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THE EFFECT OF *ALOE VERA* VS REPARIL® GEL ON PREVENTION OF THROMBOPHLEBITIS IN PARTIAL PARENTERAL NUTRITION (DOUBLE BLIND CONTROLLED TRIAL)

CHORTIP KOCHARSANEE

ลิขสิทธิ์ของบัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล

A THESIS SUBMITTED IN PARTIALS FULFILLMENT
OF THE REQUIRMENT FOR
THE DFGREE OF MASTER OF SCIENCE
(NUTRITION)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2002

ISBN 974-04-1903-8

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Thesis

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Was submitted of Faculty of Graduate Studies, Mahidol University for the degree of Master of Science in Nutrition (Clinical medicine)

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ACKNOWLEDGEMENT

I would like to express my sincere attitude and deep appreciation to Professor Dr. Chulaporn Roongpisuthipong, my advisor, for her invaluable supervision, guidance, kindness, constructive critism, and tremendous assistance throughout my study.

I am particularly grateful to Associate Professor Dr.Busba Chindavijak and Assistant Professor Dr.Sriwatana Songchitsomboon, my co-advisors, for offering an opportunity to perform this research at Ramathibodi Hospital, as well as valuable suggestion and kind assistance regarding my research work.

I appriciate to thank very much all physician, nurse and staff of Surgery Department, Ramathibodi Hospital for their cooperated.

And special thanks to all my friends and senior gratitude at the ICU 5, Ramathibodi Hospital for their help and encouragement

Finally, I am extremely grateful to my parents and brother for their love, encouragement and everything's given to me throughout this study.

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4136753 RANU/M : MAJOR : NUTRITION ; M.Sc.(Nutrition)

KEYWORDS : THROMBOPHLEBITIS, PPN

CHORTIP KOCHARSANEE : THE EFFECT OF *ALOE VERA* VS REPARIL® GEL ON PREVENTION OF THROMBOPHLEBITIS IN PARTIAL PARENTERAL NUTRITION (DOUBLE BLIND CONTROLLED TRIAL) THESIS ADVISORS : CHULAPORN ROONGPISUTHIPONG .MD, ABN. BUSBA CHINDAVIJAK D.Sc.(Pharm), Ph.D. , SRIWATANA SONGCHITSOMBOON D.Sc. (Nutrition). 90 Pages. ISBN 974-04-1903-8

The purpose of the study is to compare the effect of topical *Aloe vera* gel and Reparil® gel on the episode and degree of severity of thrombophlebitis while on PPN treatment .

There were 99 patients (50 males and 49 females) who were on surgical wards at Ramathibodi Hospital , receiving PPN treatment during the period between November 1999 to February 2001. The PPN formular was 10 %D/N/2 1000ml + Addamel 1 amp + OMVI 1 amp with 10% Aminosol 500 ml . There were 135 catheters in the experimental design, that were randomly assigned into 3 groups (45 catheter per group), group 1 was the control group, group 2 received Reparil® gel , group 3 received *Aloe vera* gel . Group 2 and 3 were applied of gel to the cannulation site about 0.3 ml and then rubbed along 10 cms after the start of PPN cannulation site and then every 8 hrs. We recorded degree of severity of thrombophlebis by pain, redness, swelling, erythema,and induration as the same applied time. ANOVA statistical analysis was chosen for statistical significance.

The results showed that, there was no significant difference in age, height, weight, BMI and serum albumin level among the 3 groups. The episodes and severity of thrombophlebitis had highly significant correlation with longer infusion in all groups , (P< 0.05).The number of catheters and degree of severity of thrombophlebitis in group 2,3 were significant lesser than group 1 every time study after 16 hrs ,(P<0.05). At 40 hrs of prolonged catheter, it was found that *Aloe vera* gel group also had least number and degree of severity of thrombophlebitis than other, respectively(P<0.05).

Thus, the application of *Aloe vera* gel and Reparil® gel at the cannulation site on hyperosmolal are benifical in preventing and reducing thrombophlebitis. However *Aloe vera* gel can reduced thrombophleblitis better than Reparil® gel when prolonged used of catheters at 40 hrs are used.

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4136753 **RANU/M** : **สาขาวิชา : โภชนศาสตร์ ; วท.ม. (โภชนศาสตร์)**

ช่อทิพย์ คชเสนี : ผลของ เจล ว่านหางจระเข้, เรพาริล เจล ต่อการเกิดภาวะหลอดโลหิตดำอักเสบส่วนปลายในคนไข้ที่ได้รับสารอาหารทางหลอดเลือดดำส่วนปลาย (THE EFFECT OF *ALOE VERA* VS REPARIL® GEL ON PREVENTION OF THROMBOPHLEBITIS IN PARTIAL PARENTERAL NUTRITION;DOUBLE BLIND CONTROLLED TRIAL) คณะกรรมการควบคุมวิทยานิพนธ์ ; จุฬาภรณ์ รุ่งพิสุทธิพงษ์ พบ,วว, อายุรศาสตร์, บุษบา จินดาวิจักษณ์, ภ.บ.,วท.ม. ศรีวัฒนา ทรงจิตสมบูรณ์ ปร.ด. (โภชนศาสตร์) 90 **หน้า. ISBN 974-04-1903-8**

การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อศึกษาผลของการทาเจลว่านหางจระเข้ ,เรพาริลเจล บริเวณที่แทงเข็มให้สารอาหารทางหลอดเลือดดำส่วนปลายต่อการเกิดภาวะหลอดเลือดดำส่วนปลายอักเสบ. ประชากรทั้งหมดที่ศึกษาจริง 99 คน (ผู้ชาย 50 คน ผู้หญิง 49 คน) เป็นคนไข้แผนกศัลยศาสตร์โรงพยาบาลรามาธิบดี โดยได้รับสารอาหารทางหลอดเลือดดำส่วนปลาย ช่วงระยะเวลาที่ศึกษาระหว่างเดือน พฤศจิกายน 2542 – กุมภาพันธ์ 2543 สูตรของสารอาหารทางหลอดเลือดดำส่วนปลาย คือ 10 %D/N/2 1000 ซีซี + Addamel 1 ขวด + OMVI 1 ขวด และ 10% Aminosol 500 ซีซี . จำนวนตัวอย่างที่ศึกษาคิดตามจำนวนเข็มที่แทงให้สารอาหารทางหลอดเลือดดำส่วนปลายทั้งหมด 135 ตัวอย่าง แบ่งจำนวนตัวอย่างเป็น 3 กลุ่ม กลุ่มละ 45 ตัวอย่าง กลุ่มที่1 เป็นกลุ่มควบคุม กลุ่มที่ 2 เป็นกลุ่มที่ ทาเรพาริล เจล และกลุ่มที่ 3 เป็นกลุ่มที่ ทาเจลว่านหางจระเข้ กลุ่มที่ 2 และ3 จะได้รับการทาเจล จำนวน 0.3 ซีซี บนผิวหนังบริเวณที่แทงเข็มให้สารอาหารและทายาวขึ้นไป10 เซนติเมตร โดยเริ่มทายาตั้งแต่เริ่มแทงเข็มให้สารอาหาร และ ทายา ทุก 8 ชั่วโมง (เวลา 6, 14 และ 22 นาฬิกา) โดยระยะเวลาที่ใช้ศึกษาทั้งหมดนาน 40 ชั่วโมง ประเมินระดับการอักเสบของหลอดเลือดดำส่วนปลายโดยสังเกต อาการ แดง ร้อน บวม ปวด ในเวลาเดียวกับที่ทายา. เปรียบเทียบผลของทั้งสามกลุ่มศึกษาใช้สถิติวิเคราะห์ ความแปรปรวน

ผลการศึกษาพบว่าอายุ ส่วนสูง น้ำหนัก ดัชนีความหนาแน่นของร่างกาย และระดับอัลบูมิน ในเลือดของกลุ่มตัวอย่างทั้งหมดไม่แตกต่างกันทางสถิติ ระยะเวลาที่คาเข็มให้สารอาหารนาน ๆ เกิดภาวะหลอดเลือดดำอักเสบมากกว่าระยะเวลาที่คาเข็มสั้นกว่าในทุก ๆ กลุ่มที่ศึกษาอย่างมีนัยสำคัญทางสถิติ ($P<0.05$) . กลุ่มที่ใช้เจลว่านหางจระเข้และเรพาริลเจล พบจำนวนตัวอย่างและ ระดับความรุนแรงของการเกิดภาวะหลอดเลือดดำอักเสบน้อยกว่ากลุ่มควบคุมหลังจากชั่วโมงที่16 ทุกช่วงเวลาที่ศึกษาอย่างมีนัยสำคัญทางสถิติ ($P<0.05$) กลุ่มที่ใช้เจลว่านหางจระเข้เกิดภาวะหลอดเลือดดำส่วนปลายอักเสบน้อยกว่ากลุ่มที่ใช้เรพาริลเจล หลังจากที่คาเข็มให้สารอาหารนาน 40 ชั่วโมง อย่างมีนัยสำคัญทางสถิติ ($P<0.05$).

ดังนั้นผลของเจลว่านหางจระเข้ และเรพาริลเจล สามารถลดอุบัติการณ์การเกิดภาวะหลอดเลือดดำส่วนปลายอักเสบได้ และการใช้เจลว่านหางจระเข้จะให้ผลในการลดการเกิดภาวะหลอดเลือดดำส่วนปลายอักเสบได้ดีกว่าเรพาริลเจล เมื่อคาเข็มให้อาหารทางหลอดเลือดดำส่วนปลาย PPN นาน 40 ชั่วโมง

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CONTENTS

	Page
ACKNOWLEDGEMENT	III
ABSTRACT IN ENGLISH	IV
ABSTRACT IN THAI	V
LIST OF TABLES	VIII
LIST OF FIGURES	X
LIST OF ABBREVATIONS	XI
LIST OF APPENDIC	XII
CHAPTER	
I INTRODUTION	
Background	1
objective	5
II LITERATURE REVIEW	
Infusion Thrombophlebitis	6
Medaitors of inflammatory response	8
Cause of Thrombophlebitis	9
Prevention of infusion thrombophlebitis	13
III MATERIALS AND METHOD	
Study design	30
Research Tools and Instruments	
Part I Preliminary study	30
Determination of osmolality	31

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CONTENTS (CONT.)

	Page
Determination of *Aloe vera* gel	36
Determination of sample size	45
Part II Experimental part	51
IV RESULTS	
The Characteristic of study popution	54
The relationship between including variables	
And thrombophlebitis by ANOVA	
V DISCUSSSION	65
VI CONCLUSION	71
REFERENCE	72
APPENDIX	78

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LIST OF TABLES

Table		Page
1.	Caloric value, osmolality and pH of PPN solution	35
2.	Details of treatments in each group {*Aloe vera* gel}	37
3.	Percentagr of application and data recording during trained	40
4.	Degree of thrombophlebitis in *Aloe vera* gel dose A	41
5.	Degree of thrombophlebitis in *Aloe vera* gel dose B	41
6.	Degree of thrombophlebitis in *Aloe vera* gel dose C	42
7.	Degree of thrombophlebitis in *Aloe vera* gel dose D	42
8.	Degree of thrombophlebitis in *Aloe vera* gel dose E	43
9.	Degree of thrombophlebitis in *Aloe vera* gel dose A-E at 40 hrs	43
10.	Details of treatments in each group { Reparil® gel and control }	47
11.	Demographic data of patients in control, Reparil® gel, and *Aloe vera* grlgroup	48
12.	Degree of thrombophlebitis in Reparil® gel group	49
13.	Degree of thrombophlebitis in Control group	49
14.	Indications for peripheral intravenous nutrition	55
15.	Number of patients	55
16.	Demographic data of patients	56
17.	Caloric value, osmolality and pH of PPN solution	56
18.	Reasons for stopping intravenous infusion	57

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LIST OF TABLES (CONT.)

Table **Page**

19. Number of catheters stratified according to degree of thrombophlebitis in control group 57

20. Number of catheters stratified according to degree of thrombophlebitis in Reparil® gel group 58

21. Number of catheters stratified according to degree of thrombophlebitis in *Aloe vera* gel group 58

22. Mean degree of thrombophlebitis during 40 hr in experimental 59

23. Number and percentage of thrombophlebitis during 40 hr in Experimental 60

24. Graph mean degree of thrombophlebitis at 16 hr comparing 3 group 61

25. Graph mean degree of thrombophlebitis at 24 hr comparing 3 group 62

26. Graph mean degree of thrombophlebitis at 40 hr comparing 3 group 63

27. Graph mean degree of thrombophlebitis at 40 hr comparing 3 group 64

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LIST OF FIGURES

FIGURE **PAGE**

1. Development and effects of the acute phase response 8

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LIST OF APPENDICES

APPENDIX **PAGE**

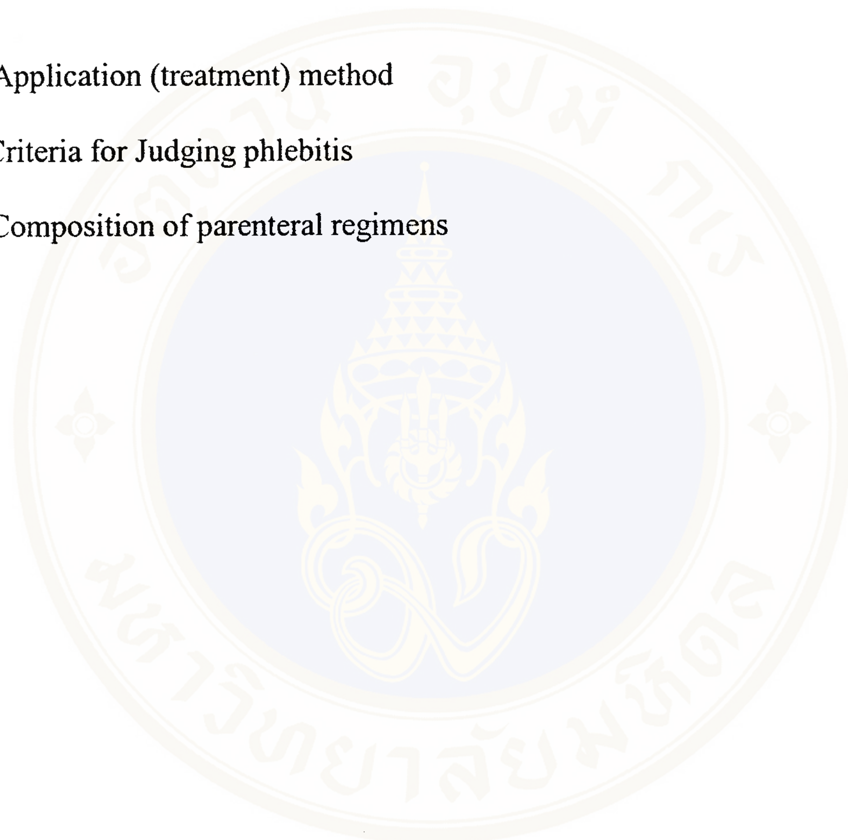
A. Osmomiter 78

B. แบบประเมินภาวะหลอดโลหิตดำอักเสบส่วนปลาย 85

C. Application (treatment) method 86

D. Criteria for Judging phlebitis 87

E. Composition of parenteral regimens 88



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CHAPTER I

INTRODUCTION

Energy balance, tissue synthesis and anabolic state in the body require adequate protein, carbohydrate, fat, water, electrolyte, vitamin and mineral components(1-3).During starvation, body protein and fat will be catabolized for energy resulting in threatening organ mass and function including skeletal and respiratory muscles, liver, kidney, heart, gastrointestinal tract and ndocrinesystem (3). Furthermore, infection due to secondary immunodeficiency, is one of the most frequent complications of malnutrition(5) . Especially in adults, malnutrition leads to increase morbidity and mortality rates and requires longerhospitalization meanwhile neonatal malnutrition results in long-term deficits in brain growth and development (6).Accordingly, nutrition therapy via either enteral or parenteral route is required. If enteral nutrition is tolerated, it is preferable to parenteral nutrition (PN). Not only because of the less complexity of enteral feeding but it also stimulates the developmentof gastrointestinal function, avoids the decreased efficiency of intestinal absorption secondary to pancreatic and small-intestine hypoplasia, and decreases the frequency to complication.

Parenteral nutrition (PN) is indicated when enteral feeding is impossible inadequate. PN is necessary in patients with various disorder states as following.

1. massive small bowel resection, radiation enteritis, disease of small intestine.
2. high dose chemotherapy, radiation, and bone marrow transplantation.

