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Hemodynamic efficacy of sequential hemoclip application using the Olympus HX-110/610 reloadable clipping device in spurting bleedings

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Background:

Hemoclip application in GI-hemorrhage has proven to be effective. Clinical experience shows that multiple clips are frequently necessary. In 2005, an easily reloadable clip-applicator was introduced. We evaluated the hemodynamic efficacy of this new device.

Material/Methods:

We prospectively compared the new clipping device (Olympus HX 110/610) in a validated experimental setting using the compactEASIE[®]-simulator for GI bleeding. The artificial blood circulation system in the simulator was connected to a pressure transducer. Four investigators of different endoscopic experience (1000–6000 endoscopies) treated 12 bleeding sources each, with up to 6 clips for each bleeding location. Pressures were recorded to objectify the additive effects of sequential clip application on the reduction in vessel diameter. The intervention was abandoned if a maximum measurable pressure of 300 mmHg was achieved.

Results:

Hemoclip application led to a significant increase of peak pressure (91±100 mmHg, p<0.001) and mean pressure (95±99 mmHg, p<0.001), representing a significant reduction in vessel diameter. Pooled data showed a significant stepwise increase in mean and maximum system pressure, resulting in reduction of vessel diameter up to the fifth hemoclip. On average, 5 clips (range 1–6) were used. More experienced endoscopists achieved a higher increase in mean pressure (167 and 118 mmHg vs 72 and 23 mmHg, p<0.05). Mean reloading time was 39 seconds (19–49 sec).

Conclusions:

Sequential application of multiple hemoclips led to an increasing effect, comparable to the results of previous clinical trials. The number of hemoclips applied correlated inversely, but not significantly, with the endoscopist's experience. Expensive single-use clips appear dispensable in view of the short reloading time.

key words:

endoscopic treatment • clip application • endoscopic hemostasis • ulcer bleeding • experimental testing

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BACKGROUND

Peptic ulcers are still the most frequent cause of upper gastrointestinal bleeding [1]. These lesions, especially those with exposed arteries and arterioles, represent a severe medical condition, with significant morbidity and mortality [2]. Endoscopic interventions, such as injection therapy, thermal coagulation and clip application, could reduce the rate of re-bleeding, as well as mortality and the need for surgical intervention [1,3–5]. Consequently, endoscopic treatment emerged as a first line therapy for upper gastrointestinal bleeding. In particular, hemoclip application combined with injection methods has shown to be one of the most effective treatments to achieve hemostasis in peptic ulcer bleedings [6]. Clip application may also prove effective in special indications such as angiodysplasia, and even in esophageal varices [7,8]. However, clinical experience, as well as clinical trials, shows that the application of multiple clips is frequently necessary to achieve bleeding cessation in peptic ulcer bleeding [9–11]. The authors report an average application of 2 to 3, and a range of 1 to 10 clips [6]. Therefore, different technical strategies were used to apply multiple clips: 1) reloadable multiple-use devices; and 2) repeated use of single-use clipping devices with 1 or, recently, even 4 preloaded clips [12]. In 2005, a new reloadable clip applicator (Olympus) was introduced with improved reloading capabilities. The use of this reloadable system is substantially less expensive, which is of special interest due to the increased financial pressure on health care systems worldwide. Thus far, there has been no prospective bench trial on the hemostatic effect of using multiple sequentially applied hemoclips for control of spurting arterial hemorrhage.

This underlying prospective trial evaluated the hemodynamic efficacy of sequential clip application in an established simulation model for upper GI bleeding used by endoscopists of different expertise. Additionally, the functionality of this new device was tested to assess its reliability and efficacy.

MATERIAL AND METHODS

Study design

The study was designed as a prospective experimental trial, comparing endoscopists of different expertise (1000, 1000, 4000 and 6000 diagnostic and therapeutic endoscopies, including at least 100 endoscopic emergency interventions) to induce hemostasis with sequential clip application. Each investigator had applied at least 100 clips in clinical cases. We used the new reloadable clipping device from Olympus (Olympus HX 110/610, Hamburg, Germany) in an established experimental setting with the compactEASIE® simulator equipped with an *ex-vivo* porcine upper gastrointestinal organ preparation for bleeding simulation [13,14].

