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Effect of Propofol and Etomidate on the Proliferation, Cell-cycle Distribution, Apoptosis and Necrosis of Pancreatic Tumour Cells

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Abstract. *Background/Aim: The influence of surgical interventions and anaesthesiological procedures on tumour progression was investigated as early as the 1920s. In current cancer management, the perioperative phase is increasingly being considered a vulnerable period with an increased risk of tumour cell dissemination due to medication, surgical manipulation, and immunosuppression. The extent to which narcotics administered in the perioperative setting influence the oncological outcomes of patients with pancreatic cancer is still unclear. Materials and Methods: To investigate the effect of propofol and etomidate on the proliferation, cell-cycle distribution, apoptosis, and necrosis of pancreatic tumour cells in vitro, PaTu 8988t and Panc-1 pancreatic cancer cells were treated with 0-1,000 μM propofol or etomidate for 24 h each. Cell proliferation was measured with enzyme-linked immunosorbent–bromodeoxyuridine assay. The apoptosis rate was analysed with annexin V staining and the cell-cycle distribution with flow cytometry. Results: Propofol at 1,000 μM induced apoptosis and inhibited cell proliferation. The cell cycle showed an increased S-phase and reduced cells in the G_1-phase. At 100 μM, propofol significantly inhibited proliferation of the pancreatic cancer cell line PaTu 8988t and reduced cells in the G_2-phase in the cell cycle. Etomidate had no effects on cell-cycle distribution, proliferation, apoptosis, and necrosis at the concentrations used. Conclusion: In this study, propofol was shown to have anticancer effects by induction of apoptosis and inhibition of cell proliferation, while etomidate did not affect pancreatic cancer cells. However, it is too early to make any recommendation for changes in clinical practice and further clinical studies are warranted to investigate the effect of anaesthetics on cancer progression.*

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Key Words: Propofol, etomidate, pancreatic cancer, cancer, proliferation, apoptosis, necrosis, cell-cycle distribution.

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The influence of surgical interventions and anaesthesiological procedures on tumour progression was investigated as early as the 1920s. In 1916, Gaylord and Simpson showed that repeated anaesthesia accelerates the growth of breast carcinoma (1). In 1977, a retrospective study by Fried *et al*. investigated the effect of anaesthetic gases on the long-term prognosis of patients with cancer (2). In current cancer management, the perioperative phase is assumed to play a key role in the progression of malignant tumours (3). The combination of surgical manipulation and perioperative impairment of the immune defence increases the risk of tumour cell dissemination, with negative consequences for the course of the disease (4).

During the perioperative phase, mechanical manipulation of tumour tissue and traumatisation of tumour vessels may result in the infiltration of tumour cells into the lymphatic and vascular system (5). The increased secretion of growth factors and the imbalance between pro-angiogenetic and anti-angiogenetic factors during wound healing may facilitate the progression of disseminated cells and micro-metastases (6). In addition, the increase in catecholamine level *via* the perioperative stress axis impedes the antitumour defence mechanisms of the immune system and reduces the number of natural killer cells, T-helper cells, and cytotoxic T-cells in the postoperative period (7). β-Adrenergic signals regulate multiple cellular processes in tumour tissue, thereby directly facilitating the proliferation, metastasis, and progression of the tumour (8). Overall, tumorigenesis is a multistep process, in which several mutations are responsible for the transformation from a normal cell into a highly aggressive tumour cell. Although the first mutations mostly cause only subtle changes in cell morphology, a carcinoma *in situ* develops in the further course of the disease. During further

