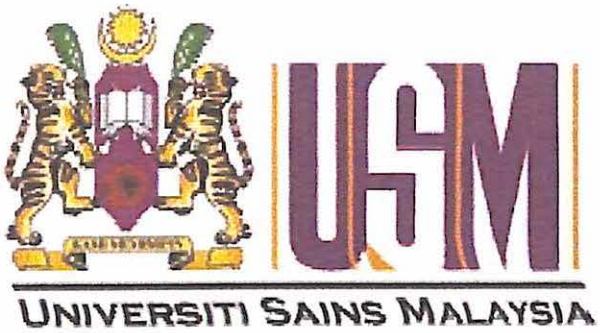
RANDOMIZED CLINICAL TRIAL COMPARING DIFFERENT METHODS OF BOWEL PREPARATION USING ORAL SODIUM PHOSPHATE FOR DAY-CARE COLONOSCOPY

By

DR. TEOH BOON WEI
M.B.,B.S. (Vellore, India)

Dissertation Submitted In Partial Fulfillment Of The Requirements For The Degree Of Master Of Medicine (SURGERY)

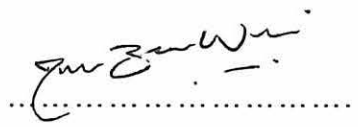


SCHOOL OF MEDICAL SCIENCES
UNIVERSITI SAINS MALAYSIA

MAY 2007

2. DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.



Dated: 5 March 2007

Dr. Teoh Boon Wei

P-UM 1164

3. ACKNOWLEDGEMENT

I would like to extend my most sincere gratitude and deepest appreciation to my supervisors; Dr. Syed Hassan Syed Abd. Aziz and Mr. Manjit Singh, for their continuous support and guidance throughout my course.

To Staff Nurse Azizon from Penang Hospital, thank you for your great help and enormous contribution in helping to coordinate the study in Penang Hospital. A special acknowledgement to the doctors and staff of the Surgical Out-Patient Department; especially the Surgeons for their ideas, invaluable advice, constructive criticisms and participation in the study. Not forgetting the patients who kindly consented to participate in the study; they are ultimately my greatest teachers.

A word of thanks also goes out to Dr. Than Winn, medical statistician, for his advice on statistical analysis of the data.

My heartfelt gratitude to my loving wife, Dr. Asha Prerna, whose prayers, encouragement and help enabled me to achieve all that I can achieve thus far; and to my parents, Mr. Teoh Chee Heong & Madam Lee Siew Heang for their care & support throughout all that I have been through.

And ultimately to God who is my Strength and my Guide. May my journey continually be blessed by You. All I have and ever hope to achieve, I owe it all to You.

4. TABLE OF CONTENTS

5. LIST OF TABLES

6. LIST OF FIGURES

7. ABSTRAK

Tajuk:

Kajian klinikal secara rambang membandingkan kaedah berlainan mencuci usus menggunakan ubat cecair sodium fosfat untuk pemeriksaan kolonoskopi.

Objektif:

Kajian ini bertujuan untuk membandingkan dua masa yang berlainan untuk mengambil ubat yang sama (cecair sodium fosfat, NaP) yang digunakan untuk mencuci usus untuk menentukan keberkesanan pembersihan usus dan keselesaan pesakit.

Tatacara:

Kajian merupakan "prospective randomized clinical trial" yang melibatkan 97 pesakit luar yang menghadiri klinik pembedahan di Hospital Pulau Pinang yang memerlukan pemeriksaan kolonoskopi. Semua pesakit-pesakit yang layak dan setuju mengambil bahagian dalam kajian ini dibahagikan kepada dua kumpulan secara rambang dan diberi arahan untuk mengambil ubat mengikut kumpulan yang telah ditetapkan. Satu kumpulan mengambil NaP pada selang masa 4 jam (1500j daan 1900j pada hari sebelum pemeriksaan kolonoskopi) and kumpulan yang satu lagi pada selang masa 12 jam (1800j pada hari sebelum pemeriksaan kolonoskopi dan 0600j pada hari pemeriksaan kolonoskopi). Pesakit-pesakit menjawab borang pertanyaan sebelum prosedur dijalankan. Selepas prosedur berkenaan, doktor yang menjalankan pemeriksaan kolonoskopi itu akan mengisi borang pertanyaan masing-masing. Data-data kemudian dikumpulkan untuk dianalisakan.

