Effect of Antiplatelet Therapy on Surgical Blood Loss and Post-Pancreatectomy Hemorrhage in Patients Undergoing Pancreatoduodenectomy

Takahisa Fujikawa, Hiroshi Kawamoto, Akira Tanaka

AIM: The aim of the study was to assess the feasibility and safety of pancreatoduodenectomy (PD) in patients with preoperative antiplatelet therapy (APT) for arterial thromboembolic risks.

METHODS: Consecutive 100 patients receiving PD at our institution between 2005 and 2016 were retrospectively reviewed. APT was regularly used in 31 patients (31%) in this series. Our perioperative management (“Kokura Protocol”) included maintenance of preoperative aspirin monotherapy and early postoperative reinstitution in patients at high thromboembolic risks. Outcome variables of patients with APT (APT group) were compared with those of patients without APT.

RESULTS: This series included 31 pancreatic cancer, 27 bile duct cancer, 19 ampullary cancer, 13 intraductal papillary mucinous neoplasms, and 10 others. In APT group, 18 (18%) required preoperative continuation of APT. APT group showed significantly high frequency of history of cerebral infarction and percutaneous coronary intervention. Totally 18 significant pancreatic fistulas (grade B,C, 18%) were observed but no perioperative death was experienced. There was only 1 thromboembolic event (1.0%, cerebral infarction) in a whole cohort, whereas increased surgical blood loss ($\geq 1,000$ mL) and post-pancreatectomy hemorrhage (PPH) occurred in 11 (11%) and 6 (6.0%, totally grade B), respectively. Multivariate analysis showed that high body mass index ($\geq 30$ kg/m$^2$) is the only significant risk factor for both increased blood loss and PPH (risk ratio = 13.64 and 27.27, $p < 0.05$), whereas either APT or preoperative aspirin continuation did not affect perioperative bleeding complications.

CONCLUSION: Even in APT-burdened patients with arterial thromboembolic risks, PD is safely performed under the Kokura Protocol without any increase of blood loss and PPH, although this patient population is still challenging and should be rigorously managed to prevent both bleeding and thromboembolic complications.

Key words: Antiplatelet therapy; Bleeding complication; Harmonic FOCUS®, Pancreatoduodenectomy, Pinch-burn-cut technique; Thromboembolic complication

© 2018 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Fujikawa T, Kawamoto H, Tanaka A. Effect of Antiplatelet Therapy on Surgical Blood Loss and Post-Pancreatectomy Hemorrhage in Patients Undergoing Pancreatoduodenectomy. Journal of Gastroenterology and Hepatology Research 2018, 7(2): 2561-2568 Available from: URL: http://www.ghrnet.org/index.php/joghr/article/view/2237

INTRODUCTION: Lately, patients who have histories of cardiovascular or
cerebrovascular diseases have been seen more often with aging of patients, and those patients frequently receive antiplatelet therapy (APT) for the purpose of primary and secondary prevention of arterial thromboembolic diseases. While indications for APT use have expanded, antithrombotic management during gastrointestinal and/or hepatobiliary-pancreatic surgery is still difficult and often bothersome because of increased risks of perioperative bleeding or thromboembolic events \[1-4\]. In our institution, a protocol of risk stratification and perioperative antithrombotic management has been established for APT-burdened patients (“Kokura Protocol”), which includes preoperative continuation of aspirin monotherapy in patients with high thromboembolic risks \[5, 6\]. So far, the safety of both open and laparoscopic abdominal surgeries under the Kokura Protocol have been reported with relatively low rates of bleeding and thromboembolic complications \[5-7\].

Pancreaticoduodenectomy (PD) is a highly invasive procedure and may expose patients to high risks of severe postoperative complications. Although mortality after PD has markedly decreased to less than 5% thanks to advance in operative techniques and perioperative management \[8, 9\], postoperative complication rates still remain high at 18-50\% \[8-11\]. The common types of postoperative complications are postoperative pancreatic fistula (POPF), deep surgical site infection (SSI), and post-pancreatectomy hemorrhage (PPH). PPH is related to a high mortality rate of up to 60\% \[8-10\], and its incidence is at 3-16\% after overall pancreatic resection \[16-21\], and at 8-29\% after PD \[13-14\]. When PD is performed especially in APT-burdened patients with high thromboembolic risks, rigorous perioperative antithrombotic management and meticulous intraoperative hemostatic procedures are required to prevent both bleeding and thromboembolic complications. To date, the effect of APT on perioperative complications, especially on surgical blood loss and PPH, in patients undergoing PD still remains unclear.

The aim of this study is to review consecutive 100 patients undergoing PD and to assess the safety and feasibility of PD in thromboembolic risk patients receiving APT.

