Effect of a Millipore Filter on Complications of Intravenous Infusions: A Prospective Clinical Trial

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Summary

The Millipore filter unit has been advocated as a means of reducing the chance of bacteria entering the circulation during intravenous infusion. In a prospective study no significant reduction was obtained in the incidence of thrombophlebitis or in the bacterial contamination of cannulae. The unit was inconvenient to use and in-vitro and in-vivo studies showed reduced flow rates and frequent episodes of filter blockage. Its use was further restricted by the fact that blood and fat emulsions would not pass through it.

Introduction

Intravenous administration of fluids carries its own morbidity and a small though significant mortality (Ayers, 1957; Doering *et al.*, 1967). The most frequent complication and a source of much discomfort to patients is thrombophlebitis which may result from chemical irritation or infection. Dextrose 5% (pH 4.0) has been associated with a 25% incidence of thrombophlebitis in 24 hours (Jones, 1967). In the past the high incidence of venous thrombosis at the site of blood transfusions was due to the leaching of toxic constituents from the rubber tubing (Hadfield-Jones and Lewis, 1952) and this incidence was reduced when plastic tubing was introduced (M.R.C. Report, 1957). Recent evidence suggests that plastic tubing may not be without risk (*British Medical Journal*, 1973 a) as it has been shown that the toxic plasticizer di-2-ethyl hexylphthalate may be leached from polyvinyl chloride (Jaeger and Rubin, 1970, 1972). The fluids administered may contain bacteria either as a result of inadequate sterilization at the time of manufacture, as occurred in the Devonport disaster (Department of Health and Social Security, 1972 a), or subsequent contamination resulting from the use of imperfect glass bottles or ill-fitting rubber plugs (Department of Health and Social Security, 1972 b). In addition an amazing diversity of particulate matter has been recovered from the fluids and occasionally from the patient (Groves, 1972), including fragments of metal, glass, plant fibres, and even ants (Rupp and Forni, 1972). For these reasons the passage of fluids through a Millipore filter unit in the course of their administration to a patient would seem to be reasonable (*British Medical Journal*, 1973 b).

Previous work has shown the Millipore filter unit to be an

effective barrier to bacteria and particulate contaminants (Myers, 1972) but Goldman (1972) said that "in spite of the theoretical benefit of Millipore filters in decreasing infection, there have been no controlled prospective clinical studies to evaluate their true efficacy." The present study was therefore designed to discover whether a Millipore filter unit had any effect on the incidence of thrombophlebitis and septicaemic complications of intravenous fluid therapy.

Materials and Methods

Filters supplied by Millipore U.K. Ltd. were used with a pore size of 0.45 μ m. Standard polyvinyl chloride giving sets were used throughout as were a variety of cannulae of two main types, short cannulae of the Braunula or Medicut pattern and long cannulae of the Intracath or E-Zcath type.

Patients receiving blood, fat emulsions, and 50% dextrose solutions were excluded from the trial. The patients were divided into two groups determined by their clinical requirements. Group 1 received intravenous nutrients and group 2 received clear fluids only. Within each group patients were allocated by random selection either to filter or non-filter subgroups. All infusions were erected by the house surgeon with the usual aseptic precautions, the choice of cannula being unrestricted. A Millipore filter unit was inserted between the giving set and the cannula of patients in the filter subgroups. The filters were changed in the event of blockage, when the drip was discontinued, or every 48 hours. The filter was sent for bacteriological examination without disconnection from the giving set. The tubing of the Millipore filter unit and giving set was occluded to prevent contamination of the filter at this stage. When the infusion was discontinued the cannula was sent in a sterile container for bacteriological examination and the infusion site assessed for the presence of thrombophlebitis. In this study thrombophlebitis was recorded as present if the vein was inflamed at a distance greater than 2 cm from the point of entry of the cannula into the skin. In most cases the infusion site was changed before the phlebitis had progressed to thrombosis with the presence of a palpable cord. The filters were examined bacteriologically by filling the dome of the unit with sterile trypticase soya broth, using an aseptic technique and incubating at 37°C for 24 hours followed by subculture and identification of organisms. Quantitative bacterial cultures were not possible since the filter beds were an integral part of the sealed plastic unit and could not be removed without contamination. Organisms present on the external and internal surfaces of the cannulae tips were cultured by immersing the tips in cooked meat medium and subsequent subculture.

