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“Hemodynamic Efficacy” of two Endoscopic Clip Devices Used in the Treatment of Bleeding Vessels, Tested in an Experimental Setting Using the Compact Erlangen Active Simulator for Interventional Endoscopy (compactEASIE) Training Model

Background and Study Aims: Hemoclip therapy is a well-established procedure in the treatment of gastrointestinal bleeding. Although new products are provided periodically by the industry, comparative investigations are lacking. We compared two different hemoclip devices in an experimental setting, assessing them using objective hemostatic parameters.

Materials and Methods: We compared two disposable clip devices (Olympus HX-200L-135 (n = 40) vs. Wilson-Cook Tri-Clip (n = 40)) in an experimental setting using the compact Erlangen Active Simulator for Interventional Endoscopy (compactEASIE) training model equipped with an upper gastrointestinal-organ package for bleeding simulation. This was a randomized, prospective, controlled trial. Four investigators with different levels of endoscopic experience applied ten hemoclip devices of each type to the spurting vessels, the clips allocated using a randomized list for each investigator. The efficacy of hemostasis was determined by continuous measurement of the pressure within the afferent vessel before and after clip application and calculation of the relative reduction of vessel diameter by the clip device. The system pressure was recorded over the period from 1 minute before to 1 minute after clip application. A secondary end point was a subjective assessment of the whole clip application procedure by the endoscopist and the assisting nurse, using a visual analog scale (0 – 100, with 100 representing the best experience).

Results: A total of 39/40 clips of each type were applied successfully. Both clip devices led to a significant increase in system pressure, representing significant relative reduction of vessel diameter (Olympus $5.4 \pm 7.5\%$, $p < 0.001$; Cook $4.9 \pm 8.0\%$, $p < 0.001$). Overall, there was no significant difference between the two devices ($P = 0.756$). However, the investigator with the least experience in endoscopy (< 100 procedures) produced significantly inferior results compared with the other three investigators, who had performed between 2000 and 6000 procedures each ($P < 0.05$). We found no evidence of a learning curve from the intra-observer results. The devices received good, but not significantly different, overall ratings by the endoscopists (Olympus 69 ± 24 vs. Wilson-Cook 65 ± 16) and by the assisting nurses (Olympus 77 ± 9 vs. Wilson-Cook 70 ± 22).

Conclusions: Using an established cadaveric training model, no significant difference was found between the two types of hemoclip devices with respect to their “hemostatic efficacy”. However, the experience of the endoscopist appears to play a major role in successful clip application. The use of a feedback mechanism in emergency endoscopy training, using continuous intra-vessel pressure monitoring, may substantially enhance the efficacy of training, resulting in a similar improvement in clinical results.

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Bibliography

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Introduction

Peptic ulceration is the most common cause of upper gastrointestinal bleeding, with as many as 30 hospital admissions per year per 100 000 population and a mortality as high as 10% [1]. Standard care for patients with upper gastrointestinal bleeding entails endoscopy, both for diagnosis and for treatment; endoscopic therapy has been shown to be effective in terms of reduction of morbidity and mortality [2]. A number of treatment modalities are available for the endoscopic treatment of bleeding peptic ulcers [3], including the well-established endoclip procedure. Several randomized studies have demonstrated the clinical efficacy of this mechanical device in bleeding peptic ulcers [4–6]. The cost and the technically challenging nature of this procedure, however, are important limitations of the method [3,7,8]. In addition, the heterogeneity of clinical results suggests that individual expertise may play a crucial role in the application of hemoclips in patients with peptic ulcer bleeding [3].

Hemoclips were first shown to be effective in the management of gastrointestinal bleeding in 1988 [9]; since then, rotatable, pre-loaded, and disposable clips have been developed [4]. Very recently, a new three-pronged device (Tri-Clip; Wilson-Cook, Winston-Salem, North Carolina, USA) was introduced in place of the original two-pronged design. There has been no published experience with this device in peer-reviewed journals, however, and, in particular, comparative trials are lacking.

