Reply: Perioperative cooling to prevent adhesion formation may be counterproductive for the clinical outcome

Sir,

We thank Persson and van der Linden for drawing attention to the potential harmful effects of a decreased core body temperature (Sessler, 2001) upon immunology, vascular supply, wound healing and risk of wound infection following colorectal surgery (Kurz *et al.*, 1996). This, moreover, has stimulated research on the pathophysiology of core body temperature decrease during anaesthesia, and methods were developed to prevent this. Since mice are unfortunately too small for peritoneal cooling without affecting core body temperature, our experiments might have given the impression that we aimed to decrease core body temperature to prevent adhesion formation. We, therefore, thank you for the opportunity to discuss this in greater detail.

Our mouse model experiments have been consistent with the concept that adhesions between surgical lesions are enhanced by mesothelial trauma, i.e, mechanical trauma (Schonman R *et al.*, 2009), desiccation (Binda *et al.*, 2006), hypoxia (less than 5 mmHg O_2 partial pressure) (Molinas *et al.*, 2001) or hyperoxia (more than 70 mmHg partial pressure) (Elkelani *et al.*, 2004). Touching and desiccation clearly affect the superficial layers only, whereas the CO_2 pneumoperitoneum causes superficial hypoxia of <100 μm in depth, as evaluated by histochemistry (unpublished data). We would therefore have preferred to cool the peritoneal cavity without affecting the core body temperature in order to confirm the hypothesis that mesothelial cells are more resistant to hypoxia at lower temperature. Unfortunately, subsequent experiments in larger animals will be necessary to prove this.

Certainly, the potential harmful effects of decreasing core body temperature will have to be evaluated and monitored closely organizing trials to translate the observations on mice experiments into clinical medicine. A full discussion of cooling only the abdominal cavity in human was beyond the scope of our original article, and in addition this would have been speculative to a large extent. We therefore restricted the discussion to the fact that adhesion formation increased exponentially with core body temperature in mice (Binda et al., 2004, Binda *et al.*, 2006).

Cooling the peritoneal cavity directly contradicts the clinically widely used heating of CO_2 gas during endoscopic surgery. To the best of our knowledge, however, this protocol was introduced clinically with little evidence of a beneficial effect of temperature alone. Indeed, almost invariably cold and dry gas was compared with warmed and moistened, and little attention was given to the associated desiccation shown clearly in the mouse model to increase adhesion formation (Binda *et al.*, 2006). Moreover, circumstantial evidence suggests that cooling the peritoneal cavity without affecting core body temperature might not have an important deleterious effect in women. For over 20 years, we have been using high-flow insufflators for smoke evacuation during CO_2 laser surgery (Koninckx and Vandermeersch, 1991). During the first years, dry and freezing cold CO_2 was used; later, we used the Thermoflator together with a humidifier. Since the tubing is not isolated, this results in CO_2 at room temperature but with 100% relative humidity because of condensation. Upon entry into the abdominal cavity, the CO_2 gas is heated up and intraperitoneal temperature ranges between 28°C and 34°C depending on the flow rate and the localization in the abdomen, given the compartmentalization of the peritoneal cavity (unpublished observations). Heating of the CO_2 is unavoidably associated with some desiccation, contributing in itself to the cooling of the peritoneal cavity. Although proper trials have not been performed to evaluate the effect upon wound infection, our incidence of wound infections has been negligible, below 0.5%, and this notwithstanding the really low peritoneal cavity temperatures and an abdominal wall which clinically felt cold. This low incidence of wound infection might be explained by the fact that the core body temperature remained unaffected during these surgeries.

Given the increased risk of wound infections with lower core body temperatures, we should consider the risk of increasing intraperitoneal infections, especially following full thickness endometriosis resection of the bowel. In our historical data collected over the last 20 years, of over 100 full thickness endometriosis resections and a peritoneal cavity temperature below 34°C, peritoneal infections have been rare; however, this might also have been a consequence of the systematic use of antibiotics. In order to avoid desiccation, the humidified CO_2 gas should preferably be cooled slightly upon entrance, thus causing some condensation. For this reason, we consider the peritoneal cavity cooling should be performed by a third and independent means. Preliminary observational data indicate that in absence of desiccation, peritoneal temperatures at least as low as 29°C will not affect core body temperature suggesting that cooling is fairly superficial. Indirectly, this also seems to confirm that desiccation has a major contribution to cooling core body temperature.