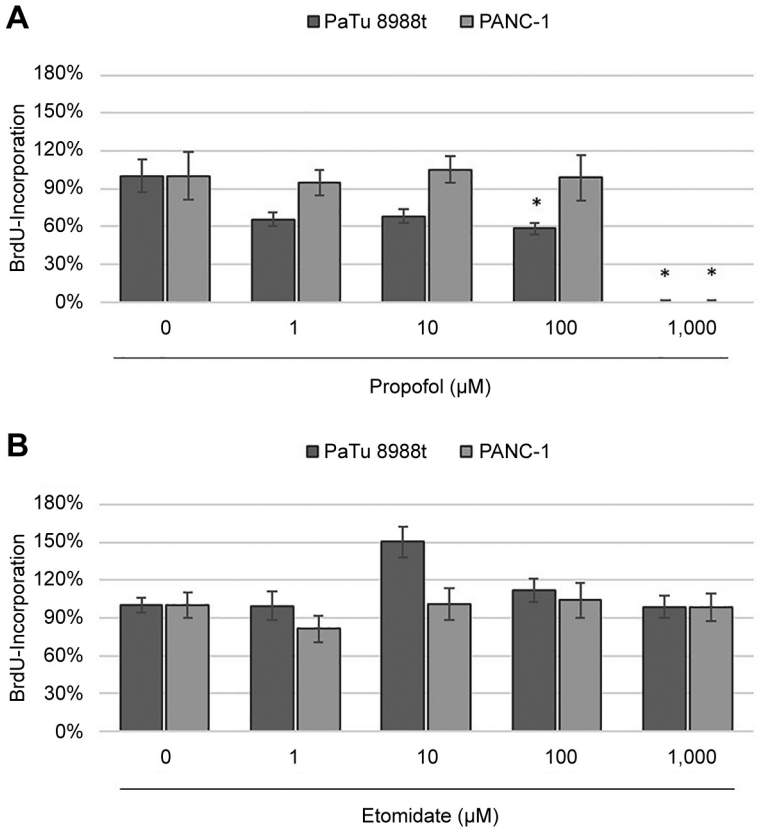

Figure 1. *The effects of propofol (A) and etomidate (B) on the proliferation of the pancreatic carcinoma cell lines PaTu 8988t and PANC-1 in vitro. Cell proliferation was quantified by measuring bromodeoxyuridine (BrdU) incorporation. *Significantly different at p<0.05 compared to the untreated control.*

transformation, aggressive tumours develop, which are marked by destructive growth and later also by invasion and metastasis (9). This process also applies to pancreatic adenocarcinoma, one of the most aggressive types of malignant tumour in humans (10).

During the past two decades, increasing interest has been focused on the impact of anaesthesia on cancer progression and oncological outcome (11). A large number of preclinical and clinical studies examined whether a patient`s oncological outcome can be influenced by the choice of specific anaesthetic technique [reviewed in (12)]. While the effect of propofol was investigated in several tumour entities [reviewed in (13)], knowledge of the influence of etomidate on cancer cells is limited [reviewed in (14)]. For this reason, the aim of this study was to compare the effects of both these intravenous anaesthetic agents on two pancreatic cancer cell lines.

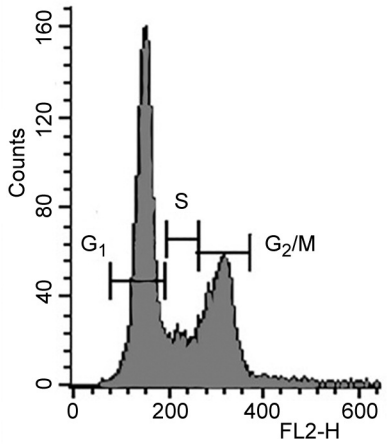

Figure 2. *Typical histogram of the cell-cycle distribution after marking the cell nuclei with propidium iodide in standard growth medium.*

Materials and Methods

Cell lines. The human pancreatic cancer cell lines PaTu 8988t and PANC-1 were obtained from Professor Ellenrieder (Philipps University of Marburg, Germany). PaTu 8988t and PANC-1 cells were maintained in Dulbecco's modified Eagle's medium (Sigma-Aldrich, St. Gallen, Switzerland) supplemented with 10% foetal calf serum (Sigma-Aldrich) and 5% Myco Zap (Lonza Verviers SPRL,