**PATIENTS AND METHODS**

Between March 2005 and April 2016, totally 506 patients received major hepatobiliary and pancreatic surgery at our institution, among which pancreatic resection was performed in 155 patients. After excluding patients receiving distal or other pancreatectomy, 100 consecutive patients undergoing PD were included in the current study (Figure 1). Background, perioperative and outcome variables of the patients were collected through a standardized review of the electronic surgery database as well as hospital and clinic charts. The status of patients’ symptoms and functions regarding ambulatory status was described according to the ECOG Scale of Performance 

- **Safety of pancreaticoduodenectomy in antiplatelet-burdened patients**

Pancreaticoduodenectomy (PD) is a highly invasive procedure and may expose patients to high risks of severe postoperative complications. Although mortality after PD has markedly decreased to less than 5% thanks to advances in operative techniques and perioperative management \[8-10\], postoperative complication rates still remain high at 18-50\% \[8-11\]. The common types of postoperative complications are postoperative pancreatic fistula (POPF), deep surgical site infection (SSI), and post-pancreatectomy hemorrhage (PPH). PPH is related to a high mortality rate of up to 60\% \[8-10\], and its incidence is at 3-16\% after overall pancreatic resection \[16-21\], and at 8-29\% after PD \[13-14\]. When PD is performed especially in APT-burdened patients with high thromboembolic risks, rigorous perioperative antithrombotic management and meticulous intraoperative hemostatic procedures are required to prevent both bleeding and thromboembolic complications. To date, the effect of APT on perioperative complications, especially on surgical blood loss and PPH, in patients undergoing PD still remains unclear.

The aim of this study is to review consecutive 100 patients undergoing PD and to assess the safety and feasibility of PD in thromboembolic risk patients receiving APT.

**PATIENTS AND METHODS**

Between March 2005 and April 2016, totally 506 patients received major hepatobiliary and pancreatic surgery at our institution, among which pancreatic resection was performed in 155 patients. After excluding patients receiving distal or other pancreatectomy, 100 consecutive patients undergoing PD were included in the current study (Figure 1). Background, perioperative and outcome variables of the patients were collected through a standardized review of the electronic surgery database as well as hospital and clinic charts. The status of patients’ symptoms and functions regarding ambulatory status was described according to the ECOG Scale of Performance Status \[17\].

Surgical procedures in this cohort included classical PD (PD with two-thirds distal gastrectomy), pylorus-preserving PD, and subtotal stomach-preserving PD (SSpPD). Our technical aspects during PD, especially in antiplatelet-burdened patients, was previously reported with satisfactory short-term outcomes \[18\]. Briefly, we used modified Pinch-Burn-Cut (PBC) technique (the technique from living-donor liver transplantation \[19,20\]) in combination with ultrasonically activated shears with a curved thin tip (Harmonic FOCUS®, Ethicon Endo-Surgery, Cincinnati, OH) \[21\] during PD to minimize surgical blood loss and this modality was also useful even under continuation of preoperative aspirin monotherapy. All procedures were performed by or under the guidance of one of the attending surgeons at our institution.

We established and conducted our perioperative antithrombotic management system for abdominal and general surgery, which consisted of thromboembolic risk stratification and perioperative antithrombotic management protocol (“Kokura Protocol”), and have shown that both open and laparoscopic abdominal surgeries in patients with antiplatelet therapy can be performed safely under the Kokura Protocol \[17\]. The protocol generally consisted of interrupting APT one week before surgery and early postoperative reinstitution in low thromboembolic risk patients, although in case of high thromboembolic risks such as patients with drug-eluting coronary stent (DES) implantation or those with cerebrovascular reconstruction within 3 months, aspirin monotherapy was continued preoperatively, followed by early postoperative reinstitution.

Postoperative complications were assessed and categorized by Clavien-Dindo classification (CDC) \[22\] and CDC class II or higher was considered significant. POPF was defined according to the definition of the International Study Group of Pancreatic Fistula (ISGPF) \[23\]. PPH was defined according to the definition of the International Study Group of Pancreatic Surgery (ISGPS) \[20\], and the condition was classified on the basis of three parameters; time of onset, location, and severity. Three different grades of PPH were classified using these parameters. Postoperative thromboembolic complication was defined as previously described \[21\], including myocardial infarction, cerebral infarction, mesenteric infarction, and pulmonary thromboembolism. Operative mortality included death within 30 days after surgery.

The primary outcome included excessive intraoperative blood loss (1,000 mL or more), PPH, and postoperative thromboembolic complications. Background characteristics, perioperative factors, and outcome variables were compared between patients receiving APT (APT group) and those without APT (non-APT group). Univariate and multivariate analyses were performed to assess the risk factors for excessive intraoperative blood loss and PPH.

