



# Correlation of Treatment of Peptic Ulcer Bleeding by Argon Plasma Coagulation (APC) via Contact Heat Probe Method (heater probe) with Epinephrine Injection

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## ABSTRACT

### BACKGROUND

This clinical investigation aimed to compare the efficacy of treatment of peptic ulcer hemorrhage by argon plasma coagulation (APC) via contact heat probe method (heater probe) along with epinephrine injection.

### METHODS

100 patients who underwent endoscopic treatment, were randomly divided into two groups consisting of 50 patients each. In the first group, an intervention was performed using foot pedal and 2.3 mm and 3.2 mm argon probes placed in a 2 to 8 mm distance of delivery place leading to plasma coagulation, sufficient necrosis and hemostasis. In the second group, wound press contact probe was used for wound healing with 15 watts of heat for about 25 degrees, causing coagulation and hemostasis. To evaluate and compare the ulcer treatment in both groups, the patient progress results were monitored for a period of one month from the day of discharge. Statistical analyses of data were performed using SPSS software version 22 along with Chi-square test and T-test.

### RESULTS

No significant difference observed in two groups in term of age, sex and clinical symptoms, but patients treated with APC method had higher hemoglobin levels ( $p < 0.001$ ). The duration of intervention and abdominal bloating in APC group was significantly higher with two cases of re-admission. In HP group, 3 cases (6.3%) had treatment failure and an average transfused blood was significantly higher in the HP group ( $p < 0.001$ ).

### CONCLUSION

Endoscopy treatment duration was significantly lower in patients treated with the HP method due to separate washing route. HP method seems to be more appropriate for treatment of cases with abdominal bloating, distal gastric lesion and HP bulbs.

### KEYWORDS:

Peptic hemorrhage, Plasma argon, Heat probe, Epinephrine.

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## INTRODUCTION

The upper gastrointestinal bleeding (UGIB) incidence is one of the most common emergency condition associated with the mortality and morbidity with the prevalence of 50-170% per 100,000.<sup>1-3</sup> The incidences responsible for the pathogenesis in the patients includes age, non-steroidal anti-inflammatory drugs, accompanying disease, re-hemorrhage and volume of transfusion, and the choice of treatment.<sup>4,5</sup> Today, it is known that the most common role in



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the inflammatory response is peptic ulcers, resulting in the adverse outcome of the ulcers showing visible vessels with active bleeding, typically causing high-risk wounds.<sup>6</sup> Presently, for GI bleeding, especially peptic ulcer hemorrhage, the endotherapy methods are considered as the first line of treatment. Although, recent advances showed improvements in induction, with many potentialities in therapeutic techniques, including interventions such as injections around the wound, and thermal coagulation. It has been reported, that thermal coagulation has contributed to positive outcome in the treatment by creating an immediate homeostasis and preventing recurrent hemorrhage, whereby heat induces the vessel to coagulate and close the base of the vein through probe heat (HP) or non-contact argon plasma coagulation (APC).<sup>7</sup>

Combination therapy have been recommended and accepted for a promising successful endoscopy efficacy in homeostasis by injection of epinephrine enabling coagulation. However, the APC method is identified to be preferable in comparison to HP, although it is largely unknown and does not have enough research support.<sup>8</sup> Overall, the rate of success of treatment in these two methods have revealed to show some beneficial efficacy and as well as some disadvantages. The beneficial effects of APC include ease of use, fewer side effects, repeatability and minimal tissue damage.<sup>9,10</sup> On the other hand, several researches have revealed comparable rates of success including superficial coagulation, inadequate hemostasis and high cost of this APC method. Moreover, HP method has a lower cost and timing with deeper coagulation than APC, however, it has a higher perforation odds.<sup>11</sup> In an animal study, it was reported that APC-induced damage existed in the muscularis propria region, which was related to the strength, duration, and intensity of the used energy, but the thermal coagulation technique was associated with a higher perforation chance.<sup>12</sup> Remarkably, several methods have been subsequently developed as new treatment methods in the therapeutic implications, and the choice of a therapeutic plan depended on novel technologies for the endoscopic hemostasis.<sup>13</sup> Despite major progress for successful induction in the endoscopic interventions showing tangible improvements, the burden of the cases along with consequent mortality of the disease remain high. Notably, considering the differences in the effectiveness and safety of the two therapeutic treatment of peptic

ulcer and the lack of a comprehensive internal study along with challenges in active bleeding cases, whereby making it difficult to achieve the desired results. In such instances, further investigation can give potential advantages of developing appropriate approach for alternative methods of endotherapy, in order to achieve more effective outcome in controlling GI bleeding.

