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Intraoperative CO_2 insufflation can decrease the risk of surgical site infection ☆

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Summary Surgical wound infections may ruin otherwise successful operations, and are associated with extended hospital stay, extra costs, and high mortality rates. In open surgery the wound's exposure to ambient air increases the risk of wound infection via several independent factors. The open surgical wound is subjected to airborne bacterial contamination, desiccation, and heat loss that increase the bacterial load, cause superficial necrosis, and impair tissue oxygenation and cellular immune functions, respectively. The present hypothesis is that topically applied carbon dioxide in the open surgical wound can be used intraoperatively to avoid these risks, and thus help to prevent postoperative wound infection. We also criticize existing methods and describe the theoretical background and supporting evidence for our suggested method. If the hypothesis would prove to be correct in a clinical trial, the new method may be an effective complement, or even an alternative, to antibiotics in preventing surgical site infection.

Introduction

Wound infection is a serious complication after open surgery resulting in increased hospital stay, costs, and mortality [1]. Despite the progress in modern medicine, postoperative infections are still common. Factors that influence the frequency of surgical wound infection include: use of ultra-clean air ventilation in the operating room, antibiotic prophylaxis, perioperative hypothermia, tissue oxygen tension, presence of bacteria in the wound, and duration of surgery [2]. Operating room ventilation is a generally accepted method for the prevention of airborne contamination. However, the use of laminar ultra-clean airflow from the ceiling downward to the operating table may actually help to convey airborne particles from the surgical team into the operating field. It has been reported that when the surgeon leans over the wound in such an airflow, as he usually does, he increases the risk

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of airborne wound contamination 27-fold [3]. In an experimental study we reached similar findings that confirmed this surprising deficiency [4]. Moreover, the continuous downward airflow also increases desiccation and cooling of the exposed wound tissues, which further increases the risk of wound infection [5,6]. Antibiotics have been widely used for prophylaxis and treatment of infection for many decades now. However, the emergence of methicillin-resistant *Staphylococcus aureus* and the recent identification of strains of *S. aureus* with resistance to vancomycin pose a significant public health threat, and alternatives to antibiotics are sought for. Since most wound infections are established intraoperatively [2,7], and since the risk of surgical wound infection increases with the duration of the operation [1,2], it seems logical to apply new countermeasures intraoperatively.

Hypothesis

Intraoperative insufflation of the open surgical wound with carbon dioxide (CO_2) may be such a countermeasure. This method is dependent on a new gas insufflation device (CarbonAid[TM] Gas diffuser, Cardia Innovation AB, Stockholm, Sweden) which the authors recently developed in order to create a local atmosphere of CO_2 in the open surgical wound [8]. The original purpose was to evacuate air from the surgical field to prevent arterial air embolism and ensuing neurological damage in open-heart surgery [9]. The present paper demonstrates that CO_2 possesses a number of potent biomedical and physical properties that may help to decrease the risk of surgical site infection (Table 1). Thus, we present the following hypothesis: *Continuous insufflation of CO_2 with a gas diffuser in the open surgical wound decreases the incidence of postoperative wound infection.*

Supporting evidence

Decreased airborne contamination

It has been found that over 90% of the contaminating bacteria in clean surgical wounds come from the ambient air, and a substantial part of these bacteria contaminate the wound directly [10]. Moreover, it has been estimated that as few as 10 bacteria-carrying airborne particles are sufficient to cause deep surgical wound infection [11]. This implies that preventing only a few airborne particles from reaching the surgical wound should have clinical significance. When considering the role that topical CO_2 insufflation might play in combating airborne infection, it should be kept in mind that when CO_2, which is heavier than air, is continuously supplied to a wound cavity, surplus CO_2 will continuously flow upwards and out of it. This continuous overflow of CO_2 from the wound opening might be able to repel and transport particles away from it and thus prevent direct airborne contamination. According to Stokes' law, which describes a particle's settling velocity in a fluid (gas or liquid), a considerable reduction of direct airborne contamination will theoretically be possible with the considered CO_2 flow rates. This prediction was confirmed in a study [12] where we found that insufflation of CO_2 at a flow of 10 L/min in an open cardiothoracic wound model could decrease the rate of direct airborne contamination with approximately 80%. Theoretically, the contamination rate could be decreased even further by increasing the flow rate and/or by making the wound opening smaller with a surgical drape, not only due to a reduced exposed area but also because of an increased upward gas velocity. In contrast, the study also revealed that CO_2 insufflation via a single open ended tube dramatically increased the rate of airborne contamination. The immediate implication of this finding is that the use of improper insufflation devices could actually lead to an increased risk of postoperative wound infection.

