New technologies and applications of laparoscopic and robotic surgery in urology

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New technologies and applications of laparoscopic and robotic surgery in urology

By

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Declaration

I hereby declare that, the contents and organization of this dissertation constitute my own original work and does not compromise in any way the rights of third parties, including those relating to the security of personal data.

Marco Oderda

2017

* This dissertation is presented in partial fulfillment of the requirements for **Ph.D. degree** in the Graduate School of Politecnico di Torino (ScuDo).

I would like to dedicate this thesis to my loving parents

Acknowledgment

And I would like to acknowledge prof Pierre Diemunsch and dr Elisabetta Cerutti for their precious assistance during the development of the clinical trial.

Abstract

Background: cool and dry gas insufflation during laparoscopy induces hypothermia and cytokine increase, with significant perioperative morbidity. Few studies have suggested that warmed and humidified insufflation leads to an improved body core temperature (BCT) maintenance, a reduction of the inflammatory response and an improved quality of postoperative course, compared with standard insufflation.

Objective: to assess if warmed and humidified CO_2 insufflation with HumiGard™ device can achieve significant benefits over standard insufflation in terms of risk of hypothermia and cytokine response, in the setting of robot-assisted radical prostatectomy (RARP).

Design: prospective, randomized, controlled clinical trial (September, 2015, June, 2016).

Setting: single center study in a tertiary hospital.

Participants: 64 patients with prostate cancer undergoing RARP were randomized, 32 to the treatment group and 32 to the control group.

Intervention: the treatment group (H+WB) received warmed, humidified CO_2 insufflation with HumiGard™ device, plus hot air warming blanket; the control group (WB) received standard CO_2 insufflation, plus hot air warming blanket.

Main outcomes and measures: BCT, plasma levels of cytokines IL-6 and TNF-α, pain scores, and intraoperative parameters. The data were analyzed according to the Bayesian paradigm.

Results: intraoperative BCT increased in both groups during surgery, with a statistically significant difference favoring group H+WB, ending at 0.2°C higher on average than group WB. The overall BCT increase was 0.088 degree per hour in the WB group, with an additional 0.064 degree per hour in the H+WB group. No difference across groups, at none of the time points, could be shown as far as mean serum cytokine levels was concerned. No statistical differences were noted for pain scores and the other intraoperative parameters.

Conclusions: during RARP, warm and humidified CO_2 insufflation with the HumiGard™ device was more effective than the standard CO_2 insufflation in maintaining the patient's heat homeostasis, even if the difference was minimal. No benefit could be shown in terms of cytokine levels and pain scores.

Trial registration: Clinicaltrials.gov Identifier: NCT02586974

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Chapter 1

Effects of warmed, humidified CO_2 insufflation on body core temperature and cytokine response: head-to-head comparison versus standard insufflation during robot-assisted radical prostatectomy

1.1 Introduction

The most commonly used gas for insufflation during laparoscopic surgery is CO_2, which is colorless, odorless and non-inflammable. The major advantage of CO_2 is its rapid dissolution in the event of venous emboli, while hemodynamic and acid-base changes are usually mild and clinically negligible for most patients.

Among the possible consequences of cool and dry gas insufflation during laparoscopic procedures are hypothermia and cytokine increase, which might cause significant perioperative morbidity **[1]**. More in detail, body core temperature (BCT) decrease during laparoscopic surgery has been calculated in humans as 0.3°C for every 50 L of cold and dry insufflation gas **[2]**. The reported temperature drop is caused by redistribution of heat and heat loss, both non-specific (due to anesthesia and environmental patient exposure) and specific (due

to peritoneal dry and cool insufflation) **[3]**. The resulting hypothermia can be severe, particularly after prolonged surgery. As for cytokine response, an increase of several pro-inflammatory cytokines has been described following the irritating effect of peritoneal **CO_2** insufflation.

In the last years, various devices providing heating and/or humidification of the insufflated gas have been investigated to evaluate the specific heat losses resulting from peritoneal insufflation, as well as the inflammatory response. Previous studies conducted on animal models and human setting have suggested that warmed and humidified insufflation leads to an improved BCT maintenance, a reduction in the degree of inflammatory response and an improved quality of postoperative course, compared with standard insufflation **[3-10]**. These findings, however, are still not conclusive as they have not been confirmed by adequate randomized controlled trials (RCTs). Furthermore, no device providing warming and humidification has demonstrated a conclusive advantage over standard cold, dry gas in terms of prevention of hypothermia during laparoscopy in the human setting **[11, 12]**.

1.1.1 Preliminary data

Warm, humidified CO_2 should maintain the physiological moist condition of the peritoneal cavity, reducing the risk of complications due to cold and dry gas insufflation. Nevertheless, according to a recent Cochrane review including twenty-two randomized controlled trials, heated and humidified gas insufflation would have only minimal benefit on body core temperature, achieving a small difference of 0.31°C in comparison to the cold CO_2 group, unlikely to be of clinical significance. Non statistically significant differences were found in terms of postoperative pain, length of hospitalization, or morphine consumption. However, the authors stated that the results of this review should be interpreted with caution due to the heterogeneity of studies in terms of design, insufflation gas temperatures, gas volumes, devices used and location of temperature probes **[12]**.

The debate about the usefulness of warmed and humidified insufflation has continued in the last years, but no definitive conclusions have been drawn. The studies conducted up-to-date are quite heterogeneous in surgical indications, type of patients enrolled and devices adopted. Furthermore, adequate randomized controlled trials evaluating the use of warming and humidification in a prolonged laparoscopic surgery are scarce, and often not controlled for the use of an external patient warming device such as a warming blanket.

Recently, an experimental study conducted on pigs has shown that a device providing heating and humidification is more effective than humidification alone

in preventing heat loss. According to this study, heated and humidified CO_2 was effective in reducing heat loss for procedures longer than 60 minutes **[6, figure 1]**.

Peritoneal irritation due to the cooling and desiccating effect of standard insufflations is difficult to assess in terms of cytokine response. Several investigators have reported that the serum and peritoneal levels of the pro-inflammatory cytokines IL6 and TNF-alfa as well as serum levels of cortisol and glucose increase after surgery and correlate with the magnitude of surgical stress. Indeed, in animal models and clinical settings a trend has been shown toward the decreased activation of pro-inflammatory cytokines after laparoscopic procedures as compared with open surgery **[5]**. In this sense, the use of warmed, humidified CO_2 has been suggested to be associated with a decreased local pro-inflammatory cytokine response. Again, however, these findings have not been confirmed; according to an experimental study, while preserving body core temperature, humidified, warmed CO_2 did not affect local or systemic trends of pro-inflammatory mediators **[5]**. Available evidence is still inconclusive.