The categorized data in each group were compared by chi-square or Fisher’s exact probability test. Continuous variables in the characteristics were expressed as a median with range and compared by Student’s T test or Kruskal-Wallis test. Non-parametric variables were also compared using Kruskal-Wallis test. Multivariable logistic regression analyses were performed to determine risk factors affecting excessive intraoperative blood loss or PPH. Statistical significance was set at \( p < 0.05 \). Data were analyzed using the SPSS package software.

Our institutional review board approved the current study.
RESULTS

Among patients in the current study, 31% (31/100) of patients undergoing PD received APT. Table 1 shows background characteristics of patients in each group. The patients in the cohort were totally Asian. The median ages in the APT and non-APT groups were 73 and 73 years, respectively. History of percutaneous coronary intervention (PCI, \( p < 0.001 \)) and coronary artery bypass graft (\( p = 0.028 \)), and history of cerebral infarction (\( p = 0.003 \)) were more common in the APT group. There was also a significant difference between the groups in the rate of anticoagulation therapy (\( p = 0.044 \)) and perioperative heparin bridging (\( p = 0.010 \)). In the APT group, 18 patients (18.0%) were classified into high risk for arterial thromboembolism, and were managed with preoperative continuation of aspirin monotherapy.

Table 2 shows operative procedures and postoperative morbidity of patients in each group. The current series included pancreatic cancer in 31 (31.0%), bile duct cancer in 27 (27.0%), ampullary cancer in 19 (19.0%), and intraductal papillary mucinous neoplasms in 13 (13.0%). There was no difference in the type of diseases between the groups (\( p = 0.091 \)). The most prevalent types of the operative procedure, pancreatic reconstruction, and texture of the remnant pancreas were SSPPD (95.0%), pancreatico-jejunostomy (93.0%), and soft pancreas (71.0%), respectively; no significant difference was observed in these factors between the groups. The duration of operation, estimated surgical blood loss, rates of intraoperative transfusion were also identical between the groups. Increased surgical

| Variables                          | Total (\( n = 100 \)) | APT (\( n = 31 \)) | non-APT (\( n = 69 \)) | \( p \) |
|------------------------------------|------------------------|-------------------|------------------------|-------|
| Age, y, median (range)             | 73 (37-86)             | 73 (60-84)        | 73 (37-86)             | 0.357 |
| Gender, n (%)                      | 0.65                   |                   |                        |       |
| Female                             | 33 (33.0)              | 9 (29.0)          | 24 (34.8)              |       |
| Male                               | 67 (67.0)              | 22 (71.0)         | 45 (65.2)              |       |
| BMI                                | 0.32                   |                   |                        |       |
| < 30 kg/m\(^2\)                    | 95 (95.0)              | 51 (100.0)        | 44 (62.9)              |       |
| \( \geq \) 30 kg/m\(^2\)          | 5 (5.0)                | 0 (0.0)           | 5 (7.2)                |       |
| Performance status, n (%)          | 0.7                    |                   |                        |       |
| 0.1                                | 92 (92.0)              | 28 (90.3)         | 64 (92.8)              |       |
| 2.3                                | 8 (8.0)                | 3 (9.7)           | 5 (7.2)                |       |
| Concurrent diseases, n (%)         |                        |                   |                        |       |
| Diabetes mellitus                  | 27 (27.0)              | 10 (32.3)         | 17 (24.6)              | 0.279 |
| Hx of congestive heart failure     | 6 (6.0)                | 4 (12.9)          | 2 (2.9)                | 0.072 |
| Coronary artery disease            |                        |                   |                        |       |
| Hx of PCI                          | 15 (15.0)              | 15 (48.4)         | 0 (0.0)                | < 0.001 |
| Hx of CABG                         | 3 (3.0)                | 3 (9.7)           | 0 (0.0)                | 0.028 |
| Hx of cerebral infarction          | 11 (11.0)              | 8 (25.8)          | 3 (4.3)                | 0.003 |
| Current hemo-/peritoneal dialysis  | 4 (4.0)                | 1 (3.2)           | 3 (4.3)                | 1     |
| Anticoagulation therapy, n (%)     | 12 (12.0)              | 7 (22.2)          | 5 (7.2)                | 0.044 |
| Periop. Heparin bridging, n (%)    | 14 (14.0)              | 9 (29.0)          | 5 (7.2)                | 0.01  |
| Preop. Aspirin continuation, n (%) | 18 (18.0)              | 18 (58.1)         | -                      | -     |

*Abbreviations: APT, antiplatelet therapy; BMI, body mass index; PCI, percutaneous coronary intervention, CABG: coronary artery bypass graft, periop.; perioperative, preop.; preoperative.*

Figure 2  Forest plots showing risk ratios of increased surgical blood loss (A) and postpancreatectomy hemorrhage (B), n=100.

