"TO STUDY EUPHORBIA PROSTRATA DRY PLANT EXTRACT VS MICRONISED PURIFIED FLAVONOID FRACTION OF DIOSMIN EFFECTIVENESS IN TREATMENT OF BLEEDING HAEMORRHOIDS IN PATIENTS ATTENDING A TERTIARY CARE HOSPITAL – A RANDOMISED CONTROL STUDY"

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LIST OF ABBREVIATIONS USED

AD	-	Anno Domini
BC	-	Before Christ
BP	-	Blood pressure
bpm	-	Beats per minute
CBC	-	Complete blood cell
COX-2	-	Cyclooxygenase 2
CVI	-	Chronic venous insufficiency
DGHAL	-	Doppler-guided hemorrhoidal artery ligation
e.g.	-	For example
GI	-	Gastrointestinal
IBS	-	Intestinal Bowel Syndrome
iNOS	-	Inducible nitric oxide synthase
IRC	-	Infrared coagulation
mg	-	Milligram
mm Hg	-	Milligram of mercury
mm	-	Millimeter
MPFF	-	Micronized purified flavonoid fraction
n	-	Total number
NSAIDs	-	Nonsteroidal anti-inflammatory drugs
OPCs	-	Oligomeric proanthocyanidin complexes
p	-	Probability
PGE2	-	Prostaglandin E2
PPH	-	Prolapsing hemorrhoids
RBL	-	Rubber band ligation

RFA	-	Radiofrequency ablation
SD	-	Standard deviation
SH	-	Stapled hemorrhoidopexy
TID	-	Three times a day
TxA2	-	Thromboxane A2
VAS	-	Visual analog scale
viz.	-	Namely

ABSTRACT

Background and Objectives

Hemorrhoids are one of the most frequent anorectal disorders encountered in the primary care sitting. The present study was aimed to assess the effectiveness of Euphorbia Prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin in control of bleeding haemorrhoids and to find the safety of Euphorbia Prostrata dry extract.

Methodology

This one year single blind randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 60 patients divided into two groups of 30 each as experimental or control group randomly by envelop method that is Group E (euphorbia prostrate) and Group C (diosmin) respectively.

Results

In the present study, the male female ratio in group E was 4:1 while in group C it was 14:1. The mean age in group E was 39.60±6.52 years compared to 43.40±10.11 years in group C (p=0.092). The mean duration of bleeding in group E was 14.6±5.41 days compared to 12.4±4.89 days in group C (p=0.109). During fifth day follow up, significantly higher number of patients in group E (53.33%) reported average reduction of bleeding compared to group C (13.33%) (p=0.001). At second and third follow up, both the groups were comparable and no statistically significant difference was noted with relief from pruritis at all the follow ups.

Conclusion and interpretation

Overall, treatment of euphorbia prostata significantly resulted in faster recovery from bleeding at first follow up on day five but further its was comparable with micronized purified flavonoid fraction of diosmin. The safety of Euphorbia Prostrata dry was comparable with micronized purified flavonoid fraction of diosmin.

Keywords

Diosmin; Euphorbia Prostrata; Haemorrhoids;

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Chapter 1

Introduction

INTRODUCTION

Hemorrhoids is one of the most common condition for which patients seek consultation from a colon and rectal surgeon. This disease is reported to affect around 10 million Americans per year with a prevalence of 4.4%.

It has been published that Caucasians of higher socioeconomic class were afflicted with a greater frequency and was theorized to be diet related.[2] However, it remains unclear if this represents limitations to the reporting of symptoms or healthcare-seeking practices. Other contributing factors include situations that increase intraabdominal pressure (pregnancy, constipation, or prolonged straining), as well as weakening of supporting tissue due to aging or genetics. It is thought that clinical disease develops as a result of dilation and distension of the veins along with weakening of the supporting connective tissue.[1]

Hemorrhoids is a common, complex, and multifaceted entity. Patients presenting with signs and symptoms of hemorrhoids should be carefully and thoroughly evaluated to exclude other diseases. Haemorrhoidal disease is most commonly associated with bleeding.[1]

There are a variety of treatments (nonoperative and operative) that have their own benefits and drawbacks. Each patient should be treated individually based on their symptoms as well as considering their other medical problems.[1]

The basic pathological factor in haemorrhoids is the dilation of the anorectal venous plexuses. In acute bleeding of internal haemorrhoids, one of the pathogenic processes implicated is the stagnation and stasis of blood in the

vascular plexuses of the prolapsed anal cushions. It has been demonstrated that stasis activates the WBC's to release inflammatory mediators and cause an inflammatory response leading to increased permeability, fragility and necrosis of the vessel wall. As a result anal cushions are easily injured by the passage of stool and bleed.[3]

Numerous modalities and techniques have been developed for treatment of symptomatic haemorrhoids. The treatment of haemorroids is often divided between nonoperative management, procedures and surgical management. The least-invasive approach should be considered given the physiologic importance of the hemorrhoid cushions and the potential self-limiting nature of many hemorrhoid symptoms. The decision on how to treat depends on multiple factors including the degree of symptoms, age, and other medical conditions. The goal of therapy should benefit from minimizing straining and avoiding constipation. Bulking of the stool facilitates this and can be accomplished by increasing dietary fiber and fluid intake. Stool softeners may also be used. Sitz baths are warm soaks that provide relief by reducing swelling and sphincter spasm.[4]

Euphorbia prostrata is a small prostrate, hispidly pubescent annual herb found all over India. This plant has traditionally been used to treat several ailments since time immemorial. The active principles in Euphorbia prostrata are chiefly flavonoids, phenolic acid and tannins. Flavonoids and phenolic acid have been reported to have anti inflammatory, analgesic, antioxidant, haemostatic, antithrombotic and vasoprotective actions. Tannins are known to possess astringent and haemostatic properties.[5]

Diosmin is a type of plant chemical found in citrus fruit. It reduces swelling (inflammation) and restores normal vein function.[4] It is one of the most commonly followed treatment regimen for haemorrhoids. The active compound in it is flavonoids.

Topical agents utilizing astringents, analgesics, and steroids help provide relief in an acute setting, but no evidence showing their benefit for prevention or long-term treatment of hemorrhoid disease is available. Surgical techniques are available for the treatment of second and third degree haemorrhoids. But pain and discomfort, anal narrowing, tags, haemorrhage, faecal incontinence and residual piles are reported complications of surgical procedures. Therefore, pharmacological agent leading to effective and rapid non-invasive control of signs and symptoms is of immense clinical value.[1]

Hence the present study was undertaken to assess the effectiveness of Euphorbia Prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin in control of bleeding haemorrhoids and to find the safety of Euphorbia Prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin.

METHODOLOGY

The study was conducted in the Pediatric Intensive Care Unit (PICU) of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, attached to KLE University's Jawaharlal Nehru Medical College, Belgaum.

Study design

Single Blind Randomized Controlled Trial

Study place

The study was conducted in the Pediatric Intensive Care Unit (PICU) of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre attached to KLE University's Jawaharlal Nehru Medical College, Belgaum

Study period

January 2012 to December 2012

Source of data

All ventilated patients admitted in PICU of KLES Dr. Prabhakar Kore hospital and medical research centre.

Sample size

$N = 2(Z_\alpha + Z_\beta)^2 \times PQ/(P_a - P_b)^2$

$\approx$ 37in each group$\approx$ 40*

Where P_A – 20%; P_B – 0%

P_A- Outcome in control group

P_B- outcome in test group (percentage decrease)

α -0.05; β -0.2 (power of 80%)

Z_α -1.96; Z_β -0.84

$P = (P_A+P_{B)}/2 = 10$

Q = 100-P = 10

10% loss due to death

10%loss due to loss of follow-up

With a total loss of 20%, the sample size was 45 in each group.

Selection criteria

Inclusion criteria

All the consecutive ventilated Patients

Exclusion criteria

- Patients with < 48 hours of ventilation (extubated, dead, DAMA or transfer out)
- Patients who developed pneumonia within 48 hours of ventilation
- Absence of written informed consent
- Known immunosuppression

Methods

Approval of study by the Institutional Ethics Committee of Jawaharlal Nehru Medical College was obtained prior to the commencement of the study. Informed consent was obtained from parents of the patients fulfilling the inclusion criteria. (Annexure–II)

Enrollment: All the patients ventilated for > 6 hrs were enrolled and randomized according to a computerized randomized table into Group A, who received conventional care, Group B who received the intervention chlorhexidine mouth wash along with the conventional care and group C who received the intervention with head end elevation along with the conventional care

At the time of enrollment, socio demographic details namely age, gender, socio economic status, ID number and a detailed history of presenting illness, past history (< 4 weeks) of hospitalization, ventilation, antibiotic use and any significant preexisting illness were recorded in a predesigned proforma (Annexure I).Number of organs affected and primary system affected were also noted down and PRISM score was calculated after 24 hours of hospital admission. (Annexure–III)

Relevant investigations like complete blood count, blood culture, arterial blood gas (ABG) and a chest x ray were obtained after intubation and at 48 hrs,72 hrs and whenever indicated

The **details of the ventilation** such as indication for intubation, date and time of intubation, the type of endotracheal tube used, number of reintubation attempts, ventilator settings used and use of sedation and its type were recorded.

After enrollment and randomization, the interventions were initiated.

Interventions

Group A: Conventional care

The components of the conventional care were:

- Hand washing before contact with any ventilated patient.
- Head end elevation between < 30°
- Mouth washes with normal saline
- Frequent change of position
- Endotracheal suction with all asepsis as required
- Chest physiotherapy

Group B: Chlorhexidine mouth wash

Along with the conventional care, patients enrolled in the chlorhexidine mouth wash group were given mouth washes with 0.2% chlorhexidine twice a day. The oral cavity was first suctioned to remove any accumulated secretions, and saline-soaked gauze was used to clean the mucosal surfaces subsequently. The allotted mouth wash was applied on to the buccal surfaces and the teeth of the patient. Strict hand hygiene was used during the procedure. The nursing staffs were trained on the method of application in order to ensure uniformity. The period of application was from the day of intubation till extubation.

Group C: Semirecumbent Position with Head of Bed Elevation:

The patients were maintained in a semi recumbent position with head end elevation maintained between 30-45° for 24 hours a day. This was followed along with the other components of conventional care.

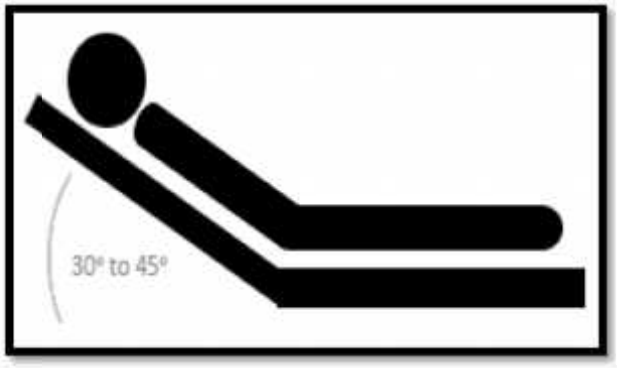


Fig 5: Monitoring

Patients were monitored for change in the clinical condition and significant physical signs were recorded. The following data were assessed daily and recorded on a monitoring chart: (Annexure–IV)

Arterial blood gas analysis, PAO2/FIO2ratio, frequency of endotracheal suction, nature of secretions, change in the color, odour and quantity of these secretions.

Clinically VAP was suspected when a patient ventilated for > 48 hours developed fever with signs of lower respiratory tract infection, with new infiltrates on chest x-ray and worsening hypoxemia on blood gas analysis. In patients ventilated for preexisting pneumonia, appearance of new radiological infiltrates and worsening of a patient after clinical improvement was considered significant. In clinically suspected cases, an endotracheal aspirate was sent for aerobic culture and sensitivity. Endotracheal aspirates were collected under all aseptic precautions .After a thorough hand wash, with the use of sterile gloves the sterile suction catheter was inserted into the endotracheal tube and advanced beyond the carina. CPIS scoring was done every day after 48 hours of ventilation. A score of > 6 was considered diagnostic of VAP[40].

Definitions used

Clinical pulmonary infection score (CPIS)

VAP was diagnosed using the CPIS criteria. CPIS uses a combination of six clinical, radiologic and microbiologic criteria: temperature, white cell count, sputum, oxygenation, culture of tracheal aspirates, and radiology; each parameter are scored from 0 to 2 and a total score of >6 points suggested a diagnosis of VAP.

Criteria	0	1	2
Temperature	>36.1 and <38.4	>38.5 and <38.9	≤36 and ≥ 39
Leucocytes	>4000 and <11000	<3.9 >11.1 and absence of band forms >11.1 and <17,no differentiation done	>11.1 and presence of band forms >17.1, no differentiation done
Tracheal secretions	Absence	Presence and non purulence	Presence and purulence
Oxygenation	>240 or ARDS		< 240 and no ARDS
Chest x ray	No infiltrate	Diffuse or patchy infiltrate	Localized infiltrate
Semi quantitative tracheal aspirate culture	$< 10^3$ No previous culture	$>10^3$	$>100^3$

Modified B G Prasad classification

SOCIO ECONOMIC STATUS	TOTAL INCOME
I	**3600 & above**
II	**1800 & 3599**
III	**1080 & 1799**
IV	**540 & 1079**
V	**< 540**

Outcomes

Primary outcome:

Incidence: The number of new cases diagnosed among the enrolled subjects during the period of study

VAP rate =

Number of ventilator-associated pneumonias x 1000
Number of ventilator-days for patients

Secondary outcomes

Risk factors: Factors known to predispose the patient to develop VAP. Risk factors used in our study were, age, gender, reintubation, prior ventilation, prior hospitalization, prior antibiotic use, use of sedation, use of uncuffed ET tube.

Duration of ventilation: Total duration of intubation.

Duration of ICU stay: Total duration that the patient was admitted in the ICU

Mortality: Death of the patient during the ICU stay

Survival: Recovery and transfer out of the patients from ICU.

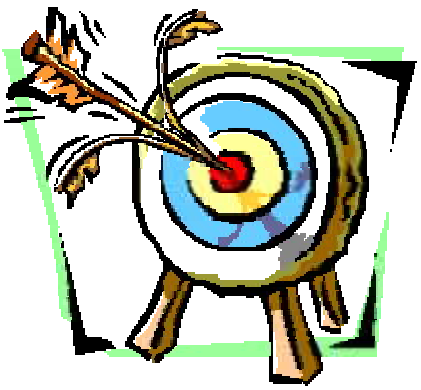
Statistical analysis

The data obtained was tabulated on Microsoft excel spread sheet and analyzed using the SPSS Statistics 21.0 software using the following tests:

- Mean and standard deviations were calculated for qualitative data like age and gender .The frequency of quantitative variables were expressed as percentages and their statistical significance was tested using student's' test, chi square and Fischer's exact t test. To determine the influence of risk factors for the VAP development, univariate analysis and multivariate analysis (logistic regression analysis) was performed in which all the risk factors were used as covariates. Rates were compared between the groups using the test of proportions. To estimate the risk of mortality and development of VAP, relative risk and odds ratio were calculated.

Chapter 2

Objectives



OBJECTIVES

The objectives of the present study were;

Primary

To study the effectiveness of Euphorbia Prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin in control of bleeding haemorrhoids.

Secondary

To assess the safety of Euphorbia Prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Haemorroids

Hemorrhoids are swollen blood vessels in the lower rectum and are one of the most common causes of anal pathology. Confusion often arises because the term "hemorrhoid" has been used to refer to both normal anatomic structures and pathologic structures. In the context of this article, "hemorrhoids" refers to the pathologic presentation of hemorrhoidal venous cushions.[7]

Hemorrhoidal venous cushions are normal structures of the anorectum and are universally present unless a previous intervention has taken place. Because of their rich vascular supply, highly sensitive location, and tendency to engorge and prolapse, hemorrhoidal venous cushions are common causes of anal pathology.[8] Symptoms can range from mildly bothersome, such as pruritus, to quite concerning, such as rectal bleeding.

Although hemorrhoids are one of the common condition diagnosed in clinical practice, many patients are too embarrassed to ever seek medical advice and treatment. Consequently, the true prevalence of pathologic hemorrhoids is not known.[9] Though hemorrhoids are responsible for a large portion of anorectal complaints, it is important to rule out more serious conditions, such as other causes of gastrointestinal (GI) bleeding, before reflexively attributing symptoms to hemorrhoids.[10]

Historical perspectives

The first known mention of this affliction is from a 1700 BC Egyptian papyrus, which advises: “Thou shouldest give a recipe, an ointment of great protection; Acacia leaves, ground, titurated and cooked together. Smear a strip of fine linen there -with and place in the anus, that he recovers immediately".[11]

In 460 BC, the Hippocratic corpus had discussed a technique for treatment of hemorrhoids similar to modern rubber band ligation: “And hemorrhoids in like manner you may treat by transfixing them with a needle and tying them with very thick and woolen thread, for application, and do not forment until they drop off, and always leave one behind; and when the patient recovers, let him be put on a course of Hellebore.”[11] Hemorrhoids may have been described in the Bible.[12,13]

Celsus (25 BC – AD 14) described ligation and excision technique, and discussed the possible complications. Galen advocated severing the connection of the arteries to veins, claiming that it reduced both pain and the spread of gangrene.[14] The Susruta Samhita, (4th – 5th century AD), was similar to the words of Hippocrates, but emphasized more on wound cleanliness.[11] In the 13th century, European surgeons such as Lanfranc of Milan, Guy de Chauliac, Henri de Mondeville and John of Ardene made great progress and development of the surgical techniques.[14]

The word "hemorrhoid" in English occurs in 1398, derived from the Old French "emorroides", from Latin "hæmorrhoida -ae".

Anatomy[1]

Hemorrhoids are not varicosities; they are clusters of vascular tissue (arterioles, venules, arteriolar-venular connections), smooth muscle (Treitz muscle), and connective tissue lined by the normal epithelium of the anal canal. Hemorrhoids are present in utero and persist through normal adult life. Evidence have indicated that hemorrhoidal bleeding is arterial and not venous. This fact is supported by the bright red color and arterial pH of the blood.

Hemorrhoids are classified by their anatomic origin within the anal canal and by their position relative to the dentate line; and hence, categorized into internal and external hemorrhoids

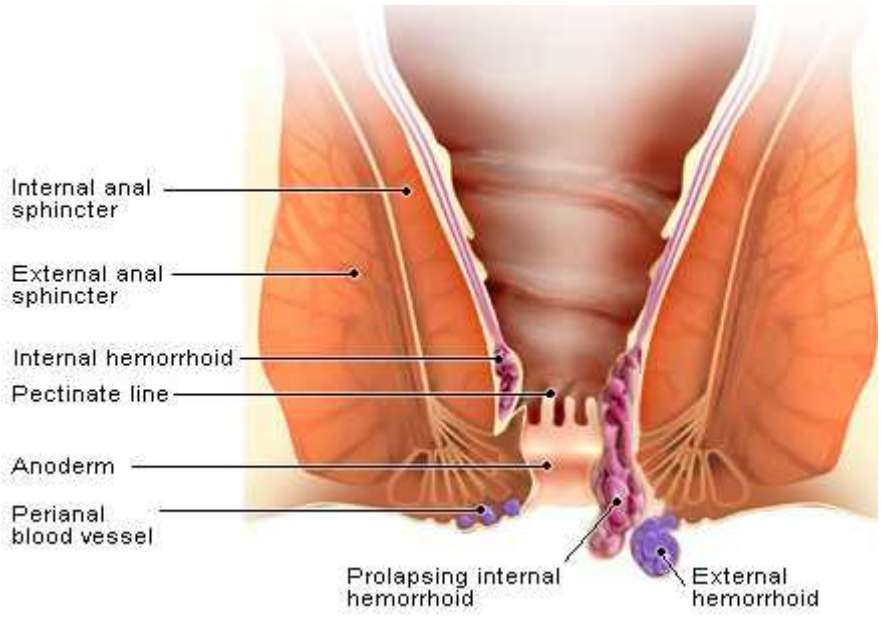


Figure 1. Anatomy of external hemorrhoid

External hemorrhoids develop from ectoderm and are covered by squamous epithelium, whereas internal hemorrhoids are derived from embryonic

endoderm and lined with the columnar epithelium of anal mucosa. External hemorrhoids are innervated by cutaneous nerves (pudendal nerve and the sacral plexus) that supply the perianal area. Internal hemorrhoids are not supplied by somatic sensory nerves and therefore cannot cause pain. Internal hemorrhoids are anchored to the underlying muscle by the mucosal suspensory ligament at the level of the dentate line

Hemorrhoidal venous cushions are a normal part of the human anorectum and arise from subepithelial connective tissue within the anal canal. Internal hemorrhoids have 3 main cushions, situated in the left lateral, right posterior (most common), and right anterior areas of the anal canal. However, it is found in only 19% of patients. Hemorrhoids can be found at any position within the rectum. Minor tufts can be found between the major cushions.

Present in utero, these cushions surround and support distal anastomoses between the superior rectal arteries and the superior, middle, and inferior rectal veins. They also contain a subepithelial smooth muscle layer that contribute to the bulk of the cushions. Normal hemorrhoidal tissue accounts for approximately 15-20% of resting anal pressure and provides important sensory information, enabling the differentiation between solid, liquid, and gas.

External hemorrhoidal veins are found circumferentially under the anoderm and hence can cause trouble anywhere around the circumference of the anus.

Venous drainage of hemorrhoidal tissue mirrors embryologic origin. Internal hemorrhoids drain into the portal system through the superior rectal vein.

External hemorrhoids drain through the inferior rectal vein into the inferior vena cava. Rich anastomoses exist between these 2 and the middle rectal vein, connecting the portal and systemic circulations.

The anal canal is 3-4 cm in length in males and slightly shorter in females, from the anal verge (lower margin of the internal sphincter) up to the puborectalis muscle. The muscular layer of the rectal wall becomes thicker on the anal canal forming the internal sphincter muscle. This muscle layer is surrounded by the conjoined longitudinal muscle, and the external sphincter muscle. The internal lining of the anal canal consists of keratinizing squamous epithelium up to the dentate line. Cranial to the dentate line the anal canal wall is lined with columnar epithelium. The zone where the anal skin and bowel mucosa meet is referred to as the transitional zone.