In this study, we aimed to explore the impact of benefits and symptoms of peptic ulcer bleeding by APC along with epinephrine injection. The contact HP method was performed in conjunction with epinephrine injection, by taking into account the clinical manifestations for achieving greater success in the treatment.

## MATERIALS AND METHODS

This prospective clinical trial study was carried out in 2017 that was conducted in Al-Zahra hospital, Isfahan which is the reference center of gastrointestinal bleeding in the Isfahan province. The target population were the patients with primary symptoms of UGIB referring to the emergency department. This research project was approved by the Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran, for all procedures performed in this study involving human participants. All individual participant included in this study gave their informed consent for the possible side effects of the drugs during treatment process which were explained to the patients.

The inclusion criteria in this study were patients with peptic ulcer bleeding with visible vessel. Exclusion criteria were as follows: UGIB patients, not having peptic ulcer, end-stage patients, coagulation-disordered or advanced disease patients, respiratory and cardiac failure, persistent hemorrhage due to esophageal or gastric malignancies, bleeding with coagulation disorders or those using anticoagulant drugs do not require endoscopic treatment were excluded. The sample size required for the study was estimated at 50 people in each group. The sampling method was non-probabilistic and the patients were randomly divided into two groups of control that were treated by APC and those with HP were in the case group. During this study, 5 patients (2 of the APC group and 3 of the HP group) were not considered in this study, and the total sample size of this research was carried out on 48 patients having treatment with APC and 47 patients having treatment with HP. This study consists of 95

**Table 1: Correlation between two groups regarding distribution of demographic variables, clinical and laboratory initial manifestations of patients.**

| Variables                       | Groups               |                 | p        |
|---------------------------------|----------------------|-----------------|----------|
|                                 | Argon plasma         | Contact thermal |          |
| Mean of age(year)               | 58.23 ± 10.38        | 56.51 ± 17.79   | 0.45     |
| Sex                             | Male                 | 40(83.3)        | 35(74.5) |
|                                 | Female               | 8(16.7)         | 12(25.5) |
| Initial demonstrations *        | * Just hematemesis   | 21(43.8)        | 16(34)   |
|                                 | Just melena          | 21(35.4)        | 16(34)   |
|                                 | Hematemesis & melena | 3(6.3)          | 11(23.4) |
|                                 | Other Symptoms       | 7(14.6)         | 3(6.4)   |
| Mean hemoglobin level (mg / dl) | 9.16 ± 1.9           | 8.76 ± 1.14     | < 0.001  |

\* The bracket numbers represent the percentage and the numbers outside parentheses represent the number.

patients, which were randomly assigned including 75 men (79%) and 20 women (21%).

This study was carried out after the diagnosis of GI bleeding in the patients in the first 24 hours, after endoscopy. The procedure was performed as soon as possible for diagnosis and the need for endoscopic treatment was determined according to the type of ulcer. All endoscopy stages were performed by an expert endoscopist with Olympus GIF1T190 series CEVIS EXERA3 Video GASTROSCOPE GIF-H190 Hamburg, Germany) based on standard protocols.

#### Drug administration:

In the procedure of APC group application, approximately 10 to 15 ml of diluted epinephrine (1/10000) was injected on the four sides of the suspected site of bleeding, and then endoscopic treatment was performed using foot pedal and two probes 2.3 and 3.2 mm of argon gas at a distance of 2 to 8 mm of the desired location, resulting in plasma coagulation, adequate necrosis, hemostasis and hemorrhages. The bleeding site was monitored through the endoscope, and if the hemorrhage stopped completely, the endoscopic treatment was terminated. The current used was 40 to 50 watts in the control group.

In the HP group after injection of epinephrine with the similar conditions as the previous one, a heat-shock probe (HP) on the wound was used in the case group which caused wound coagulation with 15 watts and heating at about 25°C. For the assessment of HP group, an effective initial hemostasis was observed for no bleeding site after the intervention. The necrosis of the wound

developed a flat or whitish area showing sufficient homeostasis. In that case, the procedure was considered to be successful and the endoscopy therapy was terminated. The calculated time of the procedure was considered from the starting point of use of the catheter until it was terminated. The patients progress results involved in this study were monitored in both control and case groups, for a period of one month from the day of discharge. The patient's follow-up survey was conducted to record the possible drug side effects, clinical complications or re bleeding until the completion of the treatment period or the death of the patients. It is worth noting that according to the protocol on the use of dual wound healing in both groups, epinephrine injection was used. Statistical analysis was carried out by using SPSS software version 22 and analyzed by Chi-square test and T-test. The significance level of *p*-value was considered less than (*p* < 0/001).

