The Effect of Inhalation and Epidural Anesthesia on Platelet Function and Coagulation Following Hip Surgery

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Introduction

Most surgical procedures require a dry operative field. Interactions of anesthesia with platelet have been implicated to aggravate the risk of perioperative hemorrhagic complications. In order to reduce the blood loss in perioperative period, we need to select the better anesthetic strategy that causes less impact on platelet function because of the preeminent role of platelets in primary hemostasis. The majority of anesthetic agents, including inhalation anesthetics, intravenous anesthetics and local anesthetics, have been reported to inhibit platelet function. Sevoflurane inhibited platelet aggregation significantly in some studies. (1-4) Patients receiving sevoflurane during anesthesia had significantly reduced platelet aggregation.(5) In contrast, there was no significant inhibition of intra- and post-operative platelet aggregation in sevoflurane- anesthetised patients in other study.(6,7) Naesh et al.(8) showed platelet aggregability was prolonged into the postoperative period in epidural anesthesia group. Some studies suggest that epidural anesthesia may be associated with an inhibition of platelet aggregation despite sub-inhibitory plasma concentrations of local anesthetics. (9-11) And several previous studies(12-15) presented that epidural anesthesia contributes to the anti-thrombotic effect although the mechanism is not known. There are virtually no data to indicate that any anesthetic regimen is better than any other for reducing perioperative bleeding or thrombotic complications. Among studies that investigated the impact of regional versus general anesthesia on the platelet aggregation and coagulation, results have been mixed. To understand the interaction of anesthesia with platelet, this report compared the effect of inhalation and epidural anesthesia on the platelet aggregation and coagulation in patients following hip surgery.

Material & Methods

The study protocol was approved by the Ethics
Table 1. Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Inhalation Group</th>
<th>Epidural Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=9)</td>
<td>(n=10)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.3±12.7</td>
<td>60.8±10.4</td>
<td>0.964</td>
</tr>
<tr>
<td>Gender (M=1/F=2)</td>
<td>1.3±0.4</td>
<td>1.5±0.5</td>
<td>0.685</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.3±13.9</td>
<td>61.6±12.5</td>
<td>0.838</td>
</tr>
<tr>
<td>ASA classification</td>
<td>1.5±0.5</td>
<td>1.6±0.5</td>
<td>0.407</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>179.0±65.3</td>
<td>137.0±37.8</td>
<td>0.753</td>
</tr>
</tbody>
</table>

Values are mean±standard deviation. Inhalation Group; Inhalational anesthesia with sevoflurane, Epidural Group; Epidural anesthesia with 2% lidocaine & 0.75% ropivacaine, Duration; anesthetic duration.

Committee of the Hospital. We informed the participants the purpose of the study and they provided their verbal consents in the presence of a relative.

Twenty patients, ASA physical status I or II, undergoing the elective hip surgery were enrolled. The hip surgery included total hip replacement, compressive hip screw fixation, bipolar hemiarthroplasty. The study was performed between January 2005 and October 2005 at our institute.

To exclude excessive alterations of the platelet function that might have masked the effects of the anesthesia, we ruled out the patients with a history of blood disease, a family history of blood disorder, diabetes mellitus, hypertension, use of nonsteroidal anti-inflammatory drugs or antiplatelet drugs during the 7 days before operation, age younger than 18 years and older than 75 years and perioperative transfusion. All of the patients received a Hartman’s solution and normal saline infusions during the surgery. Heart rate, oxygen saturation, and end tidal CO₂ (ET CO₂) values were monitored noninvasively during anesthesia. We inserted the arterial cannula into one radial artery to monitor the arterial blood pressure and take blood samples.

1. Demographic characteristics

The study was performed in 20 patients who underwent elective hip surgery (Table 1). The selection criteria were scheduled for surgery with general anesthesia and ASA status I or II. The duration of the surgery was between 45 min to 80 min, position was lateral. All patient were done in the same room by the same nurse, surgeon and assistants.

