Preoperative screening of thromboembolism using plasma D-dimer test and proximal vein compression ultrasonography in Japanese gynecologic patients

Daisuke Shigemi a, *, Tomohiko Matsuhashi a, Takashi Yamada a, Seiryu Kamoi a, Toshiyuki Takeshita b

a Department of Obstetrics and Gynecology, Nippon Medical School, Chiba Hokusoh Hospital, 1715 Kamagari, Inzai-shi, Chiba 270-1694, Japan
b Department of Obstetrics and Gynecology, Nippon Medical School Hospital, 1-5 Sendagi 1 chome, Bunkyo-ku, Tokyo 113-0022, Japan

A R T I C L E   I N F O

Article history:
Received 28 October 2016
Received in revised form 8 February 2017
Accepted 8 February 2017

Keywords:
D-dimer
Gynecologic surgery
Retrospective study
Ultrasonography
Venous thromboembolism

A B S T R A C T

Background: Venous thromboembolism (VTE) is a serious complication of surgery, including gynecologic surgery. The plasma D-dimer test and proximal/distal vein compression ultrasonography are frequently used as an easy, preoperative VTE screening method. However, targeted patients for these two examinations have not been established.

Patients/Methods: We retrospectively reviewed 380 gynecologic surgical patients who underwent preoperative VTE screening including the plasma D-dimer test and proximal/distal vein compression ultrasonography from March 2014 to February 2015. All patients underwent laparotomy or laparoscopy. In patients with a high risk of pulmonary thromboembolism, compression ultrasonography was substituted by or combined with contrast-enhanced computed tomography. With regard to D-dimer level, patients were divided to three groups: D-dimer level ≤ 0.5 µg/mL (group A), D-dimer level between 0.6 and 0.9 µg/mL (group B), and D-dimer level ≥ 1.0 µg/mL (group C).

Results: Twenty-seven cases had preoperatively detected VTE. Three patients in group B with benign disease were diagnosed with VTE before surgery. Among benign patients in group B, there was a significant difference in preoperative VTE occurrence between patients without risk factors (0/68 cases) and those with risk factors (3/54 cases). All 11 patients with benign disease having preoperative VTE had one or more risk factors.

Conclusion: Even in benign cases with low preoperative D-dimer levels (0.6–0.9 µg/mL), an imaging test should be added when the patient has one or more VTE risk factors.

© 2017 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), is a serious complication frequently occurring in surgical patients. In Japan, perioperative PTE occurs with a prevalence of 3 per 10000 surgeries, and its mortality rate is approximately 15% [1]. Gynecologic surgery has the third highest incidence rate of VTE [1]. Gynecologic patients undergoing malignant pelvic surgery have an elevated risk of VTE, and appropriate prophylaxis can reduce postoperative VTE; some studies have reported that the incidence of postoperative VTE...
decreased to 5–18% with prophylaxis from 35% without prophylaxis [2,3]. Preoperative VTE screening may be of use because prophylactic medicine for postoperative VTE is usually not prescribed in patients with benign disease. In general, preoperative VTE should be considered as an indication for anticoagulant treatment before surgery, and an intermittent pneumatic pedal compression device should not be used in patients with DVT.

The plasma D-dimer (DD) test and proximal/distal vein compression ultrasonography (CUS) are frequently used as an easy, preoperative VTE screening method in many countries, including Japan. DD is detectable in patients with VTE as it is a marker of endogenous fibrinolysis, which has a high negative predictive value (NPV). DD is highly sensitive (>95%) in excluding acute VTE at the cutoff value of 0.5 mg FEU/L, at least in patients with low or intermediate clinical probability [4]. Taira et al. reported that low clinical probability patients with negative DD (<0.5 mg DDU/ml) may not require additional and costly imaging studies [5]. Although proximal vein CUS is a highly sensitive and specific tool for diagnosing DVT, it is less sensitive to pelvic vein thrombosis and calf vein thrombosis [6]. However, targeted patients for these two examinations are different among each country, region, and hospital because the indication criteria for both examinations are unclear in surgical patients. Besides, although the cutoff value of DD is < 1.0 mg/ml (latex assay) in our hospital, we have occasionally found that patients with a low preoperative DD level (between 0.6 and 0.9 mg/ml by the latex assay) and no clinical symptoms had VTE detected on imaging examinations.

The objective of this retrospective study was to evaluate the utility of DD and CUS as a preoperative VTE screening method in 380 gynecologic patients in Japan and to establish when and how DD and CUS should be used.

1.1. Patients and methods

We retrospectively reviewed 380 gynecologic surgical patients who underwent preoperative VTE screening including the plasma DD test (latex assay) and proximal/distal CUS from March 2014 to February 2015 (Fig. 1). Approval of the institutional study board was obtained, and data was retrieved from patient case records. All patients underwent laparotomy or laparoscopy. In patients who had high risk of VTE such as swollen legs or advanced cancer, CUS was substituted by or combined with contrast-enhanced computed tomography (CT).

