Regular Review

Potential for extending survival of peripheral intravenous infusions

J F Hecker

Although many intravenous infusions run uneventfully and are stopped electively, others fail prematurely and the needle or cannula needs to be resited. Information is sparse, but the average survival of infusions in the 1950s was shorter than it is now,[1] probably less than 24 hours. This seems to have increased to one to two days in the early 1970s and is now about two to four days. The increase in survival was initially due to replacing red rubber infusion sets with plastic tubing,[2] while subsequent improvement may have been due to better quality control by manufacturers of drugs and solutions.

In the 1970s references to phlebitis were common but fewer appeared in the 1980s, suggesting that a two to four day average survival of infusions has gained acceptance and further extension is considered unimportant. Nevertheless, longer survival is feasible. I have analysed studies on survival of intravenous infusions and review here methods that may increase survival.

Infusion failure

Infusion failure is failure of an infusion site to function while needed. Phlebitis is the most common cause and extravasation is also common, whereas blockage (failure to run) and dislodging of the cannula usually account for small proportions of failures.

Most studies deal only with phlebitis.[3] A common scoring system used to describe its severity[4] ignores the fact that many infusions fail because of phlebitis but others extravasate with phlebitic signs. This leads to problems in identifying the cause of failure: extravasation is obvious at the time that the infusion is stopped, but the swelling rapidly disappears and phlebitic signs become increasingly obvious. Another problem of this scoring system is that it is influenced by the astuteness of the supervising staff as phlebitic signs will initially be slight but will increase in severity with time until they are recognised and the infusion is stopped.[4] For these reasons I have ignored differences in severity of phlebitis in this paper.

Extravasation, also called tissuing or infiltration, has received less attention because of the near universal belief that it is caused by the cannula or needle tip coming out of the vein because it has dislodged or has pierced the wall. This does occur sometimes with cannulas and is probably more common with short butterfly needles, which have sharp points that can pierce the wall. But there is another explanation. In most cases the tip probably remains in the lumen and the infusate extravasates through the hole made by the cannula or needle entering the vein.[5] For extravasation to occur by this means, the vein must constrict or be blocked near the cannula tip to stop flow. Such leakage can be shown radiographically.[6]

Venoconstriction is an early sign in phlebitis, causing the drip rate to slow.[5] Slowing of infusions in the hours immediately before failure is common, but it is rarely recognised as nurses periodically slacken infusion regulators to compensate for increased venous resistance.

Phlebitis and extravasation associated with venoconstriction are caused by irritation of endothelium. Irritation is usually caused by the infusate, although the cannula or needle tip may irritate the wall.[7] Venoconstriction stops blood flow through the vein and will intensify the irritation as the infusate will no longer be diluted with blood.[5]

Because phlebitis and extravasation are often related I have used infusion failure as a collective descriptive term. This definition affected the interpretation of one set of data, that of Sketch *et al*, in which differences were significant when total complications were used but were not when phlebitis was the end point.[8]

Statistics

Statistics in many studies of infusion failure are confusing, and the number of infusions studied often have been so small that the likelihood of detecting significant differences was low. Few studies have attempted to identify differences in failure rates due to associations with other factors, and occasionally the fact that many infusions are stopped electively has been ignored, suggesting 100% failure rates. A few papers have used paired comparisons in which volunteers received two infusions simultaneously, one with a test solution and the other with a control solution.[9-11] Other trials used clinical infusions.

Many authors have analysed numbers of infusions surviving at the end of successive 12 or 24 hour periods. When studies have examined survival at more than one time I have analysed the results for infusions surviving in the last period (48 hours,[12-17] 72 hours,[18] and 120 hours[19]).

Most studies report proportions of failed infusions and I have used these to calculate odds ratios (cross product ratios) from contingency table analyses (χ^2 tests). The odds ratio is a measure of the difference between two proportions, and a value of 1·0 indicates that there is no difference.

The method of combined logarithms of the odds ratios[20] was used to combine the odds ratios for meta-analyses of treatments. A significant homogeneous χ^2 value indicates that there are differences in odds ratios between trials while a significant association χ^2 value indicates that the pooled (overall) odds ratio is significantly different from 1·0—that is, the treatment has a significant effect.

