Clinical Case Report

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Abrupt hemodynamic changes accompanying intrapleural hyperthermic chemotherapy

Case series

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Abstract

Rationale: Intrapleural hyperthermic chemotherapy (IPHC) is the preferred method to locally treat lung cancer with pleural seeding. Anesthetic management during IPHC is a very challenging task for the anesthesiologist because of the hemodynamic instability associated with the procedure; however, there is no report on anesthetic considerations during the IPHC procedure.

Patient concerns: Three patients who diagnosed lung cancer with pleural invasion scheduled for IPHC were reported in this case series.

Diagnosis: Case 1, a 48-year-old woman, suffered from lung cancer (adenocarcinoma, T2NxM1a) with diffuse pleural seeding. Case 2, a 58-year-old female, diagnosed with lung cancer (adenocarcinoma, T3N0M1a) with pleural dissemination. Case 3, a 47-year-old male, diagnosed as sarcoma on the left lung with right pericardial invasion and right hemidiaphragm invasion (stage, T3N0M1a).

Intervention: All three patients underwent IPHC with cisplatin diluted in normal saline (2000 ml) at a rate of 600 ml/min. Inflow temperature of 42°C was using a heart-lung machine over 90 minutes. Hemodynamic changes were monitored through the procedure.

Outcomes: The patient did not require supplemental oxygenation anymore after he recovered from lung transplantation.

Lessons: There was sudden drop in the cardiac output and an increase in the pulmonary vascular resistance, which were caused by the volume and temperature of the hyperthermic chemotherapeutic drugs in the pleura during the early stage of IPHC; these changes can be a major problem during the procedure, and supportive hemodynamic management may be needed.

Abbreviations: BIS = bispectral index, CCO = continuous measurement of cardiac output, CO = cardiac output, CVP = central venous pressure, DLT = double lumen tube, ICU = intensive care unit, IPHC = intrapleural hyperthermic chemotherapy, MAP = mean arterial pressure, MPAP = mean pulmonary artery pressure, PCA = patient controlled analgesia, PCEA = patient controlled epidural analgesia, PVR = pulmonary vascular resistance, rSO_2 = regional cerebral oxygen saturation, RVEF = right ventricular ejection fraction, SvO_2 = venous oxygen saturation, SVR = systemic vascular resistance, TCI = target controlled infusion.

Keywords: anesthesia, chemotherapy, hyperthermic, intrapleural, lung cancer

1. Introduction

Patients with lung cancer with pleural seeding have a poor prognosis. The preferred method of treatment for such patients is with intrapleural chemotherapy in combination with surgery and systemic chemotherapy for local control.[1,2]

There have been many studies on anesthetic management and hemodynamic changes occurring during intraperitoneal hyperthermic chemotherapy, and many previous studies have proved the efficacy of intrapleural hyperthermic chemotherapy (IPHC).[3–5]

Anesthetic management during IPHC is a very challenging task for the anesthesiologist because of the hemodynamic instability associated with the procedure. However, there is no report on anesthetic considerations during the IPHC procedure, and there is no literature on the definite hemodynamic changes to date. In this case series, we report our experience of performing anesthesia in three cases that underwent intrapleural hyperthermic chemotherapy (IPHC).

2. Materials and methods

We obtained approval from the Pusan National University Yangsan Hospital's Institutional Review Board (approval number, 05-2012-055).

2.1. We selected 3 patients who were scheduled to undergo IPHC.

The following variables were recorded: patient's demographic information (sex, age, weight, height, diagnosis, past medical

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This case study followed the CARE guidelines for case studies. Written informed consent was obtained from the patients for publication of this case study. At the time of consent, the patients had recovered from his illness and had full capacity to make an informed decision. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

The authors have no conflicts of interest to disclose.