With respect to DD level, patients were divided into three groups: DD level < 0.5 μg/mL (group A), DD level between 0.6 and 0.9 μg/mL (group B), and DD level ≥ 1.0 μg/mL (group C).

Preoperative risk factors of VTE included 11 items: age >66 years, obesity (body mass index ≥ 25 kg/m²), hypertension, history of previous VTE, varix, angiitis, leg paralysis, prolonged bed rest, hormone replacement therapy, chemotherapy, and huge intra-pelvic tumor (>10 cm).

The results are expressed as number (%) or mean ± standard deviation. The statistical difference was determined by the chi-square test. Differences with P < 0.05 were considered significant.

This work has been reported as case series in line with the PROCESS criteria [7].

2. Result

Patient characteristics are shown in Table 1. Among the 380 patients, 292 underwent laparotomy and 88 underwent laparoscopy. With regard to malignancy, there were 122 cases of cancer; 6 cases of borderline tumors, 252 cases of benign diseases. Twenty-seven patients had preoperatively detected VTE (15 malignant cases, 1 borderline case, and 11 benign cases) (Table 1). Ovarian cancer with preoperative VTE (N = 12) included serous adenocarcinoma (5 cases) and clear cell adenocarcinoma (4 cases). Three patients who had benign disease and belonged to group B were diagnosed with VTE before surgery. Among benign patients in group B, there was a significant difference in preoperative VTE occurrence between patients without risk factors (0/68 cases) and those with risk factors (3/54 cases). All 11 patients with benign disease having preoperative VTE had one or more risk factors of eleven items. All preoperative VTE patients were treated by appropriate approach before and after surgeries, and fatal PTE has not occurred in this study.

3. Discussion

PTE is one of the most serious perioperative complications and should be prevented or diagnosed as soon as possible. Therefore, all gynecologic surgical patients should undergo preoperative VTE screening, such as a review of medical and family history, physical examination, and laboratory testing. Frequently used, noninvasive methods of preoperative VTE screening are obtaining the history and performing physical examinations. The Wells score for DVT appears to be the most commonly utilized pretest probability scoring system. Used on its own, it has high NPV for DVT (96%; 87–100%). Furthermore, the Wells score combined with a negative DD test indicates higher NPV for DVT (median value 99%; 96–100%) [8].

In this study, we focused on the preoperative DD test and CUS as a screening approach. The DD test is an invasive measure, but it can be simultaneously checked when a preoperative blood sample is obtained. A previous studies concluded that a DD level of <0.5 mg/mL by an enzyme-linked immunosorbent assay or a negative SimpliRED assay in conjunction with a low clinical probability may be useful in ruling out DVT, without the need for ultrasound testing [9]. In our study, none of 124 patients with a preoperative DD level of <0.5 μg/mL (latex assay) had DVT detected by CUS. This result indicates that patients with asymptomatic VTE or high clinical probability scoring rarely show a DD level of <0.5 μg/mL. Therefore, a DD level of ≤0.5 μg/mL (latex assay) can rule out preoperative VTE as it is a screening test with very high reliability.

Patients in group B included 4 preoperative VTE cases (4/149, 2.7%) in our study, and 3 of these had benign diseases. Benign diseases generally have a lower risk of VTE than malignant diseases [10], so preoperative screening for VTE is sometimes omitted in patients with a low clinical probability. However, an intermittent
pneumatic compression of lower extremities during surgery may lead to critical PTE if patients have asymptomatic DVT. Currently, the appropriate approach to “benign” and “low DD” patients is not well established. According to the results of our study, the 11 risk factors of VTE may be useful to screen out preoperative patients who need further imaging examination, including CUS. These factors were selected according to guidelines and recent studies [11–14].

The present study revealed two results with respect to patients with benign disease. First, among benign patients with low preoperative DD levels (0.6–0.9 mg/mL), there was a significant difference in preoperative VTE occurrence between the group without risk factors and that with risk factors. Second, all 11 patients with benign disease had low preoperative DD levels. CUS or contrast-enhanced CT should be performed in the high-risk VTE group in order to assess preoperative VTE and to perform surgeries safely.

There are several limitations to this study. Although proximal/distal leg vein CUS was mainly used as an imaging measure, CUS is less sensitive to pelvic vein thrombosis and calf vein thrombosis [6]. Furthermore, the number of patients was insufficient to identify particular preoperative risk factors of VTE among the 11 risk factors used by statistical analysis.

4. Conclusion

Even in benign cases with low preoperative DD levels (0.6–0.9 μg/mL), an imaging test should be added when the patient has one or more VTE risk factors. Although our report is only a small study, we believe that our suggestion can help to establish the best preoperative screening method for VTE.

