

# The Effects Of Sevoflurane On The Progression And Cisplatin Sensitivity Of Cervical Cancer Cells

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**Objective:** To investigate the effect of sevoflurane on the progression of cervical cancer cells, and to explore its effect on the cisplatin (DDP) sensitivity in cervical cancer cells and underlying mechanism.

**Methods:** Siha and Hela cervical cancer cells were cultured and treated with 3% sevoflurane, 10  $\mu\text{mol/L}$  DDP, or the co-treatment of sevoflurane and DDP, respectively. Cell proliferation was evaluated by the CCK8 assay. Cell apoptosis was assessed by flow cytometry. Cell migration was detected by wound healing assay. The expression of B-cell lymphoma-2 (BCL-2), B-cell lymphoma-2 associated X (BAX), Ezrin, matrix metalloproteinase 2 (MMP2), lung resistance-related protein (LRP), multiple drug resistance protein 1 (MRP1), glutathione-S-transferase- $\pi$  (GST- $\pi$ ), and P glycoprotein (P-gp) protein was determined by Western blotting.

**Results:** After treated with sevoflurane, cell proliferation and migration rate in Siha and Hela cells were significantly elevated, while cell apoptosis was decreased. In addition, the expression of migration-related protein Ezrin and MMP2 was increased accordingly, apoptotic-related protein BCL-2 expression was also increased while BAX protein expression was decreased after sevoflurane treatment. The proliferation, migration rate, and apoptosis of Siha and Hela cells in sevoflurane plus DDP group were not significantly different with those in DDP group. There was no significant difference in apoptotic-related protein, migration-related protein, and drug resistance-associated proteins expression between DDP treatment group and combined treatment group.

**Conclusion:** Sevoflurane promotes the progression but has no effect on the cisplatin sensitivity in cervical cancer cells.

**Keywords:** sevoflurane, cisplatin, proliferation, migration, apoptosis, Siha, Hela

## Introduction

Cervical cancer is the most common cancer among women in developing countries and the third leading cause of cancer mortality, with global cases and deaths estimated to be 13,170 and 4250 in 2019, respectively.<sup>1</sup> While surgery is considered the preferred treatment for patients with early cervical cancer, chemotherapy is the optimal treatment for patients with advanced, recurrent, and metastatic cervical cancer.<sup>2,3</sup> Platinum-based drugs, which effectively eradicate tumor cells, are still considered as the first-line anticancer drugs in numerous human cancers including cervical cancer, but the resistance of cancer cells to DDP seriously hinders its clinical application.<sup>4</sup>

Sevoflurane, a colorless, transparent and non-irritating volatile anesthetic, has been widely used in the surgical process of malignancy tumors including cervical

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cancer. In recent years, increasing evidence suggests that this inhaling anesthetics have impact on the biological behavior of cancer cells.<sup>5-7</sup> Additionally, previous studies reported that sevoflurane has a different effect on the chemosensitivity of cisplatin in distinct cancer cells.<sup>8-10</sup> Sevoflurane had no influence on DDP sensitivity in mouse brain cells.<sup>8</sup> However, it enhanced DDP sensitivity in non-small cell lung cancer (A549) cells,<sup>11</sup> while in renal cell carcinoma (RCC4) cells<sup>9</sup> and Ehrlich ascites tumor cells,<sup>10</sup> it attenuated the sensitivity of cells to DDP. To date, there was no published report on whether sevoflurane has effect on DDP sensitivity in cervical cancer cells, and whether patients who show resistance to DDP chemotherapy are more sensitive to sevoflurane, as well.

In the present study, the effects of sevoflurane on the proliferation, migration and apoptosis of cervical squamous cancer SiHa cells and adenocarcinoma HeLa cells and underlying mechanism were investigated. In addition, the effects of sevoflurane on the DDP sensitivity in cervical cancer cells were explored after comparing the cell viability, biological behavior, apoptotic-related protein, migration-related protein, and drug resistance-associated proteins expression between DDP treatment group and sevoflurane combined with DDP treatment group.

## Materials And Methods

### Cell Lines And Cell Culture

Human cervical cancer cells SiHa and HeLa were purchased from European Collection of Authenticated Cell Cultures. SiHa cell was established from fragments of primary tissue sample obtained after surgery from a Japanese patient. HeLa cell was a type of cervical adenocarcinoma cell line. Cells were cultured in Dulbecco's modified Eagle's Medium (DMEM, Gibco, USA) containing 10% fetal bovine serum. All the cells were incubated in a humidified atmosphere containing 5% CO<sub>2</sub> at 37°C for growth.