Table 1 Effects of intraoperative CO_2 insufflation that may help to decrease the risk of wound infection in open surgery

Expected effects of intraoperative insufflation with humidified CO_2
1. Decreased direct airborne contamination
2. Inhibited bacterial growth in the wound, via
a. Suffocation
b. Specific CO_2 effect
3. Decreased superficial tissue necrosis in the wound, via
a. Decreased desiccation
4. Increased wound tissue oxygenation, via
a. Thermal wound insulation/warming, via
— Decreased evaporation
— Greenhouse effect
— Preheated CO_2
b. Vasodilatation, via
— Increased wound and core temperature
— Specific, local CO_2 effect
c. Bohr effect in wound tissue, via
— Increased wound temperature
— Increased local pCO_2
— Decreased local pH
5. Improved cellular immune functions, via
a. Increased wound and core temperature

Decreased bacterial growth

For many years now CO_2 in high concentrations has been used in modified atmosphere packaging to prolong the shelf life of fresh food. The effect of CO_2 has been found to be especially marked in fresh meat [13]. High concentrations of CO_2 has a growth inhibiting effect on most bacteria, both aerobes and anaerobes [14,15]. The inhibitory effect of CO_2 is connected to two main mechanisms: suffocation and a specific CO_2-effect that acts directly on the bacterial cell. The latter mechanism is not yet completely understood but seems to be a result of multiple biomedical actions. In general, however, the rate of bacterial multiplication decreases with increasing levels of CO_2 [16]. The question arises why an antibacterial method that has proved to be so effective and widely used in the food industry has not been put to clinical use in open surgery to prevent postoperative wound infection. One reason may be that intraoperative methods to continuously expose an open surgical wound to 100% CO_2 have previously not been available.

Because food related research have focused on the CO_2's effects at low temperatures we studied its effects at body temperature [17]. It was found that pure CO_2 significantly decreased the growth rate of *S. aureus* at body temperature. In comparison with growth in air, where the number of bacteria increased exponentially with time, the bacterial growth in CO_2 appeared unchanged. After 4 h the bacterial count in air was almost 100 times higher than that in CO_2. The CO_2 should have a similar effect on bacteria in an open surgical wound. It may then be argued that CO_2 would not only inhibit bacteria but also immunological active cells such as macrophages in a wound. However, contaminating bacteria are located superficially in the wound and will thus be exposed directly to the topically applied CO_2 whereas immunological cells are protected by tissue and body fluids.

Decreased desiccation

When the surgeon opens the surgical wound he abruptly exposes internal tissues to a totally new environment, ambient air, which is characterized by lower temperature and, probably even more important, far lower humidity. Although the implications of this sudden change have so far not been studied very extensively it has become clear that desiccation during surgery leads to superficial tissue damage [18]. Desiccation necrosis of mesothelial layers and other sensitive tissues may not only promote adhesions but also postoperative infection.

Desiccation results from superficial water loss through diffusion and convective gas movements. The formulas that describe evaporation from a surface say that when the ambient gas is fully saturated, water loss cannot take place regardless of the gas movements above the surface. On the other hand, if the gas is not fully saturated with water, the convection, i.e. gas exchange above a surface, will be the decisive factor for desiccation. Diffusion alone is a rather slow transfer process but convection maximizes the evaporation rate by constantly exchanging the ''humidified'' gas close to the surface with ''dry'' ambient gas, i.e. the diffusion gradient is kept maximized. Thus, if it is not possible to saturate the open wound's environment, avoiding convection in the wound can theoretically still substantially reduce desiccation. We have previously found that topical insufflation of humidified CO_2 decreased the desiccation rate in a wound model with more than 90% [5]. This result has a simple explanation. The CO_2, which has greater density than air, gravitates in the wound cavity and covers it like a protective cushion, which minimizes both water diffusion and the convective air currents caused by the operating room ventilation. This explains the paradoxical result that even insufflation of completely dry CO_2 (0% relative humidity) caused a lower evaporation rate than the control which was exposed to ambient air [5,6].

Decreased heat loss

Hippocrate's statement that ''*Wounds love warmth*'' still holds true today as it is current practice to prevent peri- and postoperative hypothermia in order to reduce the incidence of surgical complications, including wound infection [7]. Mild hypothermia increases the risk of wound infection [19] partly due to a decreased tissue blood flow and tissue oxygenation [20,21]. A low oxygen tension in wound tissue has been found to be a strong predictor for the risk of surgical wound infection [22]. However, the process can be reversed by local warming which increases tissue oxygenation via locally mediated vasodilatation and increased oxygen deposition in tissue [20,23,24].