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3. moderate to severe acute pancreatitis.
4. severe malnutrition in the face of a nonfunctional gastrointestinal tract.
5. severe catabolic patients with or without malnutrition when the gastrointestinal tract is not usable within 5-7 days.
6. enterocutaneous fistulas.
7. inflammatory bowel disease.
8. moderately malnourished patients who require intensive medical or
9. surgical intervention, etc.

Administration of PN

PN can be delivered via a central or peripheral vein. The superior venacava is a large central vein used most often for central PN. Patient is percutaneously catheterized through the subclavian, the internal or the external jugular vein, with the catheter tiplying at the superior venacava-right atrial junction. With this catheter's position, very concentrated solution may be infused because of the high rate of blood flow in the superior venacava. Thus, concentrated nutrients can be delivered in relatively small volumes without causing thrombophlebitis. This method is particularly beneficial in patients who need large amount of energy and protein or who require fluid restriction (5-7).

Placement of a central venous catheter requires proper training and careful technique to minimize the chance of a mechanical complication. Common complications include pneumothorax, hemothorax, pneumohemothorax, subclauian artery injury, brachial plexus injury, thoracic duct injury, air embolism, catheter

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embolization, cardiac arrhythmia, subclavian vein thrombosia, catheter occlusion due to fibrin formation. Infected central venous catheter is one of the most common and dangerous complications. Centralvenous catheter provides direct access between the environment and the central circulation. Ideally, infected catheters should be removed and a new catheter should be placed in a different site after the infection is resolved. In some patients, sites for new catheter placement are not possible. Antimicrobial therapy should be infused in such cases through the infected catheter to treat the infection and avoid removing the catheter. The catheter exit site may also be infected. Local antimicrobial therapy may not be sufficient to treat exit-site infection and systemic antimicrobial therapy may be required. Care should be taken with dressing changes and the central line dressing change protocol should be strictly followed.

Peripheral parenteral nutrition (PPN) can be used in patients who are being weaned from central PN to a normal diets or as an adjunction to an enteral diet (6). PPN solutions are considerably less hypertonic than central PN solutions (950 mOsm/KgH2O vs 1800 mOsm/KgH2O (6-7). Actually, a solution of 600 mOsm/KgH2O is better tolerating. As the solution tonicity increases, infusion complications such as phlebitis and infiltration should be aware. A dilute nutrient solution with a final protein concentration of 3-10% and a dextrose concentration of 5-10% is thus commonly used but it is extremely difficult to meet a patient's nutritional and energy requirements, because of the large volumes of fluid required. Accordingly, concurrent infusion of lipid emulsion, the energy source with isotonic property, with dextrose to the vein, thus increases patient tolerance of

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peripheral administration.

Peripheral infusion of PN solution may cause phlebitis, swelling and edema resulting from infiltration or extravasation of PN solution which may progress to necrosis (8). Early recognition is important for successful management of these complications. Prophylactic measures, such as the addition of heparin and hydrocortisone in solution, the use of a glyceryl trinitrate patch, topical use of anticoagulant cream at the venipuncture site, and other means have been recommended to reduce the incidence of thrombophlebitis complications (18).

Aloe vera (Linn.) **Burm. f.** has been recognized as one of valuable medicinal plants. It has therapeutic abilities to penetrate tissue, anaesthetize the tissue, killbacteria, fungi and viruses, dilate capillaries and enhance blood flow (29-31).Vazquez, et al (33) showed that extracts of Aloe vera gel have antiinflammatory activity and suggested its inhibitory action on the arachidonic acid pathway via cycloxygenase. Heggers and his co-workers (30) showed that topical application of anti-eicosanoids, could reverse progressive tissue loss in each injury by actively "inhibiting" the localized production of thromboxan A2. Therefore the specific application of *Aloe vera gel* is essential in preventing tissue inflammation and phlebitis However, no one has studied about effect of *Aloe vera* gel on peripheral thrombophlebitis Thus, we were interested to study the effect of *Aloe vera* gel on reducing thrombophlebitis which was common complications of PPN. Faculty of medicine, Mahidol University in Bangkok at Ramathibodi hospital, partial parenteral nutrition (PPN) is the most popular pain way to give nutrition support in both surgical and medical patients. Infusion thrombophlebitis is the most common complication of PPN infusion which is

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characterized by erythema, edema and painful at the injection site. Thus, the site of infusion should be changed every 24 or 48 hrs, but it is not always practical.

The practical way inorder to reduce the incidence of thrombophlebitis is to use a Local Reparil® gel over the infusion site as we think Reparil® gel has claimed of its anti-inflammatory and analgesic action..

Clinical research regarding to therapeutic effect of Reparil® gel on thrombophlebitis whether or not is understudied.

Objective

To compare the effects of *Aloe vera* gel and Reparil® gel on prevention of thrombophlebitis complication of PPN.

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CHAPTER II

LITERATURE REVIEW

Infusion Thrombophlebitis

An intravenous infusion is the most commonly performed surgical procedure in hospital wards and is a frequently used therapeutic regimen for hospitalized patients encompassing the entire spectrum of patient population and disease. Infussionthrombophlebitis is the most common complication of intravenous infusion and is characterized by a painful local reaction often accompanied by erythema and edema. Symtom and signs usually last days or weeks(10, 12). As the results, it is possible to develop suppuration and septicemia.

Pathophysiology of Thrombophlebitis

Thrombophlebitis (pheripheral inflammation) is a reaction of the micro-circulation characterized by movement of fluid and leukocytes from the blood intoextravascular tissue. This is frequently an expression of the host's attempt to localize and eliminate metabolically altered cells, foreign particles, microorganisms, or antigens.Inflammation can be thought to proceed as follows (10-13).

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- Initiation of the mechanisms responsible for the localization and clearance of foreign substances and injured tissue is stimulated by the recognition that injured to tissues has occurred.
- Amplification of the inflammatory response, in which both soluble mediator and cellular inflammatory systems are activated, follows recognition of injury.
- Termination of the inflammatory response, after generation of inflammatory agents and elimination of the foreign agent, is accomplished by specific inhibitors of the mediators.

Following injury to a tissue, changes in the structure of the vascular wall lead to the following;

- Loss of endothelial cell integrity
- Leakage of fluid and plasma components from the intravascular compartment
- Emigration of both erythrocytes and leukocytes from the interluminal space into the extravascular tissue.

Specific inflammatory mediators produced at the site of injury regulate this response of the vasculature to injury. Among these mediators are vasoactive molecules that act directly on the vasculature to increase vascular permeability. In addition, chemotactic factors are generated that recruit leukocyte tissue. Once present in tissue,recruited leukocytes secrete additional inflammatory mediators that either enhance or inhibit the inflammatory response(39-42).

Medaitors of the inflammatory response

- Histamine , Serotonin, Platelet activing factor, Bradykinin, prostaglandins

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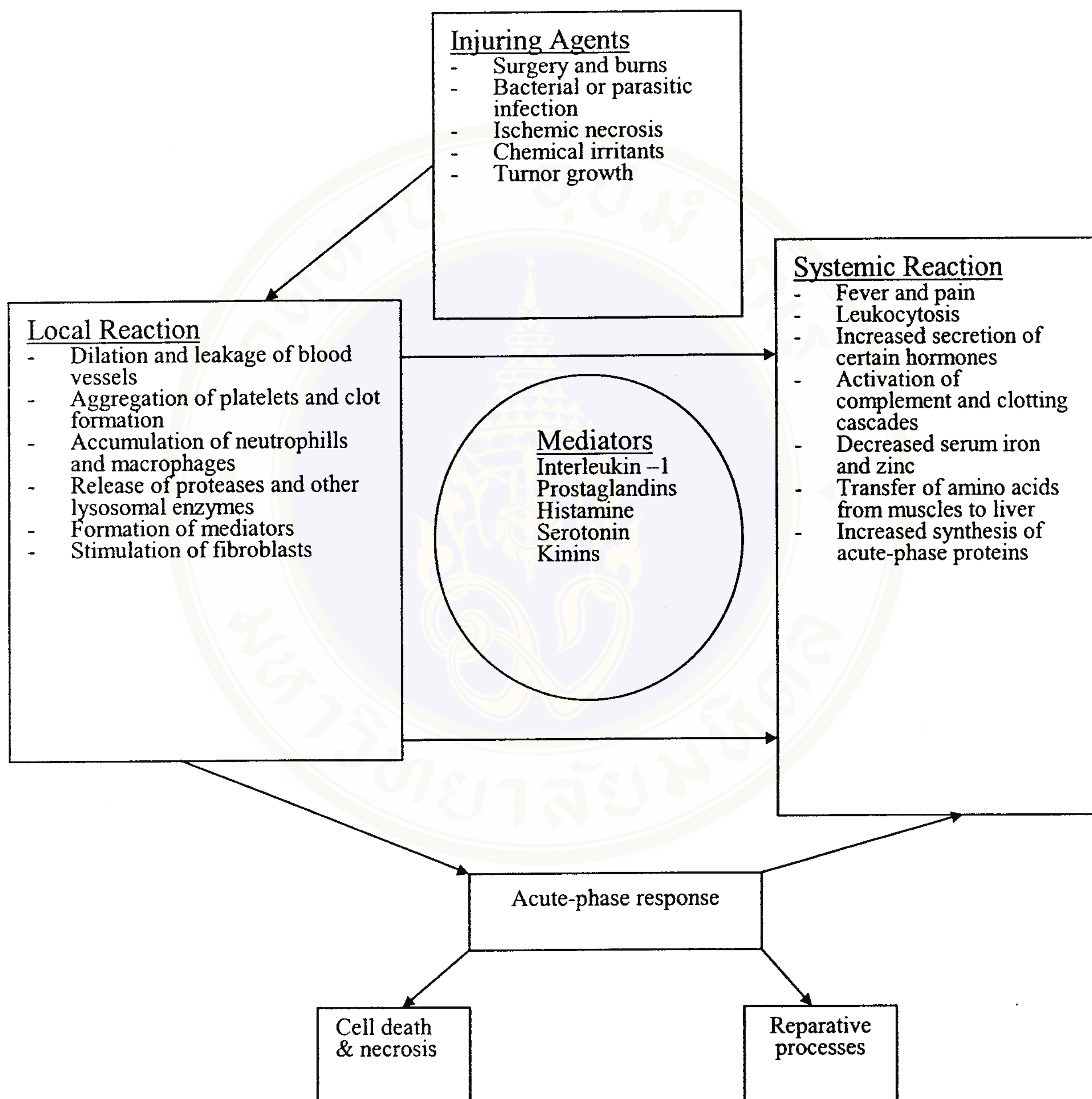
Figure 1 Development and effects of the acute phase response[44]



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Cause of Thrombophlebitis

Several factors influence the incidence of thrombophlebitis. These include site,duration of infusion, intravenous placement device, chemical and mechanical factor; pH of solution, types of solution infused, types of drug infused, osmolality of solution, rate of flow and infection (11-13).

Catheter Material and Size. The presence of a plastic catheter within the vein is contributing to all three of the classic triad of factors favoring thrombosis changes in blood flow, changes in vein wall, and changes in the blood clotting factors. The catheter interrupts the smoothness of the blood flow, producing turbulence which, in turn, may create areas of stasis. The friction of the catheter against the vein wall may damage the endothelium, exposing the collagen layer, which initiates a thrombus reaction and causes the release of histamine, producing an inflammatory reaction.

Vein Size. Considering the mechanical irritation caused by a catheter, it also seems logical that smaller veins would become irritated more easily. Peripheral veins when used for infusions will sooner or later thrombose and become inflamed. Catheters in deep veins, such as the superior venacava, decrease the likelihood of Complications because of disparity in the size of the vessel and tubing and rapid dilution of irritating solutions and activated clotting factors, however, believed the chances of infection with deep vein infusion's were greater. Despite these contradictions, no studies have been found that directly investigated the effect of different catheter sizes in different sizes.

Type of solution. Most intravenous solutions have low pH. Thus,

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solutions containing dextrose are usually of pH 3.4-5, while other solutions are around pH 5-6. Reasons given for manufacturing such acid solutions are to prevent caramellization of dextrose, and to prevent reaction with glass containers during autoclaving. Despite the flow pH, the buffering capacity of solutions is low (13). Amino acid solutions are less irritant to veins when the pH is adjusted to 7.4. A number of workers have investigated intravenous dextrose solutions. Hastbacka J Tammisito, et al (13) conducted a blind, controlled trial of dextrose solutions sterlized by autoclauing or by filtration, and found that autoclaved solutions were acid and were associated with a significantly higher incidence of intravenous thrombophlebitis than were filtered solutions of pH near neutrality . Hypertonic solutions are also irritant. Very hypertonic solutions such as aminosol and 50% dextrose can be tolerated only if given at a slow rate in large veins which have a fast blood flow. Since 1950, it has been accepted that infusion of solutions containing > 500 mOsm/KgH_2O through a peripheral vein produces thrombophlebitis so rapidly that administration of such fluids by this route is impractical. Bayer - Berger et al (8) found the incidence of phlebitis to be 48% in the first 3 days of infusion of a peripheral feed with a hyperosmolal. A retrospective study by Gagitua et al (22) found that solutions with an osmolality above 600 mOsm/KgH_2O were associated with phlebitis in all patients.

Rate of flow. It seems possible that rapid rate of flow of the infusion fluid, if directed to ward the endothelial lining, could be a source of continued slight trauma. On the other hand, a slow drip of an irritating infusion fluid is more

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damaging to the vein wall when given in a small vein that lacks ample circulating blood (12).

Duration of the infusion. Whether septic or aseptic, phlebitis seems, directly related to the length of time the catheter is left in place. Most investigators found the incidence of phlebitis higher in infusions that lasted more than 48 hours in the same vein.Collins et al (20) showed that the incidence of thrombophlebitis was 0,18,52 and 72% at 12,36,72 and > 72 hrs, respectively.

Administered drugs Antibiotics Antibiotics may also be associate with phlebitis and others routes of administration should be considered (13).Cephalosporin antibiotics have been associated with a high incidence of thrombophlebitis. Maddon RR, Rush DR, et al (15) studied the incidence and severity of thrombopflebitis associated with cefamandole, cephapirin and cephalotin, the incidence was similar for eachdrug, but phlebitis was significantly more severe with cephalothin than the other agents.

Tetracyclines added to intravenous infusions increased the risk of phlebitis (15) . Payne - James J, et al (9) found that potassium chloride ≥ 40 mEg added to infusion solution increased the risk of phlebitis.

Infection. Although any thrombus which develops around a cannula in a vein would seemingly provide an ideal site for bacterial multiplication, infection would not appear to be a major cause of phlebitis in the upper limb. If the cause were bacteria, onemight expect that antibiotic therapy would reduce the incidence of phlebitis, but there does not appear to be any study that demonstrates this. This does not exclude the possibility that phlebitis and infection may occur

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together, the infection being amenable to antibiotic therapy.

Prevention of infusion thrombophlebitis

The surest way to prevent thrombophlebitis is to avoid setting up an infusion unnecessarily. When prolonged intravenous therapy is required, it is recommended that the site of infusion need to be changed every 24 or 48 hours. However this is not always pratical in clinical pratice. Adding certain drugs to the has been shown to reduce the incidence of thrombophlebitis. LewisGB et al (13) showed a significant delay in the development of thrombophlebitis with the addition of heparin. Issacs, et al (10) added heparin 1000 u/liter 5% dextrose and reduced the incidence of phlebitis in a double-blind controlled study. Messing et al (16) also showed that the addition of heparin 1000u/liter to peripheral intravenous nutrition with an osmolality of 1130mOsm/kgH_2O decreased the percentage of patients who developed phlebitis (from 42 to 18 %) over a 48 hours period.And others study was shown that adding heparin and hydrocortisone has been shown to reduce the incidence of thrombophlebitis too . Madan, et al (14) added hydrocortisone 5 mg and heparin 500 u/liter Solution (1130 mOsm/kgH_2O) reduced the incidence of phlebitis. Maddox, et al (15) found that added hydrocortison 10 mg and heparin 1000 u/litersolution (960 mOsm/kgH_2O) decreased the incidence of phlebitis. Roongpisuthipong et al (24) showed that addition of 10 mg hydrocortisone and 500 unit heparina/liter to peripheral intravenous nutrition 860 mOsm/kgH_2O decreasedthe episode of thrombophlebitis ($P<0.004$).

