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REDUCING INFUSION FAILURE IN CHILDREN

BY THE ADDITION OF LOW-DOSE HEPARIN

TO INFUSATE

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This is to certify that the thesis entitled "Reducing infusion failure in children by the addition of low-dose heparin to infusate", submitted by Alexander Wright in partial fulfilment for the degree of Master of Applied Science by Research (Nursing) is ready for examination.

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CANDIDATES CERTIFICATE

This is to certify that this thesis has not been submitted for a higher degree to any other university or institution. The source of the information contained herein is original, and is solely the work of the author, except as indicated in the text.

Alexander Wright

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ABSTRACT

Nurses are frequently involved in the initiation and management of intravenous (IV) infusions in infants, children and adults. Many patients tend to develop adverse local venous reactions and the infusions fail. Failure of such infusions due to extravasation and/or phlebitis/infusion thrombophlebitis is probably the commonest iatrogenic sequelae to IV therapy.

The implications of this study for nursing/nurses would include fewer problems with IV solution flow rates, a reduction in medical/nursing hours associated with frequent re-cannulations, less likelihood of systemic sepsis and less patient worry and discomfort due to local venous reactions and re-cannulations. MOST IMPORTANT IS THE BENEFICIAL IMPROVEMENT OF WELFARE TO CHILDREN (directly) AND THEIR PARENTS (indirectly).

Failure of infusions due to the development of phlebitis or extravasation may cause considerable patient discomfort and pain, interfere with IV therapy, increase workload for hospital staff, cause parental worry and concern and in children, induce fear and anxiety. In patients requiring prolonged treatment, loss of veins may become problematic, thereby compromising medication and fluid administration.

The failure of intravenous infusion is common. While many studies have been performed on adults, few have been performed on children. The aim of this study (Study 1), was to report and compare the incidence of survival of peripheral infusion sites in children in three hospitals. A survey technique was used and data were collected using a standard form. Information such as type and size of cannula, sex, age, date and time of cannulation, site, signs of phlebitis/extravasation, reasons for cannula removal and type of fluids and drugs infused were recorded. Univariate (lifetable) survival analysis was performed with the significance of differences between the surveys determined by the log rank test. Results showed that survival time was greater in those children who received hydrocortisone and heparin added to the infusate. Infusion of metronidazole was also associated with reduced survival.

The use of heparin has been found to decrease the failure of intravenous infusions. In Study 2, a double-blind randomised trial was conducted where patients were allocated into control and treatment groups. The treatment group received pre-mixed IV fluids containing 1 unit of heparin per 1ml of solution whilst the control group received standard fluids. Data were collected using a standard form. Information such as type and size of cannula, sex, age, date and time of cannulation, site, signs of phlebitis/extravasation, reasons for cannula

removal and type of fluids and drugs infused were recorded. Failure incidence was analysed by Life table method and Cox's multivariate proportional hazards model.

Survival of infusion sites was considerably greater for the heparin group than the control with median survival half lives of 97 and 43 hours respectively. The difference due to the effect of heparin was highly significant (p<0.0001). Multivariate analysis confirmed this result. Other factors found to influence infusion site survival were ampicillin and flucloxacillin.

One of the limitations of Study 2 was the 12 week shelf life imposed by manufacturers for solutions containing heparin. The aim of Study 3 was to see if long-term stability of heparin in dextrose and dextrose-saline solutions could be maintained over variable time periods. Heparin sodium was added at 1 iu per ml to 500 ml bags of normal saline, 5% dextrose or 3.75% dextrose plus 0.225% sodium chloride (dextrose-saline) which were then stored at 20-25°C (room temperature). Bags of each type of fluid were removed at intervals and their pH was measured with a pH meter and a combination electrode. Activated partial thromboplastin time (APTT) and the thrombin time (TT) were then measured on aliquots mixed with equal volumes of citrated plasma. Also bags of saline and 5% dextrose with 10 iu per ml of heparin were stored at room temperature and bags of normal

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saline, 5% dextrose, 3.75% dextrose plus 0.225% sodium chloride and 2.5% dextrose plus 0.45% sodium chloride with 1 iu per ml of heparin were stored at 2.5°C; APTT and TT measurements were made on these only at 0 and 12 months. Results have shown that over a 12 month period, heparin at 1 iu/ml is stable in saline and dextrose-saline solutions but not in 5% dextrose.

Further studies are required to determine the minimal effective concentration of heparin needed to prevent infusion failure. It is also recommended that manufacturers initiate the production of dextrose-saline solutions containing 1 *i.u.* per ml of heparin for the purpose of reducing infusion failure in patients within the hospital setting.

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Definition of Terms

Thrombophlebitis may be defined as "inflammation of a vein in conjunction with the formation of a thrombus" (Taber's Cyclopedic Medical Dictionary, 1985, p1730) although other clinical definitions do exist, such as "redness and tenderness and oedema of the vein" (Hessov, Allen, Arendt & Gravholt, 1977) and "tenderness and/or erythema along the vein, incurred up to 14 days after the infusion" (Hastbacka, Tammisto, Elfving & Tiitinen, 1965).

Extravasation may be defined as "the escape of fluids into the surrounding tissues" (Taber's Cyclopedic Medical Dictionary, 1985, p591).

The terms "infusion thrombophlebitis (ITP)" and "phlebitis" will be taken to have the same meaning and are used interchangeably.

Infusion failure is failure of an intravenous infusion site to function while needed (Hecker, 1992). Causes include phlebitis, extravasation (infiltration), unintentional removal of the cannula and blockage, the most common cause being phlebitis and extravasation.

While phlebitis by itself may be easier to observe, concomitant infiltration would make the observation of phlebitis difficult.

Extravasation is an accumulation of IV fluid from the vein into the interstitial tissues (Hecker, Fisk, & Lewis, 1984; MacCara, 1983) and is always a risk associated with IV therapy. The most obvious signs of infiltration include swelling at the venipuncture site with color and temperature changes of the tissues, and patient reports of tenderness, pain, or burning (Feldstein, 1986; Hecker et al, 1984; Magdziak, 1988). In addition, a slowing of the infusion rate is often reported (Lewis & Hecker, 1991) but this may not be a dependable indicator of extravasation (Millam, 1988).

These signs are believed to result from direct trauma to the vein during placement of the cannula (Jones & Koldjeski, 1984), with or without vein wall rupture, or from irritation of the endothelium by the infusate, inducing vasoconstriction. The vasoconstriction may prevent flow, leading to increased resistance in the vein with a build up of pressure and the subsequent leakage of the infusate into the interstitial tissues from around the hole in the vessel wall made by the cannula (Hecker et al, 1984). Once infiltration has occurred, the fluid may continue to infuse until the interstitial fluid

pressure overcomes the gravity pressure of the infusion (Millam, 1988).

As venoconstriction (due to irritation of the endothelium by infusate) is believed to be initially responsible for both phlebitis and extravasation (Hecker, Fisk & Lewis, 1984; Gaukrager, Roberts & Manners, 1988; Hecker, 1989; Lewis & Hecker, 1991), for the purpose of this study, infusion failure will be defined as the occurrence of extravasation and/or phlebitis.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Intravenous Therapy - Past and Present

The first intravenous (IV) therapy in humans probably occurred in the Vatican in 1492. A blood transfusion was administered to Pope Innocente VIII by Girolamo Savonarola who is credited as the first human-to-human transfusionist (Schmidt, 1959; Kurdi, 1980; Dunn & Heath, 1981). The blood was taken from two healthy Roman citizens, the result was disasterous - all three died. Records (possibly apocryphal) have shown that animal-to-human transfusions may have been attempted prior to 1492 and the Old Testament refers to blood transfusions on a few occasions.

Perhaps the real begining of IV history could be credited to William Harvey (1572-1657) who gave a series of lectures describing the circulatory system in 1613 (Kurdi, 1980; Dutton, 1924; Plumer, 1982). In Frankfurt, 1628, Harvey published his theory of blood circulation "Execitatio anatomica de motu cordis et sanguinis in animalibus (Anatomic performance form the heart and blood motion in living beings)" (Dutton, 1924). Andreas Libavius (1546-1616), in 1615, used silver tubes to carry blood from the artery of an "elder" to the vein of a

"youth", believing that the negative effects of age would be passed on (Annan, 1896). In 1628 an Italian by the name of Giovanni Francisco (1558-1631) believed that blood transfusions given to sick patients could prolong life and went on to describe how such transfusions might be performed (Dutton, 1924; Schmidt, 1959). Francisco Folli (1624-1685), in 1654, invented a transfusion instrument, a conduit for blood consisting of a silver tube (donor cannula), a cylinder of bone (recipient cannula), an animal blood vessel connecting the two cannulae, and a side hole for the escape of air (Schmidt, 1959). In 1659, Christopher Wren (1632 - 1723) and English chemist, Robert Boyle are credited with the first injection, a bird quill fashioned into a makeshift hypodermic needle. The two inventors exposed the leg veins of dogs, cannulated them and injected them with opium from animal bladders (Dutton, 1924; Schmidt, 1959; Plumer, 1982). This experiment was the first observation of drug effects produced by infusions and hence, Boyle and Wren were able to confirm physiologically Harvey's theory of circulation.

In 1662, a German physician, Johann Daniel Major (1634-1693), was the first to give a successful IV infusion into a human. Major injected a medicine into the blood of a human (Schmidt, 1959; Plumer, 1982). Richard Lower (1631-1691) performed the first successful animal-to-animal transfusion in 1665 and his blood transfusion of

sheep-to-human was published in 1705 (Dutton, 1924; Annan, 1939; Schmidt, 1959; Plumer, 1982). He and Edmund King successfully transfused in public, one Arthur Coga who fully recovered, though he was noted to be "cracked a little in the head" (Pepys, 1896). In 1667, after reading Lower's experiments, Jean Baptiste Denis, physician, transfused patients with lamb's blood - all died. Due to these deaths and others, the French parliament, in 1678, forbade transfusions which had been sanctioned by the Royal Society in London. In 1679, churches and governments in Europe renounced the use of animal-to-human transfusions. This decree was to last over the next 100 years (Dutton, 1924; Schmidt, 1959; Petz & Swisher, 1981).

Interest in transfusions gained acceptance again at around 1792 when a British physician named Russell, experimentally exsanguinated a dog and immediately resuscitated the dog with a blood transfusion. He also transfused a dog suffering from rabies with lamb blood and the dog reportedly recovered fully (Dutton, 1924). The real resurgence of interest in IV therapy and transfusions probably did not begin until 1818 when James Blundell (1790-1878), an English obstetrician/ physiologist/gynaecologist, treated perinatal haemorrhage by transfusing human blood (Kurdi, 1980; Plumer, 1982). He believed that human blood had three advantages "promptitude, for human blood is always at hand; the

abundance with which the blood may be transfused, and most important, the opportunity it offers of throwing human blood into human veins" (Channing, 1828).

Although transfusions were plagued with high rates of infection, this "rediscovery" of blood transfusion in the early nineteenth century stimulated renewed interest in blood circulation, blood compatibility and medical treatments other than blood that could be given intravenously. Blundell realized the potential problem of transfusing incompatible blood into recipients. He experimented with blood coagulation, demonstrating that blood held in a bone syringe/needle device for less than 30 seconds would not clot and thus had no ill effects once transfused into a recipient. He also foresaw the need for the removal of air before transfusion. Blundell invented the "impellor" and the "gravitator", two devices which facilitated the transfer of blood from donor vessel to recipient vessel, and, on December 22, 1818, performed the first human-to-human blood transfusion. Blundell performed 10 such transfusions in all, five resulting in patient survival.

Dr William Brooke O'Shaughnessy (1809-1889), an English physician, continued to advance IV therapy into a more modern age with his classic publication in 1831 about fluid and solute deficits in the blood of cholera victims (Dutton, 1924). Cosnett (1989) wrote:

"The scene is Britain in 1831. Princess Victoria is 12 years old; Florence Nightingale is 8, and Joseph Lister 4. The Anatomy Act, designed to regulate human dissection, is in the throes of debate. Anaesthesia for surgery is 15 years away. An outbreak of cholera, the second pandemic, is spreading across Asia and Europe from India, where it began in 1829. England watches its inexorable progress with horror and panic. A Central Board of Health issues advice on "Preliminary steps to be taken on the first appearance of cholera". The first recognised cholera patient dies in Sunderland on October 26, 1831. There is soon no doubt that the epidemic has arrived, with its nidus in Sunderland".

While many theories arose regarding the cholera epidemic only one voice offered some form of scientific explanation. This was the voice of William Brooke O'Shaughnessy, then a recent Edinburgh graduate aged 22 years (van Heyningen & Seal, 1983). O'Shaughnessy visited Sunderland and reported on two patients with cholera. These descriptions have probably never been bettered.

"On the bed lay an expiring woman... presenting an attitude of death which ... I never saw paralleled in terror ... On the floor, extended on a

palliasse... lay a girl of slender make and juvenile
height, but with the face of a superannuated hag.
She uttered no moan, gave expression of no pain, but
she languidly flung herself from side to side ...
The colour of her countenance was that of lead - a
silver blue, ghastly tint; her eyes were sunk deep
into the sockets, as though they had been driven an
inch behind their natural position; her mouth was
squared; her features flattened; her eyelids black;
her fingers shrunk, bent, and inky in their hue.
All pulse was gone at the wrist, and a tenacious
sweat moistened her bosom. In short, Sir, that face
and form I can never forget, were I to live beyond
the period of man's natural age" (Cosnett, 1989).

After studying the blood and excreta of subjects with
cholera, O'Shaughnessy wrote:

"... the indications of cure... are two in number -
viz. 1st to restore the blood to its natural
specific gravity; 2nd to restore its deficient
saline matters... The first of these can only be
effected by absorption, by imbibition, or by the
injection of aqueous fluid into the veins. The same
remarks, with sufficiently obvious modifications,
apply to the second... . When absorption is
entirely suspended... in those desperate cases...
the author recommends the injection into the veins

of tepid water holding a solution of the normal salts of the blood" (Cosnett, 1989).

O'Shaughnessy also stated that for the treatment of cholera he "would not hesitate to inject some ounces of warm water into veins.   I would also without apprehension, dissolve in that water the mild innocuous salts... which in cholera are deficient" (O'Shaughnessy 1831-1832; O'Shaughnessy 1832; Moore, 1969).

The first practical application of O'Shaughnessy's advice was reported by Robert Lewins, MD, FRCP, of Leith in a letter dated May 15, 1832. He described witnessing the intravenous injection of a saline solution in a cholera patient. He wrote:

"To Dr Thomas Latta, of this place, is due the merit of first having recourse to this practise. He has tried it in six cases... The most wonderful and satisfactory effect is the immediate result of the injection... a large quantity must be injected, from 5 to 10 lbs in an adult, and repeated at longer or shorter intervals as the state of the pulse and other symptoms may indicate" (Cosnett, 1989).

It was Dr Thomas Latta (1790-1833) who pioneered the method of large volume IV infusions into moribund cholera patients (Latta, 1831-1832) and so was the real pioneer

in IV therapy. He put into practice the ideas of O'Shaughnessy and in 1832 presented a detailed report to the Central Board of Health, and published in the Lancet of June 2, 1832. He wrote:

"So soon as I learnt the result of Dr O'Shaughnessy's analysis I attempted to restore the blood to its natural state...". The first patient was an aged woman on whom all the usual remedies had been tried without success:

"She had apparently reached the last moment of her earthly existence, and now nothing could injure her - indeed so entire was she reduced that I feared I would not be able to get my apparatus ready ere she expired. Having inserted a tube into the basilic vein, cautiously - anxiously, I watched the effects; ounce after ounce was injected but no visible change was produced. Still persevering, I thought she began to breathe less laboriously, soon the sharpened features, and sunken eye, and fallen jaw, pale and cold, bearing the manifest impress of death's signet, began to glow with returning animation; the pulse, which had long ceased, returned to the wrist; at first small and quick, by degrees it became more and more distinct, fuller, slower and

firmer, and in the short space of half an hour, when six pints had been injected, she expressed in a firm voice that she was free from all uneasiness, actually became jocular, and fancied all she needed was a little sleep; her extremities were warm, and every feature bore the aspect of comfort and health. This being my first case, I fancied my patient secure, and from my great need of a little repose, left her in charge of the hospital surgeon; but I had not been long gone, ere the vomiting and purging recurring, soon reduced her to her former state of disability.. and she sunk in five and a half hours after I had left her... I have no doubt the case would have issued in complete reaction, had the remedy, which had already produced such effect, been repeated" (Cosnett, 1989).

Thomas Latta saved many victims of cholera in Scotland by infusing them with a mixture of several pounds of water, two drachms of muriate and two scruples of sodium bicarbonate. That was a humble beginning but the approach has been used for more than 150 years and it has, of course, advanced greatly (Dailey, 1983).

Many physicians on both sides of the Atlantic adapted Latta's work, although it was not accepted as standard

practice by the medical community, probably because many cholera patients died as a result of sepsis or air embolism (Latta, 1831-1832).

This lack of acceptance persisted for many years and in 1855, Alexander Wood (1817-1884) developed the first hypodermic needle/syringe device which aided the mechanics of IV infusions (Petz & Swisher, 1981). The observation of haemoglobinuria occurring when human and animal blood was mixed was described by Leonard Londair (1837-1902) in 1875 (Annan, 1939) and by 1900 the transfusing of animal blood into humans was not accepted. Future discoveries relating to blood reactions were also imminent. For example, ABO system in 1960 by Karl Landsteiner, MN and P system in 1927 by Landsteiner and Levine, and the Rh system in 1940 by Wiemer.

In Latta's day, IV infusions were approximately half normal saline. However, treatment with morphine, quinine, water, albumin and cow's milk were tried (Thomas, 1878). Glucose was first added to normal saline in 1911 and IV lipid in 1920. The infusate of choice was normal saline until 1925 when dextrose was added routinely, its advantages being isotonicity and caloric replacement.

In 1923 the discovery of pyrogens by Florence Seibert (Seibert, 1923), coupled with the advances in knowledge

about blood typing, types of IV solutions and anticoagulation, led to the creating of a new medical facility, the blood bank, first established in Leningrad (1932), Barcelona (1936), and Chicago (1937). The first Department of IV Therapy was established in 1940 at Massachusetts General Hospital.

By the 1920's anticoagulation, blood grouping and pyrogenic reactions were well recognised and IV solutions, needles and administration sets were widely used. However, IV access was still problematic. Up until the 1940s', three basic methods of administering IV infusions were used: 1) a new venipuncture every time IV infusions were needed; 2) a continuous infusion via a hypodermic needle and plastic tubing with scheduled infusion of medicine; and 3) venous cutdown for IV infusions (Meyers, 1945). Intra-osseous administration of fluid was suggested in 1922 (Drinker, Drinker & Lund, 1922) and used to treat pernicious anaemia in 1934 (Josefson, 1934). By mid 1940s, intra-osseous infusions in children were well accepted (Tocantins, O'Neill & Jones, 1941; Meola, 1944; Elston, Jaynes, Kaump et al, 1947). The idea of through-the-needle venous cannulation with a flexible tube was also introduced in the 1940's by B. Zimmerman and L. Meyers, thus substituting rigid needles by indwelling catheters (Meyers, 1945; Zimmerman, 1945). To overcome the problem of thrombosis within the tubing, siliconization of catheters was introduced

(Rappaport, Graham & Kendrick, 1955). These catheter-through-the-needle devices were found to be most comfortable, this being the major factor to their wide acceptance.

In 1950, Massa, Lundy, Faulconer and Ridley developed the Rochester Needle, a catheter-around-the-needle IV device which consisted of a metal needle stylet, a metal cannula hub and an indwelling plastic cannula (Massa, Lundy, Faulconer et al, 1950). By 1958 this needle was refined into a two-piece plastic catheter-over-a-plastic-stylet IV infusion set. This became the model for the current catheter-around-the-needle IV device (Lundy, 1958). Also in 1958, George Doherty, an anaesthetist, developed the idea for the present-day intracatheter, a plastic catheter-through-the-steel-needle device (Gritsch & Ballinger, 1959). Both needles (Rochester and intracatheter) were developed with adults and children in mind, although scalp vein insertion in children was a problem. Hence, the scalp vein needle was developed (Gardner & Murphy, 1950). The scalp vein device allowed for better immobilization of the IV set and was the model for the contemporary paediatric winged infusion needles.

More recent introduction of long-term Broviac and Hickman catheters for paediatric patients with chronic diseases has decreased the time spent in the treatment room attempting to secure intravenous access. However, the

level of expertise in maintenance of this skill has probably declined concomitantly. For the paediatric patient, the plea, "my kingdom for an intravenous line", continues to ring true (Orlowski, 1984).

Compared to adults, children represent an obvious challenge in attempting to place an intravenous catheter (IVC). Children generally are more anxious and uncooperative, thereby making it difficult to insert an IVC. In the toddler, generous subcutaneous fat may prevent vessel palpation as well as visualization. Not only is the caliber of vessels smaller in children, but, because of their relatively large surface-area-to-mass ratio, children tend to lose body heat readily, promoting vasoconstriction.

It is important then, that intravenous lines remain patent for as long as possible in children. This will enable maximal vein usage (for example, for medication administration) and conserve veins for future use.

Intravenous therapy has become an integral part of the daily management of both medical and surgical patients. As a consequence, the nurse's role in its management has changed dramatically. Intravenous therapy is often life-saving - and safe, successful treatment demands specialist information and skill. Given the vast increase in current knowledge concerning drugs and

fluids, it becomes ever more essential that rational and practical policies on their use should be formulated.

Infusion Failure (Phlebitis and Extravasation)

Venous cannulation for the purpose of fluid and drug administration is a common hospital procedure and many of these sites will develop complications. Intravenous infusions commonly fail due to the development of phlebitis and/or extravasation of the infusate. This causes patient discomfort, increases workload for hospital staff, and with prolonged infusions loss of veins may become problematic, thereby compromising therapy.

The incidence of phlebitis has varied widely among studies. It has been estimated that some 80% of hospitalised patients will receive IV therapy (Millam, 1988). Feldstein (1986) has reported that phlebitis will develop in 80% of patients and extravasation in approximately 28%. Similar incidence is reported by MacCara (1983) where infiltration occurred in 23% of all infusion failures and was second only to phlebitis as a cause of IV morbidity. In a study of 5161 cases of IV therapy, Tager, Ginsberg, Ellis, Walsh et al (1983) found the phlebitis rate to be only 2.3% where Tully, Friedland, Baldini and Goldmann (1981) found an incidence of 18.8%.

Earlier studies suggest that the incidence of infusion thrombophlebitis (ITP) was alarmingly high and Brown (1970) reported it to be as high as 70% in long term lines. Studies have most commonly shown that the incidence of ITP lies in the range of 30-60% (Page et al, 1952; MRC Sub committee, 1957; Collins et al, 1975; Stephen et al, 1976).

More recently, Nelson and Garland (1987) found the incidence of phlebitis in children to be 10.4% whilst Tobins (1988) reported 7% phlebitis when looking at the duration of Teflon catheters in neonates. Infiltration was the commonest reason cited for infusion failure. It is not clear why children and babies tend to have less phlebitis (and greater infiltration) than adults, but a possible explanation could be that children and neonates have proportionately smaller veins which are more reactive and veno-constrict more completely.

