Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials

Gill Schierhout, Ian Roberts

Abstract

Objective: To determine the effect on mortality of resuscitation with colloid solutions compared with resuscitation with crystalloids.
Design: Systematic review of randomised controlled trials of resuscitation with colloids compared with crystalloids for volume replacement of critically ill patients; analysis stratified according to patient type and quality of allocation concealment.
Subjects: 37 randomised controlled trials were eligible, of which 26 unconfounded trials compared colloids with crystalloids (n = 1622). (The 10 trials that compared colloid in hypertonic crystalloid with isotonic crystalloid (n = 1422) and one trial that compared colloid in isotonic crystalloid with hypertonic crystalloid (n = 38) are described in the longer version on our website www.bmj.com).
Main outcome measures: Mortality from all causes at end of follow up for each trial.
Results: Resuscitation with colloids was associated with an increased absolute risk of mortality of 4% (95% confidence interval 0% to 8%), or four extra deaths for every 100 patients resuscitated. The summary effect measure shifted towards increased mortality with colloids when only trials with adequate concealment of allocation were included. There was no evidence for differences in effect among patients with different types of injury that required fluid resuscitation.
Conclusions: This systematic review does not support the continued use of colloids for volume replacement in critically ill patients.

Introduction

Fluid resuscitation for hypovolaemia is integral to the acute medical management of critically ill patients. Although recent studies have suggested that the timing of volume replacement deserves careful consideration,[1] when it comes to selecting the resuscitation fluid doctors are faced with a range of options. At the most basic level the choice is between a colloid or crystalloid solution. Colloids are widely used, having been recommended in a number of resuscitation guidelines and intensive care management algorithms.[2 3] The American hospital consortium guidelines recommend that colloids are used in haemorrhagic shock until blood products become available and in non-haemorrhagic shock after an initial infusion with crystalloid. A 1995 survey of American academic health centres, however, found that the use of colloids far exceeded these recommendations.[4] Surveys of burn care in the United States[5] and Australia[6] found that the use of colloids for resuscitation varied without a set pattern. The choice of fluid has considerable cost implications: volume replacement with colloids is considerably more expensive than with crystalloids.

Clinical studies have shown that colloids and crystalloids have different effects on a range of important physiological parameters. Because of these differences, mortality from all causes is arguably the most clinically relevant outcome measure in randomised trials comparing the two fluid types. Although there have been meta-analyses of mortality in randomised trials comparing colloids and crystalloids,[7 8] neither of these satisfies the criteria that have been proposed for systematic reviews[9] and they predate most of the trials that have been conducted with synthetic colloids and hypertonic crystalloid solutions. The purpose of this review was to identify and synthesise all available unconfounded evidence of the effect on mortality in critically ill patients of colloids compared with crystalloids for volume replacement.

Methods

Identification of trials

Our aim was to identify all relevant randomised controlled trials available for review by June 1997. Relevant trials were those in which critically ill patients (excluding neonates) who required fluid resuscitation were assigned to colloid or crystalloid resuscitation protocols on the basis of random or quasi-random allocation. If the allocation procedure could not be fully ascertained from the published report, the author was contacted for clarification.

We included trials in which participants were critically ill as a result of trauma or burns, were undergoing surgery, or had other critical conditions such as complications of sepsis. Trials were considered unconfounded if one treatment group differed from another only in the treatment of interest. Thus a trial that compared colloid and hypertonic crystalloid with hyper-

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tonic crystalloid would be included, as would a trial which compared colloid and isotonic crystalloid to isotonic crystalloid. Trials with a "double intervention," such as those that compared colloid in hypertonic crystalloid to isotonic crystalloid, were analysed separately (for details, see longer version of article on our website). There were no language restrictions.

As the comparison between fluid type was in terms of effects on mortality, we excluded randomised crossover trials. We also excluded trials of preloading in preparation for elective surgery and trials in patients undergoing fluid loading during cardiopulmonary bypass, as in these situations fluids were given for purposes other than volume resuscitation.

Trials were identified by computerised searches of the Cochrane Controlled Trials Register, Medline, Embase, and BIDS Index to Scientific and Technical Proceedings; by hand searching 29 international journals and the proceedings of several international meetings on fluid therapy; by checking the reference lists of trials and review articles; and by contacting the authors of all identified trials, asking them about any other published or unpublished trials that may have been conducted. Further details on the search strategy are available from the authors on request. Eligibility was determined by two reviewers, who also independently extracted the data. Disagreements were resolved by discussion.

Outcome measures and data extraction

The principal outcome measure was mortality from all causes assessed at the end of the follow up period scheduled for each trial. In trials among surgical patients we sought prospectively gathered information on hospital stay and renal and pulmonary complications as the death rate in these trials was likely to be low (for details, see longer version on our website). For all trials, we extracted information on the type of participants, type of colloid and crystalloid used, duration of follow up, mortality at the end of follow up, and quality of concealment of allocation. We rated quality of concealment of allocation according the criteria proposed by Schulz.[10] We sought data in simple categorical form, and we did not extract data on time to death. When a report did not include mortality data at all, or when data were incomplete for all patients initially randomised, we sought these data from the trialists.

Data analysis and statistical methods

Before analysing the results, we identified a number of hypotheses concerning underlying differences in the studies that might require separate analyses or explain heterogeneity in an overall analysis. As efficacy of crystalloids and colloids for resuscitation is thought to differ between different patient types, we stratified the analysis by patients' injury—trauma, burns, surgery, and other conditions, including septicaemia and vascular leak syndrome. Finally, as it has been shown that studies with poor concealment of allocation tend to overestimate the effectiveness of interventions,[10] we regarded the level of concealment of allocation as a possible source of heterogeneity in study findings. We conducted an additional analysis using only trials with allocation concealment that was known to be adequate.

We calculated relative risks and 95% confidence intervals for mortality for each trial on an intention to treat basis using the Mantel-Haenszel method. We tested heterogeneity between trials with χ^2 tests, with $P \leq 0.05$ indicating significant heterogeneity. When there was no significant heterogeneity we used a fixed effects model to calculate summary relative risks and 95% confidence intervals for dichotomous data. In the event of significant heterogeneity that could obviously be related to type of injury or allocation concealment, we stratified the analyses on that dimension. As statistical tests of heterogeneity are known to lack power, we also present graphical displays for the summary effect measures of individual trials.

In order to test whether the results of the meta-analyses might have been biased because of selective publication of randomised trials with positive findings (publication bias), we used the regression approach to assessing funnel plot asymmetry proposed by Egger et al.[11] Using simple unweighted linear regression, the inverse of the variance of each study is regressed against the standard normal deviate. The larger the deviation of the intercept of the regression line from zero, the greater the asymmetry and the more likely it is that the a meta-analysis will yield biased estimates of effect. As suggested by Egger et al, we considered that $P < 0.1$ indicated significant asymmetry.

Results

We identified a total of 48 apparently randomised trials of fluid resuscitation in critically ill patients, of which 37 met the inclusion criteria. Reasons for exclusion of trials were the use of a crossover design (two trials); testing a resuscitation algorithm (three trials); and the intervention being used for maintaining serum albumin concentrations (three trials), for haemodilution (one trial), for fluid loading (one trial), and for reducing intracranial pressure (one trial).

The table gives key details of the 26 unconfounded trials that compared colloids with crystalloids (see longer version of article on our website for details of the 10 trials that compared colloid in hypertonic crystalloid with isotonic crystalloid and the one that compared colloid in isotonic crystalloid with hypertonic crystalloid). Nineteen of the 26 eligible trials reported mortality. For the other seven trials, we contacted the trialists to ask for any mortality data available for the 307 participants, but no additional information was forthcoming. Our analysis was therefore based on mortality data for 1315 participants from 19 trials. The figure shows that the summary relative risks were similar for all types of injury except surgery, for which the summary measure was imprecise because of small numbers of patients and a low overall mortality (4.7%).

In four of the trials concealment of allocation was adequate. There was no overall heterogeneity between trials ($\chi^2 = 11.67$, df = 16, $P = 0.75$). The pooled relative risk of death for all patient groups was 1.19 (95% confidence interval 0.98 to 1.45). The risk of death in the patients given colloids was 24% and the risk of death in the patients given crystalloids was 20%, giving an increase in absolute risk of mortality for resuscitation with colloids of 4% (0% to 8%). The pooled relative risk based only on trials with adequate allocation concealment was 1.29 (0.94 to 1.77), with an increase in absolute risk of mortality for resuscitation with colloids

Summary of randomised trials comparing colloid and crystalloid fluid resuscitation that met criteria for inclusion