Abbreviations: CI, confidence interval; HR, hazard ratio; APT, antiplatelet therapy; BMI, body mass index; PCI, percutaneous coronary intervention.
blood loss (≥ 1,000 mL) occurred in 11 (11.0%) patients, but no case suffering uncontrollable excessive intraoperative bleeding due to the continuation of APT and requiring platelet transfusion was experienced in the APT group.

Postoperative complications developed in 41.0% of overall patients. The most common complication was POPF (18.0%, Grade B/C according to ISGPF definition); the occurrence of POPF was similar between the groups. There was only 1 thromboembolic event (1.0%, cerebral infarction) in a whole cohort. PPH occurred in 6 patients (6.0%); all 6 PPH was classified into Grade B including 2 cases suffering uncontrollable excessive intraoperative bleeding due to the continuation of APT and requiring platelet transfusion was experienced in the APT group.

Univariate and multivariate analyses for increased surgical blood loss and PPH were performed and shown in Table 3 and Figure 2, respectively. High body mass index (BMI ≥ 30 kg/m²) was the only significant risk factor for increased surgical blood loss on both univariate and multivariate analyses [risk ratio (RR) = 13.64, p = 0.011], although use of APT or preoperative continuation of aspirin was not significantly associated. Concerning PPH, history of PCI was significantly associated on univariate analysis, although only high BMI was independently associated with PPH on the multivariate analysis (RR = 27.27, p = 0.038). Neither APT use nor preoperative aspirin continuation was a significant risk factor for PPH.

**DISCUSSION**

Our study demonstrated that the current cohort comprised 100 patients undergoing PD, among which 31% were receiving APT. According to our perioperative management protocol, aspirin monotherapy was maintained perioperatively in case of high thromboembolic risks. The rate of thromboembolic event is only 1.0% in the whole cohort, whereas the occurrence of increased blood loss and PPH were 11% and 6%, respectively. Multivariate analysis showed that high BMI is the only significant risk factor for both increased blood loss and PPH, but either use of APT or preoperative aspirin continuation did not affect bleeding complications. Thus, PD is performed safely without increase of surgical blood loss, PPH, or thromboembolic complications even in APT-burdened patients.

Since APT for prevention of cardiovascular/cerebrovascular events is widely used in patients receiving APT frequently receive surgical procedures. About 5-15% of patients who received coronary stent
implantation have undergone non-cardiac surgery within 2 years. Premature discontinuation of antplatelet agents is the known risk factor for late coronary stent thrombosis, which is rare but life-threatening sequelae with the mortality rate at 9.45%.[28-30]. We have to balance bleeding risk against thromboembolic risk in patients undergoing APT. Current guidelines of post-PCI surgical intervention specify that in the perioperative period, the continuation of APT, but not using heparin bridging, should be considered, particularly in high thromboembolic risk patients.[31-34]. In addition, recent trends in several guidelines clearly show that prevention of thromboembolism is more important since it might cause severe postoperative life-threatening complications.[35-38]. If the thromboembolic risk is low, interruption of antplatelets might be possible. However, if the risk of thromboembolism is high, continuation of at least single APT is adequate. Considering those circumstances, we have established our own perioperative antithrombotic protocol ("Kokura Protocol"), and shown that both laparoscopic and open abdominal surgery can be safely performed even in APT-prescribed patients under the Kokura Protocol.[7-]. The current study also demonstrated that the Kokura Protocol is valid and feasible in the setting of performing PD, resulting in satisfactorily low incidence of thromboembolic events and PPH even under the high prevalence of APT-burdened patients.

Concerning perioperative arterial thromboembolic complications including cerebrovascular stroke or major adverse cardiovascular event (MACE), the rates of perioperative thromboembolisms vary depending on differences in patient population, study design, and changing clinical practices. In cardiac, neurologic, and carotid surgery, the incidence of perioperative stroke is known to be high (2.2-5.2%)[39,40]; the reported incidence of stroke following noncardiac, nonneurosurgical surgery ranges between 0.1-0.4% overall, and 2.9-3.5% in patients at risk of perioperative stroke.[41-44]. In consideration of thromboembolic events after PD, the prevalence of thromboembolism seems to be higher. Haigh et al. reported that analyzing 2,610 patients undergoing PD from the American College of Surgeons-National Surgical Quality Improvement Program database, a rate of MACE after PD in the whole cohort was at 1.9%, and that in the elderly (aged > 70 years) was at 3.0%.[45]. The current study demonstrated that the incidence of perioperative thromboembolic complication was maintained at 1.0%, a relatively low rate compared to the previous report. Thus, it is suggested that PD is performed safely under the Kokura Protocol, with successful inhibition of thromboembolic events even in patients having thromboembolic risks.