The wide range of incidence of infusion failure supports the premise that it's aetiology is multi-factorial in nature. It would thus be impossible to control for all variables/factors when studying this phenomenon.

The symptoms that have been associated with phlebitis includes pain, swelling, erythema, increased warmth, and/or a palpable venous cord (thrombosed vein) at the infusion site (Deluca, Rapp, Bivins et al, 1975; Falchuk,

Peterson & McNeil, 1985; Lewis & Hecker, 1985; Khawaja, Campbell & Weaver, 1988).

Pain seems to be the most common manifestation (Wright, 1983) and Jones and Koldjeski (1984) report that in more than 50% of patients who develop phlebitis, pain is the first symptom. Pain tends to be followed by oedema and erythema. The earliest presentation of pain appears to be in the form of an initial 'single tender spot' which usually becomes apparent between 12-24 hours post cannulation. The patients are able to locate this 'spot' daily by themselves. Location is at the insertion site or at any point along the cannula's length, terminating at its tip (Wright, 1983, Unpublished results).

The occurrence of pain and erythema at an early stage can probably be accounted for by the acute inflammatory response of the vein to substances such as histamine, serotonin and kinins (Lewis & Hecker, 1985). Cording, which is a fine, hard fibrous thread felt on palpation of the vein, tends to develop later and is possibly due to fibrotic deposits once the initial irritation is withdrawn. The severity of inflammation is dependent upon the type of infusate and other additives administered IV. Mild reactions tend to occur with isotonic and heparinized solutions, the more severe reactions occurring with potassium chloride and antibiotics. Severity appears to be related to the

length of time the cannula is in situ (Collin et al, 1975; Stephen et al, 1976).

It is important then, that nurses become aware of the impending development of ITP and take appropriate action.

The severity of an episode of phlebitis has been associated with the number of symptoms, with a greater number of symptoms indicating increasing severity (Maddox et al, 1977). However, identification of IV-related phlebitis is sometimes difficult, especially in the early stages. For example, some degree of erythema is so frequently found around IV infusion sites that it easily may be disregarded by health care providers (Woodhouse, 1980) and using pain to identify phlebitis can be problematic since transient IV site pain also occurs with the administration of some medications.

The infiltration of IV fluids and/or medication outside the vein may exhibit similar symptoms. Nurses are usually able to define the extravasation of fluids when swelling of the surrounding tissue is obviously present (Millam, 1988). Other symptoms of infiltration may include a slight burning sensation or pain, blanching, coolness, or leakage from the insertion site (Feldstein, 1986).

Although differentiating phlebitis from infiltration has

been the topic of many articles (Beck, 1986; Feldstein, 1986; Millam, 1988), the nursing action is the same for either. The infusion would be discontinued in order to "conserve the structural integrity" of the IV site (Levine, 1967, 1971). Throughout the course of initiating and maintaining IV therapy, nursing actions are dedicated to protecting the structural integrity of the site and limiting the development of phlebitis and infiltration.

In an early experiment by Horvitz et al (1943), 5% and 10% dextrose solutions were infused into veins of 11 dogs. The pathophysiology seemed to follow initial vacuolation of endothelial cells with further injury leading to progressive changes and eventual death. Ghildyal et al (1975) also found swelling of endothelial cells with polymorphonuclear leucocyte infiltration to the tunica media, followed by oedema and pyknosis of the nuclei of muscle fibres of the vein. In a more recent study, Subrahmanyan (1989) showed that the earliest changes that occur in thrombophlebitis are vacuolation of endothelial cells followed by progressive cellular breakdown leading to the death of cell and destruction of endothelial lining. Sometimes fibrin was deposited on the denuded subintima forming varying degrees of thrombosis. In more severe cases, changes ranging from slight pyknosis of nuclei of muscle cells, leucocyte infiltration, haemorrhage and finally necrosis. In the

most severe cases, adventitia was also affected with oedema, leucocyte infiltration and haemorrhage.

Although the exact mechanism of ITP (infusion thrombophlebitis) is still unclear, it has been suggested that the inflammation found in ITP can be mainly attributed to chemical irritation by the infusate (Fonkalsrud et al, 1968; Lewis & Hecker, 1985) and animal experiments have shown that endothelium is very sensitive to deviations in pH (Lewis & Hecker, 1984). Following cannulation, platelet adherence occurs on the damaged endothelium which results in leucocyte infiltration and oedema of the vessel wall. The damage may spread proximally and cause intra-luminal thrombosis. These changes are enhanced by prolonged infusions (Eremin et al, 1977). Woodhouse (1980) concluded that the critical event in ITP was infiltration of the vein wall by circulating leucocytes.

Irritation, inflammation, and damage of vein wall endothelium by infusate may lead to veno-constriction (Lewis & Hecker, 1984). This may cause a reduction in blood flow, precipitating tissue ischaemia and perhaps the loss of normal vessel elastic properties. Vascular damage and blood flow stasis may therefore lead to subsequent thrombosis and an increased interaction of leucocytes with the endothelium (Simmons et al, 1987).

Chemical irritation/inflammation of endothelium may be initiated by the metabolites of arachidonic acid (Lewis & Hecker, 1985). Although the chemical interactions are complex, they are well described by Lewis and Hecker (1985) who state "prostaglandins may be released or stimulated by histamine, adenosine-5-triphosphate (ATP) and prostaglandin E_1, during the inflammatory response (Chahl & Chahl, 1976). Prostaglandins PGE_1 and PGE_2 increase local vascular permeability via histamine and 5-hydroxtryptamine in rat and man (Crunkhorn & Willis, 1971). The early histological changes observed by Ghildyal, Pande and Misra (1975), namely swelling of endothelial cells and polymorphonuclear (PMN) leucocytic infiltration to the tunica media, could perhaps be initiated by metabolites of arachidonic acid. When the vein wall is injured, platelet phospholipase A_2 is stimulated to form biologically active compounds PGE_2 and PGD_2 which increase vascular permeability and hydroxy-eicosatetraenoic acid (HETE) and thromboxane B_2 (TXB_2) which are chemotactic for PMN leucocytes (Moncada & Vane, 1978). PGG_2, PGH_2 and thromboxane A_2 are other platelet-produced arachidonic acid metabolites which are active as platelet aggregating or releasing agents and which may also be involved at the endothelial surface".

Humoral agents released in response to venous irritation may provoke veno-constriction. If the flow of blood in the vein is diminished, irritant infusates are not

rapidly diluted with blood and this, together with stasis, would predispose to ITP. Sharpey-Schafer and Ginsburg (1962) studied the effects of humoral agents on venous tone. Adrenaline, noradrenaline, 5 hydroxytryptamaine and histamine all increased venous tone in the forearm. Nitrite decreased tone whilst increasing forearm blood flow. Mason and Braunwald (1965) observed the effect of sublingual nitroglycerine on the human forearm venous tone. Forearm blood flow was increased whilst forearm vascular resistance and venous tone were decreased. It is possible that the local application of nitro-glycerine ointment near the site of an IV infusion may prevent or reduce the effects of released humoral venoconstricting substances, increase blood flow and prevent or delay the onset of ITP. Hecker, Lewis and Stanley (1983) have demonstrated the effectiveness of very small applications of nitroglycerine ointment on the dorsum of the hand as a local venodilator before venipuncture. Using this same principle, Wright et al (1985) and Khawaga et al (1988) were able to significantly reduce the incidence of infusion failure in peripherally cannulated hospital patients. Nitroglycerine stimulates the synthesis of prostacyclin by cultured human endothelial cells (Levin et al, 1981). Prostacyclin is a very potent inhibitor of platelet aggregation and is synthesized in vascular walls by prostaglandin endoperoxides (Gryglywski et al, 1976). It was suggested by Moncada and Vane (1977) that, when a

vessel is injured, endothelial damage could reduce
prostacyclin synthesis, resulting in regional
vasoconstriction. The potent vasoconstrictor thromboxane
A_2 is then produced by aggregating platelets in the
damaged area. Prostacyclin, which also relaxes smooth
muscle cells in vein walls, may be produced in increased
amounts by surrounding undamaged endothelial cells. The
maintenance of effective prostacyclin concentrations in
veins where infusions are sited may help to relax smooth
muscle, preventing veno-constriction and platelet
aggregation and possibly ITP.

Another possible group of biologically active mediators
which may be responsible for the development of ITP are
the leukotrienes. These compounds may be produced by
incubating arachidonic acid with polymorphonuclear
leucocytes (Samuelson, 1987) and these cells infiltrate
vein walls as ITP develops. By their action on smooth
muscles, leukotrienes may affect venous tone and hence
the flow rates of infusions. Leukotrienes have been
shown to increase vascular permeability in the skin of
guinea pigs (Denis et al, 1982). Samuelson (1987)
suggested that a deficiency of prostacyclin leads to the
release of arachidonic acid by means of an adenylate
cyclase mechanism. In the presence of certain enzymes,
this synthesises those leukotrienes which are known to
increase the contractility of smooth muscle causing
potent vasoconstriction. Prostacyclin may be involved in

regulation of "regional microcirculations" because of its vasodilatory ability (Oates et al, 1988). It is worthy of attention that the above results are inconclusive and further studies are needed.

Factors Affecting Infusion Site Failure

The aetiology and mechanism of infusion failure still remains unclear although several factors have been implicated. These being, mechanical trauma during venipuncture, pH of the infusate, duration of cannulation and the presence of particulate matter from the infusion bottle and giving-set tubing.

Many studies now agree that ITP is believed to be primarily a physiochemical phenomenon (Maki et al, 1973; Wright, 1993) with a variety of contributing exogenous factors. The predisposing "physical" factors to ITP include the composition of the cannula, cannula length and bore/anatomical location of the cannula, duration of cannulation and the skill of the operator and insertion technique (Turnidge, 1984). The predisposing "chemical" factors to ITP include irritant drugs, infusion rate, use of directly provocative solutions (for example, blood) (Ross, 1985) and composition of the infusate such as pH, osmolality and particulate matter (Turnidge, 1984). The third predisposing factor to ITP is that of "bacterial" contamination. Although this factor seems to play a

minor role in the aetiology of ITP (Curry & Zallen, 1973) it should not be taken too lightly, as major complications, such as septicaemia, have been well documented as arising from intravenous therapy (Maki, 1982). Rarely do the above factors independently cause ITP; in fact ITP is found most frequently to be due to a concurrent combination of these factors.

Physical Factors

Duration of Cannulation

Duration of infusion is perhaps the most important "physical" factor affecting the development of ITP. Many studies have confirmed that there is a direct relationship between the incidence and degree of ITP and the duration of cannulation (Brown, 1970; Collin et al, 1975; Stephen et al, 1976). Bolton-Carter (1951) showed that the frequency of ITP was reduced from 52% to 5% when the infusion time was restricted to under 8 hours. This was also confirmed by Page et al, (1952) and MRC Subcommittee, (1957).

The importance of the relation between infusion time and infusion rate has been studied under controlled and blind experimental conditions in ear veins of rabbits (Hessov et al, 1976). In this study a volume of acid 5% glucose solution was given within either one or five hours. The

slow (longer) infusions resulted in significantly more
inflammatory changes in the veins than the brief
(shorter) infusions. This was also the case, when brief
infusions were given twice for 30 minutes at an interval
of four hours during which the infusion needle was sealed
with heparin saline. Thus, in the animal experiments, it
was shown that a shorter infusion time reduced the risk
of inflammatory changes in the veins in spite of the
higher rate of infusion.

Although many investigators have reported that the longer
the IV cannula remains in place, the greater the
incidence of phlebitis (Cheney & Lincoln, 1964; Brown,
1970; Thomas et al, 1970; Collin et al, 1975; Tager et
al, 1983; Larson & Hargis, 1984; Larson et al, 1984).
Tager et al, (1983) reported that the phlebitis rate
dropped when the catheter was in place for 7 days or
longer. Smith et al (1990) showed no statistically
significant differences in phlebitis rates for those IV's
changed at 72 hours vs those left in longer (up to 7
days). Mulloy (1991) and King et al (1985) reported that
the duration of catheterisation was inversely associated
with the occurrence of sepsis.

Site of Cannulation

Gjores (1957) found, after injection of barbiturates,
that the incidence of ITP was higher in veins on the

dorsum of the hand as compared to those at the cubital fossa. Eerola and Pontinen (1964) found a 41% occurrence of phlebitis in veins on the dorsum of the hand as opposed to a 26% occurrence of the cubital fossa. Although Ross (1972) reported that locating the infusion in the forearm was associated with an increase in IV site symptoms, other researchers (Thomas, Evers & Racz, 1970; Hanson, 1977) reported no difference in symptoms due to the location site. Lower limb sites are associated with an increased risk of thrombophlebitis and sepsis (Benerjii, 1955; Morris, 1955; Indor, 1959).

Thomas (1970) found a lower (although not significant) incidence of complications with infusion sites in the dorsum of the hand, while Driscoll et al (1979) found that distal limb sites had more complications than proximal sites, perhaps due to the smaller calibre of veins at these sites. On the basis of this study, optimum sites for cannula placement appear to be the extensor surface of the forearm and dorsum of the hand.

Anatomic location may play an important role in the increased frequency of ITP, especially if located over mobile areas without appropriate immobilisation (Maki et al, 1973; Eremin & Marshall, 1977; Turnidge, 1984).

A study conducted by Winter and Flournay (1985) showed that shaving the cannulation site prior to insertion

increased the incidence of inflammation, probably by allowing easier access to micro-organisms through micro-abrasions caused by the shaving.

Insertion Technique

A number of authors stressed the importance of controlled insertion techniques for cannulation which may otherwise lead to development of phlebitis (Cosentino, 1977; Watt, 1977). Watt (1977) also reported that the trauma of insertion may provide bacterial access to the circulation. In a study of 200 cases, Hutton and Hall (1957) concluded that a major factor in the development of phlebitis was needle insertion. Eremin and Marshall (1977) suggested that trauma is more likely to occur to smaller veins at the time of insertion of the cannula and they felt that plastic cannulae inserted through an IV needle may be associated with less trauma to the vein than the plastic cannulae inserted as a sheath around the venipuncture needle. They found that complications were highest with the latter type of cannula and, also, highest in small veins.

Riyami (1968) implicated house officers as a cause of infusion related complications because of their lack of adherence to aseptic procedures, and reports from the United States of America state that trained IV therapy teams have a lower incidence of complications (Corso,

Agostinelli & Bandriss, 1969; Cosentino, 1977).

The vein size relative to cannula bore may also play a significant role in the occurrence of phlebitis, thrombosis, and extravasation. The relationship appears to lie in the blood flow around the cannula and that insertion of a large bore into a small vein decreases blood flow and possible nutrients to the endothelium, thereby increasing the risk of phlebitis and thrombosis (Turnidge, 1984). Other studies have shown that larger gauge cannulae are associated with more complications (Thomas et al, 1970; Tse & Lee, 1971).

Cannula Composition

Collin et al (1975) showed that long flexible Teflon cannulae significantly increased the incidence of ITP and bacterial contamination as compared to short, rigid Teflon cannulae. Thrombophlebitis has been reported to take longer to develop with Teflon cannulae with an outer diameter of 1.0 mm than with Teflon cannulae with an outer diameter of 2.0 mm (Hessov, 1985). This difference may be partly a function of the size of the peripheral vein and the flow of blood around the intravenous part of the cannula because cannulation of small veins is associated with higher rate of phlebitis than is cannulation of larger ones (Fonkalsrud et al, 1971; Gazitura, Bistrain & Blackburn, 1979).

All commercially available cannulae today are plastic. Collin et al, (1975) and Tully, Friedland, Baldini and Goldman (1981) have reported that the occurrence of ITP is greater in plastic cannulae than with steel needles. Steel catheters tend to cause extravasation whilst plastic catheters are more likely to cause phlebitis. It seems possible then that venous reactions and complications could be related to the material used in the manufacture of such cannulae (Dinley, 1976; Hecker, 1980).

Hence, the type of plastic from which the cannula is manufactured may influence the development of thrombophlebitis. Experiments have shown that catheters manufactured from silicone rubber cause little inflammatory response or thrombosis in cannulated veins, whereas those made from polyvinyl chloride or polyethylene caused severe trauma to vascular endothelium and early thrombosis (Welch et al, 1974).

Clinical studies suggest that low rates of thrombophlebitis can be obtained with polyurethane, fluoroethylene, propylene, silicone, and Teflon cannulae; however, there have been no comparative studies of different materials (Tanner et al, 1980; Rudin, 1990).

Though all investigators reported lower phlebitis rates with steel needles, results were complicated by variation

in needle size and duration of placement. Although
Teflon cannulae are said to have significantly fewer
complications, electron microscopy (Bain & Peterson,
1979) has shown surface imperfections believed to be
possible sites of thrombogenesis. No significant
difference in the incidence of complications among
cannulae was found in this study; thus the role of
cannula material as a cause of infusion complication
remains unclear. However, no account was taken of the
number of failed attempts at venipuncture, and it was
felt by the majority of staff concerned that the
'Cathlon' cannula was easier to insert.

Bacterial adherence to catheters was also claimed to be
responsible for inflammatory process leading to infusion
site complications (Ashkenazi & Mirelman, 1984) although
Tobin (1988), when comparing duration life of teflon and
stainless steel needles and associated phlebitis, found
no such connection. More recently, Vialon catheters have
been compared to Teflon catheters. In a study of 645
patients Gaukroger, Roberts and Manners (1988) conclude
that the nature of the cannula was the single most
important factor in the incidence and severity of
infusion thrombophlebitis. Vialon cannulae were
associated with a 46% lower incidence than Teflon
cannulae and McKee et al (1991) found a 36% lower
incidence of phlebitis when comparing Vialon to Teflon
catheters. Infiltration was also found to be less (18%)

when Vialon cannulae were used (Stanley, Meister & Fuschuber, 1992).

Most recent studies have compared elastomeric hydrogel catheters (Aquavene) to Teflon/Vialon (Strumpfer, 1991; Sheehan et al, 1992). The Aquavene peripheral IV catheter is manufactured from a radiopaque, bioconforming, thromboresistant elastomeric hydrogel that is stiff for insertion, like Teflon, but softens dramatically (50 times softer) after contact with body fluids to a silicone-like softness. In addition, as it hydrates and softens, it expands 2 gauge sizes larger in diameter, and the tapered tip opens to provide unrestricted flow.

Aquavene catheters have shown improved performance in prospective controlled studies performed in adult hospital patients (Hickey, Cason & Charles, 1989; Cooke, Loftus & Michelson, 1990; McClveen, Cooke & Loftus, 1990) and neonates (Walker, 1989; Risrow, Sen & Walker, 1990; Sheehan, 1990). Two studies showed substantially improved performance of Aquavene catheters in home care patients. However, the results of these studies were compared with historic controls (Crocker et al, 1990; Horton & Crocker, 1990).

Although catheter type may seem to play an important role in the development of infusion site complications, no study to date has compared all the common commercial

types whilst controlling for other factors.

Age, Gender and Race

Many workers tend to agree that age has little effect on the incidence of infusion failure in adults (Fonkalsrud, 1968; Archer & Fowler, 1977; Tager et al, 1983; Hecker, 1989). However, Wright (1993), using multivariate analyses in a study on infusion failure in children, was able to show age as a significant variable ($p<0.01$).

There are few data available to show a relationship between sex and the incidence of thrombophlebitis. Whilst Hecker (1989) found no difference between male and female babies, Hastbacka (1965), Archer and Fowler (1977) and Wright and Hecker (1991) found that adult females had a higher incidence of infusion failure than males.

Race, as a factor in the possible development of infusion phlebitis has been cited by Phelps & Helms (1987). This study found infusion failure to be higher in black babies than white babies, the reason for this difference was unclear.

Delivery System

Whilst the delivery of intravenous fluids to hospitalised patients is commonly via a "roller clamp" controller,

many specialised and acute areas are now purchasing electronic infusion devices. There remains uncertainty as to how these electronic devices effect the development of infusion complications. Jarrard et al (1987) have shown these devices increase the incidence of phlebitis whereas Rapp et al (1979) and Bivins et al (1980) report a decrease in IV complications such as infiltration and postinfusion phlebitis. Using IV infusion pumps has been questioned since severe site complications were reported as a direct result of pumping an infusion of fluids and medications into an infiltrated IV site (Upton, Mulliken & Murray, 1979; MacCara, 1983). Engler and Engler (1986) reported that the use of lower pressure infusion pumps was associated with fewer IV site symptoms.

Chemical Factors

Infusion Rate

Rate of infusion was suggested to be an important factor in the development of ITP (Hessov & Bojsen-Moller, 1976) and Ross (1972) found an increased risk of phlebitis with slower infusion rates. Other studies do not support this finding (Hecker, Duffy, Fong & Wyer, 1991) although the sample population in this study was on neonates. In a study on infusion failure Hecker (1989) found higher flow rates to be the most significant factor on multivariate analysis. Wright and Hecker (1991) in a study of 395

infusion sites, also found a significant difference between continuous and intermittent infusions. More research is needed to determine the relationship between flow rate to infusion failure.

Veno-constriction

Veno-constriction (clamping down or constricting of veins) is a concept which has attempted to explain, in part, the aetiological nature of infusion failure. It is suggested that irritation of the endothelium by the infusate induces veno-constriction (Lewis & Hecker, 1984) which in turn reduces blood flow around the cannula. This then decreases available nutrients to the endothelium as well as the ability of the blood to dilute the infusate, thus precipitating aggravation and subsequent phlebitic changes.

Extravasation is commonly encountered by many nurses, but little is known about its mechanism. The popular belief is that extravasation results from rupturing of the vein wall or cannulae perforating the vessel (Kay, 1967); this may be true, particularly if catheters are sharp, insertion technique is poor, or excessive movement of the 'cannulated site' occurs. However, Hecker, Fisk and Lewis (1984) suggested another explanation. These authors reasoned that the induction of veno-constriction by the infusate leads to infusion failure via phlebitis/

extravasation and that this occurs by two basic mechanisms. The first of these mechanisms is that if veno-constriction prevents blood flow, pressure tends to build up in the vein thereby enlarging the hole made during cannula insertion, thus leading to leakage and tissue infiltration. Second, if partial constriction occurs, this tends to allow the undiluted infusate to aggravate the endothelium for longer periods of time and thus leads to phlebitis. Severe veno-constriction is more likely to produce extravasation than phlebitis and thus the former is more common in children, who generally have smaller and more reactive veins.

If the concept of veno-constriction is true, then infusion failure should be able to be reduced by the application of some vasodilatory agent such as Glyceryl Trinitrate. The studies of Wright, Hecker and Lewis (1985) and Khawaja, Campbell and Weaver (1988) strongly support this view. Both studies reported significant decreases in infusion failure ($p<0.001$ and $p<0.0001$ respectively).

Irritant Drugs

A common belief by the medical and nursing profession is that "drugs" themselves may cause phlebitis. The evidence to support this is inconclusive. Many drugs,

including cephalosporins, penicillins, erythromycin, amphotericin B, cytotoxic drugs, and electrolytes such as potassium chloride, thiopentone and phenytoin, are chemically irritant to vascular endothelium (Maki et al, 1973; Stephens et al, 1976).