2. Groups

The patients were divided into the two groups according to the type of anesthesia used. Assignment of patients to inhalation group (group I) and epidural group (group E) was randomized. All patients in group I were intubated. The patients of group I, anesthesia was induced with an IV bolus of propofol 1~1.5 mg/kg and rocuronium 0.6 mg/kg. The ventilation was controlled with 8 ml/kg tidal volume and the respiratory rate was sufficient to maintain ET CO₂ at 35±2 mmHg. The maintenance of anesthesia was achieved by using 50% N₂O in O₂ and 1 minimal alveolar anesthetic concentration (MAC) sevoflurane. At the end of the operation, all anesthetic agents were stopped, 100% oxygen was administered and the patient was extubated.

In group E, standard epidural anesthesia was performed. We used 18G Tuhoy epidural catheter and confirmed the epidural space using the loss of resistance method. 0.75% ropivacaine and 2% lidocaine were used for the epidural anesthesia.

3. Premedication

The patients received the intramuscular premedications with 2 mg of midazolam and 0.2 mg glyco-
Table 2. Preoperative Laboratory Results

<table>
<thead>
<tr>
<th></th>
<th>Inhalation Group</th>
<th>Epidural Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>12.4±1.3</td>
<td>13.0±1.6</td>
<td>0.353</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>35.9±3.4</td>
<td>37.2±3.6</td>
<td>0.475</td>
</tr>
<tr>
<td>Collagen (%)</td>
<td>54.4±12.5</td>
<td>51.4±16.2</td>
<td>0.659</td>
</tr>
<tr>
<td>ADP (%)</td>
<td>47.8±10.7</td>
<td>38.0±20.0</td>
<td>0.155</td>
</tr>
<tr>
<td>Plt (10^3/L)</td>
<td>251.2±48.6</td>
<td>241.5±49.1</td>
<td>0.707</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>11.5±0.9</td>
<td>11.1±0.9</td>
<td>0.108</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>30.1±4.1</td>
<td>28.6±4.9</td>
<td>0.424</td>
</tr>
</tbody>
</table>

There are no differences in the preoperative laboratory results between the groups. Values are mean±standard deviation.

Inhalation Group; Inhalational anesthesia with sevoflurane, Epidural Group; Epidural anesthesia with 2% lidocaine & 0.75% ropivacaine, Hb; Hemoglobin, Hct; Hematocrit, ADP; adenosine diphosphate, Plt; platelet count, PT; prothrombin time, aPTT; activated partial thromboplastin time.

pyrolole in group I 1 hour before the anesthesia. In group E, the patients were premedicated with 2 mg of midazolam intramuscularly.

4. Sampling

The 22 gauge arterial cannula was inserted into one radial artery to take the blood samples for the platelet function tests and to monitor the arterial blood pressure with a Dinamap (electrical blood pressure to measure and record systolic, diastolic, and mean arterial blood pressure). In both groups, blood was collected 5 minutes before induction, the first hour intraoperatively, and the first hour postoperatively. Blood samples were drawn into vacuum-operated tubes that contained EDTA (Vacutainer®; Becton Dickinson, Meylan, France) for platelet count measurements were drawn into vacuum-operated tubes that contained 10% volume 2.13% trisodium citrate.

5. Platelet function test and coagulation test

1) Platelet count

We measured platelet count by using the EDTA as an anticoagulator.

2) Coagulation test

We measured prothrombin time (PT) and activated partial thromboplastin time (aPTT) by using the Ivy method.

3) Platelet aggregation

Platelet aggregation tests are performed using a modified spectrophotometer to measure the turbidity of platelet-rich plasma (PRP). The blood was centrifuged at 160 g for 5 min to prepare PRP and was centrifuged at 200 g for 10 min to prepare platelet-poor plasma (PPP) at 20℃. We added 1mcg of ADP and 1mcg of collagen to 1 mL PRP for each aggregant analysis by using a Whole Blood Lumi-Aggregometer® (ChronoLog Corporation, Havertown, PA). The light transmission was accepted as 100% through PPP and as 0% through PRP.

