General Anesthesia

The EmulSiv™ filter removes microbial contamination from propofol but is not a substitute for aseptic technique

[Le filtre EmulSiv™ élimine la contamination microbienne du propofol, mais ne remplace pas l'asepsie]

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Purpose: To evaluate the ability of the EmulSiv™ filter (EF) to remove extrinsic microbial contaminants from propofol.

Methods: Aliquots of Staphylococcus aureus (S. aureus), Candida albicans (C. albicans), Klebsiella pneumoniae (K. pneumoniae), Moraxella osloensis (M. osloensis), Enterobacter agglomerans (E. agglomerans), Escherichia coli (E. coli), Serratia marcescens (S. marcescens), Moraxella catarrhalis (M. catarrhalis), Haemophilus influenzae (H. influenzae) and Campylobacter jejuni (C. jejuni) were inoculated into vials containing 20 mL of sterile propofol. The unfiltered inoculated propofol solutions served as controls. Ten millilitres and 20 mL samples of the inoculated propofol were filtered through the EF. All solutions were then subplated onto three culture plates using a precision 1 μL calibrated platinum loop and incubated. The number of colony forming units (CFU) were counted. Data were analyzed using a one-sample t test, and a P value of less than 0.05 was selected as the level of statistical significance.

Results: The EF was able to completely remove CFU of S. aureus, C. albicans, K. pneumoniae, M. osloensis, E. agglomerans, E. coli, S. marcescens, and M. catarrhalis ($P < 0.05$). A small number of H. influenzae CFU were able to evade filtration in both the 10 mL and 20 mL samples. C. jejuni CFU were able to evade filtration in only the 10 mL sample.

Conclusions: The EF removes the majority of microbial contaminates from propofol with the exception of H. influenzae and C. jejuni. Although the EF is capable of removing most of the microbial contamination produced by H. influenzae and C. jejuni, a few CFU are capable of evading filtration. Consequently, even the use of a filter capable of removing microbial contaminants is not a substitute for meticulous aseptic technique and prompt administration when propofol is used.

Objectif : Évaluer la capacité du filtre EmulSiv™ (FE) à éliminer les contaminants microbiens extrinsèques du propofol.

Méthode: Des aliquots de Staphylococcus aureus (S. aureus), Candida albicans (C. albicans), Klebsiella pneumoniae (K. pneumoniae), Moraxella osloensis (M. osloensis), Enterobacter agglomerans (E. agglomerans), Escherichia coli (E. coli), Serratia marcescens (S. marcescens), Moraxella catarrhalis (M. catarrhalis), Haemophilus influenzae (H. influenzae) et Campylobacter jejuni (C. jejuni) ont été inoculées dans des fioles contenant 20 mL de propofol stérile. Des solutions de propofol non filtré, inoculées, ont servi de témoins. Des échantillons de 10 et 20 mL de propofol inoculé ont été passés au travers du FE. Toutes les solutions ont été ensemencées sur trois plaques à culture en utilisant une anse de platine calibrée à 1 μL de précision. Le nombre de colonies a été compté. Les données ont été analysées par le test t pour un échantillon et une valeur de P plus petite que 0,05 a été choisie comme statistiquement significative.

Résultats : Le FE a permis d'éliminer complètement les colonies de S. aureus, C. albicans, K. pneumoniae, M. osloensis, E. agglomerans, E. coli, S. marcescens et M. catarrhalis (P < 0,05). Un petit nombre de colonies de H. influenzae a pu traverser le filtre dans les échantillons de 10 et de 20 mL. Les colonies de C. jejuni n'ont traversé que le filtre dans les échantillons de 10 mL.

Conclusion: Le FE élimine la majorité des contaminants microbiens du propofol, sauf ceux du H. influenzae et du C. jejuni. Bien que le FE soit capable d'éliminer presque tous les contaminants microbiens produits par le H. influenzae et le C. jejuni, quelques colonies ont pu traverser le filtre. Par conséquent, même l'usage d'un filtre capable d'éliminer les contaminants microbiens ne peut se substituer à une technique aseptique méticuleuse et à l'administration précoce dans le cas du propofol.