### Sevoflurane And Combined Treatment

Cells were split and seeded at equal cell density in 30 mm<sup>2</sup> Petri dishes (VWR, Leicestershire, UK) and 6, 24 and 96-well plates, then incubated at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub> for growth. When the cultures reached 70%-80% confluence, the plates were placed in a 2 L purposely built gas chamber with inlet and outlet connectors. Sevoflurane mixed with 5% CO<sub>2</sub> balanced with air was delivered into the chamber by a vaporizer (Sevoflurane; Abbott, Abbot Park, IL, USA) at a rate of 2 L/min for 5 min until the

desired gas dose was reached. Sevoflurane concentrations in the chamber were monitored using an anesthetic monitor (Datex-Ohmeda, Stirling, UK) at the outlet part of chamber. When the sevoflurane concentration of the chamber reached 3%, the gas delivery was stopped and the inlet and outlet were clamped, respectively. The chamber was then transferred to a 37°C incubator (Galaxy R CO<sub>2</sub> chamber; New Brunswick Scientific, Enfield, USA) to expose the cells to 3% sevoflurane for 2 hrs. In clinical operations, the minimum effective concentration of less than 4% is usually used to maintain the anesthetic state. In our preliminary studies, the cell viability of Hela cells was increased after 1%, 2% or 3% sevoflurane treatment and the effect of sevoflurane on cell viability was concentration-dependence. Therefore, sevoflurane at a concentration of 3% was chosen in the present study to treat cells. The half maximum inhibitory concentration (IC<sub>50</sub>) of DDP on SiHa cells was 18 µmol/L and Hela cells was 18.3 µmol/L ([Supplementary Figure 1](#)). Referring to IC<sub>50</sub> value, 1 mM reserve solution (Calbiochem, USA, CAT 232120) was diluted to 10 µmol/L with DMEM to make a DDP-supplemented media. Cells were divided into four treatment groups: control group, sevoflurane group, DDP group, and a combination of sevoflurane and DDP group ([Table 1](#)). The control group was treated with 95% air/5% CO<sub>2</sub> at 2 L/min for 2 hrs. The sevoflurane group was treated with 3% sevoflurane mixed with 95% air/5% CO<sub>2</sub> at 2 L/min for 2 hrs. The DDP group was treated with 10 µmol/L DDP and immediately exposed to 95% air/5% CO<sub>2</sub> at 2 L/min for 2 hrs. The sevoflurane and DDP group were treated with 10 µmol/L DDP and immediately exposed to 3% sevoflurane mixed with 95% air/5% CO<sub>2</sub> at 2 L/min for 2 hrs. In order to be closer to the use of clinical medicines, we did not change the medium after gas exposure. Then, each group of cells were moved into a 37°C incubator for 24 hrs to subsequent experiments.

### Cell Viability Assay

To evaluate cell viability rate, 1×10<sup>4</sup> cells were plated in 96-well plates and cultured for 24 hrs for the cells to

**Table 1** Four Treatment Groups

Treatment Groups	Concentration	Exposure Time, Hour
Control		
Sevoflurane	3 vol%	2
DDP	10 µmol/L	
Sevoflurane+DDP	3 vol%+10 µmol/L	2

**Notes:** The Sevoflurane + DDP group were treated with 10 µmol/L DDP and immediately exposed to 3% sevoflurane mixed with 95% air/5% CO<sub>2</sub> at 2L/min for 2 hrs, then moved into a 37°C incubator for 24 hrs.

adhere. After DDP or/and sevoflurane treatment, the cells were cultured in a CO<sub>2</sub> incubator for another 24 hrs. Thereafter, Cell Counting Kit-8 (CCK-8, Sigma, USA) was used to analyze cell viability and the number of viable cells was assessed by measurement of absorbance at 450 nm using a Microplate Reader (Bio Tek Instruments, Winooski, VT, USA) after 2 hrs incubation. The experiments were performed at least three times for the final analyses.

## Apoptosis Analysis By Flow Cytometry

To evaluate cell apoptosis rate,  $1 \times 10^5$  cells were plated in 6-well plates and culture for 24 hrs. Apoptosis was assessed using the Annexin V-FITC/PI Apoptosis Detection Kit (BD Pharmingen, CA, USA) apoptosis detection kit (BD, Franklin Lakes, NJ, USA) according to the manufacturer's instructions. After sevoflurane or/and DDP treatment and continued culture for 24 hrs, cells were labeled with 5  $\mu$ L Annexin V-FITC and PI in dark at room temperature for 15 min. The early apoptosis was determined based on the percentage of cells with Annexin V+/PI-, whereas the late apoptosis was that of cells with Annexin V+/PI+. The total number of early apoptosis plus late apoptosis is considered to be the ultimate apoptosis rate of the cells. The percentage of apoptotic cells analyzed by flow cytometry (Beckman Coulter, Fullerton, CA, USA). The experiments were performed at least three times for the final analyses.

## Wound Healing Assay

To evaluate the migration ability of cancer cells,  $1 \times 10^5$  cells were plated in 6-well plates and cultured to a fully fused state. After DDP or/and sevoflurane treatment, an artificial gap was created by scraping with a sterile plastic pipette tip (200  $\mu$ L). By a phase-contrast microscope and digital camera (Olympus CK30, Tokyo, Japan), migrating area from the initial wound was measured from images taken. Five randomly selected scratch areas from each well were analyzed in 0 hr and 24 hrs treatment using ImageJ 1.35 (NIH, Bethesda, MD, USA) software. The experiments were performed at least three times for the final analyses.