6. Statistics

The statistics were carried out using the SPSS software (SPSS for windows 12.0). Paired T-test was adopted for the analysis of demographic characteristics and measures (collagen, ADP, platelet counts, PT, and aPTT) according to the sampling time (5 minutes before induction, the first hour intraoperatively, and the first hour postoperatively). Repeated measures analysis of variance was adopted to analyze the differences in the measurements according to the sampling time and
the different anesthetic strategies (inhalational anesthesia with sevoflurane and epidural anesthesia with 0.75% ropivacaine and 2% lidocaine). P-value <0.05 was considered as significant. Time-response curve was fitted using the Sigmaplot 2001.

**Results**

There was no difference in the demographic features and the duration of anesthesia between the groups (Table 1). There was no difference in mean arterial pressure, heart rate, oxygen saturation, and ET<sub>CO</sub>2 values during the study. There was also no difference in hemoglobin, hematocrit, collagen, ADP, platelet count, PT, aPTT between the groups according to the measurements (Table 2). Each measurements change were significantly different according to the anesthetic technique (P<0.05) and preoperative, intraoperative, and postoperative period (P<0.05). Collagen elevated intraoperatively and recovered postoperatively in both group (Fig. 1) but, collagen change have no statistical significant in both groups. ADP reduced insignificantly intraoperatively and elevated postoperatively in group I (Fig. 2). In epidural group, there was a slight reduction in intraoperative period and a remained reduction in postoperative period (Fig. 2) and ADP change in epidural group have a statistical significance (P<0.05) (Table 3). Platelet counts reduced intraoperatively and have reduced until the first hour postoperatively in both groups. There was a statistical significance in group I (P<0.01), not in epidural group. PT prolonged in intraoperative period and have prolonged until the first hour postoperatively in group I. In epidural group, PT prolonged intraoperatively and slightly recovered postoperatively. There was a statistical significance within group (P<0.01). aPTT prolonged intraoperatively and recovered postoperatively in group I, but there was no statistical significance of aPTT change. In group E, aPTT prolonged in intraoperative period and have prolonged until the first hour postoperatively although there was no statistical significance.
Table 3. Platelet Function and Coagulation Data in Perioperative Period

<table>
<thead>
<tr>
<th>Platelet function parameter</th>
<th>Group</th>
<th>N</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen ( % )</td>
<td>Inhalation Group</td>
<td>9</td>
<td>55.2±13.1</td>
<td>57.0±7.6</td>
<td>50.1±10.5</td>
</tr>
<tr>
<td></td>
<td>Epidural Group</td>
<td>10</td>
<td>49.3±16.7</td>
<td>53.2±13.5</td>
<td>50.1±18.8</td>
</tr>
<tr>
<td>ADP ( % )</td>
<td>Inhalation Group</td>
<td>9</td>
<td>47.2±11.2</td>
<td>44.8±10.0</td>
<td>56.7±10.9†</td>
</tr>
<tr>
<td></td>
<td>Epidural Group</td>
<td>10</td>
<td>36.8±18.4</td>
<td>36.5±18.7</td>
<td>35.5±15.9</td>
</tr>
<tr>
<td>Plt (10³/µL)</td>
<td>Inhalation Group</td>
<td>9</td>
<td>253.5±46.9</td>
<td>231.5±47.8‡</td>
<td>223.6±75.2‡</td>
</tr>
<tr>
<td></td>
<td>Epidural Group</td>
<td>10</td>
<td>237.4±45.9</td>
<td>214.5±40.4</td>
<td>214.6±34.3</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>Inhalation Group</td>
<td>9</td>
<td>11.7±0.8</td>
<td>12.3±0.9*</td>
<td>13.0±1.0‡</td>
</tr>
<tr>
<td></td>
<td>Epidural Group</td>
<td>10</td>
<td>11.0±0.8</td>
<td>12.0±1.1*</td>
<td>11.8±1.0*</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>Inhalation Group</td>
<td>9</td>
<td>31.0±3.0</td>
<td>31.4±2.6</td>
<td>30.6±3.4</td>
</tr>
<tr>
<td></td>
<td>Epidural Group</td>
<td>10</td>
<td>28.1±4.9</td>
<td>29.6±6.9</td>
<td>30.9±7.4</td>
</tr>
</tbody>
</table>

