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Intraoperative field flooding with warm humidified CO_2 may help to prevent adhesion formation after open surgery

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SUMMARY

Postoperative adhesion formation is a common, serious, and costly complication, which may cause organ dysfunction, difficult re-operations, and chronic pain. The formation of adhesions after open surgery is partly due to the perioperative exposure of the wound cavity to ambient air, which initiates various local processes that cause inflammation and cellular damage in mesothelial layers. These adhesiogenic processes include superficial desiccation, airborne bacterial contamination and subsequent wound infection, and exposure to atmospheric oxygen with ensuing hyperoxia and oxidative stress. Here, we describe how recent results from experimental surgical research imply that the adverse effects of air exposure during open surgery could be prevented by the use of intraoperative field flooding with warm and humidified carbon dioxide. If proven effective in a clinical trial, a decreased incidence of postsurgical adhesions would thus save a lot of suffering, time, and money for the patients and the healthcare system.

Background

The formation of adhesions after surgery is a serious complication, which may cause organ dysfunction, difficult re-operations, and chronic pain [1]. Furthermore, postoperative adhesion formation is claimed to be the most frequent complication in abdominopelvic surgery [2], where as much as one-third of the patients have to be readmitted for conditions related to adhesions [3]. The economical impact of adhesions is therefore also huge. For example, in the United States alone the annual adhesion-related expenditures in healthcare exceed one billion dollars [4].

Adhesion formation after open surgery is partly due to the perioperative exposure of the wound cavity to ambient air, which initiates various local processes that cause inflammation and cellular damage in mesothelial layers [1,5,6]. These adhesiogenic processes include superficial desiccation, airborne bacterial contamination and subsequent wound infection, and exposure to atmospheric oxygen (O_2) with ensuing hyperoxia and oxidative stress [1,7,8].

Hypothesis

It has recently become possible to establish a local atmosphere of 100% carbon dioxide (CO_2) in an open surgical wound cavity by flooding it with the gas. This has opened up new possibilities for prevention of postoperative complications in open surgery, including arterial air embolism and concomitant neurological impairment in cardiac surgery [9]. In the present article we put forth the hypothesis that: *intraoperative field flooding with warm humidified CO_2 can decrease the occurrence of adhesions after open surgery.*

Support for the hypothesis

Support for the present hypothesis is provided by results from our own previous research on CO_2 field flooding in open surgery, as well as from related research in laparoscopic surgery, after which adhesions are also common and where CO_2 is insufflated into the *closed* surgical wound cavity to facilitate endoscopy. As we will show, these results together imply that intraoperative field flooding with warm humidified CO_2 could alleviate, if not prevent, the adverse adhesiogenic effects of air exposure during open surgery.

Prevention of desiccation

Perioperative desiccation of superficial tissue in the surgical cavity is recognized as one of the most important adhesiogenic factors [1,10]. Physically, desiccation means that water evaporates and escapes from the wound surface to the open environment. Medically speaking, the desiccation of mesothelial cells activates an inflammatory process which in the end leads to adhesion formation [1,10]. We have previously found that perioperative desiccation in an open surgical cavity can be averted by topical insufflation of humidified CO_2 [11]. Being heavier than air the

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humid CO_2 acts as a protective cushion, which prevents evaporation and air draft to occur at the wound surface [11,12]. In order to be effective the CO_2 not only has to be humidified with water but also heated to body temperature. Because if room tempered humidified CO_2 is insufflated into the warm surgical wound cavity, the relative humidity of the gas will decrease as it is heated up. Consequently, desiccation will occur, even if the cold gas is saturated with water before entering the surgical cavity. Accordingly, a recent animal study showed that perioperative insufflation of *warm* humidified CO_2 could prevent the formation of adhesions after laparoscopy [13].

Prevention of surgical site infection

Since the dawn of surgery, avoiding wound infection has been of primary importance as it may cause a number of other subsequent complications that could ruin the outcome of the procedure. One of these complications is adhesion formation due to the ensuing inflammatory reactions at the infected site [1]. We have shown earlier that intraoperative CO_2 insufflation can decrease the risk of surgical site infection via several mechanisms [14]. In short, flooding the surgical cavity with CO_2 will not only prevent airborne bacteria from reaching the exposed tissue [15] but also suffocate those already there [16]. Moreover, the use of heated humidified CO_2 will also keep the surgical wound tissue warm [12], which in its turn optimizes the immune system against infection [17–19]. Thus, decreasing the risk of surgical site infection and its toxic effects should also imply a reduced risk of adhesion formation.

Prevention of oxidative stress

Postoperative adhesion formation has been associated with the occurrence of increased levels of reactive oxygen species (ROS) [8,20]. The production of ROS is an important part of the immune defense, and ROS are normally quickly detoxified by the biological antioxidant system. However, when the amount and activity of ROS increase above the power of the antioxidant system they cause deleterious oxidative stress in tissue. ROS are produced in hyperoxic environments and have accordingly been found to increase during open surgery where externalized tissues are exposed to atmospheric oxygen [7]. In air O_2 has a partial pressure of 160 mmHg (21% of 760 mmHg), which is much higher than the intracellular O_2 pressures. Consequently, the conditions during open surgery will inevitably lead to local hyperoxia and ensuing increased occurrence of ROS and oxidative stress. Laparoscopic surgery, on the other hand, does not seem to cause oxidative stress [7]. This advantage has been ascribed to the avoidance of air exposure by intraperitoneal insufflation of CO_2 [7]. Therefore, we correspondingly suggest that intraoperative field flooding with CO_2 may reduce oxidative stress and thus the risk of adhesion formation in open surgery, simply because the resulting local CO_2 atmosphere will exclude ambient air and the reactive O_2 in it [21].