We have found that humidified CO_2 provides an effective thermal insulation of an open surgical wound as evaporation and convection are reduced. Moreover, the heat emitted from the patient as well as via the light from the operation lamps can also be positively taken care of by the CO_2's greenhouse effect. (The two factors should be combined because without CO_2 in the wound, mere heating with lamps will increase the evaporation and desiccation in the wound.) We found that during insufflation of dry and humidified room tempered CO_2 the surface temperature in a wound model was kept 1.9 °C and 2.3 °C, respectively, warmer than the control without insufflation [6]. This has been confirmed in not yet published clinical measurements.

Local warming may not only have local effects in the open wound, but may also influence the body core temperature. In open surgery, a substantial amount of the total heat lost during surgery disappear through the open surgical wound via radiation and evaporation which reduces the core temperature [25,26]. Accordingly, it is known that core hypothermia is more pronounced during large than during small operations, with most of the difference presumably resulting from an increased evaporation [26]. Since anesthesia causes vasodilatation, heat is easily distributed between the core and the wound surface [26]. Thus, if the wound surface can be kept warm, the core temperature may also be kept up. In a controlled clinical trial a decrease in perioperative core temperature of only 1.9 °C, from 36.6 °C to 34.7 °C, tripled the incidence of surgical wound infection and prolonged hospitalization after colon resection [19].

Mild perioperative hypothermia not only decreases tissue oxygenation but also impairs various cellular immune functions. For example, neutrophil oxidative and phagocytic capacities are found to significantly decrease intraoperatively [27]. The production of oxidative intermediates is related to intraoperative core temperature, with an observed fourfold decrease over a 4 °C range [27]. Moreover, decreased temperatures reduce the functioning of granulocytes, which leads to a decreased rate of phagocytosis [28]. Since topically applied CO_2 can reduce heat loss in an open surgical wound, perioperatively impaired immune functions could be normalized.

Thus, even if the rest of the patient is well protected with insulating blankets and heating covers, the open surgical wound is left unprotected where a substantial heat loss takes place. Until now no practical method has been available to protect the open wound thermally. With the above in mind, it is reasonable to expect that the increased wound temperature provided by the suggested method could have a significant effect on infection rates. In addition, if warm humidified CO_2 is used this effect could be increased even further.

Specific oxygenation effects

The mere presence of CO_2 in the wound will provide additional specific effects that may contribute to increase the oxygen tension in wound tissue. It has been found that topically applied CO_2 itself increases tissue oxygenation by causing local vasodilatation and a Bohr effect [29,30], i.e. a rightward shift of the hemoglobin's oxygen saturation curve, which increases the deposition of oxygen in the exposed tissues.

Clinical evaluation

Our hypothesis that intraoperative CO_2 insufflation can be an effective method to prevent surgical site infection is based on theoretical predictions and validating experimental studies. Although these provide promising results, the total sum of the effects of CO_2 insufflation on the risk of infection can only be evaluated in a clinical trial. In fact, related clinical studies in closed surgery have shown that laparoscopic procedures where CO_2 has been used for endoscopy, have lower infection rates than corresponding open procedures (without CO_2 insufflation) [31,32]. These lower infection rates may now be explained by the very same effects as those provided by topical CO_2 insufflation in an open wound, i.e. bacteriostatic effect, vasodilatation, Bohr effect and reduced airborne contamination, desiccation, and heat loss.

Recommendations

The suggested method requires a continuous insufflation of CO_2 for its various antibacterial effects to occur. The protection against direct airborne contamination is active only when there is a CO_2 flow in the wound. Moreover, the full bacteriostatic effect and the prevention of wound evaporation are dependent on a fully developed CO_2 atmosphere in the surgical wound, which also requires a continuous CO_2 flow [33]. Because, all negative effects of the wound's exposure to air in open surgery, i.e. airborne contamination, desiccation and heat loss, accumulates during an operation, and since bacteria multiply exponentially with time, the combined risk of infection should ultimately accelerate with the time of exposure. By using the same logic in reverse, one could say that the preventive effects of topical CO_2 insufflation should be increasingly more important the longer the operation lasts. Thus, especially long procedures should benefit the most from the method.

CO_2 insufflation should be applied as long as the surgical wound is open. When used on a cardiothoracic surgical wound a CO_2 flow of 10 L/min is required [12,34,35]. For small wounds, or for those that have been made smaller with a surgical drape, a lower flow rate may suffice. As for the methods impact on the global environment, medical CO_2 is a recycled byproduct from beer and fertilizer production, and one hour of CO_2 insufflation releases approximately the same amount of CO_2 as a petroleum car during a five minutes' drive.

Implications

If the present hypothesis holds there is an effective complement, or even an alternative, to antibiotics for prevention of wound infection in open surgery. The main advantages of the suggested method would be its simplicity and, even more important, its ability to prevent infection via several independent mechanisms.

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