Trial*	Type of injury	No of patients	Treatment		Length of follow up	Mortality reported	Allocation concealment
			Colloid	Crystalloid			
Lowe et al[w1-w3]	Trauma	171	50 g albumin/200 ml Ringer's lactate	Ringer's lactate	5 days	Yes	1
Modig[w4 w5]	Trauma	31	Dextran-70 in Ringer's acetate	Ringer's acetate	To definitive reconstructive surgery	Yes	1
Nagy et al[w6]	Trauma	41	Pentastarch in 0.9% NaCl	Ringer's lactate	Unspecified	Yes	1
Younes et al[w7]	Trauma	70	6% dextran-70 in 7.5% NaCl	7.5% NaCl	To discharge	Yes	3
Vassar et al[w8]	Trauma	174	6% dextran-70 in 7.5% NaCl	7.5% NaCl	To hospital discharge	Yes	3
Vassar et al[w9]	Trauma	149	6% or 12% dextran-70 in 7.5% NaCl	7.5% NaCl	To hospital discharge	Yes	3
Evans et al[w10]	Trauma	25	Haemacell in Ringer's lactate	Ringer's lactate	Unspecified	No	2
Skillman et al[w11]	Surgery	16	25% concentrated salt-poor albumin; 1 g/kg and 5% albumin in saline	Ringer's lactate with 5% dextrose	1 day	No	2
Boutros et al[w12]	Surgery	24	Albumin in 5% dextrose	5% dextrose in lactated Ringer's; 5% dextrose in 0.45% NaCl	To 48 hours postoperative	Yes	2
Virgilio et al[w13]	Surgery	29	5% albumin in Ringer's lactate	Ringer's lactate	2½ weeks	Yes	2
Grundmann et al[w14 w15]	Surgery	20	Human albumin and crystalloid (details not reported)	Crystalloid (details not reported)	Unspecified	Yes	1
Karanko et al[w16 w17]	Surgery	36	6% dextran-70 in 0.9% NaCl or in 5% glucose	Ringer's acetate gluconate	2 weeks	Yes	2
Ley et al[w18]	Surgery	21	6% hetastarch and 5% plasma protein fraction	0.9% NaCl	To discharge	No	2
Prein et al[w19]	Surgery	18	10% hydroxyethylstarch in 154 mmol/l NaCl and plasma protein solution; 20% human albumin solution	Ringer's lactate	Unspecified	No	2
Dawidson et al[w20]	Surgery	20	3% dextran-60 in Ringer's lactate	Ringer's lactate	To discharge	Yes	2
Hartmann et al[w21]	Surgery	29	Dextran-70 in NaCl with 2.5% glucose	NaCl with 2.5% glucose	7 days	No	2
Eleftheriadis et al[w22]	Surgery	91	6% hydroxyethylstarch	Ringer's solution and 3.5% gelatine solution	Unspecified	No	2
Tollosfrud et al[w23]	Surgery	40	Haemacell; dextran-70; albumin 40 mg/ml in saline	Ringer's acetate	To 48 hours	Yes	3
Wahba et al[w24]	Surgery	22	Haemacell in Ringer's lactate	Ringer's lactate	To discharge	Yes	2
Bocanegra et al[w25]	Burns	153	Plasma with saline; whole blood supplemented with 5% glucose	Isotonic saline	To 60 hours, then unspecified	Yes	1
Hall et al[w26]	Burns	172	6% dextran-70 in 0.9% NaCl	Ringer's lactate	To 5 years	Yes	1
Jelenko et al[w27-w30]	Burns	12	Albumin in hypertonic saline (240 mEq Na^+, 120 mEq Cl^-, 120 mEq lactate, 3.5 torr/l colloid)	Hypertonic saline (240 mEq Na^+, 120 mEq Cl^-, 120 mEq lactate)	To end of resuscitation	Yes	2
Goodwin et al[w31]	Burns	79	2.5% albumin in Ringer's lactate	Ringer's lactate	To discharge	Yes	2
Rackow et al[w32-w34]	Septic and hypovolaemic shock	26	6% hydroxyethylstarch; 5% albumin	0.9% NaCl	To discharge	Yes	2
Metildi et al[w35]	Adult respiratory distress syndrome	46	50% albumin salt-poor serum in Ringer's lactate	Ringer's lactate	To discharge	Yes	2
Pockaj et al[w36]	Vascular leak syndrome	107	5% albumin in 154 mEq/l NaCl	0.9% normal saline with 154 mEq/l NaCl	Unspecified	No	2

*For list of references see longer version of article on our website www.bmj.com.

of 7% (−1% to 15%). The regression approach to funnel plot asymmetry yielded an intercept of 0.006 and P = 0.308, indicating no statistical evidence for publication bias.

Discussion

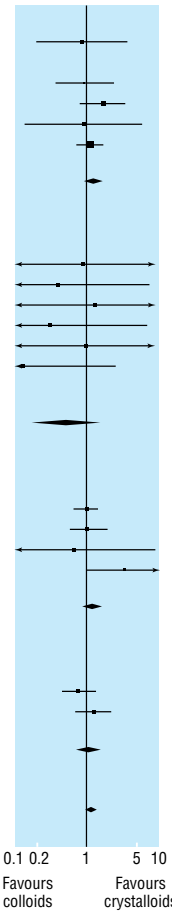
This systematic review synthesised the evidence from randomised controlled trials comparing colloid and crystalloid fluid resuscitation across a wide variety of clinical conditions. There was no statistical evidence of heterogeneity in trial results. The pooled relative risks showed no advantage for resuscitation with colloids, and when we excluded trials with inadequate allocation concealment the pooled relative risk shifted to increased mortality for colloids compared with crystalloids (relative risk 1.29 (95% confidence interval 0.94 to 1.77)).

There was no statistical evidence that the effect measure for colloids compared with crystalloids was overestimated because of publication bias. Although the regression test of asymmetry has been shown to have predictive validity,[12] the few trials in our meta-analysis (19 trials) may mean that detection of such biases would be difficult. Assuming that colloids were the "intervention," publication bias would have resulted in a pooled estimate that understated the extent to which colloids were associated with increased mortality.

Limitations of study

In common with all meta-analyses, our systematic review may have included studies in which interventions and patient characteristics were sufficiently incomparable that the calculation of a summary effect measure may be questioned. The resuscitation regimen differed between trials, with some trials randomising participants to an initial quantity of colloid or crystalloid and then proceeding with some form of standard resuscitation for all participants, and other trials resuscitating with the randomised fluid to predetermined end points, either resuscitation end points or, in the case of trauma, until corrective surgery. In addition, the type of colloid or crystalloid, the concentration, and the protocol to determine the quantity of fluid varied.

Type of injury	No of deaths: Colloids	No of deaths: Crystalloids	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Trauma					
Lowe et al[w1-w3]	3/77	4/94		2.8	0.92 (0.21 to 3.97)
Modig[w4 w5]	0/14	0/17		0.0	
Younes et al[w7]	7/35	7/35		5.5	1.00 (0.39 to 2.55)
Vassar et al[w8]	21/89	11/85		8.9	1.82 (0.94 to 3.55)
Nagy et al[w6]	2/21	2/20		1.6	0.95 (0.15 to 6.13)
Vassar et al[w9]	49/99	20/50		20.9	1.24 (0.83 to 1.83)
Subtotal	82/335	44/301		39.8	1.30 (0.95 to 1.77)
$\chi^2 = 1.68$ (df = 4)					
Surgery					
Virgilio et al[w13]	1/15	1/14		0.8	0.93 (0.06 to 13.54)
Boutros et al[w12]	0/7	2/17		1.2	0.45 (0.02 to 8.34)
Grundmann et al[w14 w15]	1/14	0/6		0.5	1.40 (0.06 to 30.23)
Karanko et al[w16 w17]	0/18	1/18		1.2	0.33 (0.01 to 7.68)
Dawidson et al[w20]	1/10	1/10		0.8	1.00 (0.07 to 13.87)
Tollosfrud et al[w23]	0/30	1/10		1.7	0.12 (0.01 to 2.69)
Wahba et al[w24]	0/11	0/11		0.0	
Subtotal	3/105	6/86		6.3	0.55 (0.18 to 1.65)
$\chi^2 = 1.75$ (df = 5)					
Burns					
Bocanegra et al[w25]	30/74	30/79		22.9	1.07 (0.72 to 1.58)
Hall et al[w26]	18/86	16/86		12.6	1.12 (0.62 to 2.06)
Jelenko et al[w27-w30]	1/7	1/5		1.4	0.71 (0.06 to 8.91)
Goodwin et al[w31]	11/40	3/39		2.4	3.57 (1.08 to 11.85)
Subtotal	60/207	50/209		39.2	1.21 (0.88 to 1.66)
$\chi^2 = 4.63$ (df = 3)					
Other					
Rackow et al[w32-w34]	11/18	6/8		6.5	0.81 (0.47 to 1.40)
Metildi et al[w35]	12/20	12/26		8.2	1.30 (0.75 to 2.25)
Subtotal	23/38	18/34		14.8	1.08 (0.73 to 1.61)
$\chi^2 = 1.48$ (df = 1)					
Total	168/685	118/630		100.0	1.19 (0.98 to 1.45)
$\chi^2 = 11.67$ (df = 16)					



Relative risks (95% confidence intervals) of death associated with fluid resuscitation with colloid solutions compared with resuscitation with crystalloid solutions

Despite these differences, all participants were in need of volume replacement, and we believe that further "fine tuning" of the intervention would have affected the size of the effect rather than its direction. Although we stratified the analyses by type of injury for which fluid resuscitation was required, these categories are crude and potentially relevant clinical conditions such as uncontrolled haemorrhage or increased capillary permeability might vary widely across and within studies. While this problem could be overcome by analyses of individual patient data from all of the trials, this may not be appropriate as there was little unexplained heterogeneity in the results.

Other studies

Our results differ from those of Velanovich's meta-analysis of mortality, which concluded that resuscitation with colloids had a beneficial effect on mortality among non-trauma patients compared with crystalloids.[7] This conclusion was based on three studies of a total of 96 non-trauma patients. Our meta-analysis, based on more than twice the number of patients undergoing surgery (191), failed to support this conclusion. For patients with burns, we also found no evidence for a beneficial effect of colloids. The effect measure for surgery was extremely imprecise, owing to the small number of patients and a low event rate.

