3. Examples of Innovation by Surgeons: Endoscopic Variceal Ligation

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Major changes in treatment of patients with bleeding esophageal varices occurred during the decade of the 1980s. Dissatisfaction with short- and long-term results of shunt operations led to the re-emergence of endoscopic sclerotherapy. This technique, initially described in the 1930s, was performed by surgeons in an operating room using rigid endoscopes and general anesthesia [1]. Sclerotherapy using flexible fiber-optic endoscopes, performed in an endoscopy suite or intensive care unit under conscious sedation, rapidly replaced the older method. Flexible endoscopic sclerotherapy was widely adopted as an inexpensive, simple to perform, and relatively effective treatment for control of variceal hemorrhage. Elective repeated sclerotherapy treatments, aimed at obliterating varices from the distal esophagus, decreased the incidence of recurrent bleeding. As experience with endoscopic sclerotherapy for esophageal varices increased, it became apparent that injection of caustic sclerosants into the distal esophagus was associated with a substantial risk of both local and systemic complications. Esophageal stricture, bleeding from sclerotherapy-induced ulcerations, chemical necrosis with perforation of the esophageal wall, and sclerosant-induced respiratory distress became recognized accompaniments of injection therapy. At a time when the mortality associated with acute variceal bleeding was as high as 50 %, these shortcomings of injection sclerotherapy seemed relatively inconsequential [2].

Elastic band ligation for the treatment of bleeding from hemorrhoids was first described in the 1960s [3]. Prior to the introduction of this technique, injection sclerotherapy performed via an anoscope, or surgery, were the two mainstays for treating this common problem. Elastic

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band ligation for treating hemorrhoids was widely accepted and employed in the United States by the 1980s. Surgical treatment became reserved for the few patients that failed band ligation or those with advanced hemorrhoid disease. Elastic band ligation was subsequently found superior to sclerotherapy for treatment of hemorrhoids and required fewer treatment sessions [4].

During the late 1970s and early 1980s, I had the privilege of working as a senior registrar and subsequently as a flexible endoscopic fellow with Professors John Terblanche and Philippus (Flip) Bornman at the Groote Schuur Hospital in the Department of Surgery at the University of Cape Town. Groote Schuur, at that time, was the epicenter for a renaissance of endoscopic sclerotherapy treatment for bleeding esophageal varices. Patients were treated under general anesthesia in the operating room using rigid esophagoscopes and long injection needles. Results were encouraging and few patients required surgical salvage [5]. The shift from operative to endoscopic treatment of bleeding esophageal varices had begun.

I returned to Denver and the Department of Surgery at the University of Colorado with substantial experience in rigid endoscopic sclerotherapy as well as diagnostic and therapeutic (such as existed then) flexible endoscopy skills. As the most junior member of the surgical faculty, my clinic assignments consisted largely of cases my senior colleagues had little interest in. Among these were a number of patients with symptomatic hemorrhoid problems, most of whom were successfully managed using the McGivney elastic band ligating device (Miltex Instrument Co., Lake Success, NY). This technique is performed via an anoscope using a clamp to grasp the hemorrhoid and pull it into the ligating chamber after which the elastic band is ejected to ensnare the captured hemorrhoid. As my experience with elastic band ligation grew, I came to appreciate the simplicity, reproducibility, and effectiveness of this treatment. I wondered if there were other potential applications in the gastrointestinal tract for elastic band ligation.

The Initial Concept

The only similarity between ano-rectal hemorrhoids and esophageal varices is their proclivity to cause problems by bleeding. Anatomically, hemorrhoids are cavernous vascular tissues as compared with esophageal varices that are large thin-walled collateral veins located in the submucosa of the distal esophagus. Could the latter be as effectively

treated as the former using elastic band ligation? My initial concept for elastic band ligation of esophageal varices consisted of an elongated McGiveny type ligation device that would be passed through a rigid esophagoscope. The varix would be grasped with a long clamp and drawn into the ligation chamber followed by ejection of the elastic band around the varix to be ensnared. This concept turned out to be little more than a thought exercise. There was no interest whatsoever in making a prototype device for this purpose among any of the manufacturers with whom I discussed the concept. The main reason there was no interest was widespread recognition that rigid endoscopy was rapidly being displaced by flexible endoscopy, including flexible endoscopic sclerotherapy for bleeding esophageal varices.

