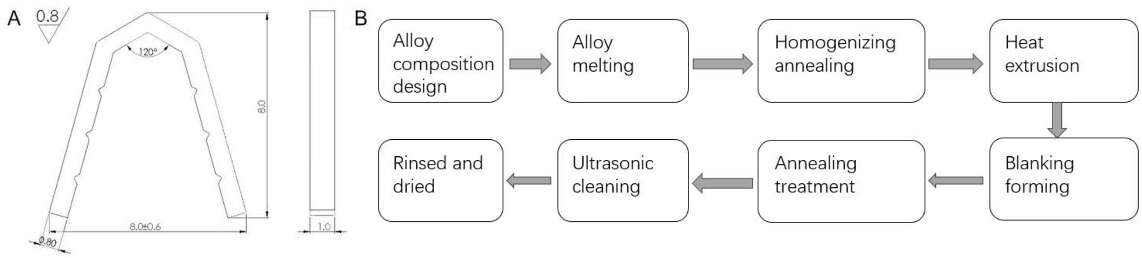


Figure 3. Degradable magnesium-based composite vascular clip. (A) Schematic diagram of the structure; (B) Processing flow chart. This figure was cited from [24].

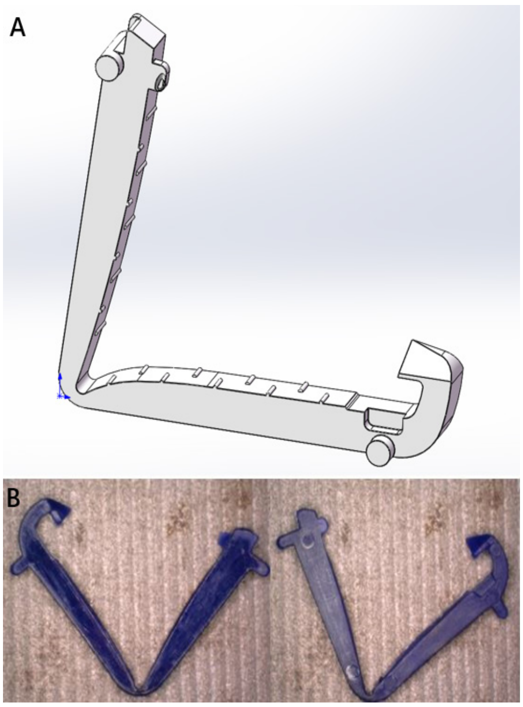


Figure 4. Vascular clip clamping. (A) American Johnson & Johnson ligature clip; (B) Sichuan Guona absorbable vascular clip. This figure was cited from [25].

still maintained a U shape, indicating a uniform degradation. In animal experiments, the air cavity gradually decreased with the passage of implantation time, and there was no obvious air cavity around the surgery. Therefore, adjusting the composition of Zn and Ca in the alloy can help to achieve uniform degradation of the alloy and gradual gas generation.

Bai et al. developed a new type of V-shaped vascular clamp using Mg-Zn-Ca alloy [23]. As shown in **Figure 3A**, the vascular clamp is designed with a 120° arc at the tail end and an angle at the connection between the tail end and the vascular clamp arm, which expands the diameter of the vessel that can be closed and reduces the possibility of tail end fracture caused by the deformation of the vascular clamp. The grooves machined on the inner surface of the clamp prevent the blood vessel from slipping behind the clamp teeth. In terms of materials, the yield strength and tensile strength of the material have been significantly improved by squeezing the plate, and the punching process along the extrusion direction has better adapted the microstructure characteristics of the material to the deformation of vascular clamps. When heated at 380 ℃, the strength of the material decreases, and the elongation reaches maximum then decreases with time. Therefore, the heat treatment time should be controlled to better meet the deformation needs of the vascular clamps. **Figure 3B** is a schematic structural view and a processing flow chart of a biodegradable magnesium-based composite material vascular clip [24].

The absorbable vascular clip of Sichuan Guona Technology Co., Ltd. and the ABSOLOK ligature clip of American Johnson & Johnson are both integrally formed with polydioxanone, and snap locks are set at the front ends of the upper and lower arms of the clip to form a joint. The gripping surfaces thereby close the vessel or tissue. The lock and linear design of the upper and lower arms of the vascular clip can effectively prevent blood vessels from slipping along the upper and lower arms, but the sharp hook design at the front end may cause damage to blood vessels. **Figure 4** shows vascular clip clamping [25].