Phelps and Helms (1987) found that the time to infiltration was significantly decreased with the intravenous administration of ampicillin, gentamicin, phenytoin and aminophylline. They concluded that the method of administration and not the drug itself was responsible for the decrease in the time to failure. Addition of potassium seems to increase failure (Crenshaw et al, 1972; Carey et al, 1986; Jakobsen et al, 1986) and Stephens et al (1976) found a significant relationship between the addition of potassium and the incidence of phlebitis. However they failed to mention other factors that may have contributed to phlebitis for example, duration of infusion or method of administration. This may have influenced their results.

Benzodiazepines, such as diazepam, are known to cause venous irritation. The incidence of thrombophlebitis with intravenous diazepam was reported to be 3.5% by Langdon et al (1973). Whereas the highest incidence was 39% reported by Hegarty and Dundee (1977). The precipitation of diazepam in water or blood was held responsible for venous irritation. Thus the variety of

solvents used as a base for diazepam was said to be responsible for the irritant action. Diazepam with benzyl alcohol has the highest incidence of infusion phlebitis, while the incidence was considerably reduced when cremophor or soyabean oil was used as a solvent (Langdon et al, 1973; Hegarty & Dundee, 1977).

Mikkelsen and co-workers (1980) compared diazepam, flunitrazepam and isotonic saline to study the role of mechanical irritation in the production of vascular damage. After an observation period of 1 month they found that, in the saline group, 9% had pain or tenderness in the arm used for the injection. Thus, it could be argued that mechanical irritation from the venipuncture and endothelial damage caused by the cannula were the principal aetiological factors.

Conflicting reports seem to exist regarding the incidence of phlebitis with diazepam (Thomas et al, 1970; Langdon et al, 1973; Hegarty & Dundee, 1977). Commonly used antibiotics such as ampicillin appear to increase the incidence of failure with cephalosporins (Thomas et al, 1970) being the worst offenders. Other drugs also include tetracycline (Hegarty & Dundee, 1977), pethidine and lignocaine (Langdon et al, 1973) and potassium chloride (Thomas et al, 1970; Stephen et al, 1976; Jakobsen et al, 1986).

The administration of medications intravenously has not conclusively been linked to the development of infusion related complications such as phlebitis. Hecker (1989) postulated that crystalloid solutions may be the main cause of vein irritation which leads to failure. These solutions are mildly acidic (Lebowitz et al, 1971) and neutralisation of such solutions can significantly reduce infusion failure (Eremin & Marshall, 1977; Lewis & Hecker, 1986). Further studies are required.

Particulate Matter

Intravenous fluids may contain particulate matter. The filtering of these particles to prevent endothelial damage and phlebitis development has been the study of many papers. Several investigators have suggested that use of IV filters reduces irritating particulate matter in solutions (DeLuca et al, 1975; Bivins et al, 1979; Rusho & Blair, 1979; Quercia et al, 1986). However, other researchers have reported no significant difference in symptom development with filter use (Collin et al, 1973; Maddox et al, 1983; Adams et al, 1986).

Osmolality/Osmolarity and PH

Composition of the infusion solution appears to be an important factor in the development of venous complications. Endothelial damage results in phlebitis

with or without extravasation (due to partial veno-
constriction). The extent of tissue damage following
extravasation is influenced primarily by the nature of
the infusate and appears to be dose-dependent.
Osmolarity and pH have been implicated as two critical
determinants (Yosowitz, Ekland, Shaw, & Parsons,
1975;Gaze, 1978; Lewis & Hecker, 1985, 1991; Crane, 1987;
Dufresne, 1987; Hagan & Hatings, 1988; McAlister &
Kisane, 1990) and produce differing tissue injuries.
Although the blood flow in the vessel dilutes the
infusate and helps to decrease the likelihood of
endothelial irritation, the endothelium is particularly
sensitive to pH and osmolarity differences found in
physiologic and nonphysiologic solutions, both of which
may differ markedly from blood. These solutions may
induce cellular injury through irritation, stimulating
the inflammatory process. The damaged tissues release
precipitating proteins with an increase in capillary
permeability which allows fluid and protein shifts to the
interstitial space. Oedema, ischaemia, vasoconstriction,
pain, and erythema are responses to these cellular
changes and may lead to tissue necrosis.

Solutions of varying osmolarity and pH have been noted to
produce widely differing injuries, with high osmolarity
agents and greater volumes of infusate associated with
greater tissue injury (Elam, Dorr, Lagel & Pond, 1991).
Low osmolar solutions appear to be tolerated much better

but do produce local inflammatory reactions (McAlister & Kissan, 1990).

The pH of most solutions containing dextrose is maintained at about 3-4 to avoid caramelization during sterilisation. The acidity of such solutions has been implicated in causing an increase in the incidence of ITP (Elfving & Saikku, 1966; Fonkalsrud et al, 1968; Fonkalsrud et al, 1971; Stephen et al, 1976; Harrigan, 1984). Lewis and Hecker (1984) showed that highly irritable solutions such as 25% dextrose caused local venous tone to respond by veno-constriction. A greater increase in tone was noted when the pH of dextrose solutions was lowered to 2.4.

When sodium bicarbonate was added to a glucose solution to raise the pH towards neutrality, the percentage of patients in whom phlebitis developed during the first 24hr of crystalloid infusion was halved from 26% to 13% (Fonkulsrud et al, 1971). In another study, thrombophlebitis was more common in patients who required potassium supplementation than in those who did not, probably because the osmolality of the feed was thus increased (Gazitura, Bistrain & Blackburn, 1979).

Infusate Composition

Infusions having a colloidal nature (for example, blood)

seem to increase phlebitis more so than crystalloids such as normal saline and 5% dextrose. This finding is supported by several authors (Dinley, 1975; Stephen 1976; Holland, 1982). Skajja (1961) however, found no difference between crystalloid and colloid solutions in causing an increase in ITP. The reason may possibly be attributed to the statistical technique used. During blood transfusions, haemolysis of the cells occurs, resulting in the release of potassium and serotonin. The veno-constriction that occurs is perhaps the result of irritation of the endothelium by these two substances.

It is important to note that the buffering capacity of blood should not be ignored, and hence blood flow around the cannula may be of importance.

Acidic drugs have been associated with the development of phlebitis (Harrigan, 1984). The addition of potassium chloride (KCL) to solutions also has been associated with more IV site symptoms (Gazitua et al, 1979; Larson, Lunche & Tran, 1984).

Hypertonic solutions of glucose have been shown in laboratory experiments to cause thrombosis and chronic inflammation of both cannulated and adjacent veins. The degree of inflammation was found to be dependent on the osmolality of the solution, and the inflammatory response was reduced by the addition of fat emulsion, which

greatly reduces osmolality (Fugiwara et al, 1984). Lipid itself has also been suggested to be veno-protective in some way other than through its effect on osmolality (Jeejeebhoy et al, 1976).

Solutions containing amino acids and electrolyte additives tend to increase venous complications by way of increasing the solutions osmolality. Osmolality concentrations in excess of 600 mmol/kg always induce phlebitis (Gazitura, et al, 1979; Turnidge, 1984).

Bacterial Factors

Infection

Infection has been suggested as a cause of phlebitis. The risk of infection following the introduction of an intravascular catheter should not be underestimated and complications such as suppurative phlebitis and septicaemia have been well documented (Sacks-Berg et al, 1987; Simmons et al, 1987; Tobin, 1988).

After the insertion of a plastic cannula, a loose fibrin sheath forms around the intravascular portion of the cannula. This acts as a potential nidus for colonising organisms, particularly those present in normal skin flora. A wide variety of predominately aerobic bacteria are capable of gaining access by way of the intradermal

wound, particularly *Staphylococcus aureus* and
Staphylococcus epidermidis, but also micrococci, Gram-
negative bacilli, diphtheroids, enterococci and *Candida*
species (Maki et al, 1973). Some of these organisms are
capable of producing significant purulent local infection
necessitating drainage, as well as septicaemia. Most
common is *Staphylococcus aureus,* but enterococci,
Staphylococcus epidermidis and facultative Gram-negative
bacilli such as *Escherichia coli, Proteus, Klebsiella,*
Enterobacter, and *Pseudomonas aeruginosa* are also seen
(Maki, 1982). The latter are particularly common in
patients receiving antimicrobial agents for other
infections.

With sensitive broth culture techniques, colonisation
rates of peripheral cannulae as high as 57% have been
reported (Maki, 1983). However, by introducing a semi-
quantitative agar-plate method, Maki has shown that
infection complications occur almost exclusively with
those cannulae which are colonised by moderate to high
numbers of bacteria (Maki, 1977). Studies employing this
technique to culture all cannulae after removal have
shown that significant bacterial contamination occurs in
1.4% - 10% of cannulae (Maki et al, 1977; Tully et al,
1981; Righter, Bishop & Hill, 1983).

Bacterial infection does not appear to be a major cause
of ITP despite providing an excellent portal of entry for

micro-organisms at the cannula insertion site. Many studies have failed to show the correlation between infection and ITP. Kay and Roberts (1967) showed that only 2 out of 23 catheters had positive cultures and no ITP. Banks et al (1970) were able to culture micro-organisms from 45% of catheter tips but only 4 out of 118 patients had bacteraemia attributable to the same organisms (0.03% with ITP). In a study of 130 patients Stephen et al (1976) obtained a positive bacterial culture of 48%, with no associated septicaemia.

It is not neccessarily true that, just because a person develops phlebitis and also has a positive culture from the catheter tip, that the two are associated. One possible explanation could be that the catheter tip becomes contaminated on withdrawal of the cannula as micro-organisms grow on the skin and around the cannula puncture site.

Skin Care

The relationship of pre-insertion and regular IV site skin care on the incidence of phlebitis has been examined. Smallman, Burdon, and Alexander-Williams (1980) reported that all 21 patients in their study who had no initial site care developed phlebitis. Other researchers (Couchonnal, Hodges, Barnes, Elmets & Clark,

1979; Thompson, Jowett, Folwell & Sutton, 1989) compared alcohol versus providone-iodine pre-insertion skin preparation and reported no statistically significant differences in symptom development. Daily dressing changes for peripheral IV sites have not demonstrated a reduced risk for developing phlebitis (Leibovici, 1989; Maki & Ringer, 1989).

The application of an antibiotic ointment to the IV site post-insertion did not affect the phlebitis rate in a well-controlled double blind study (Zinner et al, 1969). Norden (1969) also found no difference in phlebitis rates in a randomised clinical trial of the same antibiotic ointment. Couchonnal et al (1979) compared providone - iodine ointment, providone-iodine solution, and no skin preparation and reported the highest phlebitis rate in the ointment group.

Dressing Type

Still another consideration is the use and type of dressing over the IV site. A recent comparison (Hoffman, Western, Kaiser, Wenzel & Groschel, 1988) of a dry sterile dressing with transparent dressings (TP) resulted in no difference in symptoms. In other studies (Gantz, Presswood, Goldberg & Doern, 1984; Craven et al, 1985; Littenberg & Thompson, 1987) a significantly higher rate

of IV symptoms in the TP group was reported.

Tubing Change

Most intravenous therapy associated infections are cannula related as opposed to infusate related. The incidence of these infections tends to increase with the duration of cannulation (Tager et al, 1983). Thus, the Centre for Disease Control recommends that a cannula be removed and the IV infusion restarted at a new site after 48 to 72 hours have elapsed. By contrast, infections related to microbial contamination of infusate occur much less frequently than cannula related infections, and have generally resulted from intrinsic contamination which have occurred in epidemics (Goldmann et al, 1979; Maki, 1981).

Based on the findings of studies conducted during the epidemics of 1970 and 1971, hospitals began to change IV tubing routinely every 24 hours. This practice continued until 1979 when two studies (Buxton et al, 1979; Band & Maki, 1979) showed no important difference in the fluid contamination rate in tubing changed at 48 instead of 24 hour intervals. That administration sites were changed at 24 or 48 hours had no influence on the infection rate or the development of phlebitis was also supported by Nichols, Barstow and Cooper (1983), Garbed et al, 1984

and Covey et al, 1988. Because the 1979 studies revealed that contamination occurred at very low rates and in very low concentration and was unrelated to infection, questions about the need to change the tubing any more frequently than the cannula were raised (Simmons et al, 1982). This would not hold true if cannula life was prolonged for as long as 4-5 days as bacteria could accumulate (particularly in dextrose solutions) leading to potential sepsis. No studies to date have compared infection and phlebitis rates to administration set changes that have been greater than 48-72 hours.

IV Teams

Implementation of IV teams which are responsible for placement and care of intravenous catheters, has been associated with decreased septic morbidity (Bentley & Lepper, 1968; Fuchs, 1971; Maki & Ringer, 1987). It has also been demonstrated that trained intravenous therapy teams may decrease the incidence of catheter phlebitis, in part, by controlling factors related to the development of phlebitis (for example, catheter size and type, cannulation location, and dwell time). Most of these studies, however, have been of relatively short duration, 2 to 10 months, and may not have accurately demonstrated the consistency of IV teams as it regards infusion phlebitis (Cosentino, 1978; Bair & Peterson, 1979; Hershey et al, 1984; Tomford et al, 1984).

Although IV therapy teams seem to be able to reduce IV complications, the primary benefit of an IV therapy team may relate more to other activities such as standardisation of policy, procedure, and IV products, as well as promotion and adoption of national standards of practice. These activities lead to increased quality of care, efficiency of intravenous therapy, and decreased patient morbidity with associated reduced health care costs.

As can be seen from this review, the factors leading to or causing infusions to fail are many and no _one_ factor has been shown to be responsible for failure. The ideal would be zero infusion failure, this, however is not possible.

The prolongation of peripheral infusion sites is desirable, especially in particular groups such as children and babies, where infusions only tend to last up to a couple of days. There have been many strategies used for the prevention and reduction of infusion failure, some of these strategies will now be discussed.

Methods Used to Reduce Infusion Failure

Investigations into the aetiology of infusion failure have resulted in an awareness of the need to prevent or minimise such complications, and hence various strategies

have been implemented. Examples of such strategies include frequent changing of cannula site, the use of steroids and heparin, venodilation, in-line filtration and the buffering of acidic solutions. All reduce the frequency of phlebitis to some extent, but due to the multi-aetiological nature of ITP, it still remains a common problem.

Length of Cannulation

Since duration of cannulation seems to be one important contributing factor in the development of infusion failure many, if not all, clinical settings have recommended that the infusion site be changed every 48-72 hours. This is not always practical and difficult to police. In certain patient sub groups, for example, neonates and oncology patients may have few veins and hence the veins in use are allowed to run until they fail.

Neutralisation of Solutions

The pH of an infusate has commonly been implicated as a cause of ITP (Elfving, 1966; Fonkalsrud et al, 1968). Most infusates of dextrose have an acid pH of around 4, this is necessary to prevent caramelization during sterilisation. Animal experiments have shown that the endothelium is very sensitive to pH. Following

cannulation, platelet adherence occurs on the damaged endothelium which results in leucocyte infiltration and oedema of the vessel wall. The damage may spread proximally and cause intra-luminal thrombosis. These changes are enhanced by prolonged infusions and reduced by solutions of neutral pH (Eremin & Marshall, 1977).

In a study by Fonkalsrud et al (1968) buffered solutions produced less damage than did unbuffered solutions when infused into the veins of dogs. Local veno-constriction was also substantially reduced in the veins of sheep ears when 25% dextrose was neutralised (Lewis & Hecker, 1984). Hessov and Bojsen-Moller (1976) showed that less histological damage occurred in ear veins of rabbits when 5% dextrose was neutralised. Bolton Carter et al (1952) found no connection between low pH and thrombophlebitis. However, at that stage, red rubber infusion tubing was used and perhaps this interaction of rubber and pH of the solution had some bearing on the reported results.

Solutions containing dextrose have a pH of around 3.4 - 5, while other solutions a pH of 5-6 (Tse & Lee, 1971) and hence, most studies have shown that the buffering of acidic solutions to near neutralisation reduces the incidence of ITP (Page et al, 1971; DeLuca et al, 1975; Eremin & Marshall, 1977; Bivins et al, 1979; Hecker et al, 1991). Hecker et al (1991) were able to show beneficial effects in premature babies by the

neutralisation of TPN. The median survival of infusion sites increased from 21 to 33 hours. When dextrose in TPN given through peripheral veins was replaced by glycerol (non acid) the incidence of phlebitis decreased from 68% to 27% (Rypins et al, 1990).

The common buffers used are bicarbonate and phosphate. The addition of buffer has probably not been widely practised because of the risk of environmental contamination and manufacture of these neutralised solutions does not seem feasible.

In-line Filtration

Since infusions, in particular those to which medications have been added, contain microscopic particles, the use of filtration has shown to be effective in delaying the onset of phlebitis and prolonging infusion survival time. Dramatic effects were noted with infusions to which antibiotics were added (Allcutt, Lort & McCollum, 1983; Falchuk, Peterson & McNeil, 1985). In two controlled doubleblind studies by Collin et al (1973) and Thayssen et al (1977) the use of in-line filters had no effect. Other studies, such as that by Ryan et al (1973), reported a reduction in the incidence of phlebitis from 50% to 10% after filtration. Results from studies using different size filters is also conflicting with seemingly little difference on phlebitis rates; Maddox et al (1977)

used 0.2 um; Evans et al (1976) 5 um and Rusho and Bair (1979) 0.45 um.

Patients requiring filtration would include those with immunodeficiency disorders, those receiving parenteral nutrition, and any patients receiving infusions to which medications of a high particulate load have been added, for example, drugs requiring reconstitution (Adams et al, 1986), however, this may not be cost effective.

In-line filters may also effect drug administration. In-line filters are able to retain inadvertent contaminants such as bacteria, particulates and microbubbles which may arise during the setting-up and manipulation of IV sets. Due to the filter retaining these contaminants, the likelihood of an infection occurring in the IV line itself is reduced (Quercia et al, 1986). Effectiveness of line filters in the prevention of phlebitis, but ineffectiveness in preventing systemic infection has been reported (Simmons, Hooton & Wong, 1982). However, it seems to be important to use in-line filters in view of infection prophylaxis in the paediatric field, particularly for neonates who are, in a sense, the immunocompromised host, even though they are healthy.

In adults, the effect of in-line filtration on delivery seems of little importance because of the relatively high flow rate, the exception being absorbable medications and

some medications which are delivered in small dosages (DeLuca, 1979; Butler, Munson & Deluca, 1980). However, in the neonate, the flow rate is very low and may therefore constitute a serious drug administration problem in utilising the in-line filter, particularly with a drug having a narrow safety margin of drug concentration in the blood.

Vasodilation

The concept of veno-constriction leading to infusion failure has previously been discussed. Lewis and Hecker (1984) have shown that veins react to irritant solutions by constricting, thus reducing blood flow immediately surrounding the cannula. They also showed that an increase in venous tone occurred less frequently in the presence of vasodilators. The two substances used to provide vasodilation were percutaneous Nitroglycerine and intravenous Papaverine which was added to the infusate.

If veno-constriction is a major contributing factor in the development of infusion failure, then the possibility of reducing its frequency by keeping infused veins dilated exists. Wright, Hecker, and Lewis (1985) showed that the incidence of infusion failure due to phlebitis and extravasation could be significantly reduced by the application of transdermal Glyceryl trinitrate (GTN) patches at the cannula site, thereby supporting their

hypothesis. The problem with the study by Wright et al (1985) was that patients came from different wards where the nature of the cannulae and cannulation techniques employed may have been different. Khawaja et al (1988) replicated the above study in 340 patients and found a highly significant difference ($p<0.0001$) in the infusion failure rate using GTN patches (55% to 19% reduction). The median time to survival was 74 hours vs 127 hours in the control group compared to the treatment group respectively. In a further study using transdermal GTN for peripheral TPN infusions, Khwaja et al (1991) were again able to significantly reduce the incidence of infusion failure.

Venous access in children and neonates is a problem with many sites failing within 36 hours (Alpan et al, 1984). The only study conducted in neonates using transdermal GTN in an attempt to reduce infusion failure was by Hecker (1990). He reported that GTN was ineffective in prolonging IV infusion sites, this is in contrast to previous studies done on adults. Glyceryl trinitrate induces vasodilation and hence increases local blood flow around the cannula. This increase in blood flow helps dilute the infusate and buffer its acidity (Ansel, 1971). In neonates, the venodilation is not sufficient to allow such dilation and buffering, and so this "tight fit of cannula" may actually impede blood flow resulting in site failure (Hecker, 1990).

Since vasodilation is a crucial step in the preparation of neonatal veins for venipuncture and is also a preventative measure to reduce infiltration which is the predominant complication of neonatal IV therapy, other methods may need to be employed. These methods may include, an adequate heat source to the neonate to promote vasodilation and minimise neonatal distress; placing the neonate's extremity in a dependent position and allowing gravity to increase venous volume; applying a warm pack to the planned insertion site; and removing the vent plug from the catheter flashback chamber and pre-flush the small gauge IV catheter allowed fluid to exit through the stylet and bevel. The use of heparin to prolong survival of infusion sites in neonates (Alpan et al, 1984) may also be preferable to GTN.

Steriods and Heparin

The use of heparin and corticosteroids has been investigated as a method of reducing ITP and has been found to be successful in the majority of cases (Hessov & Bojsen-moller, 1976; Stephen et al, 1976; Eremin & Marshall, 1977; Woodhouse, 1979; Bass, 1985).

The effect of steroids, for example, hydrocortisone alone in reducing the incidence of infusion failure is inconclusive. While some studies have reported steroids

to decrease the incidence of ITP (Fonkalsrud et al, 1971; Sketch, Cale, Mohiuddin & Booth, 1972), others have not (Clark, Polak & Hajnal, 1960; Bivins et al, 1979). The anti-inflammatory effect of such medications may be of relevance since they inhibit prostaglandin production via lysosomal enzyme stabilisation (Hecker et al, 1984). The dosage recommended is 10mg/litre of hydrocortisone. This has high local concentrations upon entering the vein and negligible systemic effects.

Steroids are not added routinely to infusions since they have the ability to mask inflammatory reactions that occur locally or systemically. They may also inhibit defence mechanisms and thus potentially increase the risk of septic phlebitis.

Some studies have suggested that hydrocortisone with the addition of heparin act in a synergistic manner (Messing, Levene, Rigaud et al, 1986; Reid et al, 1990). Bass, Freeman, Makavewicz, Sproule and Fairfull-Smith (1985) showed that superficial infusion phlebitis could be effectively prevented by the addition to the infusate of an "antiphlebitic mixture" comprising of heparin/hydro-cortisone/sodium bicarbonate. The dosages used were 1000 IU, 5 mg, and 2.5 mmol respectively per litre. It would appear that the combination of heparin and hydrocortisone has a preventative effect on infusion phlebitis (Fonkalsrud et al, 1971; Sketch et al, 1972; Bivins et

al, 1979). The dosage used in these studies was 1,000 units of heparin and 10 mg hydrocortisone to 1 litre of infusate.

The use of heparin has been investigated as a method of reducing the incidence of ITP and has been found to be successful in the majority of reports. It is suggested that, upon cannulation a small fibrin clot may form at the tip of the cannula (Tanner et al, 1980); this then provides a nidus for both endogenous and exogenous bacteria to grow. The addition of heparin to the infusate is believed to slow down this process of fibrin formation and hence delay the occurrence of phlebitic changes. In the study conducted by Tanner et al (1980) it was shown that the incidence of both cannula related sepsis and phlebitis was significantly reduced in those patients receiving low-dose heparin (1000 units per litre of infusate) and patients receiving sub-cutaneous low-dose heparin (5000 units eight hourly). The incidence of phlebitis was decreased from 53% to 8.3% and positive bacterial cultures from cannulae from 36% to 5.5%.