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history), operation, length of anesthesia, pain control, and hemodynamic variables during anesthesia (temperature, bispectral index, cerebral oxygen saturation, systemic oxygen saturation, mean blood pressure, heart rate, cardiac output, central venous pressure, right ventricular ejection fraction, mean pulmonary artery pressure, pulmonary vascular resistance, and systemic vascular resistance)

2.1.1. General anesthesia and monitoring. Patients were premedicated with glycopyrrolate 30 minutes before anesthesia. On arriving in the operating room, patients were attached to standard monitoring devices, and radial artery catheters were inserted under local anesthesia for continuous blood pressure monitoring. Cerebral oxymeters (INVOS 5100TM, Somanetics, Troy, MI) were applied on the foreheads of the patients for continuous monitoring of regional cerebral oxygen saturation (rSO_2). Bispectral index (BIS) was used to assess the depth of anesthesia. Anesthesia was induced using propofol or thiopental sodium combined with remifentanil. After the loss of consciousness, patients were administered intravenous rocuronium (50 mg), and left endobronchial intubation using a double lumen tube (DLT) was performed. Proper placement of the DLT was confirmed by auscultation and by inspection using a fiberoptic bronchoscope. Esophageal and rectal temperature probes were also inserted. Anesthesia was maintained with propofol or sevoflurane in combination with remifentanil. Patients were ventilated with oxygen and air (FiO_2, 50%), and the end-tidal CO_2 was maintained between 35 and 40 mm Hg.

Pulmonary artery catheter (Swan-Ganz CCOmboCCO/SvO_2, Edwards Lifesciences LLC) was inserted via the right internal jugular vein for continuous measurement of the cardiac output (CO), mixed venous oxygen saturation (SvO_2), right ventricular ejection fraction (RVEF), and right ventricular end-diastolic volume index (RVEDVI). Esophageal and rectal temperatures and urine output were continuously monitored. Hemodynamic profiles were assessed using a pulmonary artery catheter until the patient was extubated.

2.1.2. IPHC protocol. All three patients underwent the same method of IPHC. Patients were placed in lateral decubitus position during the operation, and cisplatin perfusion was performed through 2 intercostal drains (lower chest tube for infusion and upper chest tube for drainage). A standard roller pump and a heat exchanger were used. Cisplatin (200 mg per body surface area) with normal saline (2000 ml) was administered at a rate of 600 ml per minute with an inflow temperature of 42°C using a heart-lung machine (Jostra-HL 30, Maquet). IPHC was performed over 90 minutes. During cisplatin perfusion, patients were also administered chlorpheniramine maleate (4 mg), famotidine (20 mg), dexamethasone (12 mg), 15% mannitol (150 ml), 25% sodium thiosulfate (12.5 g) (all intravenously) to prevent any adverse events related to chemotherapy

2.1.3. Postoperative analgesia. Two patients used patient-controlled epidural analgesia (PCEA) for post-operative pain control. Before general anesthesia, they laid in a lateral decubitus position. The thoracic epidural space was punctured between T4 and T6 region. An epidural catheter was inserted into the epidural space, and a test dose (3 mL of 2% lidocaine with 15 μg of epinephrine) was administered via the epidural catheter to rule out misplacement of the catheter. A bolus dose of 6 mL of 0.2% ropivacaine with 50 μg of fentanyl was administered. PCEA was maintained with 0.2% ropivacaine with fentanyl after the operation.

3. Results

3.1. Case 1

A 48-year-old (height, 157.8 cm; weight, 55.3 kg) female patient was admitted in the operating room for IPHC. She had lung cancer in the left upper lobe with diffuse pleural seeding. She did not have significant past medical history. A previous surgical biopsy had revealed an adenocarcinoma, and the stage was T2NxM1a. Left upper lobectomy had been performed 8 days previously without any adverse event. There were no abnormal findings on the laboratory data or preanesthetic evaluation. Anesthesia was induced with propofol and remifentanil using a target-controlled infusion (TCI) pump, which was set at a target concentration of 4 mcg/mL of propofol and 2 ng/mL of remifentanil. General anesthesia was maintained with propofol and remifentanil with a BIS of 40 to 60. IPHC was conducted as the method described above.

