A randomised controlled trial to investigate the efficacy of heparin and hydrocortisone additive to extend the life of peripheral cannulae in children.

By
Katrina Jane Milbourne

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ABSTRACT

Repeated cannulation of children during the course of treatment is distressing for the child, their family and to their nurses. Some paediatric units endeavour to minimise re-cannulation by employing strategies to reduce complications such as phlebitis and thrombosis formation. One strategy is to infuse low dose heparin and hydrocortisone (HEPHC). However, its effectiveness in prolonging cannula survival is inconclusive. There is also concern about the potential risks of administering these preparations to children.

A randomised, controlled, blinded trial was conducted that examined the effectiveness of continuous infusion of low dose HEPHC in a group of children requiring long term intravenous antibiotics in a general paediatric unit. Comparisons of cannula complications and cannulae survival times were made in children receiving either continuous infusions of clear fluids or low dose HEPHC.

The results demonstrated that there was no statistically significant difference (Logrank statistic=1.1, $p=0.3$) in cannula survival times between the two groups. It was also found that the bacterial and fungal colonisation of cannula for these children was extremely low. Based on these findings it is recommended that routine administration of low dose HEPHC to extend cannula survival time be discontinued. The findings also support current practice of removing cannula in children only when a complication occurs on completion of treatment.

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GLOSSARY

Adult: Over the age of 16 years.

Aseptic phlebitis: Phlebitis due to chemical and mechanical factors as opposed to bacteria and fungi infections.

Cannula: Short peripheral intravenous catheter made by Ovium, (Johnson and Johnson).

Cannula complication: Cannula that experienced phlebitis, extravasation, blocking or kinking.

Cannula failure (also called event): Cannula is no longer providing access to the vein due to phlebitis, extravasation, blocking, kinking or falling out.

Cannula survival time (dwell time): The period a cannula is providing access to the vein (patent) until the cannula is no longer providing access to the vein.

Cannula censor: Cannula that is removed when no complications occur. For example completion of treatment, the cannula fell out or was removed.

Child: Under the age of 16 years.

Continuous flushing solution: Solution continually infused through a cannula when other medications are not being administered.

Dwell time (cannula survival time): The period of time a cannula is inserted into and provides access to a vein (patent) until the cannula is removed and/or no longer provides access to the vein.

Event (also called cannula failure): Cannula is no longer providing access to the vein due to phlebitis, extravasation, blocking, kinking or falling out.

Extravasation (also called infiltration and tissuing): When the cannula tip leaves the vein and infusate enters the layers of skin tissue instead of the vein.

Fibrin: Insoluable protein used to repair tissue damage.

Flushing solution: General term to describe the process of infusing a fluid through a cannula to remove chemicals and material from the catheter lumen.

Infiltration (also called extravasation and tissuing): When infusate enters the layers of skin tissue instead of the vein.

Intermittent flushing solution: Solution infused through a cannula over a short period of time to clear the cannula of medications and other material.

Patency of cannula: When a clear passage exists from the external environment to the inside of a vein, using a cannula.

Phlebitis: A general term used for inflammation of a vein, characterised by pain, redness, swelling and frequently with a palpable cord.

Septic phlebitis: Phlebitis due to bacteria and fungi colonisation as opposed to chemical or mechanical factors.

Tissuing (also called infiltration and extravasation): When an infusate enters the layers of skin and fatty tissue instead of the vein.

CHAPTER 1

INTRODUCTION

1
Introduction

1.1 Introduction

This thesis presents a trial to investigate intravenous management practices in children in a general paediatric unit. Its aim is to determine whether adding low doses of two medications, heparin and hydrocortisone, to a continuous flushing solution infused intravenously to children, is effective in prolonging cannulae dwell times. This information is important because it will guide future cannula management for children admitted to The Canberra Hospital paediatric unit. And it will add to the current knowledge about cannula in this population.

Use of peripheral intravenous cannulae is common in the treatment of hospitalised patients. However, cannulation present specific issues for children because of their limited ability to understand and cope with pain. Cannulation is painful, can be traumatic for children and this can have lasting effects. This is of concern to the child, their family and health carers. And to minimise the potential for this trauma, some paediatric units employ strategies to reduce cannula related complications in an attempt to minimise the need for re-cannulation.

Usually short peripheral intravenous cannulae (pIVC) are inserted into veins of the forearm or hand and are an important part of treatment for many hospitalised children. These devices are used to administer fluids, medications such as antibiotics, parental nutrition and blood products. Despite their benefits, pIVC have complications that can be painful, reduce the time a cannula is functional and in some cases can pose significant health risks for the cannulated person. Complications associated with these devices include extravasation, phlebitis, blocking or kinking of the cannula, colonisation, cellulitis and bacteraemia.

Best practice for cannula management involves maximising cannula survival time within recommended limits and minimising complications associated with pIVC use. Strategies employed to achieve best practice include good infection control preparation and method, and vigilant monitoring of the cannula insertion site. Studies on adult

populations suggest that the length of dwell time of pIVC is an important factor in the type of complication that will develop (Mayhall, 1997).

In contrast, there is little knowledge about pIVC survival and complication rates in children. This is because there has been limited investigation into paediatric cannula management (Oishi, 2001). Those studies that have been conducted suggest that length of dwell time of pIVC is less important in children than in adults. The reason for this difference is not clear. However, current evidence indicates that adult studies cannot be generalised to children, because cannula infection rates and inflammatory responses differ between adults and children and because many hospitals have different cannulae management strategies for these populations.

As a Clinical Nurse Consultant in a general paediatric environment that includes adolescents, I have a particular interest in the differences in adult and paediatric cannula management. My unit is the only acute paediatric unit serving the ACT and Southern NSW area. There are two cannula management policies. For older adolescents, over 16 years, cannulae are routinely replaced every 72 hours in line with adult protocols. For younger adolescents and children cannula are kept insitu until treatment is complete or when complications occur. Furthermore, children who require intravenous antibiotics for periods of greater than 3 days are routinely administered a continuous flushing solution that contains low doses of heparin and hydrocortisone (HEPHC) in an attempt to extend cannula survival time.

Use of low dose HEPHC started in my unit in 1992 after bench-marking with a Sydney children's hospital. However, without any evidence on the effectiveness of this strategy in the paediatric setting and in light of the known risks associated with using heparin and hydrocortisone, clinicians have questioned this practice. This provided the impetus for the current investigation.

Pharmacological strategies, including flushing solutions with intravenous additives, are thought to prevent thrombosis formation and phlebitis. It is important to reduce these complications for reasons of safety, comfort and cost effectiveness. Additionally, pharmacological strategies may extend cannula dwell time. However, evidence supporting this practice in children is inconclusive.

This trial was conducted to investigate the efficacy of HEPHC in extending cannula survival time in children. The remainder of this thesis presents the existing research, the methodology and findings of this investigation. Chapter 2 presents the current adult and paediatric literature on pharmacological strategies aimed at increasing cannula survival time. The discussion focuses on five methods thought to achieve longer dwell times in pIVC. It has been identified that there is a lack of literature supporting the use of intravenous medications for this purpose in children. Chapter 2 supports the need for a trial to investigate the addition of low dose HEPHC to flushing solutions administered to children in a Canberra teaching hospital.

Chapter 3 describes in detail the methodology designed for the study to determine whether HEPHC added to a flushing solution prolongs cannula survival time. It outlines a randomised, controlled double blind trial conducted on a group of children admitted to a general paediatric unit.

The findings of the analysis of this trial are presented in the fourth Chapter. This includes establishing that the two groups of the study are well matched and then presenting a survival analysis between the two conditions.

Finally, Chapter 5 will discuss these findings in the context of current literature and present recommendations for research and policy.

CHAPTER 2

LITERATURE REVIEW

2
Literature review

2.1 Introduction

Cannula failure can occur from extravasation and phlebitis. Extravasation, also called infiltration and tissuing, is a significant and potentially serious cannula related complication that leads around 23% of adult pIVC to fail. Phlebitis is a general term used to describe the inflammatory process associated with some cannula and occurs when the cells of the vein are damaged. There are two ways that vein wall damage can occur. Cells can be damaged aseptically by mechanical and chemical irritation (aseptic phlebitis), for example due to alkaline or acidic infusion fluids, or septically through (bacteriae and fungial) colonisation (Frazer, Eke and Laing, 1977).

Extravasation and phlebitis are initiated by venous-constriction in the region of the infusion site brought about by irritation of the endothelium (Hecker, Fisk and Lewis, 1984). It has been argued that vasoconstriction in children is more common because they generally have smaller, more reactive veins (Wright, Hecker and Lewis, 1985). For this reason, vasoconstriction is thought to lead more frequently to extravasation than to phlebitis in children.

Although only a few studies have focused on extravasation rates in children and infants, it appears children experience over double the rate of extravasation as do adults; at between 58% and 77% (Phelps and Helms, 1987; Shimandle Johnson, Baker, Stotland, Karrison and Arnow, 1999). Thus, the literature indicates that extravasation is more common for children, when compared with adults, while phlebitis is more common and significant for adults.

Rarely has the frequency of aseptic versus septic phlebitis been considered in adults or children. This is partly because the early stages of both types of phlebitis are visually indistinguishable (Maki, Weise, Sarafin, 1977; Maki and Ringer, 1991; Nelson and Garland, 1987; Raad, Costeron, Sabharwal, Sacilowski, Anaisie and Bodey, 1993; Roberts, Holmes, Staugas, Day, Finlay and Pitcher, 1994 and Mayhall, 1997). Additionally, the ramifications of septic phlebitis are far more severe when compared to aseptic phlebitis. Septic phlebitis can result in life threatening illnesses such as

septicaemia, septic shock, meningitis, endocarditis and renal impairment. The severity of complications associated with septic phlebitis has lead to extensive research into their causes and the strategies aimed at minimising the incidence of septic phlebitis (Mayhall, 1997).

When a cannula fails, patients frequently experience pain around the cannula insertion site and require a new cannula to be inserted. Additionally, when re-cannulation is required, the process is time consuming for health professionals and leads to higher treatment costs (Khawaja, O'Brien, Buxton and Weaver, 1988). These factors in conjunction with the risks associated with phlebitis and extravasation, which includes tissue necrosis, have fostered research into chemical factors that lead to a reduction in cannula dwell time.

2.2 Contributing Factors to Reduce Cannulae Survival Time

Several demographic and environmental factors have been identified as increasing the risk of the phlebitis and extravasation (see Appendix A). These include being very young or very old, sex (men have a higher incidence of phlebitis), personal characteristics (such as poor quality veins), certain diagnoses (including malnutrition, neutropenia, immunosuppression, diabetes or heart disease) and infection at another site in the body (Maki and Ringer, 1991).

Cannulae management and processes implicated in the development of phlebitis in pIVC include whether aseptic technique is used when preparing and maintaining the access site. Also of importance is the skill of person inserting the cannula, frequency of dressings to the cannula site, whether the cannula was inserted because of an emergency and length of time insitu (Maki and Ringer, 1991; Catney, Hillis, Wakefield, Simpson, Domino, Keller, Connelly, White, Price, and Wagner, 2001).

Other factors include catheter characteristics such as cannula material (whether it is made from Teflon or Polyurethane), cannula gauge size (smaller bores appear to have fewer complications), what part of the body the cannula is inserted into, whether it is the first or subsequent cannula and frequency of tubing changes (Maki and Ringer, 1991; Catney et al, 2001).

A number of infusate characteristics have also been associated with phlebitis. These include pH of the solution (a neutral pH is less vaso-irritating than a high or low pH), osmolarity of medication (neutral is less vaso-irritating), dose and dilution of medication, infusate flow rate (faster rates are less vaso-irritating) and presence of particulate matter in infusates (Maki and Ringer, 1991; Catney et al, 2001).

Some medications have also been implicated in the literature as being more or less irritating when infused into a vein. A scale designed by Smith, Hathaway, and Goldmann (1990) rates the degree of irritability associated with different intravenous medications. They conducted a literature review and then devised a classification for rating the irritancy of medications from 1 to 3, where 1 was rarely irritating and 3 was frequently irritating. Intravenous medications that rate as 2 to 3 on this scale included ampicillin, erythromycin, vancomycin, piperacillin, 10% glucose and flagyl. Heparin, steroids, 0.9% sodium chloride, and cephalosporins rate a 1 on this scale (Catney et al. 2001). Not included in this scale were gentamicin, ciprofloxacin and Total Parental Nutrition which has also been implicated in the literature as being vaso-irritants (Hadaway, 1998).

An understanding of the mechanisms and causes of extravasation and phlebitis have facilitated strategies to interfere with these factors. The idea that vasoconstriction resulted in extravasation and aseptic phlebitis is the premise behind many strategies aimed at extending cannula dwell time or life. Therefore, if vasoconstriction results in extravasation or phlebitis then vaso-dilation should reduce their frequency (Frazer, Eke and Laing, 1977).

It has also been reported that cannulae survival time can be reduced because of thrombosis formation. Thrombi occur when blood flow slows. Flushing solutions and anticoagulants have been trialed as strategies to reduce thrombi formation and thus minimising peripheral intravenous cannula (pIVC) complications. By flushing a solution through the cannula bore it is thought that blood movement will increase and the chance of thrombi forming, decrease (Lewis and Hecker, 1984).

There is significant debate about the effectiveness of adding preparations to extend cannula dwell time and minimising complications (Hecker, 1992). This debate focuses on the safety of increasing cannula dwell time and how cannula survival time can be

extended. The research that informs these areas has largely focused on adult and neonate populations.

Debate around the safety of extending cannula survival time comes from a body of adult focused research, which evaluated the risk of septic phlebitis and sepsis associated with pIVC. There is evidence from adult studies that the longer the dwell time of a cannula, the greater the risk of phlebitis and sepsis. Based on this literature, The American Center for Disease Control and Prevention (2000) recommended that after 72 hours adult cannulae be routinely removed to minimise the risk of catheter-related sepsis to less than 5% (Shimandle et al. 1999).

