Surg Endosc (1999) 13: 1021–1025

Surgical Endoscopy
Ultrasound and
Interventional Techniques

Influence of different gases and intraperitoneal instillation of antiadherent or cytotoxic agents on peritoneal tumor cell growth and implantation with laparoscopic surgery in a rat model

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Received: 24 February 1999/Accepted: 1 July 1999

Abstract
Background: A generally accepted approach to prevent tumor implantation with laparoscopic surgery does not exist. Alternative gases in combination with intraperitoneal instillation of different antiadherent or cytotoxic agents have not been evaluated.
Methods: The effect of taurolidine, heparin, and povidone-iodine on the growth of colon adenocarcinoma DHD/K12/TRb was measured in rats undergoing laparoscopy with carbon dioxide ($n = 40$), helium ($n = 40$), or xenon ($n = 40$). In the procedure, 10^4 tumor cells were administered intraperitoneally, and pneumoperitoneum was established over 30 min at 8 mmHg with the different gases. The rats additionally received intraperitoneal instillation with one of the following: 1 ml of Ringer's solution, 1 ml of 0.5% taurolidine, 1 ml 0.5% taurolidine with heparin (10 U/ml), or 1 ml 0.25% of povidone-iodine. Tumor growth was measured after 4 weeks.
Results: Median intraperitoneal tumor weight was lower in rats receiving taurolidine (CO_2: 10 mg; helium: 50 mg; xenon: 39.5 mg) or taurolidine with heparin (CO_2: 4 mg; helium: 4.5 mg; xenon: 46.5 mg) in all gas groups than in the control groups (CO_2: 427 mg; helium: 268 mg; xenon: 345 mg) ($p < 0.001$). Whereas povidone-iodine caused significantly lower tumor growth in the CO_2 group (56.5 mg) ($p < 0.01$), the combination of helium (145 mg) and xenon (457 mg) with povidone-iodine produced no reduction of tumor growth as compared with the control groups (helium: 268 mg; xenon: 345 mg).
Conclusions: Taurolidine and taurolidine with heparin significantly inhibit intraperitoneal tumor growth, with different gases used for pneumoperitoneum. Only povidone-iodine caused significant decrease of tumor growth in combination with CO_2. The combination of xenon and povidone-iodine should not be used in patients with cancer because of increased tumor growth.

Key words: Gas — Heparin — Laparoscopy — Povidone-iodine — Taurolidine — Tumor cell growth

Laparoscopic surgery in patients with cancer has been discussed controversially because of the high susceptibility of laparoscopic incisions for metastatic tumor growth and the development of port-site metastases [4, 17, 18, 27, 28, 30]. Although simple spreading of tumor cells might be an explanation for this phenomenon, different studies have shown that insufflation of different gases significantly influences tumor cell growth and may stimulate the development of metastases. In recent experimental studies carbon dioxide (CO_2) insufflation led to significant stimulation of extra- and intraperitoneal tumor growth, whereas helium did not influence tumor growth *in vivo* [15, 22, 32].

Nevertheless, tumor cells need distinct steps of adhesion and implantation in an appropriate tissue to survive and grow. Injury of the peritoneum and exposure of extracellular matrix proteins to tumor cell surface also may be important for metastatic tumor growth in the peritoneal cavity after open and laparoscopic surgery [7, 29, 33].

Besides the pathomechanisms of intraoperative tumor cell attachment, little is known about possible therapeutic interventions to prevent tumor metastases in laparoscopic surgery. It has been demonstrated that tumor cell attachment is suppressed by binding domains of the extracellular matrix after intraperitoneal instillation of heparin in a murine model [11].

Other studies have shown a significant decrease of tumor growth after intraperitoneal instillation of taurolidine (Taurolin®, Hoechst, Germany), a derivative of the amino

Presented at the annual meeting of the Society of American Gastrointestinal Endoscopic Surgeons (SAGES), San Antonio, Texas, USA, 24–27 March 1999
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acid taurine, in combination with heparin using CO_2 for the establishment of pneumoperitoneum [13, 14, 16]. Taurolidine inhibits the production of interleukin 1β (IL-1β), a strong growth-promoting cytokine [19], in peripheral blood mononuclear cells (PBMC) and peritoneal macrophages and has a significant antiadherence effect on pathogen microorganisms and tumor cells in the abdominal cavity [2, 3, 13].

