

Effectiveness of Moviprep® as colonic preparation – cleansing right colon for Lynch Syndrome (LS) screening

A prospective study

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DECLARATION

I, Dr David J de Villiers, hereby declare that the work on which this dissertation is based is my original work and that neither the whole work or any part of it has been, is being, or is to be submitted for another degree in this or any other university.

Signature:

Signed by candidate

Date: 12/08/2016

ABSTRACT

Purpose:

Each year, a cohort in the Northern Cape undergo colonoscopies as part of a surveillance program for individuals who have a C1528T mutation in the *hMLH1* gene that puts them at very high risk for the development of colon cancer (Lynch syndrome). A clean colon is essential as it allows a thorough evaluation and surveillance for small polyps or mucosal lesions mostly encountered in the ascending colon. This study evaluated both the subject acceptance and the effectiveness of a 2L PEG electrolyte lavage solution containing ascorbic acid and sodium ascorbate (Moviprep®) as a preparation solution.

Methods:

The screening program was divided into two stages.

Stage 1, 71 subjects were counselled individually on the importance of bowel cleansing and the use of Moviprep® as their bowel cleansing agent. Preparation was either a) 2L the night prior to colonoscopy or b) 1L the night prior to and the second litre on the morning of the colonoscopy. Subjects were encouraged to drink at least 500ml clear fluid in addition to each litre of Moviprep®. Informed consent was obtained for participation in the study.

Stage 2, approximately 6 weeks later, each subject completed a questionnaire, evaluating their experience with Moviprep® and also had their screening colonoscopy performed.

Colonoscopies were performed at 4 medical facilities in the Northern Cape. All subjects were assessed for bowel cleanliness on arrival at the facility where colonoscopy was to be

performed. If any of the subjects were found to be inadequately cleaned, extra oral preparation was given prior to colonoscopy.

The Harefield cleansing scale was used to evaluate the quality of colonic cleansing during each colonoscopy. The colon was divided into 6 segments (rectum, sigmoid, descending-, transverse-, ascending colon and cecum). Preparation was scored as A = all colon segments clean; B = at least 1 segment with residual amounts of brown liquid or semisolid stool, which can easily be displaced or removed; C = at least 1 segment with only partially removable stool, preventing complete visualization; D = at least 1 segment which could not be examined due to solid stool). Grades A or B were considered successful cleansing and grades C or D were considered a failed colonic preparation.

Results:

A total of 46 subjects had colonoscopies performed. 41(89%) of them had successful and 5(11%) failed preparation. Three of those subjects that prepared successfully had previously undergone right hemicolectomies, leaving 38 with intact colons. 22/38 (58%) subjects achieved an A grade for caecal cleansing and 16/38 (42%) a B grading. 24/38 (63%) subjects scored an A grade for the ascending colon and 14/38 (37%) a B grade.

A total of 64 subjects completed the questionnaires of which 83% (53/64) had used other colon preparations previously. When asked if they would use Moviprep® again in the future, 89% (57/64) said yes and 11% (7/64) said no. 94% of subjects (60/64) would recommend Moviprep® to friend and family.

Conclusion:

Moviprep® provided adequate colonic cleansing in 89% of subjects. In addition, nearly 90% of subjects were satisfied with the product and would use it again.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1. INTRODUCTION and LITERATURE REVIEW

1.1 Lynch syndrome

Ten to twenty percent of colorectal cancers appear to have evidence of genetic predisposition. The most common inherited precursors of Colorectal Cancers (CRCs) are Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colon Cancer or Lynch Syndrome (LS).¹⁻⁶

Both FAP and LS are the result of specific germ line mutations. FAP, as inherited precursor, accounts for less than 1% of CRC's. LS is the most common form of inherited precursor colorectal cancer, accounting for 2 – 7% of all colorectal cancers diagnose in the U.S. annually.¹⁻³

Hereditary Non-Polyposis Colon Cancer or Lynch Syndrome is an inherited bowel cancer syndrome and arises from a mutation in the mismatch repair genes. It is an autosomal dominant condition and is characterized by the development of colorectal cancer in patients at a young age. Extra colonic malignancies also commonly occur.¹ If a patient is found to have a mutation or defect in the mismatch repair gene, he or she might belong to a Lynch Syndrome family. Germ-line mutations in any of four DNA mismatch repair genes, MLH1, MSH2, MSH6 and PMS2, may be responsible for Lynch syndrome.⁷ Carriers of a mismatch repair gene mutation in MLH1 or MSH2 have a lifetime risk of 85 – 90% risk of developing any type of cancer.⁷

The most frequent cancer amongst Lynch Syndrome patients are colorectal- and endometrial cancer with a respective cumulative risk of 60 – 80% and 30 – 50%.⁷

Colonoscopic surveillance significantly reduces the incidence of colorectal cancer and increases survival.⁷ The presence of a mismatch repair mutation may alter the extent of surgery and type of adjuvant chemotherapeutic agents used in young patients with colorectal carcinoma. The DNA mismatch repair mutation plays a role in the toxicity of a number of DNA-damaging drugs that might be considered in cancer chemotherapy.⁸⁻⁹

Also, one might consider more extensive resection in this group of patients, as they are young and have a higher risk of developing another cancer in the future.

Previous studies have identified a cohort of individuals with Lynch Syndrome as a result of a C1528T mutation in the *hMLH1* gene who live in the Northern Cape.¹⁰ Those at risk for the development of colonic carcinoma are offered annual screening colonoscopy (biennial if under 30). The lesions/polyps are most prevalent in the right side of the colon hence emphasizing the importance of proper and complete colon preparation prior to colonoscopy.¹⁰

1.2 Options for early detection of colonic disease

Multiple screening modalities are available aimed at early detection of colorectal carcinoma, but few are specific with regard to establishing the diagnoses of colorectal carcinoma.

Screening of the general population is not feasible in the South African context due to cost involved and limited recourses. Patients are thus risk stratified into either high or low risk for the probability of development or presence of colorectal carcinoma. Clinical history,

presentation and examination play a major role in this risk stratification process which identifies patients for surveillance.

Surveillance modalities range from minimally invasive laboratory testing, such as tumour markers and stool for occult blood, to more invasive modalities such as contrast enemas, flexible sigmoidoscopy, CT colography and colonoscopy.