Values are mean±standard deviation. T1; sampling before the induction of anesthesia, T2; sampling the first hour intraoperatively, T3; sampling the first hour postoperatively, Inhalation Group; Inhalational anesthesia with sevoflurane, Epidural Group; Epidural anesthesia with 2% lidocaine & 0.75% ropivacaine, Plt; platelet count, PT; prothrombin time, aPTT; activated partial thromboplastin time. *P<0.05 compared with T1, †P<0.05 compared with T1, ‡P<0.05 compared with T2, §P<0.01 compared with T2, ¥P<0.05 compared with groups, ¶P<0.05 compared among sampling time.

Discussion

Platelets play a central role in normal hemostasis. The series of the platelet events during hemostasis follows: (1) platelets adhere to extracellular matrix at sites of endothelial injury and become activated (2) on activation, they secrete granule products (e.g. adenosine diphosphate ([ADP]) and synthesize thromboxane A2 ([TXA2]) (3) platelets also expose phospholipid complexed important in the intrinsic coagulation pathway (4) injured or activated endothelia cells expose tissue factor, which triggers the extrinsic coagulation cascade (5) released ADP stimulated formation of a primary hemostatic plug, which is eventually converted (via ADP, thrombin and TXA2) into a larger definitive secondary plug (6) fibrin deposition stabilizes and anchors the aggregated platelets. After vascular injury, platelets encounter extracellular matrix constituents, which are normally sequestered beneath and intact endothelium; these include collagen (most important), proteoglycan, fibronectin, and other adhesive glycoproteins. The interaction with von willebrand factor and collagen mediate the platelet adhesion to extracellular matrix.(16) ADP is a potent mediator of platelet aggregation and also augments further ADP release from other platelets.(17)

The primary goal of the present study was to compare the effects of general anesthesia with sevoflurane to epidural anesthesia with 0.75% ropivacaine and 2% lidocaine on the platelet function and coagulation in platelets undergoing elective hip surgery. In both groups, there was inhibition of ADP-induced platelet aggregation, reduction of platelet counts and prologation of PT and aPTT in intraoperative period. In addition, only epidural anesthesia with 0.75% ropivacaine and 2% lidocaine influenced until postoperative period was observed.

The normal platelet count is 150,000~450,000/µL and spontaneous bleeding is uncommon if the platelet count is above 20,000/ µL. However, if platelet function is abnormal, prolonged or spontaneous bleeding can at higher platelet count.(18) Lower platelet count indicated diminished platelet adherence at damaged vessels, decreased generation of thrombin, and
Fig. 3. The changes of platelet counts. Values are mean ± standard deviation. T1; sampling before the induction of anesthesia, T2; sampling the first hour intraoperatively, T3; sampling the first hour postoperatively, Inhalation Group; Inhalational anesthesia with sevoflurane, Epidural Group; Epidural anesthesia with 2% lidocaine & 0.75% ropivacaine. * means platelet count has significantly reduced until the first hour postoperatively.