In addition to adding drugs as prophylactic of thrombophlebitis,a different

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regimen was adopted by Woodhouse (25), who used a local heparin and hydrocortisone cream at the infusion site. He found that 15 of 49 control patients, compared with only eight of 48 treated patients, developed thrombophlebitis. Patients in the treatment group took longer time to develop thrombophlebitis . Eerola and potinen (18) investigated the prophylactic effect of two anticoagulant ointment, Thrombosol forte (containing heparin) and Hirudoid (containing a heparinoid). Following infusions for an average duration of 4-5 h, 21.4% of the arms with Hirudoid or Thrombosol forte treatment showed signs of thrombophlebitis. The corresponding figure in the untreated group was 25.9%.The duration of thrombophlebitis, when it developed, was shorter in the treatment group.

Prostaglandins and related compounds are involved in the process of haemostasis and thrombosis. Aspirin, indomethacin and phenylbutazone inhibit prostaglandin synthesis. Thromboxane A_2, which is synthesized by platelets and other cells, induces platelet aggregation, whereas PGI_2, which is synthesized by vascular wall cells, inhibits platelet aggregration (40, 41). Aspirin inhibits the release reaction by acetylating platelet cycloxygenase and so inhibits the synthesis of prostaglandins and thromboxane A2(27-28). Aspirin inhibits PGI synthesis by the vessel wall. The dose of aspirin required for different effects is different, so when aspirin is used as an antithrombogenic agent, the dose used may inhibit platelet prostaglandin synthesis without affecting PGI_2 formation by the vessel wall. It is now thought that the analgesic antiinflammatory actions of aspirin-like drugs are mediated via inhibition of prostaglandin biosynthesis.

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As the results, adding topical used of reparil gel and aloe vera gel has been shown to reduce the incidence of thrombophlebitis.

REPARIL® GEL

Amorphous aescin, ascin sodium polysulfate, diethyl amine salicylated(27-28).

Reparil® gel contains a triterpene glycoside, a heparinoid analgesic, is an anti- exudative/ anti-inflammatory preparation for cutaneous application.

The site of action of aescin is the vessel wall. Under condition of abnormally increased premeability, aescin inhibits exudation by reducing the outflow of fluid into the tissues and accelerating the removal of preexisting edema. Its mechanism of action is change in the premeability of the affected capillary wall openings.

Aescin enhances capillary resistance, inhibits inflammatory processes and improves the states of the microcirculation i,e., Aescin sodium polysulfate is a heparinoid, i.e., an agent with heparin-like effect.

Heparin/heparinoid Heparin is a physiologic substance. The factor inhibiting blood coagulation was called "heparin". Today it is known that heparin occurs throughout the organism. Heparinoid on the other hand is a substance synthesized according to the structure of heparin. Its chemical structure is similar but not identical, and so is its effect (weaker). The more favourable therapeutic range of heparin than that found in heparinoids results from the higher molecular weight and the lower content of sulphur. The activity of heparin is at least by 1/3 higher than that of heparinoids. This means : the same amounts of active substance provide an effect which is 33% higher for heparin or, in other words, only 2/3 of the required amount of heparinoid is needed to achieve the same effect as heparin.

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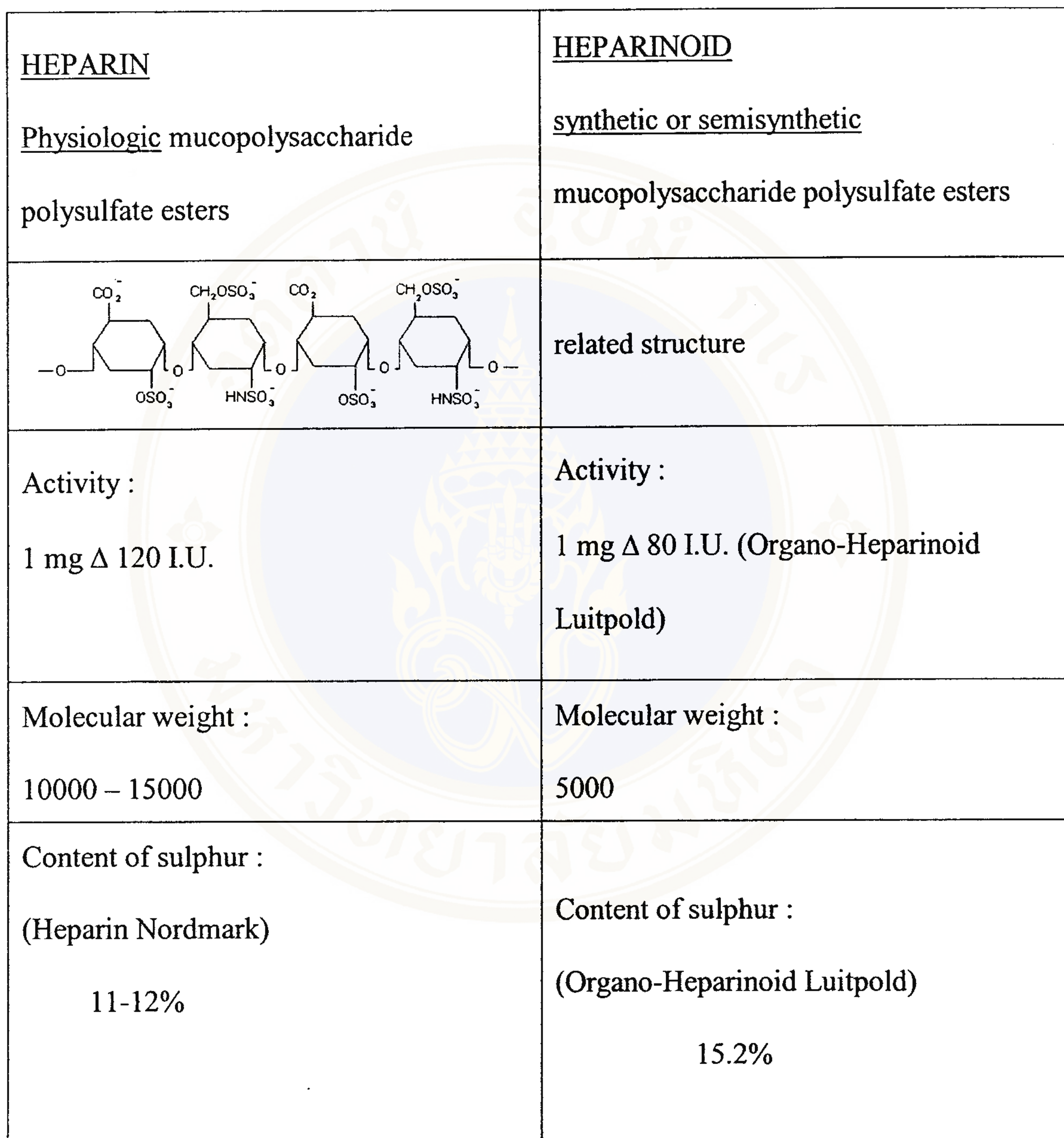
Considering the action of heparin and hepariniod into account, heparin is more favourable than hepariniod

<u>HEPARIN</u> <u>Physiologic</u> mucopolysaccharide polysulfate esters	<u>HEPARINOID</u> <u>synthetic or semisynthetic</u> mucopolysaccharide polysulfate esters
	related structure
Activity : 1 mg Δ 120 I.U.	Activity : 1 mg Δ 80 I.U. (Organo-Heparinoid Luitpold)
Molecular weight : 10000 – 15000	Molecular weight : 5000
Content of sulphur : (Heparin Nordmark) 11-12%	Content of sulphur : (Organo-Heparinoid Luitpold) 15.2%

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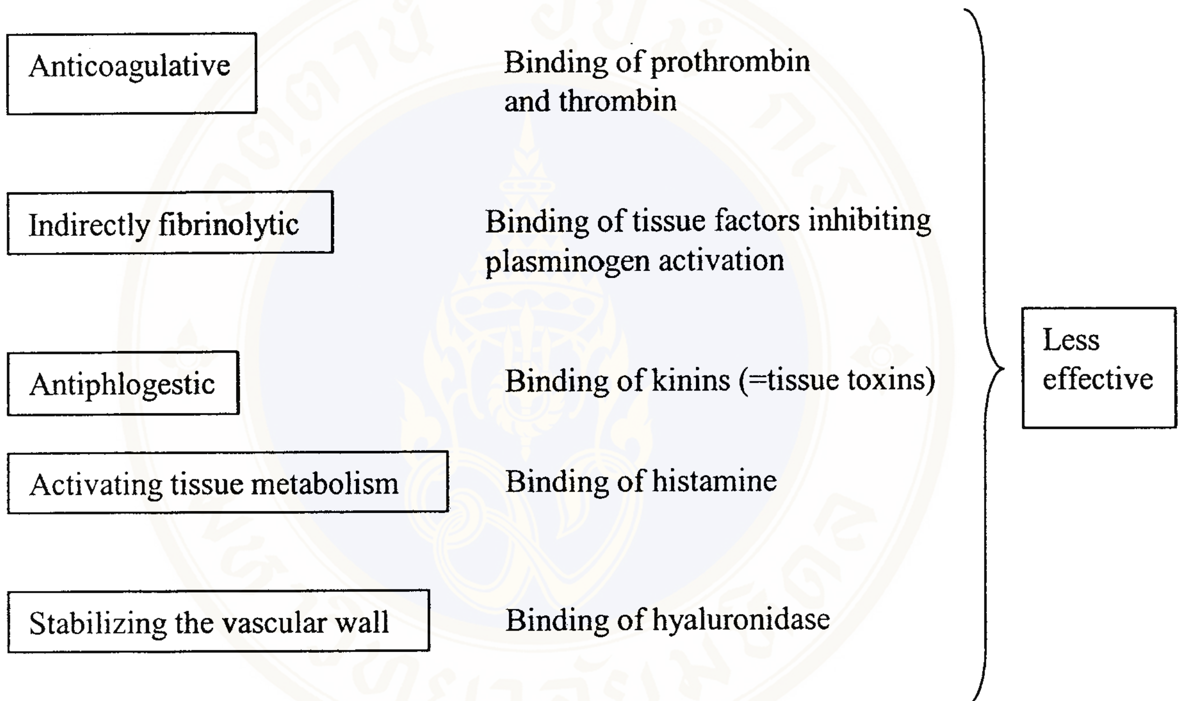
Action of Heparin and Heparinoid

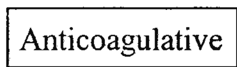
1. Blocking of alkaline protien.

Due to their acid sulphate groups, heparin and heparinoids are able to combine with alkaline proteins and thus make them ineffective.



2. Activation of an enzyme reaction

Explanations to the mode of action



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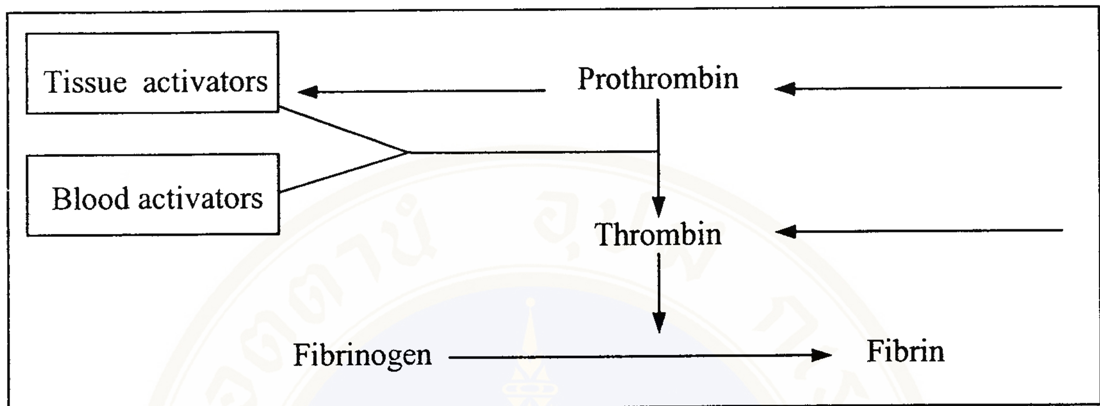
Sites of action for heparin in blood coagulation: (←———)



The decisive phase during blood coagulation is the activation of the proenzyme prothrombin which is thereby converted into thrombin. After thrombin has formed, fibrinogen is converted into fibrin, which in polymeric form represents the final stage of coagulation.

Finally, heparin and heparinoids is combined with prothrombin and thrombin,block them in their action, blood coagulation is stopped.

Indirectly fibrinogen

Fibrinolysis counteracts blood coagulation, i.e., it leads to the lysis of the polymeric fibrin. The decisive step in fibrinolysis is the activation of plasminogen which is thereby converted into plasmin. Heparin now acts indirectly fibronolytically in that it renders tissue factors ineffective which otherwise would inhibit the plasminogen activator.

Antiphlogistic

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Kinins are tissue toxins which keep up the inflammatory process. By binding thekinins, the couse of inflammation is checked.

Stabilizing the vascular walls

Histsmine whose action, among others, increase capillary permeability, is Bound and thus a stabilization of the vascular walls is achieved.

Activating tissue metabolism

Hyaluronic acid is the intercellular cement substance of the connective and supporting tissues. Hyaluronidase is an enzyme that depolymerises this substance (i.e., it converts the compound into a smaller one and thus destroys the structure of this substance). Binding of hyaluronidase and its resulting inactivation will activate tissue metabolism.

Antilipemi

Lipoprotein lipase makes absorbed fat well transportable. An activation of lipoprotein lipase promote the elimination of lipemic state or reduce fat accumution in blood.

Diethylamine salicylate (DEAS) has powerful pain relieving effects. It permeates freely through the skin and exerts it analgesic powers deep down in the affected area. This produces rapid symptomatic improvement, which in turn facilitrates the application of other therapeutic measures. The anti – inflammatory effect which DEAS also possesses, enhances the anti-inflammatory action of Reparil® gel, so that it attacks not only subjectively perceived symptoms, but also causal factors involved in the inception of the

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complaint.

Studies of transdermal absorption were performed in mice, rats and pigs by applying aescin to the skin of the back or abdomen and covering the application site with an occlusive dressing. In all 3 species, absorption (as measured by the amounts excreted within 1-2 days) was slight, amounting to only 1-3% of dose applied. However, beneath the application site and in the more deeply situated muscles, high aescin concentrations were found. For example, in pigs 24 hours after application the skin, the level of nonvolatile radioactivity in the subcutis and the underlying muscles was 50 times higher than in the blood. Thin layer chromatography showed that roughly 50% of this radioactivity was attributable to substances identical with aescin. Maximum blood levels were reached between 3 and 6 hrs after application of the gel. The aescin concentration in the tissue beneath the application site was considerably higher after transdermal application than after IV injection of the same amount, through concentrations in internal organs. Local application of aescin, therefore, produces high concentrations of active substance at the site of application, without imposing any undue load on the internal organs. Elimination takes place mainly via the bile.

Transdermal absorption of diethylamine salicylate has been studied in rats after application of the 14C-labelled substance. Maximum blood levels were reached at roughly 6 hours. Elimination of the salicylic acid and its metabolites (salicyluric aci and conjugates of both acids) takes place mainly via the kidneys (15% of the dose applied).

INDICATIONS : Painful lesions of the vertebral column (cervical disc

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syndrome, lumbago, sciatica, etc), sprains, contusions, bruises, haematomas, tenosynovitis. Varicoseveins, superficial thrombophlebitis following injections and infusions. Reparil® Gel may be used in combination with Reparil® ampoules or tablets for the treatment of serious spinal pain syndromes or post-traumatic states.

DOSAGE & ADMINISTRATION : Apply a thin layer of gel to the skin and rub overthe affected area once daily or more often. It is not essential to massage the gel into the skin, but this may be done if desired. If the skin is ulcerated, apply to the surrounding skin area only.

OVERDOSAGE : Not so far reported.

CONTRAINDICATIONS : Not to be applied to broken skin, mucous membranes or skin areas exposed to radiotherapy.

WARNING : None.

SIDE EFFECTS : Allergic skin manifestations may occur in very isolated cases.

INTERACTIONS : None so far reported.

Aloe vera (linn.) Berm. f.

The nomenclature of *Aloe vera* has been very confused, and plant has been known under various names(29-30). *Aloe barbadensis* Mill, *Aloe vera* Tourn. Ex. Linn., *Aloe* vulgaris Lamarck, *Aloe vera* N.L. (Neutan 1979) and *Aloe* perforliata. At present, he official name is *Aloe vera (L.)* Burm. f. or *Aloe barbadensis* Mill.