At the end of procedure, patient-controlled analgesia (PCA) was started through the epidural catheter. Pyridostigmine (10 mg) and glycopyrrolate (0.4 mg) were administered to reverse the muscle relaxation. The DLT was removed after confirmation of normal spontaneous respiration and of recovery of consciousness. The patient was transported to the intensive care unit (ICU), where she was administered oxygen through a nasal cannula at 3 L/min, and her vital signs were maintained as follows: SpO_2, 96%% to 98%; BP, 100 to 110/60 to 70 mm Hg; and HR, 70 to 80 beats/min. Her body temperature was maintained at 36.8 to 37°C during the ICU stay. There were no abnormalities observed until she was transferred to the ward.

3.2. Case 2

A 58-year-old (weight, 65.3 kg) female patient was admitted in the operating room for IPHC. She was diagnosed with lung cancer (left lower lobe, adenocarcinoma, T3N0M1a) with pleural dissemination. She had undergone superior segment wedge resection on the left lower lobe, mediastinal lymph node biopsy, and parietal pleura biopsy six days previously. There were no abnormal findings on laboratory data or preanesthetic evaluation. An epidural catheter had already been inserted in the thoracic epidural region during the lobectomy six days previously. Patient-controlled analgesia via the epidural catheter was stopped when the patient arrived in the operating room. General anesthesia was induced with 250 mg of thiopental sodium, 8 vol% of sevoflurane, and remifentanil (0.2 mcg/kg/min). After the loss of consciousness, the patient was administered 50 mg of intravenous rocuronium bromide, and tracheal intubation was performed using a DLT. General anesthesia was maintained with sevoflurane during the procedure, maintaining the BIS in a range of 40 to 60.

The patient was placed in a right lateral decubitus position, and IPHC was performed using the same method described above. After cisplatin perfusion was stopped, patient-controlled analgesia through the epidural catheter was re-started. After confirmation of normal spontaneous respiration and recovery of consciousness, the DLT was removed, and the patient was transferred to recovery room. The patient was administered oxygen through a nasal cannula at 3 L/min, and her vital signs remained stable. She did not exhibit abnormal signs during the stay in the recovery room and she was transferred to a general ward.

3.3. Case 3

A 47-year-old male patient was diagnosed to have a sarcoma on the left lung with right pericardial invasion and right

hemidiaphragm invasion. He had undergone surgery to remove the mass one year previously, and he had been diagnosed to have right pericardial invasion and right hemidiaphragm invasion on preoperative CT imaging (stage, T3N0M1a). He was admitted in the operating room to undergo chest wide excision and IPHC. We conducted general anesthesia with thiopental sodium (200 mg) and remifentanil (0.2 mcg/kg/min). After the loss of consciousness, the patient was administered intravenous rocuronium bromide (50 mg), and tracheal intubation using DLT was performed. Anesthesia was maintained with sevoflurane in O_2 and air.

Initially, the patient was positioned in a right lateral decubitus position; the surgeon performed wide excision of the left side of the chest wall that included the mass and scapular tip. Then, the patient was positioned on left lateral decubitus position, and resection of the pericardium and hemidiaphragm with placement of a Gore-tax patch and mediastinal lymph node biopsy were performed. To control pleural seeding, we conducted cisplatin-IPHC for 90 minutes using the same method described above. The patient refused to use PCA for postoperative pain control. After performing IPHC, we planned for postoperative ventilation, and the patient was sent to intensive care unit while still intubated.

