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Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator

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Abstract
Background: Multimodal therapy is used increasingly in advanced gastrointestinal tumors. Potential benefits of using an intraoperative adjuvant therapy during laparoscopy for cancer have been documented in animal studies. The aim of this study was to develop a device that could deliver such an intraoperative drug therapy.
Methods: We developed a micropump suitable for minimally invasive surgery procedures that allowed microdroplets of therapeutic substance to be distributed into the pneumoperitoneum (CO_2), creating a "therapeutic pneumoperitoneum." A closed-loop control system regulates drug delivery according to the gas flow. In vitro, the micropump is able to aerosolize various aqueous and ethanol solutions, including cytostatic and bacteriostatic drugs and adhesion-modulating agents. The size of the microdroplets has been optimized to prevent visual artifacts.
Results: The micropump was tested in an animal model (pig). The system was inserted into a 5-mm trocar. After insufflation of a 12-mm CO_2 pneumoperitoneum, laparoscopic sigmoid colon resections could be performed with no special difficulties. No fog developed, and no system-related complication was observed. At autopsy, the active principle was distributed to all exposed peritoneal surfaces.
Conclusions: As opposed to conventional peritoneal washing, therapeutic pneumoperitoneum reaches the entire peritoneal surface, allowing an optimal drug distribution. Drug diffusion into the tissues is enhanced by the intraperitoneal pressure. Precise determination of the instantaneous and total drug quantity is possible. Therefore, this drug delivery system has several advantages over conventional irrigation. Its potential domains of application are locoregional cancer therapy, prevention of port-site recurrences, immunomodulation, analgesia, peritonitis, and prevention of postoperative adhesions.

Key words: Pneumoperitoneum, physiopathology — Laparoscopy, side effects — Locoregional therapy — Technology, medical

The automated carbon dioxide (CO_2) pneumoperitoneum, introduced by Semm [21] in 1980, is now the accepted standard for exposing the abdominal cavity during laparoscopic procedures. In the meantime, it has been claimed that CO_2 pneumoperitoneum has several side effects. In particular, it recently has been documented that CO_2 stimulates tumor growth after laparoscopy for cancer [14], and that it increased bacterial translocation in peritonitis [3].

Gasless laparoscopy has been proposed as a solution for these side effects [5, 17, 26], but limited exposure might prevent the use of this technique for advanced laparoscopic procedures such as colonic resections. Alternative types of gas have been proposed for expanding the abdominal cavity. In particular, helium has inhibitory effects on tumor growth [8, 12], but this gas is not resorbable and therefore carries a potential risk of lethal gas embolisms in the case of venous lesions [4, 22].

We propose a different solution to prevent some side effects of CO_2 without increasing the technical difficulty of the surgical procedure nor the risks for the patient. The CO_2 might be used not only as an abdominal wall expander, but also as a drug carrier, introducing the novel concept of "therapeutic pneumoperitoneum." Thus, therapeutic pneumoperitoneum not only might prevent the side effects from CO_2, but also might improve the results of minimally invasive surgery in selected indications by allowing intraoperative multimodal therapy. Arguments for using a drug in aerosol form carried by the insufflation gas rather than as a

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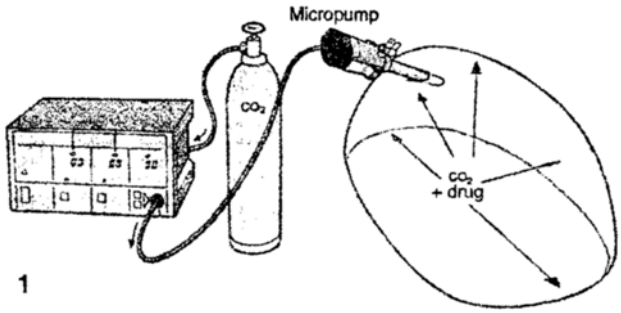


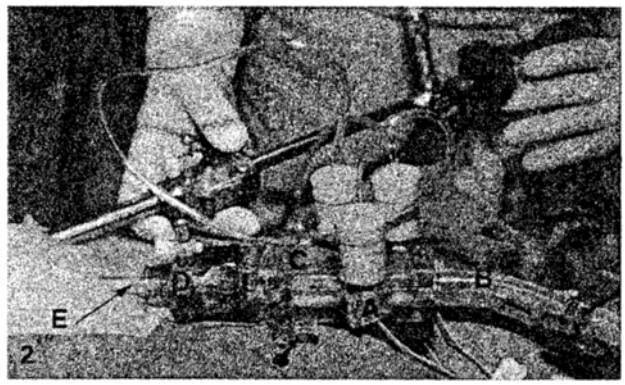


Fig. 1. The micropump is inserted between the gas insufflator and the abdominal cavity of the patient.