Key messages

- For decades there has been controversy over the relative benefits of colloid and crystalloid solutions for fluid resuscitation of hypovolaemic patients
- Although more expensive than crystalloids, use of colloids far exceeds current recommendations
- In this systematic review of randomised controlled trials we found that, compared with crystalloids, use of colloids was associated with an increase in absolute risk of mortality of 4%
- There was no evidence for differences of effect among different types of injury necessitating fluid resuscitation

Conclusions

Resuscitation with colloid solutions was associated with an absolute increase in the risk of mortality of 4% (95% confidence interval 0% to 8%), or four extra deaths for every 100 patients resuscitated. As colloids are not associated with improved survival and are considerably more expensive than crystalloids, it is hard to see how their continued use outside randomised controlled trials in subsets of patients of particular concern can be justified.

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Contributors: GS designed the protocol, undertook the literature searches, discussed core ideas about the study design and interpretation of results, and jointly wrote the paper. IR initiated the project, participated in all aspects of the research, and jointly wrote the paper. IR is guarantor for the paper.

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Conflict of interest: None.

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Is day care equivalent to inpatient care for active rheumatoid arthritis? Randomised controlled clinical and economic evaluation

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Abstract

Objective: To test the clinical equivalence and resource consequences of day care with inpatient care for active rheumatoid arthritis.
Design: Randomised controlled clinical trial with integrated cost minimisation economic evaluation.
Setting: Rheumatic diseases unit at a teaching hospital between 1994 and 1996.
Subjects: 118 consecutive patients with active rheumatoid arthritis randomised to receive either day care or inpatient care.
Main outcome measures: Clinical assessments recorded on admission, discharge, and follow up at 12 months comprised: the health assessment questionnaire, Ritchie articular index, erythrocyte sedimentation rate, hospital anxiety and depression scale, and Steinbrocker functional class. Resource estimates were of the direct and indirect costs relating to treatment for rheumatoid arthritis. Secondary outcome measures (health utility) were ascertained by time trade off and with the quality of well being scale.
Results: Both groups had improvement in scores on the health assessment questionnaire and Ritchie index and erythrocyte sedimentation rate after hospital treatment ($P < 0.0001$) but clinical outcome did not differ significantly between the groups either at discharge or follow up. The mean hospital cost per patient for day care, £798 (95% confidence interval £705 to £888), was lower than for inpatient care, £1253 (£1155 to £1370), but this difference was offset by higher community, travel, and readmission costs. The difference in total cost per patient between day care and inpatient care was small (£1789 (£1539 to £2027) *v* £2021 (£1834 to £2230)). Quantile regression analysis showed a cost difference in favour of day care up to the 50th centile (£374; £639 to £109).
Conclusions: Day care and inpatient care for patients with uncomplicated active rheumatoid arthritis have equivalent clinical outcome with a small difference in overall resource cost in favour of day care. The choice of management strategy may depend increasingly on convenience, satisfaction, or more comprehensive health measures reflecting the preferences of patients, providers, and service commissioners.

Introduction

Admission to hospital for treatment of active rheumatoid arthritis has been shown in controlled trials to be more effective than intensive outpatient care.[1–4] The information available, however, is insufficient to assess whether inpatient care is more cost effective than management strategies that use outpatient or day care.

In an earlier pilot study we showed that day care, which preserves the benefits of multidisciplinary care, is acceptable to patients and might be less costly than inpatient care.[5] The study was too small to draw firm conclusions regarding differences in clinical outcome, but the results suggested that day care did not compromise outcome.

Using a randomised controlled clinical trial with an integrated cost minimisation economic evaluation, we tested the hypothesis that inpatient and day care management of patients with uncomplicated active rheumatoid arthritis are clinically equivalent and that the resources needed are equivalent.

Subjects and methods

Subjects

A total of 118 consecutive patients attending the rheumatic diseases unit, for whom admission for management of active rheumatoid arthritis was indicated, were randomised to either day care or inpatient care. The basic criterion for admission was active rheumatoid arthritis, defined as deteriorating functional status, active synovitis, the need for review of second line drug regimen, and the need for physical or psychological treatment.

Exclusion criteria were medical complications of rheumatoid arthritis requiring immediate hospitalisation; inpatient care specifically requested by the general practitioner; and inability to reach hospital by 10 am, when the programme started. The method of randomised consent was used.[5 6] Sealed envelopes containing random treatment assignments were used to allocate individual treatments. Results were analysed on the basis of intention to treat. Ethical approval had been obtained for the study.

Patient management protocols

Multidisciplinary care and medication were left to the discretion of the attending doctor. Whereas inpatients were treated during one continuous episode until discharge, day patients received treatent in hospital between 10 am and 4 pm, interspersed with periods at home, where they followed prescribed treatment. Patients were assessed twice each week, and treatment ended when there was no further clinical improvement. The intensity of hospital based and primary care intervention was recorded. If subsequently there was relapse of disease requiring admission, the patient remained in his or her original group and resumed treatment. At the conclusion of the study all patients were requested to state whether they would prefer day care or inpatient care for future flares of active rheumatoid arthritis.

Clinical assessments

Disability, measured with the modified health assessment questionnaire,[7] the Ritchie index,[8] and erythro-

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cyte sedimentation rate (Westergren method); psychological status, measured with the hospital anxiety and depression scale[9]; and Steinbrocker functional class[10] were recorded on admission, discharge, and 12 month follow up. Secondary outcome measures were health utility, measured using the method of time trade off[11] and the quality of well being scale.[12]

Economic assessments

Costs were measured from the perspective of the health service and the patient. They comprised the direct costs of hospital based and community care intervention, transport costs, and the indirect costs incurred by patients involving forgone production as measured by cost of wages.[5] A unit cost per day was calculated for each group; this consisted of patient care costs (salaries, medication and investigations), patient services (catering, laundry), overheads (energy consumption, capital charge, maintenance), and opportunity cost. The total hospital cost was then derived by multiplying the number of days of hospital treatment by the appropriate unit cost. Community costs consisted of costs of attending the general practitioner's surgery, practice or district nursing, and paramedical services; for social support and domestic help; and for drugs not supplied on prescription. Transport details, including distance from home to hospital and to the surgery, number of journeys made, and method of travelling were recorded. Costs were based on total distance by ambulance car. Use of resources in the community and changes in employment status reported by the patient were verified by interviewing all patients. Primary care records were checked on a random sample of 10 patients in each group.

Table 1 Clinical and socioeconomic characteristics of patients with active rheumatoid arthritis

Characteristics	Day patients (n=56)	Inpatients (n=57)	Unable to travel (n=60)
Median (range) age (years)	59 (28-78)	55.5 (31-78)	57 (25-76)
Median (range) duration of disease (years)	6 (0.1-34)	4 (0.1-33)	8 (0.5-40)
No of women	40	41	47
No of patients with erosions	28	33	48
Steinbrocker class II	21	19	25
Steinbrocker class III	35	38	30
No living alone	10	13	37
No in paid employment	13	11	13
No unemployed	12	6	10
No on sick leave	2	5	2
No medically retired	12	15	11
No retired	17	16	22

Table 2 Description of treatment for active rheumatoid arthritis

Treatment	Day patients (n=56)	Inpatients (n=57)
Intra-articular steroid injections:		
No of patients	51	50
No of injections	148	120
Second line therapy:		
Started or restarted	26	27
Changed	15	18
Dose increased	7	10
Rheumatology outpatient visits	69	56
Community service visits:		
General practitioner	588	828
Practice nurse	703	800
District nurse	97	68
Physiotherapist	65	4
Occupational therapist	42	27
Chiropodist	73	43
Orthotist	4	4

Statistical and economic analysis

To test clinical equivalence, the largest acceptable clinical differences in outcome between groups were chosen as >0.25 points on the health assessment questionnaire (the main outcome measure), >20 mm/h difference in erythrocyte sedimentation rate, or >3 points on either the anxiety or depression scale of the hospital anxiety and depression scale. A total sample size of 105 patients was required to detect this difference in the health assessment questionnaire, between unpaired groups, with a power of 90% at the $P<0.05$ level (two tailed test).

Repeated measures analysis of variance were applied to data obtained at admission, discharge, and 12 month follow up to establish whether there were significant differences over time and between day patients and inpatients. Multivariate models were also used to explore the effect of baseline variables on outcome.

The clinical and economic evaluations were integrated in the trial design and execution.[13] The cost minimisation technique[14] for the economic evaluation followed published decision rules for cost effectiveness analysis.[15] The equivalence trial design to test the null hypothesis of no significant difference in outcomes[16] was followed, using a range of specific clinical assessments and health related utility measures.

The distribution of resource outcomes was compared by using generalised quantile regression to estimate cost quartiles, conditional on inpatient or day patient treatment. The impact of heteroskedasticity on standard errors and confidence intervals of coefficients was considered by comparing estimates based on analytical methods and bootstrap resampling.[17] Non-parametric bootstrap methods[18 19] were also used to calculate confidence intervals for arithmetic means of total resource use. All confidence intervals are based on 1000 bootstrap replications.[20]

Results

Analysis of admissions

Between May 1993 and January 1995, 557 rheumatology outpatients who required admission to hospital and were screened for the study. Of the 200 patients with active rheumatoid arthritis, 118 satisfied the entry criteria and were randomised to receive day care (59 patients) or inpatient care (59 patients). Sixty patients were unable to travel and 22 had medical complications. In each group, 51 patients completed the trial and eight were lost to follow up. During the study 11 day patients transferred to inpatient care, five owing to travelling difficulties, two for clinical reasons, two for domestic reasons, and two out of preference. Two inpatients requested day patient care and were transferred. The groups did not differ significantly in the baseline clinical and socioeconomic characteristics (table 1).