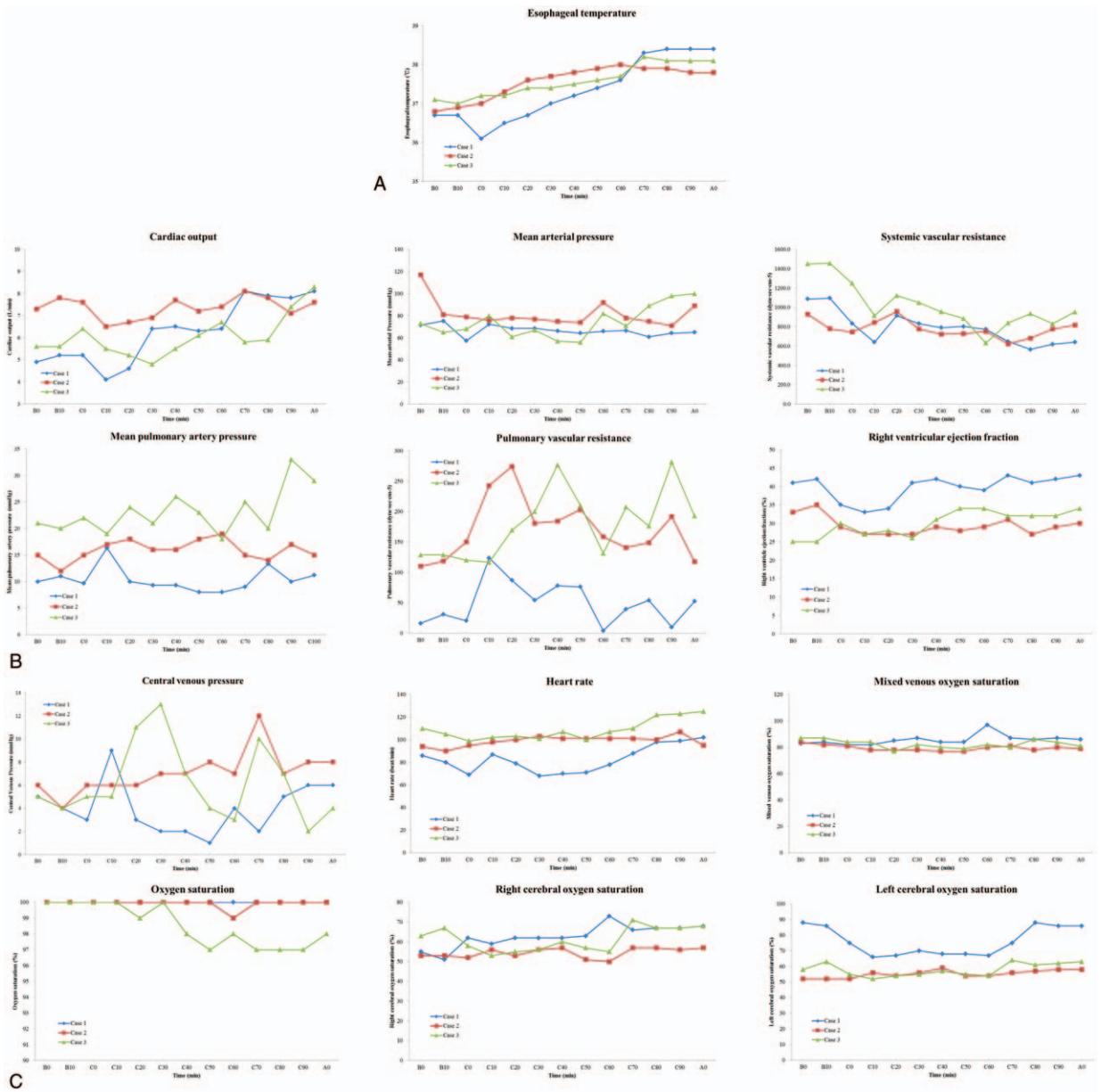

Figure 1. Hemodynamic changes among 3 cases. All data were measured over time. The time before intrapleural hyperthermic chemotherapy (IPHC), during IPHC, and after IPHC are denoted as B, C, and A, respectively, on the x-axis. Values were recorded every 10 minutes. (A) Esophageal temperature increased to around 38°C. (B) Cardiac output (CO), mean arterial pressure (MAP), and systemic vascular resistance (SVR) decreased. Mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance (PVR) had an increasing pattern. Right ventricular ejection fraction (RVEF) decreased. (C) Central venous pressure (CVP) increased. Heart rate remained stable but slightly increased toward the end of the procedure. Cerebral oxygen saturation, oxygen saturation, and mixed venous oxygen saturation did not change. (B—Before IPHC; C—During IPHC; A—After IPHC. All data were recorded every 10 minutes.) MAP = mean arterial pressure, MPAP = mean pulmonary artery pressure, PVT = pulmonary vascular resistance, RVEF = right ventricular ejection fraction, SVR = systemic vascular resistance.