Reduction of intraoperative blood loss and PPH is another important goal when PD is performed, and various technical development has been introduced.[31,32,46]. In our institution, the rate of APT-burdened patients requiring major hepatobiliary and pancreatic surgery is almost 30-40%, and the number is expected to be increasing. For this reason, a simple but strong hemostatic devices and technique should be adopted and utilized especially in this critical patient population. In this aspect, the combination of modified PBC technique and Harmonic FOCUS® is one of the preferred technical options during PD to minimize surgical blood loss.[18]. It was reported that several operations such as hip arthroplasty, neurosurgical surgery, or gastrectomy might be associated with increased surgical blood loss and postoperative hemorrhage when performed in patients receiving antithrombotic agents.[47,48]. Concerning the pancreatic surgery, however, only one report from Japan reported the effect of antplatelets and anticoagulation on PPH after pancreatic resection[17], and they concluded that rigid thromboplasty including antplatelet continuation and heparin bridging was significantly related to PPH. The incidence of PPH in their study was relatively high with the rate of 11.4% (18/158), among which 7 (4.4%) patients were grade C and PPH-associated mortality rate was 16.7%. In the current study, the incidence of PPH in the whole cohort was 6.0%, and there was no patient with grade C PPH and the mortality was zero; it is concluded that use of APT and occurrence of PPH was independent in the current series. Active intervention for rigid hemostasis using several techniques and devices could reduce intraoperative surgical blood loss, as well

### Table 3 Univariate analysis of increased surgical blood loss (>=1,000 mL) and postpancreatectomy hemorrhage in the cohort, n=100.

| Variables                        | Increased surgical blood loss | Postpancreatectomy hemorrhage |
|----------------------------------|------------------------------|-------------------------------|
|                                  | present/total (%) | P     | present/total (%) | P    |
| Total                            | 11/100 (11.0)  | 0.182 | 6/100 (6.0)       | 0.197 |
| Age                              |                          |       |                  |      |
| >>80 years                       | 8/86 (9.3)        | 0.209 | 5/92 (9.8)       | 0.092 | 0.271 |
| <80 years                        | 3/14 (21.4)      | 0.009 | 4/86 (4.7)       | 0.009 | 0.271 |
| Gender                           |                          |       |                  |      |
| Female                           | 3/33 (9.1)        | 0.213 | 0/33 (0.0)       | 0.213 | 1.000 |
| Male                             | 8/67 (11.9)      | 0.174 | 6/67 (9.0)       | 0.174 | 1.000 |
| BMI, n (%)                       |                          |       |                  |      |
| <30 kg/m2                        | 8/95 (8.4)        | 0.213 | 5/95 (5.3)       | 0.213 | 1.000 |
| >=30 kg/m2                       | 3/5 (60.0)       | 0.174 | 1/5 (20.0)       | 0.174 | 1.000 |
| Performance status               |                          |       |                  |      |
| 0.1                              | 9/92 (9.8)        | 0.009 | 6/92 (6.5)       | 0.009 | 0.213 |
| 2-4                              | 2/8 (25.0)       | 0.009 | 0/8 (0.0)        | 0.009 | 1.000 |
| Diabetes mellitus                |                          |       |                  |      |
| Yes                              | 3/27 (11.1)      | 0.213 | 2/27 (7.4)       | 0.213 | 1.000 |
| No                               | 8/73 (11.0)      | 0.174 | 4/73 (5.5)       | 0.174 | 1.000 |
| Hx of CI/TIA                     |                          |       |                  |      |
| Yes                              | 1/11 (9.1)       | 0.513 | 1/11 (9.1)       | 0.513 | 1.000 |
| No                               | 10/89 (11.2)     | 0.042 | 5/89 (5.6)       | 0.042 | 1.000 |
| Hx of PCI, n (%)                 |                          |       |                  |      |
| Yes                              | 0/15 (0.0)       | 0.209 | 0/15 (0.0)       | 0.209 | 1.000 |
| No                               | 11/85 (12.9)     | 0.174 | 3/85 (3.5)       | 0.174 | 1.000 |
| APT used                         |                          |       |                  |      |
| Yes                              | 1/31 (3.2)       | 0.027 | 4/31 (12.9)      | 0.027 | 1.000 |
| No                               | 10/69 (14.5)     | 0.072 | 2/69 (2.9)       | 0.072 | 1.000 |
| Preop. aspirin continuation      |                          |       |                  |      |
| Yes                              | 0/18 (0.0)       | 0.545 | 0/18 (0.0)       | 0.545 | 1.000 |
| No                               | 11/82 (13.4)     | 0.197 | 6/82 (7.3)       | 0.197 | 1.000 |
| Anticoagulation used             |                          |       |                  |      |
| Yes                              | 3/12 (25.0)      | 0.588 | 1/12 (8.3)       | 0.588 | 1.000 |
| No                               | 8/88 (9.1)       | 0.182 | 4/88 (4.7)       | 0.182 | 1.000 |
| Periop. heparin bridging         |                          |       |                  |      |
| Yes                              | 3/14 (21.4)      | 0.009 | 2/14 (14.3)      | 0.009 | 1.000 |
| No                               | 8/86 (9.3)       | 0.174 | 4/86 (4.7)       | 0.174 | 1.000 |
| Texture of the remnant pancreas  |                          |       |                  |      |
| Yes                              | 0.266 (71.9)     | 0.174 | 4/29 (13.8)      | 0.174 | 1.000 |
| No                               | 0/18 (0.0)       | 0.197 | 0/18 (0.0)       | 0.197 | 1.000 |
| Presence of major pancreatic fistula |                          |       |                  |      |
| Yes                              | 11/82 (13.4)     | 0.588 | 6/82 (7.3)       | 0.588 | 1.000 |
| No                               | 2/27 (7.4)       | 0.213 | 0/27 (0.0)       | 0.213 | 1.000 |