Keputusan:

Pesakit-pesakit lelaki dan perempuan dibahagikan secara sekata antara kedua-dua kumpulan dengan purata umur 52.5 tahun. Sebab utama pesakit-pesakit menjalani pemeriksaan kolonoskopi adalah untuk menyiasati perubahan dalam tabiat pembuangan air besar, diikuti oleh pendarahan, kesakitan perut, penyaringan dan akhir sekali kekurangan darah. Antara kesan-kesan sampingan yang disiasati, tiada perbezaan didapati antara kedua-dua kumpulan. Kebanyakan pesakit-pesakit boleh tahan pembersihan usus dengan selesa dan markah "median" untuk kesan-kesan sampingan adalah 6 di mana markah maksimum adalah 24. Walaubagaimanapun, pesakit-pesakit yang mengambil ubat NaP dalam masa dua hari (Kumpulan 2) lebih mengalami perasaan pening bila bangkit berbanding dengan mereka yang mengambil ubat NaP dalam masa satu hari (Kumpulan 1). Pesakit-pesakit Kumpulan 2 juga perlu membuang air besar lebih kerap (10.46 ± 5.32 kali berbanding 7.96 ± 3.24 kali untuk Kumpulan 1) dan mengalami lebih kesusahan untuk menghabiskan proses pembersihan usus mereka. Biar pun begitu, pesakit-pesakit Kumpulan 2 sanggup menjalani proses yang sama jika perlu pada masa hadapan seperti pesakit-pesakit Kumpulan 1. Jumlah markah untuk kebersihan usus Kumpulan 2 adalah 3.17 ± 2.97 berbanding 4.90 ± 2.98 untuk Kumpulan 1. Ini bermakna pesakit-pesakit Kumpulan 2 mempunyai usus yang lebih bersih daripada pesakit-pesakit Kumpulan 1.

Kesimpulan:

Bila faktor-faktor seperti jantina, umur dan sebab menjalani pemeriksaan kolonoskopi diseimbangkan dengan pemilihan rambang, adalah didapati bahawa kejadian kesan-kesan sampingan dalam kedua-dua kumpulan adalah sama kecuali kejatuhan tekanan darah bila

bangkit yang lebih kerap didapati dalam pesakit-pesakit Kumpulan 2. Pesakit-pesakit Kumpulan 2 juga lebih kerap buang air besar dan oleh sebab itu, mereka mengalami lebih kesusahan menghabiskan proses pembersihan usus mereka. Oleh sebab itu juga, kebersihan usus mereka lebih sempurna. Jikalau kesan kejatuhan tekanan darah bila bangkit dapat diatasi dengan meminum lebih banyak air, kita mendapati bahawa proses pembersihan usus dengan mengambil ubat NaP dalam masa dua hari lebih baik. Walaubagaimanapun, ia adalah disyorkan bahawa kaedah ini digunakan secara terpilih untuk pesakit-pesakit yang sihat dan tidak mengalami penyakit serius sahaja. Paling penting adalah pertimbangan klinikal diperlukan untuk pemilihan kaedah yang sesuai untuk seseorang pesakit.

8. ABSTRACT

Title:

Randomized clinical trial comparing different methods of bowel preparation using oral sodium phosphate for day-care colonoscopy

Objectives:

To compare two different timings for a similar bowel preparation agent (oral sodium phosphate, NaP) and determine the quality of bowel cleansing plus patient tolerance, compliance and acceptability.

Methodology:

This is a prospective randomized clinical trial involving 97 out-patients attending the surgical clinic of Penang Hospital who were planned for elective colonoscopy. All eligible patients who agreed to participate were randomized into two groups (one group was required to take NaP at a 4-hour interval (1500h and 1900h on the day before the colonoscopy) and another group at a 12-hour interval (1800h on the day before the colonoscopy and 0600h on the day of the colonoscopy). Instructions for bowel preparation were given accordingly. The subjects were given a questionnaire to complete prior to their procedure. After the procedure, the colonoscopists (who were blinded to the patients' assigned group) were in turn given a questionnaire to fill. Data were then collected and compiled for analysis.

