

The Effects of Analgesics on the Migration of Pancreatic Cancer Cells

MANUELA MALSY¹, CHRISTINA HACKL², BERNHARD GRAF¹,
DIANE BITZINGER¹ and ANIKA BUNDSCHERER¹

¹Department of Anesthesiology, University Medical Center Regensburg, Regensburg, Germany;

²Department of Surgery, University Medical Center Regensburg, Regensburg, Germany

Abstract. *Background/Aim:* Adenocarcinoma of the pancreas is one of the most aggressive malignant diseases in humans. Characteristics of this tumour type are poor response to radiotherapy and chemotherapeutic agents as well as metastasis in the absence of an organ capsule. The best therapeutic option is surgical removal of the tumour followed by chemotherapy or radiotherapy. Yet, even after surgical R0-resection, the 5-year survival probability is only about 20% because of the high recurrence rate of this tumour and complications due to metastases. Furthermore, recent studies have shown that the perioperative period is a particularly vulnerable phase, during which tumour progression and metastasis may be facilitated. The effects of analgesics administered during the perioperative period are still unknown. The present work investigated the effects of analgesics on pancreatic cancer cell migration *in vitro*. *Materials and Methods:* The migratory potential of pancreatic cancer cells was analysed using a Cell Migration Assay Kit with a Boyden chamber, in which cells migrate through a semi-permeable membrane under different stimuli. Cell concentration was measured by reading fluorescence (Ex/Em=530/590 nm) in a plate reader. *Results:* Migration in PANC-1 pancreatic cancer cells was significantly decreased after 24 h stimulation with 100 µM of ropivacaine, 100 nM of sufentanil, 1,000 µM of ropivacaine and 1,000 nM of sufentanil. In the PaTu 8988t cell line, incubation with 10 µM of ropivacaine caused a slight but statistically significant increase in migration, whereas

lidocaine, metamizole and paracetamol did not significantly affect migration. *Conclusion:* The risk of tumour progression and metastasis seems to be increased during major oncological surgical interventions. The recent advances in the molecular and biological understanding of pathogenesis of pancreatic cancer have not yet significantly improved patient outcome. Therefore, further studies are needed to identify the underlying mechanisms of this aggressive tumour and establish new therapeutic options for the future.

Adenocarcinoma of the pancreas is one of the most aggressive malignant diseases in humans. More than 9 of 10 patients with pancreatic cancer die within 5 years of diagnosis (1, 2). This type of tumour is marked by poor response to radiotherapy and chemotherapeutic agents as well as by early lymphogenic, perineural, haematogenic and peritoneal metastasis in the absence of an organ capsule (3-5). Furthermore, pancreatic adenocarcinoma does not present any characteristic early symptoms, and appropriate screening tests are lacking (6). First symptoms are usually caused by the invasion of the tumour into surrounding anatomic structures such as the stomach or colon, but may also be due to distant metastases, for instance in the liver or lungs (7). Thus, at the time of diagnosis, most tumours are already classified as non-curative and have a poor prognosis (8).

The best therapeutic option is surgical removal of the tumour followed by chemotherapy or radiotherapy (9). Yet, even after surgical R0-resection, the 5-year survival probability is only about 20% because of the high recurrence rate of this tumour and complications due to metastases (10, 11). Furthermore, recent studies have shown that the perioperative period is a particularly vulnerable phase, in which tumour progression and metastasis may be facilitated (12). The effects of analgesics administered via peridural anaesthesia or as lidocaine infusion during the perioperative phase or for postoperative pain management are still unknown. The aim of this study was to investigate the effects of analgesics on pancreatic cancer cell migration *in vitro*.

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Correspondence to: Manuela Malsy, MD, Department of Anesthesiology, University Medical Center Regensburg, Franz Josef Strauss Allee 11, 93053 Regensburg, Germany. Tel: +49 9419447801, Fax: +49 9419447802, e-mail: Manuela.Malsy@ukr.de