An in-vitro study of the rate of flow of various fluids through the Millipore filter unit was made after difficulties in achieving adequate in-vivo flow rates, especially with intravenous nutrients. A constant pressure arrangement was used (Ferguson and Gary, 1952) consisting of a standard giving set from which all air was evacuated. The fluid under test was run for one minute through an 18-gauge, 2-in (5-cm) Medicut cannula (Aloe Medical, St. Louis) from a height of one metre with and without a Millipore filter unit interposed. Repeated estimations were made, and three filters were used. In a similar manner the maximal rate of flow of normal saline from a height of one metre was determined in two patients, a volume measuring device being incorporated in the administration set.

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Results

A total of 60 separate infusions were studied in 43 patients. Altogether, 45 filters out of 84 required replacement at less than 48 hours due to blockage (table I).

TABLE I—Number of Filters which needed Replacing due to Blockage at less than 48 hours

	Total Filters	Filter Blockages	Significance
Group 1 (intravenous nutrients)	46	34	$\chi^2 = 32.53$ $P < 0.0005$
Group 2 (fluid replacement)	38	11	

The culture of 80 filter units yielded 17 positive cultures (21%), and 30 positive cultures were obtained from 52 cannulae (58%). Seventeen isolations of organisms were cultured from the filter units and 34 from cannula tips (table II).

TABLE II—Organisms Isolated from Filter Units and Cannula Tips

Organism	No. of Isolations			
	Millipore Filter (n=80)	Cannula Tip (n=52)		
		Total	Filter	Non-filter
<i>Staphylococcus epidermidis</i> ..	11	23	14	9
<i>Staph. aureus</i>	1	2	1	1
<i>Diphtheroids</i>	1	2	1	1
<i>Anthraxoids</i>	2	2	1	1
<i>Streptococcus faecalis</i> ..	1	3	—	3
<i>Pseudomonas aeruginosa</i> ..	1	2	1	1

The number of positive cannula tip cultures in the filter and non-filter subgroups are compared in table III.

TABLE III—No. of Positive Cultures from Cannula Tips in Filter and Non-filter Subgroups

	Groups 1 and 2 (Filter)	Groups 1 and 2 (Non-filter)
Cannulae total	29	23
Positive culture	16	14
Negative culture	13	9
Per cent. positive	55	61

$\chi^2 = 0.17$. $P > 0.6$.

Comparison of the incidence of thrombophlebitis in filter and non-filter subgroups (table IV) failed to show a significant difference.

TABLE IV—Comparison of Thrombophlebitis Incidence in Filter and Non-filter Subgroups

	No. of Infusions	No. of Cases of Thrombophlebitis	Significance
Group 2:			$\chi^2 = 0.33$ $P > 0.5$
Filter	22	9	
Non-filter	18	9	$\chi^2 = 0.15$ $P > 0.6$
Groups 1 and 2:			
Filter	33	13	
Non-filter	27	12	

There was no correlation between the presence of thrombophlebitis and a positive cannula tip culture (table V).

The results of the in-vitro study are given in table VI in order of flow rates with a filter in place. In all cases the rate of flow of fluids through a cannula is greatly reduced by the interposition

of a Millipore filter unit. In the case of 50% dextrose the flow rate with the filter in place was found to be too low to allow its use in vivo.

TABLE V—Correlation between Presence of Thrombophlebitis and Positive Cannula Tip

Groups 1 and 2	Cannula Cultures	
	Positive	Negative
Thrombophlebitis present	12	9
Thrombophlebitis absent	18	14

$\chi^2 = 0.004$. $P > 0.9$.