The key question remains—what would be the optimal pneumoperitoneum temperature to decrease adhesion formation without serious adverse side effects. At present, we can only speculate. Adhesion formation decreased with temperature in mice (Binda *et al.*, 2004) with most of the effect observed at 32°C (Binda *et al.*, 2004, 2006). This, together with the observations of the intraperitoneal temperatures during our endoscopic surgery, might suggest an ideal intraperitoneal temperatures range between 28°C and 34°C. Only constant and controlled cooling will allow detailed investigation of the relationship between peritoneal temperature and temperature gradients in intraperitoneal organs and the eventual risk of peritoneal infections. In conclusion, we postulate that we should distinguish clinically between the effects of even slight core body hypothermia (Kurz *et al.*, 1996; Sessler, 2001) and surgical conditions that do not affect the core body temperature, such as traditional laparoscopy with some desiccation and some decrease of pneumoperitoneum temperature. The effects of a pneumoperitoneum with a decreased peritoneal temperature without desiccation should be investigated in rigorous clinical trials.

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Philippe R. Koninckx[1], Roberta Corona[1], Bernard Vanacker[2] and Maria M. Binda[1,3]

[1]*Department of Obstetrics and Gynaecology, University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium*

[2]*Department of Anesthesiology, University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium*

[3]Correspondence address. Leuven Institute of Fertility and Embryology (LIFE), Tiensevest 168, B3000 Leuven, Belgium. Tel: 32-16-270-190; Fax: 32-16-270-197; E-mail: mercedes.binda@gmail.com

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Combating endometriosis by blocking proteasome and nuclear factor-κB pathways

Sir,

I have read with great interest the article by Celik *et al.* (2008) regarding experimental treatment of mouse endometriosis by inhibiting proteasome and nuclear factor-κB (NF-κB). The findings are in good concordance with recent works suggesting NF-κB to be a major factor in the pathogenesis of endometriosis (Guo, 2007). In fact, pyrrolidine dithiocarbamate (PDTC) and other dithiocarbamates are NF-κB inhibitors because of creating copper complexes in the body and inhibiting proteasome (Cvek and Dvorak, 2007); hence, PDTC is *proteasome inhibitor* as well as bortezomib. On the other hand, bortezomib as a proteasome inhibitor inhibits NF-κB pathway as well in humans (Orlowski and Kuhn, 2008). Thus, both bortezomib and PDTC represent the same therapeutic approach towards endometriosis: NF-κB blockage is a consequence of proteasome inhibition. Therefore, we suggest that it is worth investigating if proteasome inhibitors (bortezomib and disulfiram are available in the clinic even now, cf. Cvek and Dvorak, 2008) would be sufficiently effective (and safe) against endometriosis in human patients.

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Boris Cvek[1]

Department of Cell Biology and Genetics, Faculty of Science, Palacky University, Olomouc, Czech Republic

[1]Correspondence address. E-mail: cvekb@seznam.cz

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Reply: Combating endometriosis by blocking proteasome and nuclear factor-κB pathways

Sir,

I am pleased with the kind feedback from Dr Cvek, regarding our experimental work on the treatment of endometriosis by inhibiting proteasome and therefore nuclear factor-κB in rats (Celik *et al.*, 2008). As has been pointed out by Dr Cvek, both pyrrolidine dithiocarbamate and bortezomib are proteasome inhibitors, and we showed that they represent almost the same therapeutic approach towards endometriosis because of creating copper complexes in the body and consequently causing NF-κB blockage (Cvek and Dvorak, 2007; Celik *et al.*, 2008). Dr Cvek has suggested that disulfiram, which is currently used to support the treatment of chronic alcoholism, could be sufficiently effective (and safe) against endometriosis in human patients with almost the same success rate as the proteasome inhibitors we used in animals, and so needs to be investigated.

The fact is that proteasome inhibitors are drugs that block the action of proteasomes, cellular complexes that break down proteins, particularly being studied in the treatment of cancer (Cvek and Dvorak, 2008). Disulfiram creates complexes with metals such as dithiocarbamate complexes, which inhibit proteasomes (Cvek and Dvorak, 2007; Wickström *et al.*, 2007). It is used in the treatment of chronic alcoholism, cocaine dependence and protozoal infections (Nash *et al.*, 1998; Lövborg *et al.*, 2006). There are ongoing clinical trials of disulfiram with copper gluconate against liver and lung