Considering the rural location of our study population and minimal access to health care facilities, modalities other than colonoscopy, are not practical or definitive enough as a single surveillance modality. These would include both faecal occult blood and contrast enemas. CT colonography, which is also known as virtual colonoscopy, reconstructs an interior view of the colon by utilizing low dose radiation CT scanning. Again, this would only be possible in a tertiary medical institution. More than 95% of colorectal cancers arise from benign adenomatous polyps. These polyps grow very slowly and may develop over many years. A powerful method of secondary prevention of the development of colorectal cancer within these adenomatous polyps, is interruption of the adenoma-carcinoma sequence. This is accomplished by resecting adenomatous polyps. The procedure of choice for the diagnosis and resection of colorectal polyps is Colonoscopy.¹¹

For individuals with Lynch syndrome, the entire colonic mucosa needs to be visualised. The lesions that require detection are too small to be reliably detected with other methods. This is the reason why colonoscopy remains the gold standard for surveillance in our population group. These patients are from a rural and isolated part of South Africa, with limited medical resources. Colonoscopy offers each patient an opportunity at surveillance as well as diagnoses with one investigative tool.

1.3 Why is colonoscopy the best option?

A colonoscopy is an endoscopic procedure using a flexible scope to assess the integrity, mucosal lining and general luminal surface anatomy of the colon. A flexible scope is passed trans anally and navigated with care through the entire colon, from rectum up to caecum and ileo-caecal junction (figure 1). During this procedure the wall and mucosa of the colon is assessed and inspected for pathology. The colonic lumen is examined for any growth or abnormal lesion, bleeding foci or disruption in or narrowing of the lumen. The technique of a complete and thorough colonoscopy takes years of experience and bowel preparation plays a major role in achieving this goal and gaining the much needed experience. Colonoscopic screening reduces death from colorectal carcinoma and can decrease the incidence of disease through removal of adenomatous polyps.¹

Preparation and polyp miss rate plays a major role in the quality and accuracy of surveillance with colonoscopy.

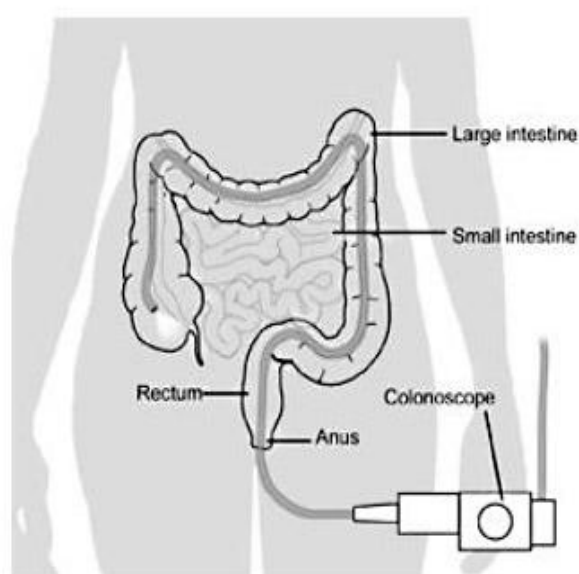


Figure 1

Even in this rural environment, colonoscopic surveillance is offered locally to this group of Lynch syndrome patients on an annual basis.

Colonoscopy can cause considerable patient discomfort. Poor preparation requires more air insufflation with added discomfort. Discomfort will impact on patient compliance during the procedure with negative impact on surveillance. What makes our study population unique is that most of the colonoscopies performed are performed on multiple members of high risk families. One unpleasant, painful or distressing colonoscopy on one member of a family could trigger reluctance to further colonoscopic surveillance within the rest of that family. Good preparation is thus essential as only a minimal amount of sedation can be offered in the rural setting.

1.4 Polyp miss rate

In a systematic review, van Rijn et al reviewed polyp miss rate looking at both polyp size and polyp type. A total of 465 patients were included. All 465 patients underwent two, same day colonoscopies with polypectomy.¹³ For any size polyp, the pooled miss rate was 22%. More specifically the adenoma miss rate was 2.1% for polyps larger than 10mm, 13% for adenomas 5 – 10mm and 26% for adenomas of 1 – 5mm.¹³ It was concluded that polyps larger than 10 mm are rarely missed at colonoscopy, but the miss rate increases significantly as the polyp size decreases. In their review of the literature, they found that one in five polyps is missed at colonoscopy.¹³ Larger polyps are less likely to be missed, but some big adenomas might be overlooked. One in four adenomas (1-5mm) may be missed. Unfortunately the number of studies looking at this specific topic is small.¹³

Bressler et al reviewed the miss rate of right sided colon cancer in 4920 patients. 2654 (53.9%) had had a colonoscopy within 3yrs prior to their diagnosis and of those patients, 96% had their most recent colonoscopy up to 6 months before admission, thus viewed as detected cancers.¹⁴ 105 patients or rather 4.0% had their most recent colonoscopy between 6 and 36 months prior to admission, categorizing them as missed cancers. The miss rate of right sided cancers in usual clinical practice was found to be 4.0%.¹⁴

Several studies established that in preventing colorectal cancer, colonoscopy is less effective in the proximal compared to the distal colon. Reasons for this might be (1) poor colon preparation prior to colonoscopy affecting the visibility more on the right than on the left or (2) polyps in the proximal and distal colon tend to differ in both polyp size and type.¹⁵⁻¹⁷ Serrated, flat and depressed polyps being more prevalent proximally.¹⁸⁻²⁰

1.5 What do we need to achieve quality colonoscopy?

For a complete and thorough colonoscopy examination, the colon needs to be cleansed of any stool or obstructing debris. If this is not done, it can result in:

- Sub optimal visualization
- Missed lesions
- Technically difficult procedure
- Patient discomfort and emotional trauma

- Poor surveillance compliance
- Mucosal damage and potential perforation

Even under optimal circumstances, polyp pick up rate is not 100%. To give the endoscopist the best possible chance of identifying most of the polyps, the colon needs to be clean.

Patients need to be compliant with preparation product instructions to ensure a clean colon prior to endoscopy. This is not always possible as most bowel preparations are poorly tolerated contributing to poor compliance.

1.6 What is unique about our population?

Our cohort resides in a number of small, remote and rural towns in the Northern Cape Province. Many only have basic medical services and support systems in place. This makes annual surveillance colonoscopies a logistic and financial challenge. As not all of the patients have adequate bathroom facilities and have to travel considerable distances to have their colonoscopies, some patients do not cope with the bowel cleansing regime during preparation. The end result is a poorly prepared colon and an incomplete colonoscopy. Their local medical facilities can unfortunately not offer them colonoscopies or alternative screening modalities. With the outreach surveillance program, colonoscopy, as a screening and diagnostic tool, is now offered to these patients locally on an annual basis.

This population group undergoes a single colonoscopy each year during the outreach program. If for any reason the colonoscopy cannot be done, a year will pass before the next scope.

What makes this study population so unique is the fact that none of them have used Moviprep® as colonic preparation previously. Prior to 2013, preparation was either a 4 litre polyethylene glycol containing solution or a small volume phosphate soda preparation. The latter solution now carries a FDA red label warning because of the possibility of development of nephrocalcinosis.

The large volume of the traditional PEG was poorly tolerated. This was the perfect opportunity to try and improve compliance and quality of bowel cleansing in the view of optimizing the surveillance program.