Botanical Description

Aloe vera (Linn.) Burm. f. or *Aloe barbadensis* Mill. Belongs to Liliaceae family.The common names of this plant are Mediterranean aloe, True aloe,

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Star cactus. Waan haang jarakhe, Waan faimai (Northern) and Haang takhe (Central). It is a short-stemmed succulent herb. The succulent leaves are crowded on the top of their stems, spreading, grayish green and glaucous; spotted when young, 20-50 cm long, 3-5cmwide at the base, tapering gradually to the point tip, 1-2.5 cm thicked; having edges spiny, and bitter latex inside. Flower borne on the upper part of a slender stalk, 50-100 cm height. The yellow perianth is divided into 6-lobes, about 2.5 cm long, with scattered small bracts. Each flower has 6 protruding stamens and 3-celled ovary with long style. Forms of the species vary in sizes of leaves and colors of flowers (30).

The epidermis of the leaves has a thick cuticle and beneath is a zone of parenchyma. The central bulk of the leaf contains the colorless mucilaginous pulp, consisting of large thin-walled mesophyll cells containing the aloe gel. Along the junction between the pulp and the parenchyma, the numerous vascular bundles are found with accompanying inner bundle sheath cells. The bundle sheath cells at the phloem poles are thin-walled and axially elongated, and contain the bitter yellow sapwhich exudes from the leaves when they are cut (29-30).

Medicinal components of the aloe leaf

The aloe leaf contains two different parts for medicinal use, the mucilage (or raw gel) and the latex(29-34).

The Aloe vera gel

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The raw aloe gel or the mucilage in the parenchyma tissue is found in the internal portion (the pulp) of the leaves of *Aloe Barbadensis* Mill. The gel firm consistency appears only in the fresh leaf. During processing and purification, the thin walled cells are disrupted and removed. The gel becomes watery and only slightly colloidal. Aloe gel is defined by the third edition of CTFA Ingredient Dictionary as… "the mucilage obtained as the juice expressed from the leaves of curacao aloe, *Aloe vera*". This transparent slippery mucilage is produced by the thin-walled tubular cells found in the inner central zone (parenchyma) of the leaf. Hair-like connective matrices may be observed in the raw gel which are somewhat reminiscent of colorless gelatin in appearance.

The *Aloe vera* gel normally does not contain anthraquinone or anthroglycoside except it may be contaminated in trace amounts. The raw unpreserved gel contains approximately 0.5% solids and 99.5% water and has a pH of 4 to 5. The solids are composed mainly of carbohydrates and proteins. The carbohydrate constituents can be categorized as monosaccharides (e.g. glucose, mannose, arabinose, galactose andxylose), polysaccharides (e.g. glucomannan, cellulose, hemicellulose, dextrin, starch and pentose) and glycosides which are sugar that are condensed with non sugar material.
A large number of amino acids, pro-vitamins and minerals and enzymes such asbradykininase, carboxypeptidase, catalase, amylase and oxidase are present in *Aloe vera* gel. Certain triterpenoid and steroid are also identified in the *Aloe vera* gel.

At least four different partially acetyled glucomannans are thought to be responsible for producing the thick, stringy mucilage – like properties

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that are characteristic of the raw *Aloe vera* gel. When these glucomannans are subjected to hydrolysis, viscosity of the gel is reduced.

Fresh *Aloe vera* gel is unstable. The mucilagenous (gel like) properties of the fresh parenchyma "pulp" are slowly lost after exposure to air and light with subsequent discoloration which progressed from pinkish to purplish and finally to brown. Anthraquinones has been suggested as the cause of discoloration. Enzymatric degradation and micro-biological decomposition are probable causative processes of thefresh *Aloe vera* gel instability phenomenon. Hence, after the leaves of the plants are cut, they should be stored in a darkly chilled place to maintain their aerobic respiration to allow the continuation of the carbohydrate and the organic acid metabolism inside the leaf and also continuation of forming the protective coating which hinders microbial .

The mineral are also found in the *Also vera* gel. Ten elements are quantitatively detected (ppm); Ai, B, Ca, Fe, Mg, Mn, Na, P and Sr. It is showed that *Aloe vera* belongs to a group of calcium-rich vegetables, which contain a little more magnesium, phosphorus and sodium.

Fatty acids such as lauric acid, myristic acid, pentadecanoic acid, palmitoleic acid,palmitic acid, stearic acid arachidonic acid are identified in the acetone extract of the *Aloe vera* gel. The acetone fraction also consists of dehydroabietic acid derivatives.The *Aloe vera* gel also contains glycoprotein, aloctin A and aloctin B. Aloctin Aand Aloctin B are peptides having molecular weight of 18000 and 24000, respectively. Aloctin A composes of two peptide subunits of 10500 and 75000. Aloctin B composes of two subunits each of 12000Aloctin A has been reported to

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have several bioactivities including immunomodulation, mitogenic for lymphocyte and binding human alpha 2 macroglobulin, antiinflammatory activity, antitumor activity, antiulcer, and inhibition of gastric secretion and gastric lesion.

The *Aloe vera* latex

The *Aloe vera* latex (Aloe sap or Aloe leaf exudate) is the bitter yellow liquid contained in the pericyclic cells of the rind, a principal constituent of which is aloin. The compounds found in the *Aloe vera* latex are composed of 3 major groups of chemicals; namely, anthracene derivatives, phenolic compounds (which comprise chromone derivatives and derivatives of 6-phenylpyran -2-one) The anthrancene derivatives can be divided into anthraquinones, anthranols and anthrones. A number of anthraquinones have been recognized both in the free state and as glycosides. Free anthraquinones seem to be present at low levels in aloes and are more prominent in various bound forms. Aloe-emodin is typical of and widespread in the genus. It was estimated that the total aloe-emodin released from leaf eluates following hydrolysis was only about 10-14% and present as the free anthraquinone. Glycosylated anthraquinone structure with C-glycosidic bonds from plant resources have been described more frequently than those with O-glycosidic bonds perhaps because of their medicinal properties and the occurrence in well-known plant drugs. Barbaloin (aloin) is the main anthraquinone-derived constituent of commercial bitter aloes and its structure has been shown to be that of a C-glycoside of aloe-emodin anthrone.

Pharmacological activities of *Aloe vera*

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The aloe species possesses a variety of biological effects. The *Aloe vera*

gel and latex show many physiological activities as follow.

Healing effect

Aloe vera has been recognized as a good medicine for the treatment of thermal and radiation burns. There are many factors in the gel involves in the healing activity. The watery composition has been shown to increase themigration of epithelial cell for the improvement of wound healing. *Aloe vera* improves healing with tissue regeneration by dilating capillaries to increase blood flow to injured area providing the more oxygen available for collagen formation by fibroblasts. Natural substances contained in *Aloe vera* such as enzymes, amino acids, vitamin C, vitamin E and Zinc arethe important ingredients necessary for wound healing. Acemanan, an acetylated β the wound healing by two mechanism. First, it is a potent macrophage-activation agent and may thereforestimulate the release of fibrogenic cytokines. Alternatively, growth factors may bind directly to acemannan, promoting their stability and possibly prolonging theirstimulating effects on granulation tissue formation.

Aloe has been also to inhibit thromboxane A_2 (a potent vasoconstrictor) synthesisat the injury tissue and maintain a homeoatasis within the vascular endothelium as well as the suronding tissue.

Antiinflammatory activity

Aloe extract and aloe gel exhibited antiinflammatory activity. Topical preparation of aloe when given to the rabbits every 6 hours showed the blockade of thromboxane production. The activity was increased when the combination of topical preparation of *Aloe vera* (Linn.)Burm f., methimazole (1 mg/kg) were used.

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Aloe was proved to be effective for a treatment of fracture in guinea pig forelimb-injuries. Aloe preparation of decolorized and colorized aloe were tested for antiinflammatory activity. The results indicated the decolorized aloe preparation gave better activity than colorized aloe preparation which contained anthraquinones. Aloe showed antiinflammatory in diabetic rats and gave a similar results to gibberellin, therefore the active compound may be gibberellin like substance. Many active compounds, aloetic bradykininase anthraquinone, aloe gel, a loctin A, aloctin B were isolated. Aloe gel was proved to be effective against inflammation via the inhibition of prostaglandin synthesis. Eventhough anthraquinones in latex exhibited antiiflammatory activity aloin and 1,8 dioxyanthraquinone increased prostaglandin formation of colon tissue. Therefore it is likely that the compounds responsible for the activity of *Aloe vera* (Linn.) Burm f. are restored in the gel part. Aloctin A, a glycoprotein isolated from aloe gel consisted of 2 subunits with molecular weight 7500 and 10,500 was proved to inhibit prostaglandin synthesis. Aloctin A when intravenously injected to rats at the dose of 50 mg/kg showed antiinflammatory activity via inhibition of PGE_2 synthesis from arachidonic via cycloxygenase. It has been suggested that, its activity to decrease the number of neutrophils migration into the peritoneal cavitty. This potential to reduce carrageenan-induced edema.

Bradykininase in aloe gel may play an important role in antiinflammatory activity.This enzyme destroys bradykinin, the tissue hormone responsible for vasodilation, inflammation and pain. Since this enzyme is carboxypeptidase, it can convert the angiotensin I to angiotensin II, the vasopressor. Therefore

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both bradykinin and angiotensin II were decreased and the inflammation was inhibited. Moreover, angiotensin II stimulates adrenal gland to excrete steroids, aldosterone which caninhibit inflammation and decrease edema(32).

Magnesium lactate isolated from aloe, inhibits the formation of histamine from histidine in the mast cells of lungs, liver and gastric mucosa. Histamine is a potent vasodilator. Therefore magnesium lactate is effective against inflammation via this machanism. All these finding led to the conclusion that the possible mechanism of antiinflammatory of aloe gel is due to the activities of bradykininase, magnesium lactate and aloctin A (33).

Many clinical uses of aloe has been reported as follows. *Aloe vera* (Linn.) Burm f. soaked polyethylene oxide gel dressings were used in three patients with chronic osteoma cutis secondary to acne vulgaris who were treated with the dermabrasion Loo-punch-excision technique. After treatment only a few small residue blue "dot" lesions remained. Wound healing acceleration was shown when stabilized aloe gel was used for the treatment of full face dermabrasion. Experimental ischemia by classical frostbite rabbit ear model clearly defined the role of thromboxane as a mediator of progressive dermal ischemia in frostbite injuries. *Aloe vera* (Linn.) Burm f. showed 28.2% tissue survival while methimazole, aspirin and methylprednisolone showed 34.3, 22.5 and 17.5% respectively. Later topical antiiflammatory activity of *Aloe vera* (Linn.)Burm f. measured by ear swelling was reported. Frostbite was treated successfully using aloe cream to combat local vasoconstrictive effects of thromboxane and oral administration of ibuprofen to decrease systemic levels of

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thromboxane. Aloe was used topically with ribonucleic acid and vitamin C on adjuvant arthritis. An ointment containing levomycetin, methyluracil, and aloe extract was used in plastic operation with transplantation of free flaps of the mucosa or skin. In USSR, aloe was used for treatment of chronic inflammation diseases of the internal female genitalia of nonspecific etiology. *Aloe vera* (Linn.) Burm f. was also useful for the treatment periodontosis due to its antiiflammatory activity. It was effective for first and second stages of gingivitis.[34] Aloe was effective in the treatment of periodontosis and its influence on the phosphorus-calcium metabolism. *Aloe vera* (Linn.) Burm f. is also recommended for dental care. Later, the experiment showed that *Aloe vera* (Linn.) Burm f. was a good vehicle for hydrocortisone, it enhanced the antiinflammator activity of cortisone.

Antihistaminic activity

The antihistaminic compounds of aloe are aloe ulcin and aloin, which isolated from aloe latex. They have an inhibitory effect on aromatic amino acid decarboxylase and on histidine decarboxylase, a histamine synthesizing enzyme. However, there was a report on histamine stimulating activity of anthraquinones.

Toxicity assessment

Toxicity studies were carried out on both latex and gel of aloe leaves. The toxicsymptoms were observed when aloe extract or anthraquinone portion were tested. High dose of anthraquinone depressed respiration, decreased blood pressure and stimulated heart rate. Aloe extract produced chronic inflammatory condition in genitals and the connective tissue are hypertrophy in rabbits.

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The toxicity of anthraquinones was observed in jaundice patient. One patient

receiving the drug composed of aloe, rhubarb and sennadied after administration. The autopsy showed the destruction of liver, kidney, heart and lungs. Intravenous injection of aloin in dog at the dose of 0.10-0.12 g/kg caused a marked rise in body temperature for 24 hours. During the rise of fever, increase in gas exchange, urea excretion and accumulation of uric acid in some organs, were observed. The cathartic portion of aloe may cause hypokalemic metabolic alkalosis. Oral administration of lyophilized aloe gel at the dose 0, 1, 4, 16 and 64 mg/100g body weight, twice a day, in rats showed only slight adversed effect on kidneys and liver.[32] Allergic symptoms of aloe were reported in 31 years old woman who had been given 1 ml of aloe subcutaneous. Feeling of tightness of chest, loss of breath, vomitting, seizures, vertigo and loss of conciousness, were observed. However she has a history of allergic tendency. Contact dermatitis of aloe was reported in 66 years old male patient. The allergic symptoms may be due to histamine releasing activity. Widespread dermatitis was reported when aloe was used in chronic leg ulcers and stasis dermatitis. Aloe extract showed allergic symptoms in animal experiment. The allergic symptom was alsoreported when an aloe juice was administered to the nose. Three women and one man aged forty-one to sixty-five years experienced a severe burning sensation following the application of *Aloe vera* (Linn.) Burm. f. that had been subjected to a chemical peel or dermabrasion. Anaphylactic shock after aloe injection was reported in USSR. However, contrary result was reported.

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CHAPTER III

MATERIALS AND METHOD

We were unaware of any reported effect osmolality of PPN solutionand effect of *Aloe vera* gel, Raparil® gel and control on peripheral thrombophlebitis of a hyperosmolal, before starting experimental design, a preliminary study was done to determine appropriate osmolality of PPN ,dose of Aloe vera gel and population size.

Thus, in this study has 2 Parts;

<u>Part I</u> Preliminary study [Period from November 1999 to February 2000]

<u>Part II</u> Experimental period [Period from March 2000 to February 2001]

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Part 1

Preliminary study

There are 3 objectiv in this study

1. Determine appropriate Osmolality and pH of PPN solution
2. Determine appropriate dose of Aloe vera gel for part 2
3. Determine appropriate population size for part 2

1. Determine appropriate Osmolality and pH of PPN solution

There are many PPN solution used in surgical ward for example;

- 10% D/N/2 1000ml+OMV I 1 amp+Addamel 1 amp iv rate 80 cc/hr with 10% Aminosol 500ml iv rate 20 cc/h
- 10% D/N/2 1000ml+vitamin B complex 1 amp iv rate 80 cc/hr with 10% Aminosol 500ml iv rate 20 cc/hr
- 10% D/N/2 1000ml iv rate 80 cc/hr with 10% Aminosol 500ml iv rate 20 cc/hr
- Vitrimix 1000 ml iv rate 80 cc/hr

Some solution was add electrolyte, vitamin ,OMVI , and Addamel. We unknown the osmolality and pH of PPN solutuon,thus we determine appropriate as the following;

Tools and method

1. Determination of osmolality is conducted with Micro-osmometer,
2. PPN solution formular

- 10% D/N/2 1000ml+OMV I 1 amp+Addamel 1 amp iv rate 80cc/hr with 10% Aminosol 500ml iv rate 20 cc/hr

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- 10% D/N/2 1000ml+vitamin B complex 1 amp iv rate 80 cc/hr with 10% Aminosol 500ml iv rate 20 cc/hr
- 10% D/N/2 1000ml iv rate 80 cc/hr with 10% Aminosol 500ml iv rate 20 cc/hr
- Vitrimix 1000ml iv rate 80 cc/hr

3. Determination of pH solution from research office floor 8 , Ramathibodi Hospital.

After started PPN canulation ordered by physical 1 ml of PPN solution was drawed for determine osmolality and sent 1ml at research office floor 8 for determination pH solution.

method

1. Moisten the end of a Chamber Cleaner with distilled water, insert it firmly into the Sample port, rotate two or three times, and withdraw. Follow with a dry Chamber Cleaner to dry out the sample chamber. This procedure will assure a clean chamber. Leave the Chamber Cleaner in place until ready for sample insertion.
2. Secure a 3MO825 20-Microliter Sample and a quantity of Disposable Sample Cells and Chamber Cleaners (reorder these together as a 3MA800 Micro-Sample Kit as needed). Mount one sample cell firmly on the sampler.
3. Carefully open an ampule of Clinitrol™-M 290 mOsm/kgH_2O Reference Solution.
4. Firmly depress the sampler plunger, insert the tip of the mounted sample cell into the ampule about ¼" below the fluid surface and release the plunger to load a 20-ul sample.
5. Remove the sample cell from the ampule and blot the barrel with absorbent

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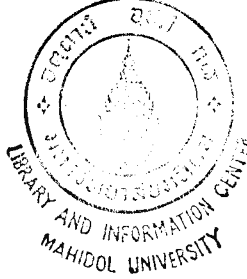
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tissue so that fluid does not extend *beyond* the end of the tip. Be careful not to wick out the sample. The fluid meniscus can be slightly concave.