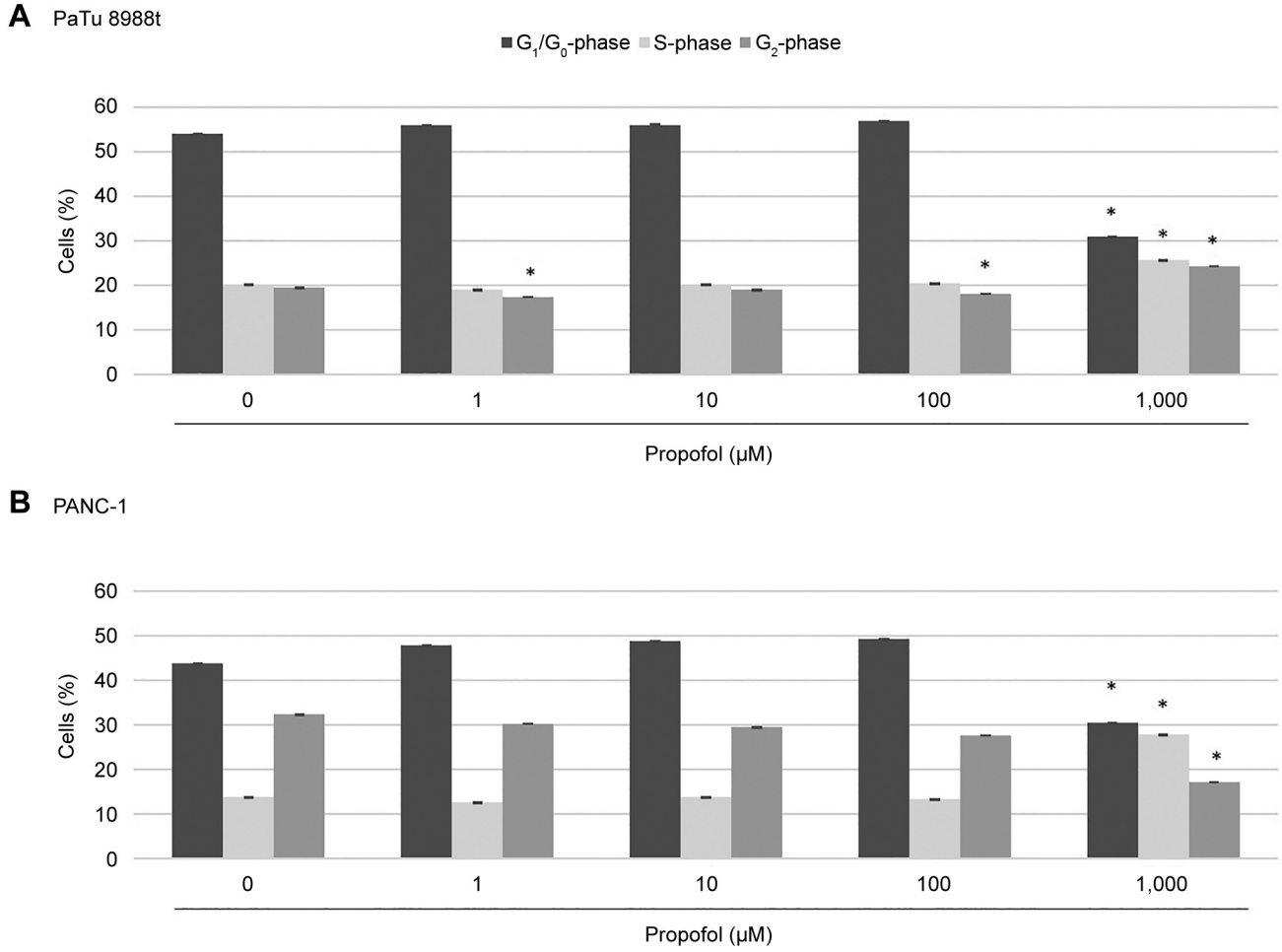

Figure 3. *Cell-cycle distribution in PaTu 8988t (A) and PANC-1 (B) pancreatic cancer cell lines after treatment with 0 μM, 1 μM, 10 μM, 100 μM and 1,000 μM propofol for 24 h. Cell cycle was analysed by means of flow cytometry after staining with propidium iodide. *Significantly different at p<0.05 compared to the untreated control.*

Verviers, Belgium). Cells were cultured at 37˚C in humidified atmosphere with 5% CO_2 and maintained in monolayer culture. Experiments were carried out with cells at ~70-80% confluence.