The mean duration of the initial hospital treatment episode was similar for day patients (13.2 days) and inpatients (13.6 days). Twelve day patients and seven

inpatients required readmission. The mean duration of readmission was similar for day patients (11.6 days) and inpatients (12.7 days). The mean number of days in which a bed was actually occupied during the initial treatment episode was significantly less for day patients (8.8 days) than inpatients (13.6 days); this is accounted for by day patients spending part of the treatment episode at home. Table 2 shows the hospital and community treatment received.

Clinical evaluation

On admission the erythrocyte sedimentation rate, Ritchie index, and hospital anxiety and depression scale scores were similar in the two groups, but day patients were slightly more disabled on the health assessment questionnaire score ($P = 0.04$, unpaired t test) (table 3). The erythrocyte sedimentation rate, health assessment questionnaire, and Ritchie index scores differed significantly over time ($P < 0.0001$, analysis of variance) but did not differ significantly between inpatients and day patients. Substantial improvement in disability (health assessment questionnaire), joint score (Ritchie index) and erythrocyte sedimentation rate were seen in both day patients and inpatients between admission and discharge ($P < 0.0001$, analysis of variance). Although small differences were observed in hospital anxiety and depression scale depression scores, these were not considered to be of clinical importance. During follow up after discharge from hospital, the health assessment questionnaire and Ritchie index scores deteriorated significantly in both groups ($P < 0.0001$, analysis of variance), but the erythrocyte sedimentation rate and the hospital anxiety and depression scale score did not ($P > 0.5$). The difference in health assessment questionnaire and Ritchie index remained highly significant after baseline variables were included as covariates in the models (table 3). Thus the groups showed equivalent clinical improvement with the initial hospital treatment and similar deterioration over the next year.

At baseline there was no significant difference in health utility between day patients and inpatients as recorded by time trade off or the quality of well being scale ($P > 0.1$, unpaired t test). Over the 12 months of follow up, both scores improved significantly ($P = 0.025$ and $P = 0.001$, respectively; analysis of variance), and were similar in day patients and inpatients. The magnitude of change in these measures was small and the clinical significance is uncertain (table 3).

Economic evaluation

The mean hospital cost per patient for day care, £798 (95% confidence interval £705 to £888), was lower than for inpatient care, £1253 (£1155 to £1370), but this difference was offset by higher community, travel and readmission costs. The difference in total cost per patient between day care and inpatient care was therefore small (£1789 (£1539 to £2027) *v* £2021 (£1834 to £2230)) (table 4).

The cost difference between day patients and inpatients was further examined using quantile regression (table 5). The cost quartiles for inpatient care are given by the coefficient reported for inpatient care. The sum of the inpatient and day patient coefficients provide an estimate of the cost quartiles for day patient care. The coefficients reported for the day patient group, which also represent the difference between day patients and inpatients, are negative at the 25th and 50th centiles and significantly different from zero. The cost differential, while still in favour of day patient care, diminishes towards the upper end of the distribution, as indicated by the small absolute difference at the 75th centile of around 5% in overall costs.

During the 12 month follow up, none of the 23 day patients and 27 inpatients who were previously on sick leave or medically retired due to rheumatoid arthritis resumed active paid employment. Of those in full time

Table 3 Summary of clinical outcome data. Values are means (SD) determined by repeated measures analysis of variance corrected for baseline scores

Variable	Admission	Discharge	Follow up after 12 months
Ritchie index*			
Day patients	27 (15.2)	15.2 (11.6)	22.4 (12.3)
Inpatients	27 (14.5)	17.6 (11.7)	20.6 (10.1)
Erythrocyte sedimentation rate*			
Day patients	54 (34)	36 (32)	33 (27)
Inpatients	48 (32)	33 (28)	33 (25)
Score on health assessment questionnaire*			
Day patients	1.74 (0.42)	1.37 (0.65)	1.63 (0.6)
Inpatients	1.54 (0.44)	1.28 (0.57)	1.47 (0.55)
Anxiety (hospital anxiety and depression scale)			
Day patients	7.7 (3.4)	6.2 (3.5)	7.0 (4.5)
Inpatients	7.8 (4.2)	7.6 (4.3)	7.7 (4.6)
Depression (hospital anxiety and depression scale)			
Day patients	7.2 (3.0)	5.8 (3.0)	6.1 (3.5)
Inpatients	7.4 (3.5)	6.9 (3.8)	6.9 (4.1)
Score on quality of well being scale†			
Day patients	0.49 (0.05)	—	0.51 (0.06)
Inpatients	0.49 (0.06)	—	0.51 (0.05)
Score for time trade off†			
Day patients	0.76 (0.29)	—	0.80 (0.27)
Inpatients	0.66 (0.32)	—	0.76 (0.30)

*No significant difference (P>0.05) over time between day patients and inpatients for any of the variables, but significant improvement in erythrocyte sedimentation rate, health assessment questionnaire, and Ritchie index between admission and discharge (P<0.0001) and subsequent deterioration in health assessment questionnaire and Ritchie index between discharge and follow up (P<0.0001).
†Significant improvement between admission and follow up at 12 months (P<0.0001) for both groups but no difference between day patients and inpatients.

Table 4 Mean (95% confidence interval) resource costs (£/patient) by treatment regimen and resource category

Resource category	Day patients	Inpatients
Hospital	798 (705 to 888)	1253 (1155 to 1370)
Community	323 (247 to 463)	298 (258 to 337)
Travel	417 (370 to 472)	293 (251 to 340)
Readmission	218 (96 to 384)	143 (38 to 306)
Total	1789 (1539 to 2027)	2021 (1834 to 2230)

Table 5 Quantile regression comparing total costs of inpatient and day care

	Coefficient	95% CI *
25th centile:		
Inpatient	1635	1447 to 1823
Day patient	–364	–647 to –82
50th centile:		
Inpatient	1930	1717 to 2143
Day patient	–374	–639 to –109
75th centile:		
Inpatient	2271	1929 to 2613
Day patient	–121	–769 to 527

*Based on standard errors estimated using bootstrap resampling.

employment at entry to the study, only two of the six inpatients and five of the eight day patients continued full time work. Of those in part time work, none of the five inpatients and two of the five day patients continued in work.

At the end of the study 31 (62%) of the day patients and 21 (42%) of the inpatients (52% overall) expressed a preference to be a day patient in the future.

Discussion

This study has shown that the clinical outcome of day care for patients with active rheumatoid arthritis is equivalent to that of inpatient care, but there is a small reduction in resource cost. This finding may be relevant to other medical specialties in which day care is a possibility.

Several randomised studies have confirmed the clinical benefit of multidisciplinary inpatient care for active rheumatoid arthritis,[1–3] which was suggested by earlier unrandomised studies.[4] However, the cost of such treatment has restricted its application, and more cost effective strategies have been sought. Three studies that compared inpatient care with outpatient care concluded that inpatient care gave the better clinical outcome.[2–4] Only one randomised study included a complete economic evaluation, and it found that inpatient care was more cost effective than outpatient care.[3]

In Canada a randomised controlled trial comparing inpatient with day care for active rheumatoid arthritis used similar inclusion criteria to our own study.[21] As in our study, functional outcomes were not significantly different between the groups at discharge.

Duration of benefit

There is conflicting evidence regarding the duration of benefit after intensive medical intervention for active rheumatoid arthritis. Our study and most others suggest that improvement is short term. This may reflect inadequate outpatient care rather than a shortcoming of the initial intervention. Nevertheless, for the expenditure on intensive intervention to be economically and clinically worthwhile it is crucial that benefits are maintained for as long as possible. Guidelines on the management of rheumatoid arthritis have been published recently, and these emphasise the importance of regular, long term follow up.[22 23] Although implementing these recommendations may require additional resources, failure to preserve the benefits of intensive intervention may also carry heavy financial penalties in terms of greater subsequent demand for health care, particularly orthopaedic surgery, earlier loss of independence, and loss of productivity. Further controlled trials are needed to test the effectiveness of these recommendations.

Financial considerations

Financial rather than clinical considerations have driven many of the recent changes in the delivery of health care in Britain, and it is appropriate to consider whether the benefits of inpatient treatment for active rheumatoid arthritis could be achieved in a more cost effective way.[24] This study shows that day care is only slightly more cost effective than inpatient care. It is also uncertain whether the potential savings from implementing a day care facility and freeing beds would be realised in practice; a day patient unit would probably generate additional workload and the spare inpatient capacity would be redeployed.

Key messages

- Day care and conventional inpatient care are clinically equivalent for patients with active rheumatoid arthritis
- The overall resource costs of day care are slightly lower than those of inpatient care
- Day care is associated with lower hospital costs but higher costs to patient and family; nevertheless half of all patients studied expressed a preference for day care
- Clinical benefit from either day care or inpatient care is short lived

Day care has been shown to be cost effective for selected patients in other specialties,[25–27] but our study shows that one consequence of implementing this model for active rheumatoid arthritis might be to transfer costs from the hospital sector to patients and their families. Whether this is reasonable for patients with chronic disease, who are already subject to adverse social, health, and economic consequences, is questionable.

This and other studies highlight the failure to maintain improvements in health after intensive medical intervention and a failure to reduce patients' incapacity for work. Further prospective controlled evaluation is needed to show that improved outpatient care as has been recommended[22 23] is of benefit in these respects.

Contributors: CML and NPH had the original idea for the study. Together they developed the protocol, coordinated the trial, and analysed the clinical data. JFF contributed to the discussion of core ideas, helped design te protocol, and analyed the economic data. AL contributed to the discussion of core ideas and supervised the database design and data collection. MM collected the clinical and economic data. GN contributed to the discussion of core ideas, helped to develop the protocol, and edited the manuscript. The paper was written by CML, NPH, and JFF. CML is guarantor for the paper.