In contrast, these guidelines are silent about removal of pIVC in children. This is because of the modest number of paediatric studies examining the safety of extending cannula survival time. These studies report that the incidence of phlebitis in cannulae placed in children is approximately half that of the adult rate (Nelson and Garland, 1987).

A literature review examining the risks of not replacing pIVC in children found that there was no evidence to support routine replacement of pIVC in children (Oishi, 2001). Therefore, it is generally accepted that cannulae are left in place in children until the treatment is complete or a complication occurs. It has been noted that studies in children should be performed to provide a more substantial basis for specific paediatric guidelines (Shimandle et al. 1999).

The remainder of this review will examine the research into five pharmacological strategies to extend cannula survival times. The discussion will focus on a critical review of the literature on: use of glyceryl trinitrate applied to the cannula insertion area, use of buffering of infusates to achieve a neutral pH, use of low dose infusions of either hydrocortisone or heparin and the concurrent infusion of heparin and hydrocortisone.

2.3 Pharmacological approaches to extend cannulae survival time

2.3.1 Transdermal glyceryl trinitrate to extend cannulae survival

Transdermal glyceryl trinitrate (tGTN) applied as a patch has been demonstrated to be effective as a strategy for extending cannula survival in adults. Generally, it is accepted that tGTN reduces vasoconstriction in the presence of irritant solutions (Lewis and Hecker, 1984). It has been hypothesised that applying tGTN to the skin where the cannula is inserted leads to vaso-dilation and an increase in local blood flow. This then makes an infusate less irritating because it becomes diluted in the blood more quickly (Hecker, 1992).

Support for this strategy has been obtained through a number of studies. One double blind trial conducted in Australia examined 208 adult patients who had tGTN applied to their cannula sites (Wright, Hecker and Lewis, 1985). They found that application of tGTN to skin near cannula sites improved cannula dwell time ($p < 0.001$) and reduced cannula related complications ($p<0.01$). They also found that application of tGTN to the area around cannula sites resulted in a reduction in the rate of infusion failure when compared to normal cannula.

Additionally, the study by Wright et al. (1985) found that the mean cannula dwell time was 81 hours for cannula sites without tGTN as compared to 145 hours for cannula sites where tGTN was applied. An unexpected finding of this study was that smaller rather than larger cannula remained patent for longer, regardless of the treatment. An explanation offered for this finding was that smaller cannula allow for higher blood flow around the catheter tip and resulted in a more rapid dilution of medications when compared to larger cannula.

The reliability of the findings from this study were criticised because patients were recruited from different wards where techniques of cannula siting, size, use and care of infusions could have differed (Khawaja, O'Brien, Buxton, and Weaver, 1988). To address these perceived flaws, Khawaja and colleagues replicated this study. In this replication, 340 patients were examined to determine the effectiveness of tGTN using a randomised controlled trial. These patients were receiving Total Parental Nutrition

(TPN) infusions via pIVC. Despite the criticisms made by Khawaja and colleagues, the study supported the findings of Wright and his colleagues. The group that received tGTN had a reduction in the incidence of infusion failure (19%) compared to the group that did not receive tGTN (55%) ($p<0.0005$). They also found that the median survival time was longer for the tGTN group at 127 hours as compared to 74 hours for the control group ($p<0.0001$). They concluded infusion phlebitis is common and applying tGTN can reduce its incidence.

Only one study (Hecker, 1990) has examined the use of tGTN as a strategy for prolonging cannula survival in paediatrics. This study focused on neonates and found tGTN to be ineffective in enhancing cannula survival time. One explanation for this offered by Hecker (1992), was that the size of cannula used in neonates, although small in comparison to adults, were proportionally large compared to the vein size of neonates. This remains unresolved, as there is no evidence to support this argument.

No trials have investigated the effectiveness of tGTN in children as opposed to neonates. One explanation for this is that some children do not tolerate patches and tend to pull then off. They may also chew and eat the transdermal patch, hastening the absorption of glyceryl trinitrate into the body and increasing the chance of receiving higher doses and being exposed to side effects. Another good reason for tGTN not routinely being using in children is that side effects such as headaches are quite common (Tighe, Wong, Bpharm, Martin and McMahon, 1995).

2.3.2 Buffering as a method to extend cannulae survival time

The pH of a solution has been implicated in animal experiments as a cause of phlebitis. This has lead to buffering solutions being explored as a pharmacological strategy to increase cannula dwell time. Studies examining the effectiveness of buffering solutions have provided mixed results. Buffering solutions such as sodium bicarbonate neutralise the pH of an infusate. A British study examined adding prophylactic sodium bicarbonate to prevent pIVC failure from aseptic phlebitis in 186 adult patients in a three arm blinded randomised study (Fonkalsrud, Carpenter, Masuda, and Beckerman, 1971). Thirty patients were then excluded for a number of reasons, including the development of infiltration, leaving a sample of 156 patients.

Of the three groups in this study, one group (n=60) received a control solution without the addition of a buffer, the second group (n=52) received the same solution with the addition of sodium bicarbonate to a pH of 7.2-7.5, while the third group (n=51) received the control solution with additive of low dose heparin and hydrocortisone (HEPHC). Phlebitis was then rated using a scale of +1 for mild, +2 for moderate and +3 for severe. A finding from this study was that buffering infusates were effective in halving the incidence of phlebitis. Adding low doses of HEPHC was also demonstrated to be moderately effective in reducing the incidence of phlebitis.

A criticism of this study was that steel needles were used. This makes comparisons with current practice, where no butterfly needles and only plastic cannulae were used, inappropriate, because the incidence of extravasation has been shown to be higher in steel needles as compared with plastic cannula (Tully, Friedland, Baldini and Goldmann, 1981). Another potential flaw in this trial was that patients who demonstrated signs of extravasation were excluded from analysis. As it is difficult to discriminate between the early stages of extravasation and phlebitis, it is possible that Fonkalsrud and his colleagues biased their sample by incorrectly excluding some cannulae from their analysis.

Another study focusing on neonates has added support to the literature indicating that buffering increases cannula survival and reduces the incidence of phlebitis (Rypins, Johnson, Reder, Sarfeh and Shimoda, 1990). Rypin and colleagues examined the effect of neutralising the pH of TPN given to a group of premature babies. Like Fonkalsrud and his team, they found that cannula survival time increased when the infusate had a neutral pH. In this study, the group that received the buffered TPN had an incidence of phlebitis of 27% as compared to 68% in the group that received the un-buffered solution.

Not all studies support the practice of adding buffering solutions to increase pIVC dwell time and reduce phlebitis rates. Bolton-Carter, Milne and Whittet (1971) found that pH did not affect cannula survival time in adult patients. However, this study has been criticised because the highest pH in their study was 6.05 (still acidic) (Hecker, 1992).

It has been argued that the equipment used in the early studies may have contributed to conflicting findings. Improvements such as making cannulae from inert plastic, aseptic

preparation, improved quality of infusates and advances in techniques to manage cannulae have occurred over the past 30 years. For example rubber infusion sets which have been demonstrated to increase the risk of phlebitis are no longer used, being superseded by a plastic set which is less likely to contribute particulate matter to the infusate (Maki and Ringer, 1977).

Only one neonatal study has not supported the used of buffering (Hecker, Duffy, Fong, and Wyer, 1991). Hecker and his colleagues examined the effect of buffering TPN in a group of neonates and found that the median cannula dwell time increased from 21 to 33 hours. A 12 hour increase in cannula dwell time is negligible and would need to be carefully weighed against the risk of receiving additional medications.

The majority of literature supports the use of buffered infusates to enhance cannula dwell time. However, addition of buffers has not been widely practiced because of the risk of environmental contamination and manufacture of these agents is not feasible (Wright, 1996). There is also the potential for a serious accident, especially if an error in the medication dosage for sodium bicarbonate was made in a child or infant.

2.3.3 Corticosteroids as a method to extend cannulae survival

Infusions of corticosteroids for severe asthmatics commonly run for prolonged periods of time without failing (Hecker, 1992). This observation has lead to the inclusion of anti-inflammatory medications, such as hydrocortisone, being trialed as a method for prolonging cannula survival time. Hydrocortisone has an anti-inflammatory effect, possibly by inhibiting prostaglandin production via lysosomal enzyme stabilisation (Hecker, 1992; Kohlhardt, 1994). It has been suggested that certain infusates initiate an inflammatory response and addition of low dose hydrocortisone counters this (Wright, 1996).

The corticosteroid dose generally recommended in the literature for prolonging cannula survival is 10mg to 20mg per litre infused at a rate of between 5 and 20 mL per hour. This dosage is thought to have negligible systemic effects but acts locally to reduce inflammation (Hecker, 1992). Corticosteroids at high doses can have deleterious effects. Risks of hydrocortisone at high doses include masking inflammation reactions at local and systemic levels and potentially increasing the risk of septic phlebitis

because it interferes with the inflammatory response (Wright, 1996). However, there is no literature outlining the systemic effects of low dose hydrocortisone over a period of time in adults or children.

It has also not been established that adding low doses of hydrocortisone is effective in extending cannula survival time (Wright, 1996). Some studies report that steroids decrease the incidence of phlebitis (Fonkalsrud et al. 1971; Sketch, Cale, Mohiuddin and Booth, 1972) while others do not report this (eg Bivins, Rapp, DeLuca, McKean, and Griffen, 1979). Fonkalsrud and colleagues (1971) compared hydrocortisone, heparin and a buffer with using buffer alone. They found a negligible increase in phlebitis when hydrocortisone was used. In contrast, Subrahmanyam (1988) demonstrated a marginal decrease in phlebitis with continuous hydrocortisone plus six hourly boluses of heparin. Even though numbers in trials are often small and findings were not always significant, a meta-analysis reported that hydrocortisone does appear to decrease infusion failure (Hecker, 1992).

2.3.4 Heparin as a method to extend cannulae survival time

Heparin has been trialed as a strategy for prolonging cannula dwell time. Heparin is widely used in the prevention and treatment of deep venous and arterial thrombosis and it has been observed that these infusions commonly run for prolonged periods of time (Hecker, 1992). It is also used as an anticoagulant for procedures such as haemodialysis, heart infiltration, and cardiac surgery (Chong, 1992). Heparin is thought to prevent or reduce the formation of a fibrin sheath at the tip of the catheter and it is thought that fibrin formation can occlude the cannula lumen (Kohlhardt, 1994, Apian, Eyal, Spinger, Glick,Goder and Armon, 1984; Daniell, 1973). Wright (1996) suggests that heparin also works at a cellular level to inhibit mast cell mediated allergic inflammation. Thus, heparin may inhibit mast cell degranulation directly or limit the oedema associated with mediator release.

Heparin appears to have several other effects. Heparin has tissue healing properties (Wright, 1996) and decreases the incidence of phlebitis (Schafermyer, 1974). However, heparin may also interfere with healing through inhibiting neutrophil activation and

complement dependent inflammation (Wright, 1996). Like many drugs, heparin may cause adverse effects including bleeding, osteoporosis, skin allergic reactions and thrombocytopenia (Chong, 1992). Life threatening side effects associated with heparin use are heparin-induced thrombocytopenia (HIT), thrombolytic and haemorrhagic complications (Ranze, Ranze, Magnani and Greinacher, 1999). The incidence of HIT for adult patients receiving therapeutic anti-coagulant doses of heparin ranges in the literature from 1-30% but it is also known to be associated with very low doses such as 1unit per mL (Chong, 1992).

In contrast, the incidence of HIT in children is not known although it appears to be relatively low because only several cases of HIT in infants and children have been reported (Potter Gill, Scott and McFarland, 1992 and Spadone, Clark, James, Laster, Hoch and Silver, 1992). A literature review of reports of HIT in children cited 8 cases where children from 3 months to 15 years as well as 14 neonates suffered HIT (Ranze et al. 1999). These children had received heparin for a variety of reasons, including for pIVC patency. An explanation for the low incidence of HIT in young paediatric patients was that the immune system is still not fully developed and that in this immature state, an effective immune response is not possible (Potter et al. 1992). In contrast, adults have an active immune system that can be induced to destroy thrombocytes which results in a higher incidence of HIT.

There are several other explanations for this low incidence of HIT observed in children. Heparin use is rare in children (Potter et al. 1992). Additionally, Potter and colleagues state that thrombocytopenia may be overlooked or attributed to other non-specific causes, such as suspected but unproven infection, and not attributed to HIT. Based on the current lack of literature on heparin use in children, several articles have recommended that children receiving heparin therapy should regularly have their platelet counts monitored (Potter et al. 1992; Wright, 1996).

Heparin has been used as an intermittent flushing agent and in a continuous infusion to prevent thrombosis formation. A Western Australian randomised controlled trial investigated whether heparinised saline (10 units/mL) was a superior intermittent flushing agent to 0.9% normal saline in a paediatric population of 152 children aged 2 months to 18 years (Robertson, 1994). This study found no significant difference in the duration of cannula survival between the two groups of the study ($p=0.1$) or the

incidence of phlebitis ($p=0.19$), and concluded that intermittent normal saline flushes should be considered as an alternative to heparinised saline.

As a continuous infusion, the effectiveness and dosage of heparin for maintaining cannula patency has not been determined (Randolph Cook, Gonzales and Andrew, 1998). In a study comparing 0, 0.01, 0.25, 0.5 and 1unit/mL of heparin in 10% dextrose added to an infusate of TPN and given to premature infants, found no difference between 0.5 and 1unit/mL concentrations (Hecker, 1992). There was further evidence supporting no difference in the effectiveness of 0.5 and 1 unit/mL concentrations of heparin in prolonging pIVC survival when added to TPN and infused into neonates (Monclair, Hecker, Willson and Bates, 1991).

Two meta-analysis studies have evaluated heparin and 0.9% sodium chloride (normal saline) as flushing solutions for peripheral intermittent infusion devices (Goode, Titler, Ones, Kleiber, and Small, 1991; Peterson and Kirchhoff, 1991). Both analyses concluded that the effect of the heparin flushes on cannula patency was equivalent to flushing with normal saline. However, the majority of studies in both meta-analysis groups were conducted on adults.