Fig. 4. The changes of PT (thromboplastin time). Values are mean ± standard deviation. T1; sampling before the induction of anesthesia, T2; sampling the first hour intraoperatively, T3; sampling the first hour postoperatively, Inhalation Group; Inhalational anesthesia with sevoflurane, Epidural Group; Epidural anesthesia with 2% lidocaine & 0.75% ropivacaine. * means PT has significantly reduced until the first hour postoperatively.

low platelet-associated factor XIII, which promotes clot stabilization and platelet interaction. The PT measures the integration of the extrinsic and common pathways of coagulation whereas the aPTT measures the integration of the intrinsic and common pathways of the coagulation. Standard coagulation tests including PT, aPTT, fibrinogen and platelet counts are important parameters to monitor the perioperative hemostatic capacity in relation to the formation of fibrin clots.(16) Variants of tests can be used to assess the platelet function and coagulation test. Platelet aggregation has a biphasic response that is characterized by a decrease in absorbency spectrophotometrically. Primary aggregation is a direct in consequence of stimulation with an agonist (i.e. ADP), whereas secondary aggregation is mainly a response to TXA2 secreted from platelets.(11)

The majority of anesthetic agents, including intravenous induction agents, volatile anesthetics and local anesthetics, have been reported to inhibit platelet function. The magnitude of inhibitory effects reported to vary among the different agents. The mechanism through which anesthetics inhibit platelet function is largely unknown and probably varies among the different agents. There are virtually no data that indicates that any general anesthetic regimen is rather than any other for reducing perioperative bleeding or thrombotic complications. Among studies that investigated the impact of regional versus inhalational anesthetics, results have been mixed.(8) Although the results of many studies have been conflicting, it appears that sevoflurane (probably with propofol) inhibits platelet function in a reversible and dose related manner at concentrations used clinically.

The proposed platelet inhibitory mechanism of sevoflurane involves that suppression of TXA2 formation.(2) In this study, inhalational anesthesia with sevoflurane showed the recovery of ADP. Many in vitro studies investigating the effects of lidocaine, cocaine and bupivacaine showed inhibition of platelet
aggregation.\textsuperscript{(19-21)} The authors noted that the concentration of local anesthetics required the inhibit platelet aggregation much higher than the peak plasma concentration occurring in vivo. In contrast to the above studies, clinical concentration of bupivacaine had no antiplatelet effect in the thromboelastogram and on platelet aggregation in vitro.

In this study, however, epidural anesthesia with 0.75% ropivacaine and 2% lidocaine influenced. This study presented that inhalation anesthesia with sevoflurane and epidural anesthesia with 0.75% ropivacaine and 2% lidocaine inhibited ADP-induced platelet aggregation, reduction of platelet count and prolongation of PT and aPTT in intraoperative period. Group I showed the recovery of ADP-induced platelet aggregation and aPTT, the remained reduction of platelet count and the remained prolongation of PT in the first postoperative period. Group E represented the remained inhibition of ADP-induced platelet aggregation, the remained reduction of platelet count, the recovery of PT and the recovery of aPTT in the first hour postoperative period. Our study revealed that only epidural anesthesia with 0.75% ropivacaine and 2% lidocaine influenced ADP-induced platelet aggregation until postoperative period (Table 3 and Fig. 2). There was intraoperative inhibition and no postoperative inhibition of platelet aggregation test performed by ADP in group I.

Several studies have shown the epidural anesthesia reduced the incidence of thrombotic events. These effects may be attributed either to physiologic changes induced by neuraxial anesthesia or to pharmacologic effects of local anesthetics on the coagulation system. The effect of the epidural administration of bupivacaine on platelet aggregation was studied by Odoom et al. They considered that ADP-induced inhibitory platelet aggregation effect explained bupivacaine accumulation with the platelets as explanation for the time lag. Some studies presented that epidural anesthesia per se may be associated with an inhibitory of platelet aggregation despite subinhibitory plasma concentrations of local anesthetic. The mechanism whether epidural anesthesia reduced platelet aggregation in this manner is not known. Nevertheless, it is possible that this inhibition of platelet aggregation contributes to the anti-thrombotic effect of epidural anesthesia which has been observed in several previous studies. Low concentration of ADP inhibit the arachidonic acid pathway to the release reaction. So it is possible to conclude that inhalational anesthesia with sevoflurane had no more effect on arachidonic acid pathway when they were stopped, but epidural anesthesia with 0.75% ropivacaine and 2% lidocaine had prolonged effect on arachidonic acid pathway. That is the similar effect of nonsteroidal anti-inflammatory drugs.