Fig. 2. Prototype of the vaporizator with three spraying units (**A**) in this case. The CO_2 tube (**B**) is connected to the micropump (**C**) that has been inserted into a 5-mm trocar (**D**). Condensation of microdroplets is visible downstream (**E**).

peritoneal wash are a better distribution of the drug in the abdomen and better drug diffusion into the tissues by the pressurization of the peritoneal cavity.

To create such a therapeutic pneumoperitoneum, an intracavitary drug delivery device suitable for minimally invasive surgery procedure is necessary. After designing and manufacturing such a prototype, we performed in vitro experiments to determine the behavior of the micropump with various kinds of solutions and to assess the flow rate, the influence of viscosity, the optimal delivery rate, and the optimal droplet size. Then we conducted in vivo experiments to test the intra-abdominal delivery rate and the peritoneal coating uniformity, and to detect possible unexpected events caused by the device during surgical procedures. The results of these experiments are reported in the current feasibility study.

Material and methods

The current invention is an intracavitary drug delivery device suitable for minimally invasive surgery procedures, allowing the creation of a therapeutic pneumoperitoneum. The efficiency of the therapeutic pneumoperitoneum depends on the activity of the substance (which depends on the composition), the place of impact (i.e., the place at which it may carry out its activity), dose repeatability (i.e., the fact that the volume of each dose remains constant), and, if indicated, the concentration repeatability (meaning that the drug flow remains constant with the gas flow).

Design of the prototype

The device consists of two elements: a micropump and a monitor. The micropump delivers the drug (in liquid form) as a dispersion of atomized droplets, thanks to the incorporated monodispersive spray device. The device is located between a gas insufflator and the body cavity where the surgery is to be performed (Fig. 1), which allows the device to aerosolize microdroplets of the therapeutic substance into the pneumoperitoneum. The liquid is aerosolized by excitation of a piezoelectric element.

Figure 2 shows in detail a prototype of the micropump built directly into a commercially available (Endopath, Ethicon Endosurgery, Norderstedt, Germany) 5-mm trocar. The monitor is placed in the vicinity of the gas insufflator. Flow rate, concentration, and amount of drug delivery are regulated according to the gas flow in a closed-loop control system. The control system allows for weighted-factor drug delivery according to the patient's condition and the level of intervention (EPO application 95908180.3). It is therefore possible to know precisely at each moment of the operation the amount of therapeutic substance that has been administrated to the patient.

Results

In vitro trial

The aim of the in vitro trials was to work out the kind of solutions including that can be aerosolized by the micropump, the influence of viscosity, the maximal flow, and the optimal droplet size.

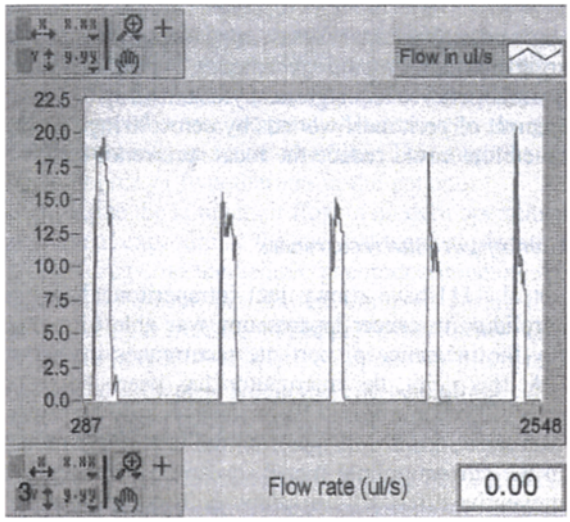
Kinds of solutions. We have shown that the micropump is able to aerosolize liquids such as water, ethanol, and various solutions including these:

- taurolidine (Taurolin, Geistlich, Wolhusen, Switzerland)
- 5-fluorouracil (Wyeth-Lederle, Wolfrathshausen, Germany)
- mitoxanthronhydrochlorid (Novantron, Wyeth-Lederle, Wolfrathshausen, Germany)
- betadine (Betaisodona, Mundipharma, Limburg, Germany), with some limitations due to PVP adhesive characteristics.