This mucocutaneous junction, or the dentate line, is a drainage site for anal glands into the crypts of Morgagni. Plenty of sensory nerve fibres end at this level. The mucosa and submucosa above the dentate line form an asymmetric mucosal wall including the haemorrhoid cushions or piles.

These have a relatively constant position; the left lateral position, right anterior and right posterior pile.[15]

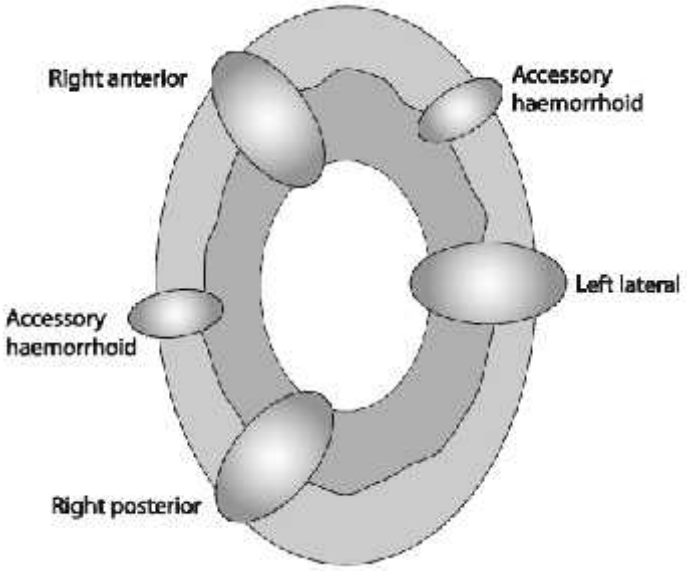


Figure 2. The invariable positioning of the anal cushions (haemorrhoids) in human

Microscopically, the epithelial layer is more thicker on the cushions with a concentration of smooth muscle fibres and connective tissue in the submucosa contributing to the bulkiness. Furthermore, there is a concentration of vascular plexa (internal haemorrhoidal plexus) in the cushions that allows them to vary in size. The smooth muscle fibres in the cushions can be seen histologically in a foetus as a continuation of the conjoined longitudinal muscle and internal sphincter muscle.[16,17]

These bundles of muscles together with an organized connective tissue stroma (Trietz fibres) are believed to be the anchoring system that attaches the blood vessels of the cushions and the overlying mucosa to the muscle wall.[17]

The suspended cushions, present in the upper part of the anal canal, are considered to form a valve that contributes to the continence for gas and liquid

stool. It means, when the pressure in the distal part of the rectum increases, the return of blood flow from the haemorrhoidal venous plexus decreases with enlargement of the cushions as a result. The three enlarged cushions seal the inlet of the anal canal like a valve to prevent leakage of liquids and gas.

Lestar et al[18] suggested haemorrhoids contribute approximately 15-20 % of the mechanism of anal closure.

Vascular nature of haemorrhoids

There exist haemorrhoidal plexa (internal and external) formed by three arteries. The internal haemorrhoidal plexus is located above the dentate line whereas the external haemorrhoidal plexus located peripheral to the anal verge. The superior haemorrhoidal arteries originate from the inferior mesenteric artery and are the terminal branches of the superior rectal artery. Additional blood supply is received from the middle haemorrhoidal artery, originating from the internal iliac artery, and the inferior haemorrhoidal artery originating from the internal pudendal artery. There is a variation in the contribution of blood supply to the haemorrhoidal plexus. For instance, in specimen studies an average of 5 branches (0-8) from the superior rectal artery were found to form the superior haemorrhoidal arteries.[15]

Furthermore, 70 percent of the specimens had blood supply to the anal mucosa from the middle haemorrhoidal artery and 42 percent from the inferior haemorrhoidal artery.[15]

The superior haemorrhoidal veins arise from the internal haemorrhoidal plexus and drain into the portal venous system, whereas the middle and inferior haemorrhoidal veins arise from the external haemorrhoidal plexus and drain into the caval venous system. However, there is free communication between the internal and external plexus. Hence this communication between the internal and external venous plexus makes it unlikely that a portal vein obstruction can lead to haemorrhoidal disease. The lymphatic drainage also demarcates at the dentate line. Above the dentate line the lymphatic drainage follows the superior haemorrhoidal artery and vein and drain into the para-aortic lymph nodes while the lymph vessels below the dentate line drain into the inguinal nodes. It is suggested that the arrangement with drainage to different venous systems has importance with reference to spread of infection or malignant disease.[19]

The theories and mechanisms of symptomatic haemorrhoids

Sliding and lining theory:

Treitz (1853) was the first to describe the anchoring connective tissue and smooth muscle deriving partly from the longitudinal conjoined muscle and partly from the internal sphincter into the submucosa of the anal canal. He explained how these layers of meshwork act as supporting scaffold to the haemorrhoidal venous plexus, thereby supporting the mucosa itself and preventing its prolapse into the anal canal when passing a motion.

This submucosal muscle and connective tissue layer has been named "sustentator tunica ani" by Kohlrausch (1854), "corregator tunica ani" by Ellis (1854), "muscularis submucusae ani" by Fine (1940), "Parks' fibres" (1954) after

Sir Alan Parks at St Mark's, and finally "muscularis canalis ani" by Hansen (1976).

The anatomical study by Thomson names this mucosal layer after its discoverer as the "*Treitz´s muscle*". He showed that this muscle was easily found in all specimens; emerging from the internal sphincter muscle and distributed in three ways to form a network around the haemorrhoidal venous plexus, to fan out into the perianal skin and to rejoin to the conjoined longitudinal muscle surrounding the distal portion of the internal sphincter8. He described the thickening of the anal submucosa as cushions with a constant triradiate configuration without correlation to the arterial anatomy.

Microscopically, Haas was able to show a parallel thin and compact layer of connective tissue in the submucosal layer. With advancing age this same layer becomes thicker, looser, disintegrated and broken. The age related changes and scar formation have been proposed to cause descensus and prolapse of the anal cushions.[20]

This theory corresponds to clinical experience where "haemorrhoids" are indeed a mucoanal prolapse rather than vascular pathology. Despite the anatomical, histological and clinical evidence, it is still debated whether mucoanal prolapse or vascular enlargement is the core event of haemorrhoidal disease.[21]

Varicous vein theory:

Thomson illustrated that haemorrhoidal veins were normal structures and present from birth and found in every adult as normal parts of the human body.[15,22] With the assumption that the varicous vein theories are a result of secondary pathological changes found in the haemorrhoidal venous plexus, Thomson could demonstrate its invalidity as primary importance.

It was thought that elevation of the venous pressure results in the development of haemorrhoids. Morgagni believed that the human upright posture was the reason for haemorrhoids. Lack of valves in the portal vein or even a rise in abdominal pressure were thought to contribute the development of haemorrhoids.

Studies show the same incidence of haemorrhoids in patients with portal hypertension as in the general population.[23-25] Graham-Stewart and Burkitt[26,27] suggested that distended haemorrhoidal veins were secondary to straining at defecation. Recently, an increased calibre and greater arterial flow in the branches of the superior rectal artery was correlated with the presence of haemorrhoids. The increased calibre was thought to be associated with advancing age.[28]

Vascular hyperplasia theory:

According to this theory piles are a result of a vascular erectile metaplasia. Virchow (1863) and Allingham (1973) considered the piles to be haemangiomatous in nature. There is little evidence in support of this theory.

EPIDEMIOLOGY

Man has been tormented by hemorrhoids since antiquity. It is among the earliest conditions recorded in the history as a cause of perpetual discomfort of humans, affecting young and old, rich and poor alike. The exact prevalence in general population is not known, since many patients do not seek surgical advice. However, Buie reported a prevalence of 52% in a large series of patients examined proctoscopically at the Mayo clinic. The exact figure probably approaches 75% of the adult population.[29]

The prevalence of hemorrhoids has been estimated at 4.4 percent of U.S. adults, with the highest in those between 45 and 65 years of age.[30] Factors that increase intra-abdominal pressure (prolonged straining, constipation, pregnancy, ascites) contribute to this condition.

Though hemorrhoids are very common cause of rectal bleeding and anal discomfort, the true epidemiology is unknown because patients have a tendency to use self-medication rather than to seek proper medical attention.

A study by Johanson et al[31] in 1990 showed that 10 million people in the United States complained of hemorrhoids, corresponding to a prevalence rate of 4.4%. In both sexes, peak prevalence was between age 45-65 years. Whites and higher socioeconomic status individuals were affected more frequently than blacks and those of lower socioeconomic status. However, this association may be due to differences in health-seeking behavior rather than true prevalence.

In the United Kingdom, hemorrhoids were reported to affect 13-36% of the general population.[32,33] However, this estimation may be higher than actual incidence because the community-based studies mainly relied on self-reporting and patients may attribute any anorectal symptoms to hemorrhoids.[34]

Constipation and prolonged straining are believed to cause hemorrhoids because hard stool and increased intraabdominal pressure could cause obstruction of venous return, resulting in engorgement of the hemorrhoidal plexus.[35]

Hard fecal material increases shearing force on the anal cushions. However, recent evidence questions the importance of constipation in the development of this common disorder.[36] Many investigators have failed to demonstrate any significant association between hemorrhoids and constipation, although some reports suggested that diarrhea is a risk factor.[36]

Increase in straining for defecation precipitates the development of symptoms like bleeding and prolapse in patients with a history of hemorrhoidal disease. Pregnancy predisposes to congestion of the anal cushion and symptomatic hemorrhoids, which resolves spontaneously soon after birth. Dietary factors include low fiber diet, spicy foods and alcohol intake, but reported data are inconsistent.[35]

In India approximately 40,723,288 people are reported to have hemorrhoids. 1 million new cases are reported annually, 47 per 1000 and increases with age. Around 50-85% 0f people around the world have hemorrhoids and in India 75% of the population is estimated. Current statistics

suggest that almost half of people in their fifties have piles. Age is not the only factor though, and hemorrhoids can affect people of any age group or gender.[37]

CLASSIFICATION AND GRADING OF HEMORRHOIDS

A hemorrhoid classification system is useful not only to help in choosing between treatments, but also to allow the comparison of therapeutic outcomes among them. Hemorrhoids are classified on the basis of their location and degree of prolapse. Internal hemorrhoids originate from the inferior hemorrhoidal venous plexus above the dentate line and are covered by mucosa, while external hemorrhoids are dilated venules of this plexus located below the dentate line and are covered with squamous epithelium. Mixed (interno-external) hemorrhoids arise both above and below the dentate line.[34]

Internal hemorrhoids are further graded based on their appearance and degree of prolapse, (Goligher's classification):[38]

(1) First-degree hemorrhoids (grade I): The anal cushions bleed without prolapse;

(2) Second-degree hemorrhoids (grade II): The anal cushions prolapse through the anus on straining but reduce spontaneously;

(3) Third-degree hemorrhoids (grade III): The anal cushions prolapse through the anus on straining or exertion and require manual reduction into the anal canal;

(4) Fourth-degree hemorrhoids (grade IV): The prolapse is irreducible. Acutely thrombosed, incarcerated internal hemorrhoids and incarcerated thrombosed hemorrhoids involving circumferential rectal mucosal prolapse are also fourth-degree hemorrhoids.[39]

Some proposed classifications based on anatomical findings of hemorrhoidal position, described as primary (at the typical three sites of the anal cushions), secondary (between the anal cushions), or circumferential, and based on symptoms as prolapsing and non-prolapsing.[40,41] However, these classifications are in less widespread use.

The current classification as described by Goligher grades haemorrhoids from grade I to grade IV. First degree haemorrhoids project slightly into the lumen of the anal canal when the veins are congested during defecation. Second degree haemorrhoids form larger swellings that protrude into the anal canal and descend towards the anal orifice; may appear externally during straining but return spontaneously after defecation. When the piles protrude during defecation and require digital replacement, they are graded as third degree. Fourth degree haemorrhoids are manually irreducible.[38]

Several classifications have been documented for haemorrhoids. It is not unusual to read the description of haemorrhoidal grade in the randomized trials as “prolapsing internal haemorrhoids”, “symptomatic prolapsing haemorrhoids” or “all 3rd and 4th degree haemorrhoids”. The correlation between the symptoms and grade of prolapse is poorly documented. Attempt has been made to combine

the symptom of bleeding with degree of prolapse,[40,41] but all symptomatic haemorrhoids do not bleed.

Other symptoms like soiling, pruritus, and pain are also considered. A disadvantage with the current classification is that the presence of skin-tags is disregarded though they may become symptomatic. A chronic inflammation of the skin-tags may result in fibrosis and patients have been known to attempt to digitally reduce the external component in the absence of mucosal prolapse. The definition of grade IV is "skin covered components which cannot properly be returned to the anal canal". If a prolapse is irreducible, a skin-covered component is always present. It is the anodermal part of the prolapse that is irreducible.[38,42]

Major classification schemes proposed in the literature

	Goligher[38]	**Lunnis**[40]	**Morgado**[43]	**Thomson**[44]
Grade 0	-	Non prolapsing anal cushions	-	-
Grade I	Merely project into the lumen of the anal canal	Non prolapsing small haemorrhoids	Bleeding Haemorrhoid disease	Bleeding
Grade II	Piles may appear Externally whilst the patient is straining but return spontaneously	Prolapsing intermediate haemorrhoids Prolapse but return spontaneously. Bleed frequently	Prolapsing Haemorrhoid disease	Prolapse at defecation (with or without bleeding) with Spontaneous return to anal canal
Grade III	Protrude during defecation, remain prolapsed until they are digitally replaced within the anus	Large haemorrhoids that prolapse and need aid to reduce. Bleed frequently and often profusely	Thrombotic Haemorrhoid disease	Prolapse (with or without bleeding) requiring replacement.
Grade IV	Skin-covered components cannot be properly returned to the anal canal.	Very large haemorrhoids. Prolapse, which is permanent and irreducible. Bleed profusely.	Mixed Haemorrhoid disease	-

Many grade II haemorrhoids are misclassified into grade III haemorrhoids when doctors are misled by the size of the haemorrhoid during examination with the proctoscope.[40] In a published randomized trial of 60 patients the authors found 19 patients with grade III haemorrhoids and 27 patients with grade IV haemorrhoids in the whole study population. In the following sentence they describe the presence of symptoms and emphasize a total of 3 patients complaining of prolapse.[45]

In trial conducted in Taiwan, 596 patients with grade III prolapse haemorrhoids were included. Of these, only 22.7 % had prolapse as the leading complaint.[46] This indicates the need of a standardized classification for wider application. A classification of haemorrhoid prolapse is of interest as the treatment may be selected based on the stage of prolapse. It is also important to ascertain grade specific treatment modalities and scientifically describe outcome by stratifying to the prolapse grade. With stage specific results the understanding of the effectiveness of each treatment is enhanced.

The classification used now-a-days could be improved by including the external component as a separate entity. A reliable and easy to use classification of the anodermal, haemorrhoidal as well as the mucosal prolapse is important for several reasons. The mucosal prolapse is evident in patients who digitally reduce a prolapse and easily diagnosed by asking the patient about this need. The anodermal prolapse reveals itself as anal tags and polyps on the surgeon's inspection of the anus. If the treatment aims to remove both features, a before and after record should reliably assess the potential of each treatment method in these respects.

PATHOPHYSIOLOGY

The exact pathophysiology of hemorrhoidal development is not clearly understood. For years the theory of varicose veins, which postulated that hemorrhoids were caused by varicose veins in the anal canal, had been popular but now it is obsolete because hemorrhoids and anorectal varices are proven to be different entities. In fact, patients with portal hypertension and varices do not have an increased incidence of hemorrhoids.[47]

Today, the sliding theory of anal canal lining is widely accepted.[15] This proposes that hemorrhoids develop when the supporting tissues of the anal cushions disintegrate or deteriorate. Hemorrhoids are therefore the pathological term to describe the abnormal downward displacement of the anal cushions causing venous dilatation. There are typically three major anal cushions, located in the right anterior, right posterior and left lateral aspect of the anal canal, and various numbers of minor cushions lying between them.[48]

The anal cushions of patients with hemorrhoids show significant pathological changes. These include abnormal venous dilatation, vascular thrombosis, degenerative process in the collagen fibers and fibroelastic tissues, distortion and rupture of the subepithelial muscle in anus. In addition to the above findings, a severe inflammatory reaction involving the vascular wall and surrounding connective tissue has been demonstrated in hemorrhoidal specimens, with associated mucosal ulceration, ischemia and thrombosis.[43]

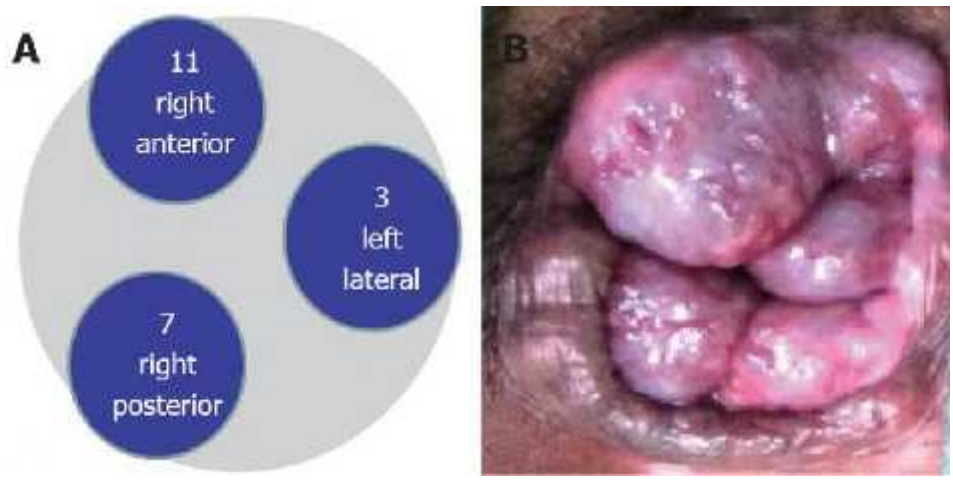


Figure 3. Diagram of common sites of major anal and internal hemorrhoids. A: Diagram of common sites of major anal cushions; B: Common sites of internal hemorrhoids.[34]

Figure 4. Pathological changes in hemorrhoids. *: Marked dilatation of hemorrhoidal venous plexus; #: Fragmented anal subepithelial muscle (the Treitz's muscle or mucosal suspensory ligament) (Scale bar = 1 mm).[34]

CLINICAL EVALUATION OF HEMORRHOIDS

One of the most common manifestation of hemorrhoids is painless rectal bleeding associated with bowel movement, described by patients as blood drips into toilet bowl. The blood is typically bright red as hemorrhoidal tissue has direct arteriovenous communication.[49]

Positive feacal occult blood or anemia should not be attributed to hemorrhoids until the colon is adequately evaluated especially when the bleeding is atypical for hemorrhoids, when no source of bleeding is evident on anorectal examination, or when the patient has significant risk factors for colorectal neoplasia.[39]

Prolapsing hemorrhoids may cause perineal irritation or anal itching due to mucous secretion or feacal soiling. In patients with large hemorrhoids a feeling of incomplete evacuation or rectal fullness is also reported . Pain is not usually caused by the hemorrhoids themselves unless thrombosis has occurred, particularly in an external hemorrhoid or if a fourth-degree internal hemorrhoid becomes strangulated. Anal fissure and perianal abscess are more common causes of anal pain in hemorrhoidal patients.[34]

The definite diagnosis of hemorrhoidal disease is based on a thorough patient history and careful examination. Assessment should include a digital examination and proctoscopy in the left lateral position. The perianal area inspected for anal skin tags, external hemorrhoid, perianal dermatitis from anal discharge or feacal soiling, fistula-in-ano and anal fissure. Some physicians prefer patients sitting and straining in the squatting position to watch for the

prolapse. Although internal hemorrhoids cannot be palpated, digital examination will detect abnormal anorectal mass, anal stenosis and scar, evaluate anal sphincter tone, and determine the status of prostatic hypertrophy which may be the reason for straining as this aggravates descent of the anal cushions during micturition. Hemorrhoidal size, location, severity of inflammation and bleeding should be noted during proctoscopy. Intrarectal retroflexion of the colonoscope or transparent anoscope with flexible endoscope also allow excellent visualization of the anal canal and hemorrhoid, and permit recording pictures.[50]

Symptoms of mucoanal prolapse

The five cardinal symptoms of haemorrhoids are:

- Anal pain
- Bleeding on defeacation
- Anal soiling
- Anal irritation and pruritus
- Mucoanal prolapse

Bleeding is one of the most common symptom described in the literature besides the prolapse. In those elected for surgery it has been attempted to correlate the severity of the symptoms with the grade of prolapse. The symptoms, however, seem weakly correlated to the extent of the prolapse. The symptoms in each patient can vary over time especially with regard to the intensity of bleeding. Deteriorated bowel habits like Intestinal Bowel Syndrome (IBS) is often associated with increased frequency of bowel movements that may cause

inflammation of the prolapse within the anal canal. External prolapse, once established, will be present every time the patient moves the bowel.

Anal pain

Pain is present as a symptom in almost 43% of the patients.[51] Pain is therefore a common symptom with a specific character in haemorrhoidal disease. It is related to the prolapse and is relieved when the prolapse is digitally reduced. Acutely thrombosed and prolapsed haemorrhoids are associated with severe pain. Consumption of capsin in red chili after haemorrhoid surgery did significantly increase postoperative pain and anal burn sensation.[52]

Bleeding

Bleeding is the most common symptom of haemorrhoids[44,53,54] Bleeding occurs commonly during defecation. The blood is never incorporated in the stool but seen as stains on the stool or on the toilet paper and occasionally colouring the cabinet. A prolapse of the cushions will give an impaired venous return and venous stasis if not reduced. This can cause inflammation of the cushions with erosion of the epithelium resulting in bleeding.[55]

The bleeding from haemorrhoids rarely causes anaemia. If present, a GI-tract investigation should be carried to exclude other causes of anaemia.[56,57] In adults, it is relevant to exclude primarily malignancy as a cause to this symptom.