The Subsequent Concept

Months later, I was supervising a resident performing a flexible sigmoidoscopy. The resident proudly proclaimed he had found an unusual polyp. I peered through the teaching head (video endoscopy was barely introduced then) and advised him that he was the cause of the "polyp." I was demonstrating to the resident how a "suction polyp" is created by inadvertently aspirating mucosa into the biopsy channel, when suddenly a light bulb flashed on. If one had an open ended cylinder mounted on the distal end of a flexible endoscope, could one create a large "suction polyp" that would be amenable to ligation with an elastic band? Suction was the potential key to making elastic band ligation with flexible endoscopes a reality and was a decidedly more elegant solution than grasping a fragile thin-walled vein with a clamp and then pulling on it.

The next step was to get a prototype device built in order to prove the concept was mechanically viable. I was reluctant to disclose many details of what I envisioned the ligating instrument would look like or how it would function, if it functioned at all. I first consulted Mr. Warren Bielke who was national sales director for Pentax Precision Instruments (Orangeburg, NY). I told him I had a concept that I outlined in sketchy detail. I needed a flexible endoscope with the old style screw on (threaded) end cap that could be used to attach an instrument in order to do some animal studies. Pentax Precision Instruments would have first rights to commercialize the device if the concept worked and they were interested. He generously loaned the equipment and we were over the first hurdle.

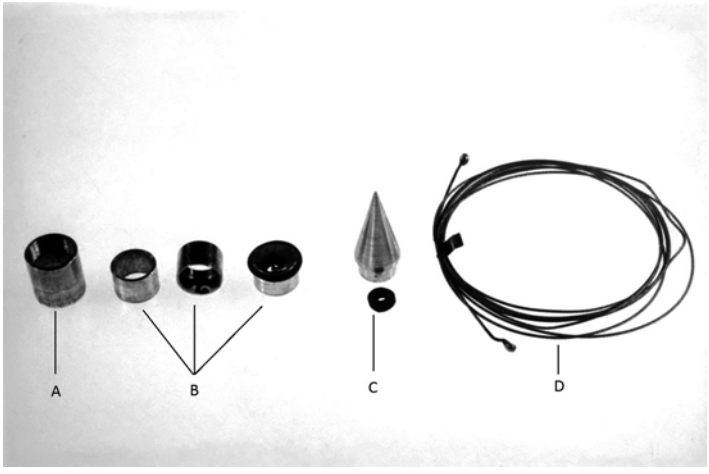

Fig. 3.1. Components of the original endoscopic ligating device prototype. The large cylinder (**a**) attached to the endoscope via screw threads. The inner (banding) cylinders (**b**) were preloaded with elastic bands using the loading cone (**c**). The trip wire (**d**) passed through the biopsy channel and attached to the inner cylinder. All components were stainless steel. (From Stiegmann et al. [6], with permission from Elsevier).

The second hurdle was designing and building a prototype device. The estimate for creation of a medical grade reusable instrument that could be screw mounted to a flexible endoscope was 5000 dollars. An unexpected opportunity to consult for a start-up company that was developing a flexible vascular endoscope resulted in the funds needed to engineer and manufacture one device. The specifications for the original device were driven by the diameter of the endoscope since mounting of the external housing cylinder to the endoscope was to be accomplished using a threaded connection. A shorter, smaller diameter inner (ligating) cylinder, over which an elastic "O" ring was stretched, fit inside the housing cylinder and was connected by cable running through the biopsy channel of the endoscope to the operator. The final component was the loading cone that fit into the inner (ligating) cylinder and facilitated stretching the elastic "O" ring in place over the ligating cylinder. (Figs. 3.1, 3.2, 3.3, and 3.4)

Fig. 3.2. The “O” ring is being loaded onto the banding cylinder using the loading cone. (From Stiegmann et al. [6], with permission from Elsevier).