Results:

There was equal distribution of male and female patients for both groups with an average age of 52.5 years. The commonest indication for elective colonoscopy was for altered bowel habits, followed by bleeding, abdominal pain or discomfort, screening and finally anaemia. Of the side-effects questioned, none differed significantly from each other. Most patients tolerated both bowel preparations well with a median total patient score of 6 out of a possible maximum score of 24. However, patients who took NaP over two days (Group 2) had significantly more incidence of postural hypotension than the other group which took NaP over one day (Group 1). Group 2 patients also had more number of bowel movements (10.46 ± 5.32 versus 7.96 ± 3.24 in Group 1) and found it harder to complete their bowel preparation. Even then, Group 2 patients were just as willing as Group 1 patients to take the same bowel preparation again if colonoscopic examination was required in the future. Total score for quality of bowel preparation was 3.17 ± 2.97 in Group 2 as opposed to 4.90 ± 2.98 in Group 1. That means overall, Group 2 patients had better bowel cleansing than Group 1 patients.

Conclusion:

With other factors such as gender, age and indication for colonoscopy neutralized by randomization, it was found that the incidence of side-effects following either bowel preparation regimen is the same except for postural hypotension which is more common in Group 2 patients. Group 2 patients also had more bowel movements and that is why they found it harder to complete their bowel preparation. Since Group 2 patients had more bowel movements, they also had the better prepared bowel. If the effects of postural

hypotension caused by hypovolemia can be negated by increased fluid consumption, we would find that taking NaP over the course of two days would definitely be superior. However, it is recommended that this method be prescribed selectively for fit patients with no major medical illness and ultimately, clinical discretion need to be employed to decide on the appropriate bowel preparation method for a particular patient.

Chapter 1
Introduction

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

With the advent of colonoscopy in the late 1960's, detection and treatment of colorectal pathology has become easier and more reliable. It is a mainstream procedure routinely used as a screening and treatment tool for diseases of the large bowel. The focus has been changing of late from the development of newer techniques to enhancing the efficacy and quality of current fundamental techniques.

One of these fundamental techniques involves bowel preparation. For a proper assessment of the colon, a clean luminal environment is imperative. If the bowel is poorly prepared, colonoscopy will be difficult to perform leading to equipment failure (due to blockage of suction port) and persistence in performing the colonoscopy despite poor bowel preparation may lead to inadvertent perforation which can be disastrous. This poorly prepared bowel will result in greater peritoneal contamination and peritonitis compared to a well prepared bowel (Tooson and Gates Jr., 1996).

The accuracy of this procedure can also be compromised if the bowel is poorly prepared, thus providing unsatisfactory visualization of the investigated segment of bowel. In such a case, any abnormality can be overlooked which can lead to a devastating outcome. Plainly put, the accuracy of a colonoscopic examination is only as reliable as the quality of the bowel preparation. Therefore, of late research attention has been directed towards discovering the ideal bowel preparation which is both safe and effective whilst being well tolerated by the patient.

1.2 AVAILABLE METHODS

1.2.1 Traditional methods

Traditional bowel preparation entails some form of diet restriction, purgation, enema and wash-out. Diet is restricted to 1 – 4 days of clear fluids or foods which leave a minimal colonic faecal residue (DiPalma *et al.*, 1984). Patients are encouraged to take clear fluids, both to prevent dehydration as well as to overcome the feeling of hunger. A variety of purgatives are also required for adequate cleansing. These include magnesium sulphate, magnesium citrate, sodium sulphate, senna or bisacodyl which all cause some degree of abdominal colic. Most traditional preparations conclude with some form of enema and wash-out. Obviously, this form of bowel preparation is time consuming, fraught with discomfort and inconvenience for the patient and ultimately results in poor compliance. For these reasons, alternative forms of bowel preparation were developed.