## Western Blot Analysis

Cells were cultured in 6-well plate ( $1 \times 10^6$  cells per well). After sevoflurane or/and DDP treatment and an additional 24 hrs cultured, the proteins expression of  $\alpha$ -tubulin,  $\beta$ -actin, BCL-2,

BAX, Ezrin, MMP2, LRP, MRP1, GST- $\pi$ , and P-gp in cells was fractionated with sodium dodecyl sulfate-polyacrylamide gel electrophoresis, followed by transferring onto Polyvinylidene fluoride (PVDF) membrane. The membranes were incubated overnight at 4°C with the primary antibodies as following: anti-Ezrin (1:1000, Cell Signaling Technology, Denver, MA, USA), anti-MMP2 (1:1000, Cell Signaling Technology, Denver, MA, USA), anti- $\alpha$ -Tubulin (1:1000, Cell Signaling Technology, Denver, MA, USA), anti-BCL-2 (1:1000, Cell Signaling Technology, Denver, MA, USA), anti-BAX (1:1000, Cell Signaling Technology, Denver, MA, USA), anti- $\beta$ -actin (1:3000, Cell Signaling Technology, Denver, MA, USA) and anti-LRP (1:1000, Abcam, San Francisco, CA, USA), anti-MRP1 (1:1000, Abcam, San Francisco, CA, USA), anti-GST- $\pi$  (1:1000, Abcam, San Francisco, CA, USA), anti-P-gp (1:1000, Abcam, San Francisco, CA, USA). After washed with Tris-buffered saline with Tween (TBST), the membranes were incubated with horseradish peroxidase-conjugated goat anti-rabbit IgG (1:2000, Biosharp) or rabbit anti-mouse IgG secondary antibody (1:4000, Biosharp) at 37°C for 1.5 hrs. Protein signals were detected using enhanced chemiluminescence reagent (Millipore, USA). The intensity of proteins was quantified by densitometry using Bio-Rad Quantity One software (Bio-Rad, Hercules, USA). The experiments were performed at least three times.

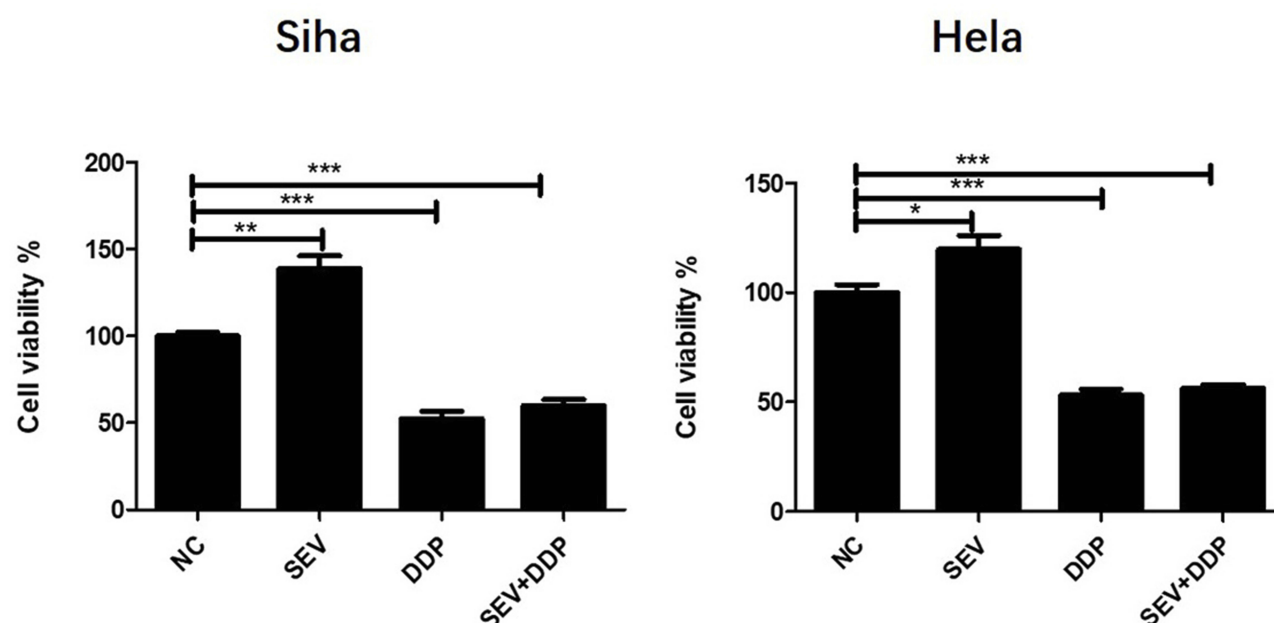
## Statistical Analysis

Data analysis was performed with Statistical Product and Service Solutions (SPSS) 19.0 statistical software (IBM Corporation, Armonk, NY, USA). Data were expressed as mean  $\pm$  standard deviation. Differences among groups were assessed using one-way ANOVA, followed by least significance difference method. Differences were considered statistically significant at a 2-sided *P*-value  $< 0.05$ .