T HE incidence of patient-acquired infections from anesthetic practices is unknown. Nonetheless, it was presumed to be insignificant.[1] However, following the introduction of propofol, this presumption was challenged. The documentation of postoperative infections and sepsis acquired from the use of propofol during anesthesia has clearly implicated failures in aseptic anesthetic technique as the cause of these infections.[2,3] These inadvertent contaminations occurred despite the manufacturer's recommendations that strict aseptic technique be used when handling propofol. The recommendations also included the following guidance: the contents of an open propofol vial or ampule must be immediately withdrawn into a sterile syringe or administration system; the propofol must be administered within six hours after removal from its vial or ampule, or within 12 hr when continuous infusion is used; and finally, propofol is to be utilized only as a single patient use product.[4]

The Centre for Disease Control (CDC) reported seven separate outbreaks of perioperative or postoperative infectious complications related to the administration of inadvertently contaminated propofol between 1990 and 1993.[3,5] Two deaths occurred. Additional outbreaks and deaths were subsequently reported to the CDC in 1993 and 1994.[3] The microbial agents included Staphylococcus aureus (S. aureus), Candida albicans (C. albicans), Klebsiella pneumoniae (K. pneumoniae),[6] Moraxella osloensis (M. osloensis), Enterobacter agglomerans (E. agglomerans), Escherichia coli (E. coli) and Serratia marcescens (S. marcescens).[3] The CDC concluded that "no single other *iv* agent has been associated with such widespread outbreaks of extrinsic contamination or has been contaminated by such a wide variety of organisms".[3]

Substandard anesthesia practices were implicated as a vector of these nosocomial infections.

The EmulSiv™ filter (EF; Pall Biomedical Products Co., East Hill, NY, USA) is a filter specifically created for use with lipid emulsion based drugs like propofol. This 0.45 micron rated filter is purported to provide protection from accidental microbial contamination, particulate contamination and entrained air while maintaining the integrity of the emulsion. The Pall Biomedical Products Company has challenged this filter with propofol inoculated with C. albicans, K. pneumoniae, and M. osloensis and demonstrated complete removal of the contaminating organisms. In addition, they reported that 99.8% of S. aureus was removed from inoculated propofol.[A]

The purpose of this investigation was to determine the ability of the EF to remove contaminating microbial agents from propofol. S. aureus, E. coli, M. osloensis, K. pneumoniae, E. agglomerans, C. albicans and S. marcescens were evaluated because of the documented outbreaks of propofol contamination associated with these microbes. In addition, Moraxella catarrhalis (M. catarrhalis), Haemophilus influenzae (H. influenzae), and Campylobacter jejuni (C. jejuni) were assessed either because of their unusual structure or small size.

Methods

American type culture collection (ATCC) organisms are stored in glycerol at -70°C. The following organisms were subplated from the frozen stock cultures: S. aureus (ATCC 25923), E. coli (ATCC 25922), C. albicans (ATCC 14053), K. pneumoniae (ATCC 13883), M. catarrhalis (ATCC 25240), H. influenzae (ATCC 49247) and C. jejuni (ATCC 38291). Overnight cultures were diluted to a density of 0.5 McFarland units (approximately 10^8 microorganisms) with 0.9% sterile non-bacteriostatic saline using a Baxter Microscan® turbidity meter (Baxter Diagnostics, Inc., Deerfield, IL, USA). Each organism was further diluted 1:50 with sterile non-bacteriostatic saline. Wild type strains of M. osloensis, E. agglomerans and S. marcescens were prepared in a similar fashion. Aliquots of 0.6 mL of each organism were inoculated into 20-mL vials of propofol (Abbott Laboratories Ltd., Saint-Laurent, Quebec, Canada). After the organisms were added, each vial was vortexed for one minute. The unfiltered inoculated propofol solutions served as the controls. The study solutions consisted of 10 mL and 20 mL samples of

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A) Providing an extra measure of protection for propofol (Diprivan®) patients. Pall Medical Products Company 1997.

TABLE I Characteristics of the microbes studied[7,8]