1.7 Methods of colonic preparation prior to colonoscopy

The 2013 European Society of Gastrointestinal Endoscopy (ESGE) guideline (Hassan et al), recommended a combination of low fibre diet prior to colonoscopy and a split regimen of 4 L of polyethylene glycol (PEG) solution (or a same-day regimen in the case of afternoon colonoscopy) for routine bowel preparation. A split regimen (or same-day regimen in the case of afternoon colonoscopy) of 2 L PEG plus ascorbate or of sodium picosulphate plus magnesium citrate may be valid alternatives. The ESGE advises against routine use of sodium phosphate.²¹

In a randomised study, Katz et al compared sodium picosulfate and magnesium citrate (P/MC) with 2 L polyethylene glycol solution and two 5 mg bisacodyl tablets.

Overall cleansing of the colon was equivalent, but patients reported that acceptability and tolerability was greater for P/MC. ²²

Komeda et al published an article in 2012 of factors associated with failed polyp retrieval at screening colonoscopy and found that small polyp size and rectal snare removal were found to be associated with polyp removal failure. Human factors such as fatigue or lapses in concentration conceivably could play a role in failure to retrieve polyps. However, there were no significant correlations found between retrieval rate and the number of polyps per patient, quality of bowel preparation, or length of procedure. ²³

Arora et al studied the efficiency of various bowel preparations in accomplishing colonic cleansing for optimal mucosal visualization during colonoscopy. Powder PEG 350 alone and in combination with oral sodium phosphate was observed to be statistically superior to magnesium citrate. ²⁴

“Preparation for colonoscopy is essential before a colonoscopy” (Lozeno-Zúniga et al 2012).

This allows us to conduct a thorough examination of the entire colonic mucosa. The ideal method of colon cleansing should be fast, safe with minimal discomfort to the patient.

Although the efficiency of most preparations is comparable, it is patient preference and the degree of compliance with product instructions, which greatly influence the results. ²⁵

1.8 Preparation expectation and experience

What do we, as clinicians, require from a preparation for colonic cleansing? As mentioned before, colonic cleansing is essential and without thorough cleansing a thorough, safe and tolerable colonoscopy is not possible. What patients expect from a colonic preparation and what they experience during the preparation period will impact on both the clinical findings and colonoscopic experience itself.

In a systemic review conducted by McLachlan et al, the primary concern of patients (regardless of whether they had direct experience of a colonoscopy or whether they were considering it) was discomfort and inconvenience due to the use of laxative bowel preparation. A significant majority judged this to be the worst part of the process, and the main barrier.²⁶

Guidelines on the technical performance of colonoscopy have not recommended specific targets for rates of adequate preparation²⁷⁻²⁸ because these rates are partly related to patient factors, such as poor socioeconomic status that typically vary between populations.²⁹⁻³⁰

Efficacy and tolerability are related, and together constitute the main ingredients of effectiveness. If the preparation is not well tolerated, it will not be ingested and will be less effective, even if otherwise efficacious.³¹ Thus, both efficacy and tolerability are important. Selection of a preparation would be easy if one preparation was clearly superior at both efficacy and tolerability, but such a preparation does not yet exist.³¹

Ideally the optimal bowel preparation should be uncomplicated to prepare, easy to consume and have a low side effect profile when considering fluid and electrolyte shifts, nausea and vomiting, abdominal discomfort, abdominal cramps. Unfortunately a bowel cleansing regime

like this does not exist and one needs to tailor the specific needs, expectations, socio-economic circumstances, disease profile and personality of each individual patient, to a specific bowel preparation regime.

1.9 Evidence behind Moviprep®

In a randomized trial comparing low volume PEG plus ascorbic acid to a standard 4L PEG plus electrolyte solution, by Christian Ell et al, it was found that there was no difference in gut cleansing or safety profile. The only difference shown, was the combination of ascorbic acid and PEG solution (2L in total) reduced the volume patients had to consume for bowel cleansing compared to PEG and Electrolyte combinations (4L in total). The low volume PEG + Ascorbic acid preparation was more acceptable to patients and should improve effectiveness in routine practice.³²

Pelitari et al evaluated the effect of additional clear fluid intake to the standard Moviprep® regime. Low volume 2L PEG and ascorbic acid (Moviprep®, Norgine Pharmaceuticals) has been demonstrated to be as effective as other bowel cleansing agents and has greater patient tolerability. They evaluated whether the addition of clear fluids to the standard regime would improve bowel cleansing. Patients were randomised to either receiving the standard 2L Moviprep® or standard 2L Moviprep® with an additional 1.5L clear fluid. It was found that increasing the volume of clear fluid intake with Moviprep® improves cleansing in the distal colon and improves polyp detection rate.³³

Kastenburg et al compared the colon cleansing efficacy of a 2L PEG + ascorbic acid to a 4L PEG solution. The scoring system used in US NaP trials were used to grade overall colonic

cleansing (excellent: >90% mucosa seen, mostly liquid colonic contents, minimal suctioning for adequate visualization; good: >90% mucosa seen without significant suctioning needed; fair: >90% mucosa seen with a mixture of liquid/semisolid colonic contents, could be suctioned and/or washed; inadequate: >90% mucosa seen, contents could not be suctioned or washed). High overall colon cleansing rates were observed for both 2L PEG and 4L PEG (88% and 96% respectively).³⁴

Moviprep®, as a product, has been proven to be effective with equal cleansing outcomes when compared to other preparations. In this study we planned to assess (1) the overall patient experience with Moviprep® and (2) the cleanliness of the colon after Moviprep® bowel preparation.

A colonoscopy, in summary, needs to be done by a skilled and specialized clinician. For maximal visualization of the mucosa during colonoscopy the colon needs to be clean and empty as the lesions in the above mentioned study group mostly populate the right side or ascending colon.

2. AIM

To evaluate the efficacy of Moviprep®, within the setting of a rural outreach program in the Northern Cape Province, in providing adequate right colon preparation for surveillance colonoscopy.

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CHAPTER 2

PUBLICATION-READY MANUSCRIPT

2.1 TITLE PAGE

2.1.1 Title of paper

2 L Polyethylene glycol ascorbic acid preparation provides effective preparation for colonoscopy in a rural setting.

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2.1.3 Supplementary information

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Reprints: No reprints

2.2 ABSTRACT

Background: A cohort of subjects with Lynch Syndrome, undergo colonoscopic surveillance in the Northern Cape Province of South Africa over 1 week, annually. Excellent preparation of the colon is essential to detect small right sided lesions. This is difficult to achieve particularly in rural areas. Distances to endoscopy facilities are also vast.