Soiling

The mucoanal prolapse disrupts the closing mechanism of the normal piles. There is a significant difference between faecal soiling due to anal incontinence of weak sphincters and the mucus soiling due to the mucosal prolapse. The mucous discharge (soiling) may also occur during daily activity and in between defecations.

Pruritus

Anal pruritus is due to irritation of the perianal skin. Without a functional cushion valve sealing of the anal canal, a chronic exposure to moisture from the mucus discharge will cause anal irritation.[38] Skin tags can cause a moist environment in its folds and also cause irritation. Anal pruritus is common in anorectal disorders and may also be idiopathic.

Prolapse

The fragmentation of the connective tissue that supports the anal cushions results in descensus of the same cushions. Prolapse can involve single cushion or there may be a total circumferential prolapse (all cushions). The prolapse may be minor with spontaneous reduction or manifest, requiring digital replacement.

Anal incontinence

Faecal incontinence occurs in 2.2% of a normal population according to telephone interviews[58] and 4.1 percent in women over the age of 65 years.[59] In case of loose stools, 10.9% of women and 9.7% of men suffered from faecal

incontinence in 1600 randomly selected subjects from a Swedish community. With solid faeces the prevalence dropped to 1.4 percent in women and 0.4 percent in men.[60]

Symptoms of incontinence are potentially more common in patients with haemorrhoidal prolapse as the prolapsed cushions normally contribute to the mechanism of anal closure. There are reports describing the presence of impaired continence before surgical treatment of haemorrhoids.[61] There are also reports of high incidence of disturbed anal continence after haemorrhoidals surgery.[62]

Resolution of symptoms

The rationale of the surgical treatment is to either excise the prolapsing piles or to restore the normal anatomy with fixation of the piles at the upper end of the anal canal. Because the symptoms are a consequence of the prolapse, the restoration of the anal anatomy will resolve the symptoms, in part or entirely. If each symptom is measured before and after a treatment, the difference is an estimate of the capacity of the treatment to resolve the symptoms.

Fueglister et al[51] studied pre and postoperative frequencies of each symptom after stapled haemorrhoidopexy. After surgery, 24% of the patients complained of prolapse, 20% of bleeding, 25% of anal pain, 31% of faecal soiling and 44% of the patients complained of local discomfort. 65% of the patients with positive symptoms were satisfied despite the residual symptoms. Other studies have also shown persistent symptoms of haemorrhoids after surgery.[63]

There are two common ways to describe and analyze subjective data as provided by the patient: Firstly by assigning each symptom an intensity value using Lickert scales or a visual analog scale (VAS).[64,65]

In such methods, patient is asked to rate the symptom from little to much alternatively, by assessing the symptom according to its frequency.[66,67] In such methods the patient is asked to rate the occurrence of the symptom from rarely to always. Patient may have different thresholds for a symptom. For instance, the intensity of bleeding for one patient can be described quite differently by another patient. Measures based on frequency may be easier to understand because the underlying time frame is common to patients and researcher.

Diagnosis

Hematologic Tests

A complete blood cell (CBC) count may be useful as a marker for infection. Anemia due to hemorrhoidal bleeding is possible,[10] but rare (0.5 cases per 100,000 patients), and its presence should raise suspicion of an alternate diagnosis. Hematocrit testin suggested if excessive bleeding with concomitant anemia is suspected.

Coagulation studies are indicated if the history and physical examination suggest coagulopathy.[7]

Anoscopy and Flexible Sigmoidoscopy

Anoscopy is mandatory for viewing internal hemorrhoids. The anoscope should be a side-viewing one. When angled well, the side-viewing anoscope allows the soft hemorrhoidal tufts to fill the beveled end of the scope and to be appropriately evaluated. Prolapse can be observed when patient performs a Valsalva maneuver.[7]

Flexible sigmoidoscopy is performed to exclude proximal disease. Having a patient strain while sitting on a toilet may reproduce prolapse most accurately; and can be very helpful in examining in indeterminate cases.[7]

Other Diagnostic Imaging Studies

Proctoscopy may be performed, and proctography may be indicated in rectal prolapse. Colonoscopy, virtual colonoscopy, and barium enema are reserved for cases of bleeding without an identified anal source. These symptoms are not attributable to hemorrhoids and are considered to be non–outlet-type bleeding. Barium enema study or virtual colonoscopy also suggested if proximal colonic and intestinal diseases must be excluded and if endoscopy is not very helpful. Full evaluation of the large bowel with colonoscopy is recommended for patients with significant abdominal symptoms, weight loss, change in bowel habits, age older than 50 years, or other risk factors for colonic malignancy.[7]

Histologic Features

Routine histologic examination of hemorrhoidal tissue is usually unrewarding, especially if it is grossly examined by an experienced anorectal

surgeon. Any suspicious tissue should be sent for microscopic evaluation. External hemorrhoids are classified by the underlying pathology and symptoms, that include thrombosed veins, bleeding from eroded blood clots, and skin tags causing hygiene problems.[7]

Treatment

Current management of internal hemorrhoids

Treatments	**Grade** I	**Grade** II	**Grade** III	**Grade** IV	**Acute thrombosis or strangulation**
Dietary and lifestyle modification	×	×	×	×	×
Medical treatment	×	×	×-selected		
Non-operative treatment					
Sclerotherapy	×	×			
Infrared coagulation	×	×			
Radiofrequency ablation	×	×			
Rubber band ligation	×	×	×-selected		
Operative treatment					
Plication		×	×		
DGHAL		×	×		
Hemorrhoidectomy		×-selected	×	×	×-emergency
Stapled hemorrhoidopexy			×	×	

Treatment of hemorrhoids is recommended only when the patient complains of them. The old saying that it is hard to make an asymptomatic patient better applies here. No matter how bad the hemorrhoids look, they should not be treated unless they bother the patient. Treatment of hemorrhoids is divided by the cause of symptoms, into internal and external treatments. Accurately classifying a patient's symptoms and the relation of the symptoms to internal and

external hemorrhoids is important.[7] Therapeutic treatment of hemorrhoids ranges from dietary and lifestyle modification to radical surgery, depending on degree and severity of symptoms.[13,68] The current management of internal hemorrhoids is illustrated in Table.

Internal hemorrhoids

Internal hemorrhoids do not have cutaneous innervation and can therefore be destroyed without anesthetic, and the treatment may be surgical or nonsurgical. Internal hemorrhoid symptoms often respond to increased liquid and fibre intake and to avoidance of straining and prolonged toilet sitting. Nonoperative therapy works well for symptoms that persist despite the use of conservative therapy. Most nonsurgical procedures currently available are performed in the clinic on outpatient basis.[7] The following is a quick summary of treatment for internal hemorrhoids by grade:[7]

- Grade I hemorrhoids are treated with conservative medical therapy and avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs) and spicy or fatty foods.

- Grade II or III hemorrhoids are initially treated with nonsurgical procedures.

- Very symptomatic grade III and grade IV hemorrhoids are best treated with surgical hemorrhoidectomy.

- Treatment of grade IV internal hemorrhoids or any incarcerated or gangrenous tissue requires prompt surgical consultation

Stapled hemorrhoid surgery, or procedure for prolapsing hemorrhoids (PPH), is an excellent alternative for treating internal hemorrhoids that have not responded to conservative or nonoperative approaches. Short- and medium-term results are excellent. Patients with minimal external tags and large internal hemorrhoids are easily treated with procedure for prolapsing hemorrhoids and skin tag excision. Operative resection is sometimes required to control the symptoms of internal hemorrhoids.[7]

External hemorrhoids

External hemorrhoid symptoms are generally divided into problems with acute thrombosis and hygiene/skin tag complaints. Thrombosed haemorrhoids well to office excision (not enucleation), whereas operative resection is reserved for the latter. Remember that therapy is directed solely at the symptoms, not at aesthetics.

When performed well, operative hemorrhoidectomy should have a 2-5% recurrence rate. Nonoperative techniques, such as rubber band ligation, have recurrence rates of 30-50% within 5-10 years. However, these recurrences can usually be addressed with further nonoperative treatments.[69] Long-term results from procedure for prolapsing hemorrhoids are unavailable at this time.[70-72]

Dietary and lifestyle modification

Since shearing action of passing hard stool on the anal mucosa may cause damage to the anal cushions and lead to symptomatic hemorrhoids, increasing intake of fiber or providing added bulk in the diet might help eliminate straining

during defecation. In clinical studies of hemorrhoids, fiber supplement reduced the risk of persisting symptoms and bleeding by approximately 50%, however it did not improve the symptoms of prolapse, pain, and itching.[73]

Fiber supplement is therefore regarded as an effective treatment in non-prolapsing hemorrhoids; however, it could take up to 6 wk for a significant improvement to be manifest.[74] As fiber supplements are safe and cheap, they remain an integral part of both initial treatment and of a regimen following other therapeutic modalities of hemorrhoids.

Lifestyle modification should also be advised to the patients with any degree of hemorrhoids as a part of treatment and as a preventive measure. These changes include increasing the intake of dietary fiber and oral fluids, reducing consumption of fat, having regular exercise, improving anal hygiene, abstaining from both straining and reading on the toilet, and avoiding medication that causes constipation or diarrhea.

Medical treatment

Oral flavonoids

These venotonic agents were first described in the treatment of chronic venous insufficiency and edema. They appeared to be capable of increasing vascular tone, reducing venous capacity, decreasing capillary permeability,[75] and facilitating lymphatic drainage[76] as well as having anti-inflammatory effects.[77]

Although their precise mechanism of action is not clear, they are used as an oral medication for hemorrhoidal treatment, particularly in Europe and Asia.

Micronized purified flavonoid fraction (MPFF), consisting of 90% diosmin and 10% hesperidin, is the most common flavonoid used in clinical treatment. The micronization of the drug to particles of less than 2 μm not only improved its solubility and absorption, but also shortened the onset of action.[34]

A recent meta-analysis of flavonoids for hemorrhoidal treatment, including 14 randomized trials and 1514 patients, suggested that flavonoids decreased risk of bleeding by 67%, pain by 65% and itching by 35%, and also reduced the recurrence rate by 47%.[78]

Some investigators reported that MPFF can reduce rectal discomfort, pain and secondary hemorrhage following hemorrhoidectomy.[79]

Oral calcium dobesilate

This is another venotonic drug commonly used in diabetic retinopathy and chronic venous insufficiency as well as in the treatment of acute symptoms of hemorrhoids. It was well demonstrated that calcium dobesilate decreased capillary permeability, inhibited platelet aggregation and improved blood viscosity; thus resulting in reduction of tissue edema.[34]

A clinical trial of hemorrhoid treatment showed that calcium dobesilate, in conjunction with increased fiber intake, provided an effective symptomatic relief from acute bleeding, and was associated with a significant improvement in the inflammation of hemorrhoids.[80]

Topical treatment

The primary objective of topical treatment aims to control the symptoms rather than to cure the disease. Thus, other therapeutic treatments could be subsequently required. A number of topical preparations are available including creams and suppositories, and most of them can be bought without a prescription. Strong evidence supporting the true efficacy of these drugs is lacking. These topical medications can contain various ingredients such as local anesthesia, corticosteroids, antibiotics and anti-inflammatory drugs.[34]

Topical treatment may be effective in selected groups of hemorrhoidal patients. Tjandra et al[81] showed a good result with topical glyceryl trinitrate 0.2% ointment for relieving hemorrhoidal symptoms in patients with low-grade hemorrhoids and high resting anal canal pressures. However, 43% of the patients experienced headache during the treatment.

Perrotti et al[82] reported the good efficacy of local application of nifedipine ointment in treatment of acute thrombosed external hemorrhoids. It is worth noting that the effect of topical application of nitrite and calcium channel blocker on the symptomatic relief of hemorrhoids may be a consequence of their relaxation effect on the internal anal sphincter, rather than on the hemorrhoid tissue *per se* where one might anticipate a predominantly vasodilator effect.

Apart from topical medication influencing tone of the internal anal sphincter, some agents targets vasoconstriction of the vascular channels within hemorrhoids such as Preparation-H® (Pfizer, United States), which contains 0.25% phenylephrine, petrolatum, light mineral oil, and shark liver oil.

Phenylephrine is a vasoconstrictor having preferential vasopressor effect on the arterial site of circulation, whereas the other ingredients are considered protectants. Preparation-H is available in many forms, including ointment, cream, gel, suppositories, and medicated and portable wipes. It provides temporary relief of acute symptoms of hemorrhoids, such as bleeding and pain on defecation.[34]

Non-operative treatment

Sclerotherapy

This is currently recommended as a treatment option for first- and second-degree hemorrhoids. The rationale of injecting chemical agents is to create a fixation of mucosa to the underlying muscle by fibrosis. The solutions used are 5% phenol in oil, vegetable oil, quinine, and urea hydrochloride or hypertonic salt solution. It is important that the injection be made into submucosa at the base of the hemorrhoidal tissue and not into the hemorrhoids themselves; otherwise, it can cause immediate transient precordial and upper abdominal pain. Misplacement of the injection may also result in mucosal ulceration or necrosis, and rare septic complications such as prostatic abscess and retroperitoneal sepsis. Antibiotic prophylaxis indicated for patients with predisposing valvular heart disease or immunodeficiency because of the possibility of bacteremia after sclerotherapy.[34]

Rubber band ligation

Rubber band ligation (RBL) is a simple, quick, and effective means of treating first- and second-degree hemorrhoids and few patients with third-degree

hemorrhoids. Ligation of the hemorrhoidal tissue with a rubber band causes ischemic necrosis and scarring, leading to fixation of the connective tissue to the rectal wall. Placement of rubber band too close to the dentate line may cause severe pain due to the presence of somatic nerve afferents and requires immediate removal. RBL is safely performed in one or more than one place in a single session with one of several commercially available instruments, including hemorrhoid ligator rectoscope and endoscopic ligator which use suction to draw the redundant tissue in to the applicator to make the procedure a one-person effort.[34]

The most common complication of RBL is pain or rectal discomfort, which is usually relieved by warm sitz baths, mild analgesics and avoidance of hard stool by taking mild laxatives or bulk-forming agents. Other complications include minor bleeding from mucosal ulceration, urinary retention, thrombosed external hemorrhoids, and rarely, pelvic sepsis. The patients should stop taking anticoagulants for one week before and two weeks after RBL.[34]

Infrared coagulation

The infrared coagulator produces infrared radiation which coagulates tissue and evaporizes water in the cell, causing their shrinkage. A probe is applied to the base of the hemorrhoid through the anoscope and the recommended contact time is between 1.0-1.5 s, depending on intensity and wavelength of the coagulator. The necrotic tissue is seen as a white spot after the procedure and eventually heals with fibrosis. Compared with sclerotherapy, infrared coagulation (IRC) is less technique-dependent and avoids the potential

complications of misplaced sclerosing injection. Although IRC is a safe and rapid procedure, it may not be suitable for large, prolapsing hemorrhoids.[34]

Radiofrequency ablation

Radiofrequency ablation (RFA) is a new modality of hemorrhoidal treatment. A ball electrode connected to a radiofrequency generator is placed on the hemorrhoidal tissue and causes the contacting tissue to be coagulated and evaporized. By this method, vascular components of hemorrhoids are reduced and hemorrhoidal mass will be fixed to the underlying tissue by subsequent fibrosis. RFA can be performed on an outpatient basis similar to sclerotherapy. Its complications include acute urinary retention, wound infection, and perianal thrombosis. Although RFA is a virtually painless procedure, it is associated with a higher rate of recurrent bleeding and prolapse.[34]

Cryotherapy

Cryotherapy ablates the hemorrhoidal tissue with a freezing cryoprobe. It has been claimed to cause less pain because sensory nerve endings are destroyed at very low temperature. However, several clinical trials have reported that it was associated with prolonged pain, foul-smelling discharge and a high rate of persistent hemorrhoidal mass.[83] It is therefore rarely used.

There are two meta-analyses comparing outcomes among the three common non-operative treatments of hemorrhoids (sclerotherapy, RBL and IRC).[84,85] These two studies demonstrated that RBL resulted in the fewest recurrent symptoms of hemorrhoids and the lowest rate of retreatment, but that it

led to a significantly higher incidence of pain following the procedure. Hence, RBL could be recommended as the initial non-operative modality for treatment of grade I-III hemorrhoids. In a British survey of almost 900 general and colorectal surgeons,[86] RBL was the most common procedure performed, following by sclerotherapy and lastly hemorrhoidectomy.

Operative treatment

An operation is indicated when non-operative approaches have failed or have led tocomplications. Different philosophies regarding the pathogenesis of hemorrhoidal disease creates different surgical approaches.

Summary of different philosophies regarding the pathogenesis of hemorrhoids and related surgical approaches

Theory	Short description	Surgical approach
Sliding anal cushions	Hemorrhoids develop when the supporting tissues of the anal cushions disintegrate or deteriorate	Hemorrhoidectomy, plication
Rectal redundancy	Hemorrhoidal prolapse is associated with an internal rectal prolapse	Stapled hemorrhoidopexy
Vascular abnormality	Hyperperfusion of arteriovenous plexus within anal cushion results in the formation of hemorrhoids	Doppler-guided hemorrhoidal artery ligation

Hemorrhoidectomy

Excisional hemorrhoidectomy is the most effective with the lowest rate of recurrence compared to other modalities. It can be performed using scissors, diathermy, or vascular-sealing device such as Ligasure (Covidien, United States)

and Harmonic scalpel (Ethicon Endosurgery, United States). Excisional hemorrhoidectomy can be performed safely under perianal anesthetic infiltration as an ambulatory surgery. Indications for hemorrhoidectomy include failure of non-operative management, acute complicated hemorrhoids such as strangulation or thrombosis, patient preference, and concomitant anorectal conditions such as anal fissure or fistula-in-ano which require surgery. In clinical practice, the third-degree or fourth-degree internal hemorrhoids are the main indication for hemorrhoidectomy.[34]

A major drawback of hemorrhoidectomy is postoperative pain. There has been evidence that Ligasure hemorrhoidectomy results in less postoperative pain, shorter hospitalization, faster wound healing compared to scissors or diathermy hemorrhoidectomy. Other postoperative complications include acute urinary retention (2%-36%), postoperative bleeding (0.03%-6%), bacteremia and septic complications (0.5%-5.5%), wound breakdown, unhealed wound, loss of anal sensation, mucosa prolapse, anal stricture (0%-6%), and even fecal incontinence (2%-12%).[34]

Recent evidence has suggested that hemorrhoidal specimens can be exempt from pathological examination if no malignancy is suspected.[87]

Plication

Plication is capable of restoring anal cushions to their normal position without excision. It involves oversewing of hemorrhoidal mass and tying a knot at the uppermost vascular pedicle. However, there are still a number of potential complications following this procedure such as bleeding and pelvic pain.[68]

Doppler-guided hemorrhoidal artery ligation

A newer technique based on doppler-guided ligation of the terminal branches of the superior hemorrhoidal artery was introduced in 1995 as an alternative to hemorrhoidectomy. Doppler-guided hemorrhoidal artery ligation (DGHAL) has become increasingly popular in Europe. The rationale of this treatment was later demonstrated that patients with hemorrhoids had increased caliber and arterial blood flow of the terminal branch of the superior rectal arteries. Therefore, ligating the arterial supply to hemorrhoidal tissue by suture ligation may improve hemorrhoidal symptoms. DGHAL is most effective for second- or third-degree hemorrhoids. Notably, DGHAL may not improve prolapsing symptoms in advanced hemorrhoids. Short-term outcomes and 1-year recurrence rates of DGHAL did not differ from those of conventional hemorrhoidectomy.[34]

Given the fact that there is the possibility of revascularization and recurrence of symptomatic hemorrhoids, further studies on the long-term outcomes of DGHAL are still required.[34]

Stapled hemorrhoidopexy

Stapled hemorrhoidopexy (SH) has been introduced since 1998. A circular stapling device is used to excise a ring of redundant rectal mucosa proximal to hemorrhoids and resuspend the hemorrhoids back within the anal canal. Apart from lifting the prolapsing hemorrhoids, blood supply to hemorrhoidal tissue is also interrupted.[34]

A recent meta-analysis comparing surgical outcomes between Stapled hemorrhoidopexy and hemorrhoidectomy, that included 27 randomized, controlled trials with 2279 procedures, showed that SH was associated with less pain, earlier return of bowel function, shorter hospital stay, earlier return to normal activities, and better wound healing, as well as higher degree of patient satisfaction.[88]

However, in the longer term, SH was associated with a higher rate of prolapse. Considering the recurrence rate, cost of stapling device and potential serious complications including rectovaginal fistula and rectal stricture, SH is generally reserved for patients with circumferential prolapsing hemorrhoids and having ≥ 3 lesions of advanced internal hemorrhoids.[34]

These two recent surgical options, DGHAL and SH, aim to correct the pathophysiology of hemorrhoids by reducing blood flow to the anal canal (dearterialization) and eliminating anorectal mucosal prolapse (reposition), respectively.[34]

A recent retrospective study of 18-month outcomes of DGHAL (n = 51) and SH (n = 63) for grade III hemorrhoids revealed that both procedures were safe and effective. DGHAL had less pain, shorter hospital stay, and faster functional recovery; however, it was associated with higher recurrence rate and lower patient satisfaction rating.[89]

Lately, a smaller prospective trial comparing DGHAL to SH for grade II-III hemorrhoids showed similar short-term and long-term outcomes of the two

procedures.[90] Nevertheless, patients undergoing DGHAL returned to work quicker, and had fewer complication rates than those receiving SH.