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Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials

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Abstract

Objective: To evaluate the effect of heparin on duration of catheter patency and on prevention of complications associated with use of peripheral venous and arterial catheters.
Design: Critical appraisal and meta-analysis of 26 randomised controlled trials that evaluated infusion of heparin intermittently or continuously. Thirteen trials of peripheral venous catheters and two of peripheral arterial catheters met criteria for inclusion.
Main outcome measures: Data on the populations, interventions, outcomes, and methodological quality.
Results: For peripheral venous catheters locked between use flushing with 10 U/ml of heparin instead of normal saline did not reduce the incidence of catheter clotting and phlebitis or improve catheter patency. When heparin was given as a continuous infusion at 1 U/ml the risk of phlebitis decreased (relative risk 0.55; 95% confidence interval 0.39 to 0.77), the duration of patency increased, and infusion failure was reduced (0.88; 0.72 to 1.07). Heparin significantly prolonged duration of patency of radial artery catheters and decreased the risk of clot formation (0.51; 0.42 to 0.61).
Conclusions: Use of intermittent heparin flushes at doses of 10 U/ml in peripheral venous catheters locked between use had no benefit over normal saline flush. Infusion of low dose heparin through a peripheral arterial catheter prolonged the duration of patency but further study is needed to establish its benefit for peripheral venous catheters.

Introduction

Almost all patients admitted to hospital require a peripheral intravenous catheter to provide access for administration of drugs and fluids and parenteral nutrition. In addition, many critically ill patients require arterial catheterisation for haemodynamic monitoring and blood sampling. Maintenance of the patency of these indwelling catheters is important for minimising patients' discomfort and the expense associated with replacement. Vascular thrombosis,[1] visible scarring, and infection related to the catheter[2] are complications associated with use of these indwelling vascular devices.

The anticoagulant properties of heparin led clinicians to use heparin flushes or heparinised infusion in an attempt to prevent thrombus formation and to prolong the duration of catheter patency. The effective dose of heparin, however, has not been clearly established for venous and arterial catheters. Two meta-analyses evaluating use of heparin flush solutions for peripheral intermittent infusion devices concluded that the effect of heparin flushes was equivalent to that of 0.9% sodium chloride flushes. Both meta-analyses combined the results of controlled and uncontrolled trials.[3 4] Goode et al included 17 studies (seven randomised controlled trials)[3] and Peterson et al included 20 studies (three randomised controlled trials).[4] Peterson et al combined trials that evaluated continuous infusion of heparinised solution with trials that assessed intermittent flushing in catheters locked between use.[4] None the less, these results led some organisations to state that sodium chloride injection should be the standard of care for maintaining intravenous catheters used for peripheral intermittent infusion.[5]

Despite its beneficial antithrombotic effects, decreasing unnecessary exposure to heparin is important to minimise the complications resulting from sensitisation. Autoimmune mediated thrombocytopenia induced by heparin occurs in about 3% of patients exposed to unfractionated heparin, which greatly

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increases the risk of thrombotic events.[6 7] Heparin induced thrombocytopenia is a risk even in newborns.[8] Other risks of heparin use include allergic reactions and the potential for bleeding complications after multiple, unmonitored heparin flushes.[5]

A large percentage of heparin exposure in patients in hospital is through heparin use in peripheral venous catheters. If the risks associated with heparin use are considered what is the benefit of using heparin in peripheral venous or arterial access devices? Individual trials of heparin in peripheral venous catheters are contradictory, and there are no systematic reviews assessing various heparin dosing strategies for arterial catheters. We therefore conducted this systematic review to resolve and synthesise the conflicting literature. We have critically appraised the clinical trials evaluating use of heparin in continuous and intermittent infusion solutions on the duration of patency of peripheral venous and arterial catheters and on phlebitic complications.

Methods

Study identification

Trials included in this review were identified by cross referencing the following MeSH terms from Medline from 1966 to April 1997: "catheterisation" and "catheters, indwelling" and "heparin" with "randomisation," "random allocation," "randomised controlled trial(s), randomised response technique," and "(controlled) clinical trials, randomised." Embase was searched from 1974 through 1996 by using the search terms "catheter" and "catheterisation, intravascular, random," and "heparin." After examining the full manuscripts of all abstracts deemed potentially relevant we reviewed the reference lists of each retrieved article and obtained the manuscript of any reference considered to be a randomised controlled trial. The trials included in two meta-analyses[3 4] were retrieved. Package inserts from catheter kits were searched for references regarding published and unpublished data. We also contacted companies manufacturing heparin bonded catheters regarding other unpublished and published randomised controlled trials. In addition, we hand searched the *National Intravenous Therapy Association Journal* from 1985 to 1992.

Study selection

The following selection criteria were used to identify studies for inclusion in this analysis: study design—randomised controlled clinical trial; population—adult or paediatric patients; intervention—heparin infused through the catheter via intermittent or continuous flush versus a control group with no heparin; outcomes—catheter patency, catheter related phlebitis, catheter thrombus, infusion failure.

We excluded studies in which over 40% of patients were excluded from analysis after randomisation.

Data abstraction

Data abstraction was conducted by two investigators; disagreement was resolved by consensus. To evaluate agreement we calculated a quadratic weighted κ for each item. Data on the number of catheters or the numbers of patients, or both, were abstracted in the form in which they were reported. Catheters were the unit of analysis when data were pooled because this was the way that most results were reported. We tried to contact authors to provide further information when the data necessary for critical appraisal or analysis, or both, were missing or unclear.

Definitions

The following definitions of terms were used. Duration of catheter patency was the number of hours the catheters were in place. Loss of patency was removal of the catheter because of inability to flush it. Catheter thrombus referred to a clot adherent to or occluding the catheter. Catheter related phlebitis indicated the presence of any one or more of the following: pain, erythema, induration, or a palpable venous cord at the catheter site. Infusion failure was loss of patency, phlebitis, or infiltration resulting in premature removal of the catheter.

Data analysis

We combined data to estimate the relative risks and associated 95% confidence intervals across studies by using the DerSimonian and Laird random effects model.[9] We tested for heterogeneity (major differences in the apparent effect of the interventions across studies) by using the method proposed by Fleiss.[9] We have reported tests of heterogeneity of variance in the results only when they were significant ($P < 0.05$).

A priori we decided to analyse the data in clinically relevant categories on the basis of similar heparin dosing strategies when sufficient data were available. This was possible for heparin flush of peripheral intravenous catheters at the most common dose of 10 U/ml and at 100 U/ml used intermittently at a minimum of 6 to 12 hour intervals. We separately examined the effect of adding 1 U/ml of heparin to continuous infusions. Because heparin bonding is only on the outside of some catheters and lasts from 30 minutes to 48 hours depending on the type of bonding used (personal communications, technical support staff, Cook, Arrow, Medcomp, Abbott, and Baxter catheter manufacturing companies) we excluded trials of heparin bonding.

Results

Study identification and selection

Twenty six trials of heparin use in peripheral venous catheters were identified in which random assignment was used, and 13 were included—12 published trials[10–21] and one unpublished (FD Craig and SR Anderson, Harrison Methodist Fort Worth Hospital, personal communication). Two trials of heparin use in peripheral arterial catheters were identified in which random assignment was used and both were included.[22 23] Three trials claiming random allocation that actually used alternate assignment or assignment by odd-even hospital number were excluded.[24–26] Five trials were excluded that randomised by hospital unit or wards instead of individual patient because only two units were randomised and a before-after design was applied within each unit.[27–31] One randomised study was excluded because all patients received 5000 U heparin subcutaneously for prophylaxis of deep

Table 1 Study design of randomised trials of heparin infusion and bonding

Author	Population	Heparin	Catheters		Methods	
			No	Gauge	Blinding	Exclusion*(%)
Peripheral venous catheters						
Kleiber et al, 1993[11]	124 Infants and children	10 U every 6 hours†	124	22,24	Double	2%
Craig et al, 1991‡	173 Adults, medical	10 U every 8 hours†	274	18-22	Double	0
Shoaf et al, 1992[12]	260 Adults, cardiac surgery	10 U every 8 hours†	260	NA	Double	15%
Ashton et al, 1990[14]	32 Adults, intensive care unit	10 U every 12 hours	321	8-22	Double	0
Hamilton et al, 1988[15]	241 Adults, medical-surgical	100 U every 8 hours†	307	18-22	Double	34%
Meyer et al, 1995[16]	65 Adults, obstetric	100 U every 6 hours†	65	18	Double	2%
Daniell et al, 1973[17]	166 Adults, coronary care	1 U/ml infused	221	18	Double	9%
Alpan et al, 1984[18]	826 Neonates, intensive care unit	1 U/ml infused	227	22	Double	0
Wright et al, 1995[20]	80 Children, medical	1 U/ml infused	80	22, 24	Double	0
Moclair et al, 1991[10]	16 Adults, surgical	1 U/ml infused	16	18	Double	0
Sketch et al, 1972[21]	Adults, coronary care	1 U/ml infused	239	NA	Double	NA
Messing et al, 1985[19]	65 Adults, medical-surgical	1 U/ml infused	65	NA	Double	0
Tanner et al, 1980[13]	72 Adults, surgical	1 U/ml infused	72	NA	None	0
Peripheral arterial catheters						
Clifton et al, 1991[22]	30 Adults, intensive care unit	4 U/ml normal saline	30	20	Double	0
AACC Nurses, 1993[23]	5139 Adults, medical-surgical	Variable	5139	18-22	None	2%

*Patients excluded after randomisation; catheters included in analysis after randomisation.
†Flush solution (control or heparin) used after medications in addition to or in place of scheduled flush.
‡Craig FD, Anderson SR. Comparison of normal saline versus heparinised saline in the maintenance of intermittent infusion devices. Harrison Methodist Fort Worth Hospital. Unpublished.
NA=data not available.

venous thrombosis.[32] Three randomised studies were excluded because more than 40% of observations were not reported after randomisation.[33–35] One randomised study was excluded because only half the patients were randomised and the rest were allocated to treatment arms at the discretion of the physician.[36] The authors of one unpublished trial were unable to provide the necessary primary data (N Bell, D Brown, L Poon, Eden Hospital Medical Centre, California, personal communication). One randomised trial of peripheral venous catheters was performed in patients treated with cephalothin[37] and another was done in patients receiving a lignocaine infusion,[38] both of which are associated with higher rates of phlebitis leading us to exclude these trials from our analysis. We were unable to include the results of one unpublished randomised study because they reported the number of events per patient, many of whom had more than one catheter, and the primary author could not re-extract the data (A Kasparek, J Wenger, R Feldt, Mercy Medical Centre, Iowa, personal communication).