Survival analysis[21] is a common tool in investigations on cancer and is preferable for infusion failure as it

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BMJ 1992;**304**:619-24

takes into account the variable time course of failure and also allows information to be used from infusion sites when infusions are stopped electively. Analyses of failure of intravenous infusions have usually used univariate or "life table" survival analysis.[22-28] However, multivariate survival analysis (usually with Cox's proportional hazards model[29]) may be preferable as it can take important prognostic factors into account. Survival analysis is particularly important for infusions in neonates,[25 26] where few infusions are stopped electively and the average time that infusions survive is the pertinent variable.

Some papers present failure rate ratios from univariate survival analyses. Even though failure rate ratios are similar to odds ratios they cannot be combined into meta-analyses. When both were available and both seemed to describe the response to a treatment similarly, the odds ratio was used in preference as it could be incorporated into the meta-analysis. Odds ratios and failure rate ratios were usually comparable if the average duration of infusions in both groups was similar and the effect of a treatment was to decrease the incidence of failure, as in most trials in adults. A few trials which cited proportions also indicated that the mean life increased (from 79 to 206 hrs[19] and from 2·1 to 5·2 days[30]) and so odds ratios underestimate their results. The only inconsistency between failure rate ratios and odds ratios in adults was in the data of Allcutt *et al*,[22] in which differences in the odds ratios but not the failure rate ratios were significant.

Most treatments in neonates had little effect on the high incidence of failure but increased the duration, and so failure rate ratios are given for these studies. Alpan *et al*, however, found that heparin both decreased the proportion failing and increased catheter patency time from 26·1 to 57·8 hours.[31]

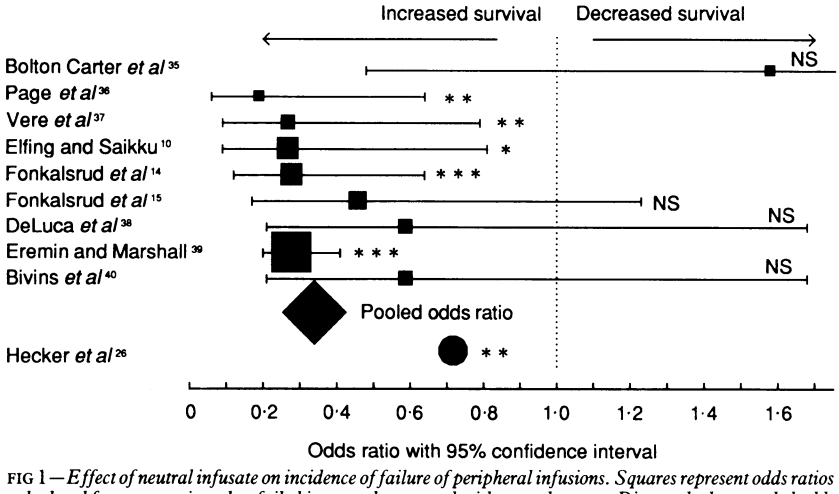

FIG 1—*Effect of neutral infusate on incidence of failure of peripheral infusions. Squares represent odds ratios calculated from proportions that failed in treated compared with control groups. Diamonds show pooled odds ratios and circles the ratio of relative failure rates of treated to control groups calculated by univariate survival analysis. Size of squares, diamonds, and circles indicate numbers of sites studied. *p<0·05, **p<0·01, and ***p<0·001. End points were phlebitis and thrombosis[36]; phlebitis, extravasation, and thrombosis[39]; failure[26]; or else phlebitis*