1.2.2 Elemental diets

Elemental diets have been tried in the past which require them to be used for at least 5 – 7 days along with some form of distal preparation like enema or wash-outs to clear residue from the large bowel (Keighley, 1982). Most patients find elemental diets unpalatable when taken by mouth but the alternative of passing a nasogastric tube does not make the situation any more tolerable but in fact worse. Therefore the trend of using elemental diets for mechanical bowel preparation seems to be over (Bounnos and Devroede, 1974).

1.2.3 Whole bowel irrigation

Irrigation of the bowel with saline or balanced electrolyte solutions is another method of bowel preparation. The irrigation solution can be administered orally or by nasogastric tube but large amounts of solution varying from 7 to 12 litres is usually necessary.

1.2.3.1. Electrolyte solution

Originally, isotonic saline was used for irrigation (Hewitt *et al.*, 1973), but it consistently caused fluid and sodium retention and was contraindicated in elderly patients with renal, cardiac or hepatic failure unless used with frusemide (Crapp *et al.*, 1975). The infusion also caused a loss of potassium and the use of a diuretic further increased the risk of hypokalemia. Ringer's lactate was therefore recommended (Wolthers *et al.*, 1994) but because large volume of solution is required (between 1 and 8 litres); it is still contraindicated in patients with cardiac and renal failure.

1.2.3.2 Osmotic agents

Newstead and Morgan (1979) introduced the concept of drinking an osmotic agent and the oligosaccharide mannitol was chosen since it was not absorbed or digested during rapid transit through the small bowel, thereby achieving an osmotic catharsis. However, mannitol was associated with dehydration and sodium loss (Gilmore *et al.*, 1981) and there were also reports of occasional fatal explosion probably due to methane production as a result of Escherichia coli fermentation (Zanoni *et al.*, 1982). Therefore, mannitol was discontinued.

1.2.3.3 Electrolyte solution and osmotic agents

Gilmore *et al.* (1981) suggested that if osmotic agents were combined with an electrolyte solution there should be no fluid or electrolyte disturbance. Davis *et al.* (1980) therefore formulated an osmotically balanced electrolyte lavage solution, polyethylene glycol-electrolyte lavage solution (PEG-ELS, Colyte®, Schwarz Pharma, Inc., Milwaukee, WI; Golytely®, Braintree Laboratories, Inc., Braintree, MA.). Polyethylene glycol, an inert, non-absorbable, non-fermentable compound is used as the osmotic agent whereas sodium sulphate rather than sodium chloride is used as sulphate inhibits sodium reabsorption, thereby minimizing the risk of sodium and water retention. The formulation also included sodium bicarbonate to prevent acidosis and some sodium supplements to minimize potassium loss.

In an attempt to improve compliance by decreasing the salty taste and 'rotten egg' smell from sodium sulphate, a sulphate-free-polyethylene glycol electrolyte lavage solution (SF-ELS, NuLytely®, Braintree Laboratories, Inc., Braintree, MA) was developed. SF-ELS has even less absorption or secretion of water or electrolytes than PEG-ELS.

1.2.4 Purgation alone

1.2.4.1 Sodium picosulphate and magnesium citrate (NaPS + MgC, Picolax®)

Sodium picosulphate and magnesium citrate (NaPS + MgC) which is marketed as Picolax® (Ferring Pharmaceuticals, Langley, UK) belongs to the group of osmotic laxatives. Until recently NaPS + MgC has been the most widely used preparation in United

Kingdom. Two sachets are given 4 – 6 hours apart, 24 hours before the procedure, followed by clear fluids thereafter. Patient compliance is good even though there is colic which is troublesome but it is usually transient. Generally high-quality of preparation is achieved. However, NaPS + MgC bowel preparation has a significant dehydrating effect, which can be minimized by administering a simultaneous volume of intravenous fluid (mean 2 litres in this study) (Sanders *et al.*, 2001).

A colonoscopy trial and a surgery trial to compare NaP with NaPS + MgC indicated that the quality of bowel preparation with NaP was superior to that with NaPS + MgC even though there was a transient rise of serum phosphate with NaP but no change in calcium levels with either group (Yoshioka *et al.*, 2000).