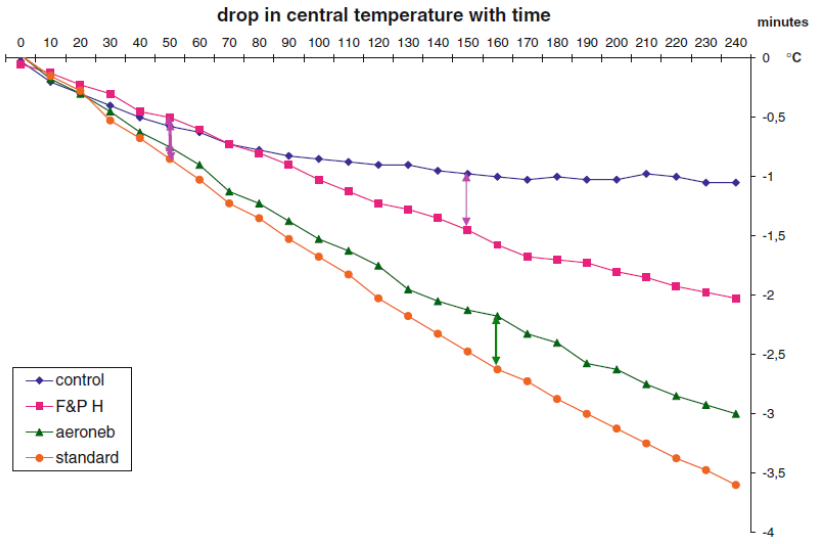


Figure 1: Benefit of warm and humidified insufflation (F&P H) versus humidified (aeroneb) or standard insufflation in terms of prevention of hypothermia.

1.1.2 Study aims

Aim of this prospective, randomized study was to assess if warmed and humidified CO_2 insufflation with HumiGard™ device can achieve significant benefits over standard insufflation in terms of risk of hypothermia and cytokine response, in the setting of robot-assisted radical prostatectomy (RARP).

1.2 Methods

1.2.1 Study design

This was a prospective, single-blinded, RCT. All patients undergoing RARP at Città della Salute e della Scienza Hospital between September 2015 and June 2016 were screened for inclusion. Exclusion criteria were as follows: age >80 years, ASA status >3, allergic status needing corticosteroid premedication, refusal to sign the informed consent, cognitive disability, conversion to open surgery. Enrolled patients were randomized into two groups, as shown by CONSORT Diagram (**figure 2**):

- **Group H+WB (32 patients)** received warmed, humidified CO_2 insufflation with the HumiGard™ device, along with the hot air warming blanket routinely used in our institution (forced air warming blanket at 40°C: Smiths Medical® applied on neck and upper thorax).
- **Group WB (32 patients)** received standard CO_2 insufflation, along with the hot air warming blanket routinely used in our institution (forced air warming blanket at 40°C: Smiths Medical® applied on neck and upper thorax).

The study was single-blinded as patients were not told about which system was used to maintain BCT homeostasis during surgery.

The study was granted Institutional Ethics approval in September 2015 (committee reference number 894/2015). The trial was prospectively registered online on ClinicalTrials.gov (NCT02586974, 23/10/2015, principal investigator dr Marco Oderda).

Clinical trial: effects of warmed, humidified CO_2 insufflation

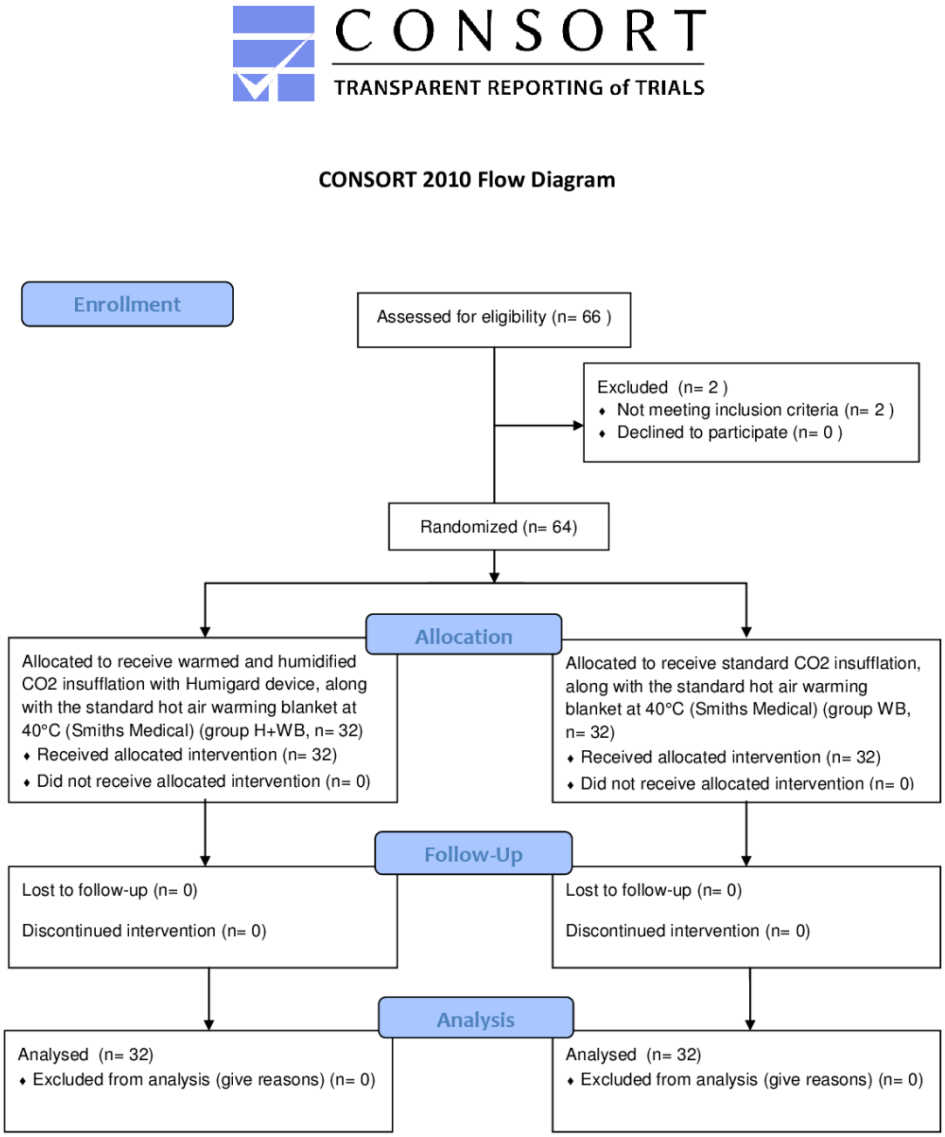


Figure 2: CONSORT flow diagram

1.2.2 Study endpoints

The primary goal was to evaluate whether the HumiGard™ device is more effective than standard CO_2 insufflation in maintaining BCT of patients undergoing RARP.

Secondary endpoints were to evaluate if the HumiGard™ device affects the response of the pro-inflammatory cytokines IL6 and TNF-α, and if it is beneficial in terms of postoperative pain, bowel transit and hospital stay.

1.2.3 Standardized anesthesia protocol

Premedication was done with midazolam. Induction of anesthesia was performed with Sufentanil (0.3γ/kg) and Propofol (2-2.5 mg/kg). Muscle relaxation was obtained with a bolus of Rocuronium (0.5-0.6 mg/kg). After tracheal intubation, maintenance was performed with Sevoflurane (MAC 0.8-1). Intraoperative analgesia was obtained with Sufentanil and deep neuromuscular blockade was achieved with Rocuronium infusion. Patients were ventilated with Pressure Regulated Volume-Controlled mode (ventilator Flow-i Maquet), with a tidal volume of 8 ml/kg and a frequency of 14-16/min. Adjustments of the ventilatory setting were made according to the measured peak and plateau pressures, serial blood gas analyses, and arterial-to-end-tidal CO_2 pressure gradients. At the end of surgery, reversal of neuromuscular blockade was obtained with Sugammadex according to train-of-four (TOF) values.