Prognosis

Most hemorrhoids resolve spontaneously or with conservative medical therapy alone. However, complications include thrombosis, secondary infection, ulceration, abscess, and incontinence. The recurrence rate with nonsurgical techniques is 10-50% over a 5-year period, whereas that of surgical hemorrhoidectomy is less than 5%.[7]

Regarding complications from surgery, well-trained surgeons should experience complications in less than 5% of cases. Complications include stenosis, bleeding, infection, recurrence, nonhealing wounds, and fistula formation. Urinary retention is directly related to the anesthetic technique used and to the perioperative fluids administered. Limiting fluids and the routine use of local anesthesia can reduce urinary retention to less than 5%.[7]

Euphorbia Prostrata dry extract for control of bleeding haemorrhoids

Bioflavonoids, particularly diosmin, oligomeric proanthocyanidin complexes (OPCs), and hesperidins, have demonstrated efficacy in the treatment of hemorrhoids. These bioflavonoids exhibit phlebotonic activity, vasculoprotective effects, and antagonism of the biochemical mediators of inflammation. OPCs, diosmin, and hesperidin have been the subject of numerous clinical trials on efficacy and safety in the treatment of varicose veins and hemorrhoids.[91]

Euphorbia prostrata is a small prostrate, hispidly pubescent annual herb found all over India. This plant has traditionally been used to treat several ailments since time immemorial. The active principles in Euphorbia prostrata are chiefly flavonoids, phenolic acid and tannins. Flavonoids and phenolic acid have been reported to have anti inflammatory, antioxidant, analgesic, haemostatic, antithrombotic and vasoprotective actions. Tannins are known to possess astringent and haemostatic properties. Preclinical studies carried out on the extract have confirmed its wound healing and anti-haemorrhoidal activity.[92]

Euphorbia Prostrata dry extract is indicated for the treatment of bleeding haemorrhoids. *Euphorbia prostrata* is an annual herb, which belongs to family Euphobeaceae and is abundantly found in Africa and India. It is been traditionally used in several digestive system disorders.[93] The active principles in *Euphorbia prostrate* are chiefly flavonoids, phenolic acid and tannins.

Flavonoids and phenolic acid have been reported to have anti-inflammatory, antioxidant, analgesic, haemostatic, antithrombotic and vasoprotective actions.[94]

The chemical analysis of *Euphorbia prostrate* revealed that it contains phenolic compounds like Gallic acid which activates Hageman factor that causes hypercoagulability and ellagic acid which suppress histamine release. It also contains flavonoids like apigenin, which inhibits I kappa B and suppresses inflammatory mediators and luteolin, which inhibits protein tyrosin phosphorylation and IkB mediated inflammation.[91]

Tannins are known to possess astringent and haemostatic properties. Preclinical studies carried out on the extract confirmed its wound healing and anti-hemorrhoidal activity.[95] Symptomatic hemorrhoid is not only a subject of interest for coloproctologists, but is also encountered in the practice of gynecology, gastroenterology, urology and family medicine.[91]

Numerous medications in the form of oral preparation or as local application have been proposed, used and studied since the time of Hippocrates. There are many oral antihemorrhoid preparations widely prescribed by physicians in the treatment of acute symptoms of hemorrhoids. These preparations contain semi synthetic agents or plant extracts such as escin, diosmin, and rutin related compounds that have been shown to have regulatory effects on veins, venules, and capillaries.[78]

Bioflavonoids, particularly diosmin, oligomeric proanthocyanidin complexes (OPCs), and hesperidin, have demonstrated efficacy in the treatment of hemorrhoids. These bioflavonoids exhibit phlebotonic activity, vasculoprotective effects, and antagonism of the biochemical mediators of inflammation.[96] Animal studies have shown that flavonoids reduce neutrophil activation, mediate inflammation, and decrease soluble endothelial adhesion molecules. Human trials have shown ability of flavonoids to improve venous tone and vein elasticity assessed by plethysmography and to decrease plasma markers of endothelial activation.[97]

Euphorbia prostrata is an annual herb, which has traditionally been used to treat several ailments like asthma, diabetes mellitus, bloody dysentery and

sores.[98] Tannins are known to possess astringent and haemostatic properties. Preclinical studies carried out on the extract have confirmed its wound healing and anti-hemorrhoidal activity.

Beneficial effects of *Euphorbia prostrata* in hemorrhoids have multiple mechanisms,[99] which include improvement of venous tone, increased lymphatic drainage, protection of capillary bed microcirculation, inhibition of inflammatory reactions, and reduced capillary permeability.

Flavonoids in Euphorbia are potent inhibitors of prostaglandin E2 (PGE2) and thromboxane A2 (TxA2) as well as being inhibitors of leukocyte activation, migration, and adhesion. Five new compounds were discovered and identified by the inventors in *Euphorbia prostrata* namely luteolin, 6-methoxyquercetin-glycoside, quercetin, and glycosides of luteolin and apigenin. The extract of *Euphorbia prostrata* is water soluble.[91]

The pharmaceutical composition containing the standardized extract of *Euphorbia prostrate* as the active ingredient contains 35-62% flavonoids. Of this, apigenin glycoside amounts to 30-45%, luteolin glycoside to 3-9%, 6-methoxy quercetin glycoside is 1-6% while quercetin and luteolin is 1-2%. Studies with the standardized extract of *Euphorbia prostrata,* when administered orally showed an inhibition of both carrageenan-induced and histamine-induced edema.[100]

Ellagic acid is one of the major constituents of *Euphorbia prostrata* extract reported to suppress histamine release mediated by histamine liberators. This property has been seen to control anal pruritus in majority of patients in this

study. It is speculated that analgesic, anti-inflammatory and antioxidant activity of various flavonoids components of *Euphorbia prostrate* extract may contribute in healing of inflammatory tissue damage in hemorrhoidal conditions.[91]

Phenolic acids have been reported to activate intrinsic blood coagulation by activation of Hageman factor and cause a state of hypercoagulability. It is well reported that tannic acid has antimicrobial properties, which is associated with the ester linkage between gallic acid and other sugar or alcohol groups.[91]

This investigation has confirmed that *Euphorbia prostrata* is quite effective in controlling hemorrhoidal bleeding and alleviating symptoms of the disease because of the various contents it has. It is non-toxic and may be given orally without loss of efficiency.[91]

This reinforces data found in previous clinical trials using varying dosages and of different study lengths, in which flavonoids was more effective than placebo in reducing the intensity and duration of symptoms (*e.g.*, bleeding, pain, and anal discharge) of acute hemorrhoid attacks.[101] Bleeding from non prolapsed internal hemorrhoids resolved more quickly with flavonoids.[102]

Studies have shown that flavonoid is an “edema- protective” drug in treatment of acute hemorrhoids.[103] It has been hypothesized that the positive effect of flavonoids on anal mucosa is through decreasing the edema. This may be the reason that patients in this study who felt that the hemorrhoids have been regressed after treatment with Euphorbia Prostrata actually had experienced reduced hemorrhoidal edema, as anoscopic examination did showed presence of residual hemorrhoids in most of the patients with grade 2 hemorrhoids.[91]

As with all diseases, the primary treatment for hemorrhoids is the prevention. Patients with risk factors for developing these conditions should be identified through history and physical examination and helped out with conservative treatment lest an aggressive intervention is called for. The use of diet, lifestyle, and hydrotherapy in addition to *Euphorbia prostrata* can effectively intervene in the initial stage of pathogenesis of decreased vascular integrity and can help prevent time-consuming and expensive complications of hemorrhoids.[91]

In a study conducted by 476 investigators and enrolling 1836 patients, Euphorbia Prostrata dry extract 100 mg tablets were given to patients of bleeding hemorrhoids for 14 days. At the end of the study, it was found that symptoms of patients such as bleeding, pain, itching and prolapse were significantly reduced as compared to baseline.[92]

According to Indian Folklore, the Euphorbia prostrata has anti-inflammatory properties and is also considered a blood purifier. Euphorbia prostrata is documented in the ancient medical science of India or Ayurveda for its various properties like in bronchial asthma. The active principles in Euphorbia prostrata are chiefly flavonoids (apigenin -7-glucoside, luteolin-7–glucoside), phenolic acid and tannins. Apigenin is a most potent inhibitor of transcriptional activation of both COX-2 and iNOS enzyme in lipopolysaccharide activated RAW 264.7 macrophages. Such type of modulation of COX-2 and iNOS by apigenin may be important in the prevention of inflammation and carcinogenesis .[92]

Cholbi et al, reported that luteolin inhibits protein tyrosin phosphorylation, nuclear factor-kB mediated gene expression and pro-inflammatory cytokine production in murine macrophages.[104]

Singla and Pathak also reported anti-inflammatory effects of Euphorbia prostrata in carrageenan, histamine, and bradykinin-induced pedal inflammation.[105]

These flavonoids are well reported for analgesic, anti-inflammatory, antioxidant, antiangiogenic, anti–allergic, antiviral and antimutagenic activity.[92]

Ellagic acid is one of the major constituents of Euphorbia prostrata dry extract also reported to suppress histamine release mediated by histamine liberators (compound 48/80, dextran and polymyxin B sulphate) in vivo. Phenolic acids are reported to activate intrinsic blood coagulation by activation of Hageman factor and cause a state of hypercoagulability. Although the hypercoagulable state persists for as long as 4 hours after IV administration but no thrombotic phenomena has been reported.[92]

Tannins, a time tested astringent, toughens the mucosa by precipitating the surface proteins and has been used in bleeding haemorrhoids as suppositories due to its haemostatic properties.[92]

In a retrospective analysis, Euphorbia prostrata extract was administered in humans in the form of capsules and cream, over a period of 26 years (1970-1996) in approximately 32,000 patients of bleeding haemorrhoids and anal fissures.[106]

Retrospective analysis of the data generated from this population reveals that use of Euphorbia prostrata provides excellent relief in symptoms like bleeding per rectum, pruritus, anal pain and discomfort. Overall, the product was well tolerated and the side effects, primarily gastrointestinal, were mild in intensity and transient in nature.

In another study conducted by Arora et al, a total of 125 patients with first and seconddegree haemorrhoids were enrolled in a 10-day trial to determine the optimal dose, efficacy, safety and tolerability of the capsule formulation (50 mg and 100 mg) of Euphorbia prostrata extract. The reduction in signs and symptoms of acute haemorrhoidal attack (viz. bleeding, anal discomfort, anal discharge, pain at prolapse and proctitis) at day 10 was found to be significantly greater with 50 mg or 100 mg capsules as compared to placebo.[107]

A phase III trial across India,[108] evaluated the efficacy of Euphorbia prostrata Dry Extract (100 mg tablets) in the treatment of internal haemorrhoids in first and second degree haemorrhoids. A total of 120 patients were enrolled in the trial and achievement of cessation of per rectal bleeding was assessed at the 14th day. There was a statistically ($p < 0.001$) and clinically significant improvement in cessation of bleeding from the baseline to the end of the therapy. Beneficial effects of the Euphorbia prostrata in haemorrhoids have multiple mechanisms and are due to its active constituent flavonoids, tannins and phenolic acid.

Micronized purified flavonoid fraction of diosminin for control of bleeding haemorrhoids

Drug treatment for various anorectal conditions has been known since ancient times. Today, modern as well as traditional drugs are being increasingly used in all grades of symptomatic haemorrhoids. These drugs (oral and local) are used as a part of conservative management or as an adjuvant to invasive outpatient procedures. Flavonoids, in the new formulation of micronised purified flavonoid fraction (MPFF) or as part of the ancient traditional medicine derivative of the Ginkgo tree, are used for relief of acute symptoms (for control of bleeding and re-bleeding in all grades of haemorrhoids). MPFF has been recommended for control of acute bleeding in patients waiting for a definitive outpatient treatment. Similarly, better known drugs such as calcium dobisilate (used in diabetic retinopathy and chronic venous insufficiency), nitrates and nifedipine have also been effective and well tolerated in the medical treatment of haemorrhoids. However, drug treatment is not aimed at curing haemorrhoids. The prime objective of drug therapy is to control the acute phase (bleeding) so that definitive therapy (banding, injection sclerotherapy, infrared photocoagulation, cryotherapy or surgery) can be scheduled at a convenient time.[109]

Micronised purified flavonoid fraction (MPFF) [Daflon 500 mg], an oral phlebotropic drug consisting of 90% micronised diosmin and 10% flavonoids expressed as hesperidin, improves venous tone and lymphatic drainage, and reduces capillary hyperpermeability by protecting the microcirculation from inflammatory processes. The absorption of diosmin is improved by its micronisation to particles with a diameter <2 microm. Compared with placebo,

MPFF 500 mg twice daily significantly decreased ankle or calf circumference, and improved many symptoms of chronic venous insufficiency (CVI) and plethysmographic parameters in two randomised, double-blind, 2-month studies. Improvement in symptoms was parallelled by an improvement in health-related quality of life in a nonblind, 6-month trial. Significantly more venous leg ulcers </=10 cm in diameter completely healed with MPFF 500 mg twice daily plus standard management (compression and local treatment) for 2-6 months than with standard management alone or with placebo in a nonblind and a double-blind trial. The addition of MPFF to standard management was cost effective in a retrospective pharmacoeconomic analysis of the 6-month trial. Compared with placebo, the duration and/or intensity of individual symptoms of grade 1 or 2 acute internal haemorrhoids improved significantly with 3 tablets of MPFF 500 mg twice daily for 4 days then 2 tablets of MPFF 500 mg twice daily for 3 days. Two tablets of MPFF 500 mg daily for 60 or 83 days reduced the frequency, duration and/or severity of acute haemorrhoidal symptoms and improved the overall signs and symptoms of chronic (recurrent) haemorrhoids compared with placebo. Compared with a control group, MPFF significantly reduced the risk of secondary bleeding after elective haemorrhoidectomy. In clinical trials, MPFF had a tolerability profile similar to that of placebo; the most frequently reported adverse events were gastrointestinal and autonomic in nature. In conclusion, MPFF is a well established and well tolerated treatment option in patients with CVI, venous ulcers, or acute or chronic internal haemorrhoids. MPFF is indicated as a first-line treatment of oedema and the symptoms of CVI in patients in any stage of the disease. In more advanced disease stages, MPFF may be used in

conjunction with sclerotherapy, surgery and/or compression therapy, or as an alternative treatment when surgery is not indicated or is unfeasible. The healing of venous ulcers </=10 cm in diameter is accelerated by the addition of MPFF to standard venous ulcer management. MPFF may reduce the frequency, duration and/or intensity of symptoms of grade 1 or 2 acute internal haemorrhoids, and also the severity of the signs and symptoms of chronic haemorrhoids.[110]

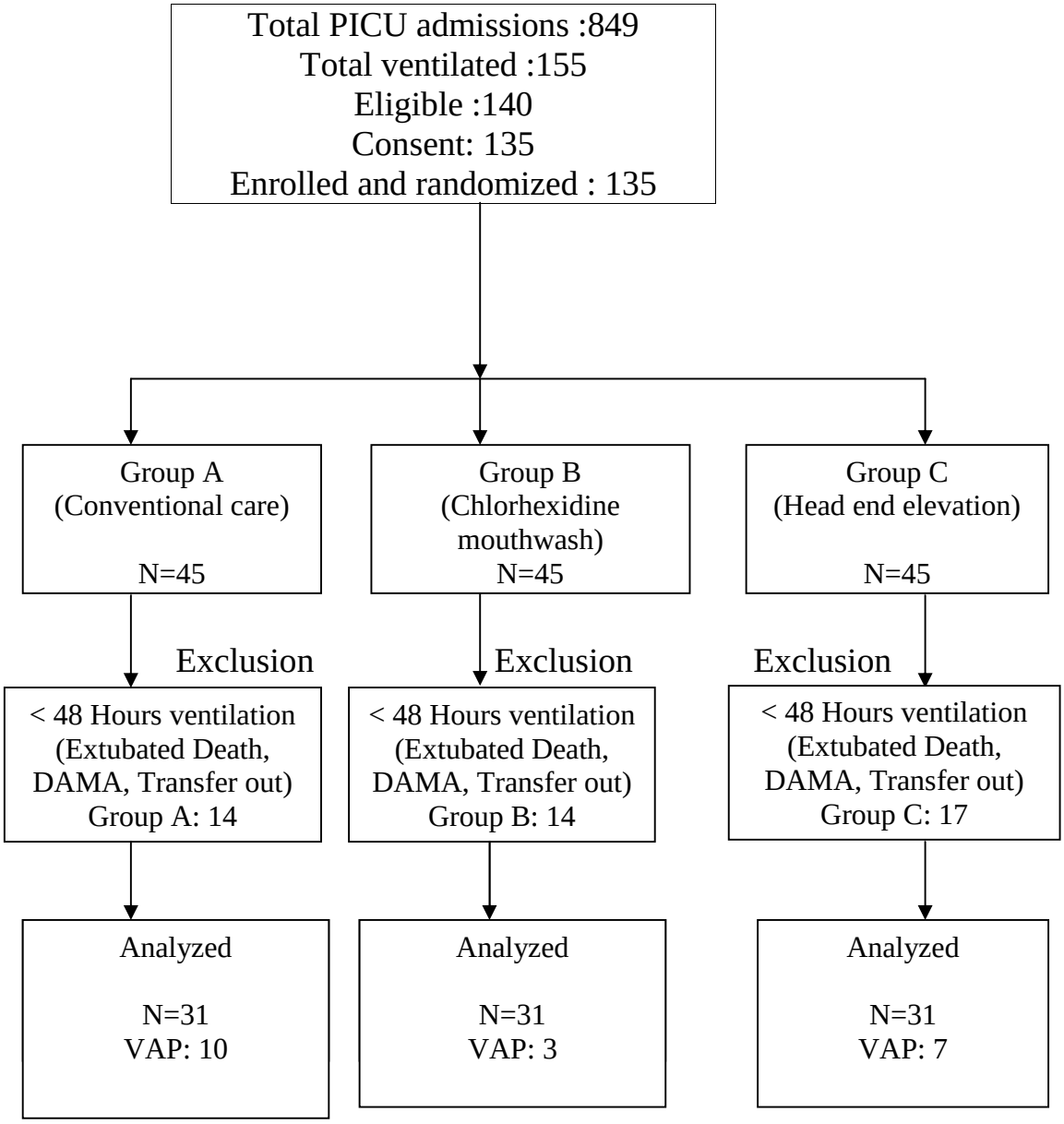
Flavonoids are widely used for the treatment of chronic venous insufficiency (CVI). In clinical trials, micronized purified flavonoid fraction (MPFF, 450 mg diosmin plus 50 mg hesperidin, Daflon 500 mg) has demonstrated its activity in CVI by improving venous tone and vein elasticity assessed by plethysmography. Randomized, double-blind, placebo-controlled clinical studies have shown an improvement in signs and symptoms related to CVI and a decrease in leg circumferences at the levels of the ankle and calf. The effect of MPFF on microcirculatory parameters suspected of participating in the pathophysiological process of venous ulceration has been investigated in patients. These include hemorheological parameters and transcutaneous oxygen tension measurements, which were shown to improve after treatment with MPFF. Finally, a randomized double-blind, placebo-controlled clinical study has shown that MPFF treatment for 2 months, in addition to standard compression therapy, accelerates leg ulcer healing in patients with ulcers ≤ 10 cm.

RESULTS

The present study was conducted in the Pediatric Intensive Care Unit (PICU) of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, attached to KLE University's Jawaharlal Nehru medical college, Belgaum.

A total of 155 patients were ventilated out of 849 total admissions in our PICU during the study period.140 patients were eligible for enrollment and 135 ventilated patients consented for the study and were enrolled and randomized into three groups A, B, C. Out of these135 patients, a total of 45 patients (Group A -14, Group B-14 and Group C-17) were excluded as they were ventilated for < 48 hours for various reasons like extubation, death, discharged against medical advice or transferred out of the ward.