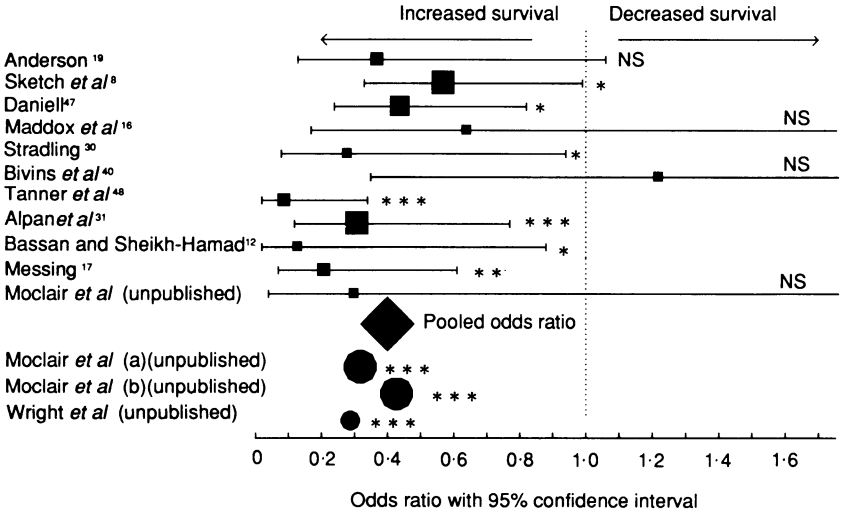

FIG 2—*Effect of heparin (1 IU/ml) added to intravenous fluids on failure of peripheral infusions. See figure 1 for explanation of symbols. End points were total complications,[8] phlebitis and spontaneous stoppages,[30] failure (Moclair* et al*), or else phlebitis. Infusions were of total parenteral nutrition into premature babies[31] (Moclair* et al *(a)), dextrose into premature babies (Moclair* et al *(b)), total parenteral nutrition into adults,[17] or else crystalloid fluids into adults. One study included lignocaine in infusions[12]*

Acidity of crystalloid solutions

Dextrose, the main solute in most intravenous fluids, provides the necessary osmotic pressure to prevent haemolysis, is not injurious to blood, and is a source of energy. The common dextrose based solutions—5% dextrose, 4% dextrose plus 0·225% saline, and 2·5% dextrose plus 0·45% saline solution—are approximately isotonic. It is commonly believed that infusion failure with these solutes is usually due to the drugs that are also given but few attempts have been made to identify which drugs are irritant.[3] Adult total parenteral nutrition solutions are based on concentrated dextrose solutions and are irritant as they induce more phlebitis in peripheral veins than isotonic solutions. Neonatal total parenteral nutrition solutions are less concentrated (usually 10% dextrose) but are still hyperosmolar and cause more rapid failure than isotonic solutions.[26]

Common crystalloid solutions, particularly those based on dextrose, are acid.[32 33] This acidity is initially due to decomposition during heat sterilisation. A recent study suggested that dextrose solutions become more acid with time as plastic bags used for packaging them allow oxygen to enter and oxidise glucose to gluconic acid (J F Hecker, G B H Lewis, unpublished data). As the pH falls the titratable acidity rises and can reach 0·1-0·2 mmol/l in 5% dextrose by the expiry date. The pH is lower in dextrose and dextrose saline solutions than in Ringer solution, but Ringer solution, which is buffered, contains 1-10 mmol/l of acid.[34] Normal saline is less acid in terms of pH, typically 5·5. Lebowitz *et al* reported that it has a similar titratable acid content to dextrose solutions,[34] but our measurements indicate that it has little acidity (J F Hecker, G B H Lewis, unpublished data).

Neutralising or buffering dextrose solutions before use reduced infusion failure in most trials (fig 1). The studies were all of crystalloid fluids into adults except that of Hecker *et al*,[26] which was of total parenteral nutrition into babies. One study compared filtered (pH 5-6) with autoclaved (pH 3·5-4) solutions.[37] The early report of Bolton Carter *et al* can be discounted as the greatest pH correction was to 6·05 and they probably used rubber tubing that leached toxic ingredients rather than plastic infusion tubing.[35] Few of their infusions lasted longer than eight hours. Red rubber infusion sets were probably also used when a considerable reduction in the incidence of phlebitis was found by Page *et al*, who adjusted the pH to 7·0.[36]

In addition, Bergqvist, who gave no details, reduced phlebitis only slightly by neutralisation[41] and DeLuca *et al* found no significant reduction in phlebitis (odds ratio=1·74) when a buffer was tested with filtered solutions (see below).[38] In the trial by Flores-Vega *et al* in which heparin was added to 77% of infusions, there was a non-significant reduction in phlebitis (odds ratio=0·72), but the time to phlebitis increased from 3·2 to 4·1 days.[42]

Total parenteral nutrition solutions have a pH of about 6·0 due to buffering of amino acids and phosphate but they require appreciable amounts of alkali for neutralisation. The only trial in which neutralised total parenteral nutrition was tested[26] showed a beneficial