*Abbreviations: BMI: body mass index; APT: antplatelet therapy; CI: cerebral infarction.; TIA: transient ischemic attack; PCI: percutaneous coronary intervention; preop: preoperative; periop: perioperative.*
CONCLUSION

Analyzing consecutive 100 patients undergoing pancreaticoduodenectomy, we showed that this procedure is safely performed even in antiplatelet-burdened patients with arterial thromboembolic risks without any increase of surgical blood loss or PPH, although this challenging group should be managed carefully to prevent severe postoperative complications.

REFERENCES

1. Fujikawa T, Maekawa H, Shiraishi K, Tanaka A. Successful resection of complicated bleeding arteriovenous malformation of the jejunum in patients starting dual anti-platelet therapy just after implanting drug-eluting coronary stent. BMJ Case Report 2012; Sep 24; 2012. [DOI: 10.1136/ber-2012-006779].

2. Fujikawa T, Noda T, Tada S, Tanaka A. Intractable intraoperative bleeding requiring platelet transfusion during emergent cholecystectomy in a patient with dual anti-platelet therapy after drug-eluting coronary stent implantation (with video). BMJ Case Report 2013; Mar 26; 2013. [PMID: 23536626]; [PMID: PMC3618701]; [DOI: 10.1136/ber-2013-009848].

3. Mitake K, Ito H, Murabayashi R, Sueyoshi K, Nabetani M, Kamasako A, Koizumi K, Hayashi T. Postoperative bleeding complications after gastric cancer surgery in patients receiving anticoagulation and/or antplatelet agents. Ann Surg Oncol 2012; 19(12): 3745-3752. [PMID: 22805680]; [DOI: 10.1245/s10434-012-2508-6].

4. Thachil J, Gatt A, Marleve L. Management of surgical patients receiving anticoagulation and antplatelet agents. Br J Surg 2008; 95(12): 1437-1448. [PMID: 18991253]; [DOI: 10.1002/bjs.6381].

5. Fujikawa T, Tanaka A, Abe T, Yoshimoto Y, Tada S, Maekawa H. Effect of antiplatelet therapy on patients undergoing gastroenterological surgery: thromboembolic risks versus bleeding risks during its perioperative withdrawal. World J Surg 2015; 39(1): 139-149. [PMID: 25201469]; [DOI: 10.1007/s00268-014-2760-3].

6. Fujikawa T, Tanaka A, Abe T, Yoshimoto Y, Tada S, Maekawa H, Shimoike N. Does antiplatelet therapy affect outcomes of patients receiving abdominal laparoscopic surgery? Lessons from more than 1,000 laparoscopic operations in a single tertiary referral hospital. J Am Coll Surg 2013; 217(6): 1044-1053. [PMID: 24051069]; [DOI: 10.1016/j.jamcollsurg.2013.08.005].

7. Fujikawa T, Yoshimoto Y, Kawaiura Y, Kawaiura H, Yamamoto T, Tanaka A. Safety and feasibility of laparoscopic liver resection in antiplatelet-burdened patients with arterial thromboembolic risks. J Gastroenterol Hepatol Res 2016; 5(5): 2165-2172.

8. Darnis B, Lebeau R, Chapin-Lally X, Adham M. Postpancreatectomy hemorrhage (PPH): predictors and management from a prospective database. Langenbecks Arch Surg 2013; 398(3): 441-448. [PMID: 23435636]; [DOI: 10.1007/s00423-013-1047-8].

9. Yekabas EF, Wolfram L, Cataledegirmen G, Habermann CR, Bogoevski D, Koenig AM, Kaifi J, Schurr PG, Bubenheim M, Nolte-Ernsting C, Adam G, Izibicki JR. Postpancreatectomy hemorrhage: diagnosis and treatment: an analysis in 1669 consecutive pancreatic resections. Ann Surg 2007; 246(2): 269-280. [PMID: 17667506]; [PMID: PMC1933568]; [DOI: 10.1097/01.sla.0000262955.77735.db].