Therefore, a total of 90 patients with 31 in group A, 31 in group B and 28 in group C were analyzed for the study


Total PICU admissions :849
Total ventilated :155
Eligible :140
Consent: 135
Enrolled and randomized : 135
Group A
(Conventional care)
N=45
Group B
(Chlorhexidine mouthwash)
N=45
Group C
(Head end elevation)
N=45
Exclusion
Exclusion
Exclusion
< 48 Hours ventilation (Extubated Death, DAMA, Transfer out)
Group A: 14
< 48 Hours ventilation (Extubated Death, DAMA, Transfer out)
Group B: 14
< 48 Hours ventilation (Extubated Death, DAMA, Transfer out)
Group C: 17
Analyzed
N=31
VAP: 10
Analyzed
N=31
VAP: 3
Analyzed
N=31
VAP: 7

Baseline characteristics

Table 1: Demographic characteristics

Demographic characteristics	Group A (n=31)	Group B (n=31)	Group C (n=28)	P value
Age	4.8±4.71	3.4±3.13	3.7±2.76	0.21
Gender	22	20	19	0.863
Males	9	11	9	
Females				
Socioeconomic status				
1	4 (13%)	3(9%)	0(0%)	0.08
2	16(51%)	10(32%)	18(64%)	
3	11(35%)	13(41%)	9(32%)	
4	0(0%)	13(12)	1(3%)	
5	0(0%)	1(3%)	0(0%)	
Immunization				
Complete	23	29	22	0.114
Incomplete	8	2	6	

Baseline socio demographic data like age, gender, socioeconomic status and immunization, showed no statistically significant difference between the groups and were comparable. [Table 1]

Table 2: Baseline clinical parameters

Clinical parameters	Group A (n=31)	Group B (n=31)	Group C (n=28)	**P value**
Number of systems affected				
≤2	27	29	25	0.740
≥3	4	2	3	
Primary system affected				
CVS	4	8	2	
Neurological illness	7	7	10	
Respiratory	5	9	3	
Renal	2	0	1	
Infectious disease/sepsis	3	3	4	
Hematology	1	0	0	
GIT illness	3	1	0	
Miscellaneous	6	3	8	
Indication for Ventilation				
Respiratory failure	14	14	12	
Cardio respiratory failure	4	6	2	
Cardiovascular failure	1	1	2	
Neurological illness	6	7	7	
Post operative	6	3	5	
PRISM score	4.55±4.48	3.55±3.76	4.75±4.32	0.332

The baseline clinical parameters like PRISM score, number of systems affected, indication for ventilation and primary system affected were comparable between the groups. [Table 2]

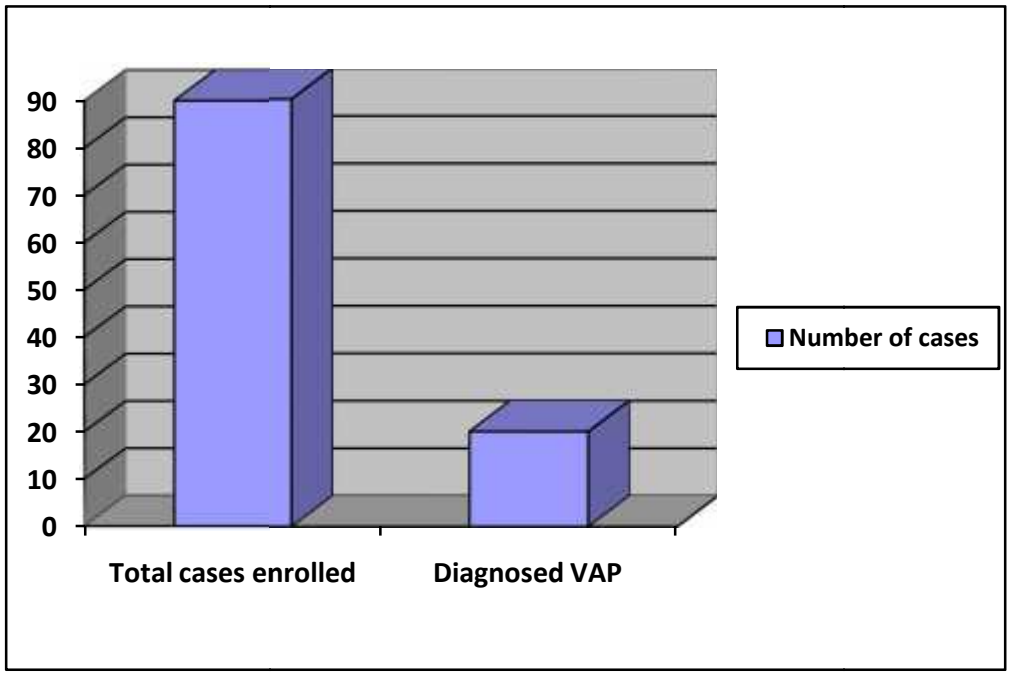
Table 3: Components of CPIS score

Score	Score	Group A	Group B	Group C
Temperature				
≥36.1 and <38.4	**0**	**17**	**22**	**21**
≥38.5 and <38.9	**1**	**12**	**7**	**4**
≤ 36 or ≥ 39 :2	**2**	**2**	**2**	**3**
Leucocytosis				
>4000 and <11000	**0**	**18**	**22**	**14**
<3.9/>11.1 and absence of band forms				
>11.1 and <17,no differentiation done	1	**12**	**7**	**6**
>11.1 and presence of band forms				
>17.1, no differentiation done	2	**2**	**2**	**8**
PAO2/FIO2 Ratio				
>240 or ARDS 0	**0**	**15**	**20**	**20**
< 240 and no ARDS	2	**16**	**11**	**8**
CXR SCORE				
No infiltrate	0	**18**	**20**	**24**
Diffuse or patchy infiltrate	1	**3**	**4**	**0**
Localized infiltrate	2	**10**	**7**	**0**
Tracheal secretions				
Absence	0	**0**	**9**	**10**
Presence and non purulence	1	**18**	**19**	**14**
Presence and purulence	2	**8**	**3**	**3**
Tracheal aspirate score				
< 10 No previous culture				
>10	0	**8**	**2**	**4**
>100	1	**1**	**2**	**0**
	2	**11**	**11**	**6**
CPIS Score (mean)		**5.04±2.90**	**3.50±2.60**	**3.87±3.28**

Mean CPIS score was less in Group B (3.50±2.60) when compared to Group A (5.04±2.90) and Group C (3.87±3.28) [Table 3]

Primary outcome: Incidence of VAP

Graph 1: Overall incidence of VAP

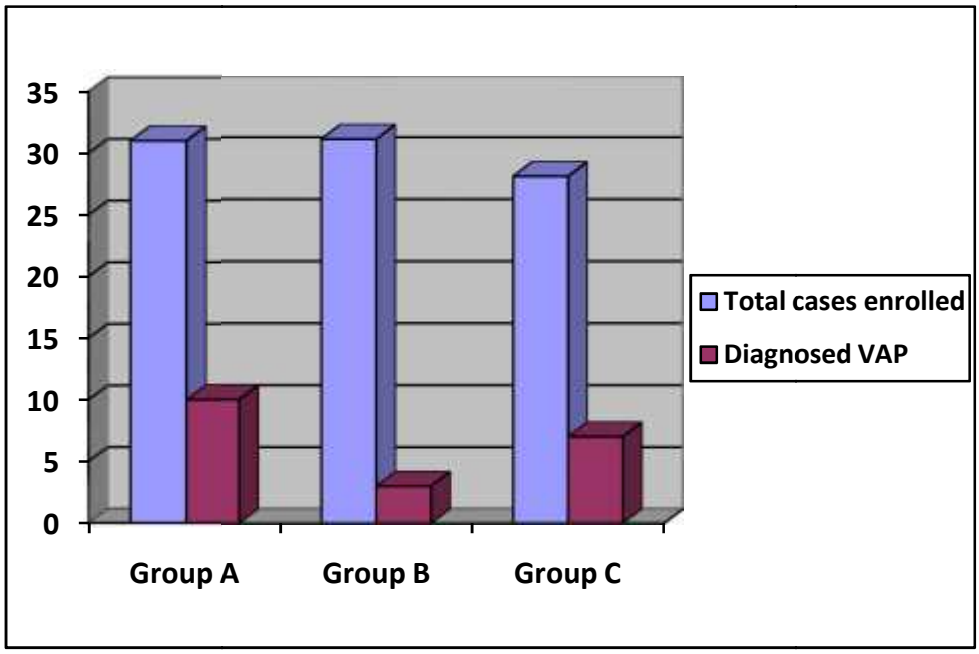


A total of 20 patients developed VAP with an overall incidence was 22.2% and a VAP rate of 51.5 cases per 1000 ventilation days with a total of 388 days of ventilation

Table 4: Incidence and VAP rate within the Groups

Groups studied	Total cases	Incidence	VAP Rate
Group A (Conventional)	31	32.25%	69.56
Group B (Chlorhexidine mouth wash)	31	9.6%	24.35
Group C (Head end elevation)	28	25%	58.41

Graph 2 : Effect of interventions on the incidence of VAP



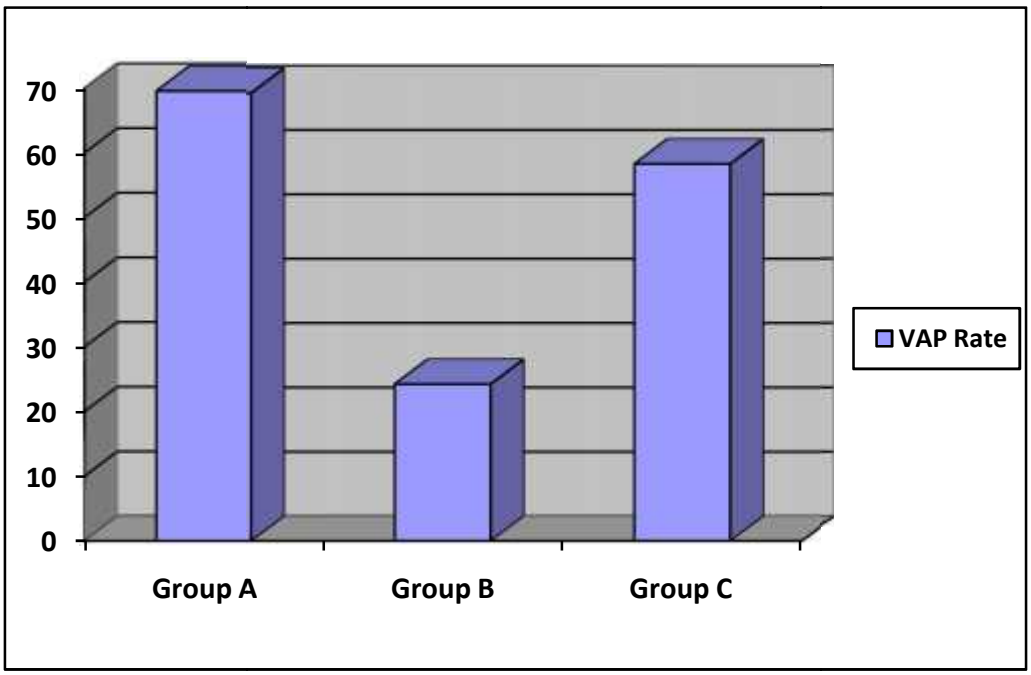
The incidence of VAP was lesser in the interventional Groups i.e. Group B (9, 6%), Group C (25%) when compared to conventional group A (32.25%).

Incidence of VAP was significantly lesser in CHX Group B when compared with conventional Group A, with an absolute risk reduction of 22.3 %(RR: 0.333, CI: 0.1207 to 0.9209, P = 0.0341)

However there was no statistically significant difference in the incidence when Group A was compared with the interventional groups B, C (P = 0.096) and between Group B and C (P=0.732). Similarly no difference in the incidence was found when Group A was compared with Group C (P = 0.5422)

(Table4)

Graph 3 : VAP rates within the groups



VAP rate was least in the interventional Group B [24.35 patients per 1000 ventilator days] followed by head end elevation Group C [58.56 per 1000 ventilator days], and highest in the conventional Group A [69.56 patients per 1000 ventilator days]. Therefore there was a higher VAP rate in the conventional group A when compared to the interventional groups.

Statistically significant difference in VAP rate was observed between Group A and Group B. (Z-Score 1.7176 P =0.0427)

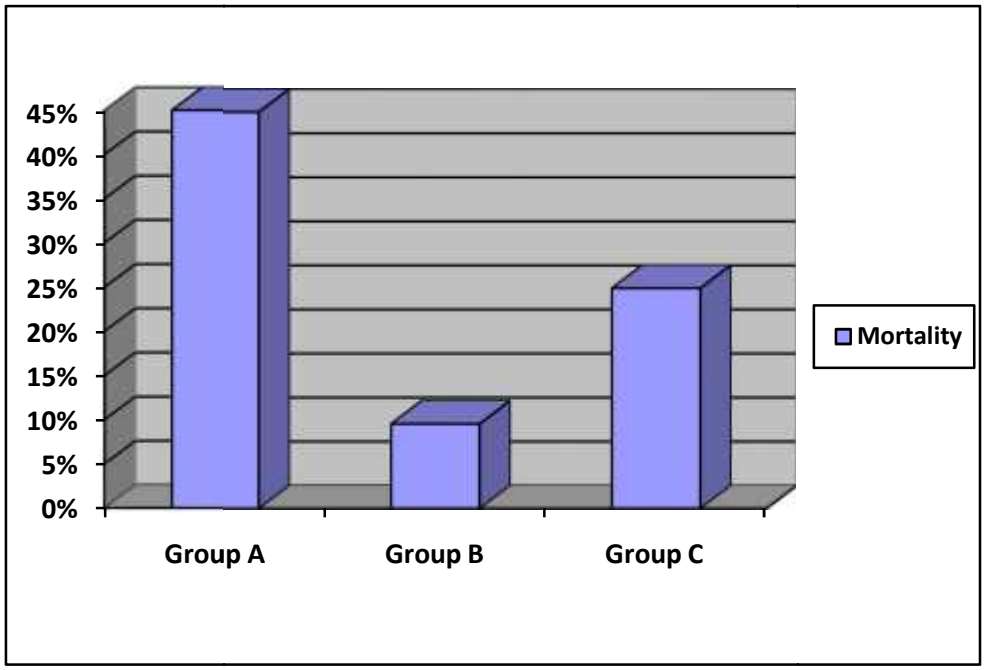
However similar observations were not seen when VAP rate was compared between Groups A and C (Z 0.3984. P 0.34458) and between Group B and C (Z-1.3182 P= 0.09342)

Secondary Outcomes

Table 5: Comparison of overall outcome between the Groups

Outcome Variables	Group A (N=31)	Group B (N=31)	Group C (N=28)	P value
Duration of ICU stay	7.25 days	6.29 days	6.60 days	0.660
Duration of ventilation	111 hrs	95.93 hrs	103.85 hrs	0.620
Mortality	14(45%)	4(9.6%)	7(25%)	**0.027**
Survival	11(35%)	18(58%)	13(46%)	**0.027**

Graph 4: Mortality within Groups



The overall mortality of ventilated patients in our study was 27.77% When the outcomes were compared between the three groups A, B, and C, a statistically significant difference was observed with respect to mortality and survival (P =0.027)

Duration of ICU stay (6.29 days in group B, 6.60 days in Group C) vs (7.25 days in Group A) and duration of ventilation (95.93 hrs in group B, 103.85 hrs in Group C) vs (111 hrs in Group A) were lesser in the interventional groups when compared to Group A . However the results were not statistically significant. (Table 5)

Table 6: Comparison of outcome between the Groups A and B

Outcome Variables	Group A (N=31)	Group B (N=31)	P value
Duration of ICU stay	7.25 days	6.29 days	0.353
Duration of ventilation	111 hrs	95.93 hrs	0.287
Mortality	14(45%)	4(9.6%)	**0.015**
Survival	11(35%)	18(58%)	**0.015**
Incidence	10(32.25%)	3(9.6%)	**0.0201**

The mortality in Group B was significantly lesser (9.6%) when compared to Group A (45 %), the difference was statistically significant (p=0.0202).

Statistically significant difference was observed with respect to mortality with Group A and Group B (RR: 0.3247, CI: 0.1253 to 0.8413, P = 0.0206) and survival (RR: 1.8595, CI: 1.1459 to 3.0175, P = 0.0120) with a higher mortality in Group A .There was a better survival (58%) in Group B compared to (41.9%) in Group A.

Duration of ICU stay (6.29 days in Group B) vs (7.25 days in Group A) and duration of ventilation (95.93 hrs in Group B) vs (111 hrs in Group A) were lesser in the interventional group when compared to Group A . However the result was not statistically significant. (Table6)

Table 7: Comparison of Outcome between the Groups A and C

Outcome Variables	Group A (N=31)	Group C (N=28)	P value
Duration of ICU stay	7.25 days	6.60 days	0.591
Duration of ventilation	111 hrs	103.85 hrs	0.657
Mortality	14(45%)	7(25%)	0.231
Survival	11(35%)	13(46%)	0.231
Incidence	10(32.25%)	7(25%)	0.542

The secondary outcomes like mortality, (RR: 0.6250, CI: 0.3132 to 1.2473, P = 0.1825) and survival (RR: 1.4773, CI: 0.8550 to 2.5523, P = 0.1619) showed no significant difference when Group A was compared with Group C.

Duration of ICU stay (6.60 days in Group C) vs (7.25 days in Group A) and duration of ventilation (103.85 hrs in Group C) vs (111 hrs in Group A) were lesser in the interventional group when compared to Group A , however the result was not statistically significant. (Table 7)

Table 8: Comparison of outcome between the Groups B and C

Outcome Variables	Group B (N=31)	Group C (N=28)	P value
Duration of ICU stay	6.29 days	6.60 days	0.764
Duration of ventilation	95.93 hrs	103.85 hrs	0.639
Mortality	4(12.9%)	7(25%)	0.298
Survival	18(58%)	13(46%)	0.298
Incidence	3(9.6%)	7(25%)	0.137

The secondary outcomes like mortality, (P = 0.298) and survival (P = 0.298) showed no significant difference when Group B was compared with Group C.

Duration of ICU stay (6.60 days in Group C) vs (6.29 days in Group B) and duration of ventilation (103.85 hrs in Group C) vs (95.93 hrs in Group B) were lesser in the interventional group B when compared to Group C, however the result was not statistically significant. (Table 8)

Table 9: Comparison of outcome between the conventional and Interventional groups

Outcome Variables	Group A (N=31)	Group B+ C (N=59)	P value
Duration of ICU stay	7.25 days	6.44 days	0.3861
Duration of ventilation	111 hrs	99.69 hrs	0.3995
Mortality	14(45%)	11(18%)	**0.0412**
Survival	11(35%)	31(52%)	**0.0412**
Incidence	10(32.25%)	10(16.94%)	**0.096**

Statistically significant difference was observed with respect to **mortality** with Conventional Group A and interventional Groups B+C (RR: 0.4677, CI: 0.2528 to 0.8653, P = 0.0155) and **survival** (RR: 1.6775, CI: 1.0406 to 2.7042, P = 0.0337) .There with a higher mortality in Group A and a better survival in the interventional Groups B+C

Duration of ICU stay (6.44 days in group B+C) vs (7.25 days in Group A) and duration of ventilation (99.69 hrs in group B+C) vs (111 hrs in Group A) were lesser in the interventional groups when compared to Group A . However, the result was not statistically significant.

There was a longer duration of ventilation and a longer ICU stay in the conventional group. (Table 9)

Table 10: Outcome in VAP cases within the groups

Outcome in VAP cases	Group A (N=10)	Group B (N=3)	Group C (N=7)	P value
Duration of ventilation in VAP cases	149±46.71 hrs	215±135 hrs	162.28±116.84 hrs	0.551
Duration of ICU stay	6.2±1.94	8.9±5.63	6.8±4.86	0.551
Mortality in VAP cases	8	0	2	
Survival in VAP cases	2	2	2	0.092 (fishers)

The duration of ventilation in Group A was 149 hours compared to 215 hours in group B and 162 hours in group C.

There was a longer duration of ventilation in group B when compared to other groups. But the difference was not statistically significant. (p = 0.551) (Table 10)

Risk factors

Table 11: Risk factors for Ventilator Associated Pneumonia

Risk factors		VAP (N=20)	No VAP (N=70)	P value
Age		2.88	4.93	**0.040**
Gender (M:F)		17:2	44:27	**0.073**
PRISM		4.40	5.90	0.246
Reintubation	Y	13	9	
	N	7	61	**<0.0001**
Prior hospitalization	Y	9	32	0.9549
	N	11	38	
Prior antibiotic use	Y	10	32	0.7347
	N	10	38	
Prior ventilation	Y	4	4	**0.036**
	N	16	66	
Sedation used	Y	13	30	**0.086**
	N	7	40	
Altered sensorium	Y	13	21	**0.006**
	N	7	49	
Type of ET	Un cuffed	10	54	**0.022**
	Cuffed	10	16	

Univariate analysis

The risk factors that were found to be significant with the development of VAP were younger age (P=0.033), male gender (P=0.023), reintubation (P<0.0001), prior ventilation (P = 0.0477), use of sedation (P = 0.0429), altered sensorium (P = 0.0044) and use of uncuffed ET tube (P = 0.0182)

The risk factors were found to be equally distributed within the groups and had no statistical significance

Group 5 : Risk factors for Ventilator Associated Pneumonia

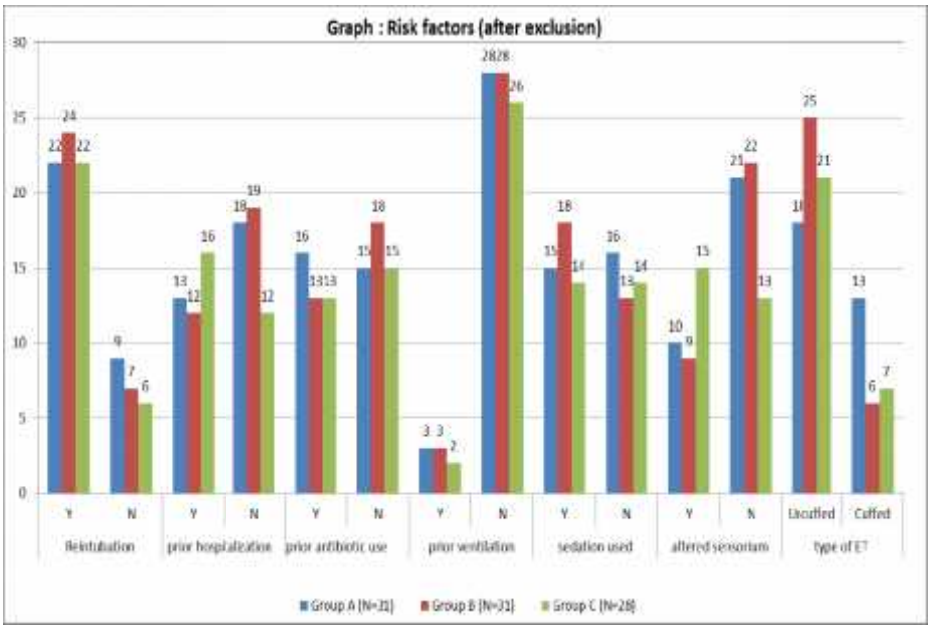


Table 12: Logistic Regression Analysis for Risk Factors of VAP

	Univariate		Multivariate		
Risk factor	95% CI	P value	Adjusted OR	95% CI	P value
Age	1.01-1.28	0.040	1.03	0.65-1.62	0.896
Male Gender	0.89-12.53	0.073	13.75	1.68-112.17	**0.014**
Reintubation	3.97-40	<0.0001	33.33	5.02-250	**<0.0001**
Prior ventilation	1.11-27.06	0.036	3.24	0.26-40.51	0.361
Sedation	0.88-6.94	0.086	8.77	1.39-55.55	**0.021**
Altered sensorium	1.51-12.40	0.006	8.51	1.61-44.81	**0.012**
Type of ET	1.19-9.54	0.022	7.24	0.3-175.18	0.223

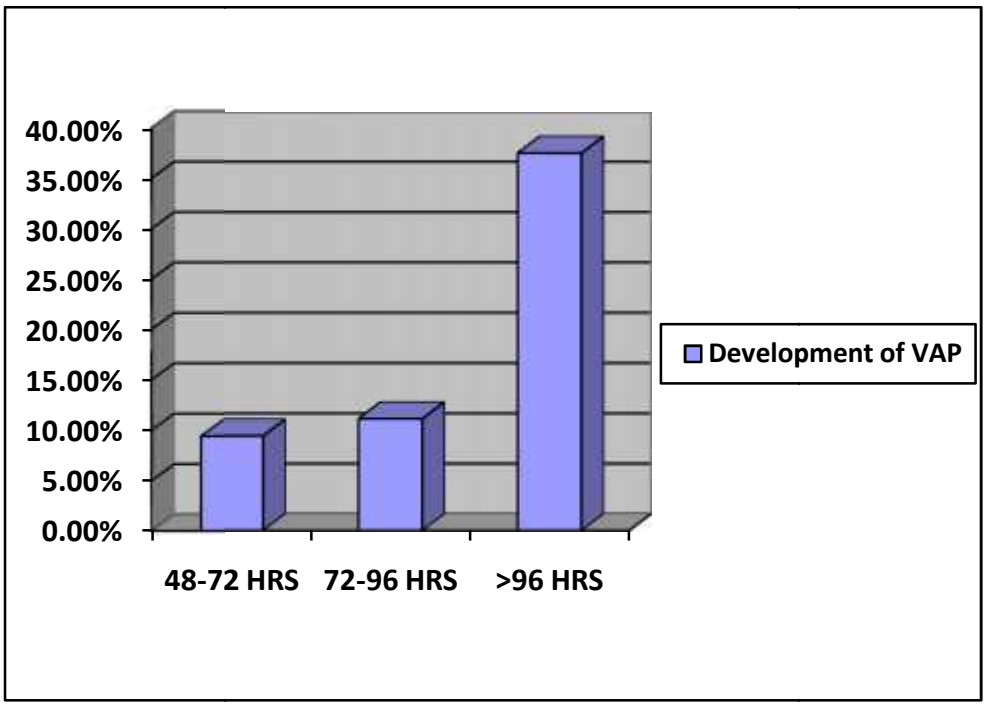
On multivariate analysis, male gender, Reintubation, Sedation and Altered sensorium were found to be statistically significant.