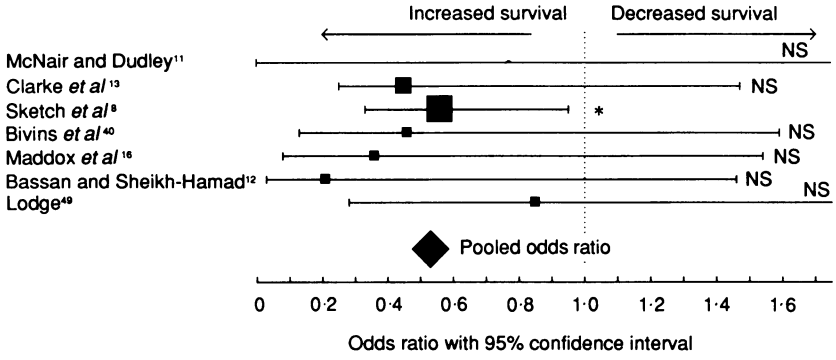

FIG 3—*Effect of adrenal steroids on failure of infusions. See figure 1 for explanation of symbols. Hydrocortisone (10 μg/ml) was added to all solutions. End points were total complications,[13] failure,[49] or else phlebitis. Crystalloid fluids were infused only into adults. Heparin was infused at 1 IU/ml except for McNair and Dudley,[11] who used 2 IU/ml, and Maddox* et al,[16] *who infused 0·5 or 1·0 IU/ml*

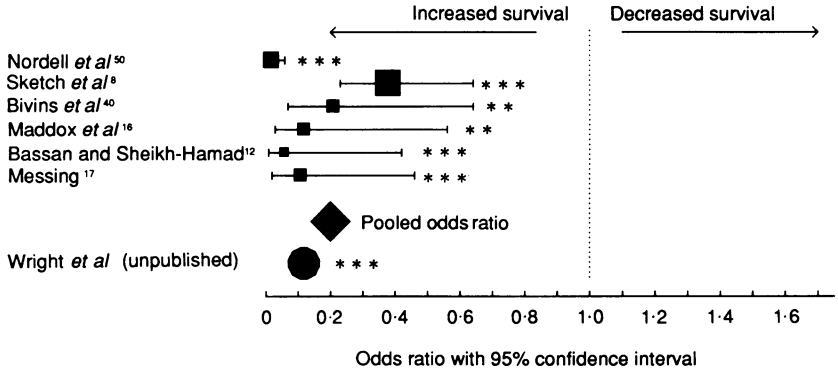

FIG 4—*Effect of heparin plus adrenal steroids on failure of infusions. See figure 1 for explanation of symbols. Heparin at 1 IU/ml (at 0·5 or 1·0 IU/ml[16]) and hydrocortisone at 10 μg/ml were added to total parenteral nutrition[13] or crystalloid fluids infused into children (Wright* et al) *and adults. End points were total complications[8] (Wright* et al) *or else phlebitis*

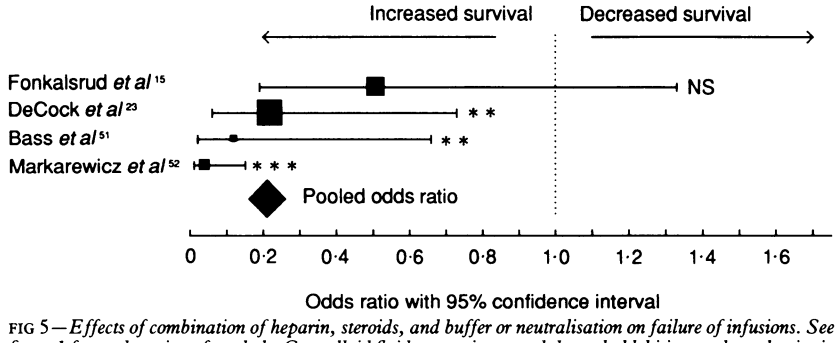

FIG 5—*Effects of combination of heparin, steroids, and buffer or neutralisation on failure of infusions. See figure 1 for explanation of symbols. Crystalloid fluids were given to adults and phlebitis was the end point in each trial*

effect in premature babies (fig 1), increasing median survival of sites from 21 to 33 hours. Rypins *et al* found that the incidence of phlebitis decreased from 68% to 27% when dextrose in total parenteral nutrition given through peripheral cannulas was replaced by glycerol[43]; glycerol is not acid.

Animal experiments support neutralisation of acidity. Infusion of common types of intravenous solutions for eight or 20 hours produced local venous damage in dogs, with unbuffered solutions causing greater damage than buffered solutions,[44] and 5% dextrose infused into ear veins of rabbits produced substantially less histological damage when neutralised.[45] Neutralisation of 25% dextrose infused into the veins in sheep's ears substantially reduced local venoconstriction.[46]

Heparin and corticosteroids

Intravenous infusions of heparin to prevent or treat deep vein thrombosis and corticosteroid infusions for severe asthma commonly run for prolonged periods without failing. These drugs are given at low flow rates and so the vein is irritated less by the carrier crystalloid solutions, but they also have local pharmacological actions which decrease venous irritation. Both drugs have been investigated in several trials in which one or both were added to infusates or applied to skin over infused veins. They usually decreased infusion failure (figs 2-5), even though numbers were often small and results not always significant. Heparin was normally used at 1 IU/ml and hydrocortisone at 10 μg/ml (Bass *et al*[51] used prednisolone). The effects of heparin and corticosteroids are additive as the pooled odds ratio is lower for the combination (fig 4) than when they were used individually (figs 2 and 3). Use of neutralised solutions with these drugs did not further improve survival (fig 5).