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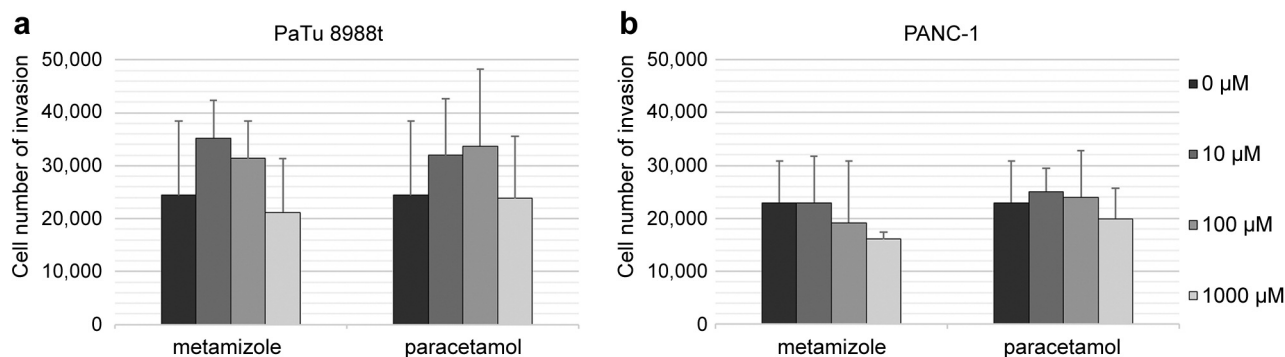


Figure 1. The effects of metamizole and paracetamol on cell migration in PaTu 8988t (a) and PANC-1 (b) pancreatic cancer cells in vitro. Cell migration was quantified by using a Boyden chamber in which cells migrate through a semi-permeable membrane under different stimuli. *Statistical significance at $p < 0.05$ compared to untreated controls.

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 (FCS) (Sigma-Aldrich) and 5% Myco Zap (Lonza Verviers SPRL, Verviers, Belgium). Cells were cultured in humidified CO₂ atmosphere (5%) at 37°C and maintained in monolayer culture. Experiments were done with cells at ~70-80% confluence.

Reagents. Commercially available ropivacaine (Fagron, Barsbüttel, Germany), sufentanil (Sigma-Aldrich) and lidocaine (Sigma-Aldrich, St. Gallen, Switzerland) were used for this study. Metamizole was purchased from Fluka (München, Germany), and paracetamol from Merck (Darmstadt, Germany). Final concentrations were obtained by diluting the drugs in standard growth media. All solutions were prepared freshly prior to use.

Cell migration assay. Cell migratory potentials were evaluated using a cell migration Assay Kit (abcam, Cambridge, UK). The test uses a Boyden chamber in which cells migrate through a semi-permeable membrane under different stimuli. In brief, cells were treated with the appropriate medication (0 μM, 10 μM, 100 μM or 1,000 μM of metamizole; 0 μM, 10 μM, 100 μM or 1,000 μM of paracetamol; 0 μM, 10 μM, 100 μM or 1,000 μM of lidocaine; 0 μM, 10 μM, 100 μM or 1,000 μM of ropivacaine; 0 nM, 10 nM, 100 nM or 1,000 nM of sufentanil or the combination of 0 μM of ropivacaine and 0 nM of sufentanil, 10 μM of ropivacaine and 10 nM of sufentanil, 100 μM of ropivacaine and 100 nM of sufentanil or 1,000 μM of ropivacaine and 1,000 nM of sufentanil) in serum-free medium for 2 h. Afterwards, 200,000 cells of the human pancreatic cancer cell lines PaTu 8988t or PANC-1 were placed into the upper chamber, and a stimulant was pitted into the lower chamber. The chambers were incubated at 37°C for 4 h. The migrating cells passed through the semi-permeable membrane and migrated into the bottom chamber or adhered to the bottom of the upper chamber. After dismantling, cell migration was directly analysed by reading fluorescence (Ex/Em=530/590 nm) in a plate reader. All tests were done with three wells per treatment group and performed as two independent experiments.

Statistical analysis. Data are presented as mean±SD. The non-parametric Mann Whitney *U*-test was used for statistical evaluation of the data. *p*-Values of <0.05 were considered significant. IBM SPSS Statistics (Version 26, IBM, New York, NY, USA) and Excel Version 2013 (Microsoft, Redmond, WA, USA) packages were employed for statistical analysis.

Results

Analysis of migration in pancreatic cancer cells. PaTu 8988t and PANC-1 pancreatic cancer cells were stimulated with 0 μM, 10 μM, 100 μM or 1,000 μM of metamizole or with 0 μM, 10 μM, 100 μM or 1,000 μM of paracetamol (Figure 1a and b). Metamizole and paracetamol did not significantly affect migration.