Moviprep is a 2l polyethylene glycol (PEG) electrolyte solution containing ascorbic acid and sodium ascorbate marketed by Norgine Pharmaceuticals. It is claimed that it provides a similar quality of preparation to the standard 4 l PEG preparation but with less volume and patient discomfort.

Aim: To evaluate Moviprep®, as a preparation for colonoscopy, in a cohort of subjects with Lynch syndrome in rural South Africa.

Patients and Methods: 6 weeks prior to the colonoscopy surveillance week, a team travelled to the area to prepare the patients for colonoscopy. After informed consent, 71 individuals with an intact left colon and known to carry a C1528T mutation in the *hMLH1* gene, were individually counselled on the importance of bowel cleansing and the specific use of Moviprep®. During the surveillance week, 6 weeks later, colonoscopies were performed at 4 venues in the Northern Cape. Subjects completed a product acceptability questionnaire on arrival for surveillance colonoscopy. The questionnaire evaluated the following aspects: ease of product preparation, prior experience with the product, acceptability and taste of the preparation, prior colonoscopy experience, volume of prep taken and occurrence of nausea and vomiting.

The quality of preparation was assessed visually at colonoscopy by a single individual (DJdV). The preparation was graded using the following criteria (The Harefield Cleansing Scale): A = all colon segments clean; B = at least 1 segment with residual amounts of brown liquid or semisolid stool, which can easily be displaced or removed; C = at least 1 segment with only partially removable stool, preventing complete visualization; D = at least 1 segment which could not be examined due to solid stool). Grades A or B were accepted as successful preparation and C or D would be considered failed preparation.

This study was passed by the Research Ethics committee of the University of Cape Town (HREC REF:249/2013).

Results: 64 of 71 (90%) subjects seen on the preparation trip completed the questionnaire. 53 of 64 (83%) had used other colon preparations previously. 57 of 64 (89%) would prefer Moviprep® for their next colonoscopy. A total of 46 subjects of the 64 underwent colonoscopy. 41 of the 46 (89%) had acceptable colonic preparation as judged at endoscopy.

Conclusion: Moviprep® provides adequate colonic cleansing in 89% of subjects undergoing surveillance colonoscopy in a rural setting. A similar number would choose the same preparation for their next colonoscopy.

2.3 MAIN PAPER

Introduction

One of the factors that negatively affect polyp detection is an inadequately prepared colon. A cohort of individuals with Lynch Syndrome, (*hMLH1* mutation C1528T), undergo a surveillance colonoscopy in small rural hospitals where endoscopy is not usually available as part of an outreach project. There are major resource constraints within the region. The nearest routine colonoscopy service is between 600 and 1200km away from where the at risk individuals live.

The only bowel preparation available previously in the region was an oral phosphate soda type preparation. There was some concern about this preparation because of the inability to ensure adequate fluid intake and pre-preparation fitness. We therefore sourced a 4L PEG solution but compliance was an issue because of the large volume. The availability of a 2L PEG ascorbic acid solution may address both the safety and compliance concerns.

Aim

The aim of this study was to assess the efficacy and acceptability of a 2L preparation of PEG with ascorbic acid and ascorbate. The primary endpoint was the quality of colon preparation and the secondary endpoint was subject acceptability of the preparation.

Methods

The study was conducted in two main phases:

Phase one.

All known at risk individuals who require colonoscopic surveillance were identified. A 1 week preparation road trip was undertaken into the western part of South Africa from 7 July 2013 until 12 July 2013. The team consisted of a professional nurse specialised in genetics, a genetics registrar, a professional endoscopy nurse, a representative of the Norgine pharmaceutical company and a registrar in general surgery.

14 towns were visited in the Northern Cape. Subjects received counselling on the importance of good bowel preparation for colonoscopy and each received an information sheet detailing the aim, methods and possible risks involved in this study in their home language.

Where subjects could not be seen in person, a family member or the primary health care worker was requested to convey the information. All subjects were given the choice between their usual bowel preparation, Klean-prep®, or using Moviprep® for the first time. During this session, it was made clear to the patient that Moviprep® is not an experimental colonic preparation and that it has been well proven and studied in its efficacy and side effect profile. This study aimed to look at the efficacy and patient opinion of Moviprep® in a rural setting.

Moviprep® includes a detailed instructional pamphlet. This pamphlet served as the standardised instruction during the counselling sessions. This aided informing subjects on dietary requirements the day prior to colonoscopy, extra clear fluid intake and instructions on mixing the product.

Each subject was given a choice on when to drink the two litres of Moviprep®. Either a single dose which consisted of two litres of Moviprep® at 05h00 the morning of the colonoscopy or a split dose, consisting of two litres of Moviprep® split up in one litre the night prior to- and the second litre the morning of the colonoscopy.

Informed consent was obtained from all subjects participating in the study which included consent for the use of Moviprep® as bowel preparation as well as completion of a product acceptability questionnaire.

Phase two.

A weeklong trip was undertaken from 26 August 2013 till 30 August 2013 to the Northern Cape, with a 19 member team. 4 Pre-planned destinations included: Upington, Nababeep, Garies and Vredendal Hospitals. Fully equipped endoscopy units were set up in each centre.

Questionnaires were completed by the patients awaiting their colonoscopies which assessed:

- Compliance
- Product satisfaction
- Side effect profile
- Comparison to other preparation products

Prior to colonoscopy each subject's colonic cleansing was assessed by a nurse who inspected the stool consistency. Each subject noted to have particulate matter in his or her stool, was given an additional litre of bowel prep (Moviprep®).

Every colonoscopy was evaluated and scored on cleanliness and quality of preparation by a single observer who was not doing the colonoscopy (DJdV). The scoring was done during the course of each endoscopy using a validated colonic preparation scoring system, "The Harefield Cleansing Scale".

The Harefield Clensing Scale divides the colon into 6 segments (rectum, sigmoid, descending-, transverse- and ascending colon and cecum). A grade ranging from A to D is awarded to each segment as follows:

A = all colon segments clean;

B = at least 1 segment with residual amounts of brown liquid or semisolid stool, which can easily be displaced or removed;

C = at least 1 segment with only partially removable stool, preventing complete visualization;

D = at least 1 segment which cannot be examined due to solid stool).

Grade A or B was considered as a successful cleansing. Grade C or D was considered a failed colonic preparation. (Appendix C)

All data processing was done with the aid of Microsoft Office Excel 2007.

Results

Phase one

During the initial phase of the study a total of 71 boxes of Moviprep® were distributed to subjects. 48/71 (68%) were directly counselled and consented by DJdV and 16/71 (23%) received their counselling indirectly from a family member who attended the counselling session, or a professional nurse known to the patient. For a further 7 (10%) subjects, preparation was delivered to the local clinic but it was not possible to provide personalised instruction. None of these 7 subjects arrived for their colonoscopies during the second phase of the study.