Table 13: Association of duration of ventilation with VAP

Duration of ventilation	VAP (N=20)	No VAP (N=70)	Total
48-72 hrs	3 (9.4%)	29(90.6%)	32
72-96 hrs	2(11.1%)	16(88.4%)	18
>96 hrs	15(37.5%)	25(62.5%)	40
Total	20	70	90

P=0.008

Group6: Association of duration of ventilation with VAP



There were 20 VAP cases diagnosed.3(9.4%)of them developed VAP between 48-72 hrs of ventilation.2 (11.1%)cases were diagnosed between 72-96 hrs of ventilation and the rest 15(37.5%) cases developed the infection with >96 hrs of ventilation. 9.4% of ventilated patients developed VAP in the first 48-72 hours which increased to 37.5% after 96 hours of ventilation. The result was statistically significant (p=0.008) indicating that longer duration of ventilation as a risk factor for the development of VAP. Patients ventilated for > 96 hours had 3.75 times higher risk for development of VAP when compared with patients ventilated for < 96 hours. (RR: 3.75, P = 0.0050) (Table 13)

Table 14: Comparison of outcome between VAP and Non VAP groups

Outcome variables	VAP(N=20)	No VAP(N=70)	P value
Duration of ventilation hrs	163.95±88.30	86.4±33.97	< **0.0001**
Length of hospital stay days	11.2	5.44	< **0.0001**
Survival	6(30%)	38(54.3%)	**0.0292**
Mortality	9(45%)	14(20%)	**0.0292**
DAMA	5(25%)	18(25%)	0.5121

The outcome of patients with and without VAP was studied using duration of ventilation, length of hospital stay, survival and mortality as criteria

The patients who were diagnosed with VAP had a significantly higher duration of ventilation i.e. 163 hours compared to 86.4 hours in patients who were ventilated for > 48 hours but did not develop VAP. (P<0.0001)

The mean hospital stay in VAP patients were 11.2 days compared to 5.44 days in Non VAP cases(p<0.0001).

Patients with VAP had a higher duration of ventilation and a longer duration of hospital stay when compared to patients who did not develop VAP.

The survival of patients with VAP was 30% compared to 54.3% in patients who did not develop VAP. Survival was poor once patients develop VAP (p=0.0552)

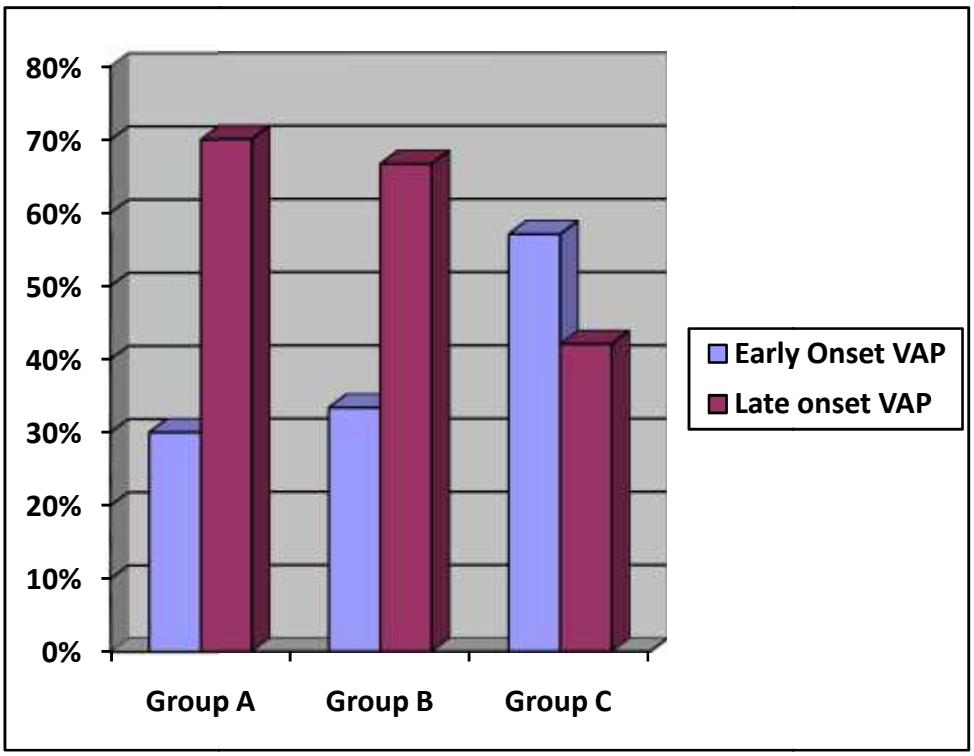
Mortality rate was higher (45%) among patients with diagnosed VAP compared with patients who did not develop VAP (20%) (RR: 2.25, CI: 1.2117 to 4.0987, P = 0.0099)

Table 15: Type of VAP and Distribution within Groups

Type of VAP	Group A (N=31)	Group B (N=31)	Group C (N=28)	Total
Early onset	3(30%)	1(33.3%)	4(57%)	8(40%)
Late onset	7(70%)	2(66.6%)	3(42%)	12(60%)
Total	10	3	7	20

P value =0.514

Group7: Type and Distribution of VAP within Groups

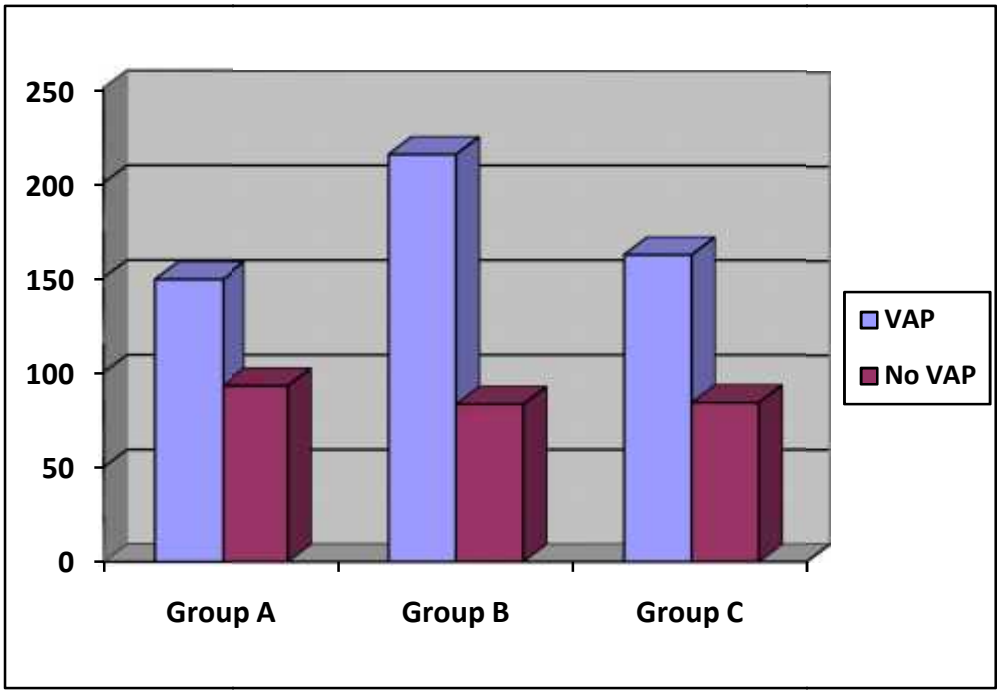


60% of the cases diagnosed were of late onset VAP. There was a higher proportion of late onset VAP in Group A (70%) compared to 42% in Group C

Table 16: Duration of ventilation in VAP cases among the groups

	Group A (N=10)	Group B (N=3)	Group C (N=7)	P value
VAP	149 hrs	215 hrs	162.28 hrs	0.031
No VAP	92.85 hrs	83.17 hrs	84.04 hrs	

Group8: Duration of ventilation in VAP cases among the groups



Statistically significant difference was observed with respect to duration of ventilation. (P=0.031). Patients with VAP had a longer duration of ventilation.

When we compared the duration of ventilation in Group B with Group A, the result was statistically significant (P =0.0128). Similar significance was not obtained when Group A was compared with Group C (P = 0.3471)and Group B with C (P =0.1350). (Table 16)

Table 17: Duration of ICU stay in VAP cases among the groups

Duration of ICU stay	Group A (N=10)	Group B (N=3)	Group C (N=7)
VAP	11.3 days	12.66 days	10.42 days
No VAP	5.33 days	5.6 days	5.33 days

The duration of ICU stay in patients diagnosed with VAP in Group B was 12.66 days which was higher than head end elevation.

Group9: Duration of ICU stay in VAP cases among the groups

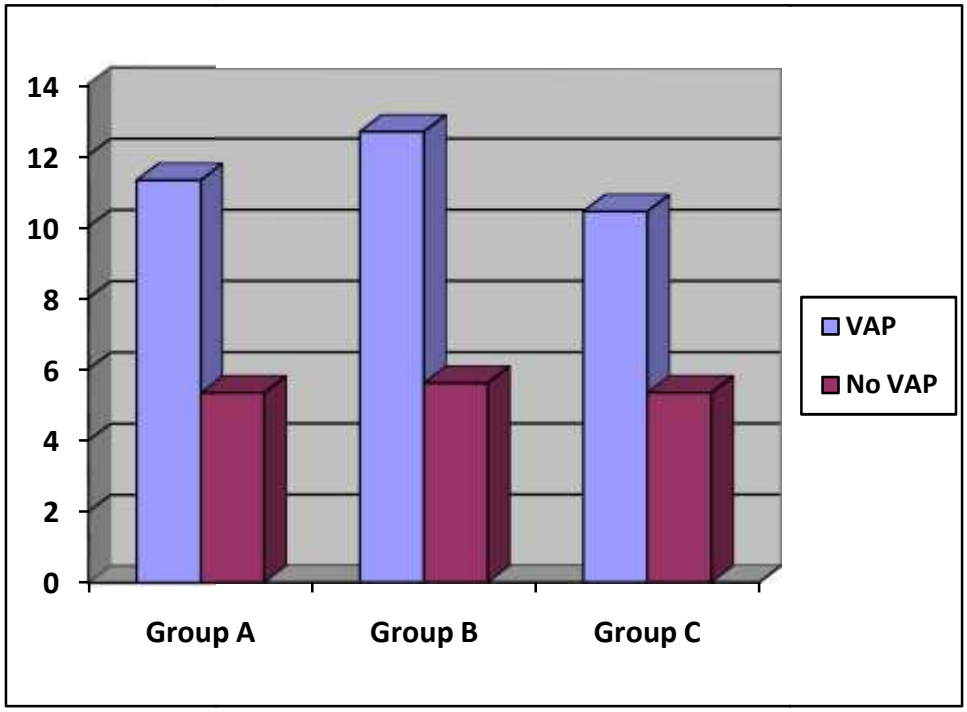


Table 18: Mortality in VAP cases among the groups

Mortality	Group A (N=31)	Group B (N=31)	Group C (N=28)	P value
VAP	8/10(80%)	0/3(0%)	2/7(28.5%)	
No VAP	6/21(28.5%)	4/28(14%)	5/21(23%)	0.092

Mortality rate was 80% among patients in the conventional group A followed by 28.5% in Group C. 2 of the 3 patients survived in Group B

Group10: Mortality in VAP cases among the groups

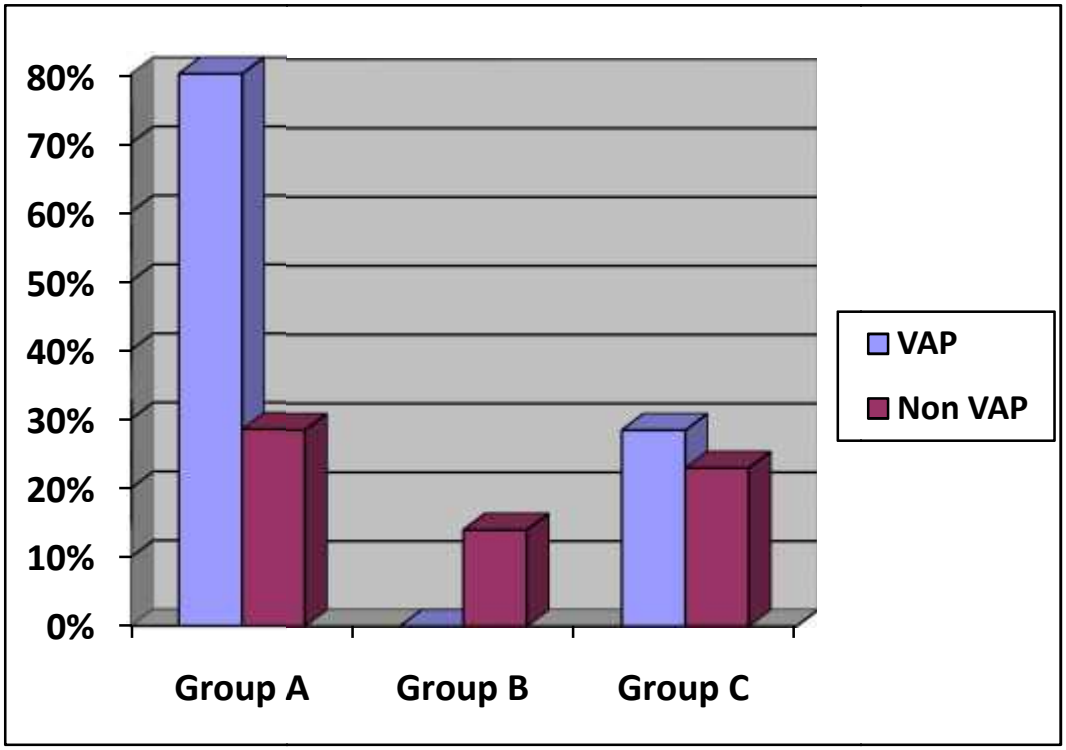


Table 19: Survival in VAP cases among the groups

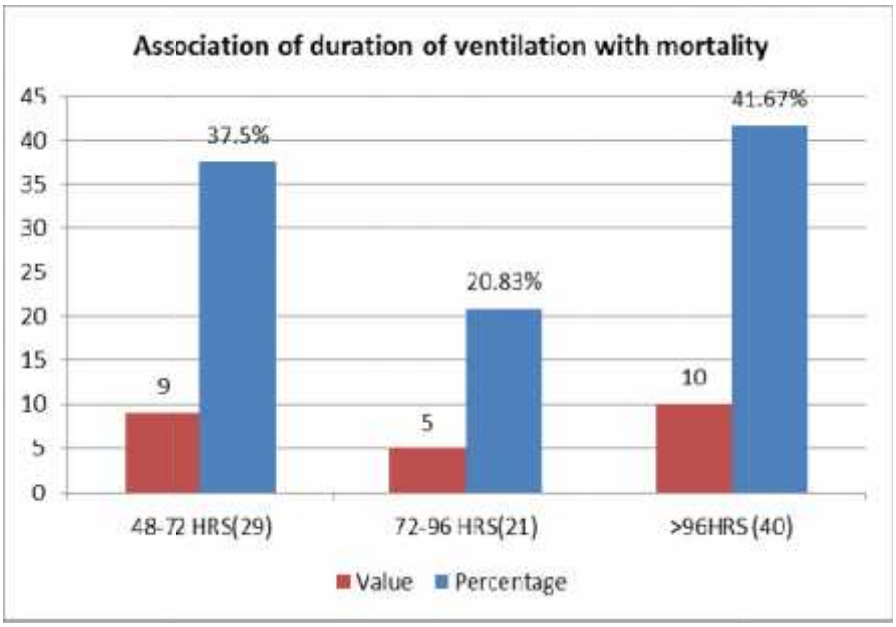
Survival	Group A	Group B	Group C	P value
VAP	2/10(20%)	2/3(66.6%)	2/7(28%)	
No VAP	9/21(42%)	16/28(57%)	11/21(52%)	0.862
Total	11	18	13	

There was a better survival rate of 66.6 % in VAP patients in the CHX group B and least in the conventional Group A. (20%)

Table 20: Association of duration of ventilation with mortality

Duration of Ventilation	Mortality	P Value
48-72 HRS(29)	9(31%)	
72-96 HRS(21)	5(23%)	P = 0.8076
>96HRS (40)	10(25%)	

Group11: Association of duration of ventilation with mortality



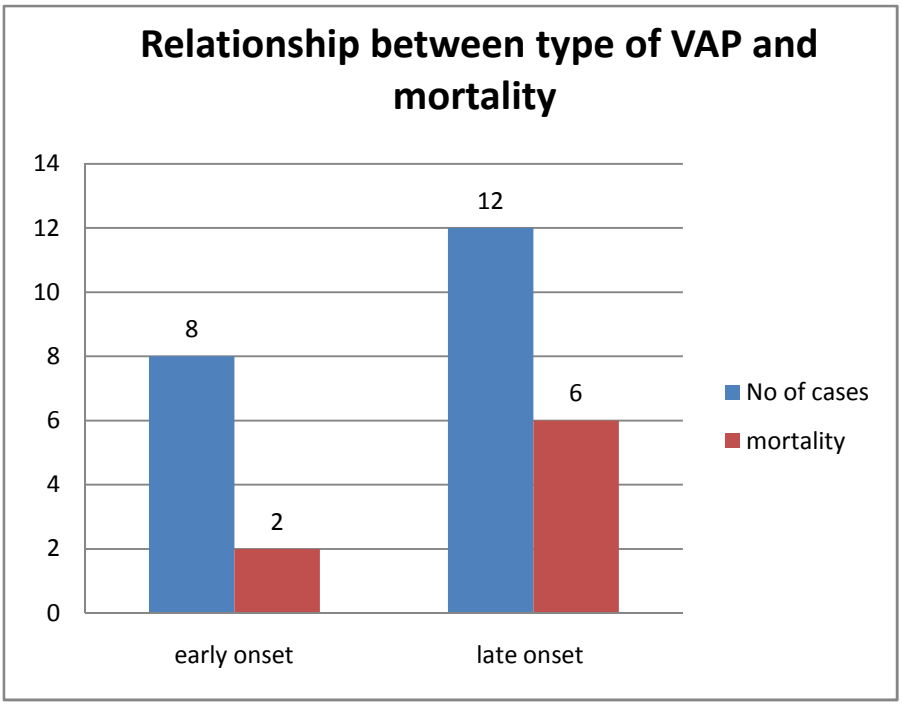
We looked at the relationship between the duration of ventilation and mortality.

The mortality was highest in the first 48-72 hours of ventilation (31%). Duration of ventilation is not significantly associated with mortality. (Table 20)

Table 21: Relationship between type of VAP and mortality

Type of VAP	No of cases	mortality
Early onset	8	2(25%)
Late onset	12	6(50%)

Group12 : Relationship between type of VAP and mortality



8 out of 20 cases were diagnosed to have early onset VAP and 12 were diagnosed to have late onset VAP. 2 patients with early onset VAP expired (25%) compared to 6 (50%) in late onset. The mortality rate doubles once the patient develops late onset VAP. The risk of mortality with late onset VAP was three times more than early onset VAP. (OR: 3.0 with 95% CI: 0.4226 and 21.298 and P=0.2719 (Table 21)

Table 22: Endotracheal culture positivity in VAP cases among the groups

	Group A (N=31)	Group B (N=31)	Group C (N=28)	Total
VAP(20)	9/10	2/3	4/7	15
No VAP(70)	4/21	4/28	3/21	11
Total	13(41.9%)	6(19.3%)	7(25%)	26

Group13: Endotracheal culture positivity in VAP cases among the groups

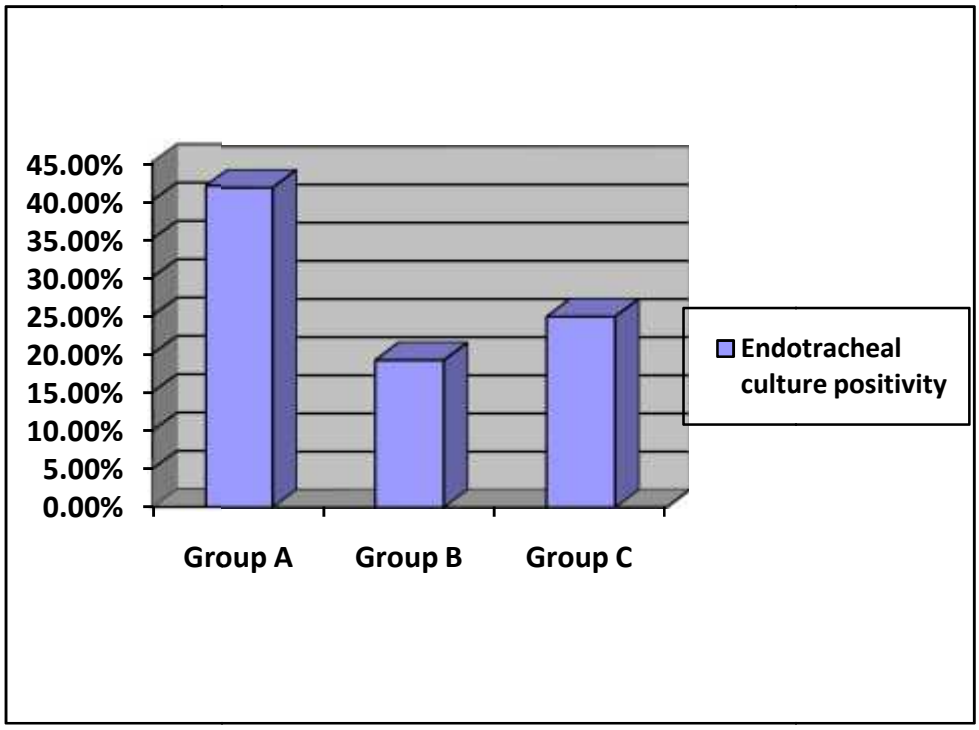


Table 23: Organisms isolated on Endotracheal aspirate

Organism isolated	Number
Aceinitobacter	5
E.coli	1
Pseudomonas	6
Enterobacter	2
Candida	1
B.cepacia	3
S.aureus	2
Klebsiella	3
Coagulative negative staph aureus	1
Chryseobacterium	2

Chapter 4

Methodology

METHODOLOGY

This randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2012 to December 2012.