Reagents. Commercially available propofol was purchased from Sigma-Aldrich and etomidate from Piramal Critical Care (Hallbermoss, Germany). Final concentrations were obtained by diluting drugs in standard growth media. All solutions were prepared freshly prior to use.

Cell proliferation. Quantification of cell proliferation was based on the measurement of bromodeoxyuridine (BrdU) incorporation during DNA synthesis. The test was performed according to the manufacturer's protocol (cell proliferation ELISA-BrdU; Roche Applied Science, Basel, Switzerland). In brief, cells were incubated with 0, 1, 10, 100 or 1,000 μM propofol or etomidate in a serum-free medium for 24 h. After incubation, cells were additionally treated with BrdU-labelling solution for 16 h. The culture medium was then removed, the cells were fixed, and DNA was denatured. Afterwards, the cells were incubated with anti-BrdU-peroxidase solution for 90 min and washed three times to remove antibody conjugates. Immune complexes were detected using TMB substrate for 15 min and quantified by measuring absorbance at 405 nm and 490 nm. All tests were performed in duplicates; eight wells per treatment group were used, and tests were repeated at least three times.

Cell cycle analysis. For flow cytometric analysis, cancer cells were incubated with 0, 1, 10, 100 or 1,000 μM propofol or etomidate in serum-free medium for 24 h. After incubation, detachment by standard trypsinisation and cell counting, the cells were fixed in 100% ethanol at room temperature for 30 min. The cells were then treated with 1 mg/ml RNase A. After incubation for 30 min, cells were stained with 100 μg/ml propidium iodide (Sigma-Aldrich) and analysed with flow cytometry using FACS Calibur (BD Bioscience, Haryana, India) and Cellquest Pro software (BD Bioscience); 10^4 cells were counted for each sample. All tests were performed in duplicate and repeated three times.