10. Corea-Gallego C, Brennan MF, D’Angelica MI, DeMatteo RP, Fong Y, Kingham TP, Jarnagin WR, Allen PJ. Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. J Am Coll Surg 2012; 215(5): 616-621. [PMID: 22921325]; [DOI: 10.1016/j.jamcollsurg.2012.07.010].

11. Roulin D, Caronlal Y, Demartines N, Schaf er M. Systematic review of delayed postoperative hemorrhage after pancreatic resection. J Gastrointest Surg 2011; 15(6): 1055-1062. [PMID: 21267670]; [DOI: 10.1007/s11605-011-1427-8].

12. Mita K, Ito H, Takahashi K, Hashimoto M, Nagayasu K, Murabayashi R, Asakawa H, Hayashi T, Fuji no K. Postpancreatectomy Hemorrhage After Pancreatic Surgery in Patients Receiving Anticoagulation or Antplatelet Agents. Surg Innov 2016; 23(3): 284-290. [PMID: 26611788]; [DOI: 10.1177/155350615618288].

13. Ricci C, Casadei R, Buscemi S, Mimm F. Late postpancreatectomy hemorrhage after pancreaticoduodenectomy: is it possible to recognize risk factors? JOP 2012; 13(2): 193-198. [PMID: 22406600].

14. Welsh T, Eisele H, Zschabitz S, Hinz U, Buchner MW, Wente MN. Critical appraisal of the International Study Group of Pancreatic Surgery (ISGPS) consensus definition of postoperative hemorrhage after pancreaticoduodenectomy. Langenbecks Arch Surg 2011; 396(6): 783-791. [PMID: 21611815]; [DOI: 10.1007/s00423-011-0811-x].

15. Sanjay P, Fawzi A, Fulke JL, Kulli C, Tait IS, Zealley IA, Polignano FM. Late post pancreatectomy haemorrhage. Risk factors and modern management. JOP 2010; 11(3): 220-225. [PMID: 20442515].

16. Rumstadt B, Schwab M, Korth P, Samman M, Trede M. Hemorrhage after pancreatectomy. Ann Surg 1998; 227(2): 236-241.

17. Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer 1999; 6(3): 773-775. [PMID: 8471434]; [PMID: PMC1968363].

18. Fujikawa T, Yoshimoto Y, Kawamoto H, Tanaka A. Combination of modified Pinch-Burn-Cut (PBC) technique and Harmonic FOCUS® for pancreaticoduodenectomy under preoperative continuation of antiplatelets in patients with high thromboembolic risks. J Gastroenterol Hepatol Res 2017; (in press).

19. Park YK, Kim BW, Wang HJ, Xu W. Usefulness of the Pinch-Burn-Cut (PBC) technique for recipient hepatectomy in liver transplantation. Korean J Hepatobiliary Pancreat Surg 2012; 16(1): 13-16. [PMID: 26388900]; [PMID: PMC4575015]; [DOI: 10.14701/jkhbs.2012.16.1.13].

20. Tanaka K, Inomata Y, Kaihara S. Living-donor liver transplantation: Surgical techniques and innovations. Barcelona, Spain: Prous science 2007.

21. Salvia R, Mallego G, Marchegiani G, Butturrini G, Esposito A, Bassi C. Pancreaticoduodenectomy with harmonic focust curved shears for cancer. Dig Surg 2014; 31(4-5): 249-254. [PMID: 25323993]; [DOI: 10.1159/000363071].

22. Sato S, Yanagimoto H, Toyokawa H. Use of the new ultrasonically curved shear in pancreaticoduodenectomy for periampullary cancer. J Hepatobiliary Pancreat Sci 2011; 18(4): 609-614. [PMID: 21331806]; [DOI: 10.1007/s00534-011-0570-0].
23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240(2): 205-213. [PMID: 15273542]; [PMCID: PMC1360123].

24. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: an international study group (ISGF) definition. *Surgery* 2005; 138(1): 8-13. [PMID: 16003309]; [DOI: 10.1016/j.surg.2005.05.001].

25. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Buchler MW. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007; 142(1): 20-25. [PMID: 17629996]; [DOI: 10.1016/j.surg.2007.02.001].

26. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. *Arterioscler Thromb Vasc Biol* 2004; 24(11): 1980-1987. [PMID: 15388526]; [DOI: 10.1161/01.ATV.0000145980.39477.a9].

27. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten WW, Schaff HV, Whitlow PL, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol* 2008; 51(2): 172-209. [PMID: 18191745]; [DOI: 10.1016/j.jacc.2007.10.002].