Therefore, it is possible that epidural anesthesia with 0.75% ropivacaine and 2% lidocaine may contribute to
abnormal bleeding in a similar manner to other antiplatelet drugs, or may reduce the incidence of thrombotic complications in a similar manner to other antiplatelet drugs. These considerations are suspected at present and further studies are required to determine whether epidural anesthesia with 0.75% ropivacaine and 2% lidocaine affects the incidence of bleeding or thrombotic complications in clinical practice.

Abstract

고관절 수술시 혈소판에 미치는 흡입마취와 경막외마취의 효과

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마취과 의사가 각기 다른 마취방법이 혈소판의 기능에 영향을 줄 수 있는 임상적 변화를 이해하고, 수술 중 혈소판이 염 영향을 미치는 마취방법을 선 택할 필요가 있다. 이 연구는 혈소판의 기능과 응집 에 대한 흡입 마취와 경막외 마취의 효과를 비교하 였다. 정규 고관절 수술이 예정된 미국 마취과학회 신체등급분류 1 또는 2에 해당하는 19명의 환자를 대상으로 실시하였으며 무작위적으로 sevoflurane 이용한 흡입 마취(9명)과 2% lidocaine과 0.75% ropivacaine을 이용한 경막외 마취군(10명)으로 분류 하였다. 모든 군에서 마취유도 전 5분, 마취유도 후 1시간 쯤, 수술 종료 후 1시간에 각각 혈액을 채취 하였고, 혈소판 기능은 혈소판 수, 프로트롬빈 시간, 부분트롬보플라스틴 시간을 이용하여 측정하였고, 혈소판 응집은 collagen과 adenosine diphosphate (ADP) 를 이용하여 측정하였다. 경막외 마취군에서 수술 후 1시간까지 ADP에 의한 혈소판 응집이 억제되었 다. 마취방법에 따른 혈소판 수와 프로트롬빈 시간, 부분트롬보플라스틴 시간, 그리고 collagen의 변화는 통계학적으로 의미가 없었으나, 수술 중과 수술 후에 대한 변화가 있음을 각각적으로 알 수 있었다. 이번 연구에서 흡입 마취군에서 ADP에 의한 혈소판 응집이 마취종료 후 더 이상 나타나지 않음과 경막 외 마취군에서는 ADP에 의한 혈소판 응집이 마취종 존 후까지 억제됨을 볼 수 있었다. 수술 후 혈액상 정성의 관점에서 다른 위험인자가 없다면 경막외 마취보다 흡입마취가 먼저 고려되어야 할 것이다. 또한 수술 후 높은 출혈 위험이 있는 환자에게서 경막 외 마취는 조심스럽게 선택되어야 할 것이다.

중심단어: 경막외마취, 로피바카인, 리도카인, 세보 플루란, 전신마취, 혈소판기능

Conclusions

1. Inhalation anesthesia with sevoflurane and epidural anesthesia with 0.75% ropivacaine and 2% lidocaine showed inhibition of ADP-induced platelet aggregation, reduction of platelet counts and prolongation of PT and aPTT in intraoperative period.

2. Inhalation group showed the recovery of ADP-induced platelet aggregation and aPTT, the remained reduction of platelet counts and the remained prolongation of PT in the first hour postoperative period.

3. Epidural group represented the remained inhibition of ADP-induced platelet aggregation, the remained reduction of the platelet counts, the recovery of PT and the recovery of aPTT in the first hour postoperative period.

4. Only epidural anesthesia with 0.75% ropivacaine and 2% lidocaine influenced ADP-induced platelet aggregation until postoperative period.

References

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