These solutions have pH values between 6.0 and 9.0.

Influence of viscosity. Because all the aforementioned solutions have low viscosity coefficients (<300 centipoises), we were not able to observe any negative influence of viscosity.

Maximal flow. Gas and drug flow calculations were based on measurements using input and output pressure sensors for determination of the differential pressure. Flows between 6 and 20 μl/s were achieved with one spraying unit (Fig. 3). Because of a redundancy of spray devices (e.g., three in the current prototype), a continuous reliable operation of the drug delivery system and an enhanced peak flow were obtained in vitro.



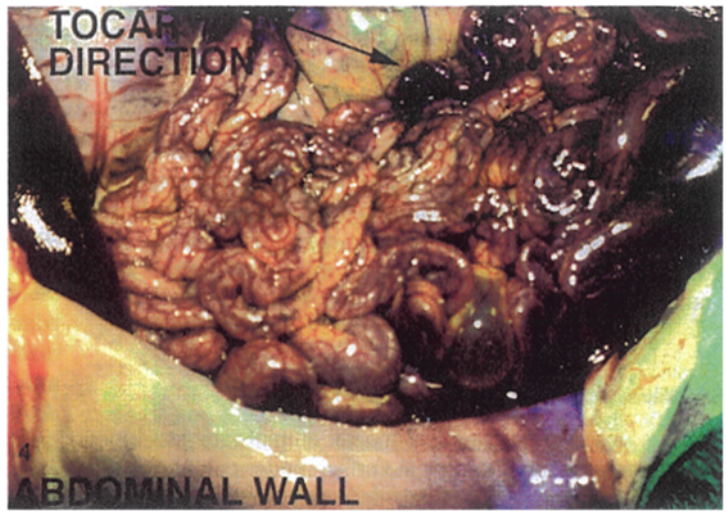


Fig. 3. Volume (and quantity) of drug aerosolized by the microvaporisator can be determined precisely by integrating the surface under the flow curve.

Fig. 4. Distribution of 3 ml of a 50% methylene blue solution after 30 min pneumoperitoneum, showing a diffuse staining with an enhanced concentration in the axis of the trocar (*arrow*) where the tumor is located.

Droplet size. A microdroplet size smaller than 10 μm was selected to allow maximal diffusion. It was observed that droplet size is inversely proportional to the excitation frequency of the monodispersive spray unit.

In vivo trial

The decision to use taurolidin in the current animal trial was based on a study of Jacobi [11] showing that application of taurolidin in the rat model was able to reduce significantly the incidence of port-site recurrences. Furthermore, toxicity of taurolidin in the pig is known to be low (data on file, Geistlich, Wolhusen, Switzerland).

Surgical procedure. After official permissions were obtained, two German land race pigs (weight, 21.3 and 20.4 kg, respectively) were anesthetized using routine protocols. Pneumoperitoneum of 12 mmHg was established using a Veres needle. At the beginning of the procedure, a further 5-mm commercially available trocar (Endopath) was inserted into the left upper quadrant, and the introducer was replaced by the micropump. A laparoscopically assisted resection of the sigmoid colon with transanal double-stapling was performed in both animals, using a four-trocar technique. Operating times were 90 and 97 min, respectively. The CO_2 volumes were 156 and 195 liters. (An artificial leak was created by opening a valve on the right lower trocar.) During the operation, a solution of taurolidin 2% was aerosolized into the abdominal cavity.