We performed a randomized, controlled trial in order to address the issues of the “hemostatic efficacy” of two different types of hemoclip device and the influence of the endoscopist’s experience on the clipping procedure.

Material and Methods

The study was designed as a prospective trial, comparing two disposable endoscopic clipping devices for endoscopic hemostasis in an experimental setting using the compact Erlangen Active Simulator for Interventional Endoscopy (compactEASIE) training model [10]. The Olympus single-use clipping device (HX-200L-135; Olympus Endo-Therapy Europe, Hamburg, Germany) was compared with the novel 7-Fr Wilson-Cook Tri-Clip device. Both clip devices have an aperture width of 10 mm but the length of the prongs differs (Olympus, 6 mm vs. Wilson-Cook, 12 mm).

Experimental Set-Up

The experimental set-up is shown in Figure 1. The compactEASIE was used for the testing of the two endoscopic devices, as described previously [10]. We used 14 stomachs prepared for upper gastrointestinal bleeding simulation, which were designed with six bleeding sites per stomach. Short segments (around 2 cm) of pig splenic arteries were sutured into the anterior wall of the corpus and approximately 2 mm of vessel stump was visible from the inside. The outer part of the artery was fixed onto a large-bore “ball tip” cannula and connected to an artificial blood perfusion system driven by a pulsatile roller pump (SP 04 GBR16; Otto Huber GmbH, Böttingen, Germany) using standard infusion lines. The pump can be regulated electronically to operate at a specific number of revolutions, which guarantees a constant

Figure 1 The experimental set-up used in the study, showing the compact Erlangen Active Simulator for Interventional Endoscopy (compactEASIE) training model.

flow and produces a permanent pressure in the artificial blood perfusion system. The blood substitute was prepared by mixing two bags of cherry-red food colorant into 1 liter of water (Früchte-Rot Kirsch, Art.-No. 2103; Brauns-Heitmann GmbH & Co. KG, Warburg, Germany).

Using a bypass, the perfusion system was connected to a measuring system for arterial blood pressure monitoring, which consisted of a disposable pressure-measurement chamber (REF I-95-VI-024; Smiths Medical Deutschland GmbH, Kirchseeon, Germany) linked to a Siemens SC 6002 XL monitoring system (Siemens AG, Munich, Germany). The “arterial pressure” of the afferent vessel was continuously monitored and documented using this system. The perfusion rate (in ml/minute) was measured over the period from 60 seconds before to 60 seconds after each clip application. The flow proved to be constant, due to the continuous flow provided by the roller pump.

The pressure curve of each clip was documented with a Panasonic digital video camera (NV DX100; Panasonic, Hamburg, Germany) for 1 minute before and 1 minute after clip application: 20 pressure measurements were recorded per minute (i.e. every 3 seconds) in order to identify both the pre-interventional and the postinterventional pressures.

Four investigators with differing endoscopic experience participated in this study: investigator 1 had performed more than 6000 endoscopies, investigator 2 and investigator 3 had performed more than 2000 endoscopies each, and investigator 4 had performed fewer than 100 endoscopies. Each investigator used ten clips of each type. Overall, 80 hemoclips (40 of each type of device) were applied. Random allocation of clips was achieved using a randomized list for each investigator. Each clip was applied to a new, previously untreated spurting arterial bleeding site in the compactEASIE model.

After each clip application, the endoscopist and the assistant rated their subjective overall impression of the device (with regard to handling, positioning, and deployment of the clip) using

a visual analog scale that ranged from 0 to 100 (0 = poorest overall impression, 100 = best or optimal overall impression).

An Olympus 160 video processor with a light source and an Olympus GIF Q160 video endoscope (Olympus Europe, Hamburg, Germany) were used for the endoscopy.