3.4. Hemodynamic variables during IPHC

Hemodynamic changes in the three cases are shown in Figure 1. The hemodynamic parameters remained stable until IPHC was started. From the moment IPHC started, body temperature gradually increased to about 38°C (Fig. 1A). At the beginning of IPHC, cardiac output (CO) and mean arterial pressure (MAP) acutely decreased, and they returned to the baseline level after initiating an intravenous infusion of dopamine. Systemic vascular resistance (SVR) also decreased. On the other hand, mean pulmonary artery pressure (MPAP) fluctuated although it tended to increase, and pulmonary vascular resistance (PVR) increased abruptly from the beginning (Fig. 1B). Right ventricular ejection fraction (RVEF) acutely decreased at the beginning of IPHC, and it gradually increased to the baseline level (Fig. 1B). Central venous pressure (CVP) fluctuated widely during the procedure, and it decreased suddenly at the start of IPHC (Fig. 1C). Heart rate seemed to be stable, but it gradually increased. BIS, cerebral oximetry, and oxygen saturation did not change during the procedure (Fig. 1C) with respect to laboratory data, ABGA did not have any characteristic change. At the end of the procedure, the vital signs and the hemodynamic profiles remained relatively stable. Patients' characteristics and anesthesia methods are summarized in Table 1.

4. Discussion

IPHC can be a good choice of treatment for a lung cancer with pleural seeding. Regional hyperthermic chemotherapy can be advantageous because the tumor is directly exposed to higher drug concentrations, whereas a lower incidence of toxic side effects may be expected. The hyperthermic effect on the mass is due to increased level of drugs within cells; significant enhancement of the DNA cross-linking effect of the drugs; and heat-induced inhibition of DNA repair.[2]

The causes of complications associated with IPHC include abrupt volume loading, regional, and systemic hyperthermia, and toxicity of the chemotherapeutics.

At the start of the chemotherapeutic perfusion, sudden volume loading with cisplatin occurs. The volume load causes an increase in the intrathoracic pressure and leads to an obstruction of the inferior and superior vena cava. Decreased venous return causes a decrease in cardiac output. In addition to a reduction of the preload, direct cardiac compression also reduces the cardiac output.[6]

In our cases, the patients developed hypotension and decreased cardiac output at the beginning of cisplatin perfusion.

During the IPHC, the pleural space temperature is increased up to 42°C. Increased regional temperature can cause an increase in systemic temperature. Regional hyperthermia causes dilatation of systemic and peripheral vessels. Dilatation of vessels results in decreased systemic vascular resistance with decreased venous return, which causes hypotension. Vasodilatation associated high temperatures increases the metabolic rate and systemic oxygen demand, which increase the heart rate and end-tidal CO_2 that causes metabolic acidosis.[7] However, the cases in this study did not develop metabolic acidosis, coagulopathy, or abnormalities of gas exchange. We immediately administered inotropes or vasopressors when hypotension occurred; therefore, hypotension and tachycardia were mild in these cases. There was no severe hyperthermia over 40°C in these cases, and there were less adverse effects of hyperthermia than those reported in previous reports.

During intraperitoneal hyperthermic chemotherapy, patients have been observed to develop significant hemodynamic (hypotension, tachycardia, and hyperthermia) and metabolic (acidosis, coagulopathy, and deterioration of gas exchange) perturbations.[4]

These changes were caused by heat stress; one of the body's initial responses to heat stress is dilation of the peripheral vasculature, which increases heat loss from the core to the environment. Heart rate increases to maintain cardiac output in the face of decreasing peripheral vascular resistance.[5,8]

Actually, increased temperature has a vasodilating effect: the compliance of the pulmonary vessels increases and PVR decreases.[9] However, an acute increase of PVR with increased PAP occurred in all 3 cases in this report. This can be explained by 2 mechanisms: passive increase or active increase. Passive increase of PVR results from reduced pulmonary blood flow. Immediately after IPHC begins, venous return is decreased due to cisplatin volume filling, which in turn compromises the right ventricular preload and pulmonary blood flow.