28. King SB, 3rd, Smith SC, Jr., Hirshfeld JW, Jr., Jacobs AK, Banerjee S, Cash BD, Fisher L, Harrison ME, Fanelli RD, Fukami N, Ikenberry SO, Jain R, Khan K, Krinsky ML, Lichtenstein DR, Maple JT, Shen B, Strohmeyer L, Baron T, Dominitz JA. Management of antithrombotic agents for endoscopic procedures. *Gastrointest Endosc* 2009; 70(6): 1060-1070. [PMID: 19889407]; [DOI: 10.1016/j.gie.2009.09.040].

29. Anderson MA, Ben-Menachem T, Gan SI, Appalanieni V, Angiolillo DJ, Laupacis A, Libby P, Lichtenstein DR, Maple JT, Strohmeyer L, Baron T, Dominitz JA. Management of antithrombotic agents for endoscopic procedures. *Gastrointest Endosc* 2011; 73(5): 445-461. [PMID: 21547880]; [DOI: 10.1055/s-0030-1256317].

30. Cardona-Tortajada F, Sainz-Gomez E, Figuerido-Garmendia J, de Robles-Adusaur AL, Morte-Casabo A, Giner-Munoz F, Artazcoz-Oses J, Vidan-Lizari J. Dental extractions in patients on antithromplate therapy. A study conducted by the Oral Health Department of the Navarre Health Service (Spain). *Med Oral Patol Oral Cir Bucal* 2009; 14(11): e588-592. [PMID: 19680200].

31. Center for Science Information ASI. Anticoagulant and Antiplatelet Medications and Dental Procedures. American Dental Association Website. Accessed December 29, 2016.

32. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl): e265S-305S. [PMID: 22315266]; [PMCID: PMC3278059]; [DOI: 10.1378/chest.11-2298].

33. Fliescher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol* 2009; 54(22): e13-e118. [PMID: 19926002]; [DOI: 10.1016/j.jacc.2009.07.010].

34. Korte W, Cattaneo M, Chassot PG, Eichinger S, von Heymann C, Hofmann N, Rickli H, Spannagl M, Ziegler B, Verbeugt F, Huber K. Peri-operative management of antithromplate therapy in patients with coronary artery disease: joint position paper by members of the working group on Perioperative Haemostasis of the Society on Thrombosis and Haemostasis Research (GTH), the working group on Perioperative Coagulation of the Austrian Society for Anesthesiology, Resuscitation and Intensive Care (OGARI) and the Working Group Thrombosis of the European Society for Cardiology (ESC). *Thromb Haemost* 2011; 105(5): 743-749. [PMID: 21437351]; [DOI: 10.1160/TH10-04-0217].

35. Poldermans D, Bax JJ, Boersma E, De Hert S, Eckhout E, Fowkes G, Gorenek B, Hennerici MG, Iung B, Kelm M, Kjeldsen KP, Kristensen SD, Lopez-Sendon J, Pelosi P, Philippe F, Pierard L, Ponikowski P, Schmid JP, Sellerovde OF, Sicari R, Van den Berghe G, Vemmassen F. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J* 2009; 30(22): 2769-2812. [PMID: 19713421]; [DOI: 10.1093/eurheartj/ehp337].

36. Boustiere C, Veitch A, Vanbiervliet G, Bulois P, Deprez P, Laquiere A, Laupacis A, Libby P, Lichtenstein DR, Maple JT, Strohmeyer L, Baron T, Dominitz JA. Management of antithrombotic agents for endoscopic procedures. *Gastrointest Endosc* 2009; 70(6): 1060-1070. [PMID: 19889407]; [DOI: 10.1016/j.gie.2009.09.040].

37. Borges VP, Nascimento RM, Caparros L, Ferreira AP, Mazi s CC, Coelho CG, Ribeiro JF, De Souza LS, Ong BC, Zanatta J, Ribeiro H, Costa FC, Cunha TA, Vasconcelos R, Santos FL, Barreiro C. Safety of pancreaticoduodenectomy in antiplatelet-burdened patients and results of a survey. *Annals Surg* 2004; 240(2): 205-213. [PMID: 15273542]; [PMCID:PMC1360123].
Ren K et al. Valproic acid in oxaliplatin-induced neuropathy

master pancreatic surgeons to avoid hemorrhage during pancreaticoduodenectomy. *BMC Surg* 2015; 15: 122. [PMID: 26608343]; [PMCID: PMC4660662]; [DOI: 10.1186/s12893-015-0109-y]

47. Nuttall GA, Santrach PJ, Oliver WC, Jr., Horlocker TT, Shaughnessy WJ, Cabanela ME, Bryant S. The predictors of red cell transfusions in total hip arthroplasties. *Transfusion* 1996; 36(2): 144-149. [PMID: 8614965]

48. Palmer JD, Sparrow OC, Iannotti F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. *Neurosurgery* 1994; 35(6): 1061-1064; discussion 1064-1065. [PMID: 7885549]