Primary End Point – Measurement of Mean Vessel Diameter

The primary end point of the study was the difference in the vessel diameter before and after one hemoclip application to a bleeding site (comparing the Olympus and Wilson-Cook devices). The change in the vessel diameter due to clip application was calculated as follows: according to Ohm's law, the relation of velocity (v), pressure difference (ΔP), and resistance (R) in a vascular systems is:

$$v = \Delta P / R$$

The law of Hagen–Poisuille was applied for calculating the relative reduction of the vascular diameter (where r = radius; l = length of the vessel; η = viscosity of the fluid):

$$v = (r^4 \times \pi \times \Delta P) / (8 \times \eta \times l)$$

Given that the postarterial pressure is 0, the diameter (d) of the vessel was calculated as follows:

$$d = 2 \times r = 2 \times \sqrt[4]{[(v \times 8 \times \eta \times l) / (\pi \times P_{\text{mean}})]}$$

Because π , viscosity (η), vessel length (l) and velocity (v) are constant, as stated in the study protocol, their fourth root may be determined as a constant (c). The reduction of vessel diameter that occurs from the pretreatment diameter (d_1) to the post-treatment diameter (d_2) could be calculated as follows:

$$\begin{aligned} (d_1 - d_2) / d_1 &= [c \times \sqrt[4]{(l / P_{1\text{mean}})} - c \times \sqrt[4]{(l / P_{2\text{mean}})}] / c \times \sqrt[4]{(l / P_{1\text{mean}})} \\ &= [\sqrt[4]{(l / P_{1\text{mean}})} - \sqrt[4]{(l / P_{2\text{mean}})}] / \sqrt[4]{(l / P_{1\text{mean}})} \end{aligned}$$

Secondary End Points

Secondary end points of our study were the inter-investigator differences, the investigators' learning curves (demonstrated by differences between the first and the second half of each investigator's experience with each type of clip), and the overall subjective assessment of the clip application procedure as rated by the endoscopist and by the nurse assistant, using a visual analog scale (ranging from 0 to 100, with 0 being the poorest experience and 100 the best, or optimal experience).

Statistical Analysis

The sample size calculation was performed using Sample Power 2.0 (SPSS Inc., Chicago, Illinois, USA). According to this pre-testing, it was calculated that it was necessary to apply a total of 40 clips of each type in order to show a significant difference for a two-tailed test with a P value of 0.05 and a statistical power of 0.99, a difference of 8 mm Hg with a standard deviation of 8 mm Hg. Data analysis was performed with SPSS Software Ver-

sion 11.0. When describing approximately normally distributed continuous variables, the mean and median values are given, together with the standard deviation and the minimum and maximum values. ANOVA was used for the comparison of unpaired samples of normally distributed continuous data. The Mann-Whitney U test was used for the comparison of unpaired samples of continuous variables that were not normally distributed. Two-tailed P values of 0.05 or less were considered to be significant.

Results

A total of 80 clips were applied, 40 of each type. Complete pressure curves (from 1 minute before to 1 minute after clip application) were recorded for 39/40 of the Olympus clips and for 39/40 of the Wilson-Cook clips; the postinterventional time period for was not recorded for one clip of each type due to a technical problem.

Clip application using either device led to a significant increase in the system pressure (Figure 2), representing a significant change in the vessel diameter. The mean pressure increased from 118 ± 45 mm Hg to 152 ± 63 mm Hg for the Olympus clips ($P < 0.001$), and from 122 ± 44 mm Hg to 160 ± 83 mm Hg ($P < 0.001$) for the Wilson-Cook clips. These pressure changes resulted in a reduction in the vessel diameter of $5.4 \pm 7.5\%$ (Olympus) and $4.9 \pm 8.0\%$ (Cook), respectively. Overall, there was no significant difference between the types of clip with regard to the reduction of vessel diameter ($P = 0.698$).

Peak pressure was achieved 3 seconds after clip application with the Olympus clips and 6 seconds after clip application with the Tri-Clips. Overall, the maximum increase to peak pressure was not significantly different for the two clip types (98 ± 86 mm Hg for Olympus clips vs. 68 ± 93 mm Hg for Wilson-Cook clips, $P = 0.283$). In addition, when results were analyzed after separating them out for each investigator as well as for the first and second half of the investigators' experience with each clip type, no significant differences were observed between the two devices. Again, the maximum reduction of the vessel diameter was not significantly different.