#### RESULTS

The clinical results of these research are presented in the following three tables. According to table 1, the distribution of demographic variables and laboratory tests and clinical manifestations of patients in both groups was illustrated. No significant difference was observed between the two groups in term of age, sex and clinical symptoms, but patients treated with APC method had higher hemoglobin levels (*p* < 0.001).

According to the results of endoscopy, the most common anatomical location of the site of bleeding or wound in both APC and HP regions was observed to be D1 (25 and 22 cases respectively) and antrum (12 and 11 cases

**Table 2:** Comparison between two groups regarding the frequency distribution of the anatomical location of the wound.

| Wound location | Group                      |                               | <i>P</i> |
|----------------|----------------------------|-------------------------------|----------|
|                | Argon plasma (Number = 48) | Contact Thermal (number = 47) |          |
| Cardia         | 3(6.3)                     | 3(6.4)                        | 0.08     |
| Fundus         | 3(6.3)                     | 0(0)                          |          |
| Body           | 2(4.2)                     | 10(21.3)                      |          |
| Antrum         | 12(25)                     | 11(23.4)                      |          |
| D1             | 25(52.1)                   | 22(46.8)                      |          |
| D2             | 3(6.3)                     | 1(2.1)                        |          |

respectively) showing no significant difference between the two groups ( $p = 0.08$ ). In the both the groups, the wounds showed visible vessels.

Regarding table 2, the most common anatomical location of the wound is summarized on bases of endoscopic monitoring. It should be noted that in 7 patients (5 of the APC group and 2 of the HP group), the anatomical site of the wound was D1 and D2.

As it is seen in table 3, the effects of two selected modalities of APC and HP are summarized along with the site of bleeding. The patients progress results involved in this study were monitored and follow up in both control and case groups, for a period of one month from the day of discharge. During the patient's follow-up period no specific complication was observed, such as no cases of death casualty, re-hemorrhage, and re-endoscopy and wound perforation in both the two groups but there were three cases (3.6%) of treatment failure in the HP group, which required the use of other modalities. However, the duration of endoscopy and the presence of abdominal bloating and anesthesia were eight hours. The procedure period was significantly lower in patients treated with the HP method (Table 3).

## DISCUSSION

Due to high prevalence of the upper GI bleeding incidence, which is recognized as a common emergency risk factor and problem responsible for the mortality and morbidity in patients. In the existing paradigm and in connection with the management of endoscopic treatment methods, particularly for the more serious manifestations of GI bleeding incidence continue to be hypothetical, requiring further more research to create the extent and importance of these different methods. Endoscopic hemostasis success depends

not only on the procedural proficiency of the performing endoscopists but also depends on the required hemostatic tools in order to gain the desired results.<sup>13</sup> Different methods of endoscopic treatment have been considered to reduce repetition of bleeding, surgery, mortality rates, and therefore, endoscopic therapies is a procedure that is employed in acute GI bleeding. Many novel endoscopic methods have been reported in the recent decades, for hemostasis of GI bleeding like heat probe coagulation, direct injection of fluids like use of diluted epinephrine or either distilled water into the bleeding lesion, endoscopic hemostatic clips, and APC.<sup>14</sup> Several studies have reported about the capability of these methods in GI bleeding.<sup>15-18</sup>

Generally injection therapy is used in an endoscopic treatment for ulcer bleeding, with a proportion of 1:10000 diluted epinephrine as the injected solution.<sup>18</sup> For initial bleeding control, the mechanical compression of injected solution plays the most significant role, some studies have reported that large amount of endoscopic injection therapy can help in preventing re-bleeding by the same mechanism as compression effect.<sup>19,20</sup> Due to the above reason the injection therapy was used in this study for treatment of ulcer bleeding. In the present study, no significant difference was observed in the two groups in terms of age and sex distribution and clinical manifestations, and the confounding effect of these factors on results of the study was not observed. The patients treated with APC method had higher hemoglobin levels ( $p < 0.001$ ).