One randomised controlled trial has examined a group of 150 children (LeDuc, 1997). This study found that cannula dwell time was similar whether heparin or normal saline solution flushes were used. Thus, continuously infused heparin in low doses may not be as effective as previously thought.

A meta-analysis of randomised controlled trials examining the benefits of heparin in peripheral venous and arterial catheters has also been conducted (Randoph et al. 1998). The Randoph et al. (1998) analysis included 13 studies on peripheral venous catheters and used a standardised phlebitis definition. They found that there was not enough evidence to draw any firm conclusions about the benefit of adding heparin to continuously infused solutions administered via pIVC, recommending further studies be conducted.

An important criticism of this meta-analysis is that it included data from adults, children and neonatal studies. Combining these groups could be a methodological flaw as the incidence of phlebitis differs widely between adults, children and neonates (Oishi,

2001). Furthermore, based on current knowledge, different management practices are currently employed in the management of pIVC for these groups. In adults, cannulae are routinely removed after 48-72 hours to reduce the risk of septic phlebitis while no such guideline exists for the management of paediatric cannula (American Center for Disease Control and Prevention, 2000).

A neonatal study was conducted after the meta-analysis by Randolph and colleagues (1996). This study assessed pIVC dwell times in 112 neonates who were randomly assigned to receive a continuous infusion of 0.5 units/mL of heparin (n=63) or normal saline (n=49) (Scaaf Treas and Latinis-Bridgese, 1991). This study indicated that heparin improved cannula survival time, which was double the mean survival time (63 hours, $p=0.0001$) of the group that did not receive heparin.

One study has examined the effectiveness of heparin as a continuous flushing solution, in prolonging cannula dwell time in a general paediatric population (Wright, Hecker and McDonald, 1995, also reported as Wright, 1993). This study was a double blind randomised trial examining eighty children in a general medical ward. Thirty-six children received a solution of 0.225% saline plus 3.75% dextrose with 1 unit/mL of heparin added while forty four children received the solution without heparin. A median cannula survival half-life of 97 hours was obtained for the heparin group and 43 hours for the control group. Using Kaplan Myer survival curves they demonstrated a three fold improvement in cannula duration before failure (odds ratio 3.33). The only other variables, flucloxacillin and ampicillin, were found not to reduce cannula survival time when compared with other antibiotics.

A limitation of this study was that patients in the group that received heparin also received fewer antibiotics, 12 as compared to 19 in the control group. As previously discussed, a number of antibiotics are known vaso-irritants. The type and number of antibiotic given could have been a significant confounding variable if these factors were not controlled for between each group of the trial. For this reason, further research should be conducted and an attempt made to ensure that the irritability of the medications is matched.

2.3.5 Combined heparin and hydrocortisone to extend cannulae survival

The concurrent administration and application of both heparin and hydrocortisone (HEPHC) is another method routinely used in many major centres as a way of prolonging cannula dwell time (Roongpisuthipong, Puchaiwatananon, Songchitsomboon and Kanjanapanjapol, 1994). Studies investigating this preparation suggest that heparin in combination with hydrocortisone acts in a synergistic manner (Wright, 1996; Hecker, 1992; Tighe et al. 1995). It has been reported that a low dose HEPHC is the best method for reducing cannula complications and extending cannula survival time (Hecker, 1992; Bassan, and Sheikh-Hamad, 1983).

The application of HEPHC in a topical cream has been investigated (Woodhouse, 1979). In this study, a cream called Movelat containing 1% adrenocorticosteriod, 0.2% organo-heparin and 2% salicylic acid was applied 3 times a day to the skin at the cannulae insertion site. The 97 patients involved in this study were well matched for demographics. It was found that the phlebitis rate was halved for the experimental group (p=0,05) and cannula that received this cream took 40% longer to develop signs of thrombophlebitis. The mean duration of the cannula dwell time was 54.7 hours for the group that received the cream and 46.7 for the control group, an increase of less than twenty hours. Of concern is that a definition of phlebitis was not provided. Secondly, a preparation that included salicylic acid would not be appropriate for use on children as salicylic acid is thought to increase the risk of Reyes Syndrome (Molitor, 1985).

A review of literature and meta-analysis on the effectiveness of low dose HEPHC in prolonging pIVC survival was conducted by Hecker (1992). Hecker (1992) included in his data an unpublished and undated work on HEPHC use in children by Wright and colleagues. Otherwise, all the data used in this analysis focused on adults. In addition to this, the doses of HEPHC were not consistent in his data set.

This meta-analysis indicated that cannula survival time could be increased and complications experienced by cannulae could be reduced when HEPHC were infused together. This combination was reported to have lower odds of removal and thus was better than infusions of either alone, with a buffer or with tGTN ($p<0.001$, pooled odds ratio=0.2 with 95% confidence interval).

One study has been conducted since this meta-analysis study, in which the effectiveness of low dose HEPHC in prolonging cannula dwell time was examined. A randomised trial conducted in Thailand examined the incidence and degree of infusion phlebitis in surgical adult patients receiving pIVC TPN by randomly assigning them into 2 groups (Roongpisuthipong et al. 1994). Seven patients received only the feed solution and 8 patients received the feed solution with an addition of 10mg of hydrocortisone and 500 units of heparin per 500mL of fluid. This study found that the low dose of HEPHC additive significantly reduced the frequency of phlebitis ($p<0.004$), but did not significantly increase cannula dwell time. The control group had a mean dwell time of 47 hours as compared to the HEPHC group, which had a mean dwell time of 67 hours. They concluded that infusing low dose HEPHC reduced the severity of phlebitis. However, this conclusion is based on a small sample size and there is a possibility of confounding variables (eg differences in the type of surgery performed).

In contrast, another recent randomised study compared cannula survival time when HEPHC and tGTN were used in adult patients receiving TPN via pIVC (Tighe et al. 1995). In this Trial, 46 participants, suffering a variety of illnesses, were randomised into one of two groups. The first group (n=23) received a standard TPN while the other group (n=23) received the same feed with the addition of heparin (1500 units/2.5liter), hydrocortisone (15mg/2.5liter) and 5mg transdermal glyceryl trinitrate patch. A finding of this trial was that subjects who received HEPHC and tGTN had half the phlebitis rate ($p<0.05$) as compared to the control group and a median onset of phlebitis in the control group of 7 days as compared to 22 days in the triple therapy group (log rank=18.96, $p<0.001$). They recommended HEPHC and tGTN be used routinely.

It is unclear how HEPHC affects colonisation and infection rates of pIVC. However, due to the seriousness of septicaemia, it is imperative that prolonging pIVC dwell time does not place patients at risk of serious complications. This could be a problem as corticosteroids, like hydrocortisone, can inhibit local defence mechanisms. However, there are no reports of sepsis due to suppression of the immune system due to low dose hydrocortisone (Wright, 1996). As previously mentioned, heparin may reduce the risk of infection and two trials have shown significant reductions in positive tip cultures of long lines when heparin was added to the infusions. However, further studies,

particularly on children, are required to compare and evaluate these methods for safety and efficacy.

Only one published study has investigated the effectiveness of using low dose HEPHC in children (Roberts et al. 1994). This Australian randomised, non-blinded trial was conducted on a group of 101 children with cystic fibrosis who were receiving antibiotics through pIVC. The trial compared the effectiveness of low dose HEPHC with in-line filters. One group of children (n=50) received a continuous infusion of 4% glucose and 0.18% sodium chloride with HEPHC additive (500units of heparin and 10mg of hydrocortisone in 500mL) along with their antibiotic regime. The other group (n=51) received the solution without the HEPHC additive along with their antibiotic regime. Roberts and his colleagues demonstrated no difference in cannula survival time between the two pIVC groups using survival trends ($p=0.39$, logrank test), with the median cannula survival time being 3.8 days (i.e. 93 hours) for both groups.

People with cystic fibrosis differ genetically to people without cystic fibrosis. For this reason comparisons with normal children should be cautiously considered. Cystic fibrosis affects the skin, sweat glands, mucus secretion and in some cases can affect the liver, leading to abnormal counts of clotting factors (Whaley and Wong, 1989). Furthermore, children with cystic fibrosis experience frequent cannulation and this causes vein damage resulting in poor vein access as children get older. Finally, it is common for children with cystic fibrosis to receive oral steroids. This was not reported in the study and possibly not controlled for. Consequently, the use of oral steroids could have been a confounding variable as the group who did not receive HEPHC may have received a different form of steroid as part of their routine treatment.

At The Canberra Hospital continual flushing with low dose HEPHC has for the past 10 years, been used routinely to maintain cannula patency in children who require intravenous antibiotic treatment for greater than three days. The rationale for this practice was derived from literature suggesting that cannula survival can be maximised with this combination (Hecker, 1992). However, more recently this finding has been questioned in children. Cannula dwell time was not found to be increased when a continual flushing solution of low dose HEPHC was compared to in-line filtering (Roberts et al. 1994). Unfortunately, no control condition was included in this study.

Furthermore, the study focused on a specific population of children and this means that the findings cannot be extrapolated to other groups of children.

The current practice of continuous flushing with low dose HEPHC at The Canberra Hospital has not been substantiated by the literature. There are risks associated with continuous administration of heparin and hydrocortisone over long periods of time. There is also a lack of information about the effects of these preparations at low doses. Thus, further research into the effectiveness of low dose HEPHC as a strategy to prolong dwell time of cannula in children is necessary.

2.4 Summary

Hospitals commonly use intravenous cannulae. While uncomfortable and potentially problematic for everyone, they pose unique problems for children because of their comprehension levels. Children do not understand or cope well with the pain associated with cannula insert and when complications occur. The trauma associated with these events can have a lasting effect on a child and lead to significant distress in the event of future interactions with health carers. This has motivated health professionals to employ other strategies to minimise the need to re-cannulate. However, well meaning as these strategies are, they could potentially be doing more harm than good.

The literature indicates that complications associated with pIVC differ for adults when compared to children. Thus, findings from studies on adult cannulae cannot be used to inform management of cannula in children. Additionally, there has been little research on cannula management in children and this lack of information has led to different cannula management practices being adopted as hospital policy. Although some institutions have applied adult management practices to children and removed cannulae every 72 hours, others have not. Instead, policies in these hospitals recommend leaving cannula in children until a complication occurs or treatment stops.

Some hospitals have added medications to infusion fluids in an attempt to maximise cannula survival time. The purpose of these medications is to reduce the processes known to cause complications and cannula failure, such as extravasation and phlebitis by increasing blood flow to the cannulated area, minimise the inflammatory response and reduce fibrin formation.

Unfortunately, medications used to prolong cannula dwell time have a range of side effects some of which are potentially serious. Additionally some preparations may not be safe for use in children. Glyceryl trinitrate can cause headaches, even when absorbed through the skin and children could ingest it. Heparin in both high and low doses can cause bleeding problems and HIT while hydrocortisone in high doses can mask the immune response. Unfortunately, little is known about the risks associated with the long-term use of these preparations in low doses in children. It is also not known what impact these preparations have on a childs developing immune system. For these reasons caution has been recommended when pharmacological preparations are used in children.

The literature is also inconclusive on the effectiveness of pharmacological strategies as a method of increasing cannula dwell times in children. Although a meta-analysis study has suggested that low dose HEPHC is the most effective method for prolonging cannula survival time, the analysis may have been flawed. For example, the meta-analysis study did not consider the difference in cannula survival times between adults and children, instead pooling these groups together.

A more recent study that assessed the effectiveness of low dose HEPHC in prolonging cannula survival time in children raises more questions. This study by Roberts et al. (1994) on children suffering from cystic fibrosis found that HEPHC was no more effective than in-line filters (which remove particulate matter) in prolonging cannula dwell time. Unfortunately without including a control group there was no way of establishing whether a solution containing HEPHC was more effective than one without. Furthermore, findings of this trial cannot be generalised to other children because of the specific nature of their medical condition.

The purpose of the current trial is to investigate intravenous management practices for children at The Canberra Hospital. Its aim is to determine whether adding low dose HEPHC to a continuous flushing solution administered intravenously to children is effective in prolonging cannula survival time in a normal paediatric population. The findings from this study will be used as a basis for future pIVC management in this paediatric unit and add to the current knowledge of cannula in this population.

CHAPTER 3

METHODS

3
Methods

3.1 Introduction

The literature review indicates there is a lack of information about the effectiveness of adding low doses of HEPHC to prolong the effective life of pIVC in children (Roberts et al. 1994). This trial was designed to determine whether the addition of low dose HEPHC significantly prolongs cannula survival time in children.

This chapter will present the method used to assess whether adding low dose HEPHC does prolong cannula survival time in children. It will outline the research design, population and sample considered and discuss the selection of measurement tools and describe the data collection process. Finally, this chapter will outline the process of data analysis, present an interim analysis and outline limitations of the trial methodology.

3.2 Research Design

The current trial compared a continuous infusion of low dose HEPHC with a placebo (Clear Fluid) that contained the same base solution but no HEPHC additive. It was hypothesised that a continuous infusion of low dose HEPHC does not significantly prolong cannula survival time in children and a randomised, controlled, double blind trial was chosen as the most appropriate design to answer this question.

A Trials Co-ordinator in the Pharmacy department randomly assigned children recruited to the trial to one of the two groups using a 1:1 allocation. This resulted in half the children receiving the HEPHC infusate and the other half receiving the placebo solution. This design also ensured that all staff working with the children remained blinded to the infusate properties.

During the trial phase, data were collected on a number of variables that were known to influence cannula dwell times. Comparisons between the data collected for both groups were made during the analysis to identify if either group was likely to be biased.

In general, the study design chosen for an experiment, is dependent on the type of question being asked. In the current trial, an experimental design was chosen to evaluate the length of pIVC survival time in children and the effects of HEPHC on this. The survival time was measured for each condition and compared to determine whether the trial solution influenced cannula survival time.