The findings of Tanner et al (1980) are consistent with those of Daniell (1973) in that heparin added to the infusate significantly reduced the frequency and severity of ITP. Other studies also support these findings (Wessler & Rogers, 1952; Sketch et al, 1972). The reduction of infusion phlebitis from 21% to 14%, 44% to

9% and 53% to 8% was reported by Sketch et al (1972), Daniell (1973) and Tanner et al (1980) respectively. The addition of heparin to TPN infused through peripheral veins has also been found to prolong the survival of infusions in adults (Messing, 1985) and in neonates (Alpan et al, 1984).

Reasons why heparin is not routinely added to the infusate include bacterial contamination and the fact that a rare but serious risk of thrombocytopenia may be induced. Surgical patients may also be at risk from bleeding.

The use of Hirudoid ointment (containing heparinoid) has also been employed with encouraging results although its use appears limited (Hastbacka & Tammisto, 1967; Woodhouse, 1979). In the study by Woodhouse (1979) Movelat cream (containing hydrocortisone and heparinoid) was used. As heparin is a large molecule, and its absorption through skin is questionable, the results reported by Woodhouse are probably due to a hydrocortisone effect. The topical effect of these creams in the prevention or reduction of infusion thrombophlebitis needs further investigation.

Although the addition of heparin to infusate to prevent infusion failure is well documented in adults, there is little data available for the paediatric population.

Alpan et al (1984) conducted a controlled study of heparinisation of total parenteral alimentation solutions administered through peripheral veins in premature infants. Heparin was found to double the duration of patency of intravenous catheters and to reduce significantly the incidence of phlebitis. The sample group, however, was small and incompletely controlled for several confounding variables relating to catheter life, the incidence of phlebitis, or both.

In a study of 113 neonates using low-dose heparin infusion, Treas and Latinis-Bridges (1991) were able to increase the mean duration of catheter patency from 27.3 hours to 62.7 hours. The occurrence of infection, bleeding and extravasation was reported to be zero. The amount of heparin used was 0.5 units per ml of solution. In another study on neonates Moclair, Hecker, Willson and Bates (1992) prolonged the survival of peripheral intravenous sites in premature infants by using heparin added to TPN solutions. The amount of heparin used in this study was 0.1 iu/ml 0.25 iu/ml, 0.5 iu/ml, and 1 iu/ml of solution (iu = international unit).

All published studies to date conducted on the paediatric population have been on neonates. Only one study has looked at children. In a double-blind randomised trail, Wright, Hecker and McDonald (1995) were able to significantly reduce infusion failure in children. The

median time to failure was 97 hours and 43 hours with an without heparin respectively. The amount of heparin used was 1 iu/ml of solution. The minimum effective concentration of heparin needed to reduce infusion failure in adults has not been determined. However, Moclair et al (1992) have found that the addition of 0.5 iu/ml to be as effective as 1 iu/ml.

The number of methods reported to reduce infusion failure have been many. They range from in-line filtration (Deluca et al, 1975) and changing of lines (Covey et al, 1988) to neutralisation of acid dextrose solutions (Fonkalsrud et al, 1968; Lewis & Hecker, 1984) and the administration of steroids (Decock, Vermeij & Stijnen, 1984), heparin (Schafermeyer, 1974; Messing, 1985; Alpan et al, 1984) and glyceryl trinitrate (Wright et al, 1985). All these strategies have reduced infusion failure to some extent. However, a meta-analysis (Hecker, 1992), suggests that steroids, heparin or glyceryl trinitrate are most effective.

Bacterial colonisation and thrombus formation are believed to result from fibrin deposits forming along the catheter and intravascular portions of the vessel upon cannulation (Tanner et al, 1980; Maki, 1982). This may result in blockage and development of infusion phlebitis/ extravasation with serious deleterious effects such as systemic sepsis and possible tissue necrosis.

The pharmacological action of heparin in reducing thrombus formation has been the premise behind its ability to prolong infusions and reduce complications. Studies have also demonstrated other beneficial properties such as anti-inflammatory (Simmons, Burdick & Schaub, 1987), anti-irritant (Ekre et al, 1986), tissue healing (Majack & Borstein, 1985), and the maintenance of endothelial integrity and homeostasis (Hiebert & Jaques, 1976).

It may be possible that the above effects of heparin also contribute to reducing the failure of infusions. No study to date has been conducted linking these specific properties of heparin to reducing infusion failure.

Aims of Research

The aims of this study were to:-

1. determine and compare the incidence of infusion failure in a given paediatric population;

2. test the efficacy of low-dose heparin for increasing the survival of intravenous infusions and vein usage in children;

3. test the stability of heparinized solutions over a period of time.

Research Questions

1. What is the incidence of infusion failure in given paediatric population (Study 1).

2. Does the addition of low-dose heparin to infusate increase the survival of intravenous infusions in children (Study 2).

3. Do various heparinized intravenous solutions maintain their stability over time (Study 3).

Research Hypotheses

1. The addition of low-dose heparin to infusate will decrease infusion failure in children (Study 2).

2. Various heparinized intravenous solutions will maintain their stability over time (Study 3).

CHAPTER 2

CONCEPTUAL FRAMEWORK

The use of conceptual frameworks or models is a common inclusion in many theses. This study draws upon (in part) the theories of Levine and Roy as well as incorporating a physiological model. Before discussing the above a brief outline of the advantages and disadvantages of model application is in order.

Nursing Models

Positive and negative results can ensue from the use of models for depicting aspects of a practice-oriented profession such as nursing. The following advantages of models are set forth by Lippitt (1973) and have transferability to nursing practice. First, models allow experimentation without risk. By using model building techniques, a wide range of alternative interventions for any given problem can be addressed without actually altering the status quo. Such an approach takes a "what if" orientation. The model builder might initially set forth the current situation and then experiment with a variety of variables by considering: "What would be most likely to happen if I did.... ?" The range of human reactions and responses to any change in the status quo cannot always be accurately predicted, but some ideas can

be gleaned by considering the responses of the persons involved to previous change events.

A second advantage of using models, especially as a preliminary state in the change process, is that models tend to be good predictors of system behaviour and performance. However, models may be more accurate as describers than as predictors. Any attempt at prediction must consider the wide range of human variables which could easily influence the outcome of the process.

A further advantage of model development for nursing practice is that models promote higher levels of understanding of the system than have been previously held. To construct a model of a real world situation, careful attention must be paid to looking at each element as well as the relationships between them. By providing a careful assessment of the situation under consideration the model-building process promotes heightened awareness of the relative significance of each component. For example, if any change in A would most likely affect B, C, and then D, then A is central to the situation or problem being considered. Moreover, model building may often indicate where missing data exist. If a situation is being graphically depicted and there suddenly appears a gap in information, then the process has been useful.

The disadvantages inherent in model development may

include a tendency to overgeneralise in an attempt to fit all the information available into a pre-established set of categories. The model builder may be tempted for the sake of simplicity and convenience to make the situation fit the model rather than trying to fit the model to the situation. Models have no truth in and of themselves; their accuracy lies in how well they describe reality.

The lack of readily available evaluative tools also may be a disadvantage in model building. Once the model is built there may not be a clear-cut way to evaluate its effectiveness.

The separate theories (models) of Levine and Roy and the commonality of these models are used as the theoretical basis for this study. A physiological model will also be utilized.

Theoretical Framework

M. Levine (Conservation Model)

In order to understand Levine's theory of nursing, it is necessary to consider her definition of nursing. Levine's definition of nursing makes three assumptions: (1) Nursing is an human interaction. (2) Nursing is a discipline based on the idea that people are dependent on their relationships with other people. (3) Nursing is

based on intervention that supports or promotes the patient's adjustment.

There are four major components to Levine's theory.

1. The patient is in the predicament of illness.

2. The nurse must recognise the organismic manifestation of the patient's adaptation to illness.

3. The patient's environment includes the nurse.

4. The nurse must recognise the organismic response of the patient, must make an intervention in the patient's environment and must evaluate the intervention as therapeutic or supportive (Fawcett, 1986, p.116-125).

Levine views each individual as a holistic being whose response is "organismic" as he/she attempts to adapt to the environment. To the individual society is the total environment which incorporates the nurse, the individual's family and significant others (Chinn & Jacobs, 1987, p.51).

Illness depicts the normal balance within the individual and so the goal of nursing is to restore a holistic balance (Fawcett 1986, p.121-122). Health practices tend to relate to illness and "Nursing is viewed as supportive and therapeutic interventions based on scientific or theoretical knowledge. Supportive interventions are

designs to maintain a state of wholeness as consistently as possible with failing adaptation. Therapeutic interventions are designed to promote adaptation that contributes to healing and restoration of health. All nursing actions are based on conservation of energy, structural integrity, personal integrity, and social integrity" (Chinn & Jacobs, 1987, p.51).

Levine explicity identified the assumptions underlying her model as the "conservation principles". Her presentation of the model indicates that she values a holistic approach to nursing care of the ill person. She also values the unique individuality of each person, as noted in such comments as:

"Ultimately, decisions for nursing intervention must be based on the unique behaviour of the individual patient .... A theory of nursing must recognise the importance of unique detail of care for a single patient within an empiric framework which successfully describes the requirements of all patients" (Levine, 1973, p.6).

"Patient centred nursing care means individualised nursing care. It is predicated on the reality of common experience: every person is a unique individual, and as such requires a unique constellation of skills, techniques, and ideas

designed specifically for them" (Levine, 1973, p.23).

In Levine's theory of nursing, nursing is human interaction. This is based on the idea that people are dependent on their relationships with others. The nurse has the responsibility to intervene in the patient's situation after recognising the patient's organismic response. Nursing interventions are supportive (maintain the status quo) or therapeutic (promote healing and restoration). The nurse's interventions are based on the four conservation principles. These are: 1. conservation of energy, 2. conservation of structural integrity, 3. conservation of personal integrity, and 4. conservation of social integrity. These conservation principles provide a guideline for viewing the individual in a holistic manner.

The first two principles, conservation of energy and conservation of structural integrity appropriately support the reduction of infusion failure in children.

By decreasing the risk of infusion failure and by lowering the incidence of phlebitis and extravasation, energy would be conserved. Otherwise, this same energy would be needed by the child to help overcome the possible serious complications to IV therapy, for example, septicaemia, which could indeed prolong the

child's hospitalization. The second principle of Levine's model is the promotion of physiological or structural integrity. During infusion failure, the vein wall becomes damaged due to various physical, microbial and chemical processes. This damage results in loss of structural integrity and eventually loss of vein function. By reducing the incidence and risk of vein loss, structural integrity of the childs vein is conserved.

Although four conservation principles are used by Levine as viewing the individual as a holistic being, the principles of conservation of energy and structural integrity may be directly linked to preventing the failure of intravenous infusions in children. One must bear in mind, however, that all four are inter-related.

Levine's theory does relate to the concepts of humanity, society, health, learning, nursing, and the nursing process. Its major limitations, however, may relate to its focus on the individual, on illness, and on the patient.

C. Roy (Adaptation Model)

The other model which may be used as a basis for this study is that of Roy who used the underlying assumption of 'adaptation' as her conceptual model.

In Roy's model, the individual is a biopsychosocial being who is whole and who interacts constantly with the environment. The individual can adapt to environmental change through psychosocial adaptive mechanisms. The need for adaptation and the level of adaptation take the form of focal, contextual and residual stimuli. There are four basic needs of adaptation: 1. physiologic, 2. self-concept, 3. role function, and 4. interdependence. Adaptation hence ensures when excesses or deficits in need occur (Fawcett, 1986, pp.251-253).

Roy saw the environment as being conceptually central in that there are constant interactions with the individual providing energy, matter and information to the person. Stimuli originate in the environment (Fawcett, 1986, pp.253-254).

She viewed health as a continuum from death to peak wellness, the central area of which was 'normal health'. Health is a state of human functioning in which cultural adaptation occurs. Maladaptation to environmental change results in poor health (Fawcett, 1986).

Nursing is viewed as "an interpersonal process that is initiated by the individual's maladaption to change in the environment. Nursing actions are directed to reducing or removing stimuli and to enhancing the adaptive level of the individual" (Chinn & Jacobs,

1987).

Roy stated the assumptions upon which her conceptual model was developed clearly and concisely. She also explicated four basic values implied by the model. These values are:

1.   Nursing's concern with the person as a total being in the areas of health and illness is a socially significant activity.

2.   The nursing goal of supporting and promoting patient adaptation is important for patient welfare.

3.   Promoting the process of adaptation is assumed to conserve patient energy; thus nursing makes an important contribution to the overall goal of the health team by making energy available for the healing process. This point is consistent with the 'conservation of energy principle' put forward by Levine.

4.   Nursing is unique because it focuses on the patient as a person adapting to those stimuli present as a result of their position on the health-illness continuum (Roy, 1980).

Roy identified the recipient of nursing care as an adaptive system (Roy, 1976). Adaptive responses promote the integrity of the person as related to survival. Ineffective responses do not promote the person's

integrity as a system (Roy, 1976). By viewing the child as an open adaptive system (Roy, 1976), the effects of stress, both internal and external are apparent. By responding to the environment, the child interacts with stressors to an end product of either adaptive (survival) or maladaptive (deterioration in condition) behaviour. The frequent attempts of recannulation (due to infusion failure) and the associated pain, interact with other stressors to determine the adaptive level of children.

This study will show heparin to be effective in reducing infusion failure in children. Use of such a strategy, then, reduces the amount of stress, both physical and psychological, to which the child is exposed. With this stress reduced, the child will have a higher adaptive level with which to respond to the other stressors in the environment. This highly adaptive level increases the child's potential for adaptive responses and thereby increases chances for survival.

Physiological Framework

The models of Levine and Roy have been used as the theoretical basis for this study. A physiological conceptual basis may also be used, and in fact, complements the theories of Roy and Levine.

Over the past 35 years, the administration of fluids and

medications intravenously has become routine, particularly for patients hospitalised for a variety of medical and surgical conditions and diseases. The use of the IV route for therapy has been associated with the general increase in phlebitis, an inflammation of the vein itself.

Phlebitis occurs as the result of inflammation of the walls of a vein. In IV therapy, the vein is pierced by a needle and causes injury and direct trauma to the wall of the vein. This injury may cause only pain and discomfort of a temporary nature to some patients, with no inflammation. For other patients, the initial injury and trauma to the vein are the first steps in the inflammation process associated with phlebitis.

Once in progress, phlebitis causes warmth, redness at or around the site, and oedema of the affected vein, often with pain and tenderness. This inflammatory process involves a series of physiologic and chemical responses to tissue injury. Almost immediately after venipuncture occurs, the damaged tissue releases large quantities of histamine, bradykinin, and serotonin. This histamine stimulates dilation of the blood vessel and causes an increased blood flow to the area, which in turn causes redness and warmth to develop at the puncture site. An increase in capillary permeability allows fluid and protein to shift from the intravenous to the interstitial

space. This results in oedema, pain and some loss of function at the site area. As this process increases with continued therapy, the defence mechanisms of the body cause leucocytes to concentrate at the site and, in time, oedema and pus formation occur. The dying leucocytes release endogenous pyrogens, which are picked up by the blood and circulated to the hypothalmus, thus triggering a rise in general body temperature. Pyrogens also circulate to the bone marrow, where they stimulate the release of leucocytes into the blood stream, which results in an elevated white blood cell count (Taylor, 1983).

In general terms, this study is able to utilise the underpinnings of the previously mentioned theorists Levine and Roy. There seems to be a common thread, either implicit or explicit, which links these theories. This thread is that of the attainment and/or maintenance of holistic individual well-being/welfare.

Both theories support the notion of adaptation, structural integrity and energy conservation (re-direction). By reducing the failure of intravenous infusions by the addition of low-dose heparin to infusate due to phlebitis and extravasation, this intervention strategy will enhance positive adaptation by the child, maintain structural integrity of the vein and promote positive energy which the child may use to 'cope' with

other aspects of illness.

Levine, in Fawcett (1986) states, "the goal of all nursing care should be to promote wholeness, realising that for every individual that requires a unique and separate cluster of activities. The individual's integrity - his one-ness, his identity as an individual, his wholeness - is his abiding concern, and it is the nurse's responsibility to assist him to defend and to seek its realisation".

One of the prime goals, then, of nurses should be the attainment and maintenance of patient welfare. This is reflected in the quotations "the nurse participates actively in every patient's environment, and much of what she does supports his adaptations as he struggles in the predicament of illness" (Levine, 1973) and "but even in the presence of disease, the organism responds wholly to the environmental interaction in which it is involved, and a considerable element of nursing care is devoted to restoring the symmetry of response - symmetry that is essential to the WELL-BEING of the organism" (Levine, 1969b).

The above models can thus be employed to guide nursing assessment and intervention (both physical and psychological) of children who are at risk of infusion failure. The holistic approach (physiological,

psychological, social) will enable stressors to be identified. Once identified, these environmental stressors, as well as the patient's own stress (anxiety) may be reduced. The child's well-being or welfare is thus preserved.

By improving the infusion survival rate of the child, various physical, physiological and psychoemotional needs are met, energy is conserved, structural integrity is maintained, and adaptation ensues.

CHAPTER 3

ANALYSES AND ANALYTICAL TECHNIQUES

Introduction

One of the features of this project is the "type" of data to be analyzed. Whereas many studies use a combination of attributes and measurements, the majority of data in this study relate to the time taken for an event, for example, infusion failure, to occur.

In the past, most studies have used the statistical analytical methods of Chi square and t-tests to analyze such data. Because infusions can be discontinued over variable time periods, the number that remain, and hence could then fail, decreases with time. To compare failure incidence, studies have used methods that collected data at successive time intervals, usually 12 or 24 hours (Holland, 1982; Bassan et al, 1984; McMullen, 1993). Although the time to diagnosis of phlebitis may have been analyzed, the differences in proportions of infusions has largely been ignored (Hershey et al, 1984) whilst other studies have ignored "time" effects (Eremin & Marshall, 1977; Tanner et al, 1980; Van der Broek, 1989). Previous studies also have failed to acknowledge the point that if infusions are electively discontinued this then reduces the number that could potentially fail.

Such studies report numerous variables as being "significant", few have attempted to determine which of these factors have been due to associations with other factors.

Since the data to be collected reflect the "survival" of infusions, a more appropriate method of analysis would be the use of Life Table (Univariate) and Cox's Proportional Hazards Model (Multivariate) survival analysis. The advantage of these methods is that they take into consideration both the differences in the duration of infusions and the fact that, since many cannulae are removed for reasons other than failure, the number of infusions still functional and which therefore can fail decreases with time.

Survival analysis has been used in the past to obtain information on cancer patients (Peto et al, 1977) and was first used by Alcutt et al (1983) for data on intravenous infusion failure. One can draw an analogy between cancer and infusion failure in that death from cancer and failure of infusions occur over variable time periods during which subjects are continually lost - through elective discontinuation of infusions and through other causes of death for cancer patients.

The survival time of a patient with cancer is a major criterion for evaluating the treatment the patient

received.   In carcinogenesis experiments, the time to
development of tumour is an important endpoint, as is the
proportion that develop tumors, in the analysis of animal
experiments in which potentially carcinogenic agents are
administered.   In the evaluation of individual or
combinations of agents in transplanted animal systems,
the survival time of the animal is a major (and sometimes
the only) endpoint in the analysis of the study.   Hence
it is worthwhile to consider methodology for analyzing
survival times.   "Survival time" is used in the broad
sense, so that for example the times may be; length of
response, time to recurrence of the disease, time from
start of treatment to first response time, or some other
function or response.

The survival time studies considered are planned studies
(for example, clinical trials or laboratory experiments)
in which a primary purpose was to characterize and
compare survival experience following the administration
of two or more treatments.   Analysis of a consecutive
series of cases with a particular disease was also
considered in which possible aims of the study were to
characterize the survival time and to delineate patient
characertistics related to longer survival.

When there is no prior experience for a particular
survival study, the first objective is to characterize
the data obtained.   Secondly, there is usually interest

in choosing a survival time model that represents the main features of the data with estimates of parameters of the model. Examples of models considered may include exponential, Gompertz, and lognormal.

In studies involving two or more treatments, it is usually important to test whether a real difference exists between the survival distributions for each of the treatments. The assumption is made that survival time is exponentially distributed in the groups being compared.

A special feature of survival time studies, especially in clinical trials with cancer patients, is the occurrence of so-called "censored times". Such observations occur when some individuals are alive or in a well state at the conclusion of the study or at the time of the analysis. Censored times may also occur when individuals are lost to follow-up after some period of study. For example, at the time of analysis the survival times available may be as follows (in weeks): 5, 7+, 11, 17+. The plus values refer to individuals who were observed for the given length of time but have not yet failed. Note that it is not even possible to estimate the sample mean time, since one cannot estimate how long the individuals with plus values will survive.

Put alternatively, censoring occurs when some items are prevented from occurring in a sample. In this present

study a cannula is to be followed until it fails and the time recorded, but, if the cannula is removed because it is no longer needed, then the failure time is known only to be greater than the time to removal.

The problem of testing differences between survival distributions can be considered from a parametric or a nonparametric viewpoint, depending on whether a survival time distribution is specified in the groups being compared. A nonparametric test is valid whatever the form of survival distribution. On the other hand, it is often true, especially in cancer clinical trials, that the survival time distributions are exponential or nearly so, and hence it is appropriate to consider a parametric test for that situation.

Two sampling situations may be distinguished when survival distributions are to be compared. First, groups of individuals may be observed for a fixed period of time so that the number of individuals failing in each group is a random variable. Secondly, the groups may be observed until a fixed total number of failures occur, the observation time being a random variable. In clinical trials with cancer patients, the usual process is that the trial is started at some time point and the analysis done at some fixed time later. Consequently the number of individuals failing in each group is a random variable and tests are conditional on the observed

number of failures in each group.

UNIVARIATE ANALYSIS

(LIFE TABLE METHOD)

Life table analysis (Kaplan - Meier product limit method) calculates for each group of data a "survival curve" which represents the proportion of infusions surviving at any one time. This curve is a descriptive graph drawn as a "step" function and it necessarily decreases with time. It represents the situation where no cannulae are removed electively but all are allowed to continue until they fail. The time when the curve crosses the probability of 0.5 corresponds to the median survival time i.e. the half-life of a survival curve is the time for 50% of infusions to fail.

When comparing two survival curves the "logrank" test is used. This is a non-parametric test which compares the observed number of failures with the expected number of failures in the control group and observed number of failures with the expected number of failures in the experimental group. The P values may be determined by comparing the $\frac{(O-E)^2}{E}$ with the appropriate Chi square distribution. The logrank test then, identifies the significance of differences between groups.

The "related risk of failure" (RRF) is a statistic used

to describe survival curves. The RRF in a group is the ratio of the observed number of failures to the expected number of failures (calculated by life-table analysis). A RRF value of less than 1 indicates fewer than average failures in a group and hence longer survivals.

The Failure Rate Ratio (which is the ratio of the relative rates of failure for two curves) is an estimate of the "magnitude" of differences between pairs of survival curves. For example, a value of 0.5 indicates that one type of infusion is half as likely to fail or a value of 2 would indicate that failure in one group is twice as great as in the second group.