Around one hour before the end of surgery, Paracetamol 1g plus Tramadol 100mg were administered. Post-operative analgesia was accomplished with continuous infusion of Tramadol 300mg/die (4-5 mg/kg/die) by elastomeric pump and Paracetamol 1g/8h bolus IV for 48 hours. Rescue therapy consisted of Ketorolac 30 mg bolus IV. Postoperative nausea/vomiting was managed with Alizapride. Antibiotic and anti-thrombotic prophylaxis were routinely performed. All fluids injected were at ambient temperature.

1.2.4 Standardized surgical protocol

All patients underwent RARP in steep Trendelenburg position, with or without pelvic lymph node dissection (PLND) according to the clinical case and the tumor risk class. Surgeries were performed by two urologists expert in robotics, with an experience of more than 100 RARP.

Patient preparation: after inducing general anesthesia, the patient is placed in modified lithotomic position, with the legs abducted and parallel to the

level of the bed. A 20Ch Foley catheter is inserted and the catheter balloon inflated with 5 ml. A 30-degree Trendelenburg position is obtained in order to displace the small bowel from the pelvic area. Pneumoperitoneum is established with an insufflation pressure of 15 mmHg. After trocar placement, insufflation pressure is maintained between 10 and 12 mmHg. Six trocars are placed: a 12-mm camera port 2 cm above the umbilicus, two 8-mm robotic ports bilaterally at a distance of at least 8 cm from the camera port, a third 8-mm robotic port 5 cm above the left anterior superior iliac spine. Finally, two 5-mm assistant ports are triangulated above the right robotic port. Afterwards, the robot with a 0° lens (4-arms Da Vinci Si Surgical System, Intuitive Surgical, Inc, Sunnyvale, CA, USA) is docked.

Robotic-assisted radical prostatectomy (RARP): before dropping down the bladder, care must be taken to have a free Douglas pouch in order to have a proper exposure to the prostate once the Retzius space is developed. We start by dividing the two umbilical arteries and the urachus as high as possible, the Retzius space is dissected in an avascular plane and the fat covering the prostate removed so that we identify the landmarks that help approaching the prostate laterally. Endopelvic fascia is incised bilaterally in order to isolate prostatic apex. The Santorini plexus is prudentially sutured with a Vycril 0 double stitch. Bladder neck is then identified and opened, possibly with a bladder neck-sparing approach. Successively, we gain access to the plane of seminal vesicles and vas deferens, which are isolated and dissected. Prostato-rectal space is developed until the prostatic apex. Postero-lateral dissection of the prostate is performed, according to clinical cases, either with an extrafascial, non nerve-sparing approach or with a nerve-sparing approach, with neurovascular bundles preservation. The apex dissection is completed and the urethra is divided, avoiding an extensive dissection from the surrounding muscle fibers. Vesico-urethral anastomosis is performed either with a 30-cm 3-0 V-loc, 17mm, ½ c, or with two running sutures with 18-cm 3-0 Monocryl, 26mm, ½ c. At the end of surgery, exsufflation of gas is performed before removing the trocars. The umbilical incision for the optical trocar is slightly enlarged for specimen removal.

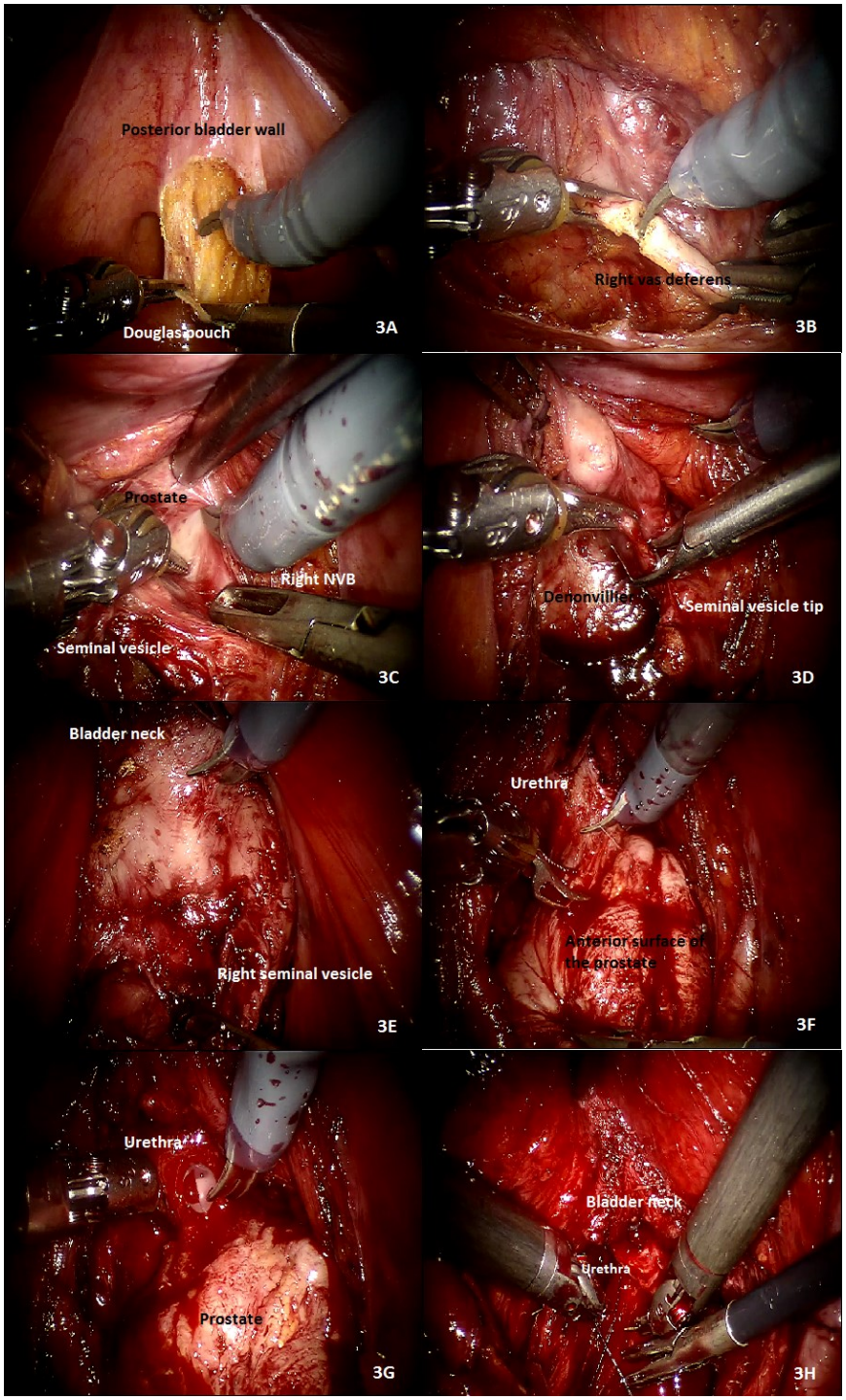


Figure 3: steps of RARP: 3A. Opening of Douglas pouch. 3B. Section of vas deferens. 3C. Exposition of the angle between prostate, neurovascular bundle (NVB) and seminal vesicle. 3D. Section of seminal vesicle tip. 3E. Section of bladder neck. 3F. Isolation of urethra. 3G. Section of urethra. 3H. Urethro-vesical anastomosis.