Trial characteristics and assessment of quality

The populations, interventions, number of patients, number of catheters, catheter gauges used, and methodological characteristics of the studies included in the final analysis are described in table 1. For peripheral venous catheters, intermittent heparin flushes varied from 10 U/ml to 100 U/ml and continuous heparin infusion was 1 U/ml. In the trial by Moclair et al all patients received a glyceryl trinitrate transdermal patch and twice daily application of hydrocortisone cream to the infusion site in an attempt to prolong vein survival and decrease phlebitis.[10] The doses of heparin used in trials evaluating continuous flush in arterial catheters varied, and the actual dose was not reported in the largest trial as it was an effectiveness study of any amount of heparin versus no heparin.[23]

Four trials evaluated multiple catheter insertions in a single patient. Two of these trials evaluated intermittent heparin flushes at 10 U every 8 hours (FD Craig and SR Anderson, Harrison Methodist Fort Worth Hospital, personal communication) and 100 U every 8 hours[15] with 274 catheters in 173 patients and 307 catheters in 241 patients, respectively. The other two trials evaluated use of 1 U of heparin per ml of infusion with 226 catheters in 26 neonates[18] and 221 catheters in 166 adult patients.[17] Three trials were in infants and children[11 18 20] and 12 were in adult patients.

Design features and methodological characteristics of the 15 published studies included in this review are described in table 1. Agreement regarding data abstraction was good (quadratic weighted κ of 0.72 to 1.00).

Duration of catheter patency

Table 2 shows the effect of heparin on duration of catheter patency in six trials. We were unable to pool the results because of differences in reporting. The two trials of intermittent heparin flushes at concentrations of 10 U/ml[11] and 100 U/ml[15] showed no effect on duration of catheter patency. Two trials showed that heparin added to the infusion to make a concentration

Table 2 Effect of heparin on duration of peripheral venous catheter patency. Figures are means with or without SD unless stated otherwise

Author	Heparin	Patency duration (hours)		Difference (hours) for heparin − control
		Heparin	Control	
Kleiber et al, 1993[11]	10 U every 6 hours*	38.2 (40)	35.4 (30)	2.8
Hamilton et al, 1988[15]	100 U every 8 hours*	44.3 (19)	45.4 (18)	–0.9
Daniell et al, 1973[17]	1 U/ml infused	88.5	57.6	30.9
Alpan et al, 1984[18]	1 U/ml infused	58.7 (45)	26.1 (20)	32.6†
Wright et al, 1995[20]	1 U/ml infused	97‡	43‡	54.0†
Moclair et al, 1991[10]	1 U/ml infused	69‡	31‡	38.0

*Flush solution (control or heparin) used after medications in addition to or in place of scheduled flush.
†Authors report P<0.05.
‡Medians.

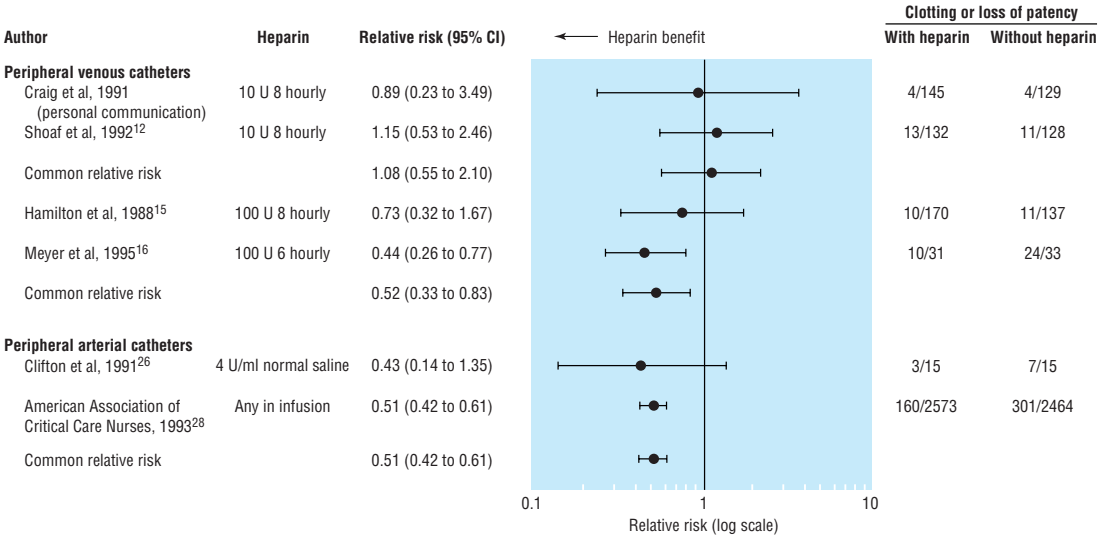

Fig 1 Relative risks (95% confidence intervals) for catheter clot formation in and loss of patency of peripheral venous and arterial catheters according to treatment with or without heparin. Last two columns are numbers of catheters with clots/total number of catheters

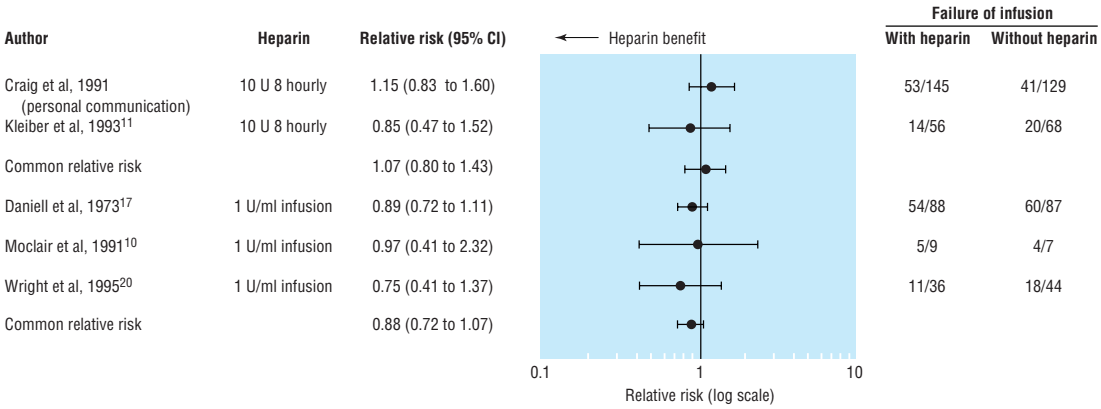

Fig 2 Relative risks (95% confidence intervals) for failure of infusion in peripheral venous catheters according to treatment with or without heparin. Last two columns are numbers of catheters with failure of infusion/total number of catheters

of 1 U/ml effectively prolonged peripheral venous catheter patency[18 20] and two trials showed non-significant trends in the direction of benefit.[10 17] The results could not be pooled because not all investigators reported the standard deviation around the mean and some reported the median. In peripheral arterial catheters, heparin significantly prolonged the duration of catheter patency in two trials,[22 23] although investigators reported the percentage of catheters patent at 72 hours (4 U/ml normal saline; 90% of heparin catheters *v* 79% of control catheters; difference 11%; $P<0.05$[23]) and 96 hours (variable dose; 86% *v* 52%; difference 34%; $P<0.01$[22]) and not the average number of hours catheters were patent.

Catheter clotting and loss of patency

Figure 1 shows that use of 10 U intermittent heparin flushes had no effect on catheter clotting compared with normal saline when the results of two trials were pooled (FD Craig and SR Anderson, Harrison Methodist Fort Worth Hospital, personal communication, and Shoaf and Oliver[12]). At doses of 100 U/ml flushed every 6 or 8 hours heparin was associated with a significantly lower loss of catheter patency when the results of two trials were pooled.[15 16] Heparinised infusion significantly decreased loss of patency in arterial catheters when the results of two trials were pooled.[22 23]

Infusion failure

Figure 2 shows that use of intermittent 10 U heparin flushes had no effect on infusion failure rates for peripheral intravenous catheters when the results of two trials were pooled (FD Craig and SR Anderson, Harrison Methodist Fort Worth Hospital, personal communication, and Shoaf and Oliver[12]). Addition of heparin at a concentration of 1 U/ml to the infusion was associated with a reduced risk of infusion failure when the results of three trials were pooled.[10 17 20]

Catheter related phlebitis

Figure 3 shows that there was a significant difference in the risk of phlebitis when the results of three trials of 10 U/ml intermittent heparin flushes versus normal saline were pooled (FD Craig and SR Anderson, Harri-

son Methodist Fort Worth Hospital, personal communication).[11 14] When the results of two trials of 100 U/ml of intermittent heparin flush were pooled phlebitis was significantly decreased.[15 16] The test of homogeneity, however, was significant (P = 0.0006) for the decreased risk of phlebitis, with one trial that used 100 U/ml every 6 hours[16] showing a much larger but non-significant trend in the direction of heparin being beneficial than the trial that used 100 U/ml every 8 hours.[15] When the data from seven trials of heparin at concentrations of 1 U/ml infusion flushed continuously through the catheter were pooled (see figure 2) there was a significant decrease in phlebitis with use of heparin.