## Results

### The Effect Of Sevoflurane And Sevoflurane Combined With DDP On The Cell Proliferation Rate Of Cervical Cancer Cells

As shown in Figure 1, compared with the control group, the cell viability of Siha and Hela cells was increased after 3% sevoflurane treatment, while the cell viability was significantly decreased after DDP treatment. Whereas, the cell viability of Siha and Hela cells was no significant



**Figure 1** The effect of sevoflurane and sevoflurane combined with cisplatin (DDP) on the cell proliferation rate of cervical cancer cells. Siha and Hela cells were treated with sevoflurane, DDP, or the co-treatment of sevoflurane and DDP. The proliferation rate was evaluated by CCK8 assay. The bars represent the cell viability rates of proliferation in each group. Data are shown as means and standard deviation of three independent experiments. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

difference between the DDP group and sevoflurane combined with DDP group. These results indicated that sevoflurane promoted the proliferation of cells, but it did not affect the inhibition of DDP on the proliferation of cervical cancer cells.

### The Effect Of Sevoflurane And Sevoflurane Combined With DDP On The Cell Apoptosis And Apoptotic-Related Protein BCL-2 And BAX In Cervical Cancer Cells

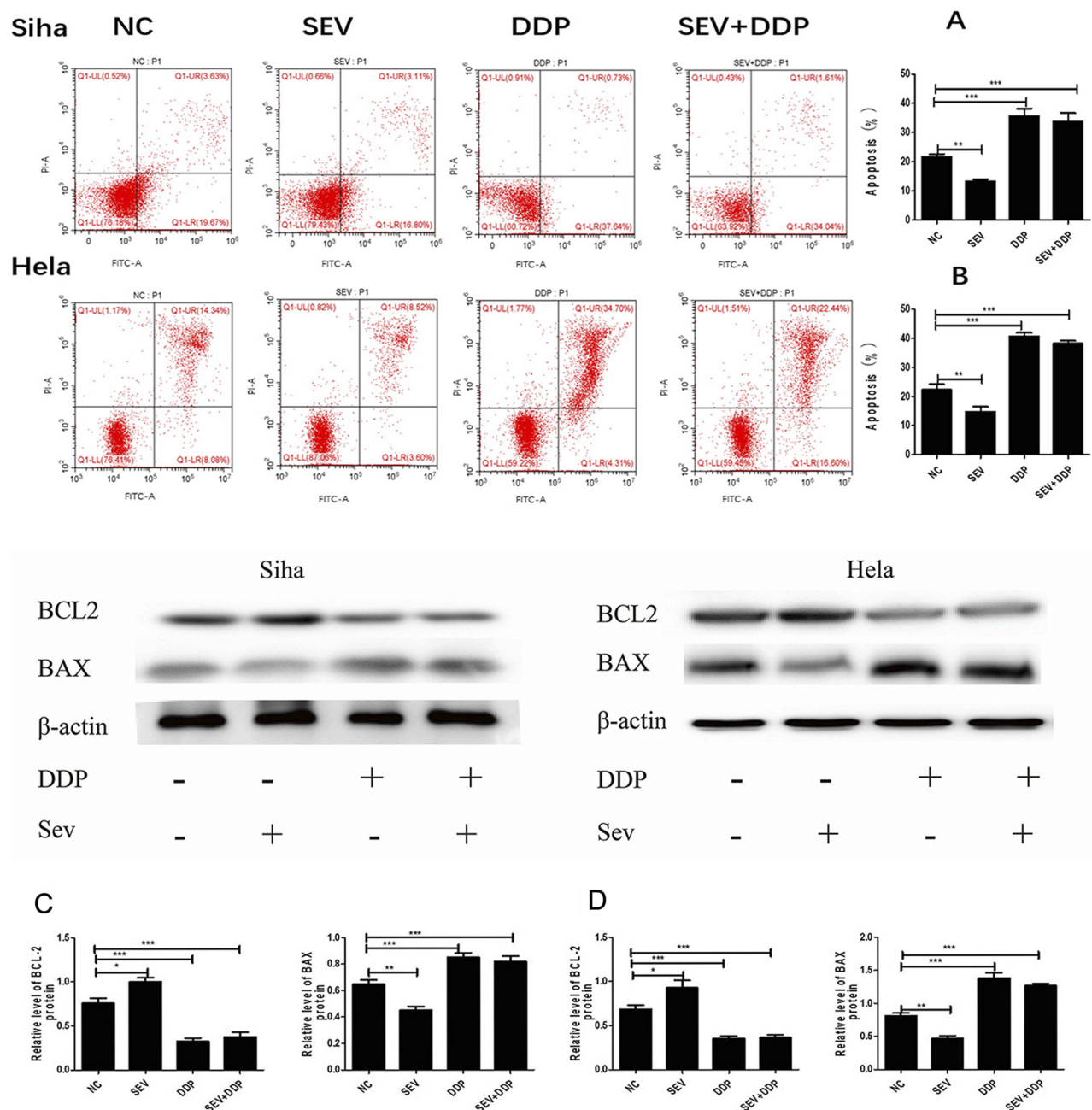
As shown in [Figure 2](#), the percentages of apoptosis of Siha and Hela cells were decreased significantly by sevoflurane treatment and increased obviously after DDP treatment when compared with control group. However, statistical analysis showed that there was no significant difference between the DDP group and sevoflurane combined with DDP group. These results suggested that sevoflurane-inhibited cell apoptosis but did not influence the promotion of DDP on the apoptosis of cervical cancer cells.