MULTIVARIATE ANALYSIS
(COX'S PROPORTIONAL HAZARDS MODEL)

This type of analysis has gained wide acceptance over the last few years with many authors now incorporating its use in infusion failure (Hecker et al, 1991; Wright & Hecker, 1991).

Cox's proportional hazards model with step wise, maximum partial-likelihood ratio selection of variables can also be used to confirm analysis by univariate techniques (life-table method). This analysis takes into account interactions between factors and selects factors in a stepwise manner until all of the factors selected have a

probability of at least p<0.01. This method can also incorporate prognostic variables such as age, concurrent administration of drugs and rate of administration of fluids. Because of the ability of this test to incorporate and handle mixtures of discrete and continuous variables it is a more powerful, versatile and sensitive test, hence giving a fuller interpretation of the data.

Any distribution of survival time can be characertized by three equivalent functions, which may be defined as follows:

1. *Survivorship function, S(t)*: Probability that an individual survives longer than t. The survivorship function is often called a survival curve.
2. *Hazard function,* λ *(t)*: Limit of the probability that an individual dies in a short interval of time, given survival to time t. The hazard function often is termed the force of mortality or age-specific failure rate. In relation to infusions, "dies" is equivalent to "fails" and mortality to "failure".
3. *Probability density function, f(t)*: Limit of the probability an individual dies in the short interval t to (t +Δ t) per unit width (Δ t).

These functions are mathematically equivalent in the sense that, given any one of the functions, the other two

can be derived (Cox, 1962).

Suppose there is population of individuals, each characterized by a non-negative random variable (T) called its survival time. The survivorship function [S(t)] is the probability (prob) that an individual survives longer than t, that is:

$$S(t) = prob\ (T > t)$$

The basic principle govering proportional hazards model is the concept of "hazard". A hazard at time t, is the probability of an infusion site failing at time t, given that it has survived up to time t. The hazard of any infusion site is its risk of failing at a given point in time.

From Kalbfleisch and Prentice (1980, p32):

If $\lambda(t;z)$ represent the hazard function at time t for an individual with covariates z, the proportional hazards model (Cox, 1972) specifies that

$$\lambda(t;z) = \lambda_0(t)e^{zB}$$

where $\lambda_0(t)$ is an arbitrary unspecified base-line hazard function for continuous T.

Put simply, the hazard model can be defined as:-

Hazard at time t of an infusion site with prognostic variable X = constant (depending on t) x constant (depending on X).

For the purpose of this project, data involving infusion failure/survival will be analyzed using life-table method and Cox's proportional hazards model, where appropriate.

The following section shows how various parts of "survival" data are analyzed (based on subjects with cancer).

Mathematical Expression of Survival

Although life table analysis may be useful in many differing situations and disciplines, for simplicity, the usual survival-time-to-death terminology will be used here.

1. **NOTATION**

   X_j time from starting event ot terminal event or censoring for case j

   w_j weight for case j

   k total number of intervals

   t_i beginning time for i^{th} interval

   h_i width of time interval i

   c_i sum of weights of cases censored in interval i

   d_i sum of weights of cases experiencing the terminal event in interval i

2.   **CONSTRUCTION OF LIFE TABLE** (Gehan (1965))

(a)   **Computation of Intervals**

The widths of the intervals for the actuarial calculations must be defined by the user. In addition to the last interval specified, an additional interval is automatically created to take care of any times exceeding the last. When calculated on a computer the algorithm is such that if the upper limits are not in ascending order, a message is printed and the run terminated. If the interval width does not divide the time range into an interval width the algorithm is reset so that the number of intervals will be the nearest integer to that resulting from the user specification.

(b)   **Count of Events and Censoring**

For each case, the interval i into which the survival time falls is determined.

$$t_i \leq X_j < t_{i+1}$$

If X_j exceeds t_k the starting time for the last interval, it is included in the last interval. The status code is examined to determine whether the observed time is time to event or time to censoring. If it is time to censoring, that is, the terminal event did not occur, c_i is incremented by the case weight. If it is time to event, d_i is incremented by the case weight.

(c) **Calculation of Survival Functions**

For each interval the following are determined:

(i) Number alive at the beginning

$$l_i = l_{i-1} - c_{i-1} - d_{i-1}$$

where l_1 is the sum of weights of all cases in the table.

(ii) Number exposed to risk of an event

$$r_i = l_i - c_i/2$$

(iii) Proportion terminating

$$q_i = \frac{d_i}{r_i}$$

(iv) Proportion surviving

$$p_i = 1 - q_i$$

(v) Cumulative proportion surviving at end of interval

$$P_i = P_{i-1}p_i$$

where $P_o = 1$

(vi) Probability density function

$$f_i = \frac{P_i - P_{i+1}}{h_i}$$

(vii) Hazard rate

$$\lambda_i = \frac{2q_i}{h_i(1 + p_i)}$$

(viii) Standard error of cumulative surviving

$$SE(P_i) = P_i \sqrt{\sum_{j=1}^{i} q_j/(r_j P_j)}$$

(ix) Standard error of probability density

$$SE(f_i) = \frac{P_i q_i}{h_i} \sqrt{\sum_{j=1}^{i-1} q_j/(r_j P_j) + P_i/r_i q_i}$$

For the first interval

$$SE(f_1) = \frac{P_1 q_1}{h_1} \qquad \frac{P_1}{r_1 q_1}$$

(x) Standard error of the hazard rate

$$SE(\lambda_i) = \sqrt{\frac{\lambda_i^2}{r_i q_i} \left\{ 1 - \left(\frac{\lambda_i h_i}{2} \right)^2 \right\}}$$

If $q_i = 0$, the standard error for interval i is set to zero.

(xi) Median survival time

If $P_k > 0.5$ the value printed for median survival time is

$$(t_k - t_1)$$

Otherwise, let i be the interval for which $P_i < 0.5$ and $P_{i-1} \geq 0.5$.

The estimate of the median survival time is then

$$Md = (t_i - t_1) + \frac{h_{i-1}(P_{i-1} - 0.5)}{P_{i-1} - P_i}$$

(3) **COMPARISON OF SURVIVAL DISTRIBUTIONS**

The survival times from the groups to be compared are jointly sorted into ascending order. If survival times are equal the uncensored data are taken to be less than the censored data. When approximate comparisons are done, they are based on the lifetables, with the beginning of the interval determining the length of survival for cases censored or experiencing the event in that interval.

(a) **Notation**

N   number of cases

$X_{(k)}$ survival time for case k, where times are sorted into ascending order so that case 1 has the shortest time and case N the longest

w_k weight for case k

g   number of nonempty groups in the comparison

W_j sum of weights of cases in group j

W_c sum of weights of censored cases

W_u sum of weights of uncensored cases

W   sum of weights of all cases

(b) **Computations**

For each case the following are computed:

(i) ULE_k sum of weights of uncensored cases with survival times less than or equal to that of case k

(ii) CLE_k same as (i) but for censored cases

(iii) UE_k sum of weights of uncensored cases with survival times equal to that of cse k

(iv) CE_k same as (iii) but for censored cases

(v) The score of case k is:

If X_k is censored:

$$S_k = ULE_k$$

If X_k is uncensored:

$$S_k = A_1 - A_2 - A_3$$

where $A_1 = ULE_k - UE_k$ uncensored cases surviving shorter than case k

$A_2 = W_c - CLE_k + CE_k$ censored cases surviving longer than or equal to case k

$A_3 = W_u - ULE_k$ uncensored cases surviving longer than case k

(c) **Test Statistic and Significance** (Lee and Desu (1975))

The test statistic is

$$D = \frac{(W-1)\ B}{T}$$

where

$$B = \sum_{j=1}^{g} SS_j^2 / W_j$$

SS_j = the sum of scores of cases in group j

$$T = \sum_{i=1}^{N} S_i^2$$

Under the hypothesis that the groups are samples from the same survival distribution, D is asymptotically distributed as a chi square with (g-1) degrees of freedom.

Study 1 (infusion site failure), will compare three surveys carried out on infusion failure in children. Two parallel studies were conducted at local Sydney hospitals, while the third at Hammersmith hospital, London.

CHAPTER 4

STUDY 1 - INFUSION SITE FAILURE[##]

Introduction

Failure of intravenous infusions is common. While many studies have been performed on infusion failure in adults (Lewis & Hecker, 1984) and several on babies (Alpan et al, 1984; Phelps & Helm, 1987; Johnson & Donn, 1988; Tobin, 1988; Hecker et al, 1991), little is known about infusion failure in children. The only information relevant to children apart from reports of skin sloughs following extravasation of drugs (Brown et al, 1979) was the study of Nelson and Garland (1987) which presented data from 286 children of mixed ages of whom 104 were babies. They reported that 11% of infusions failed with a median survival time of 69 hours. Two parallel surveys were carried out by the author at local Sydney hospitals to determine the survival (failure) of peripheral infusion sites in children. The first survey was completed at Westmead Hospital where children from a medical ward were sampled. The second survey was completed from Prince of Wales Childrens Hospital (POWCH) where it was anecdotally reported that infusions

[##] Wright, A., Hecker, J.F., McDonald, G. (1995). Extended survival of infusions in children with low-dose heparin plus steroids. Journal of Paediatrics and Child Health (submitted).

rarely failed due to the addition of small amounts of heparin and hydrocortisone added to the infusate. Whilst the above two studies were in progress, a third survey was commenced at Hammersmith Hospital, London, by a colleague of the author's. For comparative value, these data are also presented in this chapter.

Methods

Data were obtained from children in the three previously mentioned hospitals. The 44 children (68 sites) in Hammersmith Hospital, London and the 135 children (136 sites) in Westmead Hospital, Sydney, were surgical and medical patients of whom many required intravenous therapy for only one or two days. In contrast, all 44 children (56 sites) studied in the C5 ward at the Prince of Wales Children's Hospital, Sydney, had respiratory infections secondary to cystic fibrosis and were given intravenous antibiotic treatment for approximately two weeks. Low-dose heparin (1 iu/ml) plus hydrocortisone (10 ug/ml) were added to all fluids given on this ward in order to prolong survival of sites. This was standard procedure on this ward.

In each survey, data were collected using a standard form (see Appendix A). Information such as type and size of cannula, sex, age, date and time of cannulation, site, signs of phlebitis/extravasation, reasons for cannula

removal and type of fluids and drugs infused were recorded. All sites were cannulated by medical staff. Infusions were allowed to run until failure occurred or they were electively removed and the duration of survival of each site was calculated to the nearest hour.

Infusion failure was defined as the occurrence of either extravasation or phlebitis which was determined using the criteria of excessive warmth of surrounding skin, oedema, pain, erythema, and a palpable venous cord. The presence of two or more criteria signified a positive result.

Univariate (lifetable) survival analysis was performed by the method of Peto et al (1977) with the significance of differences between the surveys determined by the log rank test.

The advantage of these methods is that they take into account both differences in duration of infusions and the fact that, since many cannulae are removed for reasons other than failure of infusions, the number of infusions still functional and which therefore can fail, decreases with time. Cannulae which were electively removed were treated as "censored data" and were included in the comparison of probability of survival between groups. Differences in the proportions that failed were tested by contingency table analysis.

Results

Failure was mainly due to phlebitis and/or extravasation (tissuing). The few cannulae which dislodged, blocked or were pulled out were also classified as having failed (Table 1).

In both the Hammersmith and Westmead surveys, at least half of the infusions failed with median half lives of 56 and 52 hours respectively (Table 1, Figure 1). In contrast, only 12 infusions (21%) failed in the cystic fibrosis (POWCH) children (2 in one child) with the majority of cannulae being removed electively after periods of approximately 14 days (median duration of therapy 496 (range 214-651) hours). The median survival half life could not be calculated for these sites as the failure rate was too low but it was in excess of 269 hours. Differences between these three sets of infusions were highly significant ($Chi^2 = 68.5$; $p<0.0001$). While the difference in survival between the Westmead and Hammersmith sites was significant ($Chi^2 = 6.55$ ($p<0.05$); Failure Rate Ratio = 1.95 (survival worse for Hammersmith)), this was small when compared to the differences between the POWCH and Hammersmith data ($Chi^2 = 39.07$ ($p<0.0001$); Failure Rate Ratio = 6.6) and between the POWCH and Westmead data ($Chi^2 = 36.72$ ($p<0.0001$); Failure Rate Ratio = 6.0).

Survival analyses were performed on each set of data for age, cannula, sex, infusion site and infusion of individual drugs. Only one analysis was significant, infusion of metronidazole in the Westmead data (Table 2) which was associated with reduced survival (Chi^2 = 10.08, p>0.005).

Table 1. Data for infusion sites in children in three hospitals

VARIABLE	POWCH[#]	HAMMERSMITH	WESTMEAD
Sites			
No of children	44	44	136
No of sites	56	68	136
Males	17	25	68
Females	27	19	67
Age (months)			
Average	37.8	48.8	47.0
Median site			
survival (hrs)	>269	56	52
Cannula			
19-20 gauge	3	-	0
22 gauge	6	-	9
24 gauge	47	-	35
Site[1]			
Left	31	36	67
Right	22	25	67
Hand	24	32	76
Wrist	5	6	20
Forearm	23	11	15
Foot	1	9	3
Fate			
Elective removal	43	34	36
Tender or slightly[2]			
Swollen	17	3	17
Failed	13	19	100
Tissued	4	-	39
Phlebitis	3	-	37
Tissued + Phlebitis	1	19	10
Blocked or pulled out	5	0	14
Resited	12	13	-
Flow rate (ml/hr)	10-15	-	31

#Prince of Wales Children's Hospital, Ward C5 (patients were children with cystic fibrosis for whom heparin (500 i.u.) and hydrocortisone (5 mg) were added to each 500 ml of infusion fluids).
1 - Three, seven and two sites not recorded for POWCH, Hammersmith and Westmead data.
2 - Noted at elective removal; not classed as failed.
 - not recorded
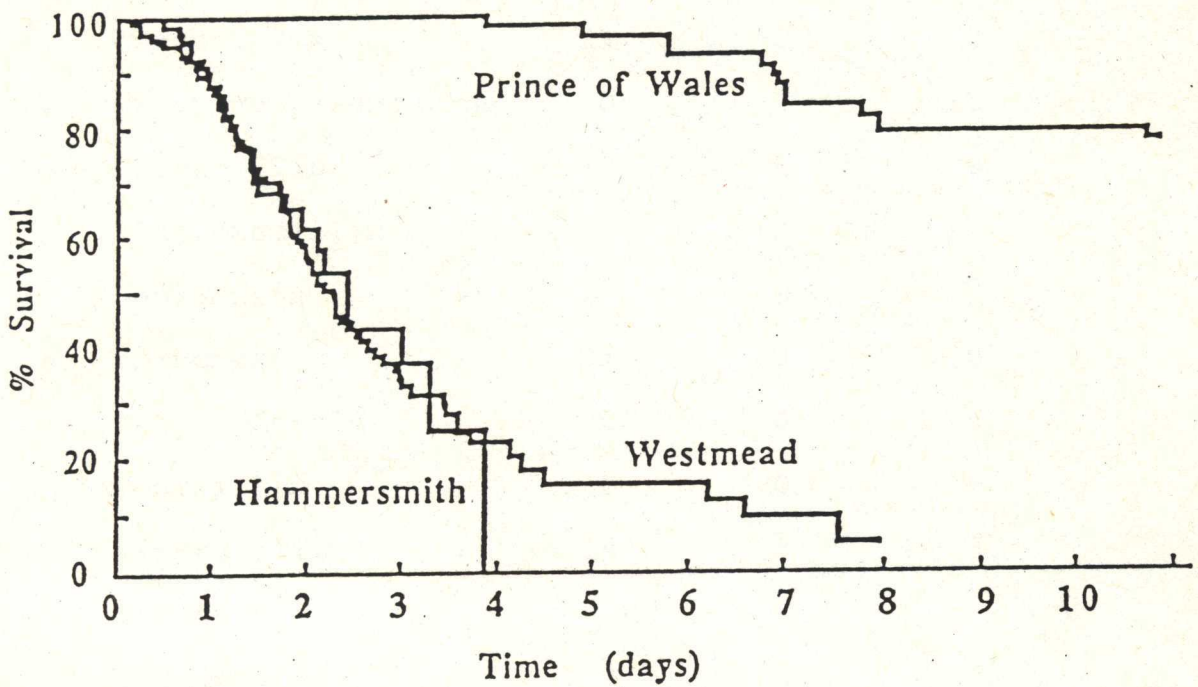
Figure 1. Survival of peripheral intravenous infusion
sites in children. Low-dose heparin plus
hydrocortisone were added to fluids for the
POWCH group

Table 2. Numbers of infusion sites receiving antibiotics in children in three hospitals

VARIABLE	POWCH[#]	HAMMERSMITH	WESTMEAD
Antibiotics			
Ampicillin	4	2	26
Ceftazidime	23	0	0
Other cephalosporins	0	2	13
Cloxacillin	28	0	0
Flucloxacillin	1	2	12
Gentamicin	11	0	7
Imepenem	23	0	0
Metronidazole	0	0	5
Penicillin	0	0	9
Piperacillin	18	3	3
Timentin	7	0	0
Tobramycin	3	0	7
Other antibiotic	44	7	68
Other Drugs			
Aminophylline	0	4	0
Phenobarbitone	0	3	0

antibiotics infused at less than four sites were:-

Amikacin, Chloramphenicol, Colistin and Ticarcillin.

Discussion

Median survival of the infusions in children at Hammersmith and Westmead hospitals appears to be greater than the median survival of infusions found in babies (Tobin, 1988) but less than that found in adults (Hecker et al, 1989). The reason for the first difference may be due to the fact that most babies are given fluids based on 10% dextrose which is hypertonic (Moclair et al, 1992).

The striking aspect of these data is the prolonged survival of the infusions in the children with cystic fibrosis even though all received antibiotics. The number of infusion sites receiving antibiotics in children in the three hospitals is given in Table 2. This long survival in the children with cystic fibrosis children could be due to two factors. First, the flow rate of infusate affects failure (Hecker, 1989; MoClair et al, unpublished observations) and flow in these infusions was usually lower than in the other children as they were given at a slow rate of 10-15 ml/hour to 'keep the vein open'. The other factor is the added heparin and hydrocortisone. Several studies have shown this combination of drugs markedly prolongs survival of infusions in adults (Sketch et al, 1972; Schafermeyer, 1974; Bassan et al, 1984; DeCock et al, 1984; Bass et al, 1985). Heparin and hydrocortisone are routinely added to

infusates at the POWCH only on this ward and it is suspected that survival of infusions on other wards in the Prince of Wales Children's Hospital would be similar to that in the other two hospitals.

These data are significant in that they showed that peripheral infusions in children can be made to survive for long periods. Addition of heparin and hydrocortisone is not without risk for there is the potential problem of platelet abnormalities such as thrombocytopaenia, a greater chance of infection from contamination of solutions if the drugs are added on the ward, and from local depression of defence mechanisms due to the steroid. In spite of these potential problems, studies have shown that the addition of similar amounts of heparin to infusion fluids reduces the incidence of positive tip cultures with central lines (Bailey, 1979; Tanner et al, 1980).

Patients with several types of diseases such as oncology and haematology as well as children with cystic fibrosis often require prolonged or repeated intravenous therapy. While the combination of heparin and hydrocortisone is not indicated for routine use, it should be considered to conserve the superficial veins of such patients.

Conclusion

Infusion failure was studied in children at three hospitals. Survival time was significantly greater in one hospital ward in which children received hydrocortisone and heparin added to the infusate.

As both heparin and hydrocortisone are known to reduce infusion failure in adults, only heparin has been studied in the neonatal population. A double-blind trial was conducted to see if low-dose heparin added to the infusate could prolong the life of the infusion i.e. reduce infusion failure (Study 2) in children. Before this second study is presented, it is important that the nature of the medication Heparin be discussed.

CHAPTER 5

HEPARIN

Heparin is a complex medication and its full biological potential is still being investigated. It is important to gain a basic understanding of the nature of this medication and hence the role it may play in preventing infusion site failure.

Heparin is a naturally occurring mucopolysaccharide produced by basophils and mast cells found in large numbers in connective tissue surrounding the capillaries, particularly those in the lungs and liver. It was first identified in 1916 by a medical student searching for a coagulant in the liver. Since 1936, heparin has been the major medication used in the prevention and treatment of deep vein thrombosis (DVT).

Heparin is composed of multiple subunits of varying molecular weights ranging from 3,000 to 30,000 and averaging 12,000. It is commercially available as a calcium or sodium salt prepared from pork and beef tissue.

Although it is not entirely clear as to how heparin may effect infusion failure, a basic understanding of the properties of this complex chemical is in order to

appreciate the possible ways by which it may influence
infusion failure.

Chemical Properties

The chemical definition of heparin has changed several
times over the years, along with refinement of methods
for purification and structural analysis of
polysaccharides. Heparin is structurally heterogeneous
because of incomplete biosynthetic modifications of its
precursors, and heterogeneous regions are unevenly
distributed in different heparin chains (Lindahl et al,
1986). Such heterogeneity, as well as possible
contamination by chemically related substances, have
certainly hampered the elucidation of even the major
structural features of heparin.

Present-day heparin is defined as a family of
polysaccharide species, whose chains are made up of
alternating, 1 - 4-linked and variously sulphated
residues of a uronic acid and D-glucosamine. Formulae of
the monosaccharide ' building blocks' identified thus far
in heparins are shown in Table 3 and the formulae of
typical heparin sequences are shown in Table 4. A
combination of unit 5 and 6 contains the binding site for
antithrombin (Lindahl et al, 1990; Cast et al, 1991;
Thunberg, Backstrom & Lindahl, 1992).