Discussion

Use of heparin as an antithrombotic agent in catheters has been widespread for over 20 years. Despite almost universal use, the benefit of heparin has not been firmly established. Half of the available trials claiming to be randomised had to be excluded because of quality considerations or the presence of potentially confounding cointerventions. The evidence supporting use of heparin in peripheral arterial catheters comes mainly from one large (5139 patients) randomised trial including 198 sites in which various heparin dosing strategies were used.[23] The limited evidence available suggests that use of heparin as an intermittent flush solution at a concentration of 10 U/ml in catheters locked between episodes of use is not beneficial. Use of heparin in peripheral arterial catheters will prolong their life and utility. Current evidence does not allow us to make firm conclusions regarding the benefit of adding heparin to the solutions infused continuously through peripheral venous catheters, but this intervention warrants further study.

Use of heparin in peripheral venous catheters

Our meta-analyses included three randomised controlled trials of intermittent heparin flushes and seven randomised controlled trials of continuous infusion of heparinised solution that were not included in the two previously published meta-analyses.[3 4] Our finding that heparin at doses if 10 U/ml for intermittent flushing is no more beneficial than flushing with normal saline alone is in agreement with the results of these meta-analyses, which combined controlled and uncontrolled studies.[3 4] This intervention has been evaluated in only four truly randomised controlled, double blind trials including a total of 652 catheters. These trials involved different populations and evaluated different outcomes. Added to the larger number of uncontrolled studies, however, the weight of the evidence supports discontinuation of use of 10 U/ml heparin flush in intermittent intravenous infusion devices.

Heparin at 100 U/ml used as an intermittent flush solution in locked catheters may increase catheter patency and may decrease catheter related phlebitis. The usual heparin dose of 10 U/ml was established from a study in dogs,[39] and, although later studies confirmed the safety of this dose, the efficacy in maintaining catheter patency was not established. The safety and efficacy of heparin concentrations of 100 U/ml used as an intermittent flush needs further study on a wider variety of patients; the study showing a significant benefit for increasing patency and decreasing phlebitis was in obstetric patients with 18 gauge catheters for serial phlebotomy[16] and the other trial in

Author	Heparin	Relative risk (95% CI)	Phlebitis from catheter: With heparin	Phlebitis from catheter: Without heparin
Ashton et al[14]	10 U 12 hourly	1.00 (0.02 to 47.56)	0/16	0/16
Craig et al, 1991 (personal communication)	10 U 8 hourly	1.23 (0.81 to 1.86)	40/145	29/129
Kleiber et al, 1993[11]	10 U 8 hourly	0.85 (0.47 to 1.52)	14/56	20/68
Common relative risk		1.09 (0.77 to 1.52)		
Hamilton et al, 1988[15]	100 U 8 hourly	0.68 (0.46 to 0.99)	35/135	38/99
Meyer et al, 1995[16]	100 U 6 hourly	0.15 (0.02 to 1.17)	1/31	7/33
Common relative risk		0.61 (0.42 to 0.88)		
Sketch et al, 1972[21]	1 U/ml infusion	0.68 (0.35 to 1.29)	10/71	35/168
Daniell et al, 1973[17]	1 U/ml infusion	0.60 (0.41 to 0.89)	26/88	42/86
Tanner et al, 1980[13]	1 U/ml infusion	0.16 (0.05 to 0.49)	3/36	19/36
Alpan et al, 1984[18]	1 U/ml infusion	0.33 (0.14 to 0.79)	6/105	21/122
Messing et al, 1991[19]	1 U/ml infusion	0.44 (0.19 to 1.01)	6/32	14/33
Moclair et al, 1991[10]	1 U/ml infusion	1.17 (0.26 to 5.19)	3/9	2/7
Wright et al, 1995[20]	1 U/ml infusion	0.75 (0.52 to 1.08)	19/36	31/44
Common relative risk		0.55 (0.39 to 0.77)		

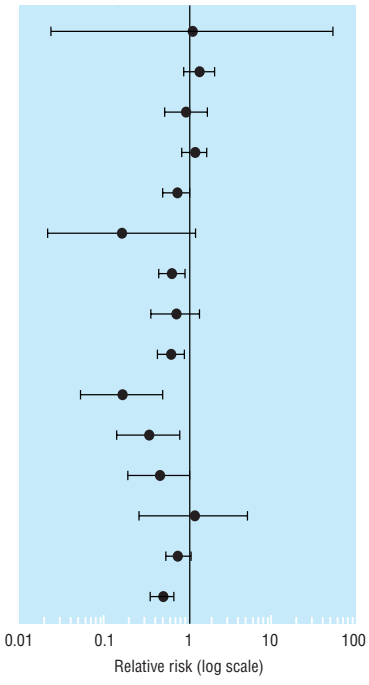

Fig 3 Relative risks (95% confidence intervals) of phlebitis from peripheral venous catheters according to treatment with or without heparin. Last two columns are numbers of catheters associated with phlebitis/total number of catheters

a more variable population of adult medical patients lost 34% during follow up.[15]

Phlebitis is associated with duration of catheter patency because red inflamed catheter sites lead to early discontinuation. Continuously infused heparinised solutions may prolong patency because they significantly decrease the risk of phlebitis. The type of solution being infused is related to the risk of phlebitis. In newborn infants with 24 gauge catheters the duration of catheter patency is prolonged, and infiltration rates are decreased with use of 10 U/ml heparin in normal saline in catheters locked between use versus 10% dextrose by continuous infusion (no added heparin).[40] Regular changing of the catheter has been advocated as an intervention to prevent phlebitis and clot formation, but in adult patients changing the heparin lock every 72 hours was shown to be of no benefit compared with leaving the catheter in place for up to 168 hours.[41]

Use of heparin in peripheral arterial catheters

Mostly on the basis of the results of one multicentre study heparin has been shown effectively to prolong the life of peripherally placed arterial pressure monitoring devices. The minimal effective dose of heparin, however, has not been established. Bolgiano et al reported no significant difference in duration of arterial catheter patency when heparin was used at 0.25 U/ml versus 1 U/ml in adults.[42] Butt et al reported that increasing the heparin concentration from 1 U/ml to 5 U/ml in 22 gauge catheters in children significantly prolonged arterial catheter patency.[43] The type of solution, however, may be important as Rais-Bahrami et al reported that neonatal peripheral arterial lines infused continuously with heparinised normal saline functioned significantly longer (107 (SD 71) hours) than those with heparinised 5% dextrose (39 (32) hours).[44] Other agents besides heparin have also been shown to be effective in prolonging the duration of patency of radial arterial catheters. Arterial catheter solutions containing papaverine[45] and 1.4% sodium citrate[46] effectively prolong the duration of catheter patency and their risk profile should be compared with that of heparin.

Conclusions

In this systematic review we have clarified that low dose heparin is beneficial for maintaining peripherally placed arterial catheters when added to the continuously infused solutions. Heparin at a concentration of 1 U/ml infused continuously through peripheral venous catheters is a promising intervention to prolong catheter life but requires further study. While the use of 100 U/ml of intermittent heparin flushes for peripheral intravenous catheters needs further evaluation, evidence currently available suggests that the current use of 10 U/ml as an intermittent flush is no more effective than normal saline flush.

We thank Derek King for statistical assistance. DJC is a career scientist of the Ontario Ministry of Health.

Contributors: AGR formulated the idea for this systematic review, searched the literature, extracted the data, analysed the data, and wrote the paper. DJC helped with the data analysis and with interpreting and presenting results in the manuscript. CAG helped with literature searching and data abstraction. MA helped with preparing the manuscript and interpreting the data. AGR is guarantor for the study.

Key messages

- Despite almost universal use, agreement has not been reached on the need to administer heparin through peripheral intravascular catheters
- The results of 13 trials on peripheral venous catheters and two trials on peripheral arterial catheters were critically appraised to clarify what evidence supports the use of heparin
- Flushing peripheral venous catheters locked between use with heparinised saline at 10 U/ml is no more beneficial than flushing with normal saline
- Heparin significantly prolongs the duration of peripheral arterial catheter patency and decreases the risk of clot formation
- In peripheral venous catheters heparin added to the infusion at 1 U/ml decreases phlebitis and may prolong duration of catheter patency and decrease infusion failure

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Use of anticonvulsants in eclampsia and pre-eclampsia: survey of obstetricians in the United Kingdom and Republic of Ireland

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Pre-eclampsia is a multisystem disorder associated with hypertension and proteinuria and is a fairly common complication of pregnancy. Eclampsia, the occurrence of fits with pre-eclampsia, is rare, but both conditions can have serious consequences for the mother and infant. Anticonvulsants are given to women with eclampsia to prevent further fits and to women with pre-eclampsia to prevent the first fit, thereby improving the outcome for mother and infant. Clinical practice, however, varies greatly worldwide. In the United Kingdom diazepam has been popular since the 1970s and phenytoin since the early 1990s, but the use of magnesium sulphate remains uncommon.[1 2] Magnesium sulphate has been widely used for decades in the United States and has recently been acknowledged as the preferred anticonvulsant for women with eclampsia.[3] There is little evidence to support or refute the use of anticonvulsants in women with pre-eclampsia.[4] We conducted a survey to determine the current use of anticonvulsants in eclampsia and pre-eclampsia.