Fonkalsrud *et al*[15] also compared heparin, hydrocortisone, and a buffer with buffer alone and found a negligible increase in phlebitis, while Subrahmanyam[53] marginally decreased phlebitis with continuous hydrocortisone plus six hourly boluses of heparin, and Schafermyer reported that heparin "greatly decreased the incidence of phlebitis."[54]

There is little evidence for percutaneous absorption of heparin and the reduced failure associated with the Movelat cream used by Woodhouse was probably due to the steroid in the cream rather than the heparin.[55] Eerola and Pontinen found that heparin creams did not reduce phlebitis.[56]

Heparin added to total parenteral nutrition infused into peripheral veins prolonged survival of infusions in adults[17] and neonates[31] (A Moclair *et al*, unpublished). An apparent paradoxical increase in phlebitis in adults when heparin was added to total parenteral nutrition[57] was probably caused by the solution with the heparin having a much higher osmolarity (and higher acidity) than that without. In contrast, the effect of hydrocortisone in hypertonic total parenteral nutrition solutions containing heparin was spectacular (mean duration increased from four to 120 hours).[58] Moclair *et al* found improved infusion survival with total parenteral nutrition solutions and heparin in patients who also had transcutaneous glyceryl trinitrate and steroid applied locally (see below).[59] Survival of sites with this combination of drugs was similar to that with routine dextrose infusions in similar patients (J F Hecker, unpublished data).

The only animal study showed that adding heparin reduced disturbances to flow in veins in the hamster cheek pouch, an effect which was confirmed radiologically in babies receiving infusions.[60]

The minimum concentration of heparin that is effective in adult infusions has not been determined. A study comparing 0, 0·1, 0·25, 0·5, and 1 IU/ml heparin in 10% dextrose or total parenteral nutrition solutions given to premature babies found that 0·5 IU/ml was as effective as 1 IU/ml (A Moclair *et al*, unpublished data).

Glyceryl trinitrate

Glyceryl trinitrate applied distal to infusion sites by means of controlled release devices (Transiderm-Nitro, CIBA, Horsham, Sussex) significantly decreased the incidence of failure of infusion by two thirds in two out of four experiments in adults (fig 6). Glyceryl nitrate probably acts by increasing local blood flow, which dilutes the infusate and buffers its acidity.[61] In one of the two other experiments in adults (G B H Lewis, J F Hecker, unpublished data) most of the 178 infusions were stopped electively and few ran for long enough to fail. In the other (M Wyer *et al*, unpublished data), glyceryl trinitrate was applied when patients returned to the ward after surgery, which was two or more hours after the infusions started. Fluids tend to be given rapidly in theatre and during recovery from anaesthesia, and significant irritation might have been caused to the veins. Khawaja *et al* increased median

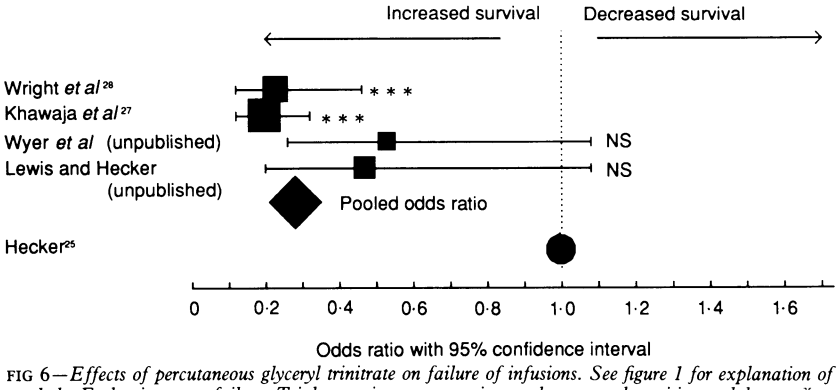

FIG 6—*Effects of percutaneous glyceryl trinitrate on failure of infusions. See figure 1 for explanation of symbols. End points were failure. Trials were in neonates using total parenteral nutrition and dextrose[25] or else in adults with crystalloid fluids*