6. Remove the Chamber from the Sample port and discard.
7. Holding the sample by its triangular plastic grip, insert the filled tip of the sample cell all the way into the Sample port until it comes to a positive stop. DO NOT push it in by the plunger handle and DO NOT attempt to inject the sample into the chamber. DO NOT remove the Sample until the test has been completed. The sample osmolality is measured on the sample inside the tip of the sample cell itself.
8. Press the Start button. If the instrument displays "Please calibrate osmometer."

There is nothing more for the operator to do during the test because the Advanced Micro-Osmometer is fully automatic. When the test is complete, the instrument will lock the reading onto the display where it will remain until the next test or the instrument is shut off.

If the Start button is pressed while a test is in progress, the test will be discontinued and the 3MO will reset itself for the next test.

9. Remove the Sampler from the Sample port after the display reads Osmalality XXX mOsm.
10. Firmly insert a clean chamber cleaner into the Sample port, rotate it 2-3 times and leave it in place until the next sample is to be inserted.
11. With the Sampler out of the instrument, press down hard enough on its plunger handle to dislodge the used sample cell. Remove and discard the sample cell.

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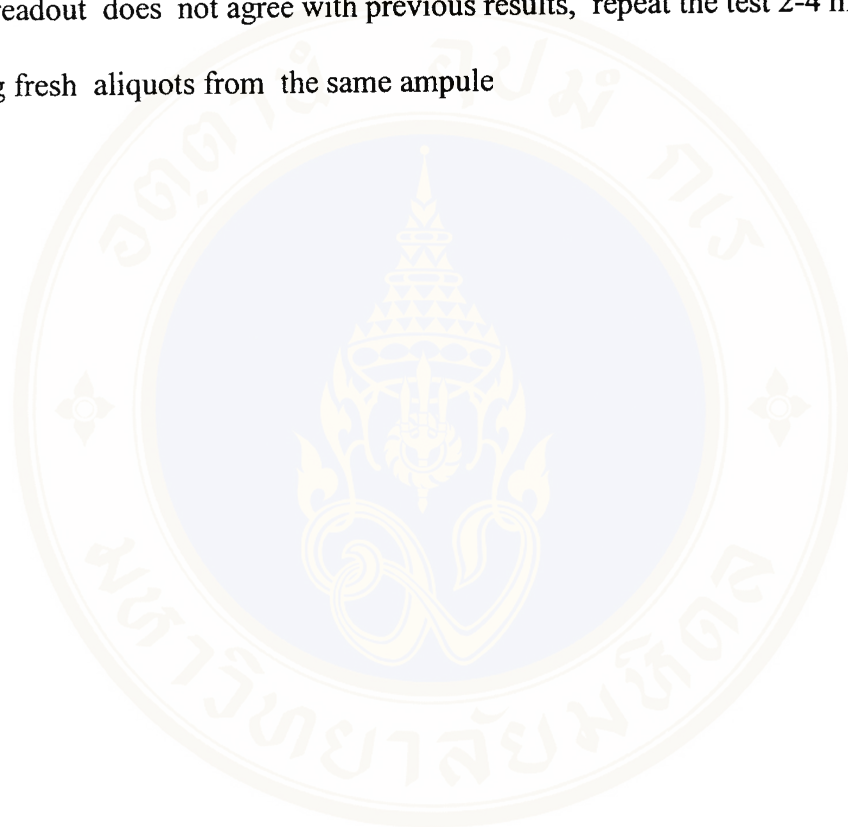
12. Blot the teflon plunger with a lint-free tissue and install a fresh disposable

137494 18

sample cell. You are now ready to run the next test. Depending upon how the readout from the just-completed test compares with previous reading, proceed as follow:

13. If you have no previous results on Clintrol™-M 290 Reference Solution or the readout does not agree with previous results, repeat the test 2-4 more times using fresh aliquots from the same ampule



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Result

Table 1 Caloric value, osmolality and pH of the PPN solution administered to patients were shown;

PPN solution	Caloric value (kcal/day)	Osmolality (mOsm/kgH_2O)	pH
1.10% D/N/2 1000ml + OMVI 1 amp + Addamel 1 amp v 80 cc/hr 10% Aminosol 500 ml v 20 cc/hr	1192	950	6.21
2.10% D/N/2 1000ml +VitaminB 1 amp v 80 cc/hr+10% Aminosol 500 ml v 20 cc/hr	1192	921	6.21
3. 10% D/N/2 1000ml 80cc/hr +10% Aminosol 500 ml v 20 cc/hr	1192	938	6.24
4. Vitrimix 1000ml v 80cc/hr	1000	1100	6.8

Most of the PPN formular used in surgical wards were 10% D/N/2 1000ml + OMVI 1 amp + Addamel 1 amp v 80 cc/hr 10% Aminosol 500 ml v 20 cc/hr which concentration osmolality was 950(mOsm/kgH_2O), pH 6.21. Thus used this formular for the study.

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2. Determine appropriate dose of Aloe vera gel for part 2

Aloe vera (Linn.) Burm. f. has been recognized as one of valuable medicinal plants. It has therapeutic abilities to penetrate tissue, inflammatory ,killbacteria, fungi and viruses, dilate capillaries and enhance blood flow However, no one has studied about effect of *Aloe vera* gel on peripheral thrombophlebitis Thus, we were study the effect of varies concentration *Aloe vera* gel reducing thrombophlebitis and selected the best used in part 2 study.

Material and method

The Subjects of the study were patients (male and female patients), aged 16-80 years old who had been treated with PPN solution, admitted in surgical wards, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, during the period of November 1999 to February 2000. They were selected by purposive sampling according to the following criterias:

Inclusion criteria

1. Subjects received PPN osmolality about 950 mOsm/kgH_2O, pH 6-7, via peripheral vein by using jellco No 22.
2. Subjects were able to receive PPN rate $\leq$ 100 cc/hr on the dorsal of the forearm or hand at least 24 hrs.
3. Subjects gave be consent to participate and follow the procedure of this study.

Exclusive criteria

1. Subjects have a disease that may effect normal peripheral venous during this study, for example, Cardiovascular disease.
2. Subjects receive chemotherapy treatment.

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3. Subjects received anticoagulant, anti-inflammatory, and vasodilator

After subjects consented to participate in the study, the 75 catheters , (with CA Esophagus, Cholangio CA, CA stomach, Pancreatitis, Peritonitis, and UGI bleed patients) were randomly assigned into 5 groups [15 catheters per group].Then each group was randomly assigned to receive one of the following treatment which are; Aloe vera gel dose A, Aloe vera gel dose B, Aloe vera gel dose C, Aloe vera gel dose D, Aloe vera gel dose E(They are different concentration each dose;Aloe vera gel from the British dispensary (L.P.)Co., Ltd.

All treatments were contained in code boxes, one box being randomly allocated to each catheter. The Double blind randomization was carried out independently and was stratified to avoid between group discrepancy in the male: female ratio. All treatments (see table 2) were applied distal to the canulation site, replaced, and recorded during the infusion followed the protocol.

Table 2 Details of treatments in each group

Group	No of catheter	Treatment
1	15	Aloe vera gel dose A
2	15	Aloe vera gel dose B
3	15	Aloe vera gel dose C
4	15	Aloe vera gel dose D
5	15	Aloe vera gel dose E

The details of procedures were received to subjects and health care providers. 10 Nurses from surgery wards who administer PPN and provide routine care to subjects were be trained 1 month to achieve standardization as follows

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1. PPN preparation, and catheter insertion

After application of an elastic tourniquet, a suitable vein was selected on the dorsal or volar surface of the forearm or hand, a 22-gauze plastic needle was inserted into the vein after disinfecting the site with 70% alcohol or betadine solution, immediately after start the PPN canulation, nurses applied distal to the canulation site, 10cm of gel by a rural from the instrument office center of Ramathibodi Hospital; There are no different from rurals . The gel containing 0.3 ml gel; used syring drawed) was extruded and rubbed into the skin with the applicators supplied, replaced every 8 hrs: at 6, 14, 22 o'clock. [Appendix C]

2. Data collection

Researcher trained nurses to recorded the thrombophlebitis data record sheet which includes data, PPN starting time, position of infusion (e.g., Rt and Lt site, pain redness, swelling, induration, leak or clot. [Appendix B]

Data was recorded every 8 hrs at 6, 14, 22 o'clock. After 40 hrs, researcher collected the data and evaluated degree of thrombophlebitis according to Maddox's criteria. [Appendix D]

3. Each infusion was continued until infiltration or local tissue reaction occur after the first infusion was discontinued, the next infusion catheter was inserted through the vein of the other forearm. If the needle was removed because infusate infiltrated the tissue within 1 hr after placing the needle, it would be excluded from the study.

4. The population number was identified numbers of inserted catheter.

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Data analysis

1. All data was analyzed by SPSS 7.5 for windows

2. Degree of thrombophlebitis was determined in score, as follows.

   Degree 0 was 0 score [no pain]

   Degree 1 was 1 score [pain,no erythema]

   Degree 2 was 2 scores[pain,erythema, but no induration]

   Degree > 3 was 3 scores[pain,erythema, and induration]

   This reported have shown no data have degree 3 from Maddox's criteria

3. Data of thrombophlebitis are presented as mean ± SD

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RESULTS

There are nothing more for error to do: applicating ,recording by nurses during the Study because the nurses be achieved to standardization

Table 3 Percentage of application and data recording during trained standardization

Nurse	Application [% correction]		Data record [% correction]
	0.3ml gel	10 cms lenght	
1	100%	100%	100%
2	100%	100%	100%
3	98%	100%	100%
4	99%	100%	100%
5	99%	100%	100%
6	100	100%	100%
7	100	100%	100%
8	99%	100%	100%
9	100%	100%	100%
10	100%	100%	100%

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Table 4 Degree of thrombophlebitis in Aloe vera gel dose A.

Degree of thrombophlebitis	Duration of experimental (hr)					
	0	8	16	24	32	40
0	15	15	9	6	3	1
1	0	0	6	4	3	5
2	0	0	0	5	9	3
≥3	0	0	0	0	0	6
Mean	0	0	0.4	0.93	1.4	1.93
± SD	0	0	0.5	0.88	0.82	1.03

Table 5 Degree of thrombophlebitis in Aloe vera gel dose B.

Degree of thrombophlebitis	Duration of experimental (hr)					
	0	8	16	24	32	40
0	15	15	10	6	5	2
1	0	0	65	4	4	4
2	0	0	0	5	6	3
≥3	0	0	0	0	0	6
Mean	0	0	0.33	0.93	1.066	1.866
± SD	0	0	0.48	0.88	0.88	1.12

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Table 6 Degree of thrombophlebitis in Aloe vera gel dose C.

Degree of thrombophlebitis	Duration of experimental (hr)					
	0	8	16	24	32	40
0	15	15	7	4	1	0
1	0	0	8	4	6	3
2	0	0	0	7	8	4
≥3	0	0	0	0	0	8
Mean	0	0	0.53	1.2	1.46	2.33
± SD	0	0	0.516	0.86	0.63	0.81

Table 7 Degree of thrombophlebitis in Aloe vera gel dose D.

Degree of thrombophlebitis	Duration of experimental (hr)					
	0	8	16	24	32	40
0	15	15	6	3	0	0
1	0	0	9	5	3	0
2	0	0	0	7	12	7
≥3	0	0	0	0	0	8
Mean	0	0	0.6	1.26	1.8	2.53
± SD	0	0	0.51	0.79	0.41	0.51

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Table 8 Degree of thrombophlebitis in Aloe vera gel dose E.

Degree of Thrombophlebitis	Duration of experimental (n)					
	0	8	16	24	32	40
0	15	15	11	9	5	3
1	0	0	4	2	6	2
2	0	0	0	4	4	6
≥ 3	0	0	0	0	0	4
Mean	0	0	0.26	0.66	0.93	1.73
± SD	0	0	0.45	0.89	0.79	1.10

Table 9 Degree of thrombophlebitis in Aloe vera gel (dose A-E) at 40 hrs.

Degree of thrombophlebitis	Aloe vera gel				
	Dose A	Dose B	Dose C	Dose D	Dose E
0	1	2	0	0	3
1	5	4	0	3	2
2	3	3	7	4	6
≥3	6	6	8	8	4
Mean	1.93	1.866	2.53*	2.33	1.73*
± SD	±1.03	±1.12	±0.51	±0.81	±1.10

*Significant difference between degree of thrombophlebitis during experiment of Aloe vera dose Dand dose E (P<0.05)

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The results of study showed that the group applying *Aloe vera* gel dose E had the least degree of thrombophlebitis at 40 hrs study . ANOVA test showed that the thrombophlebitis of catheter applying *Aloe vera* gel dose E was significantly lesser than *Aloe vera* gel dose D (P=0.024) and trend to lesser than *Aloe vera* gel dose A, B, and C. So, *Aloe vera* gel dose E was selected for the experimental part [part 2] (see table6-10)

Concentration of *Aloe vera* gel dose A-E from The British dispensary L.P. Co., Ltd. There was 95% of *Aloe* in *Aloe vera* gel dose A

There was 85% of *Aloe* in *Aloe vera* gel dose B

There was 75% of *Aloe* in *Aloe vera* gel dose C

There was 50% of *Aloe* in *Aloe vera* gel dose D

There was 100% of *Aloe* in *Aloe vera* gel dose E

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3. Determine appropriate population size for part 2

Sample size calculation

Sample size was estimated from mean independent 2 groups model. From formula

$$N_1 = \frac{2(Z_{1-B} + Z_{\alpha})^2 S^2}{d^2}$$

N_1 = Sample size that estimated from effect of Aloe vera gel dose E and no drug on thrombophlebitis in PPN osmolality about 950 mOsm/kgH_2O at 40 hr.

$$N_2 = \frac{2(Z_{1-B} + Z_{\alpha})^2 S^2}{d^2}$$

N_2 = Sample size that estimated from effect of Reparil gel and no drug on thrombophlebitis in PPN osmolality about 950 mOsm/kgH_2O 40 hr.

1-B = power of sample size = 90%

α = two-sided significant level

S^2 = Variance determined from $[(SD_1+SD_2)/2]^2$

SD_1 = Standard deviation (treatment1)

SD_2 = Standard deviation (treatment2)

d = Mean difference between group

Z_1-B = 1.96

Z_{α} = 1.2

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Because we were unaware of any seported effect of Reparil® gel , resercher must be study effect of Reparil® gel , and control on thrombophlebitis for mean and SD used for calculate size.

Tools and instruments

1. Inclusion and exclusion criteria of subjects were the same as determination of Aloe *vera* gel

2. PPN solution; osmolality about 950 mOsm/kgH_2O, pH 6-7; 10% D/N/2 1000 ml+ OMVI 1 amp + Addamal 80 cc/hr and 10% Aminosal 500 cc i.v. 20 cc/hr

3. Drugs treatment for this study, Reparil gel and control drug

- [Reparil® gel from Greater pharma Ltd., part under licences of Madaus Ag., D_51101 Koln 91, Germany

4. Thrombophlebitis data recorded sheet [Appendix B]

5. Guildline for thrombophlebitis evaluation; Maddox's criteria [Appendix D]

Method of study

After subjects consented to participate in the study, the 30 catheters (with CA Esophagus, Cholangio CA, CA stomach, Pancreatitis, Peritonitis, and UGI bleed patients) were randomly assigned into 7 groups [15 catheters per group] (clinical data of subject was shown in Table). Then each group was randomly assigned to receive one of the following treatment which are; Reparil® gel and (control group).

All treatments were contained in code boxes, one box being randomly allocated to each catheter. The Double blind randomization was carried out independently and was stratified to avoid between group discrepancy in the male: female ratio. All treatments (see table 12) were applied distal to the

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canulation site, replaced, and recorded during the infusion followed the protocol.