Study design

The study design was single blind randomized controlled study.

Study period and duration

The present study was conducted for one year between January 2012 to December 2012.

Place

This study was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

The patients presenting with complaints of bleeding per rectum, congestion, perianal itching, pruritis, congestion, prolapse and diagnosed of having bleeding haemorrhoids at Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were included in the study.

Sample size

A total of 60 patients divided into two groups of 30 each.

Sampling procedure

Data assessing effectiveness and safety of euphorbia prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin in control of bleeding haemorrhoids is scarce and hence considering this as a pilot study the effect size was determined as 30 in each group based on thumb rule.

Selection criteria

Inclusion

- Patients of either sex between age of 12 and 75 years diagnosed of having bleeding haemorrhoids having normal vital parameters.
- Patients willing to participate in the study by giving their consent for the same.

Exclusion

- Pregnant and lactating women.
- Patients undergoing any surgical procedure for haemorrhoids.
- Patients with a history of permanent anal prolapse and/or anal fistula
- Patients with associated anal fissures and/or infective anal pathology
- Patients participating in any other clinical trail.
- Patients participating in any other similar studies.

Ethical clearance

The study was approved from the Institutional Ethics and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

Eligible patients were informed about the nature of the study and a written informed consent was obtained (Annexure I).

Method of collection of data

Complete medical history of the patients was taken and examination was done to assess eligibility criteria. Demographic data such as age, sex and the presenting complaints were obtained through an interview. Patients were assessed for the bleeding per rectum at enrollment and graded as blood stained stools, slow flow of blood, number of drops of blood, jet as reported by the patients. Further these patients were subjected to thorough clinical examination and the findings were recorded on a predesigned and pretested proforma (Annexure II).

Randomization

Patients were divided into two groups of 30 each as experimental or control group randomly by asking them to pick any sealed envelope containing name of the group that is, either experimental or control group.

Photograph 1. Study drug – Euphorbia prostrata (Group E)

Photograph 2. Study drug – Micronized purified flavonoid fraction of diosmin (Group C)

Investigations

Patients were subjected to proctoscopic examinations to confirm the diagnosis and to assess the characteristics of bleeding haemorrhoids such as grade, position and congestion.

Blinding

Medicines were pre-packed in closed containers. Each container was coded with a number which was also the patients identification number.

Treatment

Experimental group

Patients in experimental group were advised to take one tablet of 100 mg euphorbia prostrata daily for 14 days.

Control group

Patients in control group were advised to take two tablets of 500 mg diosmin TID for four days and two tablets BD for three days and two tablets there after for seven days.

Follow up

Patients were followed up on days five, ten and fourteen.

Outcome variables

Bleeding

Post treatment follow up

Patients were assessed for the bleeding per rectum reported by the patients at every follow up. The end point of the study was determined as complete cessation of bleeding. The reduction of bleeding during the follow up period was graded as below.

- Excellent reduction – 71 to 100%
- Good reduction – 51 to 70%
- Average reduction – 31 to 50%
- Poor reduction – 30% or less

Pruritis

Patients were assessed for presence/absence of pruiritis at all the follow-ups.

Statistical analysis

The data obtained was coded and entered in Microsoft Excel Spreadsheet. The categorical data was expressed as rates, ratios and percentages and comparison was done using chi-square test. Continuous data was expressed as mean ± standard deviation and the comparison was done using two sample unpaired ‘t’ test with unequal variance. A ‘p’ value of less than or equal to 0.05 was considered as statistically significant.

DISCUSSION

Ventilator associated pneumonia (VAP) is the second most important cause of nosocomial infection in Pediatric Intensive Care Units [2].Incidence of VAP ranges from 9-27% of all intubated patients [1]. It is associated with a significant increase in mortality, morbidity, duration and cost of hospitalization. Studies from India have shown a high VAP rate of 32.5%-47% with mortality as high as 25-44% [2]. In view of the high frequency, associated morbidity and mortality, prevention of VAP is the need of the hour. Different VAP prevention strategies have been studied worldwide mainly in adults.

Oropharyngeal colonization with several pathogens and the micro aspiration of the colonized pathogens has been implicated as a major cause in the pathogenesis of VAP. Therefore pharyngeal decontamination with Chlorhexidine (CHX) and semi recumbent position with head end elevation are potential strategies in VAP prevention.

Evidence to demonstrate the efficacy of oral decontamination with CHX mouth wash and semi recumbent position with head end elevation to reduce the incidence of VAP, which is studied extensively in adult's shows conflicting results. However, similar results are lacking in Pediatric ICUs especially in developing countries like India. Therefore the present study was planned to test the hypothesis that oral decontamination with CHX mouth wash and semi recumbent position with head end elevation to prevent aspiration could reduce the incidence of VAP in our PICU.

The Baseline socio demographic and clinical characteristics of our study population, such as age, gender, socioeconomic status, and diagnosis, Severity of illness, number of systems affected, primary system affected at admission and indication of ventilation, were comparable between the conventional and interventional groups.

Mean age of our study population was 3.37 years, with a male preponderance similar to other Indian studies[5, 7, 12.] Our study population consisted of a younger age group, with majority of patients having grade 3 socioeconomic status, ventilated for neurological illness, and patients with preexisting infections who had received antibiotics prior to admission. Being a tertiary referral centre, sick children with multisystem involvement were admitted in our PICU.

Incidence

Incidence of VAP in our study was 22% with a VAP rate of 51/1000 ventilator days, which is similar to the trend reported previously [14]. Most studies on VAP in PICU have been carried out in developed countries, which reveal an incidence from 7-40% [1, 23.] Incidence of VAP in developing countries is 20-45%,[2,3,4,6,7,8,9] which varies considerably with various studies. Possible reasons explained could be an increased severity of illness on admission, increased prevalence of lower respiratory tract infections, malnutrition, and also the study methodology, population studied and diagnostic method used. Different diagnostic methods were used to diagnose VAP in these studies. Most of these studies have used the National Nosocomial Infection Surveillance (NNIS) and Centers for Disease Control and Prevention criteria. Our study uses the Clinical Pulmonary Infection Scoring (CPIS) criterion which has a sensitivity of 72%, specificity of 85% and accuracy of 79% at the threshold score of

6[40]. An advantage of the simplified scoring system is that it takes into account, clinical, microbiological, and radiological data and does not rely on the ET culture. Lower rate of incidence found in our study could be due to the use of interventions employed to prevent VAP.

Effect of Chlorhexidine mouth wash on the incidence of VAP

Oropharyngeal colonization by aerobic pathogens either present on admission or acquired during ICU stay has been identified as an independent risk factor. Factors such as mucosal desiccation, decreased salivary content of IgA, reduced salivary secretion, and mechanical injury induced by nasogastric and endotracheal tubes facilitate this process [4, 61]. Micro aspiration of these bacteria laden secretions track down the ET tube and contaminate the lower airways. Antiseptics like CHX reduce the bacterial load of the oropharynx and prevent infection of the lower respiratory tract.

The incidence of VAP in the CHX and the conventional group were 9.6% and 32.5% respectively in the study and were significantly lesser in the CHX group compared to the conventional group with an absolute risk reduction of 22.3 %. This observation is lesser than that reported by a recent Meta analysis, where a 36% reduction was observed.

Several studies have reported similar observations of significant benefit of CHX in reducing the incidence of VAP in medical and surgical ICUs,[52 ,59, 61]A similar observation was noted by Koeman et al[57] in adult medical and surgical ICUs, where a significant reduction in oropharyngeal colonization with gram-positive microorganisms was observed which delayed the development of VAP.

The Centers for Disease Control and Prevention guidelines recommend regular oral care with antiseptics; these highlight the lack of pediatric studies on strategies to prevent VAP and the lack of a consensus on the methodology of oral care. Little is known about the effects of oral care interventions in critically ill children. Evidence-based protocols for oral care for these children are not available. The metatanlysis of seven clinical trials by chlebicki [51] found that chlorhexidine is associated with a 30% relative reduction in the risk of VAP. The beneficial effect of CHX was demonstrated in two of the seven trials that included cardiac surgical patients. Incidence of VAP in cardiothoracic ICUs was markedly lower compared to general medicosurgical ICUs. Cardiothoracic ICU patients have a better physiological status secondary to the preoperative workup and the duration of ventilation is usually shorter. Mixed ICUs and medical ICU patients have various co morbidities and consequently a higher mortality rate [61.]

Studies that used CHX in varying concentrations from 0.1-0.2 % have failed to demonstrate beneficial effects [77]. In trials with cardiac surgery patients at low risk for developing ventilator associated pneumonia due to a short duration of ventilation, chlorhexidine 0.12% was effective in reducing ventilator associated pneumonia [77]. Tantipong et al [67] showed a significant reduction in the number of VAP episodes/1000 ventilator days using a higher concentration of 2% CHX. However, irritation of the oral mucosa was observed in 9.8% of their patients. The pediatric population that we have studied is markedly different from the adult subjects in the other studies. They are less cooperative and their oral cavities are smaller and less accessible particularly with an ET tube in situ. Chances of displacement and extubation are high in these children who are irritable, while attempting oral care.

Contrary to our observation, Pineda et al [60], Fourrier et al [53] have reported no benefit of CHX in reducing the incidence of VAP. The only Pediatric Indian RCT which evaluated the effect of CHX gel showed no effect on the incidence. The possible reasons could be the use of the CDC criteria for diagnosis which is less sensitive, and a smaller sample size. Our study was performed in similar settings and the study has shown significant benefit in reducing VAP.

The only other published data regarding the efficacy of CHX in children is the use of 0.12% CHX solution in children undergoing cardiac surgery which failed to demonstrate a beneficial effect[65] and the RCT conducted by Pedreira et al[66] where CHX was not found to be effective in decreasing the colonization.

Effect of head end elevation on the incidence of VAP

Several studies in mechanically ventilated patients have shown that aspiration of gastric contents occurs to a greater degree when patients are in the supine position than when they are in the semi-recumbent position with the HOB elevated to 30^0 to $45^{0,}$ which is facilitated by the nasogastric tube which holds the lower esophageal sphincter open. This is particularly important for patients who are receiving enteral nutrition to prevent aspiration of gastric contents.

Although statistically insignificant, there was a lesser incidence of VAP in the head end elevation group compared to the conventional group in our study probably due to a small sample size.

Other studies have reported similar observations of a lack of VAP reduction, Nieuwenhoven et al [65], Niël-Weise[70], Keeley et al [69.].Contrary to our observation,

Drakulovic et al [68] and Alexiou VG [67] have reported beneficial effects of semi recumbent position on the incidence of VAP.

Nieuwenhoven et al[65] monitored the position of the patient continuously and the targeted backrest elevation of 45°was not achieved in the study. In contrast angle of head end elevation of patients in Drakulovic[68] study was not monitored and the feasibility could not be studied. Control patients were nursed in complete horizontal position of 0° which is less than the standard of routine care and could have contributed to more VAP cases in controls. Similar findings were reported by Grap and colleagues [70]where the average backrest elevation was 21.7^0.Niel weise in their the systematic review concluded that it is uncertain whether a 45° bed head elevation is effective with regards to development of VAP.

Our study was conducted in a different situation where most of our patients were infants and there were technical difficulties in maintaining these infants in semi recumbent position.

Secondary outcomes

Overall outcome

In our study, patients who developed VAP had a significantly prolonged duration of ventilation, ICU stay and a higher mortality. Similar observations of prolonged duration of ventilation and ICU stay have been reported in other similar studies [1, 2, 18, 19, 25, and 26.]Higher mortality, similar to our findings has been demonstrated in other studies [1, 2, 3, 5, 6, 18, and 19]

Effect of chlorhexidine mouth wash on the outcome of VAP

Mortality in the Conventional group A and interventional Group B were 45 % and 9.6% respectively. The study shows a significantly lesser mortality in the CHX group compared to the conventional group, with three times higher mortality in the conventional group and a significantly lesser duration of ventilation, lesser ICU stay and better survival compared to the conventional group.

Several studies have reported similar observations of significant benefit of CHX in reducing the mortality of VAP in medical and surgical ICUs [52, 74, 76]

The recent Cochrane review confirms that the use of a combination of topical and systemic antibiotics reduces overall mortality significantly [76] .Contrary to our observation, Pineda et al[60] Snyders et al [61] Sebastian et al[4] and Chan [77] have reported no benefit of CHX in reducing the incidence of VAP. Pineda et al analyzed the studies, where most of the adult patients were ventilated following elective cardiac surgeries, where patients had different co morbid conditions and better physiological status contrary to sick children admitted in PICU. Our study has demonstrated a significant reduction of mortality in critically ill children with various co morbidities. The other possible reason could be a lesser incidence of VAP and consequently a lesser contribution of VAP to the overall mortality. The mortality in the conventional group who developed VAP was 80% compared to 0% in the CHX mouth wash group which was not statistically significant due to the small sample size. None of the studies aimed at looking at the important outcomes like duration of ventilation and mortality[51], however koeman et al[57] and deriso[52] et al have reported findings similar to ours.

Contrary to our observation, no difference in duration of mechanical ventilation, intensive care unit stay, or intensive care unit survival could be demonstrated by Fourrier et al[53.] In critically ill children, multiple factors contribute to mortality and it would be difficult to assess the attributable mortality due to VAP.

Effect of head end elevation on outcome of VAP

In our study there was a longer duration of ventilation, longer ICU stay and poor survival in the conventional group compared to the head end elevation group which was not statistically significant due to a small sample size. Similarly Alexiou [67] concluded that Patients positioned semi recumbently at 45^0 had a better clinical outcome with respect to duration of ventilation and hospital stay. Kollef et al[75] found that a supine head position during the first 24 hours was independently associated with mortality. We could not measure the angle and duration of elevation achieved, which was a limitation of our study.

Risk factors

Univariate analysis revealed younger age at presentation, male gender, reintubation, prior ventilation, use of sedation; altered sensorium and uncuffed ET were significantly associated with VAP.

Using multiple logistic regression analysis, male gender, reintubation, sedation and altered sensorium were found to be independently associated with VAP.

A significant proportion of patients who developed VAP, were of younger age group compared to the patients in the Non VAP group in our study. Since most of the studies on VAP have been conducted in adult, much literature is not available about the association of age with development of VAP.

Male gender had a significant association in our study similar to few other studies[23, 24, 29].

Reintubation is a definitive risk factor for VAP that has been shown previously by many studies [2, 3, 5, 6, 12, 14, 16, 17, 18, 26,] and our study also shows the significance of that risk factor causing VAP (P<0.0001).This finding however was contradicted by a few other studies[1] Reintubation was probably related to enhanced risk of aspiration of the colonized oropharyngeal contents during each attempt to intubate. The glottic dysfunction associated with prolonged intubation could have aggravated this.

Depressed level of consciousness and the **use of sedation** were found to be significantly associated with the development of VAP as shown by other studies. [1, 2, 14, 15, 18, 19, 23,29]. Depressed level of consciousness impairs the local defense mechanisms and predispose to aspiration.

Use of an **uncuffed ET tube** was a risk factor that was identified in this study. Similar observations have been reported previously [3, 23].Contaminated oropharyngeal secretions track down the ET and pool around the cuff of the endotracheal tube. Uncuffed ET would enhance the risk of aspiration. Use of uncuffed ET was not found to be a risk factor in these studies [1, 10] .Though significant on univariate analysis, use of uncuffed ET failed to show independent effect on multivariate analysis.

Our study found a significantly increased risk of development of VAP when the patients were ventilated for > 96 hours. In consistence with the observation of other studies[3, 5, 6, 14, 26]

Risk factors that were identified by other studies like PRISM, prior hospitalization, prior antibiotic use were not found to be associated with VAP in our study, similar to several studies [22, 23, and 24]

History of prior antibiotic use and history of previous hospitalization did not show any significant relationship with VAP in our study. A systematic review and Meta analysis by Bo Liu [18] concluded that history of prior antibiotic use was a risk factor. Findings similar to ours has been reported in other studies[2,6]

The guidelines published by American thoracic society say that prior antibiotic use and history of previous hospitalization are risk factors for multidrug resistant pathogen causing pneumonia if a patient develops VAP [24]. Few other studies have reported that prior antibiotic use confers protection [20, 21, 22, 28]

Bacteriological data

Positive endotracheal tube cultures were obtained in 19.3% of patients in Group B compared to 41.9% in Group A. with Pseudomonas being the most common isolate. This finding could be due to the lesser oropharyngeal colonization in the CHX group and a protective effect of CHX. Fourrier et al[53] and Koeman et al[57] have demonstrated that decontamination with CHX significantly reduced the colonization of oropharynx. According to the systematic review of literature by Bahubali [2], most of the cases of VAP is caused by aerobic gram negative bacteria (GNB) .The predominant gram negative bacilli associated with VAP were Pseudomonas aeruginosa and Acinetobacter spp.

To conclude, our study a single blind randomized controlled trial, is the first Indian study to demonstrate the efficacy of Chlorhexidine mouth wash in significantly

reducing the incidence of VAP. Similar effects were seen with Head end elevation though it was not statistically significant. Study also shows that the patients with the interventions had a lesser duration of ventilation, lesser ICU stay, lesser mortality and a better survival, suggesting that Chlorhexidine mouth wash and Semi recumbent position with head end elevation are effective interventions in VAP prevention.

Effectiveness of Chlorhexidine mouth wash was found to be more significant than Head end elevation. This observation may be due to the small sample size in the groups and also due to the technical difficulties in maintaining the infants in Semi recumbent position. Therefore these are the limitations of our study. We would recommend a Multicentre trial of larger study population to confirm our findings.

Chapter 5

Results

RESULTS

This one year single blind randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2012 to December 2012.

A total of 60 patients presenting with complaints of bleeding per rectum, congestion, perianal itching, pruritis, congestion, prolapse and diagnosed of having bleeding haemorrhoids were enrolled.

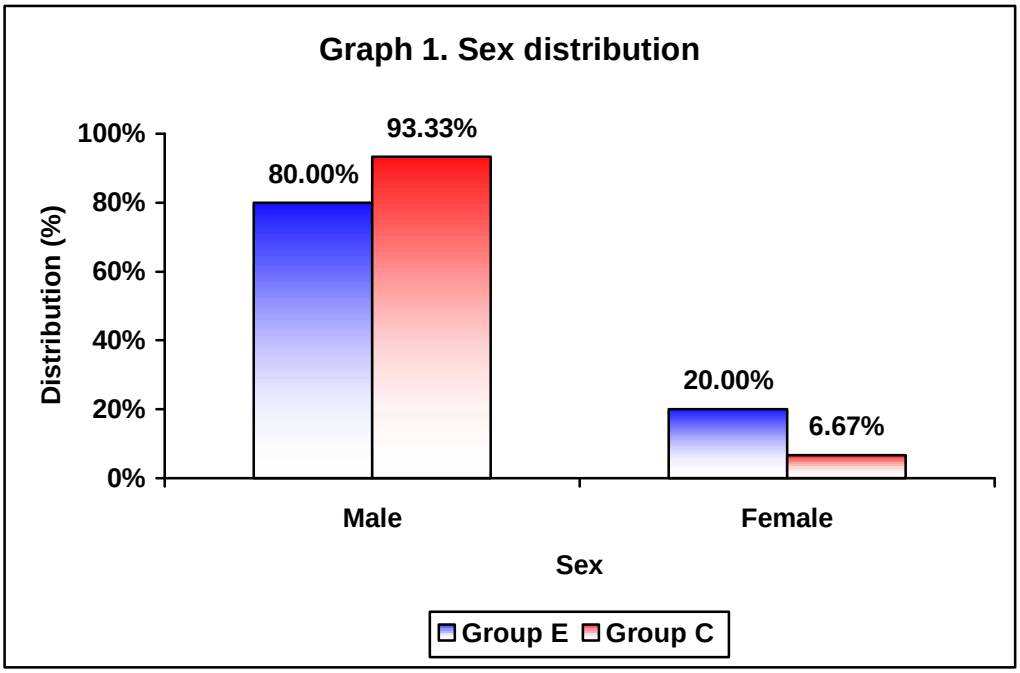
Patients were divided into two groups of 30 each as experimental or control group randomly by envelop method that is Group E and Group C respectively. Patients in experimental group underwent treatment with euphorbia prostrata and control group was treated with diosmin.

The data obtained was coded and tabulated on Microsoft excel spreadsheet. The data was anlysed and final results and observations were tabulated as below.