The major goal of any research is to draw valid conclusions (Kirk; 1982). It is therefore important to select an experimental design that reduces the impact of extraneous (external and introduced) variables and leads to a correct conclusion. Random assignment reduces the risk of bias that can lead to invalid conclusions being drawn by distributing idiosyncratic characteristics of the participants evenly between different groups (Kirk, 1982). Thus, random assignment of individuals to a test group aims to ensure that groups are equivalent such that any differences can be attributed to the treatment (Polgar and Thomas, 1995). Additionally, random assignment helps reduce bias because it reduces the risk of age and individual differences between subjects being favoured in one of the two groups. However, it does not ensure that valid conclusions are drawn or help make generalisations to other populations or settings of interest. To ensure valid conclusions are drawn, statistical procedures, internal and construct validity and external validity need to be considered. In the current trial, decisions about statistical procedures were supported by previous studies and in consultation with a statistician.

The likelihood that correct conclusions are drawn from a trial is increased if internal validity is considered. Internal validity occurs when plausible alternative explanations can be eliminated and it is identified that the factor of interest is influenced by the manipulation (Polgar and Thomas, 1995; Kirk, 1982). In the current trial, efforts to ensure internal validity focused on only manipulating the type of infusion administered to each trial group. Because of the clinical setting for the trial, a tight control of variables was not achieved. However, data collected on these variables were compared between the two groups.

To avoid the risk of a Rosenthal effect, where the researchers expectations could lead to differential treatment, participants, ward staff and researchers were blinded to the treatment being given.

Another internal control used in the current trial to ensure the conditions were consistent for both treatment groups was to ensure all the ward staff and researchers follow a protocol (see appendix B). In addition, standardised education was provided to all staff. Following this, specific training was provided with written instructions to all research associates involved in recruitment. This ensured information was given in a consistent way to each potential recruit.

External validity occurs when research findings can be generalised across populations of subjects and settings. External validity is enhanced when standard assessment tools are used. In the current trial, a standard phlebitis assessment scale and standard cannula culturing techniques and criteria were employed. Additional data items, incorporated in the collection tool (Appendix E), were derived from current literature. Finally, the tool was piloted before the data collection phase to ensure that the information required was actually collected. Through using standardised tools and methods, findings from this study will be able to be used to make comparisons with other populations and settings.

3.3 Pilot Study

Before commencing the trial, a small pilot study was conducted to determine the ease of use of the data collection tool and whether the information recorded was appropriate. Four children were selected within the paediatric unit and the tool was used for the duration of their admission. After the pilot study, feedback from ward staff lead to the layout being modified so the tool was easy to use.

3.4 Population and Sample

At the time of this trial, The Canberra Hospital Paediatric Unit had 48 beds, including 2 high dependency beds, and was part of a 450 bed tertiary accredited hospital. The Canberra Hospital is a teaching hospital and the primary referral and major trauma centre for a large catchment area including the Australian Capital Territory and surrounding southeastern New South Wales region. During the study, the paediatric unit became the only specialist paediatric facility in the region due to the closure of private paediatric facilities.

The Paediatric Unit had two wards, one for infants and children and the other for adolescent and populations requiring isolation. The unit provided general medical and surgical care to infants, children and adolescents from 0 to 18 years of age. Due to the relatively small in-patient facility, all specialty services such as oncology, cardiac surgery, endocrinology and severe renal disease were coordinated by Sydney specialists and supported by local staff.

A seasonal pattern for admissions to the Paediatric Unit was normal with an increase in population during the winter and spring periods. To maximise potential recruitments, the trial period was coordinated to include two winter seasons. A retrospective review of all patients who received low dose HEPHC additive for the two years before the trial was conducted during the planning stage of this trial. During this time, 120 children received HEPHC for prolonging cannula survival. Based on this figure, it was estimated that one to two children each week would normally be given low dose HEPHC.

3.5 Sample Selection

3.5.1 Sample Size

The sample size of children was determined by the study design and the number of cannulae required for statistical validity. It was identified during the planning stage of the trial that children who were administered HEPHC received long-term antibiotic treatment for between 3 and 14 days (72 and 336 hours), with the average length of treatment being around 7 days (168 hours). Nelson and Garland (1987) reported an average time before complications for peripheral cannulae in children of 69.3 hours +/- 39.3 hours. Based on this length of time, it was estimated that each child would receive 2.4 cannulae. After considering the number of cannulae needed for statistical comparisons, estimates were made on the number of cannulae used for a child over 7 days. From these calculations, the appropriate potential sample was determined to be around 120 children and 320 cannulae.

For HEPHC to benefit a child, it was determined that the dwell time needed to be extended to a point where there was a reduction in the average number of cannulae a child received. For example, if HEPHC extended the life of a cannula by 10%, the

average child would still require two cannulae during the admission. However, if cannulae survival time was increased by 50%, the average child would receive one less cannula and this would be of real benefit to the child.

3.5.2 Eligibility

Only children who were admitted to The Canberra Hospital Paediatric Unit were considered for the trial. An age range of 0-16 years was chosen to maximise the eligible recruits. Patients who were considered medically unstable were not recruited until their condition was stabilised; they no longer required additional fluid and they were identified as requiring intravenous antibiotics for 3 or more days. Participation in the trial ceased if the child's condition deteriorated necessitating an increase in fluid rate, or if they were transferred to another facility. If a child was re-admitted to the unit, they were treated as a new recruit. Any child who was to undergo surgery was considered ineligible to participate due to the potential anti-coagulant effect of heparin. Children with a personal or family history of allergic reactions to heparin or hydrocortisone were also excluded from participation. Those who were receiving other steroids or anti-coagulant medication were not recruited, or excluded once the medication was given as this could have confounded the results. Finally, in line with the recommended National Statement on Ethical Conduct in Research Involving Humans, any child who had participated in a trial during the previous 3 months was also excluded from recruitment.

3.5.3 Point of Entry into the Trial

Children were identified on a daily basis by medical, nursing and pharmacy staff as potential candidates for the trial and were approached by trained research nurses who offered written and verbal information about the trial by designated nurses on the ward who completed a training package. Four Research Assistants assisted with recruitment and a number of nursing staff completed education in the recruitment process and assisted follow-up of children.

Participants were those children who, after consultation with their family, gave consent to receive the trial fluid. If the child was unable to understand the trial due to cognitive

development, only the guardians' permission was obtained. The time the trial fluid started was defined as the point of entry into the trial.

3.6 Consent and Other Ethical Issues

Both the ACT Department of Health and Community Care Ethics Committee and the University of Canberra Ethics Committee approved the trial. The trial also gained financial support from the University of Canberra Industry Collaborative Grants Scheme with The Canberra Hospital Private Practice Fund providing the Industry funding. Additionally, The Canberra Hospital Pharmacy and Pathology Departments provided free and cost price services. The project was discussed widely with nursing and medical staff at The Canberra Hospital and in a wide variety of fora. The Medical Director of the Paediatric Unit and the Unit Service Management Team Leader gave support for the trial.

Ethical and legal issues outlined by the National Statement on Ethical Conduct in Research Involving Humans (1999) were addressed to protect the safety and privacy of children who participated in the trial.

3.6.1 Informed Consent

The National Statement on Ethical Conduct in Research Involving Humans (1999) states that for a child to participate in research consent must be obtained from the child whenever he or she has sufficient competency to make this decision and the parents/guardian (or any organisation or person required by law) must give consent in all but exceptional circumstances. It further states that consent cannot be given for research that is contrary to the child's best interest and a child's refusal to participate in a research project must be respected.

For the current trial, all potential participants (where appropriate for cognitive development) and their guardians were supplied with a verbal explanation of the trial and an information sheet. The information sheet is presented in Appendix C. This explanation included information on the trial, potential benefits of the information

obtained from the trial and that an interim analysis was to be or had been conducted to ensure that no child was being disadvantaged by the trial.

The consent form (Appendix D) consisted of 13 statements about the study and aimed to ensure that parents/carers and children were provided with all information relevant to the study. Additionally, contact details for the project coordinators were included on the form to facilitate contact with the researchers, should that be required. The consent form also included contact details for the ACT Department of Human Ethics and Research Complaints Committee as an independent point of contact. Only children and families who had given consent received the trial solutions. These families were provided with a photocopy of the signed consent for their personal record.

Consent was sought from children and guardians. If the child was able to understand the trial and agreed to participate, they were invited to sign the consent form with their carers. There were several instances where the guardian consented to the trial but the child did not. In these cases, the child's rights were given priority and they were not recruited.

3.6.2 Confidentiality

Confidentiality was maintained by coding participant details with a unique identification number. This number was used for all data collected and analysed. Consistent with the requirements of the two ethics committees, all data collected was stored in a locked filing cabinet in the Research Centre for Nursing Practice. Electronically stored data was placed in a restricted access database and co-research staff gave a written commitment to ensure confidentiality.

During the trial, the code to the trial fluid/identification number was kept in a locked area in the Pharmacy Department. This code was only accessed by and accessible to the intravenous pharmacist who had no contact with the investigators or participants. Additionally, the legal and ethical obligations of privacy and confidentiality were included in the trial protocol that was presented both in writing and orally for to all personnel working with subjects. The trial protocol was kept in each ward area as a reference (Appendix B).

3.6.3 Legal Responsibilities

Legal responsibilities were addressed by providing education, a trial protocol and access to written information on the National Statement on Ethical Conduct in Research Involving Humans (1999), which outlines researcher responsibilities. These responsibilities are ethical and legal and aim to ensure integrity, respect, beneficence and justice for trial participants. Guidelines pertinent to research on children and young people were also provided to highlight researcher responsibilities in ensuring well being and consent.

All potential recruits were informed about all aspects of the study both verbally and in writing. Consent was then obtained after family members had read and understood the documentation and discussed the trial with the recruitment nurse or ward delegate and among themselves.

3.6.4 Research Involving Children

The National Statement on Ethical Conduct in Research Involving Humans (1999) states that research on children is only acceptable under certain situations. Research on children is acceptable when the question posed is important to their health and well being, and when information available from research on other individuals cannot answer the question posed in relation to children. For the current trial, questions exist about the efficacy of using low dose HEPHC to prolong pIVC survival time in children and this question can not be answered using literature from adult studies.

Evidence from some literature suggested that children who received the clear fluid preparation may require more cannulae than those who received the HEPHC fluid. This could pose a risk to the health and well being of children involved in the trial. To ensure that this was not the case and to establish that no child was disadvantaged by the trial, an interim analysis was conducted to examine this question and enable early termination of the trial if necessary.

3.7 Data Collection

Data were collected on demographics, cannula details, medication and cannula dwell times. The data collection instrument is presented in Appendix E. A literature review by Maki and Ringer (1991) provided the theoretical basis for data collected in this study. Limited demographic data were also recorded for children who fulfilled the inclusion criteria but did not participate in the trial.

After recruitment to the trial, details were recorded for the cannulation process, the cannula gauge size, place the cannula was sited, number of attempts before successful cannulation and whether it was the first, second or third cannula. This information was selected because it was identified in the literature as potentially affecting cannulae survival time. It was important to establish that these factors were not overly represented in one of the treatment arms.

Again to ensure there was no bias between the groups in the trial, information about medications administered to children during their admission were recorded. Where medications were prepared was also noted.

In cases where commencement times for the trial fluids were not recorded on the data collection sheet, the researcher noted the exact time the trial fluid commenced using information obtained from the Intravenous Infusion Order Sheet. This sheet provides the most accurate information about when an infusate commences because it requires documentation of the exact time an infusion is check and administered by two nurses.

In cases where the time the trial fluid ceased was not recorded on the data collection sheet, the information was obtained from the time documented on the Fluid Balance Chart and cross referenced with the time documented in the patient notes and the time the cannula tip specimen was collected. From these times it was possible to determine how long the cannula had been insitu before the trial fluid commenced and how long the trial fluid was infused before the cannula was removed.

Complications experienced by cannulae during the trial were important to monitor because HEPHC is thought to increase cannulae survival times by reducing potential

risk factors. It is standard practice at The Canberra Hospital Paediatric Unit to observe the cannula site hourly and to cover cannulation sites with netting to allow easy visualisation. Any complications were identified on the data sheet and space for comments and actions taken was provided. A standard phlebitis scale that included guidelines for appropriate action, if phlebitis occurred, was on the back of the form.

The Phlebitis Scale used in the current trial was recommended in the Intravenous Nurses Standards of Practice Guideline (1998), and described by Maki and Ringer (1991). This provided a standard for measuring the degree of phlebitis, although criticism on it relies on individual assessment and interpretation has been made (Hecker, 1992). Another criticism of all current phlebitis assessment criteria is that it is impossible to determine whether the phlebitis is septic or aseptic in origin. This can only be determined after the cannula has been removed and cultured. However, one benefit of using this scale was that it encompassed all the common definitions in the literature. This makes comparisons between studies more meaningful.

In the current trial, the Phlebitis Scale and culturing techniques were used in conjunction to assess phlebitis. According to Sherertz (1997), the easiest way to assess for septic phlebitis through cannula colonisation is to check the catheter surfaces for bacteria by placing it in culturing broth. The two culturing techniques used in the current trial are widely accepted as standard pathology practice for determining whether pIVC have been colonised by microorganisms.

Cannulae were sent to pathology for culturing after removal. To minimise the risk of contamination, the hub of each cannula was cut from its tip using sterile scissors. The tip was then placed into a sterile specimen jar and sent to pathology where it were rolled in agar and then flushed with a culture broth. The agar plate and culture broth were then incubated for 48 hours and a colony count performed. A positive colonisation was defined as 15 or more colony forming units present after 24 hours (Maki et al. 1977).