Pelvic lymph node dissection (PLND): it is performed only when needed, according to the tumor risk class. We usually carry out the PLND prior to RARP, as we prefer to work in a "cleaner" operative space. We start by incising the peritoneum over the perceived area of the external iliac artery, lateral to the umbilical artery. The incision is cranially extended following the external and the common iliac artery until we reach the ipsilateral ureter. On the left side, we must previously free the sigmoid colon to gain access to the iliac vessels and the ureter. The lymphatic tissue overlying the external iliac vessels is longitudinally incised, and the vessels are skeletonized so that the lymph nodes can be released and removed en bloc. The lateral border of our dissection is represented by the genito-femoral nerve, whereas the distal limit is represented by the Cloquet node. The paravesical space lateral to the umbilical artery is opened until the origin of this artery from the internal iliac artery. This plane represents the medial border of our PLND. The lymphatic tissue is cleared out from the area of the iliac bifurcation and around the internal iliac artery. The internal iliac nodes are often coalesced with the obturator packet. The obturator nerve is identified distally underneath the pubic bone and the Cooper ligament. It is proximally dissected and all the lymphatic tissue is removed from the obturator fossa. The specimens are inserted in endobags.

1.2.5 CO_2 insufflation device

Airseal System (SurgiQuest, Milford, USA), used in standard modality of insufflation at 10-12 mmHg.

Figure 4: Airseal System (SurgiQuest, Milford, USA)

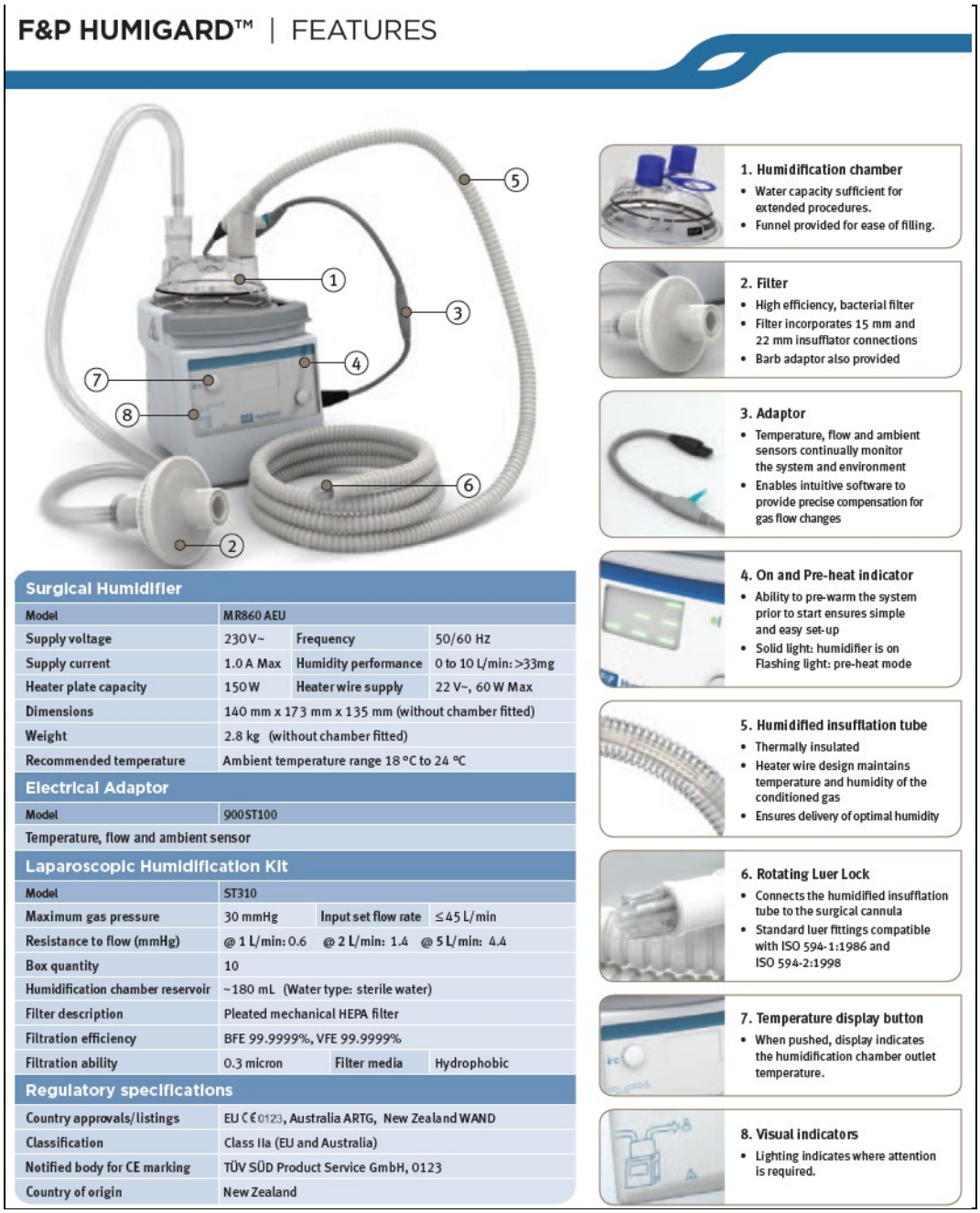
1.2.6 Gas conditioning device

Fisher and Paykel (F&P) HumiGard™ Surgical Humidification System, including F&P HumiGard™ MR860AEU surgical humidifier, F&P HumiGard™ ST310 humidified tubing set and 900ST100 Adapter.

HumiGard™ Surgical Humidification System was given to Città della Salute e della Scienza Hospital for free by Fisher and Paykel as a loan in the setting of clinical study. The costs of Humigard technology, including the cost of purchasing the equipment, tubing kits for each patient and the costs of training nurse staff, were estimated at £80.6 per treatment **[14]**.

CO_2 gas from the insufflator passes through the software-controlled humidification chamber, filled with 30 cc of saline water and sitting on a heater plate, where it actively picks up heat and humidity. The conditioned CO_2 is then delivered to the cannula via a heated insufflation tube to maintain the condition of the gas. The temperature of the gas is maintained as it travels along a heated tube to the laparoscopic port. The humidifier monitors the temperature and flow rate of the gas at the chamber outlet with a probe attachment, controlling the amount of power delivered to the heater plate to maintain the chamber set point temperature **[14]**. The system aims to condition the gas to physiological conditions: 37°C body temperature and 100% relative humidity to prevent evaporation.

When the gas enters the peritoneal cavity it will equilibrate with the internal abdominal conditions: if the gas is delivered at core temperature and saturated, no evaporation or condensation will occur. Condensation occurs when the temperature of the saturated gas is higher than the abdominal conditions: in this case, the gas will cool to the BCT and the capacity of the gas to hold water vapor will reduce, and the excess moisture will fall out as condensate. Conversely, if the gas is delivered at the same temperature as BCT with a lower relative humidity, it will absorb moisture from the patient until gas saturation. If the gas is delivered at a temperature cooler than BCT, it will absorb both heat and moisture from the patient to reach equilibrium.