The instillation of cytotoxic agent povidone-iodine also has been reported to cause significant decrease of port-site metastases after laparoscopy with CO_2 in rats [25]. Nevertheless, all antiadherent or cytotoxic agents were used in animals undergoing CO_2 insufflation, although this gas itself might stimulate tumor growth. So far, the combination of these agents with different insufflation gases such as helium or xenon has not been evaluated. Therefore, the different influences of intra-abdominal application of heparin, taurolidine, and povidone-iodine in combination with various gases (CO_2, helium, xenon) on intraperitoneal tumor growth were evaluated in a rat model.

Methods

Animals

For the animal model, 120 male inbred BD IX 2-month-old rats (Iffa-Credo, L'Arbresle, France) were acclimated to a climate- and light cycle-controlled environment for at least 7 days before investigations. The animals were allowed standard laboratory food and water *ad libitum.* All studies were performed under protocols approved by the local Committee for Animal Use and Care.

Cell line

DHD/K12/TRb (ECACC) cells were cultured in Dulbeccos MEM (Biochrom, Germany) and Hams F10 medium (Biochrom, Germany) 1:1 supplemented with 10% fetal bovine serum (Gibco BRL, Germany), 2 mmol/l glutamine (Biochrom, Germany) and 1.000 IU/ml penicillin-streptomycin (Gibco BRL, Germany). Cells were removed from the plates with 0.25% trypsin/0.02% EDTA (Biochrom, Germany), washed twice with PBS (Charité, Berlin), suspended in medium, centrifuged at 1,000 rpm for 10 min, and resuspended in medium to the desired concentration.

Study design

The influence of intra-abdominal application of taurolidine, taurolidine with heparin, or povidone-iodine on intraperitoneal tumor growth during laparoscopy with either CO_2, helium or xenon was investigated in a rat model. In the procedure, 120 rats underwent pneumoperitoneum with CO_2 ($n = 40$), helium ($n = 40$), or xenon ($n = 40$) for 30 min at 8 mmHg. Laparoscopy was accomplished through three cannulas, each 5 mm in diameter. One hour before establishment of the pneumoperitoneum, 1×10^4 cancer cells in 1 ml of culture medium were administered intraperitoneally in each animal. Directly after establishment of pneumoperitoneum in each gas group, the rats additionally received intraperitoneal application of one of the following: 1 ml of Ringer's solution ($n = 10$), 1 ml of 0.5% taurolidine, 1 ml of 0.5% taurolidine with heparin (10 U/ml) ($n = 10$), or 1 ml of 0.25% povidone-iodine ($n = 10$). Abdominal incisions were closed with a single suture after laparoscopy.

After 4 weeks, the animals were killed, and intraperitoneal tumors and trocar sites were excised. Metastatic tumor growth at the abdominal incisions was identified histologically, and intra-abdominal tumor weight was measured on a balance.

Statistics

Data are given as medians (95% confidence interval). Data between the different groups were compared using the Kruskal-Wallis or Mann Whitney *U* test for continuous data and the Fisher's exact test for categorical data, if appropriate. All *p* values less than 0.05 were considered significant.

Results

Incidence of intraperitoneal tumor growth significantly differed among all groups ($p < 0.00001$). Furthermore, the total intraperitoneal tumor weights were lower ($p < 0.001$) in rats receiving taurolidine (CO_2: 10 mg [95% confidence interval, 10.3–85.5 mg]; helium: 50 mg [95% confidence interval, 15–190 mg]; xenon: 39.5 mg [95% confidence interval, 5.5–159 mg]) or taurolidine with heparin (CO_2: 4 mg [95% confidence interval, −28–113 mg]; helium: 4.5 mg [95% confidence interval, 1.2–22 mg]; xenon: 46.5 mg [95% confidence interval, 25–84 mg]) in all gas groups than in the control groups (CO_2: 427 mg [95% confidence interval, 237–707 mg]; helium: 268 mg [95% confidence interval, 105–570 mg]; xenon: 345 mg [95% confidence interval, 194–984 mg]) ($p < 0.001$) (Figs. 1–3).

The lowest tumor weights were found in rats having the combination of taurolidine or taurolidine with heparin and either CO_2 or helium, whereas xenon led to increased tumor growth compared with the other gases ($p = 0.018$). Whereas povidone-iodine also caused significant lower tumor growth in the CO_2 group (56 mg [95% confidence interval, 17.7–178 mg]) ($p < 0.01$), the combination of helium (145.5 mg [95% confidence interval, 41–280 mg]) and xenon (457.5 mg [95% confidence interval, 275–646 mg]) with povidone-iodine produced no reduction of tumor growth compared with the control groups (helium: 268 mg [95% confidence interval, 105–570 mg]; xenon: 345 mg [95% confidence interval, 193–984 mg]).