Table 10 Details of treatments in each group

Group	No of catheter	Treatment
1	15	Reparil® gel
2	15	Control

After application of an elastic tourniquet, a suitable vein was selected on the dorsal or volar surface of the forearm or hand. A 22-gauge plastic needle was inserted into the vein after disinfecting the site with 70% alcohol or Betadine® solution, immediately after start the PPN canulation, The standardization nurses applied distal to the canulation site, 10 cm of gel [containing 0.3 ml gel; use syring drawed] was extruded and rubbed into the skin with the applicators supplied, replaced every 8hrs; at 6, 14, 22 o'clock. The time for the progression of thrombophlebitis was observed by eyes. Nurses recorded the data and time each infusion was started, location of infusion (e.g., Rt and Lt site), and finding at the infusion site (e.g., pain redness, swelling, induration along the vein, leak or clot). Data were recorded every 8 hrs during the infusion; at 6, 14, 22 o'clock. After 40 hrs, researcher collected the date and evaluated degree of thrombophlebitis according to Maddox's criteria. Each infusion was continued until it had to be stopped because of infiltration or local tissue reaction. After the first infusion was discontinued the next infusion catheter was inserted into a vein on the other forearm. If a needle was removed because infusate infiltrated the tissue within 1 hour after placing the needle, it was considered improper placement of the needle and would be excluded from the study.

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Data analysis

1. All data was analyzed by using SPSS 7.5 for windows
2. Degree of thrombophlebitis was determined in score, as follows.

   Degree 0 was 0 score[no pain]

   Degree 1 was 1 score [pain,no erythema]

   Degree 2 was 2 scores[pain,erythema, but no induration]

   Degree > 3 was 3 scores[pain,erythema, and induration]

   This reported have shown no data have degree 3 from Maddox's criteria
3. Data of thrombophlebitis are presented as mean ± SD

Results

Table 11 Demographic data of patients (N=135 catheters);control, Reparil gel,and Aloe vera gel dose A-E

Clinical data	Mean ± SD
Age (yrs)	46.8 ± 13.1
Height (cms)	156 ± 6.6
Weight (cms)	49.4 ± 5.6
BMI (kg/m^2)	20.3 ± 7.1
Serum albumin(g/ dl)	30.57 ± 4.5

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Table 12 Degree of thrombophlebitis Reparil® gel

Degree of thrombophlebitis	Time (hrs)					
	0	8	16	24	32	40
0	15	15	9	8	3	1
1	0	0	6	2	5	3
2	0	0	0	5	7	7
≥3	0	0	0	0	0	4
Mean	0	0	0.4	0.8	1.26	1.93
± SD	0	0	0.507	0.94	0.79	0.88

Table 13 Degree of thrombophlebitis of control group

Degree of thrombophlebitis	Time (hrs)					
	0	8	16	24	32	40
0	15	15	6	4	0	0
1	0	0	9	3	4	0
2	0	0	0	8	11	7
≥3	0	0	0	0	0	48
Mean	0	0	0.6	1.26	1.73	2.53
± SD	0	0	0.5	0.8	0.45	0.52

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Calculated N1: Aloe vera gel and control [used mean and SD at 40 hr study]

Formula

$$N_1 = \frac{2(Z_{1-B} + Z_\alpha)^2 S^2}{d^2}$$

$$= \frac{2(1.96 + 1.282)^2 \left(\frac{0.52 + 1.10}{2}\right)^2}{(2.53 - 2.73)^2}$$

$$= \frac{2(3.242)^2 (0.81)^2}{(0.8)^2}$$

$$= \frac{2(10.51)(0.656)}{(0.64)}$$

$$= 21.5 \approx 22 \text{ catheters}$$

Calculated N_2 : Reparil® gel and control [used mean and SD at 40 hr study]

Formula

$$N_2 = \frac{2(Z_{1-B} + Z_\alpha)^2 S^2}{d^2}$$

$$= \frac{2(1.96 + 1.282)^2 \left(\frac{0.52 + 0.88}{2}\right)^2}{(2.53 - 1.93)^2}$$

$$= \frac{2(3.242)^2 (0.81)^2}{(0.8)^2}$$

$$= 28.6 \approx 29 \text{ catheters}$$

Therefore, sample size should be used in this study was equal to 29 or 30 catheters for each group.In clinical ward the population were probably excluded during study, 50% of 30 catheter was added in each group, thus the experimental design had 30+(50% x 30) = 45 catheters in each group

- Total population size for study effect of Aloe vera gel,Reparil® gel and control on thrombophlebitis of a hyperosmolal = 45 x 3 = 135 catheters

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Part II

Experimental design

The Subjects of the study were patients (male and female patients), aged 16-80 years old who had been treated with PPN solution, admitted in surgical wards, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, during the period of November 1999 to February 2001. They were selected by purposive sampling according to the following criterias:

Inclusion criteria

1. Subjects received PPN osmolality about 950 mOsm/kgH_2O, pH 6-7, via peripheral vein by using jellco No 22.
2. Subjects were able to receive PPN rate ≤ 100 cc/hr on the dorsal of the forearm or hand at least 24 hrs.
3. Subjects gave be consent to participate and follow the procedure of this study.

Exclusive criteria

1. Subjects have a disease that may effect normal peripheral venous during this study, for example, Cardiovascular disease.
2. Subjects receive chemotherapy treatment.
3. Subjects received anticoagulant, anti-inflammatory, and vasodilator

After obtaining consent, the 135 catheters (99 patients; 50 males and 49 females with CA Esophagus, Cholangio CA, CA stomach, CA head of pancrease Pancreatitis, Peritonitis, UGI bleeding and Gut obstruction patients) were randomly assigned into 3 groups {45 catheters per group} Then each group was randomly assigned to receive one of the following treatment which are; Aloe vera

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gel dose E, Reparil® gel, and control group.

All treatment were contained in code boxes, one box being randomly allocated to each catheter. The double blind randomization was carried out independently and was stratified to avoid between group discrepancy in the male : female ratio. All treatments were applied distal to the canulation site, replaced and recorded during the infusion the same as preliminary study according the protocol.

Method (the same as preliminary study)

After application of an elastic tourniquet, a suitable vein was selected on the dorsal or volar surface of the forearm or hand. A 22-gauze plastic needle was inserted into the vein after disinfecting the site with 70% alcohol or Betadine® solution, immediately after start the PPN canulation, nurses applied distal to the canulation site; 10 cm of gel (containing 0.3 ml gel) was extruded and rubbed into the skin with the applicators supplied, replaced every 8 hrs; at 6, 14, 22 o'clock. The time for the progression of thrombophlebitis was observed by eyes. Nurses recorded the data and time after each infusion was started, location of infusion (e.g., Rt and Lt site), and finding at the infusion site (e.g., pain redness, swelling, induration along the vein, leak or clot). Data were recorded every 8 hrs during the infusion; at 6, 14, 22 o'clock. After 40 hrs, researcher collected the data and evaluated degree of thrombophlebitis according to Maddox's criteria.Each infusion was continued until it had to be stopped because of infiltration or local tissue reaction. After the first infusion was discontinued, the next infusion catheter was inserted into a vein on the other forearm. If a needle was removed because infusate infiltrated the

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tissue within 1 hr after placing the needle, it was considered improper placement of the needle and would be excluded from the study.

Data Analysis

1. The evalution of thrombophlebitis at each time was shown in mean ± SD
2. All data was analyzed by using by SPSS 7.5 for windows which is presented in mean ± SD (the same as in preliminary study)

   Degree of thrombophlebitis was determined score

   Degree 0 was 0 score [no pain]

   Degree 1 was 1 score [pain,no erythema]

   Degree 2 was 2 scores[pain,erythema, but no induration]

   Degree > 3 was 3 scores[pain,erythema, and induration]

3 The comparison thrombophlebitis of control group, Reparil® gel group and Aloe vera in during time of experiment were analyzed by ANOVA statistic analysis; 95% confident limit was chosen for statistical significant.

4. Used Q-square test comparison number /reason for stoped IV catheters between group.

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CHAPTER IV

RESULTS

The total catheter for this study were 45 catheters (99 patients; 50 males and 49 females), consisted of 45 cancer patients (13 CA Esophagus, 12 CA Lung, 10 CA Stomach, 10 CA Head of pancrease), 14 Pancreatitis, 14 UGI Bleeding, 14 UGI Obstruction, and 12 of Peritonitis. (see table 15) They were equally divided into three groups (45 catheters each group), each group was assigned to receive one of the following applie which are control (no drug), Aloe vera and Reparil® gel group. The indications for intravenous nutrition are shown in table 15. There were no difference in sex, weight, ages, BMI and serum albumin between control, Reparil® gel and Aloe vera gel group (as shown in table 17, 18) PPN formular was_10% D/N/2 1000ml + Addamel 1 amp + OMVI 1 amp iv rate 80 ml/hr with 10% Aminosol 500 ml iv rate 20 ml/hr, pH 6.21 ,osmolality was 950 mOsm/kgH_2O.There were 1 degree of thrombophlebitis in every group at 16 hrs study (table 21-23). Episodes and severity of thrombophlebitis had highly significant correration with longer infusion in all group, $p< 0.05$ (table 24-25). Reparil® gel group and *Aloe vera* gel group had decreased episode and severity of thrombophlebitis and lesser than control group respectively, $p< 0.05$.At 40 hrs of prolonged catheter, was found that *Aloe vera* gel group had significant least thrombophlebitis than other , $p< 0.05$(table 24-25).

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Table 14 Indications for peripheral intravenous nutrition

Condition	Number of patients			
	Control	Reparil® gel	Aloe vera	Total
CA Esophagus	4	5	4	13
Cholangio CA	6	3	3	12
CA stomuch	4	4	2	10
CA head of pancrease	3	3	4	10
Pancreatitis	4	5	5	14
UGI Bleeding	4	4	6	14
UGI Bobstruction	4	5	5	14
Peritonitis	4	4	4	12
Total	33	33	33	99

Table 15 Number of patients

Sex	Experiment		
	Group 1 (Control)	Group 2 (Reparil® Gel)	Group 3 (Aloe vera)
Male	16	17	17
Female	17	16	16
Total	33	33	33

Non significant difference between groups by x^2 test

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Table 16 Demographic data of patients (N=145 cetheters)

Clinical data	Experimental		
	Group 1 (Control)	Group 2 (Reparil® Gel)	Group 3 (Aloe vera)
Age (yrs.)	46.8±13.1	47.3±14.4	45.3±13.4
Height (cms.)	156.9±6.6	156±4.5	156±7.3
Weight (kgs.)	51.4±5.8	53.1±4.6	52.7±4.9
BMI (Kg /m2)	20.8±7.07	21.2±2.5	21.0±0.9
Serum albumin g/dl	35.57±4.1	36.78±4.1	37.12±4.4

Non significant difference between groups by ANOVA test

Table 17 Caloric value, osmolality and pH of the PPN solution administered to patients were shown;

PPN solution	Caloric value (kcal/day)	Osmolality (mOsm/kgH_2O)	pH
10% D/N/2 1000ml + OMVI 1 amp + Addamel 1 amp v 80 cc/hr 10% Aminosol 500 ml v 20 cc/hr	1192	950	6.21

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Table 18 Reasons for stopping intravenous infusion (each group = 45 catheters)

Reason	Experiment		
	Group 1 (Control)	Group 2 (Reparil® Gel)	Group 3 (Aloe vera)
Fluid leak	11	10	11
Clot	4	5	4
Discharge from hospital	2	2	3

Non significant difference between groups by x^2 test

Table 19 Number of catheters stratified according to degree of thrombophlebitis in control group(group 1)

Degree of Thrombophlebitis	Duration of experiment (hrs)					
	0	8	16	24	32	40
0	45	45	20	9	0	0
1	0	0	25	16	15	0
2	0	0	0	20	30	17
≥3	0	0	0	0	0	28

Degree 0 was no pain , degree 1 was pain,no erythema, degree 2 was pain,erythema, but no induration and degree 3was pain,erythema, induration

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Table 20 Number of catheters stratified according to degree of thrombophlebitis in Reparil® gel group (group 2)

Degree of Thrombophlebitis	Duration of experiment (hrs)					
	0	8	16	24	32	40
0	45	45	29	21	10	6
1	0	0	16	9	13	11
2	0	0	0	15	21	12
≥3	0	0	0	0	0	16

Degree 0 was no pain , degree 1 was pain,no erythema, degree 2 was pain,erythema, but no induration and degree 3was pain,erythema, induration

Table 21 Number of catheters stratified according to degree of thrombophlebitis in Aloe vera gel group(group 3)

Degree of Thrombophlebitis	Duration of experiment (hrs)					
	0	8	16	24	32	40
0	45	45	32	22	18	14
1	0	0	13	23	12	13
2	0	0	0	0	15	10
≥3	0	0	0	0	0	8

Degree 0 was no pain , degree 1 was pain,no erythema, degree 2 was pain,erythema, but no induration and degree 3was pain,erythema, induration

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Table 22 Mean degree of thrombophlebitis during 40 hrs. in experiment group comparing 3 group(Mean±SD) , ANOVA test

Time (hrs.)	Experiment		
	Control	Reparil® gel	Aloe vera
0	0± 0	0± 0	0± 0
8	0± 0	0± 0	0± 0
16	a 0.56± 0.5	a 0.35± 0.48	a 0.29± 0.45
24	a ,b 1.38± 0.78	a ,b 0.88± 0.88	a ,b 0.73± 0.88
32	a, b, c 1.67± 0.47	a, b, c 1.27± 0.8	a, b, 0.97± 0.83
40	a, b, c,d,e 2.56± 0.62	a, b, c,d,e 1.95± 0.95	a, b,c,e 1.26± 1.09

a; Significant difference from 0,8 hr at the same group, $p< 0.05$
Significant difference among group at 16 hr , $p< 0.05$
b ; Significant difference from 16 hr at the same group, $p< 0.05$
Significant difference among group at 24 hr ,$p< 0.05$
c ; Significant difference from 24 hr at the same group, $p< 0.05$
Significant difference among group at 32 hr , $p< 0.05$
d ; Significant difference from 32 hr at the same group, $p< 0.05$
e ; Significant difference among group at 40 hr , $p< 0.05$

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* Degree 0 was no pain , degree 1 was pain,no erythema, degree 2 was pain,erythema, but no induration and degree 3was pain,erythema, induration

Table 23 Number and percentage of thrombophlebitis patients

(each group = 45 catheters, comparing 3 group) , by x^2 test

Time (hrs)	Experiment		
	Control	Reparil® gel	Aloe vera
0	0	0	0
8	0	0	0
16	a 25 (55.5%)	a 16 (35%)	a 13 (28.8%)
24	a,b 36 (80%)	a,b 25 (53.5%)	a,b 23 (51.1%)
32	a,b,c 45 (100%)	a,b,c 35 (77.7%)	a,b, 27 (60%)
40	a,b,c,d.e 45 (100%)	a,b,c,d,e 38 (84.6%)	a,b,c,e 31 (68.6%)

a; Significant difference from 0,8 hrs at the same group, $p< 0.05$
Significant difference among group at 16 hr , $p< 0.05$

b ; Significant difference from 16 hsr at the same group, $p< 0.05$
Significant difference among group at 24 hr ,$p< 0.05$

c ; Significant difference from 24 hrs at the same group, $p< 0.05$
Significant difference among group at 32 hr , $p< 0.05$

d ; Significant difference from 32 hrs at the same group, $p< 0.05$
e ; Significant difference among group at 40 hr , $p< 0.05$

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Table 24 Graph mean of thrombophlebitis at 16 hrs. in experiment group comparing 3 group

Mean at 16hrs

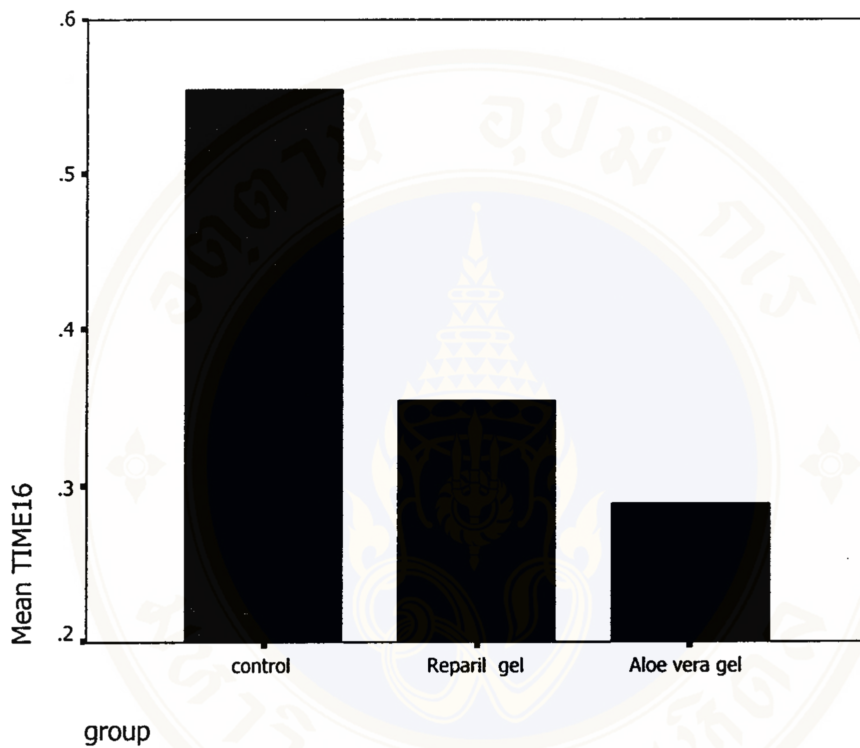

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Table 25 Graph mean of thrombophlebitis at 24 hrs. in experiment group comparing 3 group