Surgical Humidifier			
Model	MR860 AEU		
Supply voltage	230V~	Frequency	50/60 Hz
Supply current	1.0 A Max	Humidity performance	0 to 10 L/min: >33mg
Heater plate capacity	150W	Heater wire supply	22 V~, 60 W Max
Dimensions	140 mm x 173 mm x 135 mm (without chamber fitted)		
Weight	2.8 kg (without chamber fitted)		
Recommended temperature	Ambient temperature range 18 °C to 24 °C		
Electrical Adaptor			
Model	900ST100		
Temperature, flow and ambient sensor			
Laparoscopic Humidification Kit			
Model	ST310		
Maximum gas pressure	30 mmHg	Input set flow rate	≤45 L/min
Resistance to flow (mmHg)	@ 1 L/min: 0.6	@ 2 L/min: 1.4	@ 5 L/min: 4.4
Box quantity	10		
Humidification chamber reservoir	~180 mL (Water type: sterile water)		
Filter description	Pleated mechanical HEPA filter		
Filtration efficiency	BFE 99.9999%, VFE 99.9999%		
Filtration ability	0.3 micron	Filter media	Hydrophobic
Regulatory specifications			
Country approvals/listings	EU CE 0123, Australia ARTG, New Zealand WAND		
Classification	Class IIa (EU and Australia)		
Notified body for CE marking	TÜV SÜD Product Service GmbH, 0123		
Country of origin	New Zealand		

Figure 5: Fisher and Paykel (F&P) HumiGard™ Surgical Humidification System **[14]**

1.2.7 Outcome measures

The primary outcome (BCT) was measured intraoperatively at 15-min intervals using a disposable esophageal probe (Covidien). Plasma levels of cytokines IL-6 and TNF-α were evaluated with immunoassays (human sIL-6 instant ELISA, eBioscence, Vienna, Austria, and Quantikine® ELISA Human TNF-α, R&D Sistems, Minneapolis, MN, USA) just before induction of anesthesia, after 2 hours of pneumoperitoneum, 2 hours from exsufflation, and 24 hours after surgery.

Pain score was assessed through the 10 points Numeric Pain Rating Scale (NRS) at patient awakening, then every 30 minutes in the recovery room, until discharge to the ward. Successively, it was measured at 12, 24 and 48 hours, including the NRS values 1) at rest, 2) during coughing and 3) on walking where appropriate. Shoulder pain was also evaluated.

Intraoperative data included total operative time, from induction of anesthesia till awakening; duration of CO2 insufflation; total volume of CO2 insufflated; total volume of fluids infused; blood losses; shivering; Aldrete score. Postoperative data included length of hospital stay; time to recovery of gas transit; time to liquid diet; time to solid diet; patient satisfaction at the time of discharge home.

All intra- and early postoperative complications were recorded according to modified Clavien-Dindo classification **[15]**.

1.2.8 Statistical analyses

The data were analyzed according to the Bayesian paradigm. The variances were given Gamma priors. Continuous variables (and notably BCT) were analyzed with mixed effects models with fixed time and group effects with an interaction term, and a random subject effect to take account of the repeated structure of the data. This random effect was modeled with a Gaussian hyperprior. For the secondary outcomes, continuous variables were analyzed with mean comparison models with Gaussian priors (N (μ,σ)) and counts data were analyzed with Poisson regression models (Gamma priors). For the continuous variables, a lowly-informative prior was specified for each specific variable, with a variance such that the range of data were within relevant clinical values. Group comparisons on categorical data were done based on Beta distributions. Results from previous series or publications available were used to provide informative priors. In the absence of prior information for estimation of a proportion, a non-informative (Be(1;1)) prior and minimally-informative (such as Be(2;2) or Be(2;3) etc) priors were used in a sensitivity analysis. The effect size was estimated through absolute risk difference with the probability that the absolute risk difference is larger than 0

(i.e. in favor of the H+WB group) According to the Bayesian concepts, both an effect probability near 1 or near 0 indicates a worthwhile effect. We remind that Bayesian analysis does not use the (classical a.k.a. frequentist) p-value and that the probability of a worthwhile effect must not be confused with a p-value.

All computations were done with R, WinBUGS and JAGS statistical software in their most up-to-date version at the time the analysis are run with all the required packages **[16, 17]**.

Sample size calculation: the sample size was computed with the Average Length Criterion method **[18]**. The sample size was 30 subjects in each group for a total of 60 subjects. Two subjects were added in each group to take account of potential loss to follow-up, patient withdrawal and missing data. The sample size was computed for an expected proportion of subjects with a BCT larger than 36° at the end of surgery. This sample size was obtained with the following parameters: an expected average length (EAL) of the posterior credible interval for the difference between the two proportions of 0.35 (i.e. 35%), a credibility level of 0.95, and the following lowly-informative prior: Beta(5;5) in the H + WB group and Be(1;9) in the WB alone group. It must be noticed that the sample size was the same for an EAL of 0.40 with non-informative prior Be(1;1) in each group. More precisely, the computed sample size was 29 per group in each case, rounded upward to 30 per group. Finally, and only for illustrative purpose, a frequentist estimation according to Casagrande & Pikes, with a type I error rate of 5%, a type II error rate of 10% in an equitail test required 31 subjects per group to show a difference between 50 and 10%.

Randomization: the randomization list was obtained with a computer random numbers generator, with blocks of 4 patients each.

1.3 Results

Groups were well matched at baseline, with no significant differences in age, BMI, ASA, comorbidities, or PLND performed. Baseline patient characteristics and intraoperative data are shown in **table 1**. No statistical differences were found between the two groups in terms of operative time, insufflation time, fluid infusion or blood losses. An increased CO_2 volume infused was seen in group H+WB, as a consequence of longer operative and insufflation time in comparison with group WB.

Table 1. Baseline patient characteristics and intraoperative data

BASELINE CHARACTERISTICS			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB > WB)***
Age, mean (SD)	66.4 (7.0)	64.4 (9.0)	0.837
Age, median (range)	68 (53-78)	65.5 (40-81)	
BMI, mean in kg/m^2 (SD)	26.0 (2.0)	26.4 (3.3)	0.632
ASA score			0.945[1]
- I	2 (6.2%)	1 (3.1%)	
- II	27 (84.3%)	23 (71.8%)	
- III	3 (9.3%)	8 (25%)	
Comorbidities			
- Hypertension	15 (46.8%)	20 (62.5%)	0.107
- Diabetes Mellitus	0 (0%)	2 (6.2%)	0.119
- Glaucoma	3 (9.3%)	1 (3.1%)	0.821
- OSAS	3 (9.3%)	3 (9.3%)	0.503
- Cardiopathy	1 (3.1%)	4 (12.5%)	0.100
- Obesity	1 ()	5 (%)	0.196
PLND			0.397
- Yes	10 (31.2%)	11 (34.3%)	
- No	22 (68.7%)	21 (65.6%)	
INTRAOPERATIVE DATA			
	Group H+WB (n=32)	**Group WB (n=32)**	***P*[1]**
Operative time, min, mean (SD)			
- Total operative time	350.9 (55.9)	333.1 (46.7)	0.908
- Insufflation time	275.0 (48.3)	257.4 (56.0)	0.931
Total CO2 volume used, L, mean (SD)	635.5 (316.1)	522.0 (158.1)	0.962
Total fluid infusions, L, mean (SD)	2460.9 (553.7)	2429.0 (614.4)	0.581
Blood loss, cc, mean (SD)	224.4 (162.7)	214.5 (177.6)	0.588

[1] probability that the frequency of ASA score less than 3 is larger in the H+WB group.