Covidien absorbable ligation clip adopts the mechanical structure of a double-layer crocodile mouth, which is assembled with four parts: an inner clip, an outer clip, a piston, and a jacket. The outer layer material is polyglycolic acid, and the inner layer material is polyglycol carbonate. After assembly, it forms a double-layer crocodile mouth structure. The jacket has a fixed U-shaped 1cm insertion opening. The mechanism is that under the action of a special clamping tool, the inner piston of the jacket is used to push out the outer layer clips one by one according to the set track, and the duct tissue of the pipe is flattened and blocked. Due to its structural characteristics, the double-layer crocodile mouth absorbable vascular clip

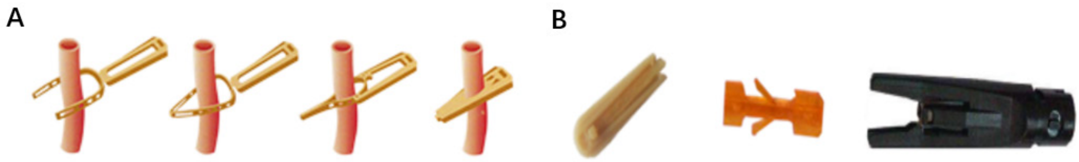


Figure 5. Covidien vascular clip. (A) Process of clamping blood vessels; (B) Picture of the clip. This figure was cited from [25].

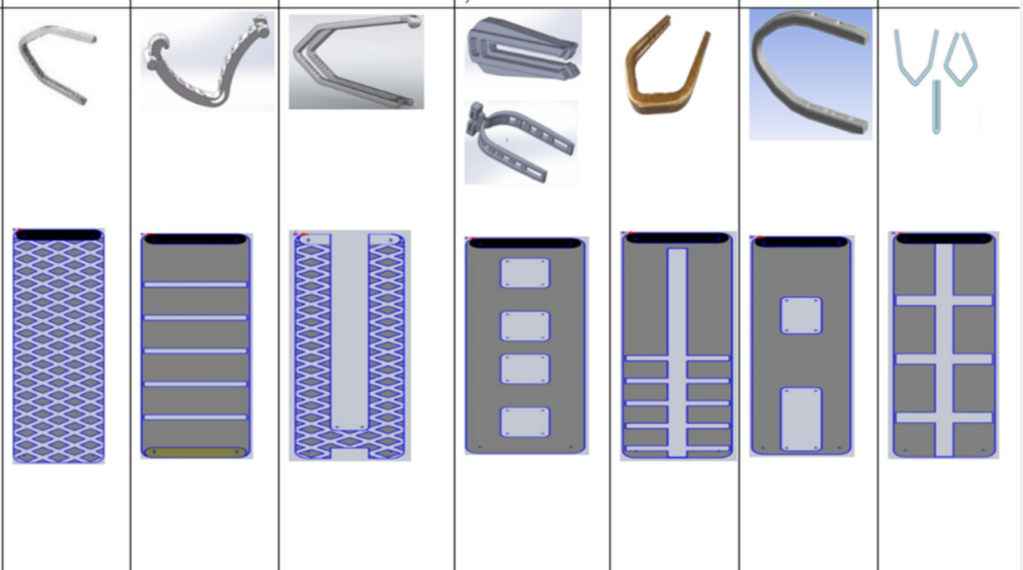
Product	SLS™ clip	Hem-o-lok®	Double-shank	Laparo-clip™	TiGold®	Endo clip™	Ligaclip®
Material	Titanium	Polymer Non-absorbable	Titanium	Polymer absorbable (2-component)	Titanium-gold	Titanium	Titanium
Profile Hinge end Jaw End							
Contact surface	Rhomboid	Transverse Raised jaw	Rhomboid w/o latch	Notches	Transverse Linear	Lock-Super Interlock™	Transverse Linear

Figure 6. Tooth profiles of different vascular clips.

can be closed without completely freeing the duct tissue. To use, the operator only needs to buckle the coat directly to the special clamping tool, which enters the body through the laparoscopic trocar, then insert the tissue intended for clamping into the U-shaped opening of the coat, and quickly close it. Therefore, only two steps are required to complete a clamping. The advantage of this structural design is twofold. Firstly, during the clamping process, the inner clip effectively prevents the blood vessel from slipping along the upper and lower arms of the vascular clip. Secondly, the inner clip is constructed from a relatively soft material where it makes direct contact with the blood vessel, minimizing the risk of blood vessel damage. The material of the outer clip is relatively hard, and it is connected with the inner clip to enhance the clamping performance and provide a closure buckle for the overall clip structure. However, because the clip has a double-layer structure, the overall size is relatively large, so it is difficult to clamp the blood vessel in the narrow and closed human body cavity. **Figure 5** shows the design and mechanism of a Covidien vascular clip [25].

Teeth design of vascular clips

Slipping and dislocation of vascular clips in the process of clamping blood vessels is likely to cause serious complications [26-28]. Reasonable tooth shape design can effectively avoid this scenario. Both the French SLS™-Clip and the German Aesculap vascular clip adopt a rhombus design, which not only increases the contact area with the blood vessel, but also enhances the clamping safety to ensure interlocking and non-slip. TiGold® and Ligaclip® have a transverse and a single longitudinal tooth design that prevents vessels from slipping in both directions. Lapro-clip™ ensures non-slippage through the gap in the inner clip for the jaw of the outer clip to pass through [28]. **Figure 6** shows the tooth profile of different vascular clips.