1.2.4.2 Oral sodium phosphate (NaP, Fleet® Phospho-soda®)

Oral sodium phosphate (NaP) which is marketed as Fleet® Phospho-soda® (C.B. Fleet Co., Inc., Lynchburg, VA) has gained attention because of its small volume and oral administration. 45 ml of the highly osmotic laxative is diluted to 90 ml with water and taken twice. Each 5 ml of NaP contains 2.4 g (20 mmol) of monobasic sodium phosphate monohydrate and 0.9 g (6.5 mmol) of dibasic sodium phosphate heptahydrate, making it very hypertonic.

1.3 RECOMMENDED METHOD AND ITS SAFETY

Many trials have been conducted to ascertain the optimal bowel-cleansing regimen and for the majority of population, NaP has been the preferred agent so far, both for patients' tolerance as well as for better bowel cleansing (Vanner *et al.*, 1990, Cohen *et al.*, 1994, Golub *et al.*, 1995, Frommer, 1997, Oliveira *et al.*, 1997). However, few studies have investigated the different timings for the same bowel preparation agent. Frommer (1997) was the only one found to compare different timings for the same agent comparing the 7 a.m./ 7 p.m. dosing of NaP on the day before to the 6 p.m./ 6 a.m. dosing over two days and found the latter to be more effective in cleansing.

However, there have been concerns in the past regarding the safety of this preparation method as there is the small risk of hyperphosphathemia and hypocalcemia. Hyperphosphatemia is dose related and more common in patients with renal failure (Afridi *et al.*, 1995). Vanner *et al.* (1990) found no significant changes in intravascular volume when compared with PEG lavage solution, although transient hyperphosphatemia was noted up to a level of 7 mg/dL.

Huynh *et al.* (1995) investigated the safety of 5-hour interval of NaP (5 p.m. & 10 p.m. the day before) for colonoscopy cleansing and found that even though there were significant electrolyte changes, i.e. hyperphosphatemia with borderline hypocalcemia and asymptomatic intravascular contraction, the 5-hour regimen is safe in most patients for colonic cleansing. Aronchick *et al.* (2000) compared the efficacy and safety of three different types of bowel preparation of which NaP was one of them. Even though it was

given over a shorter dosing interval (3 p.m. & 6 p.m. the day before), there were no adverse events with NaP.

Hence NaP is safe and effective for the majority of patients, but the biochemical effects associated with its usage raise concern. Therefore, this preparation should be avoided in patients with significant renal, cardiac or hepatic diseases or in those in whom fluid and electrolyte balance is delicate.

1.4 RESEARCH PROPOSAL

From the drug information provided by Fleet® Pharmaceuticals, the timing of two doses of diluted NaP should be as directed by the physician. Through correspondence with the Consumer Affairs Department of C.B. Fleet Co., Inc. (the manufacturer of Fleet® products), it was found that the recommended dosing is 1.5 fl.oz. (45 ml.) in the evening before the procedure and another 1.5 fl.oz. (45 ml.) in the morning of the procedure. This dosing regime is based on current clinical studies quoted in Table 1.1. In the U.S., the maximum allowable daily over-the-counter drug dosage of NaP is 45 ml., therefore the manufacturer is unable to recommend dosing regimens that use more than 45 ml. in a single day. However in the U.K. and Europe, two doses of NaP are given 10 to 12 hours apart on the same day before the procedure. From Table 1.1 it can be seen that the trend for dosing regimen is going towards a shorter dosing interval and completion the day before examination.

If the two doses of NaP are given 12 hours apart; one dose on the day before and another dose on the day of the procedure, this is associated with poor patient compliance and inconvenience. Besides the usual side effects, patients also complain of having abdominal discomfort and bowel movements while on their way to their colonoscopy appointment.

To improve on this, we propose to have a shorter dosing interval and NaP be given the day before the proposed colonoscopic examination. This way, patients will have a shorter period of bowel preparation, thus suffer discomfort for a shorter period and can complete the bowel preparation the day before and will not suffer the urgency of looking