There are several important limitations to this culturing method. The process is retrospective, as the cannula must be removed. Another limitation of this method is that as a cannula is pulled out of the body through the entry point in the skin, it can collect skin bacteria, which then grow in the culture broth and give a false positive culture. Additionally, because the organisms are left to grow over a period of time, a single

bacterium could rapidly multiply and give the same end result as 1000 bacteria. Cultures can also fail to demonstrate slow-growing and fastidious pathogens in a mixture of fast growing organisms due to competition. However, when a broth culture is negative, the probability of a catheter-associated infection is low (Sherertz, 1997).

For this trial, polyurethane cannula manufactured by Ovium, a product of Johnson and Johnson were used. The cannulae were short (less than 5.7cm) ranging in gauge size from 18-24mm. Generally, cannulae used in children are inserted under non-urgent conditions by several experienced personnel (paediatric registrars and occasionally residents). Thus, it was assumed that the insertion conditions would be similar. It was also assumed that these staff would have well-established hygiene practices and follow protocols on infection control and cannula securing.

Cannulae were classified as being inserted under emergency conditions if inserted by an ambulance officer or as part of a medical emergency. Under these conditions, it was not possible to determine if the insertion protocol and hygiene practices were adhered to. For this reason, the incidence of emergency cannulation of children before recruitment to the trial was included as a variable on the data collection sheet. This enabled comparison to exclude bias between the two groups. However, the nature of the clinical setting did not allow for tighter control of this variable.

All cannula were secured following the unit protocol (see Appendix F), which included tape, netting and an arm-board. The Interlink TM System was used on all children in the trial.

During the trial period, adherence to protocols for IVT line and flask management were monitored by asking staff to sign on the data collection form when intravenous therapy line were changed and new flasks of fluid were administered.

Intravenous antibiotics were either reconstituted by nursing staff into small volumes and given as push doses or reconstituted, through a 0.5 micro filter and under sterile conditions, by pharmacy staff into larger volumes (mini-bags of 25-50mL). Those made up by nursing staff were given within 24h hours of reconstituting while those made into mini-bags were used within 48 hours of preparation. Children requiring

antibiotics for greater than 3 days generally had mini-bags prepared by the Pharmacy Department.

3.8 Data and Analysis

3.8.1 Data Collation and Entry

During the collection phase of the trial, the research staff, co-researchers and ward nursing staff collected data. All data collected was entered into a Windows (1998) Access Database, designed specifically for the trial. The researcher and an assistant carried out data entry. After the data had been coded into the database, manual crosschecks were performed to ensure accuracy of the data entered.

The coded data transported from the Access Database into SPSS (Statistical Package for Social Sciences) 10 Database and again crosschecked with the data collection sheets to ensure accuracy of details during this process.

3.8.2 Data Analysis

All data were analysed using SPSS10. Descriptive statistics and frequencies were determined for all demographics, and selected cannula and medication data for the two treatment groups. Additional comparisons using chi-square analysis were made where a difference between certain results was possible. A significance level was set at $p<0.05$.

Cannula dwell times were determined for the pre-trial fluid time and the time the trial fluid was infused. The dwell time was then used in combination with the reason the cannula had been removed (end point survival) and plotted using Kaplan Meier survival curves.

The Kaplan Meier method of estimating survival is the best type of survival analysis for small groups because it does not divide times into intervals for analysis (Dawson-Saunders and Trapp, 1994). Rather, it is an estimate of survival each time a "death" occurs. In the current trial, a "death" occurred when the cannula lost patency and failed, while withdrawals (or censors) occurred when the cannula had not lost patency before

removal and therefore did not fail. Instead, in these cases, the cannula was removed for some other reason such as completion of treatment or it was inadvertently pulled out.

The logrank test is a frequently used method to compare the survival distributions for two groups of a trial (Dawson-Saunders and Trapp, 1994). The logrank test compares the number of observed failures in each group with the number of failures that would be expected from the losses of the combined groups (if group membership did not matter). This method therefore assumes that the control is representative of the general population (Chiang, 1984). A benefit of the logrank test is that the numbers needed to estimate the odds ratio are also obtained.

The odds ratio is an estimate of the relative risk (Dawson-Saunders and Trapp, 1994). It estimates the odds times when a person is exposed to a given risk factor divided by the occasions that a control is exposed to the risk factor (Dawson-Saunders and Trapp, 1994). In the current trial, the odds ratio was the calculated risk that HEPHC leads to a difference in cannula survival time.

3.9 Interim Analysis

Consistent with the requirements of the ACT Human Research Ethics Committee an interim analysis was conducted by an independent statistician to determine whether any child was being disadvantaged by the trial. This analysis was conducted nine months into the data collection phase, from June 2000 to February 2001. Data from twenty-nine children and thirty-nine cannulae were analysed. However, clinical staff and researchers remained blinded to the groupings.

The average age of recruited children at this time was 6 years and the range was 1 month to 14 years. Of the sample, 61% of children had been allocated to the HEPHC group while 39% were allocated to the CF group. The crude cannula failure rates were similar in both groups and the odds ratio and 95% confidence interval was 1.21 (Atlin, 2001). The median cannula failure rate was 36 hours and the range was 1 to 120 hours. Atlin noted that the Kaplan Meier curves for the two groups crossed at 3 days. Although the sample sizes were small at this time, the results did not indicate that one group was being disadvantaged (logrank statistic 0.33 on 1 degree of freedom, $p=0.6$) (Atlin, 2001). Therefore, it was recommended that the trial continue.

At the time of the interim analysis, a review of the sample size was also conducted given that recruitment was slower than anticipated. It was determined that a sample of 78 cannula would be required to detect an odds ratio of 4 at 5% significance level with 80% power. The power is the probability of not rejecting a hypothesis when it is false (Type II error). Where as a 5% significance level means that there is only a 5% chance that an odds ratio of 4 will arise in a random sample from the population when no significance difference is present. This is the probability of concluding a result is significant when there is no significance (Type I error). This odds ratio was comparable with other similar trials reported in the meta-analysis (Hecker, 1992), which accepted an odds ratio of approximately 5.

3.10 Limitations of Current Methodology

Randomising children, as opposed to cannulae, to treatment groups was determined as the most effective way to conduct the trial. Although randomly assigning each cannula to a treatment would have been more empirically sound, the randomising process was simplified by randomly assigning children to avoid confusion and errors during each admission and make the process more easily understood by children and their families.

3.11 Summary

This chapter has described the methods used to assess whether adding low dose HEPHC does prolong cannulae survival time in children. This chapter also outlined the study design, population, discussed the selection of measurement tools, and described the data collection process and storage. The chapter also described the process of data analysis using SPSS 10, presented the conclusions of an interim analysis and presented limitations of the trial methodology. The next chapter will present the findings of the current trial.

CHAPTER 4

RESULTS

4
Results

The previous chapter described the methodological approach taken to investigate the effectiveness of adding low doses of HEPHC to prolong the effective life of pIVC in children. This chapter will present the results from the eighteen-month data collection phase of that study. Demographics of the participants and cannula details are presented along with survival analysis for 'cannula life'.

4.1 Description of Participants

Eighty cannulae were inserted into fifty-nine children who were recruited from those admitted to The Canberra Hospital Paediatric Unit from June 2000 to November 2001. Participants required pIVC for intravenous antibiotics for a period of 3 days or more and were randomised into either the HEPHC (experimental) or the CF (control) group. Twenty-six children received HEPHC while twenty-seven received the clear fluid treatment. Six children were excluded from the trial after recruitment because they received steroids during their hospital stay. One child with meningitis received a single dose of dexamethasone, three received oral steroids and two others received inhaled steroids.

Limited demographic data were also recorded for twenty-six children who fulfilled the inclusion criteria but did not participate in the trial. This group had a mean age of 3 and consisted of fifteen girls and eleven boys. Seventeen of these children were not recruited because their caregivers declined to participate. Another four children declined after their caregivers had expressed interest in participating in the trial. A further three children were not recruited due to medical staff opposition, a family history of HIT (grand father and uncle) and one child was participating in another trial.

4.1.1 Participant Match

The children in the HEPHC and CF groups were similar in age ranging from small babies to adolescents. Table 1 presents the summary of demographic data for the experimental and control groups. As can be seen from Table 1, the median ages were less than a year apart.[1] The weight distributions were also very similar between the two groups.[2] The median has been presented because the distribution of age and weight was skewed to the left. From the table it is evident that the two groups were well matched for age and weight.

Table 1 Summary of Demographics of Children

Parameter	HEPHC (n=26)		CF (n=27)	
Age (yrs): Median	6.3	(0.2–16.5)	5.6	(0.2-14)
Weight (kg): Median	22	(5-60)	20	(5-60)
Sex: Male (%)	19	(73)	16	(59)
Female (%)	7	(27)	11	(41)

Double the number of males was recruited to the trial (35:18). This ratio was reflected in both the experimental and control groups. The unequal distribution of males to females was explored in each group of the trial. It was found that there was no statistically significant difference in sex ratio between the two groups (Chi-Square = 1.1, df = 1, $p = 0.3$).

Children recruited to the trial had a wide range of medical conditions reflecting the diverse case-mix admitted to this paediatric unit. The illness groups for each child based on the Diagnostic Related Groupings at hospital discharge are presented in Table 2. Cellulitis was the most frequent cause of a hospital stay of 3 days or longer for children requiring continued peripheral IVT. Cellulitis occurred in over a third of children in the CF group and half of those in the HEPHC group. Both groups also included diagnosis such as respiratory infection (pneumonia), urinary tract infections, osteomyelitis and acute lymphadenopathy.

[1] The means and SD have been provided for comparison with other studies.
HEPHC: mean = 6.5, SD = 4.4; CF: mean = 5.9, SD = 4.4.
[2] HEPHC: mean = 24.8, SD = 15.5; CF: mean = 25.7, SD = 16.6.

A group of miscellaneous illnesses was represented in only one of the trial conditions. These were infections within the head region (otitis media and meningitis), immune disorders and one gastrointestinal infection. It is difficult to determine what impact the small numbers of illnesses had on group match, as the sizes excluded statistical comparison. However, no obvious bias was observed with both groups having a higher representation of cellulitis, a few respiratory tract infections and some miscellaneous illnesses.

Table 2 Diagnosis of Children

Parameter	HEPHC (%) (n=26)		Control (%) (n=27)	
Cellulitis: Periorbital, face, body	14	(54)	8	(30)
Respiratory infection	3	(12)	3	(12)
Genital/urinary infection	2	(7)	2	(7)
Other infections within head	-		4	(15)
Osteomyelitis	3	(11)	3	(12)
Systemic illness	1	(4)	2	(7)
Acute lymphadenopathy	1	(4)	1	(3)
Acute inflammation	1	(4)	2	(7)
Immune disorder	-		2	(7)
Misc. digestive system	1	(4)	-	

4.2 Cannula Data

Eighty cannulae were inserted during the trial as a number of children required more than one cannulae during their hospital admission. Eight children in the HEPHC group required multiple cannulae during hospitalisation. Of these children, seven required a second cannula and one required a second and a third cannula. In contrast, fourteen children required additional cannulae in the CF group. Ten of the CF group children required a second cannula while four children required a second and then a third cannula (described later in Table 4).

Children who required only one cannula during their hospitalisation may differ from those who required multiple cannulae. For example, children requiring only one cannula throughout their admission may have had larger veins or different immune responses. It was noted that children who received HEPHC and only required one cannula were 2 years older than those children who received the same solution and

required multiple cannulae. In contrast, children who received the CF solution and required only one cannula for the duration of their treatment were about 3 years younger than those who received the same solution and required multiple cannulae. This observation indicates that HEPHC may improve cannulae survival in older children. However, further investigations into the questions this raised were not in the scope of the current trial. This trial focused on cannulae survival time, not child characteristics and thus each cannula was considered individually. There was no statistical difference in the dwell time of the first cannulae in either group.

4.2.1 Vaso-irritant antibiotics

Vaso-irritant antibiotics, which were administered intravenously through the cannula during the life of the cannulae, were recorded. Also noted was whether the pharmacy department had prepared all the antibiotics or if some had been prepared by nursing staff on the ward. Finally cannula insertion time, the time the trial fluid commenced and when the cannula was removed was noted. This enabled calculation of the cannula dwell time before the commencement of the trial solution (pre-trial time) and the time from the commencement of the fluid until the cannula was removed (hours in trial time).

Table 3 presents the cannula characteristics of site, gauge, administration of vaso-irritants, where the intravenous medications were prepared and survival status upon removal for the HEPHC and CF conditions.

Table 3 Cannula Characteristics

Parameter	HEPHC (%) (n=35)		Control (%) (n=45)	
Site: Hand	21	(60)	28	(62)
Cubital fossa	8	(23)	9	(20)
Foot	4	(11)	3	(7)
Forearm	1	(3)	4	(9)
Not stated	1	(3)	1	(2)
Gauge: Small (22-24Gauge)	19	(54)	16	(36)
Larger (18-20Gauge)	7	(20)	14	(31)
Unknown	9	(26)	15	(33)
Vaso-irritant given: YES > 1	26	(74)	29	(64)
YES 1	9	(26)	16	(36)
AB* Preparation: Pharmacy	22	(63)	32	(71)
Ward	10	(29)	6	(13)
Unknown	3	(8)	7	(16)
Failed	14	(40)	23	(51)
Survived	21	(60)	22	(49)

* AB (antibiotic)

A similar distribution for cannula sites between the HEPHC and CF groups can be seen from Table 3. The hand was the favoured cannulation site, being used in 60% of cases for both groups. The second most frequently used site for cannulation was the cubital fossa, which was used in 20% of cases for both groups. Other sites were used infrequently and in similar numbers for both groups.

Cannula gauge size was similar for both groups with smaller gauge cannulae (22-24 gauge) being used in 50% of cases in the HEPHC group and around 40% of cases in the CF group. Larger cannulae (18-20 gauge) were used in 20% of the HEPHC group and 30% of the CF group. Around 30% of cannulae gauges were not recorded.