Drug distribution. Distribution of the active principle within the abdominal cavity was assessed by aerosolizing 3 ml of a 50% methylene blue solution into a pig cavader after installation of a pneumoperitoneum of 12 mmHg for 30 min. This assay showed a dispersion of the microdroplets within the entire abdominal cavity, including the anterior abdominal wall where trocar sites had been placed (Fig. 4). It is important that nonexposed surfaces such as the bursa omentalis and the inferior liver aspect were not stained. The trocars were not moved during this experiment. As expected, the distribution was not homogeneous, and staining was enhanced in the vicinity and axis of the trocar where the micropump had been introduced.

Unexpected problems. Both surgical procedures, performed by two experienced laparoscopic surgeons, showed no technical difficulties. In particular, vision was not impaired. Cardiorespiratory instability was observed in both animals by the anesthesiologist, which could be explained by the hypotonic nature of the 2% taurolidine solution that should have been corrected with saline.

As soon as the relative humidity in the intraperitoneal cavity approached 100%, the micropump was not able to aerosolize any longer. For this reason, we had to create a continuous artificial gas leak through a trocar tap and a usual gas line. This allowed the micropump to function throughout the procedure, but modified the standard laparoscopic procedure, in which the gas flow usually is interrupted in the absence of any gas leak.

Discussion

We propose the novel concept of "therapeutic pneumoperitoneum," defined as the association of a carrier gas such as CO_2 with an aerosolized therapeutic substance.

Results show that it is possible to create a therapeutic pneumoperitoneum with the drug delivery device used in the current study. It was possible simultaneously to perform resections of the sigmoid colon with no special surgical difficulty. This study was a feasibility test in a large animal model. Positive or negative target effects of drugs were not assessed at this stage of development. Therefore, this study provides no proof of the interest that therapeutic pneumoperitoneum may have in clinical practice. Nevertheless, therapeutic pneumoperitoneum has several interesting properties related to intraperitoneal pharmacokinetics.

The pharmacokinetic problems in peritoneal drug ad-

ministration were reviewed recently by Dedrick and Flessner [7]. Both theory and clinical studies demonstrate that drug concentrations in the peritoneal cavity can greatly exceed concentrations in the plasma after intraperitoneal administration. This regional advantage has been associated with clinical activity [2]. Two pharmacokinetic problems appear to limit the effectiveness of intraperitoneal therapy: poor tumor penetration by the drug and incomplete irrigation of serosal surfaces by the drug-containing solution. In both respects, the current invention might have major advantages over conventional irrigation.

Exposure of the peritoneal surface

Various observations in experimental animals suggest limited exposure of the peritoneal surface under conditions of peritoneal dialysis. In general, definitive studies have not been conducted on the potential peritoneal surface area of human subjects. The likelihood exists that much of the residual tumor burden after surgery is untreated or undertreated by conventional intraperitoneal irrigation. If the peritoneal surfaces are not exposed to drug-containing solutions or if they are inadequately exposed, then the rationale for regional administration is compromised [7]. Theoretical considerations suggest that the therapeutic pneumoperitoneum should be capable of carrying microdroplets of active substances to all exposed peritonteal surfaces. These considerations were confirmed by the current pilot study conducted in two animals, in which all exposed peritoneal surfaces were stained by methylene blue, suggesting that the active principle is distributed throughout the abdomen.

Increasing drug penetration

Obtaining large increases in the tissue penetration of a drug might be difficult. Both theoretical predictions and experimental measurements suggest very limited penetration of drugs into tissues, including tumors adjacent to the peritoneal cavity. Interestingly, introducing dialysis solution into the peritoneal cavity of rats and raising the intraperitoneal pressure from 0 to 4 cm H_2O caused the extracellular space of the anterior abdominal wall to double. This likely increased the effective diffusivity [7]. However, only limited clinical data are available to substantiate these preliminary observations [13]. In this respect also, therapeutic pneumoperitoneum has theoretical advantages over intraperitoneal irrigation, by applying intra-abdominal pressures of 12 to 15 mmHg (16 to 20 cm H_2O).

Therapeutic pneumoperitoneum has numerous potential applications, in particularly in the following fields.