Behaviour of cell migration and analysis of cell concentration. PaTu 8988t pancreatic cancer cells and PANC-1 were stimulated with 0 μM, 10 μM, 100 μM or 1,000 μM of lidocaine, 0 μM, 10 μM, 100 μM or 1,000 μM of ropivacaine and 0 nM, 10 nM, 100 nM or 1,000 nM of sufentanil or the combination of 0 μM of ropivacaine and 0 nM of sufentanil, 10 μM of ropivacaine and 10 nM of sufentanil, 100 μM of ropivacaine and 100 nM of sufentanil or 1,000 μM of ropivacaine and 1,000 nM of sufentanil (Figure 2a and b). The combination of 100 μM of ropivacaine and 100 nM of sufentanil and 1,000 μM of ropivacaine and 1,000 nM of sufentanil had significantly decreased the migration of PANC-1 pancreatic cancer cells after 24 h stimulation (Figure 2b). In a PaTu 8988t cell line (Figure 2a), incubation with 10 μM of ropivacaine caused a slight but statistically significant increase in migration. Lidocaine did not significantly affect migration in either cell line.

Discussion

At the time of death, up to 80% of patients with adenocarcinoma of the pancreas are found to have metastases

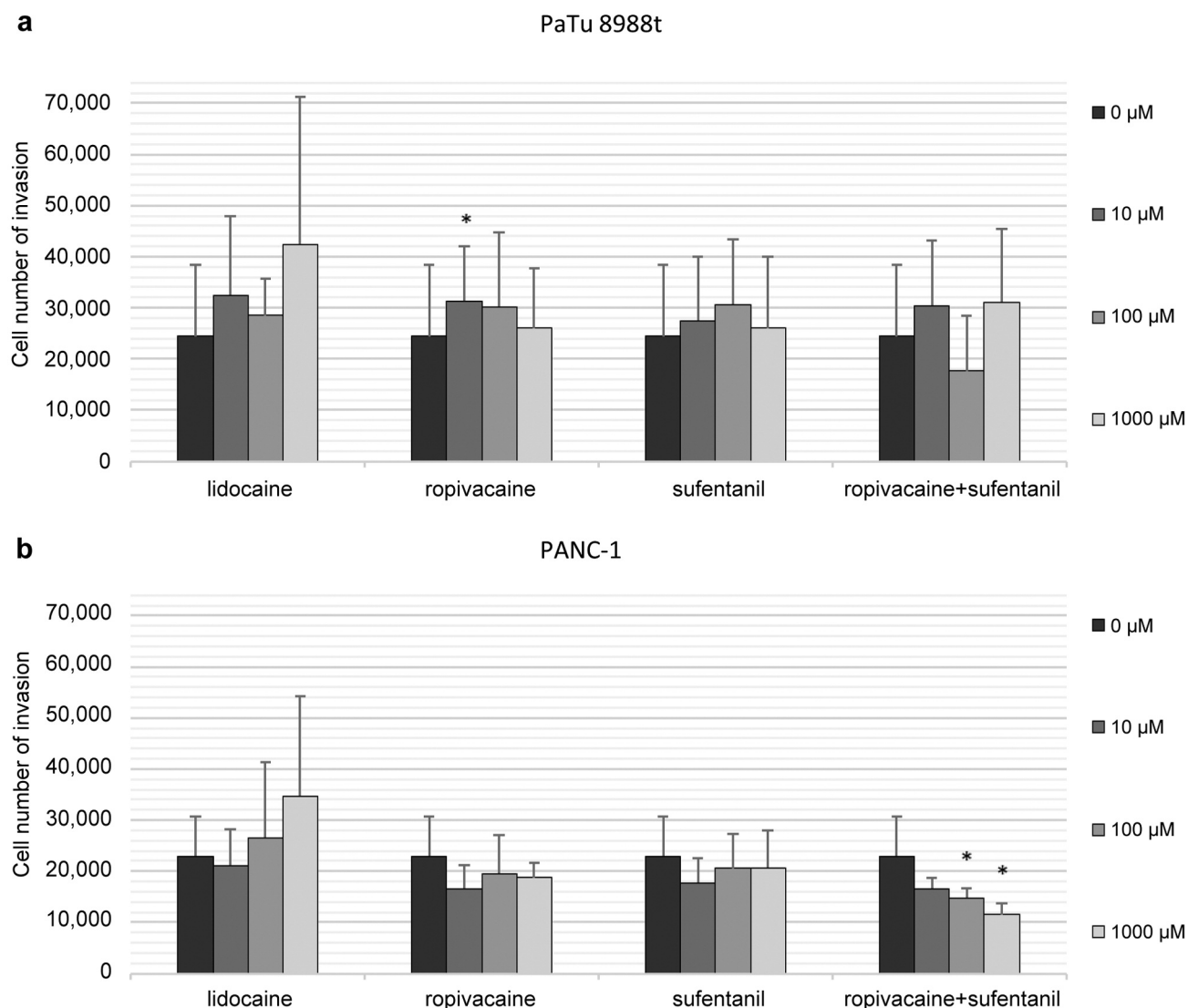


Figure 2. The effects of lidocaine, ropivacaine and sufentanil and the combination of ropivacaine and sufentanil on migration in PaTu 8988t (a) and PANC-1 (b) pancreatic cancer cells in vitro. The cell migration rate was detected by using a Boyden chamber in which cells migrate through a semi-permeable membrane under different stimuli. *Statistical significance at $p < 0.05$ compared to untreated controls.

of the liver, 60% of the peritoneum and 50-70% of the lungs or pleura (13). In carcinogenesis, metastasis of tumour cells represents the endpoint of a multi-step process (14). Metastases occur when cancer cells become detached from the original tumour, migrate with blood or lymph and re-colonise and multiply in other tissues. Molecular biological analyses have shown the loss or inactivation of cell-cell or cell-matrix adhesion molecules (15) and, in invasive tumours, the simultaneous upregulation of adhesion molecules (16).

Recent studies have indicated that the perioperative period is a particularly vulnerable phase, during which tumour progression and metastasis may be facilitated (12). The effects of analgesics administered via peridural anaesthesia

or as lidocaine infusion during the perioperative phase or for postoperative pain management are still unknown.

In the first studies analysing the effects of analgesics on metastasis in tumour cells, the selective COX-2 inhibitor celecoxib was found to reduce the gelatinolytic activity of matrix metalloproteinase 2 and 9 and to decrease the invasion capacity in oral squamous cell carcinoma (17, 18). According to Li *et al.*, celecoxib inhibited the proliferation, invasion and migration of PANC-1 pancreatic cancer cells (19). Aspirin inhibited the motility and subsequently the migration and invasion of prostate cancer cells by suppressing the binding of tumour cells to fibronectin and vitronectin (20). Indomethacin reduced the invasion capacity