Choice of cannula gauge should be determined by vein size. As previously discussed, the median age for recruits to this trial was around 6 years. Six-year-old children are about half the size of adults so it is expected that smaller gauge cannulae will be used. However, 30% of cannulae sizes were not recorded. Thus, caution is necessary when considering these figures and drawing conclusions.

Vaso-irritant antibiotics (AB) increase the incidence of chemically induced phlebitis and have been shown to reduce cannulae survival time (Falchuk, Peterson and McNeil, 1985). This trial aimed to assess the effectiveness of HEPHC in reducing phlebitis as a result of infusion of these vaso-irritants. It was therefore important to ensure that each cannula was exposed to a vaso-irritant. As can be seen from Table 3, every cannula in the trial had a vaso-irritant medication infused through it. Moreover, over 60% of all cannulae received more than one vaso-irritant for both trial groups. Thus, cannulae in this trial appeared to be at significant risk of chemically induced phlebitis.

Intravenous antibiotics were either given as a push dose (more concentrated) or diluted into pharmacy prepared mini-bags of 25 to 50mL of normal saline before being infused. The randomisation process controlled for the potential differences between the two methods of administration. Around two thirds of cannulae in both treatment groups received only pharmacy prepared mini-bags. The remaining cannulae received at least one mini-bag prepared by nursing staff or a push dose of antibiotic. Approximately the same percentages of intravenous medications were filtered in each group. Thus, preparation and administration of vaso-irritants was well matched for the HEPHC and CF groups.

The survival and failure rates are included in Table 3. Half of the cannulae had not experienced any complications and were still patent at the time of removal for both the HEPHC and CF conditions. The ratio of survived to failed cannulae in each group of the study was explored and found not to be statistically significant (Chi-Square = 1.2, df=1, $p = 0.5$). Thus, the two groups were similar for cannulae survival and failure rates.

As mentioned previously, cannula were removed either because the treatment concluded (no cannula problem), or because of a complication. Complications were classified as either "vein related" or "mechanical device related". Signs of vein related problems were classified as infiltration or phlebitis. The Phlebitis Scale (included in Appendix E) included symptoms of phlebitis such as minor swelling, pain and redness at the site. Mechanical device related problems occurred when the cannula patency was lost without vein signs. The difference between blocking and kinking was then determined by visual inspection of the cannula after its removal.

Consistent with the survival rates from Table 3, Table 4 shows that around half of the cannulae in both groups were removed without any complications being experienced. A quarter of the cannulae were removed because of vein related complications and around 20% were removed because of mechanical device related problems. One cannula in both the HEPHC and the CF groups was removed accidentally (pulled out by the child) and four cannulae in the HEPHC group were removed because a long-term device was inserted and the pIVC was no longer required. These cannulae were classified as "no problem".

Table 4 Reason for Cannula Removal

Parameter	HEPHC (%) (n=35)		Control (%) (n=45)	
No problem	21	(60)	22	(49)
Phlebitis/Infiltration	9	(26)	13	(29)
Blocking/Kinking	5	(14)	10	(22)

The number of cannulae removed because treatment ceased, due to vein complications or mechanical complications were similar for the HEPHC and CF groups. Hecker (1992) suggested that a combination of HEPHC reduces the incidence of phlebitis. However, the incidence of phlebitis in this study was similar regardless of the solution infused through the cannula. This indicates that HEPHC did not reduce the incidence of phlebitis. It is possible that HEPHC delays the onset of phlebitic symptoms but this cannot be determined from Table 4. To establish whether HEPHC delays the onset of phlebitis, the cannulae survival time must be compared for those cannulae that received HEPHC and those that received CF.

Seventy percent of all cannulae (56/80) were cultured after removal. The remaining thirty percent were not cultured because they were either contaminated or accidentally thrown out.

Six cannula had coagulase negative Staphlococcus Species in very low numbers identif.ed. Low numbers indicate contamination after or during removal. In three cases, low numbers (below 15 colony forming units) were identified in culture. Also identified in culture in low numbers was one case of Staphlococcus aureus and one of Candida albicans in the HEPHC group. Based on Maki and colleagues (1963) criteria

that significant infection has occurred when the colony count is greater than or equal to fifteen colony forming units, no cannula was found to be significantly colonised.

In summary, the HEPHC and CF groups appeared well matched for recruit demographics, cannula details and vaso-irritant medications. Cannulae colonisation by microorganisms appears to be minimal.

4.2.2 Cannula Dwell Times

This trial aimed to determine whether HEPHC prolonged the dwell time of cannulae in children. To ensure that the two groups experienced similar conditions, the mean time before the trial fluids commenced (Pre-trial time) were compared for the two groups. Then a survival analysis was conducted for each group of the trial and a comparison made between the two survival curves. For a significant difference between dwell times of the two conditions to have been meaningful for children, the dwell time for the group that received HEPHC needed to be extended so that there was a significant reduction in the number of cannulae a child required during their hospital stay. This meant that a large effect was required.

A comparison of the pre-trial time was conducted for both groups of the trial. Cannulae were frequently inserted and used before the trial fluids were started. There were two reasons for this. Often the child's medical condition was unstable and required a period of re-hydration for which the trial solution was not indicated. Families also wished to have time to discuss the trial before agreeing to participate. This time lag before the trial fluid commenced was called the "pre-trial time" and was calculated from the time the cannula was inserted to the time the trial fluid commenced.

The mean and median pre-trial times for the HEPHC and CF groups were compared. The means have been included for comparison with other studies. Only the first cannula was considered, as second and third cannulae did not have a pre-trial time. Table 5 presents the pre-trial times in hours for first cannula for the group that then received HEPHC and CF.

Table 5 Pre-Trial Times (hours)

Parameter		HEPHC (n=24)	Control (n=28)
Pre-trial:	Range	6-112	2-126
	Median	45	44
	Mean	64	49

There was no difference in the pre-trial time between the two groups, with the median time before the trial fluid commenced of just less than 2 days. The median has been considered because the start times for HEPHC and CF groups were skewed to the left. Kaplan Meier survival analysis was conducted on pre-trial times and a longrank test showed that differences were not significant (logrank statistic=1.3, $p=0.3$).

4.3 Hours in Trial

The trial time started when the trial solution commenced and continued until the cannula was removed. If the cannula was removed because treatment ceased and not because of complications, it was recorded as censored. If a complication lead to the cannula being removed, it was considered an event. Table 6 presents the range, median and mean of the hours in the trial and the survival status of the cannula upon removal.

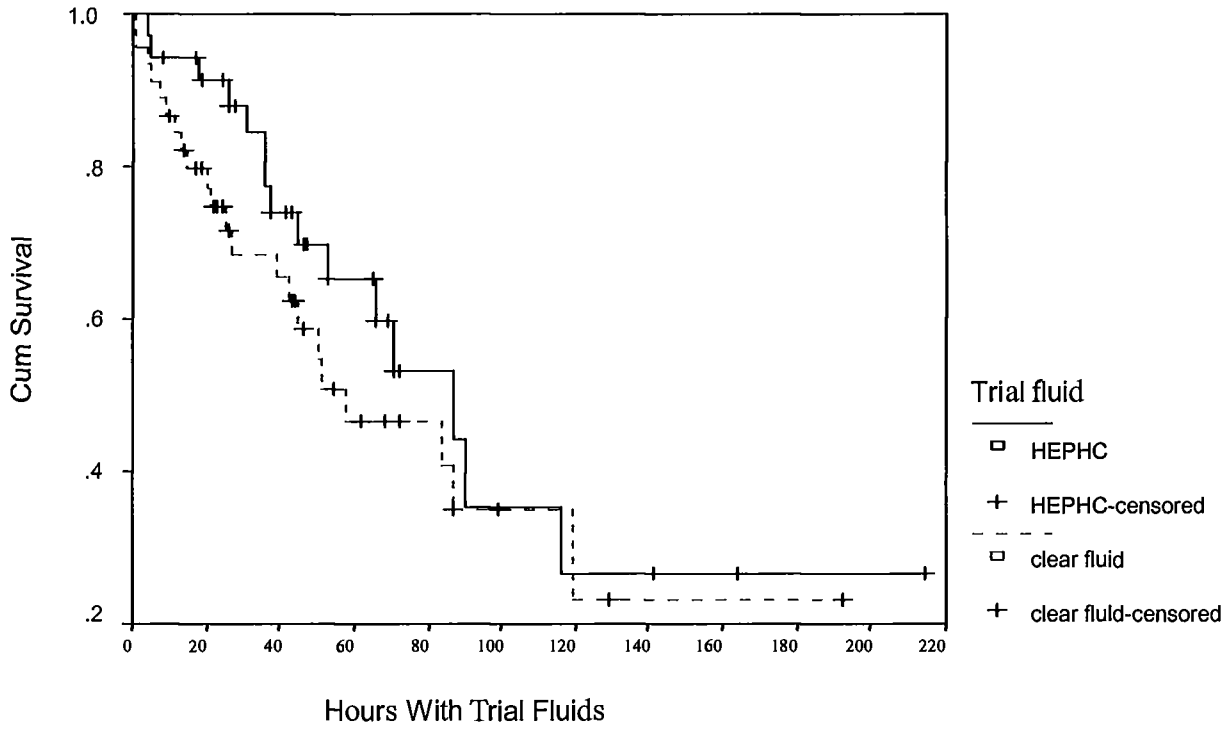
Table 6 Hours in Trial

Parameter		HEPHC (n=35)	Control (n=45)
In Trial:	Range	6-112	2-126
	Median	87	58
	Mean	102	83
Survival:	Censor	20	23
	Event	15	22

Thirty-five cannulae had the HEPHC trial solution while 45 cannulae had the CF Solution. The median time that the trial solution was administered through the cannulae for the HEPHC group was 87 (3.6 days) hours. The survival status for this group was 15 events and 20 censors. In comparison, the median times for the CF condition were around 20 hours less. The survival status for the control condition was 23 censors and

22 events. Cannulae dwell time and survival status were then plotted for each condition. These curves are presented in Figure 1. A logrank test was used to determine the odds ratio and thus the difference between the survival curves for each condition. A significant difference was considered to be an odds ratio value of greater than or equal to 4.

Figure 1 Kaplan-Meier Curve: Survival Time for HEPHC and CF Conditions



A Log Rank test produced a statistic of 1.1 (1df; $p=0.3$), which was not significant. The cannula survival times were not significantly different between the HEPHC and CF groups. HEPHC did not significantly increase the cannula survival time in this trial.

4.4 Conclusion

There was a good match between the two groups. Children in the HEPHC and CF groups were well matched for age, weight and sex. They experienced a broad range of illnesses including respiratory, skeletal, genito-urinary, systemic illness and cellulitis. Cannulae details were also similar between the HEPHC and CF groups. The cannula placement (site) and gauge sizes were similar for both groups with the most commonly

used cannula site being the hand and the most frequently used gauges sizes being 22 to 24 gauge.

Cannulae complications and reasons for removal were also similar for both the HEPHC and CF groups. In both groups, over 50% of cannulae were removed because therapeutic treatment was completed. Furthermore, the two groups were well matched for vein and mechanical related problems. Around 70% of cannulae were cultured and results showed no significant microbial colonisation for any cannula within the study.

Both groups had a similar number of vaso-irritant medications infused through the pIVC. Each child received at least one intravenous vaso-irritant medication and multiple vaso-irritant antibiotics were given to over 60% of the participants in both groups.

There was no significant difference in cannulae dwell times before or during the trial period. Both the HEPHC and CF conditions had a median time of two days before the commencement of the trial solutions. After commencement of the trial solutions, those cannulae that received the HEPHC solution had a trend for slightly longer median cannulae survival time (4.3 days or 103 hours as compared to 3.6 days or 86 hours for CF group). This difference was not statistically significant. Thus, HEPHC solution did not significantly enhance cannulae dwell times although there was a trend towards increased cannulae dwell times in this group.

In conclusion, this chapter has outlined the results of a trial to evaluate the effectiveness of adding low doses of HEPHC to prolong the effective life of pIVC in children. It has found that addition of low dose HEPHC did not prolong the effective life of pIVC in children. This finding questions the efficacy of using HEPHC to prolong cannulae dwell times in children. The next chapter will discuss these findings and their implications for paediatric nursing practices.

CHAPTER 5

DISCUSSION

5
Discussion

5.1 General Discussion

The purpose of this trial was to examine whether low dose HEPHC improved cannulae survival in children. Two well-matched groups of children were compared through a randomised, controlled double-blinded trial. No statistically significant difference was found in cannulae survival time for cannulae that received low dose HEPHC, as compared to those that did not receive the additive. Thus, this trial demonstrates that the addition of low dose HEPHC does not prolong pIVC survival time in children at The Canberra Hospital.

Some studies on HEPHC have indicated that this strategy is effective in prolonging cannulae dwell time. The meta-analysis conducted by Hecker (1992) supported HEPHC as a pharmacological strategy for extending cannulae survival time with combined cannula data from children and adults. However, the data relating to children has never been published separately for scrutiny. The literature indicates that cannulae dwell times and complication rates differ for adults and children. The current study challenges the findings of Hecker (1992) indicating that combining adult and paediatric data could be a methodological concern.

The finding on cannulae survival time of the current study supports a study from Thailand that also examined the effectiveness of HEPHC in prolonging cannulae survival time (Roongpisuthopong et al. 1994). This study on adults found that co-infusion of HEPHC with TPN only marginally increased the mean cannulae dwell time (by 20 hours) and this was not found to be statistically significant.

Additionally, this study from Thailand found that co-infusion of HEPHC with TPN reduced cannulae related complications. In the current study, the complication rates in both groups were similar. This finding adds to the evidence that complication rates differ between adults and children. Although the study from Thailand is unable to inform about HEPHC use in children because no children were included in the sample, the finding of that study and the current trial indicates that the evidence on HEPHC to prolong cannulae survival times is inconclusive.

Some methodological concerns noted in the study from Thailand have been addressed by the current study. The Thailand study randomised participants into a control and a treatment group but disclosed the treatment group to both participants and researchers. This could have resulted in different treatments for trial cannulae and complications between the two conditions (Rosenthal effect). The current study was randomised, controlled and double blinded and participants, their families, ward staff and researcher personnel did not know which treatment was being given.