We found that mean differences in the results of clip application in terms of changes in vessel diameter depended on the experience of the endoscopist, however. Investigator 1 (> 6000 endoscopies) and investigators 2 and 3 (> 2000 endoscopies each) achieved a reduction of the vessel diameter with both clip devices. These three investigators all had at least 2 years' experience in emergency endoscopy. Investigator 4 (< 100 endoscopies) did not achieve significant results with either device, despite being familiar with clip application using this particular simulator (Table 1, Figure 3). Except for this result, no other significant differences were observed between the investigators for either clip (Figure 4).

The differences between the first half ($n = 5$) and the second half ($n = 5$) of experience with each clip device, both overall and for each investigator (data not shown), did not demonstrate a learning curve.

Figure 2 Pressure curves (mean $\pm$ SD) from 1 minute before to 1 minute after clip application, showing the pressure curve for the Olympus HX-200L-135 clips (n = 40, upper curve) and the pressure curve for the Wilson-Cook Tri-Clips (n = 40, lower curve). Clip application resulted in a significant increase of system pressure for both clip types. The peak pressure level was achieved after 3 seconds for the Olympus clips and after 6 seconds for the Wilson-Cook clips, but this difference was not significant.

Figure 3 Reduction of the vessel diameter achieved by the four investigators. Investigator 4, who had performed fewer than 100 endoscopies, achieved significantly lower reductions in vessel diameter than the other three investigators ($P < 0.05$). No significant differences were observed between investigators 1, 2, and 3 (who had performed > 6000, > 2000, and > 2000 endoscopies respectively).

Figure 4 Comparison of the reduction of vessel diameter achieved by the Olympus and Wilson-Cook clips for each of the four investigators. The results were not significantly different for any of the investigators.

Table 1 Reduction of vessel diameter (mean, standard deviation (SD), median, minimum, and maximum reductions, all expressed as percentages) achieved by the four investigators, using the Olympus HX-200L-135 clips and the Wilson-Cook Tri-Clips

Investigator	Clip type	No. of clips applied	Reduction in vessel diameter, %				
			Mean	SD	Median	Minimum	Maximum
1	Wilson-Cook	10	5.2	8.7	7.1	– 11.7	15.6
	Olympus	10	8.7	8.8	9.1	– 7.0	26.1
2	Wilson-Cook	10	8.6	9.5	4.4	0.5	27.3
	Olympus	10	1.9	7.4	1.1	– 7.6	18.6
3	Wilson-Cook	10	5.9	5.1	4.5	– 2.0	13.5
	Olympus	10	8.6	6.2	9.1	1.0	18.4
4	Wilson-Cook	9	– 0.9	5.8	– 0.5	– 14.4	5.8
	Olympus	9	1.9	4.9	1.8	– 6.5	12.1
All Wilson-Cook clips		39	4.9	8.0	4.2	– 14.4	27.3
All Olympus clips		39	5.4	7.5	3.5	– 7.6	26.1

No significant difference was found between the endoscopists' overall assessment of the Olympus clips and their assessment of the Wilson-Cook clips, either for individual investigators or for all investigators (Olympus 65 ± 16 vs. Wilson-Cook 69 ± 24 , $P=0.541$); the assisting nurses' rating results similarly showed no significant difference between the devices (Olympus 77 ± 9 vs. Wilson-Cook 70 ± 22 , $P=0.054$).

Discussion

In this prospective randomized trial, in which we tested two different disposable clip devices in a cadaveric training model [10], we were not able to detect a significant difference in their "hemostatic capacity". Experience in endoscopy overall and in emergency endoscopy in particular, however, appears to play a crucial role in the efficacy of controlling gastrointestinal bleeding using such devices.