Organism	Shape	Dimensions (μm)	Other characteristics
E. coli	Rods	1.1 to 1.5 by 2.0 to 6.0	Motile or non-motile. Gram negative. Capsules or microcapsules occur in many strains. Non-sporing bacilli.
S. aureus	Cocci	0.5 to 1.5 diameter	Non-motile, non-sporing, non-capsulated, gram positive cocci. Occuring singly, in pairs and in grapelike clusters. Capable of toxin production.
K. pneumoniae	Rods	0.3 to 1.0 by 0.6 to 6.0	Non-motile, gram negative bacilli encapsulated within a large polysaccharide capsule and surrounded by extracellular slime.
M. catarrhalis	Rods or Cocci	1.0 to 1.5 by 1.5 to 2.5 0.6 to 1.0 diameter	Gram negative. Occurring in pairs or short chains. Exhibit pleomorphism. Encapsulated.
M. osloensis	Rods or Cocci	1.0 to 1.5 by 1.5 to 2.5 0.6 to 1.0 diameter	Gram negative. Occurring in pairs or short chains. Exhibit pleomorphism. Encapsulated.
E. agglomerans	Rods	0.6 to 1.0 by 1.2 to 3.0	Gram negative. Motile
H. influenzae	Variable	Less than 1.0 in width variable in length	Small polysaccharide encapsulated gram negative bacilli occurring in short chains or clumps. Non-motile. Spherical, oval or rod shaped. Marked pleomorphism.
S. marcescens	Rods	0.5 to 0.8 by 0.9 to 2.0	Gram negative bacilli. Motile.
C. albicans	Oval	2.5 to 4.0 diameter	Budding, yeast like fungus with pseudo-mycelium or pseudohyphae.
C. jejuni	Vibrioid	0.2 to 0.5 by 0.5 to 5.0	Gram negative coiled spiral. Non-spore forming. Rods have helical turns and can be as long as 8.0 μm

Escherichia coli = E. coli; Staphylococcus aureus = S. aureus; Klebsiella pneumoniae = K. pneumoniae; Moraxella catarrhalis = M. catarrhalis; Moraxella osloensis = M. osloensis; Enterobacter agglomerans = E. agglomerans; Haemophilus influenzae = H. influenzae; Serratia marcescens = S. marcescens; Candida albicans = C. albicans; Campylobacter jejuni = C. jejuni.

inoculated propofol filtered through the EF. These volumes were selected to represent a pediatric and adult propofol dose commonly used in the operating theatre. Injections through the EF were completed under ten seconds. All solutions were then subplated onto three plates using a precision calibrated 1 μL platinum loop. H. influenzae was subplated onto chocolate agar plates. C. jejuni was subplated onto camyplates. The remaining samples were subplated onto blood agar plates (BAP). The BAP were plated with filtered and unfiltered propofol samples and incubated in a 35°C carbon dioxide incubator for 24 to 48 hr. C. jejuni was incubated at 42°C in an anaerobic jar with a campyplate gas pack. With the exception of C. jejuni, all plates were manually counted at 24 and 48 hr. C. jejuni plates were counted at 48 and 72 hr because of its unique growth characteristics. The number of colony forming units (CFU) on each plate were counted by two investigators. Values for replicate determinations ($n = 3$) of unfiltered CFU are reported as the median with 95% confidence intervals. The significance of the differences between filtered and unfiltered CFU values for each organism was determined by a one-sample t test that assumed values for unfiltered CFU were derived from a Gaussian distribution.

Results

Table I lists the reported size and characteristics of the microbial agents used in this study.[7,8] Table II demonstrates the effectiveness of the EF in removing microbial contamination from 10 mL of inoculated propofol. The EF was effective in removing E. coli, S. aureus, K. pneumoniae, M. catarrhalis and C. albicans from contaminated propofol. However, a small number of H. influenzae CFU were able to pass through the filter. C. jejuni CFU successfully evaded filtration. Table III demonstrates that the EF is effective in removing extrinsic contamination from 20 mL of propofol. This represents twice the microbial load previously tested using 10 mL. M. osloensis, E. agglomerans and S. marcescens were studied as well. Only H. influenzae was successful in having a few CFU pass through the EF. Interestingly, C. jejuni failed to have any CFU escape the filter when 20 mL were used.

TABLE II The number of colony forming units (CFU) prior to and after the use of the EmulSiv™ filter - 10 mL of contaminated propofol

Organism	CFU/µL (95% CI)	CFU/mL	Total CFU Challenge	Post filtration CFU/µL (95% CI)	Filter Efficacy	P
E. coli	38 (21-56)	3.8×10^4	3.8×10^5	0	100%	0.0110
S. aureus	90 (70-100)	9.0×10^4	9.0×10^5	0	100%	0.0020
K. pneumoniae	27 (4-50)	2.7×10^4	2.7×10^5	0	100%	0.0382
M. catarrhalis	33 (28-39)	3.3×10^4	3.3×10^5	0	100%	0.0013
H. influenzae	170 (110-240)	1.7×10^5	1.7×10^6	0.7 (-2.2-3.5)	99.5%	0.0078
*C. albicans	2 (1.1-2.2)	2.0×10^3	2.0×10^4	0	100%	0.0377
†C. jejuni	50 (48-91)	5.0×10^4	5.5×10^5	11 (6.4-16.2)	81.8%	0.0043

* = culture results at 48 hr; † = culture results at 72 hr. All other samples cultured for 24 hr.