of breast cancer cells, most likely due to changes in the choline-phospholipid and triacylglycerol metabolism (21). In previous studies acetaminophen and metamizole revealed proapoptotic effects in colon cancer and antiproliferative effects in pancreatic cancer cells (22). Through increased expression of the differentiation markers, paracetamol seems to be able to change breast cancer cells into a more benign type marked by reduced tumour growth, low invasion capacity and increased sensitivity to anti-tumour agents (23). In our study, however, metamizole and acetaminophen did not significantly affect the migration of pancreatic cancer cells. Further preclinical and clinical studies are required to decide if these drugs can be safely administered in patients with pancreatic adenocarcinoma.

The effect of regional anaesthesia on tumour progression has also been the focus of many clinical studies in recent years, but the obtained data show somewhat contradictory results. For peridural anaesthesia, the long-acting local anaesthetic ropivacaine is used, a local anaesthetic of the amide type (24). Local anaesthetics act by blocking voltage-gated sodium channels of the neuronal axon. In this process, the local anaesthetic binds to the inside of the inactivated sodium channel, thus preventing the rapid influx of sodium into the cell, which is important for depolarization. The conduction of stimuli in the nerve is inhibited, and pain transmission is stopped (25). Such ion channels are not only found on the axons of peripheral nerves but have also been detected in various tumour entities, such as in cancer cells of the breast, colon and prostate (26). Thereby, increased expression of voltage-gated sodium channels seems to be associated with increased tumour metastasis (27, 28). Circulating tumour cells partially bind to vessel walls via microtentacles. Tertacaine, and to a lesser extent also lidocaine, inhibits the spread of these microtentacles, subsequently reducing the metastatic potential of breast cancer cells (29). Meanwhile, reduced expression of voltage-gated sodium channels correlates with decreased cell proliferation and invasiveness, thus inducing apoptosis in astrocytoma cells (30). Piegeler *et al.* investigated the effects of local anaesthetics on migration in adenocarcinoma of the lung. Incubation with ropivacaine and lidocaine reduced ICAM phosphorylation, which is associated with inhibited cell migration. Ester-type local anaesthetics did not produce such anti-metastatic effects. Moreover, these effects seem to be independent of the function of local anaesthetics that inhibits the sodium channel (31).