Table 3. Monosaccharide 'building blocks' identified as heparins (from Lindahl, 1989)

Name	Structure	R-group		Abridged nomenclature	Symbols
uronic acid residues					
(1) α-L-iduronic acid		(a)	R = H	IdoA	I
		(b)	R = SO_3^-	IdoA-2S	I_{2S}
(2) β-D-glucuronic acid		(a)	R = H	GlcA	G
		(b)	R = SO_3^-	GlcA-2S	G_{2S}
glucosamine residues					
(3) N-sulpho-α-D-glucosamine		(a)	R = R' = H	GlcNSO$_3$	A_{NS}
		(b)	R = SO_3^- R' = H	GlcNSO$_3$-6S	$A_{NS,6S}$
		(c)	R = R' = SO_3^-	GlcNSO$_3$-3,6S	$A_{NS,3,6S}$
		(d)	R = H R' = SO_3^-	GlcNSO$_3$-3S	$A_{NS,3S}$
(4) N-acetyl-α-D-glucosamine		(a)	R = H	GlcNAc	A_{NA}
		(b)	R = SO_3^-	GlcNAc-6S	$A_{NA,6S}$

Table 4.   Heparin sequences (from Lindahl, 1989)
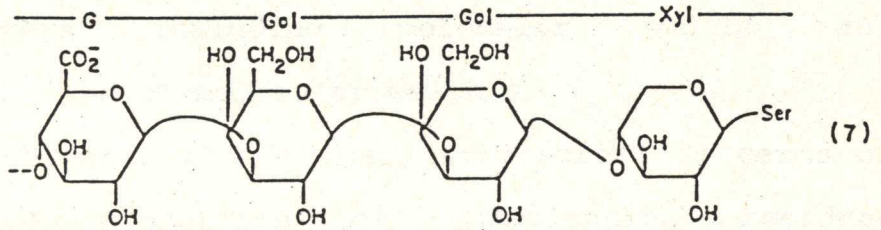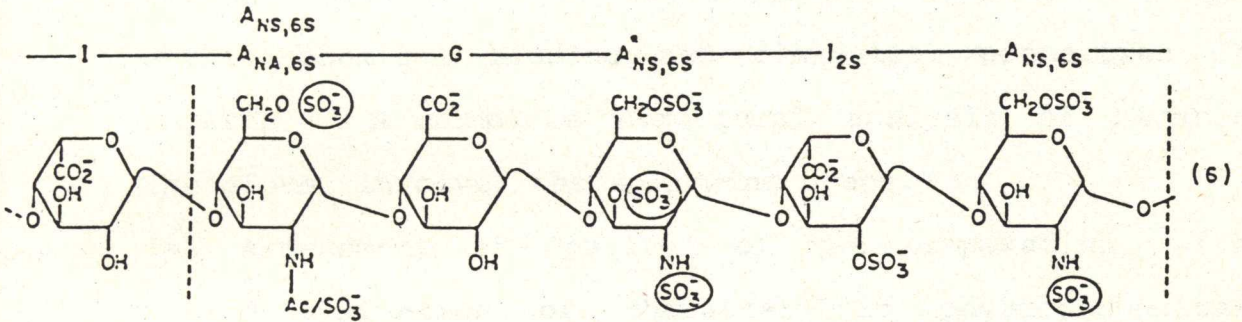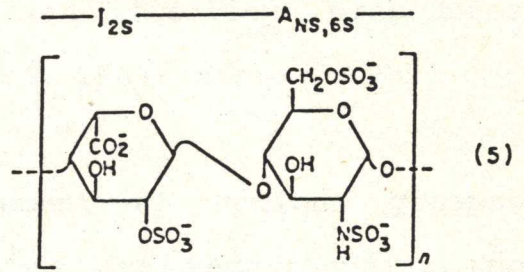
Molecular weights, on average, are in the range of 12,000 - 19,000, with degrees of dispersion also depending on "cut-offs" involved in the purification procedures (Johnson & Mulloy, 1976; Johnson, 1982; Barlow, 1983).

The three-dimensional arrangement of various groups, residues and chains is important for understanding the physico-chemical binding and biological properties of heparin. A complete structural analysis of heparin therefore, involves the following steps:

(a) Assessment of 'purity' of the preparation, with determination of characteristic physico-chemical parameters including molecular weight and distribution of molecular weights.

(b) Elucidation of the 'primary structure', in terms of relative proportion of constituting residues (compositional analysis), arrangement of these residues along the heparin chain (sequence analysis), and determination of the position and configuration of the interconnecting glycosidic bonds (linkage and configurational analysis).

(c) Determination of the 'secondary structure' - the shape of individual residues and segments of the heparin chains (conformational analysis).

It is beyond the scope of this study to delve further into the structural analysis of this drug, suffice to say that its chemical nature is complex.

Physical Properties

Many of the physical properties of heparin have been considered in the general glycosaminoglycan (GAG) reviews of Comper and Laurent (1978) and Lindahl and Hook (1978).

The physical properties of heparin derive from its primary chemical structure, conformation, chain flexibility, molecular weight and particularly its high charge density.

The conformation or shape of a molecule depends upon the torsional angle adopted at each single bond in the structure. In heparin, there are two levels of interest: the conformation adopted by individual sugar residues and the conformational relationship between adjacent residues.

The heparin chain conformation is probably best understood from X-ray fibre diffraction studies, though these were carried out in the solid or gel state and therefore may not provide entirely accurate information about the solution conformation. The unit cell dimensions of heparin samples generally yield a tetrasaccharide fibre axis periodicity of 1.59 - 1.73 nm (Nieduszynski & Atkins, 1973, 1975; Atkins & Nieduszynski, 1986). Any model for heparin conformation in the solid state must therefore obey these dimensional and symmetry constraints.

Heparin chains present in commercial preparations generally have molecular weights in the range 5,000 - 25,000 which are considerably smaller than the 60,000 - 100,000 size of chains upon the native heparin proteoglycan (Robinson et al, 1978). This depolymerisation occurs as a result of the action of tissue endoglycosidases, for example, the -D glucuronidase (Gren & Lindahl, 1985).

The main problem in the determination of the molecular weight of any heparin preparation is the long recognised polydispersity in chain size (Laurent, 1961; Ehrlich & Stivala, 1973). This constitutes a problem because the various methods of molecular weight determination (for example, measurements of osmotic pressure, sedimentation-diffusion properties, viscosity and light-scattering behaviour) tend to yield different types of molecular weight.

Heparin is a strongly anionic polyelectrolyte (Fig 2) and it has long been recognised that heparin and the other GAGs are excellent candidates for a range of functions involving the binding and release of cations (Bhavanandan & Davidson, 1985), whether these are the micro-ions (for example, the metal cations and cationic dyes) or the macro-cations (for example, the basic polypeptides or proteins) is uncertain.
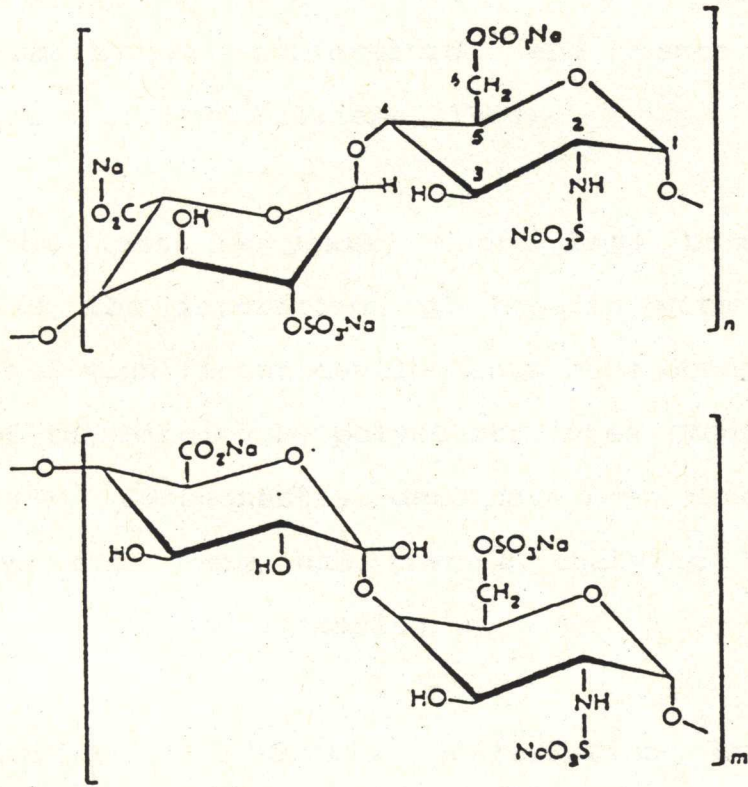
Figure 2 - Heparin Sodium (from Goodman
and Gilman, 1985, p.1340)

Much research has been stimulated by the belief that a physiologically important cation such as Ca^{2+} which is capable of reversibly binding to the multicarboxylate and sulphate centres of glycoconjugates may trigger changes in macromolecular conformation and hence influence biological activity (Williams, 1980).

During the last 25 years, there have been numerous studies of the interaction of heparin with the metal cations and significant developments have occurred in the theory of ion-binding by polyelectrolytes (Manning, 1969, 1974, 1988). Consequently, data have been interpreted in many ways and there has been a changing theoretical framework to our understanding.

The dynamics of heparin conformation has quickly developed with the realisation that two iduronate conformers are in rapid equilibrium with one another. A major goal is to identify the roles that the different iduronate conformers may play in specific interactions with antithrombin and other heparin-binding proteins. Developments in Nuclear Magnetic Resonance (NMR) spectroscopic techniques should ultimately provide a wealth of detailed information about these molecular interactions.

Biological Properties

The property of heparin which has attracted most attention and resulted in its widespread clinical use has been its anticoagulant activity. Heparin does, however, have a number of other pharmacological properties, for example, antilipaemic (Levy, 1958), antihaemostatic (Cruz & Dietrich, 1967), antihaemolytic (Bradshaw & Wessler, 1975) and antithrombotic (Jaques, 1980) effects. Heparin has been shown to inhibit several enzymes including myosin ATPase (Cruz & Dietrich, 1967), RNA-dependent DNA polymerase (Neuhoff, Schill & Sternbach, 1980), hyaluronidase, elastase and renin (Sealey, Gerten & Ladingham, 1987). Furthermore, inhibition of tumour growth (Lippman, 1965; Folkman, 1985), antibacterial activity (Corrigan, 1977), antiviral action (Vaheri, 1964) and effects on the activity of growth factors (Lobb, Harper & Fett, 1986) have also been attributed to heparin.

This broad range of seemingly unrelated activities raises the question of what the biological role of heparin actually is.

Howell (1918) has shown that water-soluble materials extracted from dog liver contained an anticoagulant activity which he also called heparin after McLean (Jaques, 1980). The purification of this activity was

initiated by Charles and Scott (1933) and Jaques, Waters and Charles (1942). These initial studies showed that several tissues, besides dog liver, contained water-soluble anticoagulant substances defined as heparin.

The advance of the chemistry and the increasing knowledge of the physiochemical properties of heparin has allowed it to be distinguished from other sulphated GAGs. This identification has been based on a number of parameters, including anticoagulant activity. The use of several techniques for defining heparin became extremely important in view of the findings that heparin preparations possess a wide range of different anticoagulant activities (Nader et al, 1974; Nader & Dietrich, 1975; Hood et al, 1976; Lam et al, 1976; Lane et al, 1988).

Since the discovery of mast cells by Ehrlich (1879) and the discovery that metachromatic activity with basic dyes was related to heparin (Holmgren & Wilander, 1937; Jorpes, Holmgren and Wilander, 1937; Wilander, 1937, 1939), there has been controversy over whether this compound is only confined to the mast cells or is also present in other cell types (Jaques & Debnath, 1980).

The peculiar distribution of heparin between foetal and adult tissues again raised the question of whether these heparins were related to the presence of mast cells.

Studies on the concentration of heparin and content of mast cells in different foetal and adult bovine tissues (Straus, Nader & Dietrich, 1982) have shown a correlation between the mast cell number and heparin concentration in all tissues analysed.

Several papers reported that mast cells could be derived from cells of thymus and lymph nodes and from the haematopoietic spleen tissue (Csaba, Toro & Moldo, 1962; Burnet, 1977); other workers inferred that mast cells could develop locally from other cell types of the connective tissue (Selye, 1965). If mast cells were derived from thymus, heparin should be absent in athymic 'nude' mice, assuming that the correlation between heparin concentration and mast cell number is valid.

Heparin is present in the skin, lung, thymus and muscle of both lines. These results indicate either that heparin in the athymic mice was not present in mast cells, or that these mice, though athymic, show the presence of mast cells.

It has since been established that mast cells originate from haematopoietic stem cells (Kitamira, Go & Hatanaka, 1978; Kitamira & Go, 1989). The presence of heparin in mast cells of the peritoneal cavity of rats (Silbert, Yurt & Austen, 1979; Metcalfe et al, 1980) and in mastocytomas (Dunn & Patter, 1957) has been extensively

documented. Previous data indicate that heparin is present only in mast cells but mast cells do not necessarily contain heparin.

Heparin was discovered in 1916 (McLean, 1916, 1959) and for the next 60 years, anticoagulation was considered to be its major, if not its sole biological activity. In 1976, however, three reports showed that less than half of this disperse molecule is anticoagulant (i.e. dependent upon its interaction with antithrombin III) (Hook et al, 1976; Anderson et al, 1976; Lam et al, 1986) and implied that other activities of heparin remained to be discovered. One year later, heparin was found to suppress the proliferation of vascular smooth muscle (Clowes & Karnovsky, 1977). Furthermore, this new activity was subsequently shown to be independent of the anticoagulant function of heparin (Castellot, Favreau, Karnovsky et al, 1982). The ability of heparin to suppress delayed hypersensitivity was reported in 1983 (Sy, Schneeberger, McCluskey et al, 1983).

Another new function of heparin, also independent of anticoagulation has become recognised, namely the involvement of heparin in the regulation of angiogenesis. This new function was related to its mitogenic effect. The observation that heparin could potentiate the mitogenic effect of endothelial cell growth factor (Acidic FGF) in vitro (Thorton, Mueller & Levine, 1983)

provided the first evidence that the affinity of heparin for endothelial mitogens could have physiological significance. It suggested that the access of endothelial cells to growth factors could be modulated by binding of these factors to heparin. In vivo evidence for such a physiological role came from a subsequent finding that basic fibroblast growth factor, (FGF), is stored in certain basement membranes (including vascular basement membrane) where it appears to be bound to heparin sulphate.

FGF has been studied in several laboratories for its potential use as a stimulator of angiogenesis in the healing of wounds, burns, fractures and chronic ulceration (Thomas & Gimenez-Gallego, 1986). As heparin can retard the degradation of FGF (Gospodarowicz & Cheng, 1986), it could be co-administered with FGF to prolong the pharmacological action of this angiogenic endothelial mitogen. Various combinations of FGF and heparin fragments may also be useful in the healing of certain corneal ulcerations where neovascularization is desirable (Guyton et al, 1980).

Although heparin or heparin fragments may be potentially valuable in augmenting the angiogenic effect of FGF, an even broader use for heparin or its analogues may exist as potentiators of angiogenesis inhibitors. The use of angiogenesis inhibitors as adjuncts to the treatment of

cancer is a clear, but as yet untested goal. There are also many non-neoplastic diseases which may be "angiogenesis dependent" (Folkman & Klagsbrun, 1987).

The most distinguishing feature of heparin-like compounds is their cellular localisation, their occurrence in the animal kingdom and their physiological behaviour. Heparin is restricted to the cytoplasm of mast cells and is not found in all animal species. Among the mammals, some species lack heparin (for example, the rabbit) and in others (for example, dog and cow) heparin occurs in many tissues and in high concentration.

There has been speculation that heparin might play a role in the protection of the organism against foreign bodies, for example bacteria and viruses (Vaheri, 1964; Regelson, 1968). Heparin (and/or mast cells) is therefore preferentially located in tissues/organs that are in direct contact with the environment (i.e. skin, lung and intestine). In Anomalocardia brasiliana, an invertebrate, this preferential location is also maintained; mast cells in this species are distributed along the gastrointestinal tract. Furthermore, when skin, lung and intestine are not functionally active (during foetal development), no heparin, or only trace amounts, can be detected. Also, the presence of heparin in liver, lymph nodes, spleen and placenta (organs that function as internal barriers against infections (Weiss,

1977) and foreign bodies) contain considerable amounts of heparin. It is significant that the maternal side of the placenta contains seven times more heparin than the foetal side (Regelson, 1988).

Results showing that there is an inverse relationship between heparin content and antibody response in genetically selected mice agree with the suggestion that heparin may function as an alternative mechanism for the surveillance of the organism against pathogens, without the direct involvement of the immune system. This lends further support to the hypothesis that heparin may have a role in defence against pathogens without the involvement of the immune system. In this context it is relevant that heparin appears at the late stages of foetal development, before the maturation of the immune system. Thus, heparin/mast cells could confer resistance to the neonate against bacterial infections or other pathogens.

It is unlikely that the biological function of heparin might be related to blood coagulation, as species with blood clotting mechanisms (for example, the rabbit) lack heparin and species without a functional coagulation system (for example, molluscs) contain large amounts of heparin.

Finally, whatever the biological role of heparin/mast cell might be, its uneven distribution suggests that it

functions in mechanisms which are not fundamental for the survival of the organisms.

Pharmacological Properties

Clinically effective anticoagulation can be achieved with the administration of either heparin or an oral anticoagulant such as warfarin. Heparin is present in mast cells and is prepared by extraction from animal tissues such as lung and intestine. Whilst it may play a part in the body's response to inflammation, its role in normal physiology is not as yet fully defined.

Heparin enhances the anticoagulant action of antithrombin III, an anticoagulant present in plasma (Figure 3).
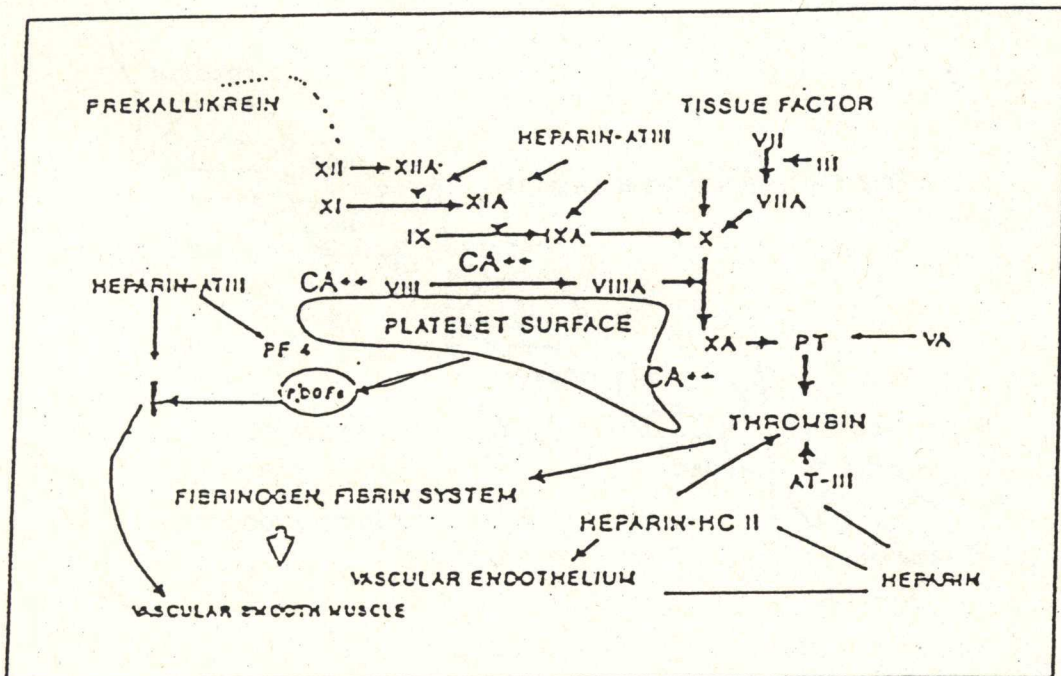
Figure 3. Actions of Heparin (from Freedman, 1992)

The anticoagulant effect of heparin is essentially immediate, and it occurs both 'in vitro' and 'in vivo'. Heparin acts indirectly by means of a plasma cofactor. The heparin cofactor, or antithrombin III is an alpha-globulin and a serine protease inhibitor that neutralises several activated clotting factors, that is, XIIa, kallikrein (activated Fletcher factor), XIa, IXa, Xa, IIa, and XIIIa. Although antithrombin III was thought to be the only macromolecule able to inactivate thrombin, other plasma proteins are now known to possess this activity. Antithrombin III and the newly described heparin cofactor II form irreversible complexes with thrombin and, as a result, the proteins are inactivated (Griffith, 1983). Binding sites for antithrombin III can be seen in Figure 4.
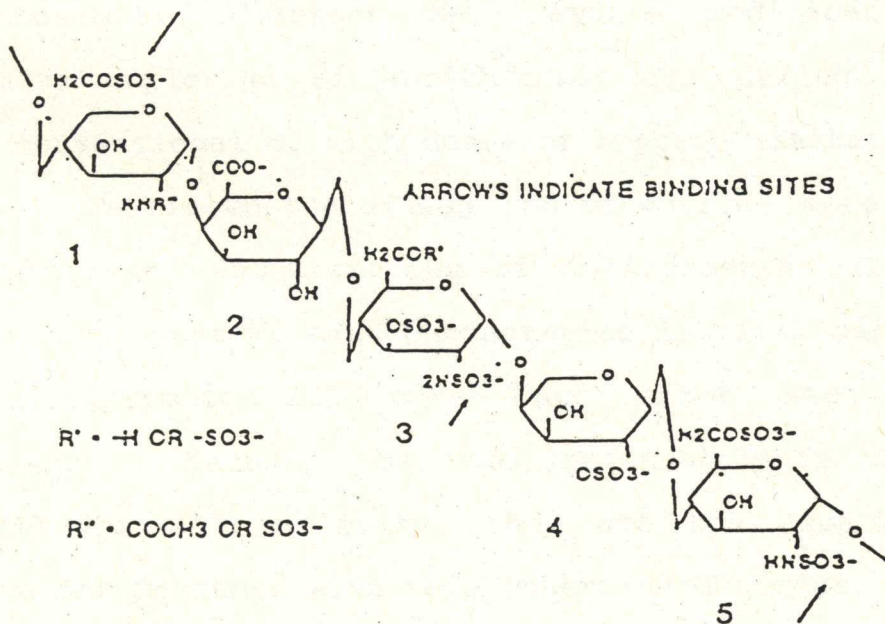
Figure 4.   AT III binding pentasaccharide
(from Freedman, 1992)

Heparin markedly accelerates the velocity, but not the extent, of this reaction. A ternary complex is apparently formed between heparin, antithrombin III, and the clotting factors (Bjork & Lindahl, 1982). Low concentrations of heparin increase the activity of antithrombin III, particularly against factor Xa and thrombin; this forms the basis for the administration of low doses of heparin as a therapeutic regimen. Patients who receive intermittent or continuous therapy with heparin have a progressive reduction of antithrombin III activity to values that approximate one third of normal (Marciniak & Gockerman, 1977). Thus, a heparin-induced reduction of the activity of antithrombin III may paradoxically increase the thrombotic tendency in humans. The standard regimens for treatment of thromboembolic diseases may require modification to minimise depletion of antithrombin III during therapy with conventional or high doses of heparin (Kakkar et al, 1980). Oestrogen-containing contraceptives also reduce the apparent concentrations of antithrombin III. The thrombotic symptoms that characterise familial deficiency of antithrombin III often are first seen during pregnancy. Because the oral anticoagulants increase antithrombin III activity, they are the treatment of choice for patients with this inherited disorder.

The above properties demonstrate that heparin is indeed a complex chemical with many apparent functions. Although

its prime action, and hence use, has been for anticoagulation, other functions have been postulated. Non-anticoagulant actions of the heparin glycosaminoglycans include regulation of angiogenesis (Folkman & Ingber, 1989), lipoprotein lipase modulation (plasma clearing effect) (Robinson, 1970; Nilsson-Ehle, Garfinkel & Schotz, 1980), maintenance of endothelial wall competence, and inhibition of vascular smooth muscle proliferation (antiproliferative effect) after endothelial injury (Clowes & Karnovsky, 1977; Guyton et al, 1980). With special reference to this last property, and of particular public health interest, has been an association frequently made between heparin administration and a beneficial effect on the evaluation of atherosclerosis (Engelbert, Kuhn & Steinman, 1956; Rosenberg, Fritze, Castellot & Karnovsky, 1984; Rosenberg, Reilly & Fritze, 1985).

No studies to date have been published that relate this endothelial function of heparin to infusion failure, although the anti-thrombotic effects have been well documented.