Experimental setting

The compactEASIE® and the experimental setting were used as described previously [13,14]. As in our prior studies, we used prepared *ex-vivo* porcine stomachs for upper GI-bleeding, with only 4 spurting bleeding sites per stomach (2 at the proximal end and 2 at the distal end of the anterior wall of the corpus) [13]. A special roller pump was

used to perfuse artificial vessels sewn into the wall of the stomach as a simulation of a spurting arterial bleed, comparable to a Forrest Ia bleeding scenario in a clinical setting. The artificial blood circulation system in the simulator was connected to a pressure transducer to objectively assess the hemostatic effect of endoclips applied on the vessel. The baseline pressure of the circuit was calibrated to 80–100 mmHg [13,14].

Four investigators of different endoscopic experience participated in the study. Investigator 1 had performed more than 6000 endoscopies, Investigator 2 more than 4000, and investigators 3 and 4 more than 1000 endoscopies. Each investigator had to treat 12 bleeding sources (3 stomachs with 4 identical allocated bleeding sites). Up to a maximum of 6 clips could be used for each bleeding source. Clip application was abandoned once the maximum measurable mean arterial pressure of 300 mmHg was reached. The reloading time (i.e., removal of the applicator from the endoscope, reloading of a new clip, introduction of the applicator back into the endoscope and repositioning for the next intervention) was documented for every clip. Assistance was provided by an experienced endoscopy nurse with more than 10 years of clinical practice.

The pressure curve of each clip was documented with a Panasonic digital video camera (NV DX 100, Panasonic, Hamburg, Germany). The baseline pressure was recorded 1 minute before the first clip application (pre-interventional pressure), during the sequential clip applications and reloading periods, and 1 minute after the last clip application. Twenty pressure measurements were recorded per minute (i.e., every 3 seconds) in order to identify each of the pre- and the post-interventional pressure levels. Peak pressure was defined as the pressure 3 seconds after clip application, as described in our prior trials [13,14].

An animal use only Olympus GIF Q 160 video endoscope (Olympus Europe, Hamburg, Germany) with Olympus Excera 160 video processor and light source was used in the study.

Primary endpoint

The primary endpoint of the study was bleeding cessation observed during endoscopy, or achieving a maximum systemic pressure of ≥ 300 mmHg (upper limit of the transducer system). Up to 6 hemoclips could be used per bleeding site. As shown previously, the increase of pressure represents a reduction in vessel diameter [14]. Therefore, step-wise increase or decrease in sequential clip application correlates with the change in vessel diameter according to the following formula [14]:

$$\frac{d_1 - d_2}{d_1} = \frac{\sqrt[4]{\frac{1}{P_{1mean}}} - \sqrt[4]{\frac{1}{P_{2mean}}}}{\sqrt[4]{\frac{1}{P_{1mean}}}}$$

Secondary endpoints

Secondary endpoints were: 1) the increase of pressure over time between each clip applied on a bleeding site (ie, effect

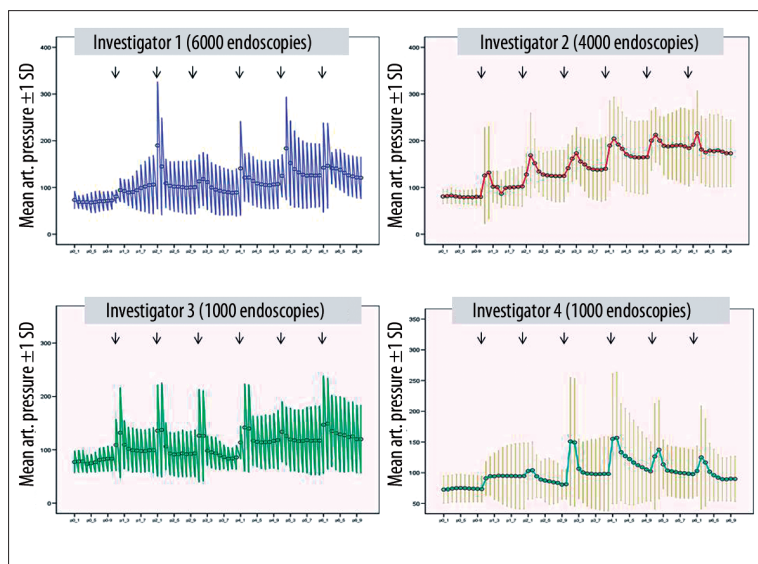


Figure 1. Pressure curves (± 1 standard deviation) for all 12 bleeding sources by investigator. The arrows indicate the time of clip application.