Fig. 3.3. The trip wire, passed via the biopsy channel, is secured into the notch of the inner (ligating) cylinder. Note the elastic “O” ring mounted on the distal end of the ligating cylinder. (From Stiegmann et al. [6], with permission from Elsevier).

Fig. 3.4. The assembled ligating device. The ligating cylinder with loaded "O" ring is positioned inside the housing cylinder that is attached by screw thread mount to the endoscope. The trip wire runs via the endoscope biopsy channel and exits at the biopsy channel entrance. (From Stiegmann et al. [6], with permission from Elsevier).

Proving the Concept I

Once manufacture of a prototype device appeared likely, we devised a plan to determine if ligating tissue inside the gastrointestinal tract with elastic bands, using a flexible endoscope, could be reproducibly accomplished. This and subsequent animal studies were made possible by a grant from the Veterans Administration that was obtained just as the original prototype was delivered. We quickly confirmed, in a small preliminary study done in normal canines, exactly what we had hoped. The procedure was relatively simple to perform using an endoscopic overtube passed into the esophagus, resulted in no immediate or short-term adverse effects we could recognize and was easy to reproduce multiple times in the same animal [6]. We were elated.

Protecting the Concept

Soon after being convinced that elastic band ligation could be reproducibly performed in animals, I sought intellectual property protection in conjunction with the technology transfer office at the University of

Colorado. The practice of that office, at the time, was to proceed with a preliminary patent filing only, until there was certainty the idea would be commercialized. This stance raised the ante for completion of animal studies, initiation of clinical trials, and finding a manufacturer interested in taking the new method to market. We discussed the advisability of publishing results, in the context of intellectual property protection, prior to obtaining a completed patent. I was erroneously advised that the preliminary filing was adequately protective. That advice was correct if one were only concerned about rights in the United States. I was sorry to learn later that our early publications had effectively eliminated the opportunity to obtain international patent protection.

Proving the Concept II

The next experimental step was a study aimed at examining the clinical and histologic effects of endoscopic ligation on esophageal varices in a portal hypertensive animal model. This work took nearly a year to complete since the dogs had to undergo a laparotomy for creation of the portal hypertension inducing venous anatomy after which several months were required for the esophageal varices that developed to enlarge and mature [7]. Animals were treated with elastic band ligation, followed by repeat endoscopy, and then sacrificed at varying intervals. Detailed histological analysis of the elastic band ligation sites was performed. This study demonstrated, in a portal hypertensive canine model, that the series of local events that occurred in treated tissues included: ischemic necrosis, acute inflammation, shallow ulcer formation, and subsequent healing with re-epithelialization of the ulcer by 14–21 days. Varices in the submucosa were obliterated by a process of dense scar formation. The underlying muscular wall of the esophagus was unaffected. More importantly, throughout this study we observed no adverse clinically apparent events in any of the treated animals [8].

As the course of this animal study progressed, it became apparent that the technique was safe to perform and, from my perspective, was ready to move into human clinical trials. At the time, our Gastroenterology colleagues were rapidly and successfully adopting flexible endoscopic sclerotherapy for treatment of their patients with bleeding esophageal varices. It was clear if we were to move forward clinically in an optimal fashion, a respected Gastroenterologist-Endoscopist needed to join the team. To that end, I invited Dr. John Goff to the animal laboratory one day as we were performing endoscopic ligation on a dog. I had worked

with Dr. Goff clinically for several years, and we had a solid relationship in taking care of patients with complex gastrointestinal and biliary problems. I showed him our sole endoscopic ligating instrument, explained how we were using it, and jokingly told him that "I wasn't sure a Gastroenterologist could figure out how to make this work." Of course, as expected, he succeeded on the first try and immediately sensed we were on to something promising. After reviewing the data that had accumulated thus far in the study, he was more convinced. When asked if he had interest in joining forces for a clinical trial, the answer was a resounding yes. That marked the beginning of a productive collaboration as we geared up to determine how endoscopic ligation compared with endoscopic sclerotherapy in patients.