Mean at 24 hrs

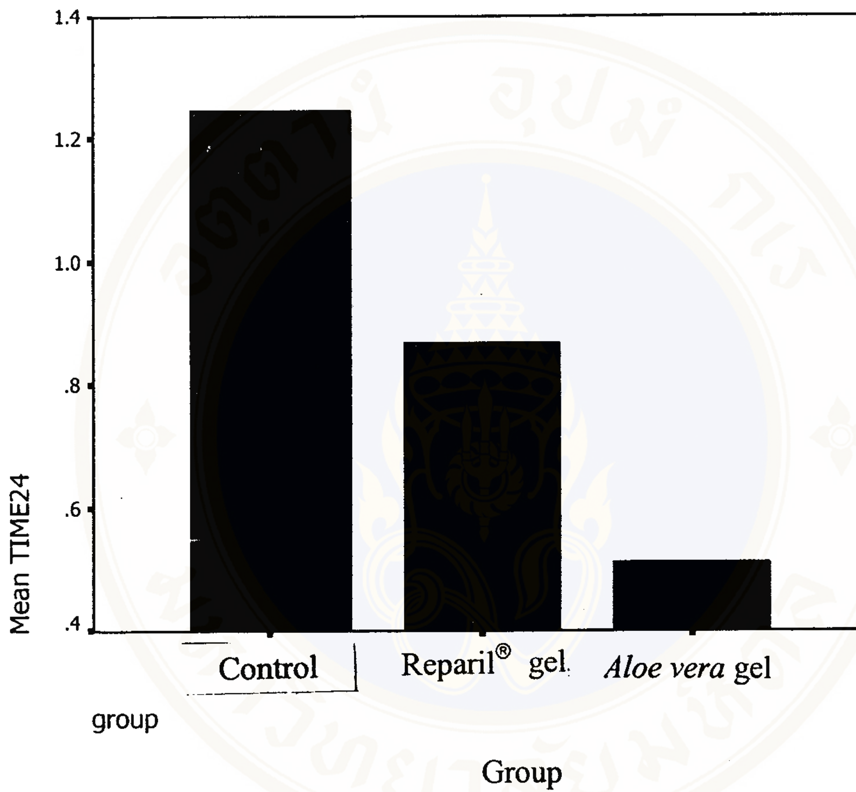

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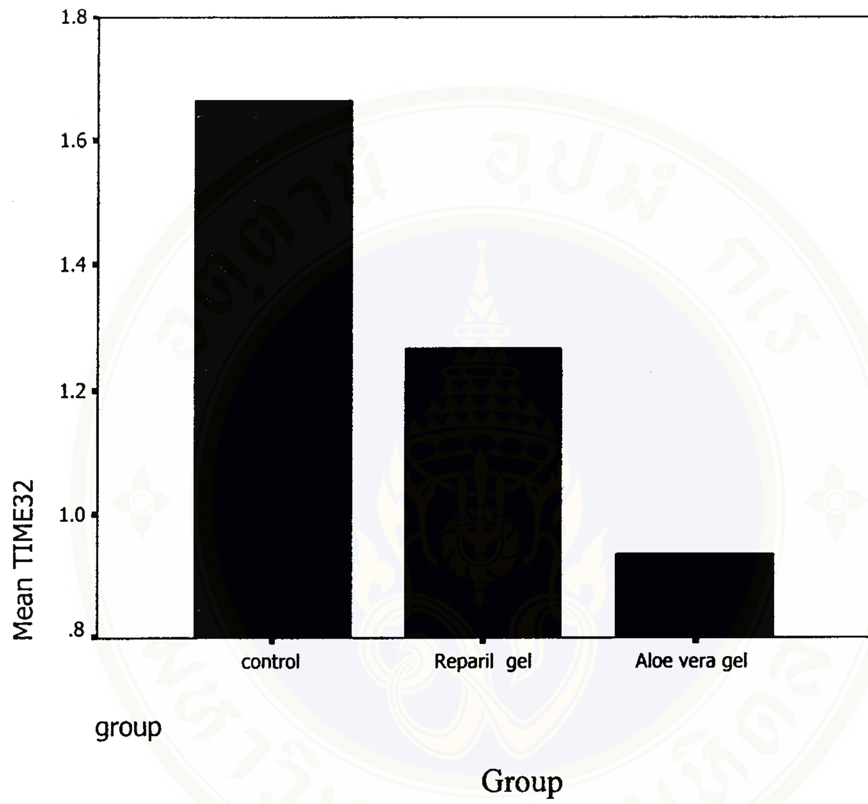
Table 26 Graph mean of thrombophlebitis at 32 hrs. in experiment group comparing 3 group

Mean at 32 hrs



Group

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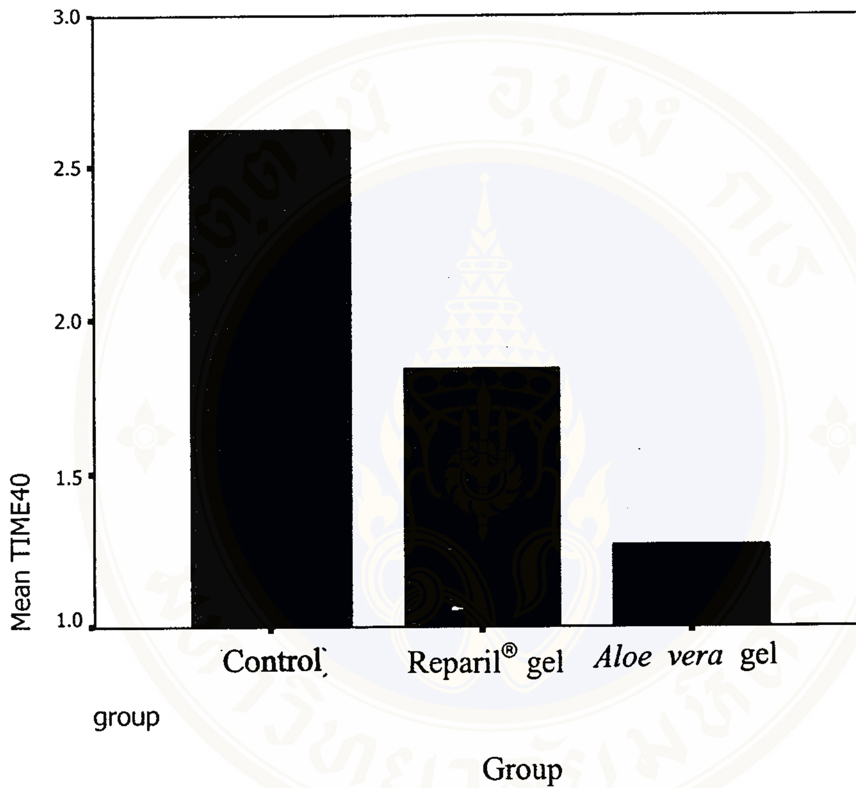
Table 27 Graph mean degree of thrombophlebitis at 40 hrs. in experiment group comparing 3 group

Mean at 40 hrs



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CHAPTER V

DISCUSSION

Adequate nutrition is essential to maintain normal function, growth and healing. Many hospitalized patients cannot maintain optimal nutrient intake, a significant incidence (25-54%) of protein calorie malnutrition was documented from many surveys of surgical inpatients (1,2).

Unquestionably, profound malnutrition cause growth retardation and lowered resistance of infection, with marked effects on cellular immunity and increased mortality, particularly among infants, and the elderly.Malnutrition is associated with slower healing. More complications, higher morbidity and mortality rates, longer length of hospital stay, and higher health care costs. In fact, health professionals agree : Good nutrition helps keep people healthy and speeds recovery when they are sick or injured, promotes vitality and independence; and scientific evidence indicates people with good nutritional status have shorter hospital stays and fewer and less costly complications(4).

Nutrition assessment, as covered in the previous publictions[6], incorporates screening, clinical data, dietary data, anthropometric data, and biochemical data along with additional questions about eating habits, living environment, and functional status. There is no simple one indicator or set of data that can be used to assesses nutritional status. Several type of data must be used.

The peripheral route of infusion for parenteral nutrition is easier and less expensive and less serious complication (e.g., pneumothorax, thoracic duct injury,

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it has been advocated for short term nutritional support(7). The energy requirementof the surgical patients without sepsis is 1500 – 2000 kcal/day, and the daily nitrogen requirement is ~ 8.5 g.[8] The provision of 6.5g., 7.5g., of nitrogen with 1400 kcal by peripheral intravenous infusion helps to reduce a large negative energy and nitrogen balance and thus lesson the detrimental effect of prolonged fasting until oral feeding is recommended(8).

The populations in the study were similar, as based on serum albumin (35.57 ± 4.1 vs 36.78 ± 4.1 vs 37.12 ± 4.4) and body mass index (BMI) (20.8 ± 7.07 & 21.2 ± 2.5& 21.2 ± 0.9).This suggest that 8.5g nitrogen of PPN solution was able to provide satisfactory nutritive support, many help to reduce a large negative energy and nitrogen balance, that mean adequate nutrition for maintain normal function, growth and healing.

The main disadvantage of peripheral intravenous is thrombophlebitis, thought to be influenced by the osmolality, composition of nutritive infusion (drugs, potassium, acidity of fluid, concentration of dextrose), size and material of the needle or cannula, duration of infusion and whether a venous dilator patch is used(10-13).

Since 1950, it has been accepted that infusion of solution containing > 500 mOsm/kgH_2O through a peripheral vein produces thrombophlebitis so rapidly that administration of such fluids by this route is impractical. Clinical studies carried out by Bayer-Berger et al (8) demonstrated that hypertonic solutions greater than 802 mOsm/kgH_2O, were associated with a high rate of thrombophlebitis (48% in 3 days), while a retrospective study by Gazitua, et al(21) found that peripheral venous nutrition containing glucose and amino acid through the

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use of hyperosmolal solution (600 to 1200 mOsm/kgH_2O) usually results in high rate of peripheral venous complications, often greater than 59% of case, however the incidence of thrombophlebitis in this study may be an effect of osmolality.

The highly significant correlation between longer infusions and the incidence of thrombophlebitis was also expected from the literature reviewed, the result followed Hastback (11) results in the group from 24 to 48 hrs. Lewis GB et al(13) showed that the incidence of thrombophlebitis was 0, 18, 52 and 72% at 12, 36, 72 and >72hr, respectively. Such results have prompted some investigations to suggest that the cannula should be changed every 8, 12 or 24 hr, However this practice is distressing for the patient and time consuming

The composition of the catheter is another factor which may be important in the genesis of thrombophlebitis, Madan et al (14) have shown that catheters manufactured from silicone or teflon cannulae , position of catheter at dorsal or forearm results in a low level of complication, with differing cannulae while the osmalality of the feed is kept constant, Inclusioncannulating a vein with a small bore cannulae (22G) manufactured, as in this study, would be expected to results in a low incidence of thrombophlebitis(21).

Considering solutions of low pH are associated with the significantly higher incidence of intravenous thrombophlebitis than solution of pH near neutral(<6.5 – 7.5), PPN solutions of this study have pH < 6.21 that near neutral, suggested that these solutions results in a low level of complication too.

Several regimens have been suggested for prophylaxis, including addtion of steroids and/or heparin to the infusate, topical application of each therapeutic agent

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at the venipuncture site such as glyceryl trinitrate 5 mg, anticoagulation cream (Thromo.gel). These topical cream have been recommended to reduce the incidence of thrombophlebbitis (25). Eerola et al (18) showed that the incidence of thrombophlebitis fell from 53% in the control group to 8.3% in the study group by the addition of 1000 U of heparin to post–operative intravenous fluids. Messing et al (16) have also shown that the addition of heparin (1000 U/L) to PPN, with osmolality of 1730 mosmol/kgH_2O, resulted in a fall in the percentage of patients who developed phlebitis over a 48 hr period. (from 61% in control group to 21% in the study group).

The clinical practice, concentrated solutions and irritant drug are given via central rather than peripheral veins because of the greater blood flow in central veins rapidly dilutes the infusate and removes the irritant, therefore the concept of increasing blood flow in peripheral veins in appealing and may reduce the development of infusion thrombophlebitis. *Aloe vera gel* and Reparil® gel have therapeutic abilities to penatrate tissue, dilate capillaries and enhance blood flow. These potentials would be helpful in preventing thrombophlebitis. John P et al (30) showed that topical application of *Aloe vera* gel, is more specific anti – thromboxane agents and could reverse progressive tissue in the partially damaged tissue. Vazgues et al(34) also showed that Aloe vera gel acts as an antiinflammatoryagent via the inhibitory action of arachidonic acid – cycloxygenase pathway. It has been shown to stimulate synthesis of prostacyclin by cultured human endothelial cell(31-33), that is a potent inhibitor of platelet aggregation and is synthesized in vascular walls by prostaglandin endoperoxides. It has been suggested that, following vascular injury, endothelial

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damage could reduce prostacyclin synthesis, resulting in regional vasoconstriction. The potent vasoconstrictor thromboxane A_2 then produced by aggregating platelets in the damaged area. Prostacyclin, which also relaxs smooth muscle cells in vein walls, may be produced in increased amounts by surrounding undamaged endothelial cell, indicated that topical *Aloe vera* gel at infusion site vein may help to relax smooth muscle cell and prevent venoconstriction and platelet aggregation, there by possibly reducing the incidence of thrombophlebitis(34). The effect of Reparil® gel may reduce the incidence of thrombophlebitis by delaying the formation of fibrin clot around the tip of an intravenous needle dwelling in the vein for 24 hr(27-28). Results of this study also showed that, at 16 hr period, the thrombophlebitis catheterapplying *Aloe vera* gel was significantly less than control group after that at 24, 32, and 40 hr period, the thrombophlebitis catheter applying both *Aloe vera* gel and Reparil® gel group were significantly less than control group, respectivly. But the frequency of fluid leak, clot and discharge from the hospital in 3 regimens were similar, suggested that application of *Aloe vera* gel and Repail® gel only reduce the incidence of thrombophlehitis, but *Aloe vera* gel may decrease thrombophlebitis faster than Reparil® gel.

While the increase in the duration of infusion related to the decrease of thrombophlebitis, this study showed that at 40 hrs period the thrombophlebitis catheter applying *Aloe vera* gel was significantly less than Reparil® gel, this possibly mean that after prolonged 40 hrs period infusion, *Aloe vera* gel had more active antiinflammatory action than Reparil® gel.