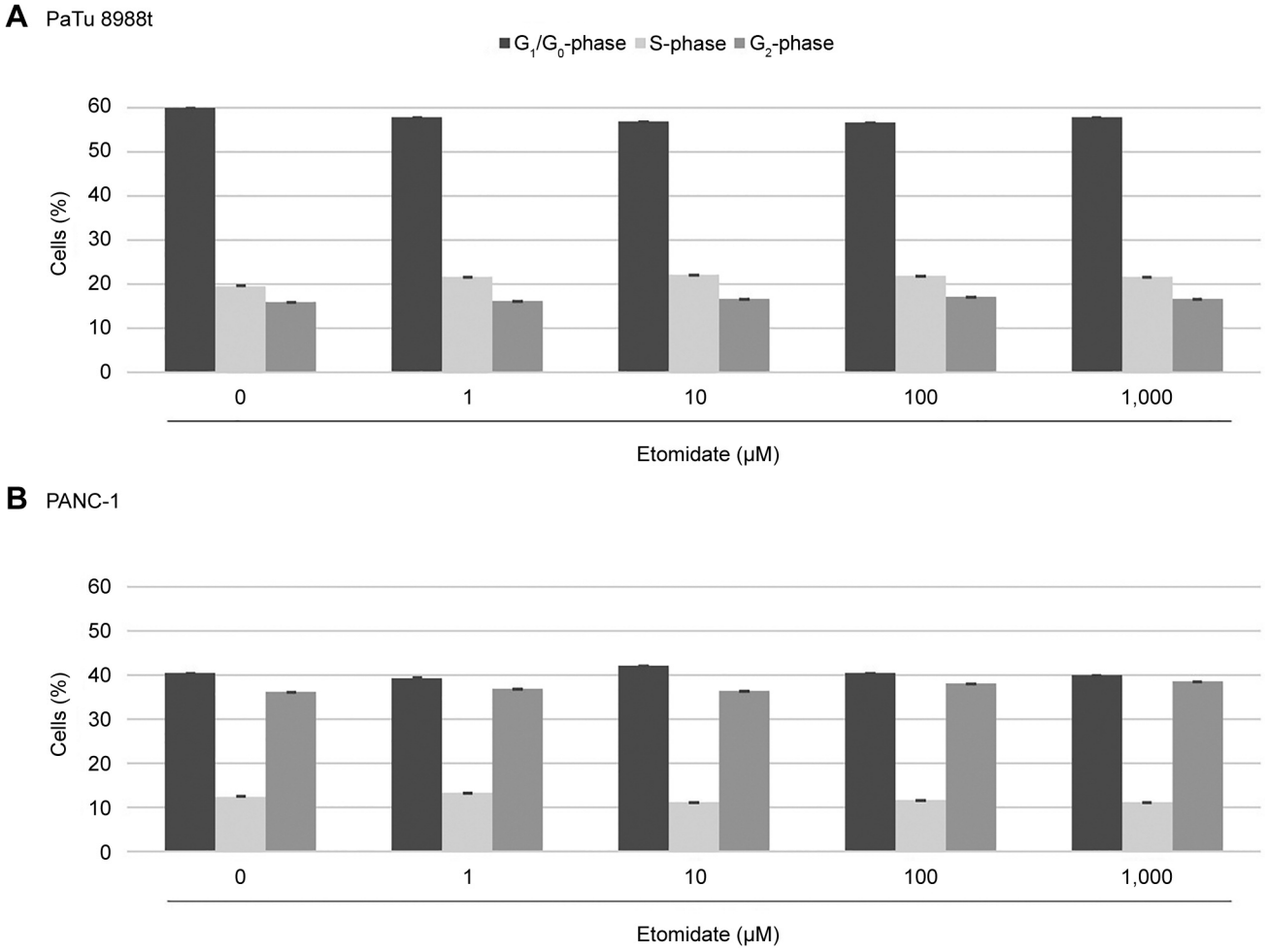

Figure 4. *Cell-cycle distribution in PaTu 8988t (A) and PANC-1 (B) pancreatic cancer cell lines after treatment with etomidate for 24 h. The cell-cycle distribution was analysed by means of flow cytometry after staining with propidium iodide.*

Apoptosis analysis. Apoptosis assays by annexin V staining were performed according to the manufacturer's instructions (BD Pharming, Franklin Lakes, NJ, USA). In brief, PaTu 8988t and PANC-1 cells were incubated with 0, 1, 10, 100 or 1,000 μM propofol or etomidate in serum-free medium. Staurosporine was used for positive control and standard growth medium for negative control. After 24 h incubation, the supernatant was decanted from the cells to preserve floating cells. Adherent cells were rinsed with warm Dulbecco's phosphate-buffered saline (Sigma-Aldrich) and harvested by standard trypsinisation. Afterwards, harvested and floating cells were mixed, washed and re-suspended in binding buffer at a final density of 10^6 cells/ml. Cell suspension containing 10^5 cells (100 μl) was re-suspended in 5 μl fluorescein isothiocyanate-conjugated annexin plus 5 μl propidium iodide, followed by 15 min incubation at room temperature in the dark. Cells were washed and re-suspended with 400 μl binding buffer. Finally, the cells were analysed by flow cytometry using FACS Calibur and Cellquest Pro software (BD Bioscience). All tests were performed in duplicate and repeated three times.

Statistical analysis. Data are presented as the mean±standard deviation. The non-parametric Mann-Whitney *U*-test was used for statistical evaluation of the data. Values of $p<0.05$ were considered significant. IBM SPSS Statistics (Version 26; IBM, Armonk, NY, USA) and Excel Version 2019 (Microsoft, Redmond, WA, USA) packages were employed for statistical analysis.

Results

Proliferative behaviour of cells. PaTu 8988t and Panc-1 pancreatic cancer cells were stimulated with 0-1,000 μM propofol or etomidate in serum-free medium for 24 h each (Figure 1). At concentrations of 100 and 1,000 μM, propofol significantly inhibited cell proliferation in the PaTu 8988t pancreatic carcinoma cell line (Figure 1A) and 1,000 μM propofol significantly reduced cell proliferation in PANC-1 cells compared to the untreated control (Figure 1A). In