Preliminary Clinical Experience

Institutional Review Board approval of the initial human pilot study was based on the findings from our experimental animal studies and substantial literature confirming the safety and efficacy of treating hemorrhoids using elastic band ligation. Our first patient was a very nice lady who worked as an AT&T telephone operator. She had portal hypertension from chronic hepatitis and was admitted with a variceal bleed. Her band ligation treatment was accomplished without problem. Humans with portal hypertension and variceal bleeding tend to have large varices in contrast to the relatively small ones that developed in our canine model. This made treatment in patients (at least the first treatment session) easier than in the canine since there was more tissue to aspirate into the device and ligate. She was kind enough to allow us to do several diagnostic endoscopies while we observed her in hospital. We observed (and subsequently confirmed in additional patients) essentially the same progression of events at ligated sites in patients that we found in the canines. The initial clinical results bolstered our confidence and set the stage for moving forward with more definitive trials [9]. Before taking the next step, however, we needed to find someone to manufacture the ligating device. All of our work to this point had been done with the original prototype. We realized how tenuous continued progress was when one day, while being washed after use, a key component of the ligating device disappeared down the sink's drain. The plumber was impressed with the number of people interested in his work that afternoon. He successfully retrieved the part.

Commercialization

Numerous representatives and delegations from flexible endoscope manufacturers and endoscopic accessory companies came to Denver. Live demonstrations, endoscopic video tapes, and experimental as well as clinical results were offered up for them. All asked for some time to think about committing to manufacture and market this new treatment concept, including our original supporters at Pentax Precision Instruments. We gained additional experience with clinical use, prepared more presentations for the spring meetings, and became more confident that band ligation was superior to sclerotherapy. Still, no one stepped forward.

At Digestive Disease Week (DDW), I was carrying around a video that demonstrated elastic band ligation in several patients with bleeding varices. Anyone interested was welcome to have a look. I spotted Warren Bielke at the Pentax exhibit and asked him if he had interest in what we had been able to accomplish with the endoscope he had lent us. I plugged the video tape into a relatively public video cassette player and pushed the play button. Several minutes into the showing a well-dressed Japanese man appeared and joined us. I was introduced to Mr Katsumi Oneda, the president of Pentax Precision Instruments. He almost immediately told Mr Bielke to please shut off the video and retrieve the tape from the machine. I was temporarily shocked. Mr Oneda then said "We should not be viewing this in public. Please bring the tape into our private office." In private, we reviewed the video tape, I explained our experimental and clinical results, and Mr. Bielke explained the role Pentax Precision Instruments had played in developing this method. With no hesitation, Mr Oneda simply said: "We want it." The game was on.

During further discussions at DDW and subsequently, I outlined steps I believed necessary to properly test and debut this new treatment in an ideal manner. The first, of course, was manufacturing the device itself. Working with engineers at a Rhode Island injection molding company, the initial production device came to life with only minor design changes that included a "slip on" method of securing the device to the new generations of flexible endoscopes that did not have threaded screw tips on the distal end of the endoscope. The production design was manufactured from molded plastic as a single-use instrument. How to make the trip wire, which in the original prototype was a braided stainless steel cable, was another question. The owner of the company had an idea. He took me out to his car and opened the trunk to reveal a collection of deep

sea fishing equipment including several rolls of high-test monofilament fishing line. We settled on the 250 lb. test line and that remains the material in use today.

Once production of devices began, I lobbied for a multicenter prospective randomized trial that would compare endoscopic ligation with endoscopic sclerotherapy. The trial would be conducted by individuals with recognized experience in endoscopic sclerotherapy at five or six centers in the United States. There was immediate question of the cost of such a trial. I believed there was enough interest from highly qualified individuals that if Pentax Precision Instruments could provide the ligating devices and an endoscope for six centers, the local principle investigators would be anxious to put the new method to the test, be an author on a high-quality randomized controlled trial, and have access to the non-Food and Drug Administration (FDA) approved ligating device well ahead of the general endoscopic public. That logic was accepted and planning for a multicenter trial began in earnest.