1.3.1 Body core temperature

The intraoperative BCT increased in both groups during surgery, with a statistically significant difference favoring group H+WB, ending at 0.2°C higher on average than group WB (**figure 2A**). The overall BCT increase was 0.088 degree per hour in the WB group, with an additional 0.064 degree per hour in the H+WB group (**table 2**, Probability of a positive interaction >0.997).

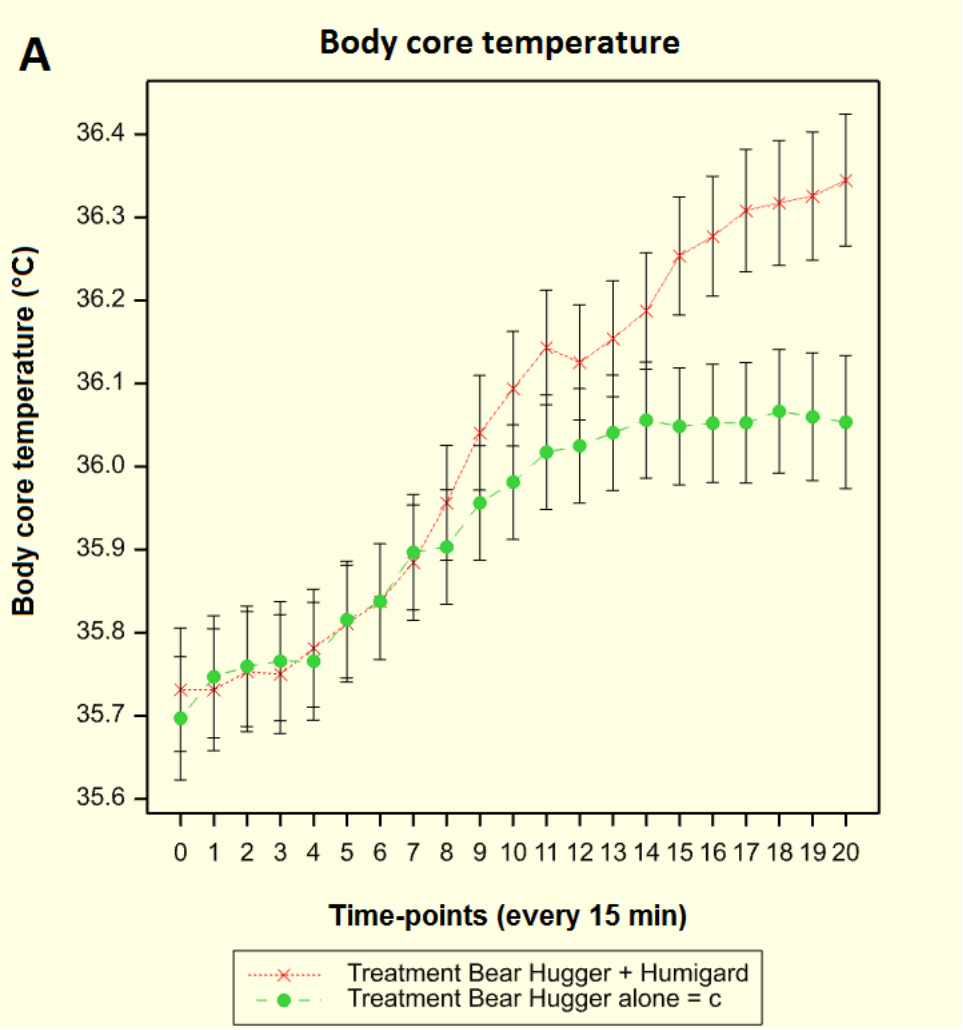


Figure 6: profiles for body core temperature

1.3.2 Cytokines

As for cytokines, there were no significant differences in the mean serum cytokine concentrations between groups at different time-points (**table 2**). In both groups, IL-6 increased after 2 hours of insufflation, reaching a peak two hours after exsufflation (**figure 2B**). No statistically significant differences were seen between groups for TNF-α, with no interaction although a quadratic effect is seen (decrease an increase of TNF-α in the WB group, Pr(effect) = 0.973) (**figure 2C**).

Table 2. Baseline patient characteristics and intraoperative data

BODY CORE TEMPERATURE			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)****
BCT, °C, mean			0.997
- Start of surgery	35.73	35.70	
- After 1h	35.78	35.77	
- After 2h	35.96	35.90	
- After 3h	36.11	36.02	
- After 4h	36.34	36.07	
- End of surgery	36.26	36.06	
SERUM IL-6			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)****
Serum IL-6, pg/ml, mean			0.666
- Start of surgery	2.13	2.20	
- After 2h of pneumoperitoneum	4.61	4.16	
- 2h from exsufflation	29.13	25.91	
- 24h after surgery	27.01	23.67	
SERUM TNF-α			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)****
Serum TNF-α, pg/ml, mean			0.112
- Start of surgery	5.74	6.29	
- After 2h of pneumoperitoneum	5.69	5.20	
- 2h from exsufflation	5.44	4.90	
- 24h after surgery	6.11	7.24	

***** Test for the time group interaction

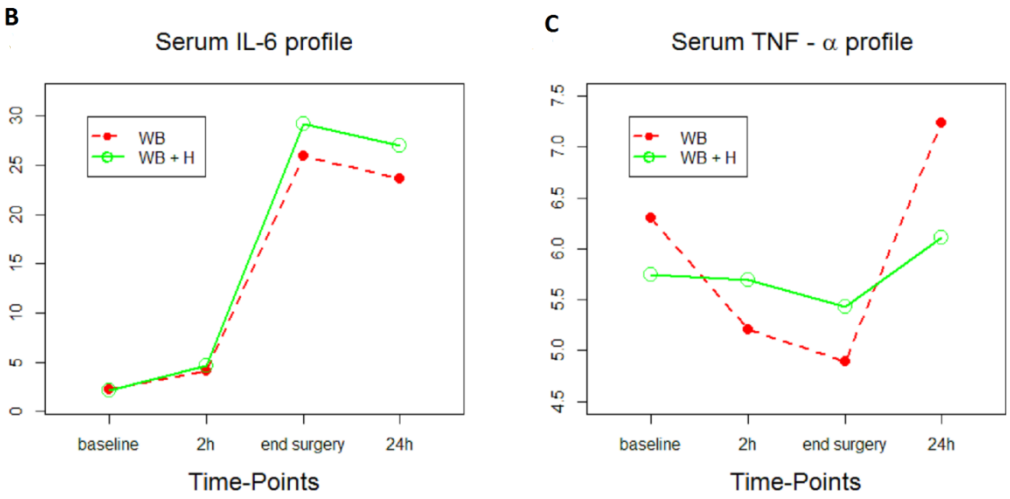


Figure 7: profiles for cytokines IL-6 (B) and TNF-alfa (C)

1.3.3 Postoperative parameters and complications

Concerning postoperative parameters, no statistical differences were seen in terms of shivering and Aldrete score at awakening, post-operative pain or shoulder pain (**table 3**). No statistical differences were seen in terms of rescue therapy administered in the recovery room. The same goes for length of hospital stay, time to recovery of gas transit, time to liquid and solid diet. Patient satisfaction was equally high in both groups.

Complications were experienced by four patients, and none was related to HumiGard™ (**table 4**).