The small sample size for the study from Thailand was also of methodological concern. In that study, only fifteen patients were investigated. This meant that less than ten participants were randomised to each treatment arm. The small sample size weakened the statistical credibility of their finding. In contrast, the current study used a sample size of fifty-three children and included eighty cannulae. This size was adequate to perform calculations and statistics required to answer the research question. Thus, the findings of the current study have greater statistical credibility when compared to the study from Thailand.

Only one published study by Roberts et al (1994) has investigated the use of low dose HEPHC to increase cannulae survival time in children. This study found that cannulae survival time was similar regardless of whether low dose HEPHC was continuously infused or medications were infused through an in-line filter. Based on their finding, Roberts and colleagues recommended using in-line filters instead of HEPHC as removal of particulate matter was shown to prolong cannulae survival and have less risks compared with HEPHC.

In the current study, in-line filters were not used and no significant statistical difference in cannulae survival time was found for clear fluids and low dose HEPHC groups. This finding, conflicts with the conclusion by Roberts et al. that both HEPHC and in-line filters prolong cannulae survival time in children. Furthermore, it highlights a methodological concern for their study. The research design of Roberts et al. (1994) did not include a control group to assess cannulae survival time when neither strategy HEPHC nor in-line filtering was employed.

Roberts and colleagues (1994) acknowledged their design flaw but justified the exclusion of a control group on ethical grounds. They stated that children in a control group would have been disadvantaged because they would not have received a strategy to prolong cannulae survival time. Therefore, there was a potential that these children were at risk of more frequent cannulation. The current study addressed this ethical concern by conducting an independent interim analysis mid-way through the trial. The aim of this analysis was to determine whether receiving only clear fluids was disadvantaging children in the control group. If a statistically significant difference between the cannulae survival times of the two groups of the trial had been identified, the trial would have been terminated. However, no statistically significant difference was found between the two groups, thus the trial continued until completion.

The study by Roberts and colleagues (1994) focused on a specific group of children with cystic fibrosis. This means that the findings of their trial cannot be generalised to all children. The current trial was conducted in the only paediatric unit in the ACT, providing a good opportunity to evaluate pIVC management practice. Unlike Roberts and colleagues, children in this trial were suffering from a wide range of illnesses. Thus, the findings of the present study have broader implications for cannulae management in children in general and particularly for the ACT.

Findings from the current trial demonstrated that adding low dose HEPHC was not beneficial in prolonging cannulae dwell times in children. Furthermore, evidence about complications associated with HEPHC and the lack of understanding about how these drugs affect developing immune systems indicates that this practice may be placing children at unnecessary risk.

Heparin has potentially serious complications such as HIT and white clot syndrome. Knowledge of these conditions in children is limited with few reported cases in the literature. However, there are incidents of death associated with heparin use in children (Hecker, 1992; Wright, 1996). There is also a view that under-reporting of HIT in children occurs because thrombocytopenia can been attributed to other factors, for example suspected but unproven infection (Potter et al. 1992). Thus, until more is known about administering these medications to children for this purpose, caution is indicated. As an interesting aside, the rigorous recruitment process in the current trial

identified and excluded a child with a family history of HIT, who might have received HEPHC if the trial had not taken place.

Health carers in the ACT, in an attempt to minimise unnecessary pain and distress to children, have employed strategies to prolong cannulae dwell times and reduce the need for frequent cannulation. The current study adds to the empirical evidence that the practice of adding low dose HEPHC to fluids administered to children via pIVC is not necessary. Additionally, this study has contributed to the general literature on paediatric pIVC management.

It has not been established that prolonging cannulae dwell time in children is safe. Although guidelines for cannula management by the Center for Disease Control and Prevention (2000) recommend routine pIVC replacement in adults to minimise the risk of cannula-related infection, no such guidelines exist for children. As stated previously, this is because of limited research into this area. Evidence indicates that serious complications associated with pIVC are less common in children when compared to adults (Mayhall, 1997), and the current study provides further evidence of this.

An Australian study reported the rate of pIVC related septicaemia in adults to be around 0.1% (Collignon, 1984), while rates of septic phlebitis were around 25% (Maki, Weise and Sarafin, 1977). It can be difficult to distinguish between early stages of phlebitis and infiltration development. Thus in the current study, these conditions were combined. The combined rate of these complications, in cannulae left in-situ for up to 10 days, was less than 30% for both study groups. This means that the reported combined incidence of phlebitis and infiltration in this study of children is similar to the septic phlebitis rate reported in the adult study. A possible alternative explanation for observing differences between the current study and those cited in the literature is that significant changes have occurred in cannula and management practices since the adult studies were conduced 20 to 30 years ago.

In contrast to the septic phlebitis rates reported in the Australian adult study (Collignon, 1984), the current study identified no cases of septic phlebitis. In the current trial, 70% of all cannulae were cultured and no significant colonisation was observed. Additionally, no cases of systemic sepsis relating to pIVC sites were identified. Only five previous studies have investigated phlebitis rates and cannulae colonisation in

children with dwell times greater than 72 hours (Fuchs, 1971; Garland, Nelson, Cheah, Hennes, and Jahnson, 1987; Garland, Dunne, Havens, Hintermyer, Bozzette, Wincek, Bromberger and Seavers, 1992; Schlager, Hidde, Rodger, Germanson and Donowitz, 1997 and Shimandle et al. 1999). In all cases, the infection rate from cannulae sites was less than 2% while the phlebitis rates were between 3 and 40%. The current study reported no infections from cannulae sites and a combined phlebitis and infiltration rate of 30%. Thus, the current study finding of a low cannula site infection rate is consistent with previous studies and provides further support that phlebitis in children is generally due to mechanical and chemical irritation of the vein as opposed to bacteria and fungal colonisation. Based on this observation, routine replacement of cannulae in children appears to be unnecessary.

Except for the addition of low dose HEPHC to extend cannulae survival time, findings from the current study support much of the current practice for pIVC management in children at The Canberra Hospital. Current practice involves diluting known vaso-irritant antibiotics and in the majority of cases includes filtering under sterile conditions. It is not clear whether filtering in the manner conducted in this trial has any effect on the incidence of phlebitis or cannulae survival time. Furthermore, the literature on in-line filtration as a strategy to prolong cannulae survival time is inconclusive.

Two controlled, double blind studies on adults have not found in-line filtration to improve cannulae survival time (Collin et al. 1973; Thayassen et al. 1977). While two recent Singapore studies demonstrated that use of in-line filters increased cannulae survival time and reduced phlebitis rates in adults (both reported in Chee and Tan, 2002). In relation to paediatrics, a Western Australian study failed to find any benefit from in-line filtration (Newall, Ranson and Robertson, 1998). It is therefore possible that intravenous fluid preparation in the current trial has no bearing on the findings.

Based on the findings of the current randomised, controlled, blinded trial, it has been demonstrated that HEPHC is not effective in prolonging cannulae dwell times in children. The literature review identified that heparin has significant complications and that there is a gap in the knowledge about the effects of administering low dose HEPHC to children over a number of days. Additionally, the current trial has contributed to the general literature on paediatric cannulae management. Specifically, it has contributed to the debate about whether cannulae should be routinely replaced in children. This

study has identified that the incidence of septic phlebitis in children is low and that a major reason that cannula fail in children is aseptic phlebitis and infiltration. Based on this finding, it appears that routine cannulae replacement in children is not necessary.

5.2 Limitations

The effect of filtering medications administered to children is controversial (Maddox et al. 1983; Roberts et al. 1994; Newall, Ranson and Roberts, 1998 and Chee and Tan, 2002). Filtering occurred for the majority of medications infused during the trial and this could have confounded the results. However, trial conditions, such as where the medications were prepared, were well matched in both groups of this trial. Thus, the overall finding that HEPHC is not necessary in pIVC management of children at The Canberra Hospital remains valid.

Another limitation of the current trial was the sample size. Although it was anticipated that the sample would be larger based on the number of children administered HEPHC in the previous years, recruitment was slow. However, the sample size of the current trial was large enough to identify any significant effects.

A small number of cannulae were discarded during the trial period. This resulted in 70% of cannula being cultured to identify contaminating agents. It would have been more rigorous if all cannula had been cultured, however, this was not possible.

Ideally, protocols and hygiene practices should be identical between the general ward and emergency environments. However, due to the pressures surrounding an emergency and the nature of designing studies in a clinical setting, it was not possible to ensure consistency in protocols and practices between these two settings.

This trial would also have had more methodological rigour if cannulae instead of children had been randomised to treatments. The decision not to randomise the cannulae was made because it was believed that this might confuse children and their families and increase the risk of errors.

In summary, no trial in the clinical setting is exempt from limitations. However, the current trial has been designed to address limitations identified in several previous studies, thus ensuring a sound basis for conclusions and recommendations to be drawn.

5.3 Conclusions and Recommendations

The present study was a randomised controlled double-blinded trial that investigated whether HEPHC prolonged cannulae dwell time in a group of children admitted to a general paediatric unit in the ACT. There was a good match between both groups of the trial for demographic details, cannulae details and medications administered. The study found that infusion of HEPHC did not extend the life of cannulae sufficiently to reduce the number of cannulations a child experienced during a course of AB therapy.

Based on this study, HEPHC does not improve cannulae dwell time in children at The Canberra Hospital. It is therefore recommended that:

1. The practice of prescribing low dose HEPHC for prolonging cannulae dwell time in children should be discontinued at The Canberra Hospital.

This study indicates that septic phlebitis is uncommon in pIVC sites of children even after long periods of time. It is therefore recommended that:

2. The current practice of unlimited cannulae dwell time in children should be continued at The Canberra Hospital.

Furthermore, based on the lack of knowledge about infection rates of cannulae with long dwell times in children, it is recommended that:

3. A cohort study of children is recruited to confirm the low phlebitis rates associated with cannulae in children despite extended dwell times, and to contribute to understanding about the ratio of aseptic and septic phlebitis in children.

In conclusion, repeated cannulation of children during the course of hospital treatment is distressing for the child, their family and to their nurses. The Canberra Hospital has endeavoured to minimise re-cannulation by infuse low dose HEPHC to reduce

complications such as phlebitis and thrombosis formation. A randomised, controlled double-blinded trial was conducted at The Canberra Hospital to examined whether low dose HEPHC improved cannulae survival in two well-matched groups of children. This unit is the only paediatric facility and tertiary referral centre for the Australian Capital Territory and South Eastern New South Wales region. Findings from this trial therefore have significant implications for paediatric practice in this region.

A finding from this trial was that no statistically significant difference existed in cannulae survival time for those cannulae that received infusions of low dose HEPHC, as compared to those that did not receive the additive. Thus, this trial demonstrated that the addition of low dose HEPHC does not prolong pIVC survival time in children at The Canberra Hospital. Based on this finding and the concern about the potential risks of administering these preparations to children this study has recommended that prescription of HEPHC for this purpose be discontinued.

Finally, the current trial has also contributed to the general literature on paediatric cannula management. Specifically, it has contributed to the debate about the need for routine replacement of cannula for children and the rate of septic and aseptic phlebitis in children. Based on the low septic phlebitis rates observed in this study, it has been recommended that The Canberra Hospital should not routinely replacing cannulae in children.

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APPENDIX

A

Summary of Factors Associated with Phlebitis

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APPENDIX

Summary of Factors Associated with Phlebitis: Maki & Ringer (1991)

IMPORTANT FACTOR	CANNULA SURVIVAL: SHORTER > LONGER
Personal characteristics	1. Age: children older > younger 2. Sex: men > women 3. Nationality: white > dark 4. Underlying medical disease: yes > no 5. Individual biological vulnerability: yes > no 6. Poor quality veins yes > no
Cannula characteristics	7. pIVC material :Teflon > Polyurethane 8. pIVC placed in emergency room > in-patient facility 9. Cannulation attempts: more > less 10. Cannula gauge size: large > small bore 11. Cannulation site in upper are/wrist > hand 12. Subsequent cannula beyond the first > one only
Environmental factors	13. Skill of person inserting pIVC: less > more skilled 14. Aseptic technique during insertion: not septic > aseptic 15. Colonisation of cannula: present > not 16. Daily dressing changes > less frequent changes 17. [1]Place medication prepared (ward > pharmacy department) 18. Time cannula was insitu: longer > shorter
Infusate characteristics	19. Ph of solution: high/low > neutral 20. Osmolarity of solution high > neutral 21. [2]Precipitation: more > less 22. Flow rate: high > maintenance

[1] Identified by Falchuk, Peterson and McNeil (1985)
[2] Identified by Mayhall, C.G., (1997)

APPENDIX

B

Trial Protocol and Check List

B

APPENDIX

Trial Protocol

How to Obtain Informed Consent.

Prior to approaching parents/patients for Informed Consent please consider the following:

- **Has the VMO been consulted?**
- **Does the patient fit the inclusion/exclusion criteria? i.e. would the patient normally have Heparin and Hydrocortisone?**

If you think the patient may be suitable for the study, approach the patient/parents. Give them a very brief outline of the trial and ask them to read the Information Sheet. (Allow them at least 10-15 minutes)

Ensure that they understand that the study is voluntary and that they have the right to not participate or to withdraw at any point without it affecting their or their child's management.

You must read the whole consent form point by point with the parent/patient and discuss any part of it that they may not understand fully. Sorry, but this is a Legal Requirement! At the end of the Consent Form, the parent/patient is invited to participate in the study.

The Consent Form must be signed and dated by the parent unless the nursing/medical staff is confident that the patient is able to fully understand the consequences of participating in the trial. In this case, the parent must sign as the witness. If the parent gives consent then the witness may be another relative or family friend or a member of the nursing or medical staff who has witnessed the explanation given.

In the absence of the Trial Investigator, the Investigator may appoint an Investigator Delegate to explain the trial to the patient/parent and to sign as the Trial Investigator.