Accelerated or induced bleeding (5%) and perforation (2% to 3%) was reported as a complication of the HP method<sup>14,15</sup> and the initial hemostasis was reported to be 78 to 100%.<sup>16,17</sup> Our finding showed that the success rate of treatment of the HP group was 96% and the APC group was 100% and these were not higher than the other studies. However, no significant difference between the two groups was observed, but in 3 patients treated with HP method, treatment failure induction bleeding was observed which was not higher as compared to other studies,<sup>14-16</sup> and our clinical findings correlates with the data referred by Cipolletti and the success rate of treatment in the APC was more favorable.<sup>16</sup>

Meanwhile, some studies have reported the efficacy of APC for treating bleeding peptic ulcer showing similar efficacy to heat probe in terms of initial homeosta-

**Table 3:** Comparison between two groups regarding the frequency distribution of need for blood transfusions, injected blood volume, feeling of bloating and abdominal pain.

| Variables                                   | Group                      |                               | P       |
|---|----------------------------|-------------------------------|---------|
|   | Argon plasma (number = 48) | Contact Thermal (number = 47) |         |
| Frequency (%) requires a blood transfusion  | 30(62.5)                   | 36(76.6)                      | 0.14    |
| Average unit of blood transfused            | 1.08 ± 1.32                | 2.36 ± 1.85                   | < 0.001 |
| Average procedure time (min)                | 1.08 ± 4.23                | 1.19 ± 3.64                   | 0.013   |
| Average hospital stay (day)                 | 1.24 ± 4.56                | 0.89 ± 4.77                   | 0.001   |
| Treatment failure (bleeding recurrence)     | 0(0)                       | 3(6.3)                        | 0.24    |
| Need to be re-admitted                      | 2(4)                       | 0(0)                          | 1       |
| Bloating and abdominal pain after endoscopy | 26(54.2)                   | 16(34)                        | 0.063   |
| Re- endoscopy due to bleeding               | 0(0)                       | 0(0)                          | 1       |

sis and the prevention of recurrent bleeding<sup>18,21</sup> which was similar to our data referred in this findings. The duration of procedure and the degree of abdominal pain in the intervention group with APC were more than the case group, which was observed that the HP method was superior and showed advantageous to the APC method at these two angles. Since the most common problem after upper endoscopy was bloating and abdominal discomfort which was reduced by use of HP method in our study and this was a significant point in comparison to data referred by this study.<sup>17</sup> It should be noted that less process time in the HP group may be justifiable for having a separate route and no need for replacement of the catheters. In this study, follow up survey of a month after the discharge of patients, did not show any specific complication except for the need for two re-admissions in the APC group, which did not show any difference in the outcome of the patients. After discharge of patients, one month's follow-up and survey was carried out showing superiority of our study in comparison to similar research. The point here is that the study of pain and discomfort was performed by experienced gastroenterologists and trained assistants by following the standard protocols as administered in patients in term of complication of treatment methods. Notably, to the best of our knowledge, this study was the first to investigate the safety and effectiveness between two treatment methods, and this is the advantage of the current study.

In addition, the average amount of blood transfusion in HP group was significantly higher (Table 3). The chance of recurrent hemorrhage in the HP procedure was

0 to 18%,<sup>15-17</sup> although in our study was 0%. The risk of perforation in APC was reported at approximately 0.3%.<sup>9</sup> However, this potential risk can be considered as a disadvantage of APC. In the present study, two cases of argon patients needed hospital re-admission due to gastrointestinal bleeding for the same cause, but there was no such problem in the other way.

Endoscopic treatment for UGIB can be challenging and is not always easy in some cases, as bleeding may be found in places that can be difficult to access, such as the duodenal posterior wall or proximal lesser curvature of the stomach.<sup>22</sup> It is important to note that studies have shown that access to bleeding places with difficult anatomy (such as small curvature) by use of the APC method is better than the contact method.<sup>18,21</sup> However, in the present study, the supporting evidence was the prevalence of most ulcers in the duodenal bolus, attenuating the shorter duration of the procedure can be justified. In future, a large randomized study, is suggested to clarify the effectiveness and safety of these two treatment methods in high-risk bleeding ulcers. The prevalence of anatomical location of the site of bleeding may pave the way for a further promising and comprehensive study of therapeutic approach of research methods by choosing a larger sample size of other GI ulcers.

## CONCLUSIONS

This finding of endoscopic therapy investigation with HP method, considering the short duration of intervention, the ease of use, the lower incidence of bloating after the endoscopy treatment in patients with underlying



diseases and those with a history of abdominal bloating was significantly lower as compared to APC method. HP method maybe more suitable and appropriate intervention choice in treatment for having good beneficial effect in preventing and controlling of GI bleeding caused by UGIB. However, with the acceptable results of this investigation, further researches with larger sample sizes regarding other GI ulcers may be able to clarify more comprehensively the differences between these two methods of APC and HP.

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### ETHICAL APPROVAL

This study with human participants was performed according to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed Consent

All individual participants attending in this study gave their informed consent.

### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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