The result of proteins revealed that the expression of BCL-2 proteins was upregulated in Siha and Hela cells after sevoflurane treatment and downregulated significantly after DDP treatment. In addition, the expression of BAX was significantly reduced after sevoflurane treatment, while

DDP treatment significantly increased its expression. But no significant difference was indicated in the expressions of both BCL-2 and BAX proteins between the DDP and sevoflurane combined DDP group, which further demonstrated sevoflurane-inhibited cell apoptosis but had no influence on the promotional effect of DDP treatment in the process of apoptosis on cervical cancer cells.

### The Effect Of Sevoflurane And Sevoflurane Combined With DDP On The Cell Migration And Migration-Related Protein Ezrin And MMP2 In Cervical Cancer Cells

The effect of sevoflurane or/and DDP on cervical cancer cells migration was assessed by determining the migration area by using the wound healing assay. As shown in [Figure 3](#), compared with the control group, treatment of sevoflurane was significantly increased the migration area of cells at 24 hrs post-treatment, while the treatments of DDP were obviously decreased the migration area. Nevertheless, there was no statistical difference between the DDP group and sevoflurane combined with DDP group, which indicates that the inhibitory effect of DDP was not affected by the promotion of sevoflurane on the migration of cervical cancer cells.

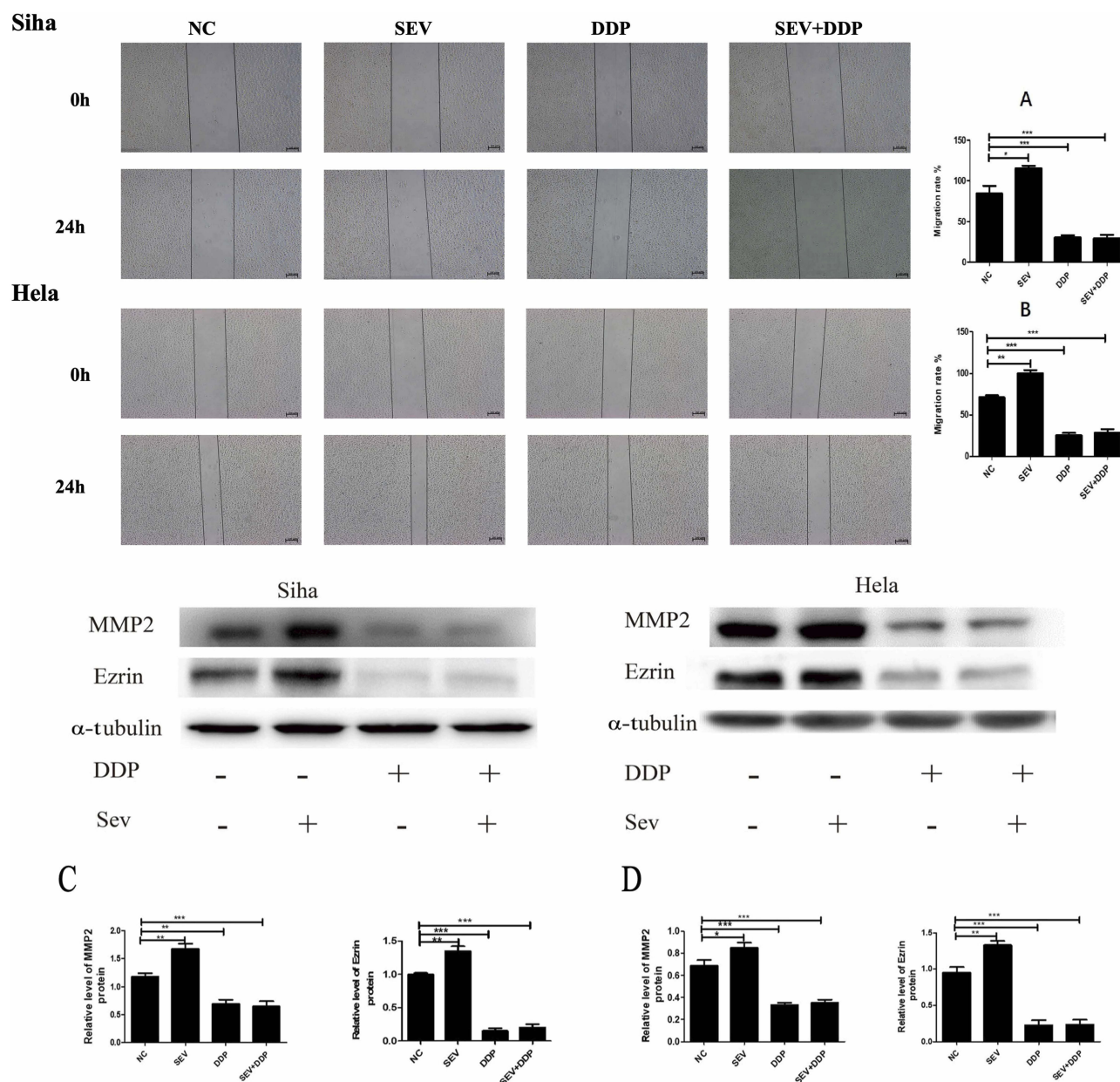


**Figure 2** The effect of sevoflurane and sevoflurane combined with DDP on the cell apoptosis and apoptotic-related protein BCL-2 and BAX in cervical cancer cells. Siha and Hela cells were treated with sevoflurane, DDP, or the co-treatment of sevoflurane and DDP. The apoptosis percentages were evaluated by flow cytometry. The bars represent apoptosis percentages of each group. Data of Siha (**A**) and Hela (**B**) are shown as means and standard deviation of three independent experiments. The expressions of BCL-2 and BAX were determined by Western blot. The data of Siha (**C**) and Hela (**D**) are presented as relative expression level of BCL-2 and BAX proteins normalized to  $\beta$ -actin. Data are shown as means and standard deviation of three independent experiments. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

The result of proteins showed that sevoflurane treatment upregulated both of the Ezrin and MMP2 proteins expression, while DDP treatment suppressed their expressions significantly in Siha and Hela cells. In view of the levels of Ezrin and MMP2 protein, there was no statistical

difference between DDP group and sevoflurane combined with DDP group. These results further demonstrated that sevoflurane promoted cell migration while had no effect on the inhibition of DDP treatment in the process of migration on cervical cancer cells.



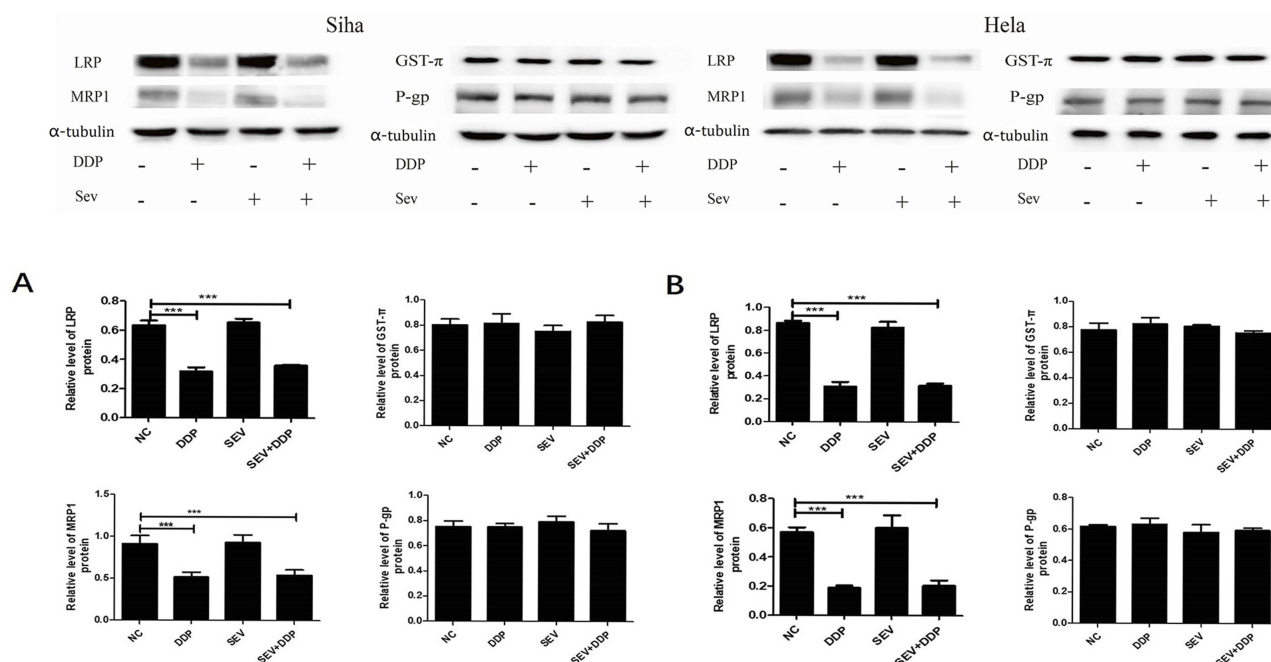


**Figure 3** The effect of sevoflurane and sevoflurane combined with DDP on the cell migration and migration-related protein Ezrin and MMP2 in cervical cancer cells. Siha and Hela cells were treated with sevoflurane, DDP, or the co-treatment of sevoflurane and DDP. Migrating area from the initial wound was measured from images taken. Scratch areas of each group were analyzed in 0 h and 24 h treatment using ImageJ. The bars represent migrating area of each group. Data of Siha (A) and Hela (B) are shown as means and standard deviation of three independent experiments. The expressions of Ezrin and MMP2 protein were determined by Western blot. The data of Siha (C) and Hela (D) are presented as relative expression level of Ezrin and MMP2 proteins normalized to  $\alpha$ -tubulin. Data are shown as means and standard deviation of three independent experiments. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