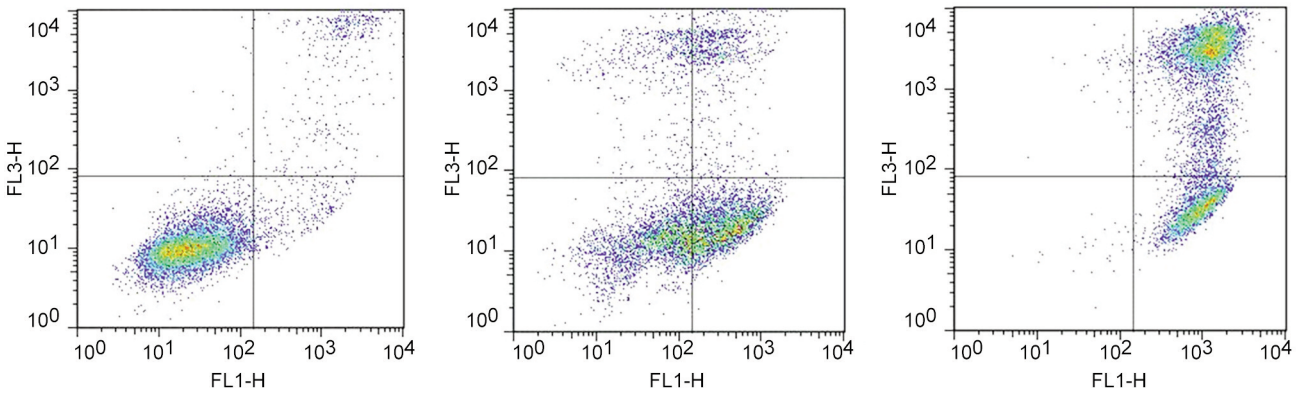

Figure 5. *Typical dot plots after double staining with annexin V and propidium iodide in standard growth medium.*

contrast, etomidate did not significantly affect growth of either cell line (Figure 1B).

Effects of propofol and etomidate on the cell-cycle progression of pancreatic cancer cells. The aim of this study was to investigate the effects of propofol and etomidate on the cell-cycle behaviour of pancreatic cancer cells. Figure 2 shows a typical histogram after marking the cell nuclei with propidium iodide. At concentrations of 1 and 100 μM, propofol significantly changed the cell distribution in the PaTu 8988t pancreatic cancer cell line, and the fraction of cells in the G_2-phase was reduced compared to the untreated control cells (Figure 3A). At 1,000 μM, propofol led to a significant increase in the S-phase, a significant decrease in the G_1-phase and a change in the G_2-phase in both the PaTu 8988t cell line and the PANC-1 cell line (Figure 3). Treatment with etomidate did not result in any changes in cell distribution, neither in the PaTu 8988t cell line nor in the PANC-1 cell line (Figure 4).

Analysis of apoptosis and necrosis. The annexin V-staining apoptosis assay was used to determine whether treatment with propofol or etomidate induced apoptosis or necrosis. Figure 5 shows typical dot plots after double staining with annexin V and propidium iodide. In the PaTu 8988t cell line, the number of vital cells was significantly increased after 24 h incubation with 1 μM propofol; 24 h incubation with 1,000 μM propofol (Figure 6A) induced significant apoptosis and reduced the vital cell fraction from 83% to 2% compared to the untreated control samples. In the PANC-1 cell line, 24 h incubation with 1,000 μM propofol significantly increased apoptosis and reduced the vital cell fraction compared to the untreated control samples (Figure 6A). Propofol at other concentrations did not result in any significant changes in the apoptosis rate. Etomidate did not induce any changes in cell death behaviour, neither in the PaTu 8988t cell line nor in the PANC-1 cell line (Figure 6B). Staurosporine, often employed for inducing apoptosis, was used as positive control for the testing procedure and induced significant apoptosis in pancreatic cancer cells (data not shown).

Discussion

To date, only a few studies have investigated the effect of narcotics on tumour cells, and some of them have yielded contradictory results.

Propofol (2,6-diisopropylphenol), a rapid short-acting intravenous general anaesthetic without any analgesic effect, acts as an allosteric modulator at pentameric ion channels such as gamma-aminobutyric acid (GABA)-A receptors and nicotinic acetylcholine receptors (15), is able to stimulate protein kinase C (16, 17) and has been classified as antioxidant (18). Propofol also inhibits the entry of calcium into muscle cells (19) and increases myofilament calcium sensitivity in ventricular myocytes (20). Propofol is the most commonly used hypnotic drug worldwide and is non-toxic for humans, even at high concentrations (3-8 μg/ml; 20-50 μM) (21). Propofol has also been classified as direct vasodilator and bronchodilator with anti-inflammatory and anticonvulsant properties (22). Although the exact molecular mechanism of action for these different properties is unknown, propofol is thought to be able to modulate not only intracellular signalling pathways but also cellular processes that influence tumour dissemination (21).