Table 3. Pain scores

Shivering and Aldrete score at awakening			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)***
Shivering	6 (18.7%)	2 (6.2%)	0.925
Aldrete score	9.3 (1.4)	9.4 (1.5)	0.931
PAIN at rest by Numeric Rating Scale			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)****
NRS, pain at rest, mean (SD)			
- Patient awakening	2.5 (2.6)	2.3 (2.8)	0.160
- At 12h	1.6 (1.8)	1.9 (2.2)	
- At 24h	1.3 (1.5)	1.8 (2.1)	
- At 48h	0.6 (1.1)	1.1 (1.9)	
PAIN on coughing			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)****
NRS, pain on coughing, mean (SD)	2.4 (2.1)	2.6 (2.4)	0.205
- At 12h	3.0 (2.1)	3.4 (2.4)	
- At 24h	1.6 (1.7)	2.4 (2.5)	
- At 48h			
PAIN on walking			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)****
NRS, pain on walking, mean (SD)	2.0 (1.9)	1.9 (1.8)	0.582
- At 24h	1.2 (1.5)	1.2 (1.7)	
- At 48h			
SHOULDER PAIN			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)****
NRS, shoulder pain, mean (SD)	0.5 (1.4)	1.1 (2.1)	0.687
- At 12hi	0.3 (1.5)	0.8 (1.7)	
- At 24h	0.4 (1.1)	0.7 (1.8)	
- At 48h			

***** Test for the time group interaction

Table 4. Postoperative recovery parameters and complications

Postoperative recovery parameters			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)***
Length of hospital stay, days, mean (SD) - To discharge criteria met - To actual discharge	 3.3 (1.3) 3.5 (1.3)	 3.2 (1.4) 3.5 (1.7)	 0.549 0.529
Length of hospital stay, days, median (range) - To discharge criteria met - To actual discharge	 3 (2-7) 3 (2-8)	 3 (2-9) 3 (2-11)	
Time to recovery of gas transit, days, mean (SD)	1.7 (0.9)	1.8 (0.5)	0.343
Time to recovery of gas transit, days, median (range)	2 (1-5)	2 (1-3)	
Time to liquid diet, days, mean (SD)	1.0 (0.2)	1 (0)	0.550
Time to liquid diet, days, median (range)	1 (1-2)	1 (1-1)	
Time to solid diet, days, mean (SD)	2.4 (0.7)	2.5 (1.0)	0.358
Time to solid diet, days, median (range)	2 (2-5)	2 (1-6)	
Patient satisfaction - Satisfied - Moderately satisfied - Not satisfied	 22 9 1	 25 4 2	0.145 *
Complications			
	Group H+WB (n=32)	**Group WB (n=32)**	***Pr(H+WB>WB)***
Patients with complications, N (%)	3 (9.3%)	1 (3.1%)	0.823
Clavien grade of complications, N (%) - I - II - III - IV	 N= 1. Postoperative urine leakage N= 0. N= 2. Intraoperative small bowel perforation (n=1), intraoperative haemorrage (n=1). N= 0.	 N= 0. N= 0. N= 1. Intraoperative ureteral injury N= 0.	

* Test for satisfied versus moderately or not satisfied

1.4 Discussion

The key to comprehend the possible adverse effects of CO_2 insufflation resides in the properties of this gas, which is easily absorbed, causing hypercarbia and respiratory acidosis. Furthermore, it is relatively cold and dry compared with the natural environment of the peritoneal cavity (36°C, virtually 100% relative humidity) **[19]**. Dry and cold CO_2 is a mild irritant to the peritoneum, causing adverse structural alterations to the mesothelial lining, local pH imbalances and changes in the macrophage responsiveness, as shown by histological studies **[21]**. These alterations could be responsible for a conscious sensation of pain which has been described in patients undergoing awake laparoscopy **[22]**.

More importantly, dry and cool CO_2 insufflation has been linked to a peritoneal hypothermia and a drop in BCT, as a result of evaporative heat loss from intra-abdominal tissue **[23]**. Hypothermia can be very dangerous for the patient, causing myocardial ischemia, cardiac arrhythmias, generalized immunosuppression, disrupted coagulation and increased risk of surgical site infections **[24]**. Thus, the prevention of perioperative hypothermia is essential during laparoscopic surgeries and usually involves the use of a forced warm air blanket around the patient. This device, however, is often not enough to contrast the cooling effect of CO_2, considering that the abdomen must remain uncovered during abdominopelvic procedures such as RARP. The use of warm and humidified CO_2 has been proposed to maintain the physiological moist condition of the peritoneal cavity and reduce the risk of such complications **[25]**. Several devices providing heating and humidification have been tested in the animal setting, showing promising results in terms of heat loss prevention; recently, an experimental study conducted on pigs has shown that heated and humidified CO_2 was more effective than humidification alone in preventing heat loss, particularly for procedures longer than 60 minutes **[6]**.

Nevertheless, studies conducted in the human setting have not shown the same results. According to a Cochrane review updated in 2016 which included twenty-two RCTs, heated and humidified gas insufflation would have only minimal benefit on BCT, achieving only a small difference of 0.31°C in comparison with standard, cool CO2 insufflation, unlikely to be of clinical significance. The authors of this review concluded that while heated, humidified gas leads to mildly smaller decreases in core body temperatures, clinically this does not account for improved patient outcomes. Therefore, to date no clear evidence supports the use of heated gas insufflation in laparoscopic abdominal surgery **[12]**. The debate has continued in the last years, but no definitive conclusions have been drawn. The studies conducted up-to-date are quite heterogeneous in surgical indications, type of patients enrolled and devices adopted. Furthermore, adequate RCTs evaluating the use of warming and humidification in a prolonged laparoscopic surgery are scarce, and often not controlled for the use of an external patient warming device such as WB.

Clinical trial: effects of warmed, humidified CO_2 insufflation

Our study is the first adequately designed to evaluate the usefulness of warm and humidified CO_2 for the endpoints considered. Sample size was accurately calculated to detect an improvement of 35% in BCT, which could reflect a clinically significant benefit given preliminary data obtained during experiments with minipigs. We chose HumiGard™ following the promising findings of Noll et al, who discovered in an animal setting an advantage of this device in preventing heat loss for laparoscopic procedures longer than 60 minutes **[6]**. In the human setting, only a few RCTs **[8, 9, 26]** have investigated the usefulness of HumiGard™, and none has shown significant benefits except for a reduction of postoperative pain **[26]**, as shown by **Table 5** and **6**.