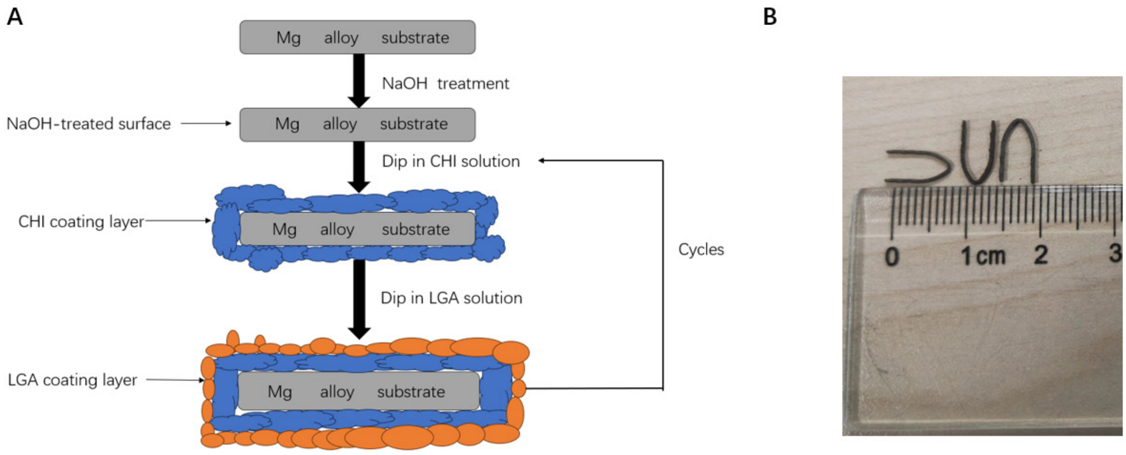


Figure 7. Hemostatic Magnesium Clip. (A) Processing flow of hemostatic coating; (B) Physical image. This figure was cited from [29]. NaOH, sodium hydroxide; CHI, chitosan; LGA, L-glutamic acid.

Coating for vascular clips

Since the hemostasis related to vascular clips is mainly aimed at the internal bleeding of blood vessels in various organs of the human body, many researchers have focused their research on coatings of vascular clips. Chang et al. applied chitosan /L-glutamic acid multilayer coating (CHI/LGA) on the surface of metal clip by adjusting the pH of solution using the principle of layer-by-layer self-assembly technology [29]. CHI/LGA can improve the corrosion resistance of the metal clamp to the expected level through the assembly of 7 layers of coating. This ensures no major mass loss and mechanical property change within three weeks after clinical surgeries, but the magnesium clamp can lose its original shape and function after five weeks of stress corrosion. In future experiments, the corrosion resistance of magnesium clips can also be improved by adjusting the thickness and number of coating layers by manipulating the concentration of CHI and LGA solution and dipping times. **Figure 7** shows the processing flow and samples of the hemostatic coating of the hemostatic magnesium clip [29].

Zheng et al. applied plasma electrolytic oxidation/phytic acid coating on the surface of hemostatic clips made of Mg-Zn-Y-Nd alloy [30]. This coating improves the early corrosion resistance of the clamp by using plasma electrolytic oxidation with a porous surface as the first layer of the composite coating. Phytic acid, used as a chelating agent, forms a conversion film with metal ions such as magnesium and zinc. This has a certain insulation effect on air and water in the middle and later stages of degradation. All these improves corrosion resistance and prevents emphysema caused by gas accumulation and tissue cell damage attributed to the rapid degradation of high concentrations of magnesium ions. Although the biocompatibility and uniform degradation performance of plasma electrolytic oxidation/phytic acid coated vascular clamps are good, in the long-term clinical application process, it is also necessary to observe whether their mechanical properties meet the mechanical requirements after three weeks.

Summary

Judging from the research status in recent years, absorbable metal and polymer vascular clips are developing rapidly. Current research primarily focuses on the improvement of vascular clips from the selection of mechanical structure and absorbable materials, so that vascular clips can be degraded after clamping the bleeding blood vessel, and not remain in the human body. Although the research on vascular clips has made great progress, there is still room for further research:

Mechanical structure: Although currently avilable vascular clips have improved the general structure and their own tails, as well as increased the overall size of the vascular clips to varying degrees, some of the improved designs did not take the degradation of the vascular clips into account.

Degradable materials: After the degradation in vivo, the degradation products are likely to cause inflammation and adverse reactions in human organs. In addition, the degradation rate of the material needs to be regulated to meet the time and mechanical performance requirements for vascular clamping of the blood vessel.

Hemostasis efficiency: The hemostasis efficiency of vascular clips still needs to be improved. The existing vascular clips may still cause bleeding at the hemostatic site during clamping, which affects the surgical field of view.

In order to make vascular clips better adapt to the needs of laparoscopic clinical surgery, future research and development should focus on reasonable mechanical structure and degradation rate, good biocompatibility of degradation products, and high hemostasis efficiency of vascular clips. At the same time, various hemostatic coatings have been applied on vascular clips in animal experiments [29, 30]. With the continuous improvement of hemostatic efficiency, mechanical structure, and degradation rate of vascular clips, future vascular clips will also have higher clinical application value.

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