Subjects, methods, and results

A questionnaire was sent to consultants in the United Kingdom and the Republic of Ireland asking about their use of anticonvulsants in women with eclampsia or pre-eclampsia. Two reminders were sent six weeks apart.

The table summarises the main results. Of the 662 respondents who used prophylactic anticonvulsants, 658 were more likely to prescribe them in the presence of signs or symptoms of imminent eclampsia and 364 would consider using an anticonvulsant if delivery was unlikely within the next 24 hours. Over half (475) of the respondents would collaborate in a placebo controlled trial of magnesium sulphate versus placebo in women with pre-eclampsia.

Comment

Compared with earlier surveys,[1 2] our survey was shorter and simpler and focused largely on anticonvulsant use. Our survey also had a slightly better response rate (table). Since 1991, when the last survey was conducted,[2] the reported use of magnesium sulphate in pre-eclampsia has risen from 2% to 40%. During 1992 only 2% of women with eclampsia received magnesium sulphate,[5] whereas 60% of respondents in our survey said that they would now use this anticonvulsant for such women. As the use of magnesium sulphate had remained at 2% for 14 years,[2] this change probably occurred after publication of evidence showing that magnesium sulphate is better than diazepam or phenytoin for eclampsia.[3] Despite this substantial shift in practice, diazepam remains the most widely used anticonvulsant for pre-eclampsia and eclampsia, and phenytoin continues to be used by a quarter of respondents. We believe that magnesium sulphate should be used in preference to diazepam and phenytoin.

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Anticonvulsants used by 860* obstetricians to treat pre-eclampsia and eclampsia

	Anticonvulsant used to treat	
Anticonvulsant	**Pre-eclampsia**	**Eclampsia**
None	198	
Magnesium sulphate	343	517
Only	183	229
With diazepam	90	215
With phenytoin	26	14
With diazepam and phenytoin	27	40
With other	17	19
Diazepam	352	573
Only	113	162
With magnesium sulphate	90	215
With phenytoin	73	104
With other	76	92
Phenytoin	227	204
Only	76	22
With diazepam	73	104
With magnesium sulphate	26	14
With other	52	64
Chlormethiazole	60	59
Only	5	5
With diazepam	23	24
With other	32	30
Other	3	1
Not answered	3	8

*1020 respondents out of 1400 (72.9%); 160 (15.7%) were not in clinical practice and were therefore excluded.

Uncertainty about the role and choice of prophylactic anticonvulsant treatment for pre-eclampsia is reflected in the variation in clinical practice. For example, an increasing proportion of obstetricians never use prophylactic anticonvulsants (16% in 1991 *v* 23% in 1996).[2] Among those who do there is no consensus on which agent to use or when prophylaxis is appropriate (data not shown). One aim of our survey was to assess the feasibility of conducting a multicentre, randomised, placebo controlled trial of magnesium sulphate versus placebo in women with pre-eclampsia. Over half of the respondents indicated their interest in collaborating in such a study compared with only 3% of respondents in the 1991 survey.[2] This confirms the increased uncertainty about the role of anticonvulsants in women with pre-eclampsia.

We thank the respondents to our questionnaire.

Contributors: LD had the original idea and participated in the design and conduct of the study. AMG participated in the design and conduct of the study and was responsible for coordination. Both authors supervised the analysis and wrote the paper and will act as guarantors for the paper. Sarah Ayers provided programming support and Caroline Busby entered the data.

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Satisfaction with clinical nurse specialists in a breast care clinic: questionnaire survey

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Specialist nurses have an established role in the management of breast cancer in helping patients to understand their disease and treatment options, and in offering counselling and emotional support[1 2]; they are not usually involved in diagnosis.

In 1987 two clinical nurse specialists were appointed to the breast care clinic at our hospital; they were given responsibility for running outpatient clinics for symptomatic patients, including new referrals. The nurses take histories, examine the women, request imaging, and perform fine needle aspirations when appropriate. Test results are given by the nurses to both the patients and their general practitioners. The specialist surgeon sees patients who have been newly diagnosed with cancer and any patients for whom the evidence is equivocal. This paper describes patient satisfaction with a nurse led clinic screening for breast diseases in London and assesses the clinical expertise of the nurses.

Subjects, methods, and results

A specifically designed patient satisfaction questionnaire was distributed to 150 consecutive new referrals seen by the nurses during six weeks in June and July 1996. Altogether 119 questionnaires (79%) were returned after a postal reminder.

Women were asked to rank their opinion of eight features of the clinic on a four point scale which ranged from very satisfied to very disappointed. Forty out of 118 (34%) women were very satisfied with the amount of time it took to obtain an appointment. Altogether 47 out of 117 (40%) women were very satisfied with the amount of time they spent waiting at the hospital, 39 out of 113 (35%) were very satisfied with the facilities in the clinic, and 75 out of 113 (66%) were very satisfied with the way the clinic was run. A total of 88 out of 117 (75%) women rated themselves as very satisfied with the speed of diagnosis or reassurance, 67 out of 115 (58%) were very satisfied with the amount of time taken

Cytological results of fine needle aspirations for all breast lesions by clinician doing the aspiration and classification of sample. Values are number of aspirations done by each type of clinician (percentage; 95% confidence interval)

	Clinician doing aspiration								
Classification	Consultant surgeon	Pathologist	Radiologist	Senior registrar*	Registrar*	Research registrar*	Clinical assistant	Clinical nurse specialist*	Total
C1 (inadequate sample)	38 (58; 46 to 70)	0	6 (11; 3 to 19)	16 (55; 37 to 73)	39 (41; 31 to 51)	32 (42; 31 to 53)	31 (24; 16 to 31)	114 (31; 27 to 36)	276
C2 (benign)	15 (23)	4 (50)	28 (50)	12 (41)	42 (44)	34 (44)	73 (55)	206 (57)	414
C3 (probably benign)	2 (3)	1 (13)	4 (7)	0	6 (6)	1 (1)	9 (7)	5 (1)	28
C4 (probably malignant)	2 (3)	0	8 (14)	1 (3)	0	0	4 (3)	11 (3)	26
C5 (malignant)	9 (14)	3 (38)	10 (18)	0	8 (8)	10 (13)	15 (11)	26 (7)	81
Total number of aspirates	66	8	56	29	95	77	132	362	825
Ratio of benign: malignant samples	0.6	1.3	2.8	NA	5.3	3.4	4.9	7.9	5.1

NA=not applicable.
*Combined results of two clinicians at each grade.

for consultation, and 83 out of 118 (70%) were very satisfied with the standard of care provided. Twenty six of 93 women (28%) were very satisfied with car parking, public transportation, or other access to the hospital.

Only five women had expected to see a nurse. All women were satisfied or very satisfied with the clinical care they received, and 19 out of 118 (16%) added specific praise to their questionnaires. Evaluation of clinical care and hospital services overall showed that the women were significantly more satisfied with the nurses (χ^2 with Yates's correction = 22.5, 1 df, $P < 0.0001$) than with other aspects of hospital care.

A postal questionnaire was sent to each woman's general practitioner; 102 out of 150 (68%) questionnaires were returned. Altogether 99 questionnaires were analysed. Sixty four out of 91 (70%) of general practitioners always or regularly referring patients to the clinic were aware of the nurses' role but only 8 out of 91 (9%) had informed their patients that the clinic was run by nurses. The most common reasons for referral to the clinic were the high standard of care and convenient location; however, some referrals were the result of a request by the patient to attend our clinic. There were no complaints about patients being misdiagnosed.

To measure the nurses' technical expertise the results of fine needle aspirations of breast lesions were audited by type of clinician who did the aspiration and classification of disease. Pathologists had the lowest percentage of inadequate samples; their samples tended to be from gross lesions detected by other team members, as indicated by the high proportion of malignancies identified (table). A lower percentage of inadequate samples were aspirated by the specialist nurses compared with other team members across the range presenting symptoms.

Comment

Both patients and purchasers of health care expect patients referred for outpatient care to be seen by specialists. Historically this has meant patients were seen by consultants. Clinical guidelines on the management of symptomatic breast disease[3] require that referrals occur rapidly. According to the same guidelines, breast care clinics should treat 100 to 150 new cases of cancer annually; this is equivalent to 1000 to 1500 new referrals. A single consultant cannot see this many patients in an outpatient clinic. Our study suggests that clinical nurse specialists can provide outpatient care in the absence of a second consultant.

In this study, being seen by specialist nurses was acceptable to patients and general practitioners; the nurses' clinical expertise compared favourably with that of other clinicians. Other studies have found that pathologists may be less likely to classify their own samples as inadequate[4] but it seems that variations in the rate of inadequate samples partially reflect the skill of the clinician doing the aspiration.

In another study patients were randomly allocated to be seen either by a nurse practitioner or a junior doctor.[5] Patients who saw the nurse practitioner expressed more satisfaction and had less anxiety than those who saw either male or female junior doctors. No difference was found in adherence to protocols between the nurse practitioners and the junior doctors. Further trials are required to determine whether any cost-benefit results from nurse led clinics.

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