Phase two

64/71 (90%) subjects decided on Moviprep® as their colonic preparation and were willing to complete the questionnaire. The remaining 7 did not attend on the day of their colonoscopy. These were the same individuals who could not be contacted during phase one of the outreach program.

In total, 46/64 (72%) patients who had used Moviprep® and signed consent for the study had their colonoscopies done. Due to logistic constraints at one of the venues, 18/64 (28%) colonoscopies could not be performed. (Figure 1)

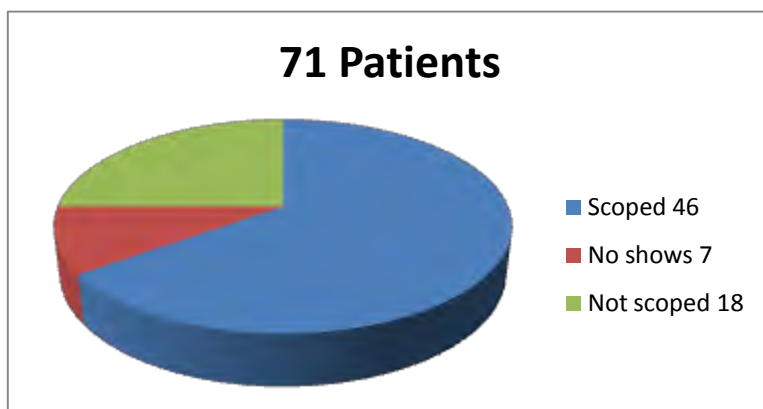


Figure 1. Breakdown of scope numbers

9/46 (19%) patients received an extra litre of preparation. Of the 46 patients who had their colonoscopies performed, 41 subjects (89%) were graded A or B. The remaining 5/46 (11%) C and D. (Figure 2)

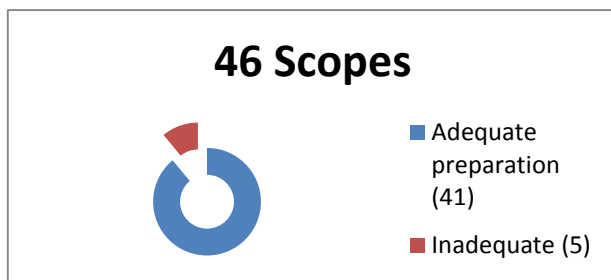


Figure 2. Cleansing results

Thus, of the 41 (89%) patients that had passed their colonic preparation, 26/41 (63%) received direct counselling from me and 15/41 (37%) indirect counselling from either a counselled family member or a professional nurse. This was found to be statistically significant. (p-value 0.02)

Of the 5 (11%) patients who failed their colonic preparation, 4/5 (80%) were counselled directly and 1/5 (20%) received indirect counselling. (Figure 3)

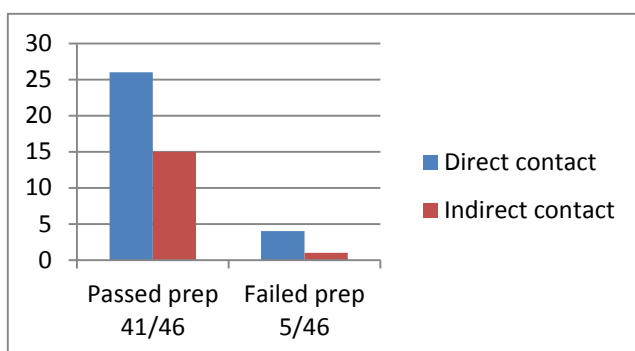


Figure 3. Contact with patient during phase one.

When comparing single or split dose preparation of Moviprep®; 33 (80%) of the 41 patients who passed their colonic preparation had used the single dose method and 8/41 (20%) used the split dose method. All the patients who had failed their colonic preparation (5/5) had used the single dose method. (Figure 4)

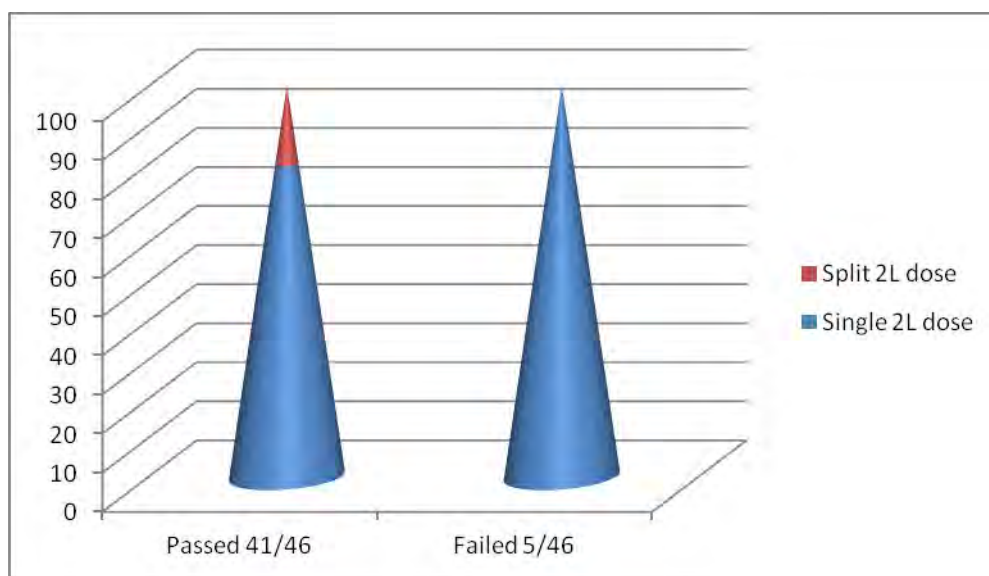


Figure 4. Single versus split preparation

A total of 18 subjects could not be colonoscoped due to logistic constraints at one of the venues. Despite this they all completed a questionnaire. At another venue, 7 patients did not arrive for their colonoscopies which brought the total of completed questionnaires to 64. Of the 64 patients, 53(83%) had used a colonic cleansing preparation in the past. None of these patients had ever used Moviprep® as colonic preparation prior to this study. 91% of the 53 patients, who had used a different type of colonic preparation in the past, preferred using Moviprep® as their colonic preparation in the future. When asked whether or not Moviprep® would be considered for future colonic preparation, 57/64 (89%) answered yes.

18/64 (28%) reported an unpleasant taste and 46/64 (72%) reported the taste as being pleasant. 56/64 Patients found Moviprep®, as a product, easy to prepare and 63/64 patients reported that they had followed the instructions regarding diet and fluid intake during the preparation process.