Escherichia coli = E. coli; Staphylococcus aureus = S. aureus; Klebsiella pneumoniae = K. pneumoniae; Moraxella catarrhalis = M. catarrhalis; Haemophilus influenzae = H. influenzae; Candida albicans = C. albicans; Campylobacter jejuni = C. jejuni.

TABLE III The number of colony forming units (CFU) prior to and after the use of the Emulsiv™ filter – 20 mL contaminated propofol

Organism	CFU/ µL (95% CI)	CFU/mL	Total CFU Challenge	Post filtration CFU/ µL (CI)	Filter Efficacy	P
E. coli	39 (26-51)	3.9×10^4	7.8×10^5	0	100%	0.0054
S. aureus	95 (30-160)	9.5×10^4	1.9×10^6	0	100%	0.0242
K. pneumoniae	25 (7-42)	2.5×10^4	5.0×10^5	0	100%	0.0260
M. catarrhalis	68 (49-87)	6.8×10^4	1.4×10^6	0	100%	0.0044
M. osloensis	20 (12-29)	2.0×10^4	4.0×10^5	0	100%	0.0098
E. agglomerans	37 (14-60)	3.7×10^4	7.4×10^5	0	100%	0.0198
H. influenzae	180 (86-270)	1.8×10^5	3.6×10^6	0.3(-1.1-1.8)	99.9%	0.0141
S. marcescens	87 (77-99)	8.7×10^4	1.7×10^6	0	100%	0.0022
C. albicans	5 (1-9)	5.0×10^3	1.0×10^5	0	100%	0.0377
†C. jejuni	15 (10-20)	1.5×10^4	3.0×10^5	0	100%	0.0059

† = culture results at 72 hr. All other samples cultured for 48 hr. Escherichia coli = E. coli; Staphylococcus aureus = S. aureus; Klebsiella pneumoniae = K. pneumoniae; Moraxella catarrhalis = M. catarrhalis; Moraxella osloensis = M. osloensis; Enterobacter agglomerans = E. agglomerans; Haemophilus influenzae = H. influenzae; Serratia marcescens = S. marcescens; Candida albicans = C. albicans; Campylobacter jejuni = C. jejuni.

Discussion

Clearly, bacteria such as E. coli were too large to pass through the EF (Table I). In contrast, although S. aureus usually occurs in grapelike clusters, single cocci capable of passing through the filter are present. Other organisms such as K. pneumoniae, which are encapuslated within a large polysaccharide envelope and surrounded by extracellular slime, are actually larger than their reported size and should therefore be easily removed by filtration. Finally, organisms such as H. influenzae, which are pleomorphic and variable in size, and C. jejuni, which is a coiled spiral, may have the capability of "squeezing" through the EF.

This independent study supports the manufacturer's contention that the EF is effective in removing extrinsic microbial contamination from propofol. In addition, the product was challenged with ten to a 100 times as many microbes as the manufacturer had reported, in an attempt to overwhelm the filter's capability. The manufacturer reported complete removal of C. albicans, K. pneumoniae and M. osloensis from contaminated propofol. They reported that greater than 99.8% of S. aureus contamination was removed. Our findings confirm these results. In our study, complete removal of S. aureus was documented. Only H. influenzae was able to consistently have a few CFU escape filtration. This may be due to the variable shape of H. influenzae. Campylobacters, including C. jejuni, are capable of passing through membrane filters (pore size 0.45 to 0.65 µm) because of their motility.[9] Alternatively, the ability of C. jejuni CFU to pass through the EF only when a 10-mL syringe was used may be related to "over pressuring". This phenomenon has been demonstrated when filters are used to remove particulate matter from *iv* anesthetic drugs when they are drawn up for injection.[10]