Due to the complex nature of heparin, and its now many functions, it is possible that it may play some role in reducing infusion failure due to its vascular endothelial properties.

Study 2 will examine if the addition of low-dose heparin to the infusate can prolong infusion-site survival (reduce infusion failure) in children.

CHAPTER 6

STUDY 2 - THE EFFICACY OF LOW-DOSE HEPARIN IN DECREASING INFUSION FAILURE IN CHILDREN[##]

Introduction

Initiation of intravenous (IV) infusions in hospital wards is a common surgical procedure. Unfortunately infusions will fail due to complications and adverse local venous reactions. The commonest sequelae to IV therapy is probably infusion failure due to phlebitis and/or extravasation.

IV infusions commonly fail because of extravasation of infusate or the development of phlebitis. This interferes with IV therapy, causes considerable patient discomfort and worry, and increases workload for hospital staff. In patients needing prolonged treatment, loss of veins may become a problem, thereby compromising fluid and medication administration.

The creation of fear and anxiety in children with other psycho-emotional implications of instituting IV procedures, may also lead to further unnecessary stress and distress (Carlquist, 1981; Abbott, 1984).

[##] Wright, A., Hecker, J.F., McDonald, G. (1995). Effects of low-dose heparin on failure of intravenous infusions in children. Heart and Lung, 24,1,79-82.

When children suffer, so do their parents who may experience special anxieties and apprehensions when confronted with infusion devices (Polchuck & Fraser, 1980). If sensed by the children, these same parental anxieties and apprehensions may further enhance fears and phobias, as well as non-compliance.

Many authors acknowledge that complications often arise when veins are cannulated and infusions started (Lewis & Hecker, 1984; Turnidge, 1984; Streckfuss, 1985; Wright et al, 1985).

The problems of intravenous therapy have been evaluated extensively in adults, however, little attention has been devoted to children and few articles cite incidences, examine the responsible variables or test methods for reducing such failure.

Heparin is effective in reducing thrombus formation and studies have also demonstrated other beneficial properties such as anti-inflammatory, anti-irritant, tissue healing, and the maintenance of endothelial integrity and homoeostasis. It is suggested that the addition of low-dose heparin to the infusate may prolong infusion site survival in children.

Methods

Informed consent (see Appendix C & D) was obtained from parents of children who were to receive intravenous therapy in a medical ward at Westmead Hospital.

An experimental design was used whereby patients considered eligible for the study were randomly allocated into control and treatment groups. The treatment group received pre-mixed IV fluids containing 1 iu/ml of heparin whilst the control group received standard fluids. Data were collected using a standard form and information such as type and size of cannula, sex, age, date and time of cannulation, site, signs of phlebitis/extravasation, reasons for cannula removal and type of fluids and drugs infused were recorded.

Infusion failure was defined as the occurrence of either extravasation or phlebitis which was determined using the criteria of pain, erythema, oedema, excessive warmth, and palpable venous cord. The presence of two or more criteria signified a positive result.

Failure incidence was analysed by Cox's multivariate hazards model, life-table method and log-rank tests. The advantage of these methods is that they take into account both differences in duration of infusions and the fact that, since many cannulae are removed for reasons other

than failure of infusions, the number of infusions still functional and which therefore can fail, decreases with time. Difference in the proportion that failed was tested by contingency table analysis.

Results

Heparin was present in the solutions given to 35 children while 44 children received solutions without heparin. There were no significant differences between these groups in factors (Table 5) such as sex ($Chi^2 = 0.09$), age ($Chi^2 = 1.20$), cannula type ($Chi^2 = 3.49$), cannula site ($Chi^2 = 3.51$; comparison between hand/arm, foot/leg and scalp), cannula size ($Chi^2 = 2.05$) or individual antibiotics and other drugs.

Table 5. **Details on patients, infusions and cause of failure**

Factor	Control	Heparin
Sex Male	24	20
Female	22	16
Age (Months)	35.0	37.5
Cannula Size:		
22 Gauge	7	7
24 Gauge	35	29
Average Infusion Rate (ML/HR)	35.7	31.8
Fate:Blocked or Pulled Out	2	4
Extravasation	11	7
Extravasation + Phlebitis	6	4
Phlebitis	14	8

The percentage of failed sites receiving heparin decreased from 73% to 53%, a difference that was statistically significant (Chi^2 = 3.86; odds ratio 2.25). Kaplan-Meier survival curves for the groups with and without heparin (Figure 5) indicate that the median survival half lives for the infusion sites were 97 and 43 hours respectively. The difference due to heparin between the two curves was statistically highly significant (Log rank test: Chi^2 = 20.32, p<0.0001). The odds ratio (a measure of the magnitude of the difference due to the heparin) was 3.33 indicating a greater than three-fold improvement due to the heparin. Much of the effect can be seen to be due to the marked reduction in the first two days.
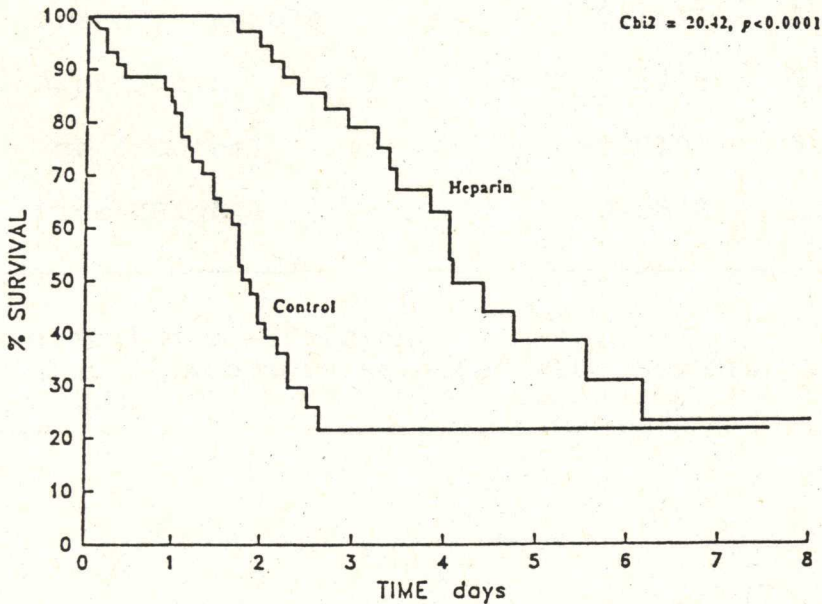
Figure 5. Comparison of survival curves (Life table analysis) for groups with and without heparin

A summary of the significant findings from the multivariate survival analysis is given in Table 6. As well as heparin, two drugs, flucloxacillin and ampicillin, age of child, type of cannula and right side were selected by the multivariate analysis. Only heparin was highly significant. Other drugs, sex, average infusion rate and cannulation site had no effect on failure.

Table 6. Results of the multivariate analysis (Cox's Model) of factors influencing infusion site survival

STEP	FACTOR	NUMBER WITH FACTOR	B[a]	CHI^2
1	Heparin	35[b]	-1.9150	27.53***
2	Flucloxacillin		-0.0514	4.00*
3	Brand 2 cannula		0.1431	3.63
4	Ampicillin		0.3405	5.63*
5	Age (Months)		-0.0101	3.57
6	Side (Right)		0.2532	2.84

[a] Regression co-efficient
[b] Number of subjects selected with factors
*** p<0.001
* p<0.05

Discussion

Guidelines frequently adopted by hospitals suggest that peripheral cannulae be replaced every 48-72 hours. In this study it was the policy of the paediatric unit to allow infusions to continue until they failed.

The risk of infection following the introduction of an intravascular catheter should not be underestimated and complications such as suppurative phlebitis and septicaemia have been well documented (Strechfuss, 1985; Sacks-Berg, 1987; Tobin, 1988). It has been suggested that upon cannulation small fibrin deposits form along the catheter and around the intravascular portions of the vessel (Hoshal et al, 1971; Peters et al, 1973; Tanner et al, 1980; Maki, 1982). This then predisposes to bacterial colonisation and thrombosis formation.

Extravasation (tissuing) is also a common phenomenon associated with failure of IV infusions. Most infiltrations will rapidly disappear once the infusion is ceased and the cannula removed. However, serious sequelae have been reported in tissue necrosis which may required surgical debridement, skin grafting, and even amputation (Yosowitz et al, 1975; Brown et al, 1979; Blair et al, 1980).

Research conducted by Fonkalsrud et al (1968) and Lewis &

Hecker (1985) suggested that the inflammation found in infusion thrombophlebitis can be mainly attributed to chemical irritation by the infusate and animal experiments have shown that endothelium is very sensitive to deviations in pH (Lewis & Hecker, 1980). Following cannulation, platelet adherence occurs on the damaged endothelium which results in leucocyte infiltration and oedema of the vessel wall. The damage may spread proximally and cause intra-luminal thrombosis. These changes are enhanced by prolonged infusions (Eremin & Marshall, 1977). Woodhouse (1980) concluded that the critical event in ITP was infiltration of the vein wall by circulating leucocytes.

Heparin administration is effective in reducing the incidence of thrombosis during central vein hyperalimentation in adults as well as preventing phlebitis during peripheral vein infusions (Daniell, 1973; Brismar et al, 1982; Tobin, 1988). It has also been reported to improve indwelling umbilical artery catheter patency (Rajani et al, 1979). In neonates, Alpan et al (1984) showed that the addition of heparin to alimentation fluids significantly reduced the incidence of phlebitis.

In this study, heparin not only reduced the proportion of infusions that failed from 70% to 53% but also increased markedly the median time at which failure occurred. The

odds ratio, a statistic which provides a combined estimate of the magnitude of these two changes was 3.33, indicating that infusion survival had been improved by greater than 3 fold.

Enhancing the survival of infusion sites (or decreasing infusion failure) in children due to phlebitis/extravasation would tend to conserve the child's energy. This energy may otherwise be utilized by the child to combat serious complications to IV therapy, for example, septicaemia. By reducing the risk of infusion failure (and hence vein damage or loss) structural integrity of the vein is also maintained/conserved.

The complications associated with IV therapy induce both physical and psychological stress in a child. By decreasing infusion failure, this same stress may be reduced, thus allowing the child to adapt at a higher level and so combat other foreign stressors within the environment. Higher levels of adaptation, hence, enable the child to increase his/her chances for survival.

By reducing the risk of infusion failure, a variety of psychological, physical and physiological needs can be met. Improving infusion site survival conserves energy, maintains structural integrity and enables adaptation to ensue.

Over the last few years concern has been raised about the administration of heparin causing heparin-induced thrombocytopenia and thrombosis syndrome. Although cases of morbidity and mortality have been reported in adults (Aburahma et al, 1991; Aburahma et al, 1992) only two have been cited in children (Oriot et al, 1990; Potter et al, 1992). The problem with previous studies of heaprin-induced thrombocytopenia has been in the methodology and few seem to agree on consistent criteria such as definitions, measurement levels and time of exposure to heparin. The seriousness of heparin-induced thrombocytopenia and thrombosis syndrome should not be underestimated and caution is advised when using heparin. No clinical evidence of heparin-induced thrombocytopenia was found in this study.

Irritation, inflammation, and damage of vein wall endothelium by infusate may lead to venoconstriction (Lewis & Hecker, 1984). This may cause a reduction in blood flow, precipitate tissue ischaemia and perhaps the loss of normal vessel elastic properties. Vascular damage and blood flow stasis may therefore lead to subsequent thrombosis and an increased interaction of leucocytes with the endothelium (Simmons et al, 1987).

The biological function of heparin is still unclear and evidence exists that it may have a modulating role in immune and inflammatory processes (Ekre et al, 1986;

Simmons et al, 1987). Bowler et al (1988) suggest that, during mast cell mediated allergic inflammation, heparin may play an inhibitory role, hence, "Heparin may inhibit mast cell degranulation directly or limit the oedema associated with mediator release" (Bowler et al, 1988). Heparin may also inhibit neutrophil activation (Laghipasini et al, 1984) and complement-dependent inflammation (Ekre et al, 1986).

Handler (1988) states that "endothelial injury or cellular loss is accompanied by platelet adhesion and release of platelet-derived growth factor (PDGF), which is a protein stored in the alpha-granules. The PDGF, which has a plasma half life of 2-3 minutes, is thought to diffuse into the vessel wall and bind to smooth muscle cell (SMC) receptors, inducing migration to the luminal surface and subsequent proliferation of these cells and generation of extracellular matrix. Repeated injuries to the endothelium are thought to result in additional episodes of PDGF release, SMC migration and proliferation, and matrix formation, a process characterised as neointimal or myointimal lesion formation".

Heparin has been shown to inhibit the production of PDGF which is chemotactic for polymorphanuclear leucocytes (PMN) (DiCorelto et al, 1984). Other beneficial properties to vessel homeostasis and integrity include an

affinity for endothelium (Hiebert et al, 1976) which prevents cellular damage from toxins, enzymes, and vasoactive amines. Whilst still others may decrease endothelial permeability and cause the neutralisation of cytotoxic cationic proteins which are released from neutrophils (Handler, 1988). Adachi et al (1986) suggest that heparin itself may be cytotoxic to leucocytes - relevant, since leucocyte infiltration is part of the pathophysiological process involved with ITP development.

A further biological property of heparin is that it may be involved in the reparative or healing phases of tissue damage and Majack et al (1985) report that the production of new vessel wall collagen by smooth muscle cells is enhanced in the presence of heparin.

Endothelial cell growth factor (ECGF) is the main polypeptide mitogen for human endothelial cells (Maciag et al, 1984) and has been linked to neovascularization (Maciag, 1984) which occurs during tissue healing. Heparin has been shown to have a modulating role in the biological activity of ECGF and when combined with ECGF heparin promotes cell growth (Thornton et al, 1982). Therefore, heparin and ECGF may indeed play significant roles in controlling human endothelial cell migration which in turn may be relevant to tissue healing (Terranova et al, 1985).

Although heparin decreased the proportion of sites which failed, the greater effect was the increase in the survival time for the sites. In these patients, the median half life for infusion sites without heparin was 43 hours. This is longer than the 34 hours for neonatal sites receiving dextrose solutions in the trial of Moclair et al (1992) but shorter than values for sites in adults (Lewis & Hecker, 1986). The 54 hour increase in median survival time with the heparin was similar to that found by Alpan et al (1984) and Moclair et al (1992) for TPN and dextrose saline solutions given to premature babies.

Previous studies on the use of low-dose heparin have used solutions where the heparin was added either in hospital pharmacies or on the ward. This is the first trial using solutions manufactured under commercial conditions. Because they were a special batch containing an additive, a shelf-life of 12 weeks was imposed by the manufacturer and this limited the number of sites that could be studied. Low-dose heparin is available in normal saline with a shelf-life of 24 months and we have evidence that the stability of heparin in dextrose solutions is such that dextrose-based solutions with low-dose heparin could have a shelf life of at least 12 months (Wright & Hecker, unpublished observations).

Some patients, especially those who require repeated

intravenous therapy, are liable to develop problems with venous access and steps should be considered to reduce the number of veins which are lost by patients who are likely to spend much time in hospitals. Local GTN significantly decreases infusion failure in adults (Wright et al, 1985; Khawaja et al, 1988) but is probably not effective in neonates (Hecker, 1990). Infusion site survival can be increased in neonates by neutralising total parenteral nutrition (TPN) (Hecker et al, 1991). This is a special situation as TPN for neonates is usually formulated in hospital pharmacies and thus can have the pH adjusted, unlike adult TPN which is usually produced ready for use by companies. It appears that the most practical of these methods for paediatric patients is low-dose heparin, especially if it were available from a manufacturer as is saline containing 1 iu/ml of heparin.

It is not suggested that such techniques for prolonging survival of infusions should be used in all patients. However, there are several identifiable subgroups of patients, such as those being treated for cancer and chronic haematological conditions, who have lost most peripheral veins from previous intravenous therapy and who are at risk of losing their remaining veins. It is likely that potential risks such as infective phlebitis and thrombocytopenia from use of low-dose heparin (possibly combined with percutaneous steroids) would be

outweighed by the maintenance of venous access through conservation of veins.

An unexpected significant finding was that of flucloxacillin and ampicillin prolonging survival. This result is contrary to other studies (Hecker, 1989; Hecker et al, 1991; Wright & Hecker, 1991) where these drugs were found to have no significant effect. One possible explanation could be that penicillin-related compounds may inhibit platelet aggregation. Another reason may be the effect of other confounding variables not accounted for during this study.

The number of methods employed to reduce infusion failure in the past have been many. They range from in-line filtration and changing of lines to neutralisation of acid dextrose solutions and the administration of steroids, heparin and glyceryl trinitrate. All these strategies have reduced infusion failure to some extent, however, meta-analysis has shown steroids, heparin and glyceryl trinitrate to be the most effective (Hecker, 1992).

This experiment used one unit of heparin per ml of infusion solution, this amount was based on previous adult studies, however, the minimum effective concentration required has not as yet been determined, and further studies are necessary.

At present, heparinized dextrose-saline solutions are available only from pharmacies. We suggest that a fluid manufacturer initiate steps for marketing approval for such a solution containing heparin.

Conclusion

Many hospitalized children will require the initiation of intravenous therapy for fluid or medication administration. It has been shown that children, more so than adults, will develop infusion site failure (due to phlebitis and extravasation) earlier. The need, therefore, exists to be able to prolong IV therapy by reducing the infusion failure rate.

This study showed, that by adding low-dose heparin to the infusate, the incidence of phlebitis and extravasation could be decreased in children; a significant reduction in the infusion failure rate could be achieved and that by prolonging infusion-site survival effective vein usage could be increased.

Nurses who work in clinical areas will always be involved in IV management as part of their role. Unfortunately infusions will always fail. The aetiology of infusion failure due to phlebitis/extravasation is probably multifactorial in nature and may include physical, chemical and bacteriological aspects. By becoming aware

of the possible factors involved and the strategies used to prevent such failure, the nurse can offer optimal patient care in relation to infusion sites.

One such strategy is the pharmacological approach, for example, steroids, heparin, glyceryl trinitrate. Caution must always be used when administering drugs to patients, particularly children, but in certain cases the benefits may outweigh the risks. This study, by the use of low-dose heparin added to infusate, was able to significantly improve infusion site survival. Nursing implications are likely to include fewer problems with IV solution flow rates, a reduction in medical/nursing hours associated with frequent cannulations, less likelihood of systemic sepsis and less patient worry and discomfort due to local venous reactions and re-cannulations. MOST IMPORTANT IS THE BENEFICIAL IMPROVEMENT OF WELFARE TO CHILDREN AND THEIR PARENTS.

One of the major limitations to this study was the 12 weeks shelf life imposed by the manufacturer. This limited the number of infusion sites able to be studied. As manufacturer's data related to stability of heparin in dextrose-saline solutions was limited, it was decided to test heparin stability in various saline and dextrose-saline solutions over time (Study 3).

CHAPTER 7

STUDY 3 - STABILITY OF HEPARIN IN DEXTROSE/SALINE SOLUTIONS[##]

Introduction

Infusion failure is a common problem in hospitals with most intravenous infusions failing due to phlebitis or extravasation. Studies on infusion failure have identified several methods which prolong the life of infusions by reducing the incidence of failure. These include neutralising acidity in solutions, applying percutaneous steroids or glyceryl trinitrate near the infusion site, using inline filters and adding low-dose heparin and/or steroids to the fluids (Hecker, 1992; Wright & Hecker, 1995). One of the more effective of these methods is adding low-dose heparin, usually 1 iu/ml (Anderson, 1951; Sketch et al, 1972; Daniell, 1973; Stradling, 1978; Tanner et al, 1980; Alpan et al, 1981; Bassan et al, 1984; DeCock et al, 1984; Bass et al, 1985; Wright & Hecker, 1995). In the published experiments, except for Wright and Hecker (1995), heparin was added shortly before use, either on the ward or in

[##] Wright, A., Hecker, J.F. (1995). Long-term stability of heparin in dextrose and dextrose-saline intravenous fluids. International Journal of Pharmacy Practice (in press).

the pharmacy. The risk of errors and of microbial contamination would be reduced if heparin could be added during manufacture. Normal saline is made for flushing cannulae with 1 iu/ml of heparin but no similar dextrose or dextrose-saline solution is available. Trissel (1983) in the only review of the stability of heparin in various solutions stated that "evaluations of the stabliity of heparin sodium in dextrose-containing solutions have appeared frequently in the literature, but the results are conflicting". He cited 13 papers in which two or more different type of solutions (saline, dextrose, dextrose/saline, Ringers) were investigated. Of these, 3 or 4 indicated incompatibility and the others compatibility with the differences being largely independent of the type of solution. Some of the inconsistency is due to a loss and then restoration of activity in the first 24 hours. Two other papers indicated long-term (1 or 7 years) stability of heparin in saline but there were no studies of its stability in dextrose or other solutions longer than 14 days.

Since Trissel's (1983) review, commercial saline with 1 iu/ml of heparin (a shelf life of 24 months) has been marketed. This could only have been done if stability tests had been done by the manufacturers. If heparin is stable in saline, then it might also be stable in dextrose-saline and dextrose solutions. This study presents data on long-term stability of low-dose heparin

which has been added to such solutions.

Methods

Heparin sodium (porcine mucous, 5000 iu in 5 mls, David Bull Laboratories) was added at 1 iu/ml to 500 ml bags of normal saline, 5% dextrose, and 3.75% dextrose plus 0.225% sodium chloride (dextrose saline). They were stored at 20-25°C (room temperature). A bag of each type of fluid was sampled at intervals of one day, one, three, six, nine and twelve months, the pH was measured and an aliquot was mixed with an equal volume of citrated plasma. Activated partial thromboplastin time (APTT) and the thrombin time (TT) were then measured (on solutions mixed with equal volumes of citrated plasma) (Bauer et al, 1974; Dacie & Lewis, 1984). Other bags of saline and 5% dextrose with 10 iu/ml of heparin were stored at room temperature and APTT and TT measurements were made at 0 and 12 months. A third set of bags (saline, 5% dextrose and dextrose-saline) with 1 iu/ml of heparin were stored at 2-5°C and APTT and TT measurements were made at 0 and 12 months.

Results

APTT and TT values remained greater than 180 and 120 seconds respectively in saline and 3.75% dextrose saline at 20-25°C over the 12 months (Figures 6 and 7). In 5%

dextrose, the APTT gradually decreased between 7 days and 9 months to about 25% greater than the control while the TT dropped suddenly to control values between 1 and 3 months (Table 7).

Table 7. Anticoagulant effects of solutions with 1 i.u. of heparin stored at 2-5°C and with 10 i.u. of heparin stored at 20-25°C

	Test	1 iu/ml:2-5°C		10 iu/ml:20-25°C	
		1 day	12 mths	1 day	12 mths
Heparinized 5%	APTT	>180	59	>180	>180
dextrose	TT	>120	15	>120	>120
Heparinized 2.5%	APTT	>180	>180	-	-
dextrose +					
saline	TT	>120	>120	-	-
Heparinized 3.75%	APTT	>180	>180	-	-
dextrose +					
saline	TT	>120	>120	-	-
Heparinized					
saline	APTT	>180	>180	>180	>180
	TT	>120	>120	>120	>120

Data are times in seconds before coagulation occurred.
APTT activated partial thromboplastin time, *TT* thrombin time
- not measured.