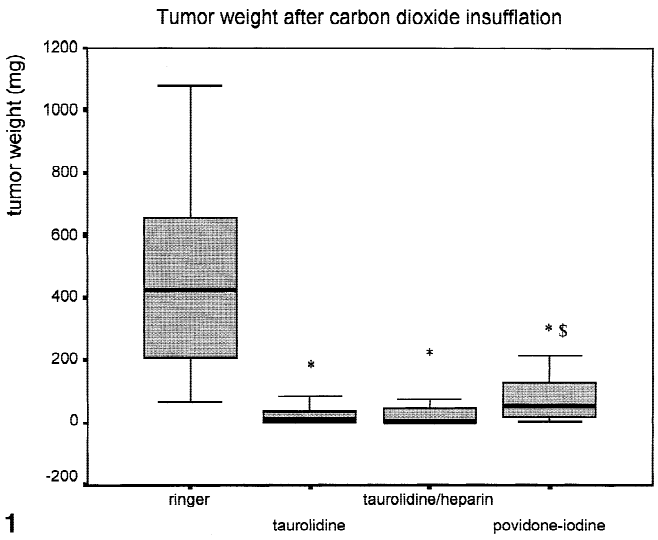
In comparison with the control group, tumor growth was even higher when povidone-iodine was combined with xenon ($p = 0.018$) (Figs. 1–3). Interestingly, fibrin layers on the peritoneal surface, liver, and spleen were found in all animals undergoing povidone-iodine instillation independent of the gas used during laparoscopy.

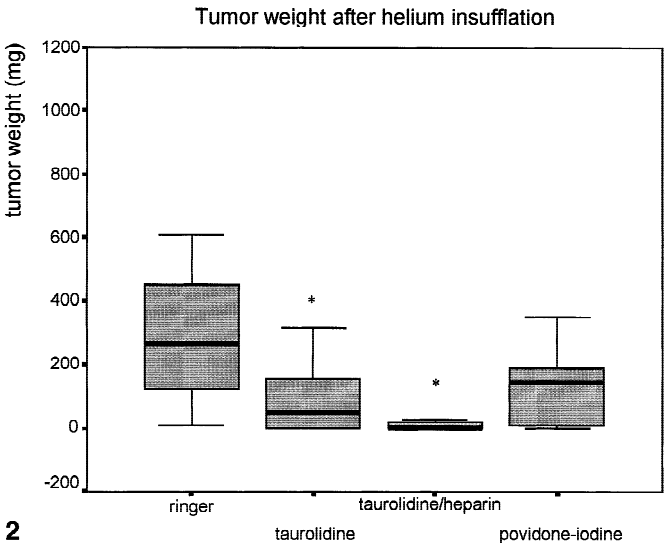
Incidence of port-site metastases also differed between the groups ($p = 0.003$). Incidence was lower at trocar incisions in the taurolidine (CO_2: 1/10; helium: 1/10; xenon: 1/10) and taurolidine with heparin groups (CO_2: 0/10; helium: 0/10; xenon: 1/10) compared with the control group (CO_2: 7/10; helium: 3/10; xenon: 7/10) for all gas groups. Instillation of povidone-iodine produced no significant therapeutic effect at trocar sites in any of the three gas groups (CO_2: 4/10; helium: 3/10; xenon: 4/10) (Table 1).

Discussion

Because port-site metastases and tumor spillage have been reported after laparoscopic resections of malignant tumors, the use of laparoscopic procedures in oncologic surgery has been discussed controversially [9, 18, 26, 30]. Nevertheless, it remains unclear whether the incidence of metastases is more likely to occur after laparoscopy than after conventional open surgery. It has been proved that surgical technique and experience play a major role in tumor metastases with either laparoscopic or conventional cancer surgery [17, 18, 20, 21, 28].