The incidence of hospital acquired propofol associated infection is assumed to be low. Using a strict aseptic protocol, the manufacturer studied propofol which had been transferred from 140 vials into sterile syringes over a 12-hr period. Of the 2,040 test samples, only two tested positive for microorganisms and were from different syringes. The very low levels of contamination of these samples were consistent with the background contamination inherent with the study protocol.[11] Consequently, it is argued that the low incidence and levels of propofol contamination pose only a minimal risk to patients. Further, the paucity of reported cases of propofol associated sepsis and infection would support this view.[12]

There is evidence that opportunities exist for the extrinsic contamination of propofol by microbial agents during the transfer of the drug from a vial or ampule to a syringe if recommended aseptic techniques are not followed. Accidental introduction of microbial contaminants on glass shards occurs with the opening of glass ampules and is particularly frequent with the larger 20 mL ampules. Furthermore, rubber stoppers and injection ports provide microbial access to propofol if they have not been carefully swabbed with alcohol.[13,14] When using aseptic protocols for handling propofol, the in-use rate of propofol extrinsic contamination in clinical practice has been reported to be 4.8 to 8.75%.[12,15–18] Bach *et al.* concluded that microbial contamination of *iv* anesthetic agents formulated in lipid solutions does occur in clinical use even when strict aseptic precautions are taken.[17] Since propofol is a medium particularly well-suited to support microbial growth, the question has been posed as to whether or not adherence to the manufacturer's recommendations is sufficient to reliably prevent the contamination of propofol.[3,5,18,19] Moreover, there is no evidence to conclusively confirm that the use of meticulous aseptic techniques in preparing propofol injections or infusion solutions can prevent such complications.[18,19]

Unfortunately, not only do anesthesia practitioners fail to practice such rigid aseptic protocols, studies and surveys of anesthesia personnel show that aseptic techniques and infection control procedures are frequently ignored in practice[20,21] despite the admonitions of the manufacturer. In clinical practice, aseptic techniques and hygienic guidelines are often neglected, ignored or broken.[14] Additionally, educational efforts directed toward anesthesia practitioners have not always been effective.[5] Thus, anesthesia practitioners can be a vector of nosocomial infection.

Inadvertent propofol contamination is not uncommon. What is unusual is that few affected patients develop clinical infection despite receiving contaminated propofol. This may be a consequence of the low microbial inoculum, the use of perioperative antibiotics,[5] and the immunological competency of most patients. Finally, the true incidence of propofol associated infections is under reported because of its widespread use and the lack of epidemiologic investigative expertise capable of identifying and reporting suspected propofol-related infections at most hospitals.[5]

Lipid based admixtures for total parenteral nutrition are routinely administered through 1.2 μm filters to remove particulate matter and reduce the risk of accidental contamination with fungi such as Candida.[22,B,C] The EF is capable of removing particulate and microbial contamination from lipid based propofol emulsions. Although filtration has not been recommended by the manufacturers of propofol, the EF has been approved by the Food and Drug Administration [FDA 510 (k) Market Clearance Number: K954331]. In order to assure the protection of our patients, the combination of strict aseptic handling of propofol and the use of filtration has been suggested. Sadly, due to limited demand, the Pall company has discontinued the production of the EF.

Filtration is not capable of removing endotoxins produced by gram-negative microbes. Endotoxins are detected in substantial levels by 24 hr in contaminated lipid emulsions and in propofol in particular.[23,24] Endotoxins themselves are capable of contributing to the morbidity and mortality of patients. The more time the contaminating organism is permitted to grow prior to its removal, the greater the accumulation of endotoxin.[24] This reinforces the manufacturer's warning that propofol must be administered within six hours of its preparation for injection or within 12 hr for continuous infusions for sedation. Consequently, even the use of a filter capable of removing microbial contaminants is not a substitute for meticulous aseptic technique and the prompt administration of propofol when the contaminating organism is capable of producing endotoxins.

The presumption that infection acquired from anesthetic practices is rare or uncommon is no longer accurate nor credible. The failure of educational programs to ensure the appropriate handling and administration of propofol underscores the necessity of proper training and monitoring of personnel who handle propofol as

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B) FDA safety alert: hazards of precipitation associated with par enteral nutrition. Public Health Service, Food and Drug Administration, April 18, 1994.
C) *Whitehead J, Jarres L.* Removal of candida albicans from total nutrient admixtures (TNA) by 1.2 micron filters, Pall Technical Report, 1994.

well as the introduction of adjuncts to prevent the exposure of patients to extrinsic microbial contamination. Hospital acquired infections and in particular nosocomial bloodstream infections increase morbidity and mortality and are accordingly expensive.[25]

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