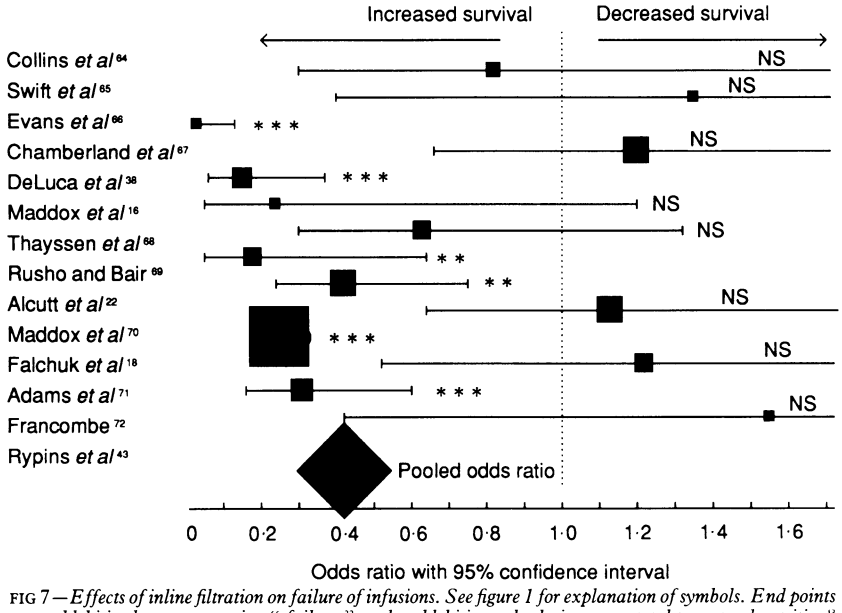

FIG 7—*Effects of inline filtration on failure of infusions. See figure 1 for explanation of symbols. End points were phlebitis plus extravasation,[66] failure,[22] or else phlebitis, and solutions were total parenteral nutrition[43] or else crystalloid fluids. In one study control infusions preceded filtered infusions.[72] Calculations on data of Rusho and Blair assume 50 patients per group and proportions calculated from data of Rypins* et al *have been rounded*

survival of total parenteral nutrition infusions in adults with local glyceryl trinitrate.[62]

The only trial of glyceryl trinitrate in neonates showed that it was ineffective.[25] This may be because veins in neonates are small and cannulas, although also small, occupy most of the vein and so venodilation may not allow an appreciable increase in local blood flow.

Inline filtration

The other well studied method for reducing infusion failure is inline filtration, which eliminates microscopic particles that remain in intravenous fluids and drugs despite manufacturers' attempts to remove them. It has been extensively reviewed by Lowe.[63] Some trials of filters have shown either a reduction in the incidence of infusion failure or an increase in time before failure (fig 7). Most studies showed no significant differences, and the publicity given to particles in recent years may have reduced particle loads in solutions and drugs compared with a decade ago so that filters are now less effective in preventing failure of infusions. Filtration was the only method for which the homogeneous χ^2 value was significant, indicating significant differences between trials.

In addition to the data in figure 7, Ryan *et al* reported a reduction in incidence of phlebitis from 50% to less than 10% but gave no details,[73] and DeLuca *et al*[38] found a reduction in phlebitis when filters were tested with buffered solutions and a small reduction when control solutions were compared with buffered, filtered solutions.

The pore size of filters has changed. All trials after 1980 used 0·2 or 0·22 μm whereas most before 1980 used 0·45 μm filters (Maddox *et al*[16] used 0·2 μm and Evans *et al*[66] 5 μm filters). Results do not seem to differ with these two sizes. Evans *et al* found a substantial decrease in phlebitis with 5 μm filters,[66] but Rusho and Bair found no effect with this size, although 0·45 μm filters had an effect.[69]

Control of infection

There is a belief that infection rather than chemical irritation causes peripheral infusion phlebitis. The evidence for this mainly comes from trials in which cultures of cannula tips after withdrawal have shown that some tips are contaminated, especially with the common skin organism *Staphylococcus epidermidis*. That organisms grow at the skin puncture site and contaminate cannula tips as they pass through the skin during withdrawal is one explanation why correlations between positive cultures and either phlebitis or the species of microorganism causing bacteraemia are usually poor.[39 74-76] Quantitative culture techniques largely eliminate the problem of skin contamination,[77] but they have not been used widely.