In recent years, several animal studies have shown a positive effect of propofol on tumour progression (22-24). Mammoto *et al.* showed that clinically relevant concentrations of propofol reduced the invasion and metastatic potential of human cancer cells, including HeLa, HT1080, HOS and RPMI-7951 (23). In mice, continuous infusion of propofol inhibited lung metastasis of murine osteosarcoma cells by modulating Rho A (24). In human HL-

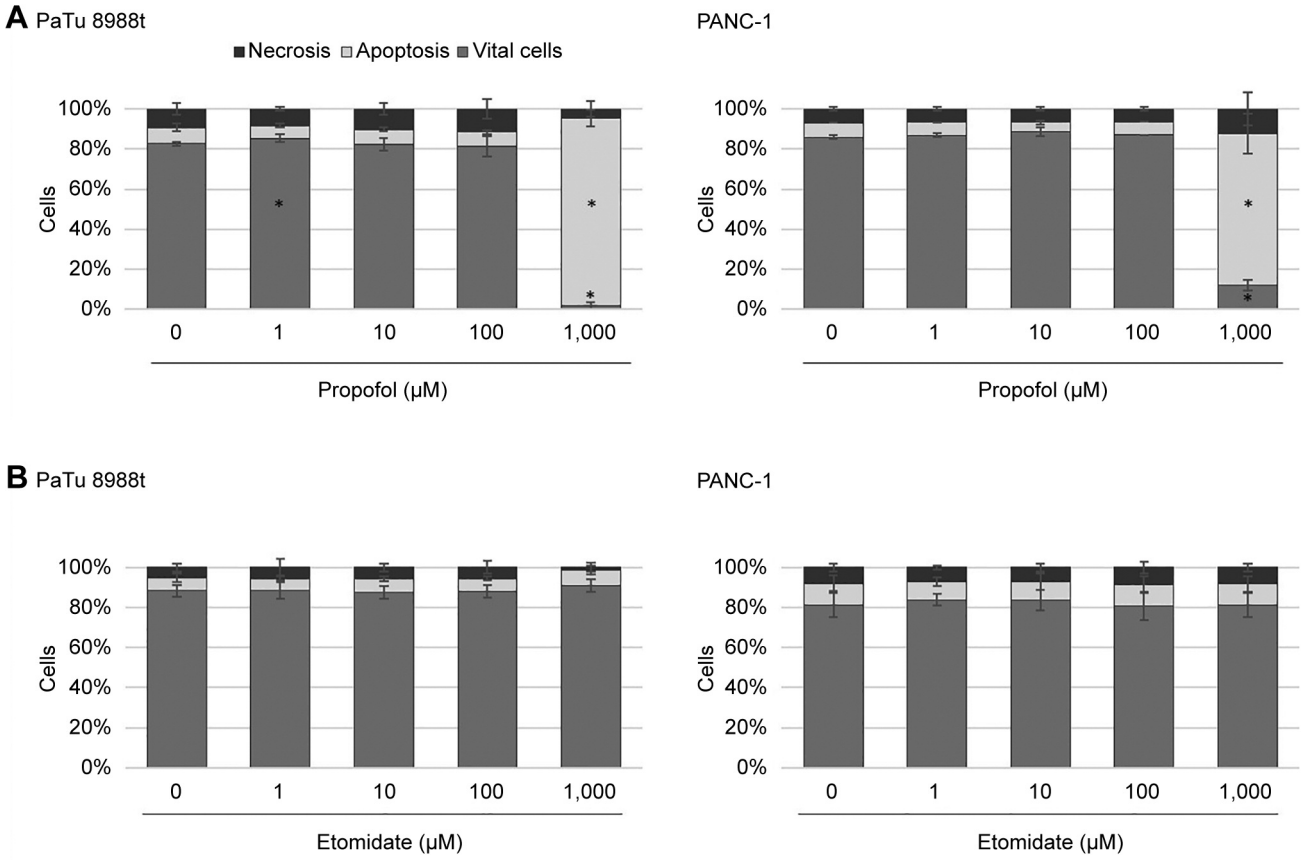

Figure 6. *The effects of propofol (A) and etomidate (B) on apoptosis in the pancreatic carcinoma cell lines PaTu 8988t (left) and PANC-1 (right) in vitro. For analysis of apoptosis, cancer cells were stained with annexin V. *Significantly different at p<0.05 compared to the untreated control.*

60 promyelocytic leukaemia cells, propofol inhibited tumour growth, induced the formation of apoptotic bodies, increased DNA fragmentation and activated caspases 3, 6, 8 and 9. Moreover, cytosol enhanced the release of cytochrome *c* (25). The conclusion of these studies was that propofol induces apoptosis *via* a cell-surface death receptor (extrinsic), as well as through the mitochondrial intrinsic pathway. In a study by Kushida *et al.* in 2007, tumour growth in mice was significantly reduced after the administration of propofol in comparison to the administration of saline (24). Propofol inhibited the invasion of lung carcinoma cells by reducing the expression of matrix metalloproteinases 2, 7 and 9, and by increasing the expression of TIMP metallopeptidase inhibitors 1 and 2 (26). Propofol also inhibited cell invasion in breast and colon carcinoma *in vitro* (27, 28).

On the other hand, Garib *et al.* found that the administration of propofol increased the potential of cell migration in breast carcinoma (29). Other studies showed it induced cell proliferation in gallbladder carcinoma (30) and neuroblastoma (31). In the present study, at 1,000 μM, propofol induced apoptosis, halted cell proliferation, and increased the S-phase whilst reducing the G_1-phase in the cell cycle. At 100 μM, propofol also significantly inhibited proliferation and reduced the G_2-phase in the cell cycle of the pancreatic cancer cell line PaTu 8988t. Thus, this study shows once again that propofol influences tumour spread, likely through modulation of intracellular signalling pathways and cellular processes.