Prevention of local recurrence after cancer laparoscopy

The main causes of local recurrence are intraoperative tumor cell implantation and inadequate excision of the primary tumor or the draining lymph nodes [1]. Because they are breaking the natural barrier formed by mesothelium and hyluronic acid [15], peritoneal wounds [25] such as those of trocar sites [14] or anastomoses are major causes of recurrence. The presence of growth factors and other cytokines in surgical wounds after cancer resections might stimulate growth of minimal residual disease. Avoidance of unnecessary surgical trauma by gentle techniques, control of spilled cells by intraoperative locoregional cytostatic drug delivery, and treatment of peritoneal wounds by aerosolizing coating agents therefore could reduce the local recurrence rate.

Prevention of port-site recurrences

Jacobi et al. [11] have shown that intraperitoneal lavage with taurolidine in cancer laparoscopy was able to reduce markedly the incidence of port-site recurrences in the rat model. At this point, the micropump has been shown to aerosolize a 2% taurolidine solution, and because the therapeutic substance reaches the anterior and lateral abdominal walls in the current animal model, it can be hypothesized that a preventive effect will be achieved. Therapeutic pneumoperitoneum also might be used in thoracoscopy. Because port-site recurrences also have been described during such procedures [9], aerosolization of taurolidine [16] or other hyaluoronates might be indicated as well.

Intraperitoneal and intrapleural chemotherapy

The response of established carcinoma or sarcoma implants to intraperitoneal and intrapleural chemotherapy is multifactorial. Two of the factors that influence the pharmacokinetics of intraperitoneal drugs are pressure [13] and heat [23]. Application of an intraperitoneal hyperpressure such as pneumoperitoneum in laparoscopy and heated CO_2 might be a promising approach to increase the drug diffusion into the tumor and to enhance the efficiency of intraperitoneal chemotherapy. These points deserve further research because in the case of colorectal adenocarcinoma there are insufficient data on which to base a clear-cut conclusion concerning real benefits [18].

Modulation of tumor immunogeneity

In the animal model, stress factors such as butyrate (associated or not with heat) in peritoneal carcinosis of colorectal origin have been shown to enhance tumor immunogenicity. In the rat model, immunomodulation followed by passive immunotherapy using intraperitoneal interleukin-2 (IL-2) application achieved some complete tumor responses in established peritoneal carcinosis [19, 20].

Benign disease

Other possible applications of therapeutic pneumoperitoneum concern benign disease such as intra-abdominal or intrapleural infections and prevention of postoperative adhesions. Because it has been shown that intraoperative bupivacain irrigation reduces both frequency and intensity of shoulder pain after laparoscopic procedures [6], therapeutic pneumoperitoneum also might be used for postoperative or even intraoperative analgesia.

It is important to note, however, that technical challenges remain. To aerosolize drug solutions into the gas

stream, it was necessary to maintain a gas flow throughout the procedure, so large volumes of CO_2 were used. Technically, this was possible by opening a trocar tap and diverting the therapeutic pneumoperitoneum over a usual line into a special waste recipient. Alternatively, the gas might be diverted into an active coal filter. This might have caused some degree of hypothermia in the patient.

Despite the laminar air flow in modern operating rooms, to prevent exposure of the surgical team to potentially hazardous drugs, no therapeutic pneumoperitoneum should be allowed to escape into the environment during the procedure. Such gas leaks should be prevented during laparoscopic cancer surgery because they appear to promote implantation and growth of free intraperitoneal tumor cells at port sites [24] and might be toxic when tissue has been cauterized [10]. In the particular case of intraperitoneal chemotherapy using cytostatic drugs, it might be necessary for the operating team to leave the room during the application of the drug (e.g., at the end of the procedure).

Using monopolar cautery in the presence of aqueous taurolidine solution was possible with no limitation. Nevertheless, further study using flammable solvents such as ethanol is necessary to identify potential hazards.

In summary, we introduce the novel concept of "therapeutic pneumoperitoneum" in laparoscopic and thoracoscopic surgery to prevent some side effects of CO_2 pneumoperitoneum without increasing the difficulty of the surgical procedures nor the risks to the patient. Expected and unexpected effects of various drugs now need to be assessed in appropriate studies. These might be exciting fields of research for engineers, pharmaceutical companies, oncologists, and laparoscopic surgeons.

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