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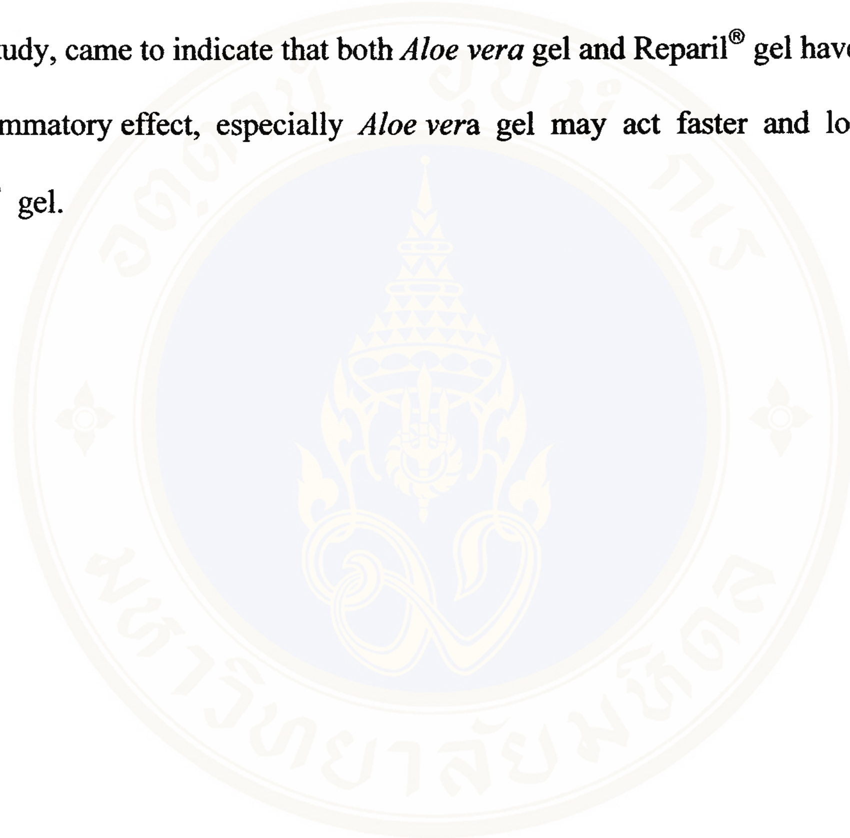
In summary, application *Aloe vera* gel and Reparil® gel both showed an Inhibitory effect of thrombophlebitis. The effect of *Aloe vera* gel was suggested to be an inhibitory action on arachidonic acid pathway via cycloxygenase but Reparil® gel was suggested to delay the formation of fibrin clot. Based on the results of this study, came to indicate that both *Aloe vera* gel and Reparil® gel have potential antiinflammatory effect, especially *Aloe vera* gel may act faster and longer than Reparil® gel.



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CHAPTER VI

CONCLUSSION

In conclusion, this study has shown that osmolality of infusion PPN about 950 mOsm/KgH_2O containing 10% D/N/2 and 10%Aminosol (ratio by volume 2 : 1) is a major factor in the causation of thrombophlebitis. There was highly significant correlation between longer infusion thrombophlebitis and infusion of the PPN. However, these thrombophlebitis could be reduced by topical application of Aloe vera gel and Reparil®gel into the skin with the applicator supplied, respectively. After 40 hr prolong catheter, Aloe vera gel had the least thrombophlebitis than Reparil® gel. Possibly, Aloe vera gel may be the best agent to be used for the prevention of thrombophlebitis.

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Appendix A

OSMOMETER

A. INSTRUMENTION

Freezing-point osmometers are devices for the extremely precise determination of the concentration of solutions by means of freezing-point measurement. They can routinely determine differences of 2 mOsm/kgH_2O[48]

These instruments basically consist of :

1. The means to carefully control the cooling and freezing of small samples.
2. An extremely sensitive electronic thermometer for the measurement and display of the freezing points of these samples.

B. FREEZING-POINT THERMODYNAMICS

What is meant by "freezing point" in osmometry and cryoscopy is that unique temperature, at atmospheric pressure, at which the solid and liquid phases of a substance will co-exist in equilibrium. For the solutions under consideration, this temperature is not only unique but simple to determine with extreme precision because, unlike the other colligative properties such as vapor pressure, isolation of the sample from the environment is inherent in the ice blanket generated when the sample freezes.

The quickest and most precise way to measure the freezing point of a solution is to supercool it several degrees below its freezing point and then mechanically induce the sample to freeze. The heat of fusion suddenly liberated causes the sample temperature to rise toward a plateau wherein an ice/water equilibrium is maintained. This equilibrium temperature is, by definition, the freezing point of

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solution. The osmometer utilizes a thermister probe in order to sense the sample temperature, to control the degree of supercooling and freeze induction, and to measure the freezing point of the sample.

The time over which phase equilibrium develops is a function of the temperature differential between the sample and its environment and the ability of the surrounding materials to conduct heat. The cooling of the sample should be rapid but not so fast that supercooling is uncontrolled. If the probe and/or sample cell are much warmer than the sample, heat will flow from them to the sample and distort the freezing curve.

The probe senses the temperature in the same cell. Because the probe sees only a small portion of the sample space, it is important that the sample temperature be uniform. If the tip of the probe is not positioned repeatably from sample to sample or if there are gradients in the freezing, the precision of the measurement may suffer.

Optimum precision by this method results from a carefully engineered instrument that assures proper probe/sample alignment and uniform cooling for each sample. Fully automatic operation minimizes imprecision due to operator technique.

C. PHYSICAL PRINCIPLES OF FREEZING-POINT OSMOMETRY

When a solute is dissolved in a pure solvent, the following properties of the solvent are changed:

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1. The freezing point is depressed.

2. The boiling point raised.

3. The osmotic pressure is increased.

4. The vapor pressure is lowered.

These are the so-called colligative properties of the solvent and, within reasonable limits, change indirect proportion to the solute concentration the *number* of particles in solution.

The proportionality constant is characteristic of the particular solvent. For water, one gram-mole (Avogadro's number) of non-ionizing solute dissolved in one kilogram of water will depress the freezing point by 1.858 °C. If the solute does dissociate, then all ionized and undissociated species must be counted.

D. DEFINITIONS

Solution. A homogeneous mixture of solute and solvent where:

1. The **solvent** is the major component;

2. The **solute** is the minor component.

Concentration. The amount of solute in a given amount of solvent. The amount of solute is usually expressed in terms of moles, i.e. gram molecular weight. Recall that one mole= 6.02×10^{23} molecules (Avogardo's number). Thus, one mole of glucose (180.2 g) and one mole of sodium chloride (58.4 g) both contain Avogadro's number of molecules. Common units of concentration are:

Molarity : moles of solute per liter of solution (temperature dependent).*

Molality : moles of solute per kilogram of pure solvent (temperature independent).

One **osmol** is defined as Avogadro's number of **particles**. Thus, one mole of glucose is also one osmol. If one mole of NaCl were to completely

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dissociate, then 2 osmols of particles would be produced : 1 mole of Na^+ and 1 mole of Cl^-. Common units of concentration are: **Osmolarity** : osmols of solute particles per liter of solution (temperature dependent).

Osmolality : osmols of solute particles per kilogram of pure solven (temperature independent).

One milliosmol (mOsm) is 10^{-3} osmols.

In reality, most ionic solutes do not completely dissociate so one should more completely define osmolality as:

Osmolality = osmols/kgH_2O = $\phi(n)(C)$, where:

ϕ = the osmotic coefficient, which accounts for the degree of molecular dissociation.

n = the number of particles into which a molecular can dissociate.

C = the molal concentration of the solution.

Freezing Point. The temperature at which the liquid and crystalline phases of a substance will remain together in equilibrium.

Freezing Point Depression. When a solute is added to a solvent, the freezing point of the solvent is lowered. In aqueous solutions, one milliosmol of solute per kilogram of water depress the freezing point by 1.858 millidegrees Celsius (m°C).

Supercooling. The tendency of a substance to remain in the liquid state when cooled below its freezing point.

Crystallization Temperature. Aqueous solutions can be induced to freeze (i.e. crystallize) most reliably when supercooled. Crystal formation is induced by

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agitating the solution (freeze pulse). Heat of fusion is liberated to the entire sample, raising its temperature and yielding a mixture of ice and water at equilibrium, by definition the freezing point of the solution. This temperature will remain constant (plateau). Advanced Osmometers and Cryoscopes can measure freezing points to ±0.002°C. This degree of precision is in part due to repeatably choosing the temperature at which crystallization is initiated.

Heat of Fusion. The heat released when the mobile molecules of a liquid are frozen into rigid crystals.

Freezing-Point Plateau. The constant temperature maintained during the time that ice and liquid exist in equilibrium after crystallization is initiated.

**One liter of water at 25 °C changes volume as the temperature varies.*

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OPERATION

A. SAMPLE PREPARATION

No special sample preparation in required. Whole blood may be used as well as serum or plasma.

B. SAMPLE HANDLING

The advanced™ 3MO825 20-Microliter Sample and the disposable sample cells in the 3MA800 Micro-Sample Kit are specially designed for freezing point depression osmometry with The Advanced™ Micro-Osmometer, model 3MO. The use of any other means of containing the sample for use in the model 3MO is not recommended. These specialized items *should not* be used in conjunction with any other laboratory procedure.

Your 3MO825 20-Microliter Sampler has been carefully calibrated at our factory and is ready to use with the Disposable Sample Cells provided. Should the user wish to check the calibration or replace the teflon sample plunger (recommended with each new package of 500 Disposable Sample Cells), complete instructions are enclosed with each 3MO825 20-Microliter Sampler.

C. 3MO INITIALIZATION

When the 3MO is first turned on, the display will read "RUNNING DIAGNOSTICS" for about 20 seconds, then display "OSMOMETER READY". If any other message appears, turn the 3MO OFF for about 5 seconds, then ON again. If "OSMOMETER READY" dose not appear after 20-30 seconds, please refer to section VII.

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After "OSMOMETER READY" appears, allow the 3MO to warm up to 20-30 minutes only if the 3MO has been off for a long period. Your 3MO Micro-Osmometer is designed to remain ON continuously for optimum operation and stability.

Your 3MO Micro-Osmometer was calibrated at the factory. The calibration is backed up by an internal, rechargeable battery so that calibration will not be lost if there is a power outage or the instrument is turned off for a brief period. Thus, when "OSMOMETER READY" is displayed, your 3MO should be calibrated and ready to run. If the battery has run down because of long storage, the display will read "Please calibrate osmometer." When you attempt to run a sample and you should refer to dection VI

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Appendix B

แบบประเมินภาวะหลอดโลหิตดำอักเสบส่วนปลาย

ผู้ป่วยชื่อ __________นามสกุล________________อายุ_____ปี H.N.

วินิจฉัย_______

ชนิดสารอาหารทางหลอดเลือดดำ_______________

ส่วนสูง _________ cms น้ำหนัก________kgs Abumin __________mg/dl

1. ผู้ป่วยได้รับสารอาหารทางหลอดเลือดดำส่วนปลาย 3 L/day
2. ใช้เข็มขนาดเบอร์ 22
3. ถ้าหากต้องแทงเข็มใหม่ ให้เปลี่ยนสลับข้างกับของเดิม และลงบันทึกเวลาที่แทง
4. ลงบันทึกการเปลี่ยนแปลงทางเส้นทุกเวร (8 ชั่วโมง เวลา 6 14 และ 22 นาฬิกา)
5. แพทย์หน่วย nutrition/ ศัลยแพทย์ จะเป็นผู้สั่งชนิดของสารอาหารPPN
6. ห้ามให้ยา เจาะเลือดผ่านทางPPN

วันที่ / เวลา	ครั้งที่	เริ่มแทงเวลา	ตำแหน่ง		สิ่งที่ตรวจพบ					
			ขวา	ซ้าย	เจ็บ	แดง	บวม	เส้นแข็ง (ความยาว)	อุดตัน	หลุด /รั่ว
6										
14										
22										
6										

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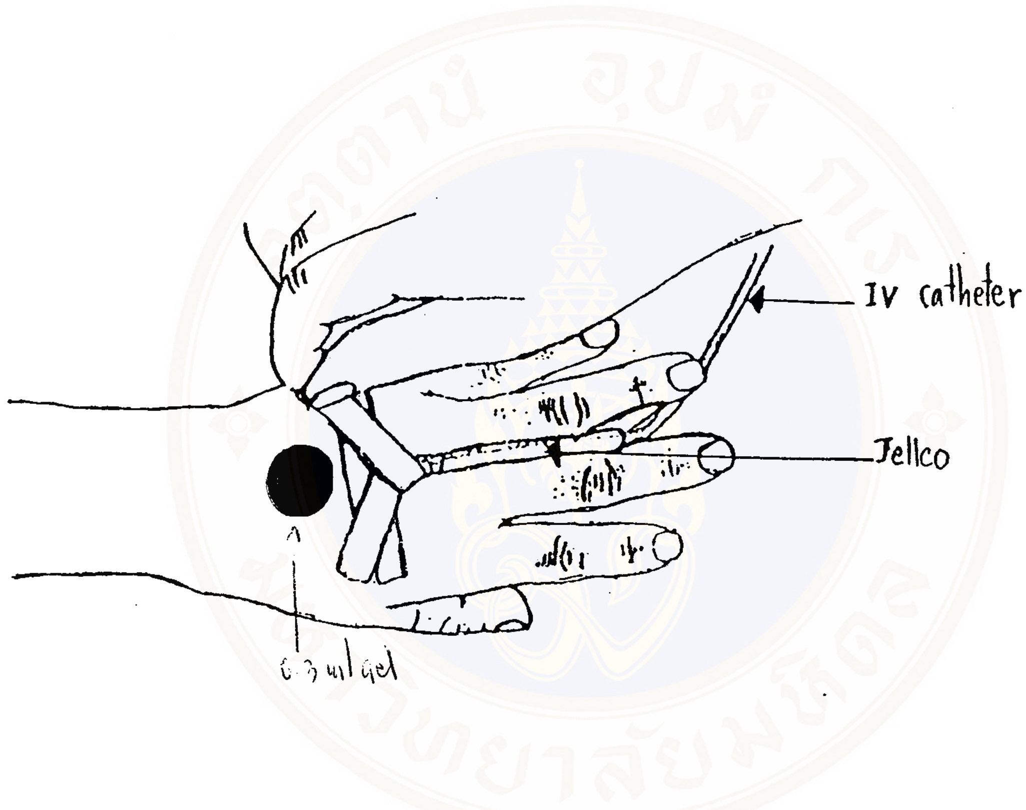
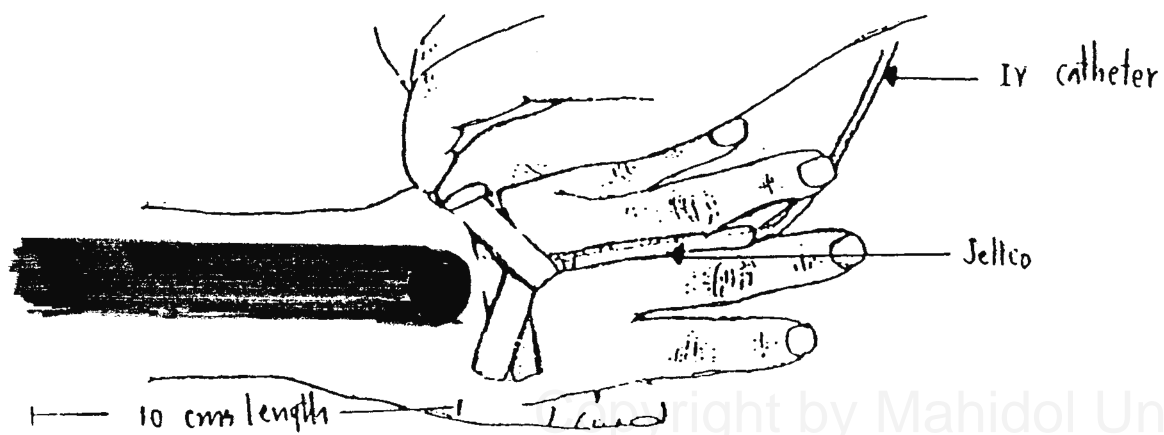
Appendix C

Figure 1 show application (treatment) method on dorsal of hand

A. 0.3 ml gel was applied distal to the cannulation site



B. extruded and rubbed gel into the skin which 10 cms length



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Appendix D

Criteria for Judging phlebitis Maddox, et al.,[15] (1977).

Severity	Criteria
0	No pain at intravenous site, no erythema, no swelling no induration, no palpable venous cord.
1 +	Painful intravenous site, no erythema, no swelling, no induration, no palpable venous cord.
2 +	Painful intravenous site with erythema or some degree of swelling, or both, no induration, no palpable venous cord.
3 +	Painful intravenous site with erythema and swelling and with induration or a palpable venous cord less than three inches above intravenous site.
4 +	Painful intravenous site, erythema, swelling, induration and a palpable venous cord greater than three inches above intravenous site.
5 +	Frank vein thrombosis along with all signs of 4+; Intravenous may have stopped running due to thrombosis.

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Appendix E

Table 28 position of parenteral regimens; 10% Aminosol® 500 ml

composition	Amount/500 ml
Amino acid (g.)	53.1
Nitrogen content (g.)	8.5
Carbohydrate (g.)	50
Electrolytes (mmol.)	
Sodium	24
Potassium	12.5
Malate	7.5
Chloride	31
Phosphorus	4.5
Calories(kcal)	412
pH	7.8

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Table29 Composition of parenteral regimens; 10% D/N/2 1000 ml

Composition	Amount /1000 ml
Carbohydrate (g.)	100
Electrolytes (mmol.)	
Sodium	77
Potassium	20
Malate	0
Chloride	77
Phosphorus	10
Calories	400
pH	.0.34

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BIOGRAPHY

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