**Table 1**

| Patients characteristics and results of preoperative VTE screening. | N = 380 | Preoperative VTE (N = 27) |
|---|---|---|
| **Age (years)** | 47 (13.45)* | – |
| **Body mass index (kg/m²)** | 23.6 (4.4)* | – |
| **Approach** | | |
| Laparotomy | 292 | 26 |
| Laparoscopy | 88 | 1 |
| **Histological type** | | |
| Benign | 252 | 11 (4.4%) |
| Border | 6 | 1 |
| Malignant | 122 | 15 (12.3%) |
| Cervical cancer | 21 | 0 |
| Endometrial cancer | 44 | 2 (4.5%) |
| Ovarian cancer | 46 | 12 (26.1%) |
| Peritoneal cancer | 5 | 1 |
| Others | 7 | 0 |
| **Plasma D-dimer level (μg/mL)** | | |
| <0.5 | 124 | 0 |
| 0.6–0.9 | 149 | 4 (2.7%) |
| ≥1.0 | 97 | 23 (23.7%) |
| Number | Number (percent) |

* Mean (SD).

**Sources of funding**

There were no sources of funding for our research.

**Author contribution**

D. Shigemi wrote the first draft and performed critical revision. T. Matsuhashi, T. Yamada, S. Kamoi and T. Takeshita commented on and revised the article.

**Conflicts of interest**

None of the authors have any conflicts of interest associated this paper.

**Research registration unique identifying number (UIN)**

Preoperative screening of thromboembolism using plasma D-dimer test and proximal vein compression ultrasonography in Japanese gynecologic patients.

researchregistry1790.

**Guarantor**

Daisuke Shigemi.

**Acknowledgments**

We thank Dr. Momoko Owada, Dr. Sayuri Kondo, Dr. Ryoko Matsui, Dr. Eri Hamano, Dr. Eiko Mori, and Dr. Mariyo Nakata from Department of Obstetrics and Gynecology, Nippon Medical School Chiba Hokusoh Hospital for the help with data collection.

**References**

[1] M. Kuroiwa, N. Seo, J. Furuya, The 18th pulmonary thromboembolism study: a investigation of pulmonary thromboembolism in 2009 (in Japanese), Shinzou 44 (2012) 908–910.

[2] S. Tateo, L. Mereu, S. Salamano, C. Klersy, M. Barone, A.C. Spyropoulos, F. Piovella, Ovarian cancer and venous thromboembolic risk, Cynecol. Oncol. 99 (2005) 119–125.

[3] M.H. Einstein, E.A. Pritts, E.M. Hartenbach, Venous thromboembolism prevention in gynecologic cancer surgery: a systematic review, Cynecol. Oncol.
D. Shigemi et al. / Annals of Medicine and Surgery 15 (2017) 52–55

105 (2007) 813–819.

[4] M. Righini, A. Perrier, P. De Moerloose, H. Bounameaux, D-dimer for venous thromboembolism diagnosis: 20 years later, J. Thromb. Haemost. 6 (2008) 1059–1071.

[5] T. Taira, B.R. Taira, M. Carmen, J. Chohan, A.J. Singer, Risk of venous thromboembolism in patients with borderline quantitative D-dimer levels, Am. J. Emerg. Med. 28 (2010) 450–453.

[6] C. Kearon, J.S. Ginsberg, J. Hirsh, The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism, Ann. Intern Med. 129 (1998) 1044–1049.

[7] R.A. Agha, A.J. Fowler, S. Rammohan, I. Barai, D.P. Orgill, The PROCESS Group, The PROCESS statement: preferred reporting of case series in surgery, Int. J. Surg. 36 (Pt A) (2016) 319–323.

[8] L.J. Tamariz, J. Eng, J.B. Segal, J.A. Krishnan, D.T. Bolger, M.B. Streiff, M.W. Jemec, F.B. Bass, Usefulness of clinical prediction rules for the diagnosis of venous thromboembolism: a systematic review, Am. J. Med. 117 (2004) 676–684.

[9] P.S. Wells, D.R. Anderson, M. Rodger, M. Forgie, C. Kearon, J. Dreyer, G. Kovacs, M. Mitchell, B. Lewandowski, M.J. Kovacs, Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis, N. Engl. J. Med. 349 (2003) 1227–1235.

[10] K.A. Bauer, Venous thromboembolism in malignancy, J. Clin. Oncol. 18 (2008) 3065–3067.

[11] K. Masayuki, Perioperative and periparturient venous thromboembolism (In Japanese), Jpn. J. Obstet. Gynecol. Neonatal Hematol. 25 (2015) 63–73.

[12] M. Cushman, L.H. Kuller, R. Prentice, R.J. Rodabough, B.M. Psaty, R.S. Stafford, S. Sidney, F.R. Rosendaal, Women’s Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis, JAMA 292 (2004) 1573–1580.

[13] E.R. Pomp, S. le Cessie, F.R. Rosendaal, C.J. Doggen, Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations, Br. J. Haematol. 139 (2007) 289–296.

[14] H.G. Gordon, A.A. Elie, C. Mark, D.G. David, J.S. Holger, Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines, Chest 141 (2012) 75–47S.