This raises the importance of skin preparation. In one trial 10 out of 29 patients given antiseptic skin preparation developed phlebitis compared with all 21 control patients, with four and 17 respectively of the cannula tips giving positive cultures (usually *S epidermidis*).[78] In contrast, another trial found that povidone-iodine ointment had no effect on the incidence of phlebitis or on the mean duration of infusions.[76] Though occlusive dressings decrease the rate of cannula tip colonisation, they may not influence the incidence of phlebitis.[79]

Appreciable lengths of central and long lines become covered with thrombus[80] with most of it in large veins. Direct seeding of thrombus by infusate borne organisms is unlikely as infusate flows away from the tip, but thrombus can readily be seeded by blood borne organisms.[81 82] Peripheral cannulas also form thrombus, but the amount is much less as cannulas are short and the small size of peripheral veins restricts the amount that forms. Again this thrombus is unlikely to be seeded by infusate borne contamination as the flow is from the cannula tip. Seeding of peripheral cannula thrombus from blood is less likely than with long lines as initial blood flow is small and will be decreased by venoconstriction associated with chemical irritation from the infusate.[5]

Other factors

Although much has been said about types of cannula, there are few sound data. Tully *et al* showed that using scalp veins were associated with significantly less phlebitis but more extravasation than cannulas.[83] The sharp tip and shorter length of a scalp vein needle would be more likely to cause it to hole the vein wall or to dislodge. Reasons for differences between cannula types are not clear but Gaukroger *et al* showed that a tendency for the tip of one brand to deform was associated with a significantly higher incidence of phlebitis.[7] Another important but often ignored factor is that infusion failure is time dependent. Many infusions are given for longer than they are needed and stopping them at the earliest suitable time would reduce problems.

Discussion

Although the numbers of infusions were small in many trials and differences in several were not significant, meta-analyses indicate that each technique signifi-

cantly decreases infusion failure. This is clear in figure 8, in which the pooled odds ratios indicate that proportions failing decreased to about 50% for steroids, 40% for heparin and filters, and 30% glyceryl trinitrate and heparin plus steroids. Neutralisation had no additional effect to heparin plus steroids.

There are fewer data on the effect on survival time than on proportions of infusions failing, but these treatments also increase the time that sites can be used if they are not automatically resited at 48 or 72 hour intervals. This is particularly so for trials with neutralisation[26] and heparin in neonates (A Moclair *et al*, unpublished data).

Should infusion sites be used for longer? The alternatives are to resite infusions every 24 or 48 hours when few have failed or to accept the status quo. Routine resiting is time consuming for junior medical staff and disliked by patients. It has been tried in many hospitals and abandoned or alternatively is still policy but often not followed. The current practice is also time consuming for staff, who have to deal with failed infusions, and is again disliked by patients. Arguments against increasing survival are mainly on the grounds of safety and cost. This raises further questions: what methods of achieving an increase are practical, cost effective, and safe, and are they worth using? The following points are relevant.

Firstly, prolonged infusions must not cause increased septic phlebitis. This could be a problem with corticosteroids, which inhibit local defence mechanisms, but has not been reported. Filtration will trap microbial contamination in infusates but changing filters daily also risks contamination, as does addition of buffers, heparin, or corticosteroids to infusates on the ward. If these drugs are to be used they should be added in a pharmacy, where the risk of contamination would be negligible. Normal saline is already available with 1 IU/ml of heparin, and other "non-irritant" intravenous fluids could be manufactured (for example, dextrose saline plus low dose heparin).

The actions of heparin and glyceryl trinitrate on local defence mechanisms at concentrations that will be present in infused veins are unknown, but microorganisms in blood are rapidly phagocytosed and so the vasodilating action of glyceryl trinitrate and the antithrombus effect of heparin may reduce the risk of infection. Two trials have shown significant reductions in positive tip cultures of long lines when heparin was added to infusions.[48,84]

Secondly, methods must have no risk to the patient.