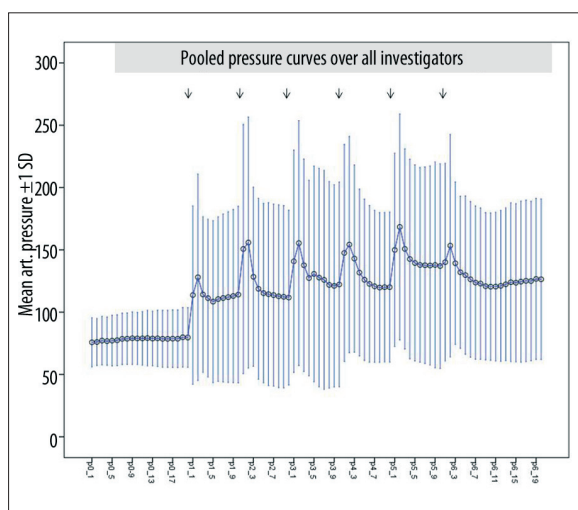


Figure 2. Pooled data of the pressure curves (± 1 standard deviation) for all 48 bleeding sources by investigator. The arrows indicate the time of clip application.

of each clip); 2) the inter-investigator difference in number of clips used to achieve hemostasis in order to demonstrate the influence of endoscopic experience in clip application; and 3) the overall functionality of the clip applicator as assessed by subjective rating of the application procedure and by measuring the reloading time.

Statistical analysis

Based on the results of the former trials [13,14], a sample size calculation was performed using Sample Power 2.0 (SPSS Inc., Chicago, IL, USA). Twelve bleeding sources were deemed sufficient to demonstrate a significant difference for 2-tailed testing with $\alpha=0.05$ and an 85% power for a reduction of vessel diameter of 30% and a standard deviation of 30%. Data analysis was performed with SPSS 15.0 software. With our normally distributed continuous data, we calculated mean values with standard deviation (SD) and range. Student t-test was used for the comparison of

normally distributed paired and unpaired samples. Tukey HSD Post-Hoc testing was used to compare inter-investigator differences. P-values of 0.05 or less were considered to be statistically significant.

RESULTS

Complete pressure curves were documented for all 48 bleeding sources. A total of 249 clips were applied. Investigator 1 (Inv.1) used a total of 59 clips for treatment, Investigator 2 (Inv.2) used 53, Investigator 3 (Inv.3) used 65, and Investigator 4 (Inv.4) used 72 clips. Clip application was stopped earlier (less than the maximum number of 6 clips) in 12 bleeding sources (25% of the bleeding sources) by achieving the maximum measurable systemic pressure of 300 mmHg. In the other 36 bleeding sources, the maximum number of 6 clips was used. Endoscopic bleeding cessation was not observed in any of the experiments. Overall, an average number of 5 clips (range 1–6) were used until hemostasis was achieved, as defined by reaching the primary endpoint with a pressure increase to 300 mmHg.

We found that systemic pressure was increased significantly by sequential clip application. A stepwise increase of system pressure after every clip application (Figure 1, 2), and a reduction of the vessel diameter up to the fifth clip, were observed by pooling the data over all investigators. A significant increase of mean pressure by 95 ± 99 mmHg ($p<0.001$) resulted in a significant reduction of vessel diameter ($13\pm 12\%$, $p<0.001$) following clip application. The peak pressure also increased significantly by 91 ± 100 mmHg ($p<0.001$) and significantly reduced the vessel diameter ($13\pm 12\%$, $p<0.001$) (Table 1).

The mean number of clips used to reach the primary endpoint was 4.58 (Inv. 2, 4000 endoscopies); 5.08 (Inv. 1, 6000 endoscopies); 5.42 (Inv. 3, 1000 endoscopies); and 6.0 (Inv. 4, 1000 endoscopies). Therefore, it appears that more experienced endoscopists tend to require fewer clips to achieve hemostasis, but the difference did not reach statistical significance. More experienced endoscopists achieved a higher mean pressure increase (167 and 118 mmHg vs 72 and

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Table 1. Increase of systemic pressure and reduction of vessel diameter by investigator.