All three signatures should be signed and dated with a black pen. The patient/parents should date their own signature. As with all Medical Forms, no white out should be used. If you require to alter anything, then you should cross it out, initial and date.

Please photocopy the Consent Form and give a copy to the patient/parent.

The person acting as "Investigator/Delegate" should use the stamp in the Case History to identify the patients enrolled in the study.

Always ensure patients/parents know about the role of the Ethics Committee in approving and controlling Clinical Research Studies for the protection of the public. Also, that ethics are available if they have any concern about the study and how it is carried out.

Parents/patients who do not understand English should still be given the opportunity to participate in the study. The hospital interpreter would be required to assist in translating the Information Sheet and Consent Form into the participant's language. This would ensure that the patient fully understands the implications of the study.

If there are any other queries, please do not hesitate to ask.

Good luck and happy recruiting!

Checklist for Patient Enrolment

Please check the following applies to patients being screened for the Management of Intravenous Therapy in Children (Mitch Study).

- The Medical Officer has identified no clinical reasons that would prohibit this patient's inclusion in the study
- Patient or parents/guardians are able and willing to give consent
- Patients age is 16 years old or younger
- Patient has no history of clotting or bleeding problems
- Patient has no history of sensitivity to Hydrocortisone of Heparin
- Patient has completed maintenance fluids
- Patient would normally have Heparin/Hydrocortisone to keep the vein open
- Patient will be receiving antibiotics for a further three days

If the patient appears to meet the criteria, please give the Information Sheet to the patient and/or parents and allow them to consider
enrolment in the study.

Thankyou

Management of Intravenous Therapy in Children (MITCH Study)

The 12 most asked questions about the study!

Who would be an appropriate patient?
Any patient who is able to be on TKVO fluids and would normally be commenced on heparin and hydrocortisone. The patient will be having antibiotics for at least a further 3 days. They should have no contra-indications to heparin or hydrocortisone.

What age of patients are we looking for?
The patient must be 16 years or under for this study.

What permission is required?
The VMO in charge of the patient's management will have to have given their approval for the patients to be involved. The parents must sign the Information Consent and the patient must have agreed if they are old enough to understand.

Can the patient sign their own consent form?
Yes, they can as long as the Investigator or research assistant is convinced that the patient fully understands the consequences of participating in the study. Also, they can only sign if a patent/guardian signs as the witness.

Who decides which fluid the patient receives?
Pharmacy will randomise the patients and allocate them a number. That number will belong to the patient for their entire admission. The trial solution will be made up in Pharmacy and only the intravenous pharmacist will know which solution is given to the patient. The code will only be broken in an emergency.

How is the trial fluid going to be available to the nurses on the ward?
The RMO will order "MITCH Study Fluids" for the patient on the standard IV Order chart. This order will go to pharmacy and a bag will be sent to the ward.

What if the trial fluid is commenced out of Pharmacy's normal working hours?
A spare bag with the next randomisation number will be available in the 4B immunisation fridge. When you collect the bag from there, please take a patient sticky label with you. There will be a form attached to the bag of trial fluids. Please put the patient's sticky label on that form and leave it on the fridge door. Check the randomisation number on the form corresponds with the number on the bag. This way, pharmacy will know who has been enrolled in the study.

What happens if a cannula is removed?
Complete the data sheet and sign and date it. The catheter tip should be sent to pathology for culture. Please cut the tip from the cannula with sterile scissors and place it in a sterile universal container. There is a special form for Pathology which is available in the MITCH Study Folder.

What happens if the cannula is then replaced? Does the patient get a new randomisation number?
No, the same number stays with the patient until they are discharged. However, you must commence a new data sheet every time a cannula is replaced.

What if I forget to fill in the data sheet?
Don't worry about it as we can usually trace the information back from the case history and medication record charts. Just please don't guess an answer to a question, we'd prefer if you left it blank.

What if I accidentally throw away the cannula tip?
Again, it's not the end of the world. Accidents will happen! Just please do not try to retrieve it from the bin or wherever else, just write "not done" and that's fine.

What I some parents or patients change their mind and want to withdraw their consent, should I try to persuade them to stay in the trial?
No, they are perfectly entitled to change their mind. Respect their decision and treat the patient as normal.

Also, please remember that it is vital to the study and the patient's safety that we adhere strictly to the protocol. Any deviation from the protocol must be reported to the Ethics Committee as soon as possible.

APPENDIX

C

Information Sheet

C

APPENDIX

Research project: Management of intravenous treatment for children

Information sheet

Dear parent,
The staff of the children's ward is conducting a study on the management of intravenous treatment for children. As your child will need a drip for four days or more we would like to involve her/him in the study. We need your permission for your child to be included. Before you decide please read the following information and if you have any additional questions please talk to one of the nurses caring for you and your child.

INTRODUCTION
Sometimes when children are in hospital they need to have an intravenous infusion (drip) as an important part of their treatment. Through this drip, fluids and/or drugs can be given to the child through a very small tube in a vein (called a cannula), usually in the arm. Frequently however the cannula becomes blocked and needs replacing, a procedure that is distressing and painful for the child. Nurses and doctors use various methods to try and prevent this blockage. One method is to use only clear fluids and another is to insert a small dose of the medications *heparin* and *hydrocortisone* to prevent blockage. Both of these methods are commonly used in hospitals throughout Australia. At The Canberra Hospital we frequently use the heparin and hydrocortisone method.

THE STUDY
We are conducting a study to see if the use of the heparin and hydrocortisone really does make a difference. The results of this study will help us to develop a policy, that is based on research, for care of intravenous treatment for children. The study is a clinical trial where both methods are used to see if the use of the medications is the best method.
If you give permission the research will proceed as follows:

- **There will be 120 children involved in this clinical trial**
- **Your child will be allocated to one of two groups.**
- **One group of children will receive the heparin and hydrocortisone method of managing the cannula and one group will receive clear fluids.**
- **No one except the pharmacy will know if your child is getting the medication or the clear fluids.**
- **The nurses will keep a record of the condition of the drip site, pain or any other symptoms and the length of time the cannula remains in the vein without becoming blocked.**
- **At the end of the trial we will calculate whether there was any difference in the life of the cannula between the two groups. In other words does the medication make the drip last longer or not.**

YOUR CHILD'S INVOLVEMENT

The following points may help you decide if your child will be involved.

1. RISK

This is not a trial for a new drug treatment. The medications in the dose we will be giving are currently used routinely in management of IV treatment but, like all medications, carry a small risk of unwanted side effects. Standard treatment has involved administration of heparin and hydrocortisone, with adverse effects including haemorrhage, however the risk of this is extremely small and this has been an acceptable part of standard therapy for the management of cannulae.

There is a risk that the children in the group receiving the clear fluids method may have to have a new drip put in more often that the children in the other group. But we do not know this for sure.

If your child appears to be allergic to something, we can stop the infusion and treat any allergy. The pharmacy will be able to tell from your child's code number if they were getting the medications or not therefore helping the doctors to diagnose if there is a problem.

2. WITHOLDING PERMISSION

Your child will not be included in the trial without your permission. If you decide not to give permission neither you nor your child will in any way be disadvantaged and you will both continue to receive all necessary care and treatment. Also if you give permission but later change your mind, your child will be withdrawn from the trial without any consequences to the quality of care they receive.

3. WHAT HAPPENS TO THIS INFORMATION?

The results of the study will contribute to treatment policy in the children's ward. The information we get from this study will be written up as an article and submitted for publication in a nursing/medical journal. At no time will any personal details about your child or yourselves be made available to any one. Your child's name will not be written on the paper we use for recording information about their drip. The people doing the calculations or writing the article will not be able to identify you or your child at all. If you are interested in the results of the trial we can make arrangements to contact you when we have the final results.

Please feel free to ask any questions if things are not clear and let us know when you have decided. Remember whatever your decision your child will get the care and treatment they need. If you would like to talk to someone not directly involved with the project you may contact the ACT Department of Health Ethics Committee Secretary on Second Floor, North Building, London Circuit, Canberra City, ACT 2601 or on phone number 02-62050846.

Thank you for taking the time to think about our request.

Anne Gardner, Assistant Director of Nursing
Jon Darvill, Paediatric Nurse Educator
Kate Milbourne, Clinical Nurse Consultant, Paediatrics
Phone extn – 3529 or page 62699004 if would like further information regarding the trial.

APPENDIX

D

Consent Form

D
APPENDIX

The Canberra Hospital and University of Canberra
Consent Form to Participate in a Research Project

I, _____
(name of participant)

being the _____ of _____
(state relationship eg parent) (name of patient)

of _____ _____ _____
(street) (suburb/town) (state and postcode)

have been asked to consent to my child's participation in a research project entitled:

Management of intravenous treatment for children

In relation to this project I have read and understood the Patient Information Sheet and have been informed of the following points:

1. Approval has been given by the ACT Department of Health and Community Care Human Research Ethics Committee and the University of Canberra Human Ethics Committee.

2. The aim of the project is to determine whether heparin and hydrocortisone additives prolong the effective life of intravenous cannulae in children. This is not a trial for a new drug treatment. Heparin and hydrocortisone, in the doses used in this research, are currently used routinely in management of IV treatment for children.

3. The results obtained from the study may or may not be of direct benefit to the medical management of my child.

4. The procedure will involve my child being allocated to one of two groups. One group of children will receive the heparin and hydrocortisone method of managing the cannula and one group will receive clear fluids. No one except the pharmacy will know if my child is getting the medication or the clear fluids. The nurses will keep a record of the condition of the drip site, pain or any other symptoms and the length of time the cannula remains in the vein without becoming blocked.

5. These are some possible adverse effects or risks related to this project which include:
   - Standard treatment has involved administration of heparin and hydrocortisone, with adverse effects including haemorrhage, however the risk of this is extremely small and this has been an acceptable part of standard therapy for the management of cannulae
   - There is a risk that the children in the group receiving the clear fluids method may have to have a new drip put in more often that the children in the other group

6. My child's involvement in this project may be terminated if any of the following circumstances develop:
   - his or her condition deteriorates requiring recommencing full intravenous fluids
   - he or she develops an allergic reaction which requires a determination to which of the two groups the child belongs

Consent Form to Participate in a Research Project

Management of intravenous treatment for children

7. An earlier analysis suggests that no child is being disadvantaged.

8. Should my child develop a problem which I suspect may have resulted from his/her involvement in this project, I am aware that I may contact:–

Anne Gardner	Phone:	6244 2375
Jon Darvill	Phone:	6244 3529
Kate Milbourne	Phone:	6244 4116

9. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the research staff, I am aware that I may contact the ACT Department of Health Ethics Committee Secretary on Second Floor, North Building, London Circuit, Canberra City, ACT 2601 or on phone number 02-62050846.

10. I can refuse permission for my child to take part in this project or withdraw from it at any time without affecting his/her medical care

11. Participation in this project will not result in any extra medical and hospital costs to my family.

12. If the results of tests or information regarding my child's medical history is published, his/her identity will not be revealed.

13. If I am interested in the results I should ring the contact people listed in question 8.

After considering all these points, I accept the invitation for my child to participate in this project.

I also state that my child has/has not participated in any other research project in the past 3 months. If he/she has, the details are as follows:

_____

Date: _____ Witness: _____
(Please print name)

Signature: _____ Signature: _____
(of participant/volunteer) (of witness)

Investigator's Signature: _____

APPENDIX

E

Data Collection Instrument

E
APPENDIX

Peripheral Inserted Catheter Study Data Sheet

Todays' date: ___/___/___ Pt Randomisation Number: ___ ___ ___

Patient Data-
DOB: __/___/____ Sex: _____ Language spoken at home:_____
Diagnosis: _____Reason for insertion:_____

Insertion Data-
Cannula Gauge: _____ Site:_____
Number of attempts: _____ Describe:_____
_____ Emergency/Elective insertion (circle)

Medications Prescribed while in-patient-

***Any IV ABs not loaded by Pharmacy: YES / NO**

Date **Heparin and Hydrocortisone started-**___/___/___

Management Data-
Daily Bag Change:(sign if attended)

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Da 14

***Second Daily Line Change** (sign if attended)*

Day __	Day __	Day __	Day __	Day __	Day __

IV/Connula Complications-

Key
Date __/__/__Problem/Action _____] (a) Blocked
Date __/__/__ Problem/Action _____] (b) Kinked
Date __/__/__ Problem/Action _____] (c)Infiltrate
Date __/__/__ Problem/Action _____] (d) Phlebitis

(PTO for key)

Removal of Cannula Data- Date: ___/____/____
Reason for removal (circle): Blocked / Kinked / Infiltrate / Phlebitis / IV meds ceased
Other: _____.
[Tip culture results: _____] **PTO for Notes/Comment**

Phlebitis Scale Guide

Stages of Phlebitis	Clinical Indicators	Nursing Interventions
0	No pain, redness or oedema at IV site	None
1+	Redness <2-3cm above IV site; no pain oedema, hardness or palpable cord	Remove the cannula
2+	Painful IV site with redness, warmth, and/or oedema >2-3cm above IV site, no palpable cord or hardness	Remove IV cannula Elevate extremity PRN apply warm pack for 20min QID until resolved
3+	Painful IV site with redness, oedema, hardness, or palpable cord < 5cm above IV site	Remove IV cannula Elevate Limb, apply warm pack as per above Inform team

Reference: Perucca and Micek (1993), Journal of IV Nursing and 1998 Nursing Standards Guidelines, Journal of IV Nursing.

Notes/Comments:_____

APPENDIX

F

Process of Cannulation at The Canberra Hospital

F

APPENDIX

1. Process of Cannulation at The Canberra Hospital Paediatric Unit

(a) Cleaning the Cannulation Site

Emla (topical anaesthetic) is removed and the skin is cleaned with chlorhexidine and then alcohol.

(b) Taping Cannula Insitu

The cannula is secured into place using leukoplast tape.

(c) Completing the securing process.