Recommendations

In case of hypoxia – add oxygen

Avoiding local hyperoxia in the open surgical wound would surely help to decrease the risk of postoperative adhesions. However, if local hypoxia is induced in the process the total effect could instead imply an increased risk of adhesion formation. Previous experimental laparoscopic research on mice has indicated that pneumoperitoneum might induce hypoxia in superficial mesothelial cells and increase the formation of adhesions as a result [22]. It was hypothesized that the intraperitoneal pressure compresses superficial blood vessels while the insufflated gas, whether CO_2 or helium, at the same time diffuses into the superficial blood and tissue. However, this should not be the case with CO_2 field flooding in open surgery. Firstly, there is no pneumoperitoneum involved as the CO_2 is insufflated into open air. Secondly, Bourdel et al. have recently found in animal experiments that a CO_2 pneumoperitoneum, created at a *low* insufflation pressure, actually increases the tissue O_2 tension in peritoneum [23]. This elevation was neither observed when air was insufflated nor when CO_2 was insufflated at a higher pressure. Thus, Bourdel et al. concluded that "...it is the biological activity of CO_2 gas that is contributing to the increase in peritoneal tissue–oxygen pressure..." and that "...a CO_2 pneumoperitoneum could increase the transport of oxygen from blood to the tissue through the Bohr effect." Since this increase is achieved through a biological mechanism the resulting O_2 pressure in tissue should still remain at normal non-deleterious levels.

Nevertheless, if future studies would show that even CO_2 flooding causes superficial hypoxia, despite the Bohr effect, there is a simple solution. Experimental laparoscopy studies in mice have shown that adding O_2, either systemically via the lung ventilation [24] or locally via insufflated CO_2 [20,25], can elevate and restore the tissue O_2 tension in peritoneum and thereby reduce abdominal adhesion formation. As for the latter way of administration, Koninckx and his group have found that mixing the insufflated CO_2 with 3–4% O_2, equivalent to the intracellular partial pressure of O_2, will provide a balance in superficial tissue O_2 tension so that both hypoxia and hyperoxia are avoided [20,25].

No cooling

The same research group has found in animal studies that lowering the perioperative body temperature decreases adhesion formation after laparoscopy [25,26]. In these experiments cooling seemed to protect superficial cells metabolically against the toxic effects of the hypoxia induced by the pneumoperitoneum. Consequently, the researchers suggested that perioperative cooling could be applied to prevent adhesions [26]. However, seen in a larger clinical perspective such cooling would be inappropriate. A randomized clinical study has clearly shown that a slight temperature drop of just a couple of degrees greatly increases the risk of surgical wound infection [19]. Part of the explanation is that cooling not only decreases the metabolic rate in cells but also reduces tissue perfusion and oxygenation [17,18]. Furthermore, general hypothermia is associated with other postoperative complications including shivering, prolonged intubation and hospitalization, as well as cardiovascular morbidity [27]. Thus, if not indicated for other reasons, cooling to prevent adhesions could be counterproductive and seriously adventure the clinical outcome. Besides, in open surgery the suggested treatment for local hypoxia would probably be superfluous anyway because, as described above, due to the absence of a pneumoperitoneum and to the CO_2's Bohr effect [23], superficial hypoxia may not even occur in the first place.

Insufflation with a gas diffuser

According to our previous research the potential preventive effects of CO_2 flooding on adhesion formation will only be attained if the gas is insufflated through a diffuser, which minimizes the outflow velocity of the gas [28]. Insufflation without a diffuser would produce a high-velocity jet and cause turbulent mixing with ambient air. This would in its turn not only result in a high O_2 concentration in the open surgical wound cavity [28], but also drastically increase the rate of both desiccation [11] and airborne contamina-

tion [15], and thereby in fact increase the risk of adhesion formation.

Testing the hypothesis

The technical and physical aspects of CO_2 flooding have already been studied extensively in laboratory settings by the authors. The next step would then be to study the method's effect on adhesion formation *in vivo*. As we have described, much related animal research has already been done in experimental laparoscopy. However, although those results may be interpreted and applied to serve our present purposes, new tests should be performed with CO_2 flooding during *open* surgery. Admittedly, animal models are very useful in adhesion research because they make it easier to quantify adhesion formation and to follow strictly standardized protocols. However, there is still always a risk that the results will not be generalizable to the human clinical setting [29]. Moreover, the present hypothesis can ultimately only be tested in a clinical trial.

Many new methods to prevent adhesions have been tried in animal experiments but few have been evaluated in patients. As we have shown, there are good grounds to believe that the suggested method should have a clinical effect. There are also many reasons why the method should be clinically safe. It is for those reasons that intraoperative CO_2 insufflation, since many decades, is being used in laparoscopy to create pneumoperitoneum and in open-heart surgery to de-air the heart and great vessels. As for the proposed modifications of the CO_2 gas, the use of heated and humidified CO_2 for pneumoperitoneum is nowadays almost regarded as standard routine in laparoscopy and should therefore not be an issue in open surgery either. The possible addition of a few percents O_2 to the insufflated CO_2 should also be a safe modification. Medically, the concentration of the added O_2 would correspond to the normal intracellular levels. Physically, the extra O_2 would not pose a fire hazard, partly because the O_2 content would be much lower than that in air, and partly because CO_2 is itself a fire extinguishing gas [30,31].

Implications

All in all, we have shown that intraoperative field flooding with warm humidified CO_2 could, via several mechanisms, help to prevent the formation of adhesions after open surgery. If proven effective in a clinical trial, a decreased incidence of postsurgical adhesions would then save much suffering, time, and money for the patients and the healthcare system.

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