	Mean pressure increase (mmHg \pm SD)	p-value*	Mean reduction of vessel diameter (% \pm SD)	p-value*	Maximum pressure increase (mmHg \pm SD)	p-value*	Maximum reduction of vessel diameter (% \pm SD)	p-value*
All investigators	95 \pm 99	<0.001	14 \pm 12	<0.001	91 \pm 100	<0.001	13 \pm 12	<0.001
Inv. 1	118 \pm 102	0.002	18 \pm 11	<0.001	93 \pm 115	0.017	13 \pm 13	0.006
Inv. 2	167 \pm 100	<0.001	22 \pm 12	<0.001	146 \pm 92	<0.001	20 \pm 10	<0.001
Inv. 3	72 \pm 88	0.016	10 \pm 13	0.018	95 \pm 107	0.011	13 \pm 12	0.005
Inv. 4	23 \pm 40	0.068	5 \pm 10	0.091	30 \pm 44	0.042	7 \pm 10	0.031

* Students t-test for paired samples, significant results in bold letters; p-values represent the comparison of pre and postinterventional values.

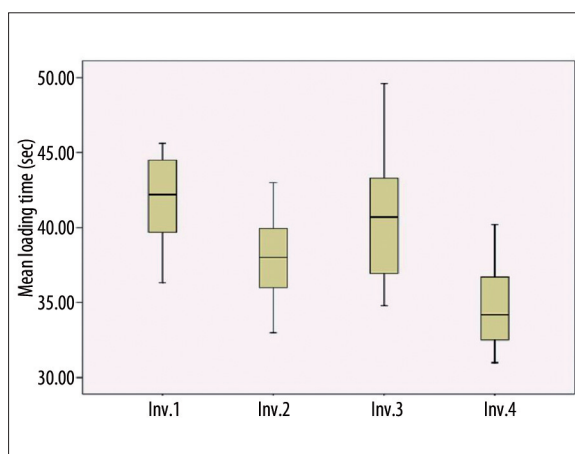


Figure 3. Reloading time by investigator representing the time for mounting of a new clip, reintroduction of the applicator into the endoscope and positioning for new clip application.

23 mmHg; $p < 0.05$) and a significantly higher reduction of vessel diameter ($p = 0.005$ and $p = 0.029$). The results of each investigator are shown in Table 1, illustrating that the less experienced endoscopists had a lower increase of mean and peak pressures.

Mean reloading time was on average 39 seconds (19–49 sec). Inv. 2 had significantly shorter reloading times compared to Inv. 1 ($p = 0.046$) and Inv. 4 compared to Inv. 1 and Inv. 3 ($p < 0.001$) (Figure 3). Differences in reloading time resulted mainly from differences in time required to introduce the endoscope and repositioning, since the other parts of the reloading procedure were performed by the same nurse (Figure 3).

DISCUSSION

In this prospective experimental study, we tested sequential clip application to induce hemostasis in a simulation model for upper GI bleeding. We demonstrated that sequential clip application led to a significant cumulative increase in system pressure. Therefore, the underlying study confirms the clinical experience that an ineffective hemostasis by the first clip can be compensated for by the consecutive application

of additional clips. Based on our results, the beneficial effect of using more clips can be noticed until the number of 5 clips is reached. The application of the sixth clip did not lead to a significant increase of pressure or reduction of the vessel diameter. This observation may be explained by the experimental setting of this study. The investigators treated a single vessel per lesion, visible above the mucosal surface passing through the wall in a perpendicular direction. This may explain why only a limited number of clips were used to reduce the vessel diameter. In clinical situations, the bleeding vessel may run at a shallower angle inside the wall, making it more challenging to achieve compression of the entire vessel. Clip application may possibly also be effective just beside a visible vessel. Additionally, clip application in ulcers is often impeded by slipping of the clip branches over the rough and scarred ulcer base during the closing procedure, resulting in malposition of the clip.