The large difference (0–25%) in the incidence of port-site metastases reported after colorectal surgery also might be explained by the experience of the surgical team, and the





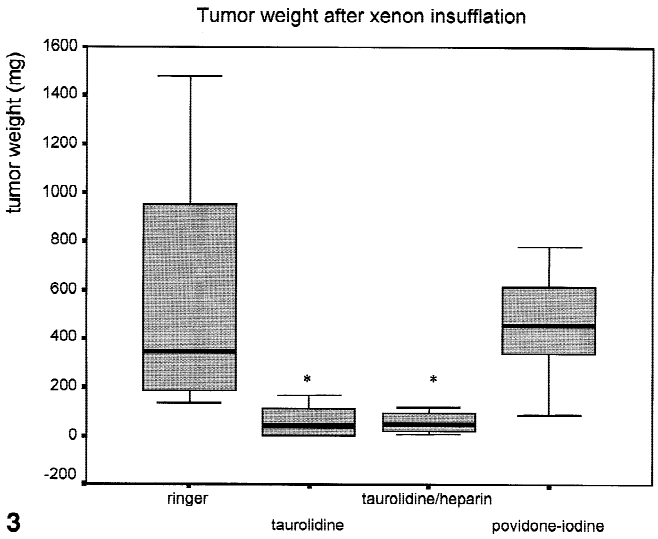


Fig. 1. Tumor weight after intraperitoneal instillation of Ringer's solution ($n = 10$), taurolidine ($n = 10$), taurolidine with heparin ($n = 10$), and povidone iodine ($n = 10$) combined with carbon dioxide insufflation (box plot: median and percentiles). In comparison with Ringer's solution, tumor growth was significantly decreased after instillation of taurolidine, taurolidine with heparin, and povidone-iodine (asterisk indicates $p < 0.01$). In comparison with povidone-iodine, tumor growth was significantly lower after instillation of taurolidine ($ indicates $p < 0.05$).

Fig. 2. Tumor weight after intraperitoneal instillation of Ringer's solution ($n = 10$), taurolidine ($n = 10$), taurolidine with heparin ($n = 10$), and povidone iodine ($n = 10$) combined with helium insufflation (box plot: median and percentiles). In comparison with Ringer's solution and povidone-iodine, tumor growth was significantly decreased after instillation of taurolidine and taurolidine with heparin (asterisk indicates $p < 0.01$).

Fig. 3. Tumor weight after intraperitoneal instillation of Ringer's solution ($n = 10$), taurolidine ($n = 10$), taurolidine with heparin ($n = 10$), and povidone iodine ($n = 10$) combined with xenon insufflation (box plot: median and percentiles). In comparison with Ringer's solution and povidone iodine, tumor growth was significantly decreased after instillation of taurolidine and taurolidine with heparin (asterisk indicates $p < 0.01$).

Table 1. Incidence of port-site metastases in the different groups ($n = 10$ in each group, Fisher's exact test)

	Carbon dioxide	Helium	Xenon	*p*
Ringer's solution	7\10	3\10	7\10	0.06
Taurolidine	1\10	1\10	1\10	1
Taurolidine with heparin	0\10	0\10	1\10	0.4
Povidone-iodine	4\10	3\10	4\10	0.9
p	0.002	0.1	0.004	

decrease of tumor recurrency reported from 1994 to 1999 seems to be caused by the learning curve of the surgeons [1, 9, 24, 27, 28, 30]. In an experimental setting, Lee et al. [21] could demonstrate that traumatic handling of a splenic tumor leads to significant higher numbers of port-site metastases than meticulous resection technique with and without pneumoperitoneum. Nevertheless, metastases also have been reported after laparoscopic resection during early tumor stages. Thus, development of port-site metastases is caused not only by surgeon-related factors, but might also by other factors related to the pneumoperitoneum itself.

Tumor cell suspension models have been used in rats, mice, and hamsters to evaluate the possible benefits or negative effects of pneumoperitoneum in cancer surgery [5, 14, 15, 23, 25, 26]. Although these models can be used to simulate intraoperative tumor spillage during laparoscopy, the number of free tumor cells after instrumental manipulation in patients is still unknown. Furthermore, the number of injected cells certainly does influence the tumor weight and development of port-site metastases, and controversial results might be the consequence [32]. Nevertheless, influences of carbon dioxide and elevated intraperitoneal pressure on tumor growth can be investigated in these models.

Other models have used retroperitoneal tumor cell injection and solid tumor models of the spleen, liver, and renal capsula [5, 10, 21]. Instrumental manipulation can be evaluated during open and laparoscopic procedures in these models, but resection of tumor-bearing organs also might lead to changes in immunologic (spleen) or renal (kidney) functions. Furthermore, all models have been established in rodents, whose immunologic functions and perioperative changes are different from those in human beings. Therefore, results of tumor models in rodents may be different from clinical findings in cancer patients.

Besides the general problems of experimental models, carbon dioxide has been shown to stimulate the growth of different colon cancer cell lines *in vitro* as well as *in vivo*

[15, 22, 23, 31]. Helium, as an alternate gas, reduced the risk of intra- and extraperitoneal metastases in different animal models and therefore might be used in patients with cancer [15, 26].