Measurements on other samples were made only at 1 day and 12 months (Table 7). Heparinized saline and heparinized 5% dextrose with 10 iu per ml of heparin at 20-25°C had APTT values greater than 180 seconds and TT values greater than 120 seconds on both occasions. One iu per ml of heparin was also added to 5% dextrose, normal saline, Hartman's solution, 3.75% dextrose plus 0.225% sodium chloride and 2.5% dextrose plus 0.45% sodium chloride

which were kept at 2-5°C. All had values for APTT greater than 180 seconds and TT greater than 120 seconds except for 1 iu per ml of heparin in 5% dextrose in which the APTT had decreased to 59 seconds and the TT to control values after 12 months.
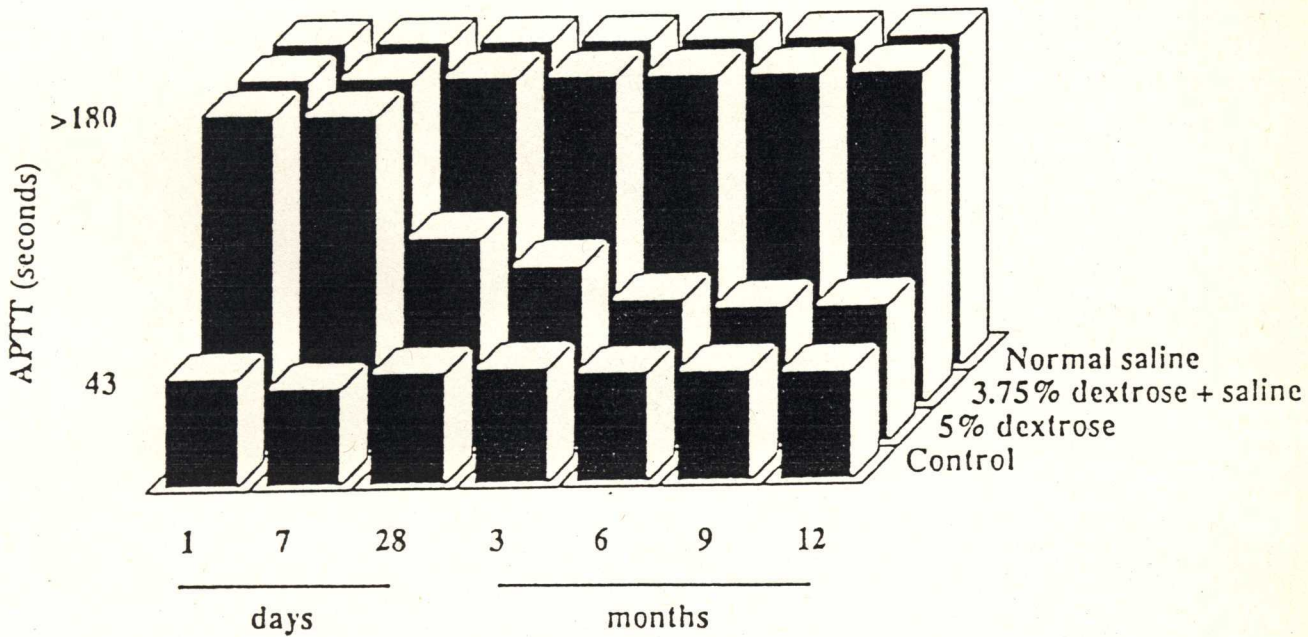
Figure 6. APTT Values

Figure 7. TT Values

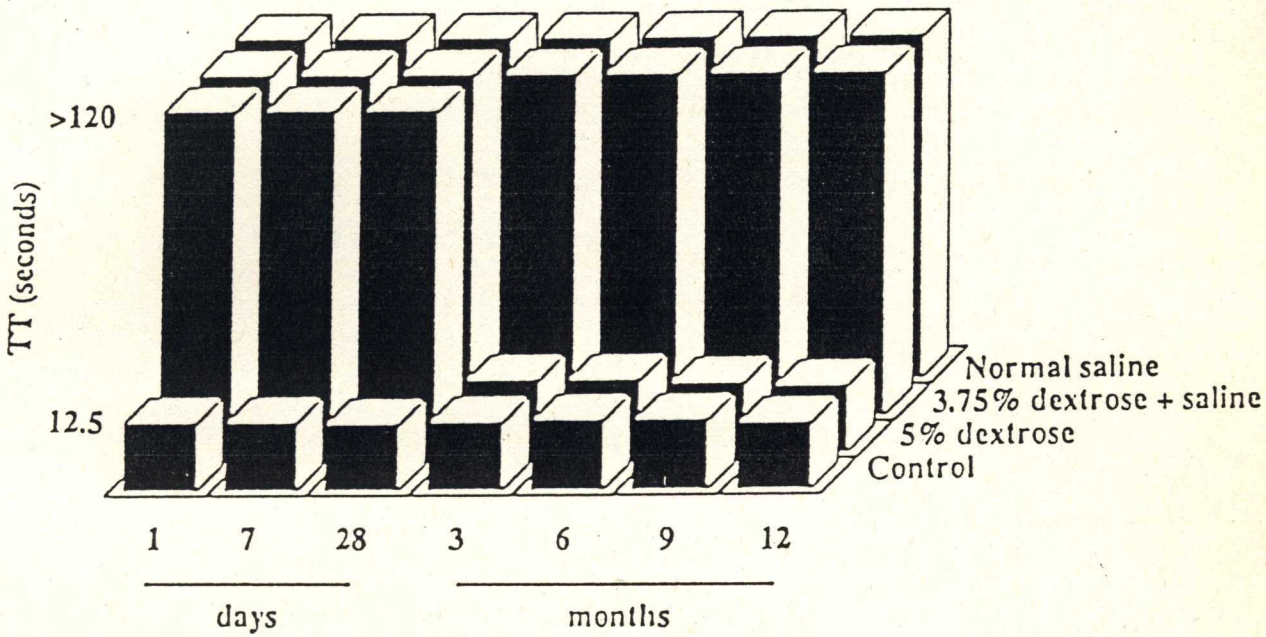## Discussion

There are two aspects to stability of heparin in solution, stability during sterilisation and stability during storage. Heparin appears to be unaffected by the approximately 120°C at which solutions are autoclaved (Bowie & Haylor, 1978; Menzies et al, 1989). These data show that heparin at 1 iu per ml is stable in dextrose-saline solutions during a shelf life of 12 months given

to intravenous fluids but not in dextrose solutions which do not contain sodium chloride ions.

The reason for this effect of sodium chloride is unknown. While Parker (1967) found no effect of ph on stability, Pritchard (1964) found loss of activity at pH values of below 5 or above 8. The present solutions had initial values of 4.85, 4.15 and 3.91 for saline, 5% dextrose and dextrose-saline respectively which decreased to 4.62, 4.10 and 3.87 after 12 months.

Meta-analysis of ways to prolong survival of infusion sites showed that the most effective method is the combination of low-dose heparin (1 iu/ml) plus steroids (hydrocortisone at 10 ug/ml) added to the solutions (Hecker, 1992). In these trials, the drugs were added shortly before use. It is not possible commercially to produce fluids containing low-dose steroids as they are unstable and also they would be adsorbed by the plastic bags packaging the fluids. However, steroids are efficacious when applied percutaneously over the infusion site (Clark et al, 1960) and so the marked additive effect of these drugs could be obtained by using percutaneous steroids plus solutions containing heparin. This trial has shown that it would be possible to produce dextrose-saline solutions with low-dose heparin which retained the heparin activity for an acceptable shelf life.

Nurses should be aware that the strategy of prolonging infusion site survival in children by the addition of low-dose heparin to the infusate may not always be possible. Potential risks such as infective phlebitis and thrombocytopenia may occur. Children suffering from cancer and various chronic haematological conditions quite often lose many of their peripheral veins from previous IV therapy and thus have fewer veins remaining for future use. For these children, it would seem desirable to prevent infusion complications by the use of low-dose heparin. The potential risks of medication (heparin) administration may be outweighed by the maintenance of venous access through the conservation of peripheral veins.

Conclusion

In study 2, it was shown that the addition of low-dose heparin to the infusate could decrease infusion failure and prolong survival of IV infusions in children. Study 3 has shown that the activity/stability of low-dose heparin when added to dextrose-saline fluids can be maintained over time (up to 12 months).

Hospitals using this technique of prolonging survival of infusions could benefit by not having to replace fluid bags every three months (a cost saving). The 3 month shelf life imposed by the manufacturer also limited the

number of available IV sites to be studied, hence, if shelf life was increased, a greater sample number could be obtained in future studies.

It is also suggested that manufacturers commence production of commercially available dextrose-saline solutions containing low-dose heparin for the purpose of decreasing infusion site failure in peripheral veins of hospitalised patients.

CHAPTER 8

CONCLUSIONS, LIMITATIONS, IMPLICATIONS AND RECOMMENDATIONS

Nurses working in the clinical area will frequently be involved in the management of intravenous infusions. Many patients, including adults, children and infants will develop complications and the infusions will fail. The most common problem associated with such failure is extravasation and/or phlebitis.

Failure of infusions due to the development of phlebitis or extravasation may cause considerable patient discomfort and pain, interfere with IV therapy, increase workload for hospital staff, cause parental worry and concern and, in children, induce fear and anxiety. In patients requiring prolonged treatment, loss of veins may become problematic, thereby compromising medication and fluid administration.

The problems of intravenous therapy have been evaluated extensively in adults however, little attention has been devoted to children and few articles cite incidences, examine the responsible variables, or test methods for reducing such failure in children.

The aims of this study were to:-

1. determine and compare the incidence of infusion failure in a given paediatric population;
2. test the efficacy of low-dose heparin added to infusate for increasing the survival of intravenous infusions and vein usage in children;
3. test the stability of heparinized solutions over a period of time.

The first study was conducted to determine the incidence of infusion failure in a given paediatric population.

The results of Study 1 indicate that survival time of infusions was markedly increased in those children who received hydrocortisone and heparin added to the infusate (median half life of >269 hours) as compared to those who did not (median half life of 52 and 56 hours respectively). Infusion of metronidazole was also associated with reduced survival.

Study 1 comprised of three separate clinical surveys and due to the multifactorial nature of infusion failure it was difficult to control for all variables. Most cannulations in this study were performed by various medical staff which may have influenced the infusion failure rate, particularly from an infective phlebitis perspective. One cannula insertion operator would have

been ideal. Another possible limitation is that two of the above surveys (Westmead and POWCH) were conducted on medical wards as opposed to a mix of medical and surgical patients. This may have affected the incidence of failure, however, no study to date has shown that infusion-site failure occurs more frequently when comparing medical to surgical patients. Due to the difference in setting and hospital practices, caution should also be used when interpreting the data from Hammersmith hospital, although it was felt the results were relevant to the overall study.

The second study tested the efficacy of low-dose heparin added to the infusate for increasing infusion site survival in children.

In a randomised double-blind trial, Study 2 showed that the survival of infusion sites was considerably greater for the experimental group than for the control, with median survival half lives of 97 and 43 hours respectively. The difference due to the effect of heparin was highly significant ($p < 0.0001$). Multi-variate analysis confirmed this result. Other factors found to influence infusion site survival were the addition of ampicillin and flucloxacillin.

Only a relatively small number of infusion sites were studied in the heparin experiment (Study 2). The reasons

for this were that only 180 bags of solutions with heparin were available and the manufacturer imposed a twelve week shelf life. Even so, the difference in survival of sites was highly significant and there is no reason to believe that a similar difference would not be produced in a much larger trial.

The first hypothesis that "the addition of low-dose heparin to infusate will decrease infusion failure in children" was supported.

The major limitation to Study 2 was the short shelf life (12 weeks) of heparin in intravenous fluids. The third study was conducted to determine if various heparinized intravenous solutions could maintain their stability over time. The results of Study 3 showed that, over a 12 month period, heparin at iu/ml was stable in saline and dextrose-saline solutions, but not in dextrose.

The possibility that stability could have been affected by poor aseptic technique is possible. Although the addition of heparin to the infusion fluids was done using an aseptic technique, sterile conditions, for example, under laminar flow, would have been preferred. The fact that pH of the solutions did not vary greatly and that coagulation times remained high over the 12 months suggests that contamination due to poor 'adding' technique was not a problem.

The second hypothesis that "various heparinized intravenous solutions will maintain their stability over time" was supported, with the exception of heparinized 5% dextrose.

Nurses who work in clinical areas will always be involved in IV management as part of their role. Unfortunately, with present technology, infusions will always fail. The aetiology of infusion failure due to phlebitis/ extravasation is probably multifactorial in nature and may include physical, chemical and bacteriological aspects. By becoming aware of the possible factors involved and the strategies used to prevent such failure, the nurse can offer optimal patient care in relation to infusion sites.

Both Levine and Roy, in describing their theoretical frameworks for practice, supported the notion of adaptation, structural integrity and energy conservation. Employing these concepts of Levine and Roy, as well as a physiological framework, nurses should consider the use of a pharmacological intervention as a means of reducing infusion failure. By reducing the failure of intravenous infusions by the addition of low-dose heparin to infusate, this intervention may enhance positive adaptation by the child, maintain structural integrity of the vein and promote positive energy which the child may use to "cope" with other aspects of illness.

Hence, by improving the infusion site survival rate of the child, various physical, physiological and psychoemotional needs are met, energy is conserved, structural integrity is maintained, and adaptation ensues.

The pharmacological approach, that is, the addition of steroids, heparin or the use of glyceryl trinitrate patches may be employed. Caution must always be used when administering medications to patients, particularly children, but in certain cases the benefits may outweigh the risks. Study 2, by the use of low-dose heparin added to infusate, was able to significantly improve infusion site survival. Although the work on this topic has traditionally been the province of medicine, implications for nurses/nursing are likely to include, fewer problems with IV solution flow rates, a reduction in medical/nursing hours associated with frequent re-cannulations, less likelihood of systemic sepsis and less patient worry and discomfort due to local venous reactions and re-cannulations. MOST IMPORTANT IS THE BENEFICIAL IMPROVEMENT OF WELFARE TO CHILDREN AND THEIR PARENTS.

Although the minimum effective concentration of heparin added to infusate to prolong infusion site survival has not been determined in adults and since the one trial in neonates (Moclair et al, 1992) has shown 0.5 iv/ml to be

as effective as 1 iu/ml, further studies are required. There will always be a sub-population of patients who may benefit from the addition of low-dose heparin to infusate to decrease infusion site failure. It is also recommended that manufacturers initiate the production of commercially available dextrose-saline solutions containing low-dose (1 iu per ml) heparin for the purpose of prolonging survival of peripheral intravenous sites in patients who are admitted to hospital.

Although the use of heparin in continuous infusions to improve infusion site survival remains controversial, it is suggested that in cases where venous access is of prime importance, that 1 iu/ml of heparin be added to the infusate to increase infusion site survival and prolong effective vein usage, thereby reducing potential morbidity.

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**Wright, A. (1993). Nursing implications of low-dose heparin to infusate to improve infusion site survival in children. <u>Australian Critical Care</u>, 6(4), 10-13.

**Wright, A., Hecker, J.F. (1991). Infusion failure caused by phlebitis and extravasation. <u>Clinical Pharmacy</u>, 10, 630-634.

**Wright, A., Hecker, J.F., Lewis, G.B.H. (1985). Use of transdermal glyceryl trinitrate to reduce failure of intravenous infusions due to phlebitis and extravasation. <u>Lancet</u>, 2, 1148-1150.

**Wright, A., Hecker, J.F., McDonald, G. (1995). Effects of low-dose heparin on failure of intravenous infusions in children. <u>Heart and Lung</u>, 24,1,79-82.

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**Denotes relevant publications to this thesis by author.

APPENDICES

APPENDIX A

DATA COLLECTION FORM

I.V. SURVEY

PLEASE RETURN FORM TO B4A

$\qquad$ N.B. Use one form per cannula.

$\qquad$ Use ticks where indicated

Unit No.: _____ Ward: _____

Sex: _____

Age: _____

CANNULA INSERTION

Type & Size: _____

Date: ___/___/___   Time: _____ (am/pm)

Site( ): Hand( ) Wrist( ) Forearm( ) Foot( )

Other: _____

Side( ): Left( )   Right( )

CANNULA REMOVAL

Date: ___/___/___   Time: _____ (am/pm)

Reason( ): Phlebitis( ) Tissued( ) Blocked( )

$\qquad$ Pulled out( ) Elective removal( )

$\qquad$ Resited as in for 48 hrs( ) Other:_____

Site at removal: Slightly tender   ( ) (Please
(may tick more   Tender   ( ) palpate
than one)   Very tender   ( ) the area)
                     Slightly red   ( )
                     Red   ( )
                     Slightly swollen   ( )
                     Swollen   ( )
                     Cording   ( )

Type of IV fluids given: Heparinized Solutions:
eg. N/4

$\qquad$ Used / Not used

$\qquad$ (Please circle)

Drugs given & Concentration:
(eg. Gentamicin 5mg in 100mls
N/2 over 20mins or Amoxicillin
250mg IV bolus over 10 mins)

APPENDIX B

RESEARCH PROCEDURE

Before the commencement of this part of the study the following will be organised:-

1. Inservice talks will again be held to reinforce correct data collection and research procedure;
2. Consent forms and 'information to parents' forms will be kept in a central location in the participating wards;
3. IV data collection sheets will be kept in a central location in the participating wards;
4. IV fluids (with and without Heparin) will be kept in the fluids area of the participating wards and will be clearly labeled,
5. A list of drugs whch are known to be incompatible with Heparin will be displayed in a central location in the participating wards (Hipwell, 1984, pp71-73; Trissel, 1983, pp214-227);
6. Although medical officers working in the area will not be directly involved, they will be informed of the study and expert guidance sought where needed.

PROCEDURE

1. Upon routine ward admission, the study will be explained and then parental consent will be sought.
2. The following information will then be recorded on the standard form; patient's initials, unit number sex, age, type and size of cannula, site, date and time of cannulation, type of IV fluid and medication administered and which group the subject belongs to (control/treatment).
3. Depending on which group the patient is in, the appropriate IV fluid (with or without Heparin) will then be started.
4. Any new IV fluids/medications ordered during the patient's stay in hospital will also be recorded on the provided form.
5. Before heparinized fluid are started, the IV medications will be noted and cross-checked with the incompatibility list. Should heparin be incompatible with the drug then standard fluids shall be started and the reason stated on the form.
6. Should an incompatible drug be ordered during the treatment with heparinized fluids then the same procedure as point 5 will be followed ie. standard fluids commenced and the reason stated on the firm.
7. Should an unpredictable incompatibility reaction occur then the infusion will be stopped and the above procedure followed.

8. If there is any doubt in the nurse's mind as to the incompatibility of medications with heparin the pharmacy will be contacted and their advice followed.

9. Daily inspection of the infusion site will be carried out and any signs of phlebitis/ extravasation reported.

10. Upon cannula removal the following will be recorded: date and time, reason for removal, and inspection of the site as to signs of phlebitis/ extravasation (tenderness, erythema, oedema and cording).

11. The total volume of fluids administered will also be obtained from the patient's records on discharge.

12. Should the infusion be suspended and the cannula capped, then the procedure for "cannula removal" will apply, the form completed, and reference to the capping be documented on the form.

13. If patients are transferred towards other than those in which the research is being conducted then this will be documented and the "cannula removal" section completed.

14. Should non-standard fluids be ordered at any time during the patients stay, and should this patient be in the treatment group, then permission will be sought from the medical officer in charge (who will be aware of the study) to add the required amount of heparin to the solution (ie. 1 unit/ml) until such time as the non-standard solutions are replaced by standard solutions (eg. n/4, n/2, 5% dext, 0.9% NaCl, Hartmans).

15. All forms will be kept in a central location in the respective wards except those in use. These will be located at the foot of the patients bed.

16. All data collection forms will be of a standard colour - PINK!.

17. Once the required number of subjects has been reached the data will be analyzed and the results made known to those participating in the study.

APPENDIX C

CONSENT FOR RESEARCH

Cumberland Area Health Service

<u>CONSENT FOR RESEARCH</u>

Title	Family Name	M.R.N.				
Given Names		C.M.O.				
Address	Street	Age	Sex	H.I.S.		
Suburb	Postcode	Adm. date				

<u>Title of Project</u>:

Decreasing intravenous problems with
low-dose heparin in children.

<u>Name(s) of Chief Investigator(s)</u>:

ALEX WRIGHT

<u>Purpose</u>:   The purpose of this study will be to see if low-dose heparin can
lower the incidence of complications associated with intravenous
infusions (drips) in children.

<u>Methods and Demands</u>:

Children will be put into two groups, one will receive fluids with
heparin, the other fluids without heparin. A standard form will be
used to record any problems these two groups develop as well as the
frequency of these problems.

<u>Risks, Inconveniences and Discomforts Which May Occur</u>:

Please see attached "INFORMATION TO PARENTS"..

I have been asked to participate in the above research study and give my
consent by signing this form on the understanding that:
1.   The research study will be carried out in a manner conforming with the
     principles set out by the National Health and Medical Research Council
2.   The general purposes, methods and demands and the possible risks,
     inconveniences and discomforts which may occur during the study have
     been made known
3.   Refusal to take part in this study will not affect the treatment of my
     condition.
4.   I am volunteering to take part in this study and I may withdraw at any
     time
5.   This research has been approved by the Cumberland Area Health Service
     Research and Human Ethics Review Committees.

Signature:_____   Date:_____
(By subject, if over 18 years, otherwise by guardian or next friend)

Witnessed by: _____   Project Approval No:_____
          of: _____

APPENDIX D

INFORMATION TO PARENTS

Many children who are admitted to hospital will require a needle (cannula) to be put into a vein for administration of medications and fluids (intravenous therapy).

Quite often the cannula site will become tender and inflammed and a new cannula will have to be put into a new vein. This may cause unnecessary discomfort and worry to the child.

This study will attempt to see if a low-dose medication (Heparin) can prevent or reduce the incidence of complications when added to the bag of fluid (infusion). This medication is regularly used in day to day medical practice to prevent clots forming in a vein.

The present study will use very low-dose Heparin to prevent clot formation and past studies on premature babies have shown this to work. Because the dose is low there have not been any reports of problems associated with this medication, however, it is remotely possible that antibodies may be produced to this medication although none have been demonstrated in children.

If this study is successful then future children who are admitted to hospital may receive trouble-free and more comfortable intravenous therapy.

Your co-operation to make this study successful will be greatly appreciated.

Confidentiality will be maintained throughout the study.

You also have the right to withdraw your child from the study at any time should you decide to.

At the completion of this study the results will gladly be shared with you if you so desire.

Thank you again,

ALEX WRIGHT (R.N., C.M. BA)
(Principal Researcher - CCHS)

APPENDIX E

PUBLICATIONS BY THE AUTHOR WHICH ARE RELEVANT TO AND RESULTING FROM THIS THESIS

Wright, A. (1983). Superficial thrombophlebitis post cannulation - a geriatric hospital study. (Unpublished manuscript).

Wright, A., Hecker, J.F., Lewis, G.B.H. (1985). Use of transdermal glyceryl trinitrate to reduce failure of intravenous infusions due to phlebitis and extravasation. Lancet, 2, 1148-1150.

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