The side effect profile was found to be similar to most bowel preparation regimes. This included nausea and/or vomiting, abdominal cramps and a feeling of “hunger” during the preparation period. Subjects were asked to rate each possible adverse reaction or event on a

scale of 1 to 5. One being the least severe, and 5 most severe. Of the 64 patients who had completed a questionnaire, 6% (4/64) experienced nausea rated at 5/5. Abdominal cramps were experienced at a rating of 2/5 in 11% of subjects and 5/5 in 5% of subject. The major adverse event experienced by subjects, were the sensation of “hunger” during the preparation phase. Of the 64 subjects, 17% (11/64) rated hunger at 5/5 and 23% (15/64) rated it at 2/5.

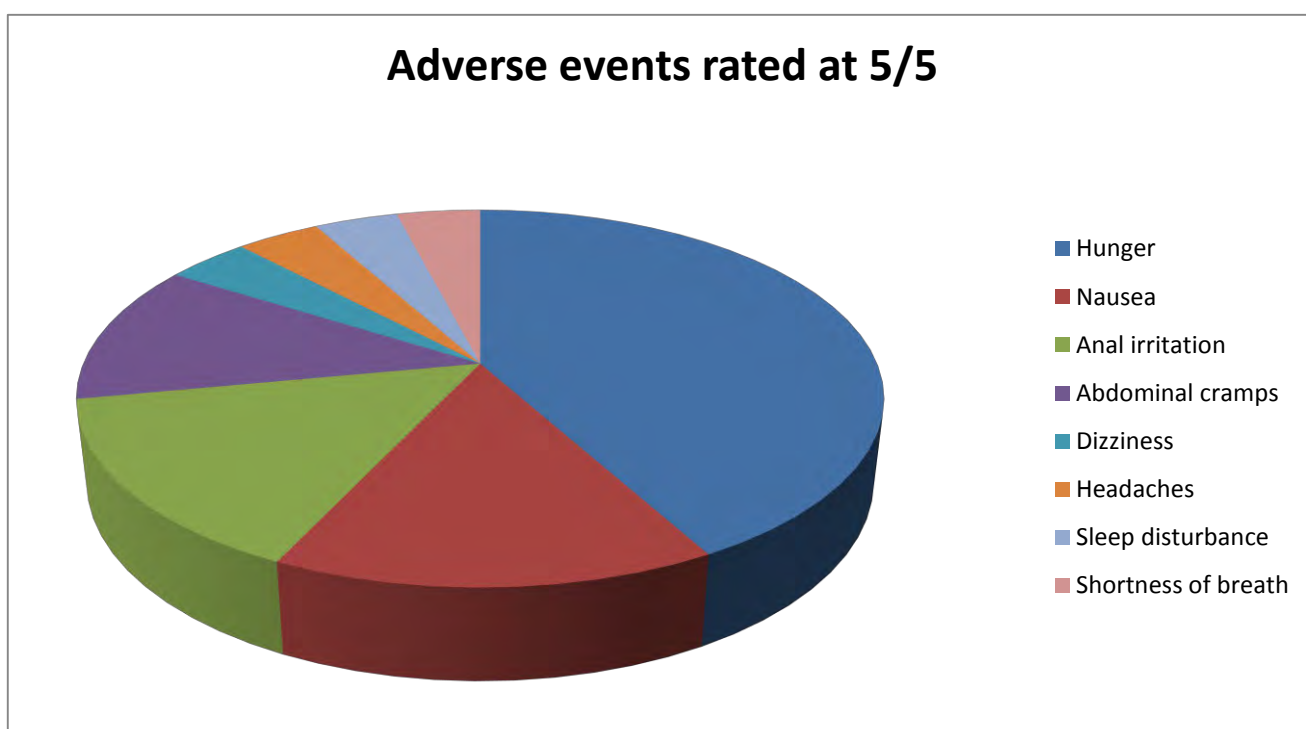


Figure 5. Breakdown of adverse events rated 5/5 in 40% (26/64) subjects

Discussion

Several studies established that in preventing colorectal cancer, colonoscopy is less effective in the proximal compared to the distal colon. Reasons for this might be poor colon preparation prior to colonoscopy or the fact that polyps in the proximal colon tend to be more difficult to detect.¹⁻³ Without proper colonic cleansing a complete and thorough investigation is impossible, not to mention the higher risk of patient discomfort and possible complications related to the procedure itself.

In this study population, colonoscopy was performed in patients with a high risk of developing colon cancer and the lesions are mostly encountered on the right side of the colon. This emphasises a clean colon even more. These patients live in a rural part of South Africa and are screened annually by colonoscopy. It is thus very important, in this rural setting, that every colonoscopy is preceded by optimal bowel cleansing.

During this study we offered a cohort of patients an alternative colonic preparation to what they are used to. This product is marketed as being half the usual volume, 2 litres compared to 4 litres, as well as having a more pleasant taste. This should make the likelihood of the patient completing his/her preparation regime much higher.

In a systematic review by van Rijn et al 2006, they reviewed polyp miss rate looking at both polyp size and polyp type. A total of 465 colonoscopies were reviewed.⁶ Adenoma miss rate was 2.1% for polyps larger than 10mm, 13% for adenomas 5 – 10mm and 26% for adenomas of 1 – 5mm. Polyps larger than 10 mm are rarely missed at colonoscopy, but the miss rate increases significantly as the polyp size decreases.⁶ In their review of the literature, they found that one in five polyps is missed at colonoscopy. Larger polyps are less likely to be missed, but some big adenomas might be overlooked. One in four adenomas (1-5mm) may be missed. Unfortunately the number of studies looking at this specific topic is small.⁶

Bressler et al reviewed the miss rate of right sided colon cancer in 4920 patients. All of these patients had established and confirmed right sided colon cancer.⁷ 2654 (53.9%) had had a colonoscopy within 3yrs of their diagnoses being made. Of the 2654 patients, 96% had their most recent colonoscopy up to 6 months before admission, thus viewed as detected cancers.⁷ 105 patients or rather 4.0% had their most recent colonoscopy between 6 and 36 months prior to admission, categorizing them as missed cancers. The miss rate of right sided cancers in usual clinical practice was found to be 4.0%.⁷

Of the 71 patients approached for this study regarding the use of Moviprep®, 64 were enrolled in the study and 46 colonoscopies were evaluated for colonic cleansing. Data clearly shows that Moviprep® can be used, for colonic preparation in the rural setting, with great success. This was proven with successful cleansing in 89% of all scoped patients. A similar percentage of patients were satisfied with Moviprep® and would prefer using it in the future for colonic preparation.

Colonic preparation will never be viewed as a convenient and easy process. What we essentially induce in our patients is diarrhoea with nausea and vomiting in some cases. With this being said, one can understand that some patients find it very difficult to complete a course of colonic preparation despite the risk of an incomplete colonoscopy. The main drive behind this study was to see if we can offer patients, in this study group, an alternative to what they are used to. While doing this, we have proven the product as being effective, even in a rural community with minimal resources.