TABLE VI—Results of In-Vitro Study

Solution	Mean Flow (ml/min)	$\pm$ S.D.	Filter Flow
			Non-filter Flow $\times 100\%$
Normal saline:			30
Filter	29.5	1.1	
Non-filter	99.5	1.1	
5% Dextrose:			29
Filter	27	0.8	
Non-filter	92	1.3	
Aminoplex 14:			26
Filter	21	2.3	
Non-filter	80	1.9	
Aminosol 10%:			22
Filter	18.5	0.6	
Non-filter	84.2	0.8	
Vamin:			18
Filter	14.5	1.1	
Non-filter	79	1.5	
Laevulose 20%:			15
Filter	13	1.0	
Non-filter	86	0.6	
Sorbitol 30%:			15
Filter	11	0.8	
Non-filter	76	0.9	
Dextrose 50%:			10
Filter	4	0.0	
Non-filter	40.5	1.8	

Maximal flow rates in the patients were found to vary greatly between observations, ranging from 0-17 ml/min with a filter in place, and from 18-44 ml/min with no filter (table VII). Clearly the rate of flow can be influenced by alteration in the state of contraction of the vein and by the rate of blood flow through the vein. Under certain conditions a head of pressure of one metre of saline was insufficient to drive saline through the Millipore filter into some veins.

TABLE VII—Flow Rates at Three Observations

Paired Observations	Flow (ml/min)					
	1		2		3	
Patient A:						
Filter	4	4	6	9	0	5
Non-filter	25	25	20	24	40	32
Patient B:						
Filter	2	1	17	15	7	0
Non-filter	28	44	22	30	18	28

Discussion

The millipore filter unit was unpopular with both medical and nursing staff owing to the difficulty in maintaining an adequate flow rate, particularly with intravenous nutrients. The subjective opinion of the staff involved was confirmed by the highly significant difference in the incidence of filter blockage between the two groups. The following two explanations seem to be possible for filter blockage. (1) Mixing of the intravenous nutrients before their passage through the filter may produce crystallization with consequent filter blockage. (2) When two giving sets are used

with a connexion, difficulty is often experienced in regulating the flow of one fluid against another; when the reserve flow capacity is reduced, as it is with a filter in place, this difficulty is increased. In such circumstances flow is often stopped completely for some time, with resultant clot formation at the cannula tip, this being recorded as filter blockage.

Bacteria may be introduced at the time of insertion of the cannula or subsequently may track around the cannula or may be present in the infusion fluid. Several studies have been made of the effects of application of antibiotic ointments at the site of the cannula. Moran *et al.* (1965) found a reduction of positive cannula tip cultures and a halving of the incidence of thrombophlebitis when using an ointment containing polymyxin, bacitracin, and neomycin, while Glover *et al.* (1971) with an identical ointment failed to find any such reduction. The practice of shaving the cannula insertion site has recently been criticized as a result of the work of Serapian and Reynolds (1971), which showed a tenfold reduction in surgical wound infection rates after replacement of razor shaving with the use of a depilatory cream.

The present study has shown that bacteria can often be isolated from a terminal filter in drip sets. However, the incidence of thrombophlebitis or of positive bacterial cultures of cannula tips is unaltered by the use of a Millipore filter. In view of the closed method of collection and culture it is likely that all organisms cultured from the filter unit were present during the time that fluids were passing through the unit. How these organisms came to be there is open to conjecture. In the case of organisms cultured from the cannula tips there can be no way of knowing whether these were present on the cannula tip while it was in the vein or whether they were acquired from the skin during removal of the cannula. No relation was found between a positive cannula culture and the presence or absence of thrombophlebitis. The overall incidence of thrombophlebitis has been found to be 42% and positive cannula tip cultures were obtained in 58% of all cannulae cultured. These figures compare with a 39% incidence of thrombophlebitis and 30% positive cannula tip cultures in Collins's series (Collins *et al.*, 1968), who also showed no relation between the two, and with 88% positive cannula tip cultures in the study by Moran *et al.* (1965). Sanderson and Deitel (1973), however, obtained only 10% positive cultures from 107 cannulae tips.

It is known that showers of bacteria can be liberated during the act of chewing and at dental extraction apparently without effect on the well being of normal persons (Wilson and Miles,

1966). In this study it has been shown that though bacteria are often trapped by the Millipore filter this was not associated with any demonstrable clinical advantage. Furthermore, it has been suggested that the filters may increase the hazard of sepsis by allowing the organisms to concentrate and discharge as a bolus if the filter becomes damaged in any way (Atkins *et al.*, 1970).

To avoid the disaster of massive bacterial contamination of infusion fluids it is necessary to rely on a continuing high standard of care in their preparation. In this connexion it is interesting to note that blood, which is the one fluid infused which cannot be sterilized at the present time, will not pass through a Millipore filter.

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