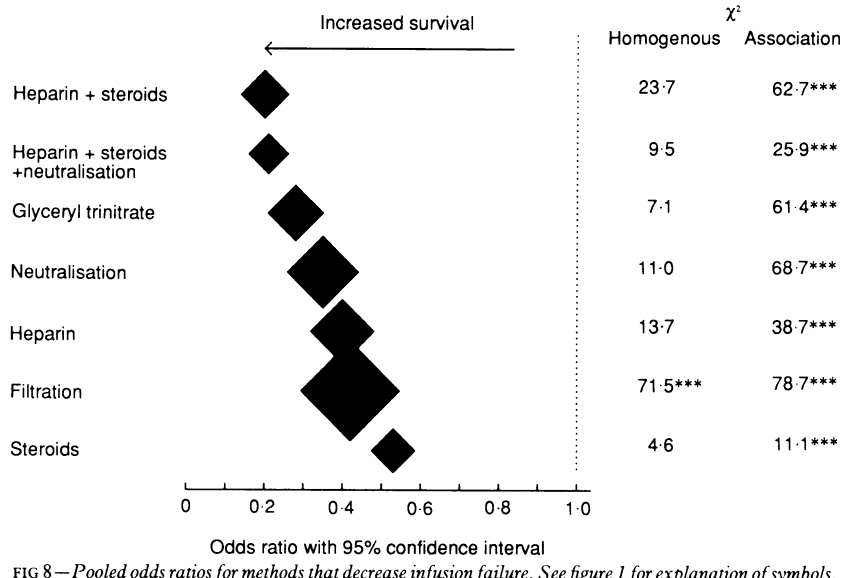

FIG 8—*Pooled odds ratios for methods that decrease infusion failure. See figure 1 for explanation of symbols. Methods are arranged in order of increasing odds ratios. χ^2 (association) indicates magnitude of differences between trials while χ^2 (homogeneous) indicates significance of pooled odds ratio*

Systems for controlled release of glyceryl trinitrate entail a small risk of a headache, but this can be treated with analgesics (few surgical patients get headaches as almost all receive analgesics after surgery). Smaller glyceryl trinitrate systems should be equally effective and cause fewer headaches. The Deponit patch (Schwartz Pharmaceutical, Chesham, Buckinghamshire) has an advantage over the Transiderm-Nitro system (CIBA) in that it can be cut into pieces to reduce the dose. There is also the problem of heparin induced thrombocytopenia.

Thirdly, methods for prolonging the survival of infusions are prophylactic and so the increased costs of infusion must be small. An increase in cost is acceptable if it is less than savings in cannulas and other items needed for resiting plus savings in staff time which would have been spent caring for and then resiting failed infusions. The only investigation of cost effectiveness of any of these methods showed that glyceryl trinitrate systems changed daily slightly reduced the cost of giving intravenous infusions.[85] However, controlled release glyceryl trinitrate systems have the advantage that only one system is needed for most infusions[28] and so cost savings would be greater if systems were not changed daily. Filters have not gained acceptance, probably because of expense, but the cost of commercially manufactured solutions containing low dose heparin would be relatively small. Unfortunately steroids may not be stable in solution for long periods and may be adsorbed on to the bag containing the solution.

To some, the idea of prolonging the life of peripheral infusion sites is heretical; yet they accept prolonged central cannulation. Central lines are associated with fewer problems (especially less phlebitis) than peripheral lines, but when problems do occur they are usually serious. These data suggest that techniques which prolong the life of peripheral sites might be used for patients needing several days' intravenous therapy who would otherwise be given a central line.

There is a further consideration. Patients receiving repeated intravenous therapy gradually lose superficial veins and some oncology patients and patients with chronic haematological conditions have few superficial veins remaining. Except for one study on oncology patients,[24] such loss has not been investigated but it is associated with endothelial damage caused by infused solutions and drugs. Few veins survive clinical phlebitis or extravasation[11] and loss would also follow the painless induration that may develop up to a week after injection of drugs such as diazepam.[86] Of the methods reviewed, percutaneous glyceryl trinitrate systems are most likely to prevent damage to the endothelium. With these systems a skin reservoir of glyceryl trinitrate seems to develop which lasts for many hours after removal of the systems, as veins tend to remain dilated. This may maintain blood flow through damaged veins to help healing. Use of controlled release glyceryl trinitrate therefore could have the bonus of helping to preserve superficial veins.

Conclusions

These data show that considerable reductions in the proportions of sites failing or increases in survival of infusions, or both, are possible, with heparin plus steroids, buffering, and transcutaneous glyceryl trinitrate being the most effective methods. Further studies are required using adequate numbers of patients to compare and evaluate these methods for safety, efficacy, and cost effectiveness. Even so, in patients who have or are likely to develop poor venous access the evidence is sufficiently strong that one or more methods should be used to conserve their remaining veins.

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(Accepted 10 December 1991)