In the clinical setting, hemoclip application is one of the best modalities in active bleeding with a visible vessel [6]. Imprecise or insufficient clip application can result in an accidental laceration of the vessel, caused by unfavorable tension effect on the surrounding tissue. In our experimental setting, in some cases we observed a decrease of pressure after clip application. This phenomenon corresponds with previously described clinical situations [14]. In clinical studies, an average of 2 to 3 clips were used to stop bleeding [9–11], but, in difficult cases, up to 10 clips have been used to achieve hemostasis [15]. Patients with spurting arterial bleeding required on average more clips than patients with oozing bleeding [11]. The number of clips needed to achieve hemostasis has been found to be lower in other studies compared to ours [9,11]. In none of the scenarios did we observe a complete cessation of bleeding, perhaps due to the experimental setting of this study. The artificial blood flow generated by the roller pump resulted in systemic pressures of more than 300 mmHg, which does not correspond to the hemodynamics of a real patient. In a clinical setting, a hemostatic effect is achieved once the vascular compression on the bleeding vessel reaches supra-systemic pressures (above approximately 120 mmHg systolic blood pressure) [13,14]. However, the experimental setup allowed us to objectively assess the hemostatic capability of clip application exceeding clinical requirements. Hepworth et al. demonstrated, in an experimental study,

that only mechanical methods such as clip application are effective in control of bleeding from vessels exceeding a diameter of 2 mm [16]. A clinical trial comparing the application of different numbers of clips in immediate and prolonged hemostasis of ulcer bleeding may be warranted.

Furthermore, we showed that the experience of the endoscopist correlated inversely, but not statistically significantly, with the number of clips required to achieve hemostasis. More experienced endoscopists achieved a significantly higher reduction of the vessel diameter. This underlines the observation that hemoclip application is technically more challenging than endoscopic injection [10,13]. A significant degree of training and experience in clip application is required. The development of new clips like the OTSC-clip (Ovesco Endoscopy AG, Tuebingen, Germany) may require less precision in application, based on the fact that more tissue surrounding the bleeding vessel is grasped and adapted due to the larger size of the clip [17]. Proper training can be effectively provided in structured training programs for endoscopic hemostasis using animal part simulators, as demonstrated in our prior studies [18,19].

Despite the effect of the endoscopist's experience on the reduction of vessel diameter, we could not show a significant difference in the number of clips needed to reach the primary endpoint, but only a trend towards a lower number of clips. Therefore, studies with a higher sample size are required to confirm the influence of endoscopic experience to a greater statistical power.

We found no difference in functionality of this new reloadable device between more or less experienced investigators. The overall assessment shows high satisfactory rating by the investigators and the assisting nurse. The reloading time, which included the time for repositioning, was very short (39 sec; 19–49 sec) and may not be much longer than using a pre-mounted disposable device, since this has to be unpacked before its use. Therefore, single-use clips appear dispensable. Nevertheless, there has been no experimental trial comparing reloadable, disposable and newly developed disposable devices with 3–4 pre-mounted clips [20] in terms of time required for reloading and repositioning.

Treatment cost is of increasing importance in the health care systems all over the world. Therefore, cost-effectiveness of reloadable and the disposable systems have to be taken into consideration. Reloadable clips (~10€ in Germany) are substantially less expensive than disposable systems (55–95€ in Germany), even though the purchase costs for the slightly more expensive applicator (~600€ in Germany) and the reprocessing cost (~5€ in Germany) have to be taken into account. The investment for the applicator may be compensated if more than 8–15 clips are used, depending on the choice of hemoclip. Therefore, if proper and careful reprocessing of the applicator is guaranteed, this reloadable clip device is time- and cost-effective, especially if it is used regularly and frequently.

Our study has some limitations. First, the sample size is small. Secondly, the EASIE®-simulator uses a roller pump with a higher power and output than observed in clinical cases, which makes the cessation of the bleeding almost impossible [14]. However, this bench setup has proven to be

effective to assess hemostatic equipment in extreme situations to objectively assess their limitations.

CONCLUSIONS

In conclusion, we showed that sequential application of multiple clips for endoscopic hemostasis led to an increasing hemostatic effect, comparable to the results of previous clinical trials. The experience of the endoscopist also plays a major role in achieving hemostasis. Disposable clip application devices appear dispensable in view of the short reloading time of the multiple-use device employed in this study.

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Dr. Maiss and Prof. Schwab have given lectures for Olympus Optical Germany. Dr. Maiss is chairman of the 'Association for Quality-Oriented Training in Endoscopy e.V., Erlangen' who supported the conduct of the underlying study. Dr. Ende, Dr. Zopf, Dr. Heide, Dr. Bernatik, Dr. Wehler and Prof. Hahn have no conflicts of interest or financial ties to disclose.

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