## The Effect Of Sevoflurane And Sevoflurane Combined With DDP On The Expression Of Drug Resistance-Associated Proteins MRP1, LRP, GST- $\pi$ And P-gp In Cervical Cancer Cells

Overexpression of LRP, MRP1, GST- $\pi$  and P-gp played important roles in chemoresistance. To explore the effects of sevoflurane on cisplatin resistance in cervical cancer

cells, LRP, MRP1, GST- $\pi$  and P-gp proteins were investigated in the cells after sevoflurane or/and DDP treatment. As Figure 4 showed, the expressions of LRP and MRP1 were almost equal in the control group and sevoflurane group, and these two proteins were found to be almost equivalently down-regulated in the DDP group and DDP combined sevoflurane group. Moreover, the expression of GST- $\pi$  and P-gp proteins was not affected by sevoflurane or/and DDP treatment. In view of the LRP, MRP1, GST- $\pi$



**Figure 4** The effect of sevoflurane and sevoflurane combined with cisplatin (DDP) on the expression of drug resistance-associated proteins MRP1, LRP, GST- $\pi$  and P-gp in cervical cancer cells. SiHa and HeLa cells were treated with sevoflurane, DDP, or the co-treatment of sevoflurane and DDP. The expressions of MRP1, LRP, GST- $\pi$  and P-gp were determined by Western blot. The data of SiHa (**A**) and HeLa (**B**) are presented as relative expression level of MRP1, LRP, GST- $\pi$  and P-gp proteins normalized to Tubulin. Data are shown as means and standard deviation of three independent experiments. \*\*\* $P$ <0.001.

and P-gp protein expression in these four treatment groups, it suggests that sevoflurane had no impact on the resistance of cervical cancer cells to DDP.

## Discussion

Hysterectomy remains the standard treatment modality for patients with early-stage cervical cancer.<sup>12</sup> Sevoflurane, a common volatile anesthetic, is extensively used in surgical oncology. Despite the primary surgical resection is often curative for these patients, the recurrence after surgery is inevitable among women with several high-risk factors including anesthetics administration.<sup>13–15</sup> Hence, it is essential for these patients to receive an adjuvant DDP-based chemotherapy with or without radiotherapy postoperatively.<sup>16,17</sup> The resistance of cancer cells to cisplatin significantly reduces the efficacy of DDP in chemotherapy. ERCC1-XPF, as a heterodimer, plays an important role in removing DNA damage caused by DDP.<sup>18,19</sup> In addition, there are evidences that the use of narcotic drugs may also contribute to cisplatin resistance. Of note, though differential effects of sevoflurane on the chemosensitivity have been reported in lung<sup>11</sup> and renal cell carcinomas,<sup>9</sup> such effect of sevoflurane in cervical cancer remains to be elucidated. In this study, we first observed that sevoflurane promoted the proliferation and

migration and inhibited the apoptosis, while had no effects on the sensitivity to DDP in cervical cancer cells.

Cell proliferation is considered as a vital indicator for cell survival or death when exposing to various conditions.<sup>20</sup> In our study, we first demonstrated that sevoflurane alone exerted a positive effect on the proliferation of SiHa and HeLa cells, but had no influence on the inhibitory effect of DDP on the proliferation of cervical cancer cells.

BCL-2 protein-mediated apoptosis blockade contributes to malignant transformation in multiple human cancers, whereas Bax protein enhances the permeability of the mitochondrial outer membrane and induces release of cytochrome c and consequently promotes apoptosis, which can be counteracted by BCL-2.<sup>21</sup> In the present study, we first observed that sevoflurane treatment apparently suppressed the apoptosis of SiHa and HeLa cells, as confirmed by Western blot analyses with a remarkable elevation of BCL-2 and sharp decline of Bax expression in both cell lines. Notably, accumulated evidences have revealed that the sensitivity to DDP is conferred by suppression of BCL-2 expression in various types of human cancers.<sup>22,23</sup> Thus, the cytotoxic effect caused by DDP in cervical cancer cells might be weakened by sevoflurane via increasing the expression of BCL-2. However, neither

the apoptotic rate nor the level of related proteins (BCL-2 and BAX) was significantly changed in DDP-treated SiHa and HeLa cells after sevoflurane contact, demonstrating that pro-apoptotic function induced by DDP was not altered by sevoflurane.

The metastasis of cancer is a complex process involving the dissemination of tumor from the primary site to distant organs.<sup>24</sup> Numerous scientific and clinical evidences have shown that Ezrin and Matrix metalloproteinase 2 (MMP2) proteins are important structural molecule controlling cell adhesion and invasive properties of cancer cells,<sup>25,26</sup> including cervical cancer.<sup>25</sup> In line with this notion, our study first detected that sevoflurane promoted the migration of both SiHa and HeLa cells, which was mediated by upregulating the expression of Ezrin and MMP2 proteins. Nevertheless, it is worth noting that cancer metastasis plays a crucial role in generating drug resistance, in which Ezrin and MMP2 were involved.<sup>25–27</sup> But fortunately, there was no significant difference found between DDP and DDP combined with sevoflurane treatment groups, supporting that DDP-induced suppression on cervical cancer cells migration was not affected by sevoflurane.