To improve the analgesic effect of peridural anaesthesia, ropivacaine is often combined with the opiate sufentanil (32). As a pure antagonist, sufentanil binds to opioid receptors of the nervous system (33) and has been shown to improve the quality of analgesia. Similarly, the addition of opioids to local anaesthetics in peridural anaesthesia leads to a faster onset of the required effect, thus enabling a dose

reduction of the individual components (34). This phenomenon can also be observed in the intravenous application of lidocaine in major abdominal surgery compared to single general anaesthesia. The decrease in peri- and postoperative pain levels also significantly reduces the need of anaesthetics and opioid analgesics (35). For opiates, data on the migration, invasion and metastatic potential of tumours have been inconsistent so far. In one study, morphine inhibited the adhesion, migration and invasion of colon cancer cells *in vitro* and the expression of MMP2 and 9 in breast cancer cells (36), whereas in other *in vitro* studies, morphine increased the migration and invasion of breast and bladder cancer cells (37, 38).

Samples from patients with non-small cell lung cancer showed a 5- to 10-fold increase in μ opioid receptor expression. In animal models, treatment of lung cancer cells with the opioid antagonist methylnaltrexone or inactivation of the μ -receptor resulted in a 65% reduction in lung metastases (39). Interestingly, opioid receptors do not always appear to be involved in mediating the effects of μ -agonists. In some studies, effects also occurred in μ -receptor-negative cells, or the observed effects could not be antagonised by naloxone. There is some evidence that the effects of opioids on tumour cells are also mediated by the nitrite oxidase system (36), the bradykinin 2 receptor (38) or the NET 1 gene (37). A study on breast cancer treatment by Exadaktylos *et al.* showed that combining general anaesthesia with paravertebral blockade for mastectomy was associated with a significantly better prognosis than general anaesthesia alone. After 36 months, recurrence-free and metastasis-free survival was 94% in the paravertebral group versus 77% in the general anaesthesia group (40). De Oliveira *et al.* found a reduced risk of recurrence for intraoperative epidural anaesthesia in patients operated on for ovarian cancer (41). In contrast, results from other retrospective studies indicated that epidural anaesthesia had no benefit on overall survival in patients undergoing cytoreductive surgery for ovarian cancer (42, 43). A meta-analysis with 14 included studies concluded that there may be a benefit of epidural anaesthesia compared to general anaesthesia in terms of overall survival but not recurrence-free survival (44).

In the present study, migration of PANC-1 pancreatic cells was significantly reduced after 24 h stimulation with 100 μ M of ropivacaine and 100 nM of sufentanil as well as with 1,000 μ M of ropivacaine and 1,000 nM of sufentanil, which underlines the positive effect of epidural anaesthesia found in preliminary studies. The potential molecular and biological background of this effect remains unclear. Tumour progression and migration is regulated of specific signaling and transcription pathways. Many proteins are involved in the carcinogenic process, which can act as transcription factors or cofactors, and have a significant impact on the regulation of target genes.

Conclusion

Recent advances in the molecular and biological understanding of the pathogenesis of pancreatic cancer (45) have not yet significantly improved patient outcome (46). The risk of tumour progression and metastasis appears to be increased during the perioperative period of major oncological surgical interventions. The perioperative period is particularly associated with the administration of a variety of substances for balanced anaesthesia and postoperative pain management. The extent to which these drugs affect the carcinogenesis of pancreatic cancer needs to be investigated in further studies. The aim is to identify the underlying mechanisms of this aggressive tumour and to establish new therapeutic options for the future.

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 have been involved in the critical revision of the manuscript with regard to important intellectual content. All authors have given 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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