Further investigations concerning the prevention of port-site metastases are rare. Neuhaus et al. [25] evaluated the therapeutic effects of intraperitoneal instillation of 10% povidone-iodine solution in rats undergoing laparoscopy and found a significant decrease of port-site metastases without systemic side effects. Unfortunately, neither tumor size nor tumor growth was influenced by povidone-iodine. The intraperitoneal or intravenous application of cyclophosphamide, as described by Iwanaka et al. [12] in a murine model, seems to reduce tumor growth at port site, but cannot be generally advocated in laparoscopic cancer surgery because of the negative side effects of chemotherapy. Previous work from our department shows that intraperitoneal instillation of taurolidine or taurolidine with heparin causes significant reduction of either intraperitoneal tumor growth or development of port-site metastases in rats after laparoscopy with carbon dioxide [13, 14, 16].

These findings can be explained partly by the inhibition of IL-1β production in peritoneal macrophages, a significant antiadherence activity, and a direct suppression of cell growth by taurolidin [2, 3, 13, 19]. Heparin seems to act on the peritoneal surface by binding domains of the extracellular matrix which might reduce tumor cell adherence [11]. However, all therapeutic approaches in the prevention of metastases with laparoscopic surgery have been performed only under the condition of carbon dioxide insufflation [12, 14, 15, 16, 26]. Helium, which does not increase tumor cell growth, has not been combined with antiadherent or cytotoxic agents to prevent perioperative metastases. Moreover, xenon has not been used in laparoscopy for malignant neoplasms.

In the current study, a tumor cell suspension model was used to investigate therapeutic approaches dealing with tumor cells spilled during laparoscopy. Tumor growth was suppressed significantly after intraperitoneal instillation of either taurolidine or taurolidine with heparin as compared with the control group for all gas groups. Because IL-1β promotes cell growth *in vivo*, it might be that intraperitoneal application of taurolidine indirectly causes decreased tumor growth by inhibiting the IL-1β production of intraperitoneal macrophages, as shown in previous experiments *in vitro* [14]. Furthermore, it seems that taurolidine acts directly on the tumor cells, inhibiting tumor cell growth itself. This suppression is not because of increased cell death, but because of decreased proliferation [13, 16]. Although it has been reported that taurolidine releases "methylol" groups (hydroxymethyl groups), becoming attached to the cell wall of bacteria and causing death of the bacteria [6], it remains unclear whether a similar mechanism is responsible for decreased tumor cell growth. The combination of taurolidine and heparin showed significant synergistic effects on suppression of tumor growth *in vivo*. It might be that taurolidine is acting more on tumor cells and peritoneal macrophages, whereas heparin is acting on the peritoneal surface. These results are not cell specific but have been confirmed in different human and rat cancer cell lines [14].

Interestingly, tumor growth was higher in the xenon group than in the helium and CO_2 groups, even when these two agents were used for intraperitoneal application. Although insufflation of xenon did not lead to stimulation of tumor growth in the Ringer's solution (control) group, it caused significant increase when combined with povidone-iodine. Povidone-iodine was used for intraperitoneal instillation because it has potential cytotoxic effects on different tumor cells, and it often has been used for intraperitoneal lavage in septic patients without major side effects [8, 25]. Although povidone-iodine caused significant tumor cell death *in vitro* [14], intraperitoneal tumor weight was significantly reduced only in the CO_2 group by this agent. Nevertheless, total intraperitoneal tumor weight was significantly higher than in the taurolidine or taurolidine with heparin groups independent of the different gases. One possible explanation for the differences between the agents may be the increased IL-1β levels after incubation of peritoneal macrophages with povidone-iodine [14]. Povidone-iodine seems to cause release of intracellular cytokines by cell death and destruction of cell membrane structure, leading to promotion of viable tumor cells *in vivo*. Furthermore, adhanced fibrin layers on the peritoneal surface were found in all animals undergoing povidone-iodine instillation. The increased fibrin production after povidone-iodine instillation remains unclear, but may be related to mesothelial cell damage. Therefore, povidone-iodine seems not to be the ideal agent for intraperitoneal instillation during cancer surgery.

Although further prospective clinical studies are needed to confirm these experimental results, application of taurolidine with heparin during laparoscopic surgery should be used either with CO_2 or helium insufflation. Because of the presented results, standardized intraoperative lavage with 1.51 taurolidine 0.5% and heparin 5,000 i.E./l is performed routinely in all patients undergoing open and laparoscopic resection of malignancies in our department.

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