Conclusion

Moviprep® can effectively be used in the rural setting for bowel cleansing with proven patient satisfaction. The feedback and data derived from this study proved the above and the author hopes that he can offer the same product, even as an alternative, to the cohort of patients along the west coast of South Africa in the future.

A lot of emphasis is placed on bowel preparation prior to colonoscopy with good reason, as stipulated before. The patients in this cohort cannot afford missing out on a single surveillance colonoscopy, especially not due to poor bowel cleansing. Here we have proven that patients were compliant to Moviprep® and would do it again.

2.4 REFERENCES

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CHAPTER 3

Appendix A

INFORMATION SHEET

Title: Effectiveness of Moviprep® as colonic preparation – cleansing right colon for Lynch Syndrome (LS) screening

Researchers

Dr. D.J. de Villiers, Surgical Registrar, UCT

Prof. P.A. Goldberg, Head of Colorectal Unit, UCT

Sr. U. Algar, Colorectal Unit, UCT

Introduction

You are invited to participate in a study evaluating the effectiveness of Moviprep® in cleaning the colon in preparation for colonoscopy. Moviprep® is a bowel preparation specifically designed for bowel cleansing.

A study group of about 100 patients who undergo yearly colonoscopy will be asked to enrol in the study.

Nature of research and purpose of the study

Moviprep® is a product manufactured by the Norgine group of Companies. It is a well established product specifically directed at bowel cleansing. Norgine donated Moviprep® to the 2013 Colonoscopy outreach programme and we decided to test its efficacy during a trial

which will run during the outreach programme. Preparation of the colon prior to colonoscopy is an essential part of the preparation process.

If the colon is not cleaned properly it is impossible to do a complete and thorough colonoscopy. This product, Moviprep®, is a bowel preparation said to be effective in cleaning the colon and easy to use. With this study we will evaluate whether or not Moviprep® cleans the bowel well enough to do a complete colonoscopy.

In general, patients in rural parts of the country use whatever product is available from their local hospital and clinic. These products, e.g. fleet enemas, laxatives etc. are not always specifically indicated for bowel preparation and are either uncomfortable or difficult to use or may result in poor bowel preparation. Poor bowel preparation may mean that the doctor cannot see all the areas of the colon necessary for proper screening.

What do I have to do if I agree to take part in the study?

The product, Moviprep®, will be supplied to you with specific instructions on its use.

The product, 2 L in total, must be taken one day before the procedure in two divided doses.

Agree to answer a few questions before or after the colonoscopy regarding your experience with Moviprep® e.g. taste, ease of preparation, ill effects etc.

Possible risks and benefits

This product is not an experimental medication and is freely available on the market since 2006 and is safe. It is a well known bowel preparation in the private sector. As with any pharmaceutical product on the market, and with most colonic preparations, one should expect possible risks of experiencing ill effects or adverse reactions.

Risks or adverse effects:

Any patient, who has used the product before and experienced adverse effects or severe allergic reactions, should not use this product again. Diarrhoea is an expected outcome of bowel preparation but other gastro-intestinal side effects can often occur. This would include nausea, vomiting, bloating, abdominal pain, anal irritation and sleep disturbance and may vary between different preparations. These might only occur when the product is used and will resolve spontaneously shortly after colonoscopy.

The risk of poor bowel preparation is very low as the product is designed to induce diarrhoea and bowel cleansing. We will specifically look at the quality of bowel cleansing that this product produces on the day of colonoscopy.

Benefits

The product is marketed as having a pleasant taste compared to other products on the market. The entire preparation consists of two oral doses of 1L each compared to other preparations consisting of 4L in total. Preparation is easy and no rectal administration required. There is also a chance that the doctor's ability to view to colon may be better with this product than with less suitable bowel preparations, e.g. fleet enemas that may be available from your local clinic or hospital.

Other options

It is your own free choice to take part in this study. If at any stage you decide against the use of Moviprep®, or not to participate in the study, we will provide you with another good quality bowel cleansing product.

Confidentiality

If you agreed to take part you will not be identified by name in any of the data or any publication of the results. The results of your colonoscopy and any other private medical information will be protected and kept confidential.

Contact details

If you have any questions regarding the product or the study please contact the following people:

Dr. D.J. de Villiers – 083 422 3162

Sr. Ursula Algar – (021) 404 5499

If you are concerned that your rights as a research participant has not been respected please contact the following committee:

Faculty of Health Sciences – Human Research Ethics Committee

Telephone: (021) 406 6626

Email: Shuretta.thomas@uct.ac.za

Appendix B

Consent Form to participate in medical research

Title: Effectiveness of Moviprep® as colonic preparation – cleansing right colon for Lynch Syndrome (LS) screening

Authors: Dr. DJ de Villiers, Prof. PA Goldberg, Sr. U Algar

Contact for research: Dr. DJ de Villiers (Tel: 083 422 3162 e-mail: devilldj@gmail.com)

I, _____ hereby agree to participate in the research project evaluating the effectiveness of Moviprep® in cleansing the right/ascending colon prior to colonoscopy being done. The risks and benefits have been explained to me by Dr. DJ de Villiers and Sr. Ursula Algar which I understand and have been given the opportunity to ask questions.

I understand that my participation in this study is entirely voluntary and as colonic preparation is an absolute necessity prior to colonoscopy I can contact Dr. DJ de Villiers or Sr. Ursula Algar if I prefer using an alternative preparation to Moviprep® and not continue with the study.

I understand there will not be any financial compensation involved for participation in this research.

If you agreed to take part you will not be identified by name in any of the data or any publication of the results. The results of your colonoscopy and any other private medical information will be protected and kept confidential.

Patient

Doctor

Witness

Witness

Date

Appendix C

The Harefield Cleansing Scale®

Objective Segmental Evaluation of Cleanliness

For each segment of the colon score the overall cleansing according to the following criteria:

| Segmental Score | 0 | 1 | 2 | 3 | 4 |
|--|---------------------------------|---|--|------------------------------|--------------------------|
| Example | | | | | |
| Description | Irremovable, heavy, hard stools | Semi-solid, only partially removable stools | Brown liquid/removable semi-solid stools | Clean liquid | Empty and Clean |
| Rectum | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Sigmoid Colon | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Descending Colon | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Transverse Colon | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Ascending Colon | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Caecum | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Use the lowest scoring segment to calculate the overall grade of colon cleansing | | | | | |
| Grade | ↓ D | ↓ C | ↓ B | ↓ A | |
| | 1 or more segments scored 0 | 1 or more segments scored 1 | 1 or more segments scored 2 | All 5 segments scored 3 or 4 | |
| Tick only one box | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| | FAILURE | | | SUCCESS | |

MP/0212/001

The Harefield Cleansing Scale®

Objective Segmental Evaluation of Cleanliness

For each segment of the colon score the overall cleansing according to the following criteria:

| Segment Score | Description |
|---------------|---|
| 0 | Irremovable, heavy, hard stools |
| 1 | Semi-solid, only partially removable stools |
| 2 | Brown liquid/removable semi-solid stools |
| 3 | Clear liquid |
| 4 | Empty and Clean |

Success Scores

| Grade | Description |
|-------|------------------------------|
| A | All 5 segments scored 3 or 4 |
| B | 1 or more segments scored 2 |
| C | 1 or more segments scored 1 |
| D | 1 or more segments scored 0 |

Segmental Cleansing Score examples

The Harefield Cleansing Scale, © Norgine® group of companies, 2008.