Etomidate is known for its short-acting properties, as well as its low cardiovascular risk profile. In contrast to other hypnotics, etomidate causes only a relatively small drop in blood pressure and is therefore suitable for patients with impaired cardiac performance (32). It has a $GABA_A$-mimetic effect by attenuating the reticular formation (33). Even a single dose of etomidate impairs adrenal cortex function, causing a drop in serum levels of both cortisol and aldosterone (34). Although etomidate is a common and widely used intravenous anaesthetic, studies on its effects on cancer cells are rare. Previous studies have shown that etomidate impeded migration and invasion of A549 lung adenocarcinoma cells by inhibiting the expression of matrix

metalloproteinases 1, 2, 7 and 9 (35). Furthermore, etomidate exerted antiproliferative effects on adrenocortical carcinoma (36) and induced apoptosis in neuroblastoma (37). In contrast, Deng *et al*. showed that etomidate increased migration of colon carcinoma cells *via* the phosphatidylinositol-4,5-*bis*phosphate 3-kinase–AKT serine/threonine kinase 1 pathway (38).

In our study, the concentrations of etomidate used had no effects on cell-cycle distribution or proliferation. Moreover, etomidate did not induce apoptosis and necrosis, neither in the PaTu 8988t cell line nor in the PANC-1 cell line.

Conclusion

The perioperative phase is suggested to be a vulnerable phase for cancer cell dissemination and progression. For this reason, it is under discussion whether the choice of anaesthetic agents can affect a patient's oncological outcome. In our study, propofol was shown to have anticancer effects by induction of apoptosis and inhibition of cell proliferation, while etomidate did not affect pancreatic cancer cells. However, it is too early to make any recommendation for changes in clinical practice and further clinical studies are warranted to investigate the effect of anaesthetics on cancer progression.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

All Authors have made substantial contributions to the conception, design, analysis, and the interpretation of this research article; they were involved in the critical revision of the article with regard to important intellectual content. All Authors gave their final approval for the version to be published 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.

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