Over the ensuing months, I learned that Mr. Oneda and his associates Messrs. Lewis Pell and Warren Bielke were highly regarded in the medical device business for developing new devices into successful products using start-up companies that were financed with venture capital. Several months later I found myself in Orangeburg New York presenting the endoscopic ligation concept and the entire context of treatment for bleeding esophageal varices to an assembled group of nonmedical venture capitalists. Several other creative new device ideas were packaged up along with endoscopic ligation and a new company called VascuCare was formed. Some months thereafter, the marketing rights for endoscopic ligation were acquired by Bard Interventional Products, a flexible endoscopy focused division of the C. R. Bard Company.

Working with Bard Interventional engineers, the design of the endoscopic ligating device was optimized and considerations for packaging and the quantities of preloaded elastic "O" rings that should be included in each kit were addressed. The main issue for Bard Interventional, however, was obtaining FDA approval in order to begin marketing the ligating device. Options included an "Investigational Device Exemption" pathway that could take several years to complete, or the 510-K pathway of demonstrating substantial equivalence to devices currently marketed. The latter was much shorter. I suggested to the team at Bard that endoscopic band ligation used for treatment of hemorrhoids was identical to elastic band ligation for hemorrhoids performed using other devices currently on the market. I further suggested that if endoscopists wanted to use band ligation for "off label" purposes, such as treating esophageal

varices, that was a medical decision left to their discretion. After about a year, the Bard endoscopic ligating device came to market approved by the FDA as a hemorrhoid treatment method. Few people using it at the time bothered to read the package inserts.

Everything was coming together. The patent filing was completed and eventually approved. Leadership at Bard Interventional was passed to Mr. David Chazanovitz who was a friend and innovative business leader. The prospective randomized multicenter trial was running smoothly and data acquisition was nearly complete. We knew, from an interim analysis, that there were strong trends favoring endoscopic ligation in almost all of the variables measured. Dr. Goff's and my biggest problem was trying to accommodate all of the invitations we received to speak on the subject. Additional data began to emerge from other institutions both in North America and abroad that confirmed our initial observations and clinical results. Then, one afternoon, I received a telephone call. The endoscopic ligating device was being removed from the market.

The Bard Cardiovascular division had apparently modified the design of one of its cardiac catheters and had not made corresponding changes in the package insert or notified the FDA of the minor changes. This was a major issue for the FDA and resulted in all C. R. Bard divisions scouring their product package inserts to make certain everything was in order. When the endoscopic ligating device package insert was reviewed, it was realized that almost all of the devices sold were being used to treat bleeding esophageal varices, an indication for which the device had not been approved by the FDA. This was a bit of a crisis; however, the timing could not have been better. We had just received word that results from our multicenter trial comparing endoscopic ligation with sclerotherapy had been accepted for publication by the New England Journal of Medicine [10]. Our trial results and additional clinical data generated by others provided solid evidence that elastic bland ligation treatment for bleeding varices was safer, more effective, and more efficient than endoscopic sclerotherapy. These data were submitted to the FDA and, ironically, resulted in the first medical device approved for a specific clinical indication based on prospective randomized clinical trial data.

Epilogue

Endoscopic elastic bland ligation has been the endoscopic treatment of choice for bleeding esophageal varices for 20 years. Development of a multifire device by Saeed, one of our multicenter study principle investigators,

greatly simplified and accelerated acceptance of the method [11]. Numerous prospective, randomized studies have reconfirmed our original findings as has meta-analysis of these data [12].

It is unclear if endoscopic elastic band ligation would have been developed if the regulatory milieu of the 1980s were similar to that of today. The complex and costly restrictions faced by today's surgical innovators were imposed with the best intentions. The consequences, however, discourage creativity and diminish progress.

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