In addition to reducing venous return, regional hyperthermia can also reduce pulmonary blood flow. There has been a report that hyperthermia reduces local pulmonary blood flow.[10] Active constriction of the pulmonary vasculature causes an increase of PVR and MPAP; this occurs due the substance causing vasoconstriction, low oxygen, or circulating catecholamines.[11]

Table 1

Characteristics of 3 cases.

	Case 1	Case 2	Case 3
Age, years	48	58	47
Sex	Female	Female	Male
Weight, kg	55.3	65.3	71
Height, cm	157.8	153.9	167
Past medical history	None	None	None
Diagnosis	Adenocarcinoma (S/P LULobectomy)	Lung ca. /c Pleural seeding (S/P Wedge resection LLL)	Chest wall sarcoma
Lung cancer staging	T2NxM1a	T3N0M1a	T3N0M1a
Operation	IPHC	IPHC	Chest wall wide excision, lobectomy, IPHC
Anesthesia drug	Propofol, remifentanil	Sevoflurane, remifentanil	Sevoflurane, remifentanil
Operation time	2 h 00 min	2 h 00 min	7 h 15 min
Anesthesia time	3 h 15min	2 h 40min	8 h 15 min
IPHC time	90 min	90 min	90 min
Postoperative pain control	PCEA	PCEA	None

IPHC = intrapleural hyperthermic chemotherapy, LLL = left lower lobe, LUL = left upper lobe, PCEA = patient controlled epidural analgesia, S/P = surgery/procedure.

To prevent an increase in PVR, hypoxemia, acidosis, and hypercapnea should be avoided. To promote pulmonary vasodilatation, oxygenation should be improved, and permissive hypocapnia applied to maintain adequate preload.[12,13]

Appropriate fluid management is another goal during IPHC. Liberal fluid administration is strongly associated with postoperative pulmonary complications, including pulmonary edema and acute lung injury.[6] Adequate fluid therapy is also important in the prevention of chemotherapy-related nephropathy. Hemodynamic monitoring using devices such as pulmonary artery catheter and Vigileo may be helpful to determine the appropriate volume status.

Hypotension with tachycardia decreases tissue perfusion and increases oxygen demand. This effect can be worse in patients who have coronary artery disease. Although invasive cardiac output monitoring or transesophageal echocardiography is not always recommended, extended invasive monitoring can be used based on the patients' medical and surgical status. Adequate fluid therapy and drugs, such as inotropes and vasopressors, are needed in the management of hemodynamic instabilities.

Maintenance of normothermia is an anesthetic goal during the procedure. Use of cooled infusions and cooling blanket for temperature control prior to IPHC has been recommended in order to avoid systemic hyperthermia.[14]

All 3 cases in this series used epidural analgesia for postoperative pain control. Thoracic epidural analgesia with local anesthetics and opioids proved to be beneficial for postoperative pain control and pulmonary function. Previous studies have shown that thoracic epidural analgesia was superior to oral opioids or nonopioid analgesics.

Although epidural analgesia has sympathectomy effect (cardiovascular instability), thoracic epidural analgesia is recommended as the best method for these operations because it is associated with less pulmonary complications and less chronic pain.

Regional cisplatin perfusion is beneficial because it is associated with less systemic chemotherapeutic toxicity. However, cisplatin has various toxicities, including nephrotoxicity, ototoxicity, gastrotoxicity, myelosuppression, and allergic reactions. To prevent nephrotoxicity, fluid management is important during the procedure.

In conclusion, we were able to directly observe how hemodynamic parameters change during IPHC. We proved that IPHC caused abrupt hemodynamic changes at the beginning of cisplatin perfusion. A sudden decrease in cardiac output and increase in pulmonary vascular resistance can potentially induce complication. Anesthesiologists should prepare for these sudden changes in vital signs.

Author contributions

Conceptualization, writing, and revise: Hyeon-Jeong Lee.
Data curation: Jihwan Yun.
Investigation: Eunsoo Kim.
Writing – original draft: Hyae-Jin Kim.

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