Multidrug resistance-related protein 1 (MRP1) and P-glycoprotein (P-gp) are the best-characterized transport proteins and commonly protect cells by effluxing chemotherapeutic agents, whose high expression in cancer cells can lead to a decrease in intracellular platinum concentration.<sup>28–30</sup> In this study, we found that the level of MRP1 and P-gp was not changed in sevoflurane group, suggesting that sevoflurane administration alone had no effect on chemosensitivity in cervical cancer cells. Additionally, the expression of MRP1 was almost equally downregulated by DDP and DDP combined with sevoflurane treatment, demonstrating that the DDP resistance of SiHa and HeLa cells was not influenced by the action of sevoflurane. Interestingly, the expression of P-gp did not change in the application of DDP and DDP combined with sevoflurane treatment. Hence, we suggested although there are several resemblances in the biochemical and pharmacological properties of MRP1 and P-gp, the major protein involved in cisplatin resistance in SiHa and HeLa cells is MRP1 rather than P-gp. Similar results were reported in one study from Cole et al,<sup>31</sup> they identified an overexpression of MRP1 rather than P-gp in doxorubicin-resistant HeLa cell lines.

Lung-resistance-related protein (LRP) and glutathione-S-transferase- $\pi$  (GST- $\pi$ ) are two kinds of non-transport

proteins which are generally considered to be associated with multidrug resistance (MDR) of various tumors.<sup>32–34</sup> Our results showed that the level of LRP and GST- $\pi$  were not altered by sevoflurane, indicating that application of sevoflurane alone had no influence on chemosensitivity in both SiHa and HeLa cells. However, the expression of GST- $\pi$  was not changed after the action of DDP or DDP combined with sevoflurane treatment. This result is similar to the findings of Li et al,<sup>35</sup> with a low expression of LRP only in DDP-resistant ovarian cancer cells rather than GST- $\pi$ .

Little effort has been made to explore the effects of sevoflurane on the biological behavior and chemosensitivity in various types of cancer cells. For example, Ciechanowicz et al<sup>9</sup> found that sevoflurane promoted the proliferation, migration and reduced the DDP sensitivity in kidney cancer cells, which were reversed by *TGF- $\beta$*  and *OPN* knockdown. Similar results were also observed in human breast cancer,<sup>7</sup> colon cancer<sup>36</sup> and hepatocellular carcinoma cells.<sup>37</sup> Conversely, two groups revealed that, in human lung adenocarcinoma cells, the metastatic potential was significantly inhibited while the anticancer effects of DDP were enhanced after sevoflurane exposure, respectively, which was associated with upregulation of nuclear Smad3 and downregulation of XIAP, Survivin and MMPs.<sup>5,9</sup> In fact, the cytotoxic effect of the combined application of DDP and sevoflurane on a variety of cells has also been investigated in vivo.<sup>8</sup> It showed that sevoflurane administration in mice induced obvious genotoxic effect in peripheral blood leucocytes, liver, kidney, brain and Ehrlich ascites tumour cells, while a synergistic effect of combined treatments was not expressed in brain and Ehrlich ascites tumor cells. Thereafter, another in vivo research<sup>10</sup> reported that apoptosis in Ehrlich ascites tumor cells was not affected under application of sevoflurane alone but was significantly attenuated after the co-treatment of sevoflurane and DDP. From the above, we suggested that sevoflurane may exhibit dual effects on behavior functions and chemosensitivity in different human cancers in a tissue and cellular context-dependent manner.

There are still some limitations that need to be interpreted cautiously in this study. First, diverse volatile and intravenous (such as propofol) anesthetics are usually used in combination in clinical practice. Thus, it is necessary to investigate the influence of sevoflurane and other types of anesthetics on cervical cancer cell lines especially with cisplatin-resistance in the future. Second, experiments in our study were all designed in vitro, which should be conducted in vivo in the future. Third, further studies need



to be carried out to explore the potential molecular mechanisms or signaling pathways regulating the effect of sevoflurane on cervical cancer cell lines which are obtained from cisplatin-resistant patients.

## Conclusion

In conclusion, despite the limitations, results of our study favor that the use of sevoflurane can affect the proliferation, migration and apoptosis of cervical cancer cells. Sevoflurane promotes the proliferation and migration of Siha and Hela cell lines, while it exerts an inhibitory function on the apoptosis of cells. But sevoflurane did not attenuate the cisplatin sensitivity in cervical cancer cells.

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## Author contributions

X.Q. Zhu and R.Y. Li conceived and designed the study. F. Xue, Y.C. Xu and W.W. Zhang acquired the data by did the experiments. Y. Z. Song and Y.C. Xu analyzed and interpreted the data. F. Xue, Y.C. Xu and W.W. Zhang drafted the article. X.Q. Zhu, R.Y. Li and Y. Z. Song revised the important intellectual content of manuscript. All authors contribute to data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the final version to be published.

## Disclosure

The authors report no conflicts of interest in this work.

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