Several studies have been undertaken to evaluate the efficacy of endoscopic hemostatic methods, both in humans and in murine models [5–8, 11–15]. Although experimental settings have frequently been used to test different methods of hemostasis and have elucidated the influence of vessel diameter, comparative trials investigating different types of clipping devices designed for hemostasis are lacking. Most commonly, canine models (live anaesthetized dogs) were used for this kind of research [12–14]. The direct application of experimental results to human clinical conditions may be open to question, however [3]. For example, experimental investigations in one study showed that commonly used hemostatic devices were unable to achieve cessation of bleeding even in small vessels [12], while several clinical studies were able to demonstrate their efficacy beyond doubt [4]. In fact, using complete cessation of bleeding as a principal end point implies the belief that total vessel occlusion is the mode of action in hemostasis. In the human clinical situation, however, other contributory factors may be of relevance, such as thrombosis of the afferent and/or efferent vessel, induced either by increased pressure of the surrounding tissue [13] or by activation of endothelial adherence factors. Under these circumstances, the reduction of vessel diameter (as calculated in our study), which may ultimately lead to thrombosis instead of complete hemostasis, appears to be of clinical significance. In this situation, the bursting

pressure (i.e. the maximal prevascular pressure measured 3–6 seconds after the application of a clip) may reflect the vital situation most closely.

We cannot rule out the possibility that a vessel may re-open, even under natural conditions, as shown in our model. Of note is the fact that the vast majority of bleeding ulcers require the application of two to three clips before complete hemostasis is achieved [6, 7, 11]. The reduction of vessel diameter by a single hemoclip as performed in our study appears to imply that this is the most important mechanism for hemostasis in bleeding peptic ulcer disease. Its relevance lies in the contribution that multiple clips make to total occlusion, in conjunction with plasma coagulation and the activation of endothelial factors.

Interestingly, we observed a decrease of pressure after clip application in some cases, which may appear to be contrary to expectations from the physical standpoint. In the clinical situation, imprecise or insufficient clip application can result in an accidental opening of the vessel, caused by unfavorable tension effects on the surrounding tissue, and this supports the contention that this experimental setting closely resembles the real-life setting.

Another interesting result was the short delay before reaching the peak pressure in the Tri-Clip arm, compared with the Olympus arm. Several mechanisms might explain this finding, such as a different releasing mechanism or delayed closing of the prongs, resulting in prolonged compression of the tissue. However, these are speculative and probably of minor clinical relevance because the two clips achieved a comparable reduction in vessel diameter within 3–6 seconds.

It was clinical experience rather than the type of hemoclip used that was shown to be of relevance for successful hemostasis in our study. The participant with the least endoscopic experience achieved significantly lower hemostasis rates than the other investigators, with the best results obtained by the most experienced investigator. This may suggest that the efficacy curve in relation to quantitative experience is asymptotic rather than continuous, although the relationship between quantitative experience and hemoclip competence is not known.

In Brief

Experimental study on an animal model for training of hemostasis which shows equivalent potency of two different clips with regards to effects on vessel pressure and diameter reduction.

Several clinical trials in the field of endoscopy have shown that experience, in terms of numbers and frequency of endoscopic interventions, determines the clinical outcome. This has been observed, for example, for sphincterotomy [16] and colonoscopy [17]. Our findings reaffirmed this observation and thus demonstrated the clinical validity of our results.

Our findings not only have implications for the understanding and evaluation of endoscopic hemostasis using hemoclips, but also highlight the need for thorough training. Endoclip application can be a challenging procedure [5,8,11], and operator experience is a critical factor [4]. Although one of our investigators (investigator 4, the least experienced) was familiar with both the compactEASIE training model and hemoclip devices, having applied several clips over the previous 2 years, he produced inferior results. None of the individual investigators demonstrated a learning curve for the different clip devices, and previous handling of the clip device itself does not seem to be the crucial point in this respect. In fact, clinical training and experience appear to be more important factors in achieving successful hemostasis.

We do not know which particular operator-specific ability accounted for the difference we observed between the investigators, but the investigators who were in active clinical practice had experience of biological feedback in clinical hemostatic interventional procedures, in terms of failure or success of hemostasis, whereas the trainee did not. In the compactEASIE model the spurting of the vessels is produced by a pump [10], making it almost impossible to stop the bleeding because of the force of the pump. In practice, therefore, the spurting may look different but keeps on going, and this does not reflect how effective the application was. We therefore believe that training models for endoscopic hemoclip therapy should include a “biofeedback” mechanism, such as the measurement of the afferent vessel pressure we used in our study. Nevertheless, further studies of the relationship between hemoclip experience, simulator training, and outcome may be helpful.