Appendix D

Questionnaire

**Effectiveness of Moviprep® as colonic preparation –
cleansing right colon for Lynch Syndrome (LS) screening**

Dr. DJ de Villiers

Supervisor

Prof. PA Goldberg

Department of Colorectal Surgery

Groote Schuur Hospital

Please tick appropriate box

1. Was Moviprep® easy to prepare?

Yes No

2. Did you follow the instructions on preparing Moviprep®?

Yes No

3. Did you follow the instructions on diet and fluid intake during preparation?

Yes No

4. Did you take 2L of Moviprep® in total?

Yes No

5. Was a litre a day for two days too much to drink?

Yes No

6. Did Moviprep®, in your opinion, have a bad or pleasant taste?

Bad Pleasant

7. Was Moviprep® easy or difficult to swallow?

Difficult Easy

8. Have you used other preparations before?

Yes No

9. If yes in question 8, was Moviprep® easier to take than other preparations?

Use a 1 to 5 scale with 1 difficult and 5 very easy

1 2 3 4 5

10. Did you experience any side effects after taking Moviprep®?

Yes No

11. Please indicate whether you experienced any of the following:

Use a scale from 1 to 5 with 1 being none and 5 severe

Nausea 1 2 3 4 5

Rash 1 2 3 4 5

Vomiting 1 2 3 4 5

A PROSPECTIVE STUDY

de Villiers DJ

| | | | | | |
|----------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| Itchiness | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Abdominal cramps | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Limb swelling | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Abdominal pain | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Hunger | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Abdominal distension | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Dizziness | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Anal irritation | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Headache | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Sleep disturbance | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| Shortness of breath | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |

12. Would you consider using Moviprep® in future as bowel preparation for colonoscopy?

Yes No

13. Would you recommend Moviprep® to a friend or family member as bowel preparation prior to colonoscopy?

Yes No

14. In your opinion, was Moviprep® effective in cleaning your bowel?

Yes No

Thank you

Appendix E

BOWEL PREPARATION PRIOR TO COLONOSCOPY

- If the preparation is to be of any value you must co-operate fully in preparing yourself for your procedure. If the bowel is not clean the procedure may have to be repeated.
- Any tablets containing iron **MUST** be stopped at least 7 days before the procedure.
- If you are prone to constipation or have been following a high fibre diet you may need to take a laxative such as MOVICOL® several days before your procedure.

TWO DAYS BEFORE YOUR PROCEDURE

- We recommend a light diet which is low in fibre and nothing that contains seeds, nuts or anything with skins eg grapes.

THE DAY BEFORE YOUR PROCEDURE

- You may eat a light breakfast e.g. poached egg on white toast. For lunch have a clear soup without any "bits". Clear fluids should be consumed as much as possible in addition to the water which is taken after each litre of MOVIPREP®.

| FIRST LITRE OF MOVIPREP® | | SECOND LITRE OF MOVIPREP® | |
|---|-------|---|-------|
| Date: | Time: | Date: | Time: |
| 1 Hour later drink 500ml of water | | 1 Hour later drink 500ml of water | |
| You should continue to drink clear fluids | | You should continue to drink clear fluids | |

Your bowel is only clear once you are only passing clear liquid without any solid components.

Stop drinking all liquids at _____ time

Examples of clear liquids which should be consumed as much as possible:

Black tea

Black coffee

Clear soup

Stock cubes dissolved in warm water

Jelly

Fruit juice (no pulp)

Clear soft drinks eg Sprite, Sprite Zero

Energy Drinks eg Powerade, Energade (no black or red coloured drinks allowed)

- You may take regular medication EXCEPT aspirin, iron, diabetic medications or warfarin with a sip of water up to 2 hours before your procedure.

YOU WILL NOT BE ABLE TO DRIVE FOLLOWING YOUR PROCEDURE.

If you have any queries please contact your doctor.

How to prepare [®]MOVIPREP[™]

1st Litre



- Pour contents of both sachets A and B into a jug
 - Add 1 litre of water
 - Stir to mix well
 - Pour into a glass and drink all of the mixture
- **Drink an additional 500ml of clear fluids**

2nd Litre



- Pour contents of both sachets A and B into a jug
 - Add 1 litre of water
 - Stir to mix well
 - Pour into a glass and drink all of the mixture
- **Drink an additional 500ml of clear fluids**

Appendix F



UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee

Professor Anwar Suleman Mall

J-45 Room Old Main Building, Groote Schuur Hospital,
Observatory 7925, South Africa

Tel (021) 406 6168/6232/6227 Fax (021) 448 6461

Email: Anwar.Mall@uct.ac.za

23rd April 2013

Dr D de Villiers
Department of Surgery
Division of General Surgery
Groote Schuur Hospital
University of Cape Town

Dear Dr de Villiers

RE: PROJECT 2013/030

PROJECT TITLE: Effectiveness of Moviprep® as colonic preparation – cleansing
right colon for Lynch Syndrome (LS) screening

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

Signed

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE

*OUR MISSION is to be an outstanding teaching and research university,
educating for life and addressing the challenges facing our society.*

The South African Journal of Surgery (SAJS) - Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; and (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

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Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

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Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to www.icmje.org.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to surgery. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results, and Conclusion*.

Scientific letters/short reports, which include case reports, side effects of drugs and brief or negative research findings should preferably be 1500 words or less, with 1 table or illustration and no more than 6 references. Please provide an accompanying abstract not exceeding 150 words.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAJS peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Obituaries should be about 400 words and may be accompanied by a photograph.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - www.icmje.org.

Manuscripts must be provided in **UK English**.

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Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

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Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

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Journal references:

Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. [<http://dx.doi.org/10.1000/hgjr.182>] [PMID: 2764753]

Book references:

Jeffcoate N. *Principles of Gynaecology*. 4th ed. London: Butterworth, 1975:96-101.

Chapter/section in a book:

Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. *Pathologic Physiology: Mechanisms of Disease*. Philadelphia: WB Saunders, 1974:457-472.

Internet references:

World Health Organization. *The World Health Report 2002 - Reducing Risks, Promoting Healthy Life*. Geneva: World Health Organization, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

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