Table 5A. Main studies evaluating warm and/or humidified gas conditioning

Author, year	Setting	N	Gas conditioning	Device
HUMAN SETTING				
Oderda, 2017 **[current study]**	Human, RCT, RARP	32 (Humigard + WB) 32 (WB)	Heating and humidification	**Humigard**
Koninckx, 2013 **[26]**	Human, RCT, laparoscopic deep endometriosis excision	25 (Humigard) 18 (controls)	Humidification only	**Humigard modified**
Tzu-Chieh, 2013 **[9]**	Human (children), RCT, laparoscopic appendicectomy	97 (Humigard) 98 (controls)	Heating and humidification	**Humigard**
Sammour, 2010 **[8]**	Human, RCT, laparoscopic colonic surgery	41 (Humigard) 41 (controls)	Heating and humidification	**Humigard**
Benavides, 2009 **[30]**	Human, RCT, laparoscopic gastric banding	40 (Stryker) 38 (Insuflow) 35 (controls)	Heating only Heating and humidification	Stryker Insuflow
Davis, 2006 **[4]**	Human, RCT, laparoscopic gastric bypass	11 (Stryker) 11 (Insuflow modified) 11 (Insuflow) 11 (controls)	Heating only Humidification only Heating and humidification	Stryker Insuflow modified Insuflow
Farley, 2004 **[29]**	Human, RCT, laparoscopic cholecystectomy	52 (Insuflow) 49 (controls)	Heating and humidification	Insuflow
Nguyen, 2002 **[23]**	Human, RCT, Nissen fundoplication	10 (Insuflow) 10 (controls)	Heating and humidification	Insuflow
Mouton, 1998 **[28]**	Human, RCT, laparoscopic	10 (modified insufflator)	Heating and humidification	Modified LINS-1000

Clinical trial: effects of warmed, humidified CO_2 insufflation

	cholecystectomy	10 (controls)		insufflator
Ott, 1998 **[7]**	Human, laparoscopic surgery	36 (Insuflow) 36 (controls)	Heating and humidification	Insuflow
ANIMAL SETTING				
Noll, 2012 **[6]**	Pigs	16 (each pig acting as it own control)	Heating and humidification Humidification only	**Humigard** Aeroneb
Schlotterbeck, 2011 **[10]**	Pigs	4 (each pig acting as it own control)	Heating and humidification Humidification only	HME-Booster Aeroneb
Schlotterbeck, 2008 **[3]**	Pigs	4 (each pig acting as it own control)	Heating and humidification Humidification only	Pall system Aeroneb
Margulis, 2005 **[5]**	Pigs, laparoscopic nephrectomy	5 (Insuflow) 5 (anti-inflammatory) 5 (controls)	Heating and humidification	Insuflow

Table 6. Main studies evaluating warm and/or humidified gas conditioning

Author, year	**Outcomes of gas conditioning**		
	Temperature	**Cytokines**	**Pain or other**
HUMAN SETTING			
Oderda, 2016 **[current study]**	Significant difference favoring heated and warmed insufflation	No statistical differences in mean serum levels of IL-6 and TNF-α	No statistical differences in pain scores
Koninckx, 2013 **[26]**	Not investigated	Not investigated	Less postoperative pain and reduction of adhesions
Tzu-Chieh, 2013 **[9]**	Not investigated	Not investigated	No significant differences in pain (VAS score) or opiate consumption
Sammour, 2010 **[8]**	No significant differences in BCT	No differences in cytokine concentrations (IL-6, IL-1, TNF-α, IL-8, IL-10)	No significant differences in MEDD usage, or any recovery parameters
Benavides, 2009 **[30]**	Not investigated	Not investigated	Warm and humidified gas reduces shoulder pain, shortens length of stay and decreases pain meds requirements
Davis, 2006 **[4]**	No significant differences in BCT	Not investigated	No significant differences in pain scores or length of hospital stay
Farley, 2004 **[29]**	Significantly less intraoperative	Not investigated	Significantly less postoperative abdominal pain

	hypothermia		
Nguyen, 2002 **[23]**	No significant differences in BCT	Not investigated	No significant differences in pain (VAS score) or opiate consumption
Mouton, 1998 **[28]**	No significant differences in BCT	Not investigated	Significantly less postoperative pain (VAS score)
Ott, 1998 **[7]**	Less intraoperative hypothermia	Not investigated	Reduced length of stay and postoperative pain.
ANIMAL SETTING			
Noll, 2012 **[6]**	Less heat loss for procedures longer than 60 minutes; more effective than humidification only	Not investigated	Not investigated
Schlotterbeck, 2011 **[10]**	Less temperature decrease as compared to standard insufflation after 160 minutes; equal efficacy as compared to humidification only	Not investigated	Not investigated
Schlotterbeck, 2008 **[3]**	Less temperature decrease as compared to standard insufflation after 160 minutes; equal efficacy as compared to humidification only	Not investigated	Not investigated
Margulis, 2005 **[5]**	Higher intraoperative and postoperative BCT than controls.	No differences in peritoneal or systemic cytokine levels (IL-6, IL-1, TNF-α)	Not investigated

Our RCT showed a statistically significant difference of BCT in favor of heated, humidified CO_2. However, this advantage became visible only after a certain amount of time, and the difference of 0.2°C on average was minimal from a clinical point of view: in fact, it did not affect the patient outcomes, in terms of cytokine levels, pain scores or other intraoperative parameters. On the other hand, this finding can be seen as promising, especially if we consider that our HumiGard™ device warmed the CO_2 only up to 36°C, and not 37°C as expected.

As for cytokine response, several investigators have reported that serum and peritoneal levels of pro-inflammatory cytokines IL6 and TNF-alfa, as well as cortisol and glucose, increase after surgery, as a consequence of surgical stress **[5]**. In laparoscopy, this increase is also linked to the peritoneal irritation due to the cooling and desiccating effect of CO_2, and could be reduced by the use of warmed, humidified CO_2 **[27]**. Only a couple of studies have evaluated this aspect: in the animal settings, Margulis et al were not able to find any differences in peritoneal or systemic cytokine levels during laparoscopic nephrectomies performed with heated and humidified CO_2 obtained with Insuflow™ versus

standard insufflation **[5]**. Sammour et al reached the same conclusions on human patients undergoing laparoscopic colonic surgery, using the HumiGard™ device versus standard insufflations. In our study, we were not able to find significant differences in IL-6 and TNF-α concentrations, at different time-points throughout the surgery.

Concerning postoperative parameters, we did not find any significant differences in terms of postoperative pain, shoulder pain, nor shivering and Aldrete score at awakening. We acknowledge that postoperative pain after RARP is usually mild and easily controlled by conventional drugs, so we did not expect huge differences in this field. No differences were seen in terms of recovery parameters such as length of hospital stay, time to recovery of gas transit or diet, and patient satisfaction. A few studies have suggested an improvement in postoperative pain, shoulder pain, or pain meds consumption **[7, 26, 28-30]**, but others have not confirmed these results **[4, 8, 9, 23] (Table 5** and **6)**.

Analyzing the results of our RCT, we acknowledge that the benefit of HumiGard™ was clinically small. Interestingly, our RCT showed a progressive increase of intraoperative BCT during surgery, pointing out that patients undergoing RARP have an increased risk of hypothermia at the beginning of the procedure. This may be due to the initial steps of robotic surgeries, including the docking of the robot, which limit the possibilities of covering the patient with standard warming blankets. In this light, conditioning of the insufflation CO2 with devices such as Humigard™, used as part of a multimodal heat loss prevention strategy, could represent a useful aid to limit the risks of hypothermia. In clinical practice, the use of this device has been estimated to be cost-effective if compared to standard care, considering also the limited cost of the system **[13, 31]**.

Limitations of study were the low baseline BCT of our patients and the fact that our HumiGard™ device never reached 37°. Amongst its strengths we acknowledge its design as RCT and the diversity of endpoints considered.

1.5 Conclusion

During RARP, warm and humidified CO_2 insufflation with the HumiGard™ device was more effective than the standard CO_2 insufflation in maintaining the patient's heat homeostasis, even if the difference was minimal and did not alter the patient outcomes. Gas conditioning with HumiGard™ did not affect plasma levels of pro-inflammatory cytokines IL-6 and TNF-α. No differences were seen for postoperative pain and other recovery parameters.

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