In conclusion, we were not able to detect a difference between the two hemoclips we studied in terms of their hemostatic efficacy, using a cadaveric training model, but found that, in general, the experience of the operator played a major role. This could have implications both for further clinical trials and for the development of training curricula for interventional endoscopy.

Competing interests: None

References

- Higham J, Kang JY, Majeed A. Recent trends in admissions and mortality due to peptic ulcer in England: increasing frequency of haemorrhage among older subjects. *Gut* 2002; 50: 460–464
- Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology* 1992; 102: 139–148
- Laine L. Endoscopic therapy for bleeding ulcers: room for improvement? *Gastrointest Endosc* 2003; 57: 557–560
- Raju GS, Gajula L. Endoclips for GI endoscopy. *Gastrointest Endosc* 2004; 59: 267–279
- Chou YC, Hsu PI, Lai KH et al. A prospective, randomized trial of endoscopic hemoclip placement and distilled water injection for treatment of high-risk bleeding ulcers. *Gastrointest Endosc* 2003; 57: 324–328
- Cipolletta L, Bianco MA, Marmo R et al. Endoclips versus heater probe in preventing early recurrent bleeding from peptic ulcer: a prospective and randomized trial. *Gastrointest Endosc* 2001; 53: 147–151
- Chung IK, Ham JS, Kim HS et al. Comparison of the hemostatic efficacy of the endoscopic hemoclip method with hypertonic saline-epinephrine injection and a combination of the two for the management of bleeding peptic ulcers. *Gastrointest Endosc* 1999; 49: 13–18
- Gevers AM, De Goede E, Simoons M et al. A randomized trial comparing injection therapy with hemoclip and with injection combined with hemoclip for bleeding ulcers. *Gastrointest Endosc* 2002; 55: 466–469
- Hachisu T. Evaluation of endoscopic hemostasis using an improved clipping apparatus. *Surg Endosc* 1988; 2: 13–17
- Hochberger J, Euler K, Naegel A et al. The compact Erlangen Active Simulator for Interventional Endoscopy: a prospective comparison in structured team-training courses on “endoscopic hemostasis” for doctors and nurses to the “Endo-Trainer” model. *Scan J Gastroenterol* 2004; 39: 895–902
- Lin HJ, Hsieh YH, Tseng GY et al. A prospective, randomized trial of large- versus small-volume endoscopic injection of epinephrine for peptic ulcer bleeding. *Gastrointest Endosc* 2002; 55: 615–619
- Hepworth CC, Kadirkamanathan SS, Gong F, Swain CP. A randomised controlled comparison of injection, thermal, and mechanical endoscopic methods of haemostasis on mesenteric vessels. *Gut* 1998; 42: 462–469
- Randall GM, Jensen DM, Hirabayashi K, Machicado GA. Controlled study of different sclerosing agents for coagulation of canine gut arteries. *Gastroenterology* 1989; 96: 1274–1281
- Swain CP, Mills TN, Shemesh E et al. Which electrode? A comparison of four endoscopic methods of electrocoagulation in experimental bleeding ulcers. *Gut* 1984; 25: 1424–1431
- Harold KL, Pollinger H, Matthews BD et al. Comparison of ultrasonic energy, bipolar thermal energy, and vascular clips for the hemostasis of small-, medium-, and large-sized arteries. *Surg Endosc* 2003; 17: 1228–1230
- Rabenstein T, Schneider HT, Nicklas M et al. Impact of skill and experience of the endoscopist on the outcome of endoscopic sphincterotomy techniques. *Gastrointest Endosc* 1999; 50: 628–636
- Tassios PS, Ladas SD, Grammenos I et al. Acquisition of competence in colonoscopy: the learning curve of trainees. *Endoscopy* 1999; 31: 702–706