Table 1. Sex distribution

Sex	Group E (n=30)		Group C (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Male	24	80.00	28	93.33
Female	6	20.00	2	6.67
Total	**30**	**100.00**	**30**	**100.00**

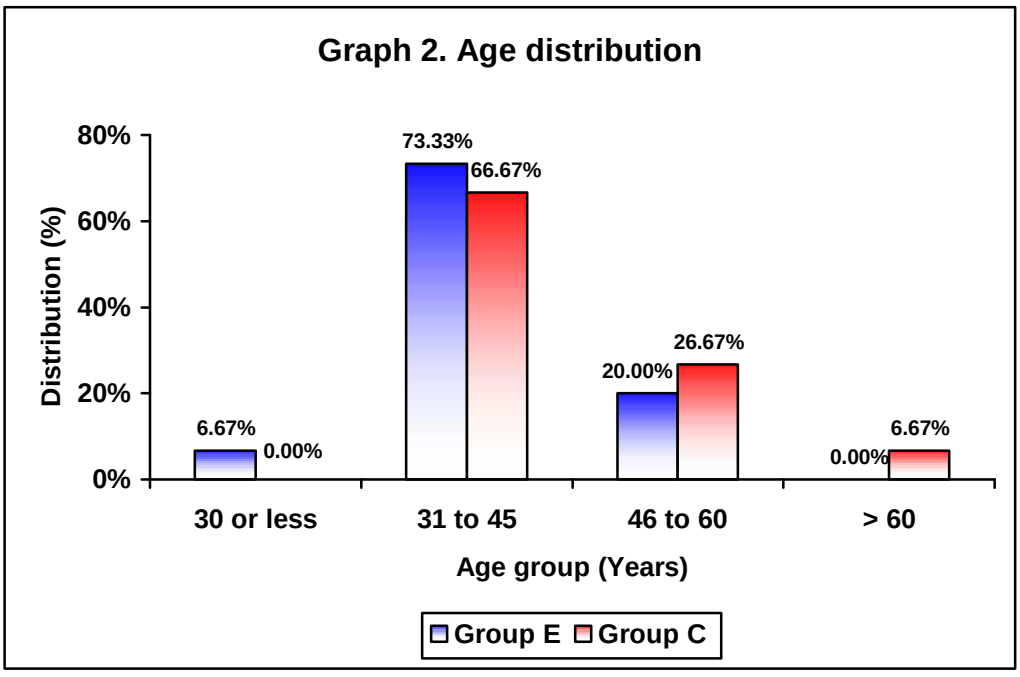
p = 0.255



In the present study, 80% of patients in group E and 93.33% of patients in group C were males. The male female ratio in group E was 4:1 while in group C it was 14:1.

Table 2. Age distribution

Age group (Years)	Group E (n=30)		Group C (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
30 or less	2	6.67	0	0.00
31 to 45	22	73.33	20	66.67
46 to 60	6	20.00	8	26.67
> 60	0	0.00	2	6.67
Total	**30**	**100.00**	**30**	**100.00**



In this study most of the patients in group E (73.33%) and (66.67%) were aged 31 to 45 years.

Table 3. Mean age

Variables	Group E (n=30)		Group C (n=30)		p value
	Mean	SD	Mean	SD	
Age (Years)	39.60	6.52	43.4	10.11	0.092

In this study the mean age in group E was 39.60 ± 6.52 years compared to 43.40 ± 10.11 years in group C and on comparison no statistically significant difference was observed between the two groups (p=0.092).

Table 4. Occupation

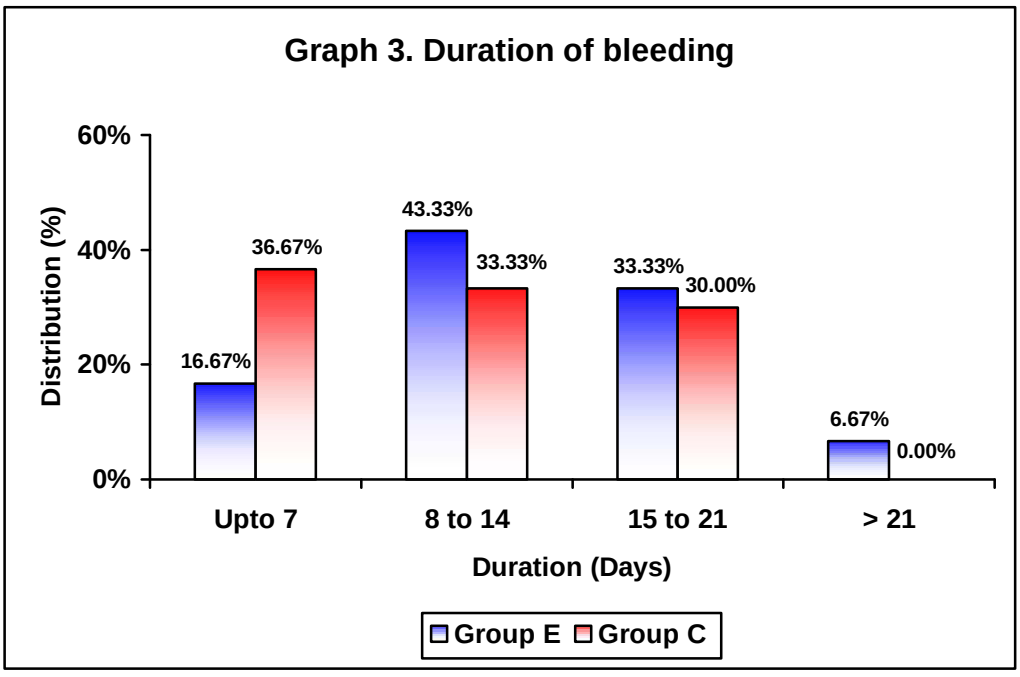
Occupation	Group E (n=30)		Group C (n=30)	
	Number	Percentage	Number	Percentage
Business	7	23.33	8	26.67
Farmer	5	16.67	11	36.67
Service	8	26.67	8	26.67
Labour	5	16.67	1	3.33
Housewife	5	16.67	2	6.67
Total	**30**	**100.00**	**30**	**100.00**

p = 0.180

In the present study most of the patients in group E were in service (26.67%) while in group C 36.67% were farmers. However no statistically significant difference was observed between the two groups (p=0.180).

Table 5. Duration of bleeding

Duration (Days)	Group E (n=30)		Group C (n=30)	
	Number	Percentage	Number	Percentage
Upto 7	5	16.67	11	36.67
8 to 14	13	43.33	10	33.33
15 to 21	10	33.33	9	30.00
> 21	2	6.67	0	0.00
Total	**30**	**100.00**	**30**	**100.00**

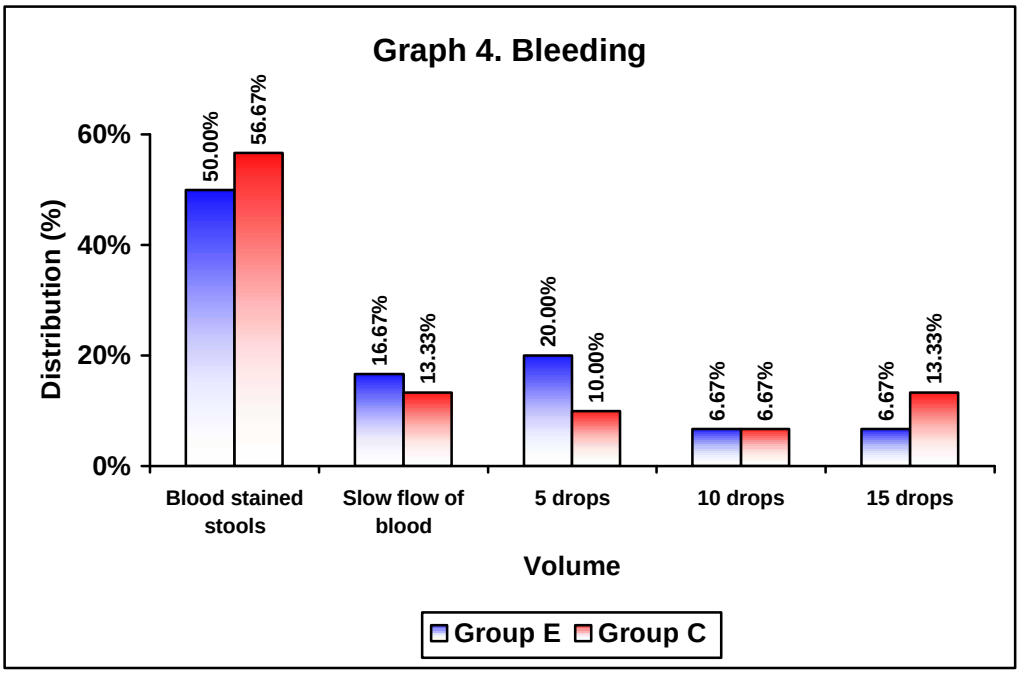


In this study 43.33% of patients in group E presented with duration of bleeding between 8 to 14 days compared to 36.67% of patients in group C with duration of less than 7 days. The mean duration of bleeding in group E was 14.6 ± 5.41 days compared to 12.4 ± 4.89 days in group C (p=0.109).

Table 6. Bleeding

Volume	Group E (n=30)		Group C (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Blood stained stools	15	50.00	17	56.67
Slow flow of blood	5	16.67	4	13.33
5 drops	6	20.00	3	10.00
10 drops	2	6.67	2	6.67
15 drops	2	6.67	4	13.33
Total	**30**	**100.00**	**30**	**100.00**

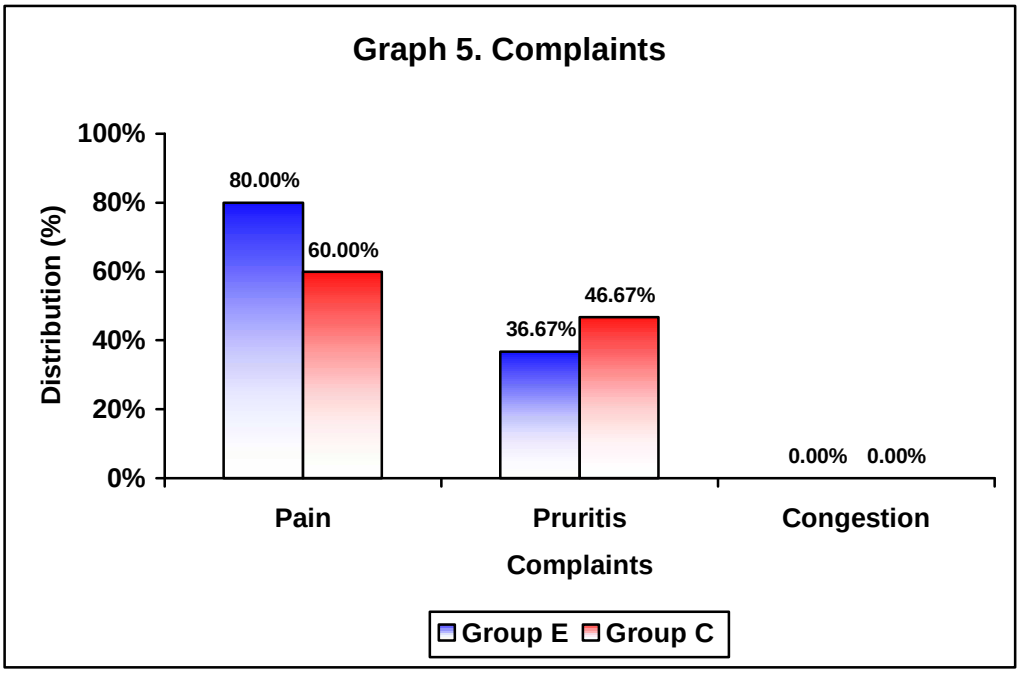
p = 0.754



In the present study blood stained stools were reported by 50% of patients in group E compared to 56.67% in group C. However this difference was statistically not significant (p=0.754).

Table 7. Complaints

Complaints	Group E (n=30)		Group C (n=30)		p value
	Number	Percentage	Number	Percentage	
Pain	24	80.00	18	60.00	0.091
Pruritis	11	36.67	14	46.67	0.432
Congestion	0	0.00	0	0.00	1.000



In the present study the presenting complaints namely, pain and pruritis were comparable in group E and C while none of the patient complained congestion.

Table 8. Vitals

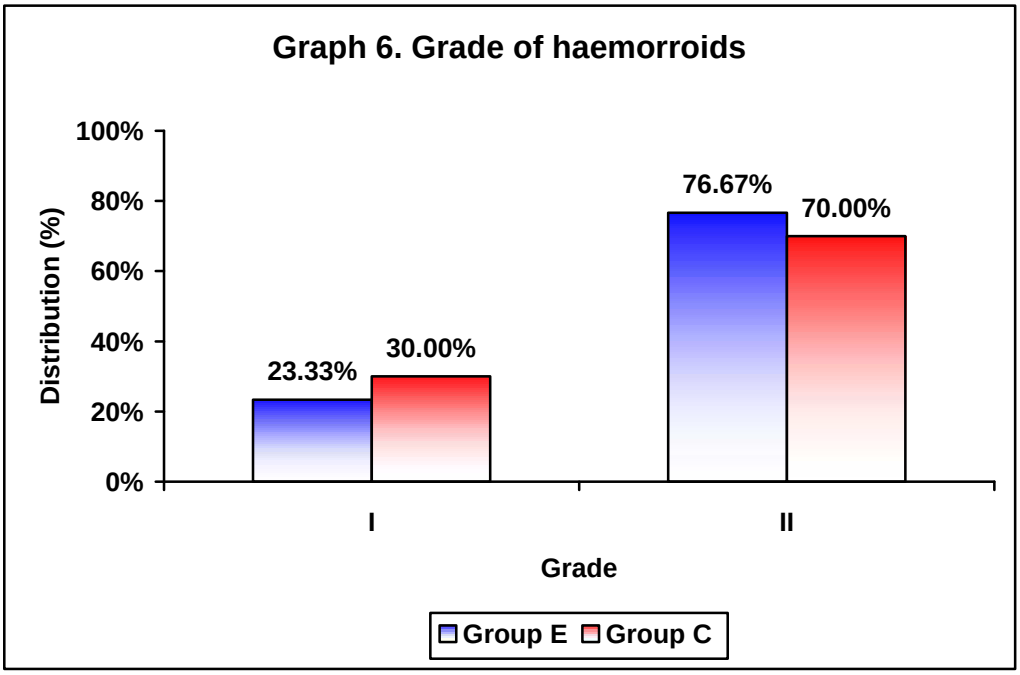
Vitals	Group E (n=30)		Group C (n=30)		p value
	Mean	SD	Mean	SD	
Pulse rate (bpm)	78.9	2.91	77.5	3.58	0.102
Systolic BP (mm Hg)	117.4	4.78	116.2	8.45	0.502
Diastolic BP (mm Hg)	76.8	4.02	77.2	5.52	0.750

In this study, the mean pulse rate, systolic and diastolic blood pressure were comparable in group E and C ($p>0.050$).

Table 9. Grade of haemorroids

Grade	Group E (n=30)		Group C (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
I	7	23.33	9	30
II	23	76.67	21	70.00
Total	**30**	**100.00**	**29**	**96.67**

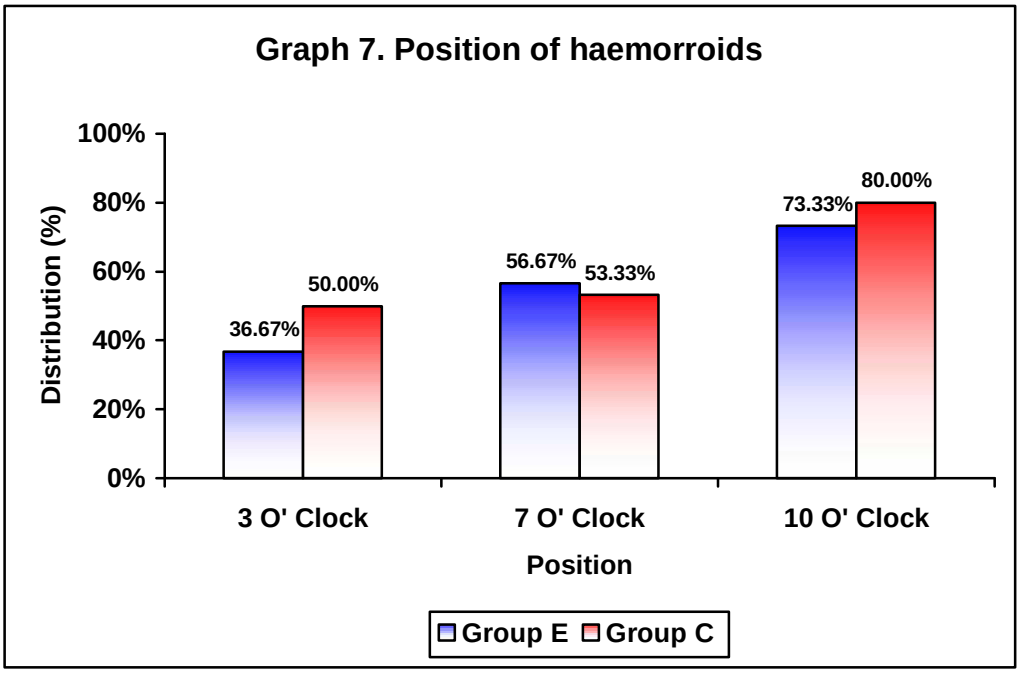
p = 0.561



In this study most of the patients in group E (76.67%) and C (70%) presented with grade II haemorroids. However the haemorroid grades in group E and C were comparable (p=0.561).

Table 10. Position of haemorroids

Position	Group E (n=30)		Group C (n=30)		p value
	Number	Percentage	Number	Percentage	
3 O' Clock	11	36.67	15	50.00	0.297
7 O' Clock	17	56.67	16	53.33	0.795
10 O' Clock	22	73.33	24	80.00	0.542

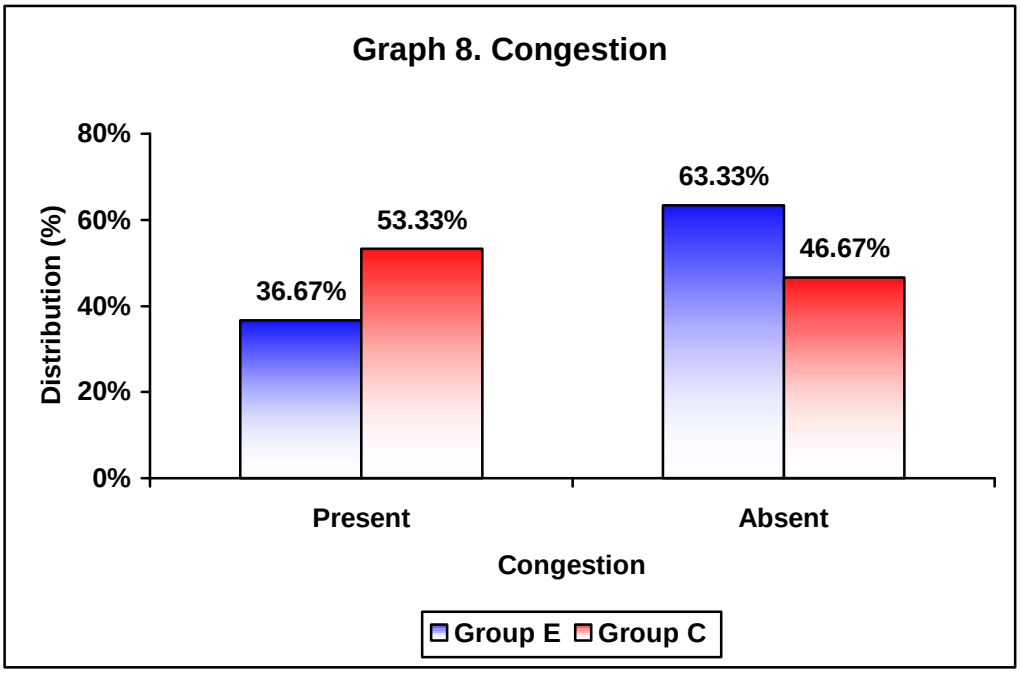


In the present study on proctoscopic examination, the 10 O'clock position of haemorroids was seen in majority of the patients with group E (73.33%) and group C (80%) (p=0.542). The 7 O' clock position was noted in 56.67% of patients in group E and 53.33% in group C (p=0.795).

Table 11. Congestion

Congestion	Group E (n=30)		Group C (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Present	11	36.67	16	53.33
Absent	19	63.33	14	46.67
Total	**30**	**100.00**	**30**	**100.00**

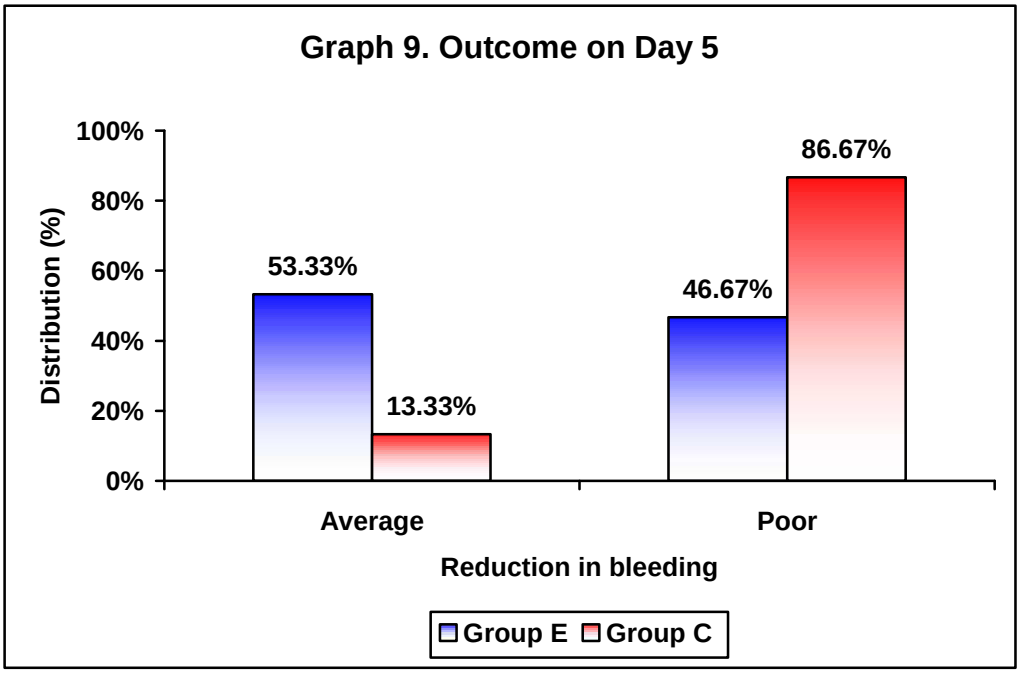
p = 0.194

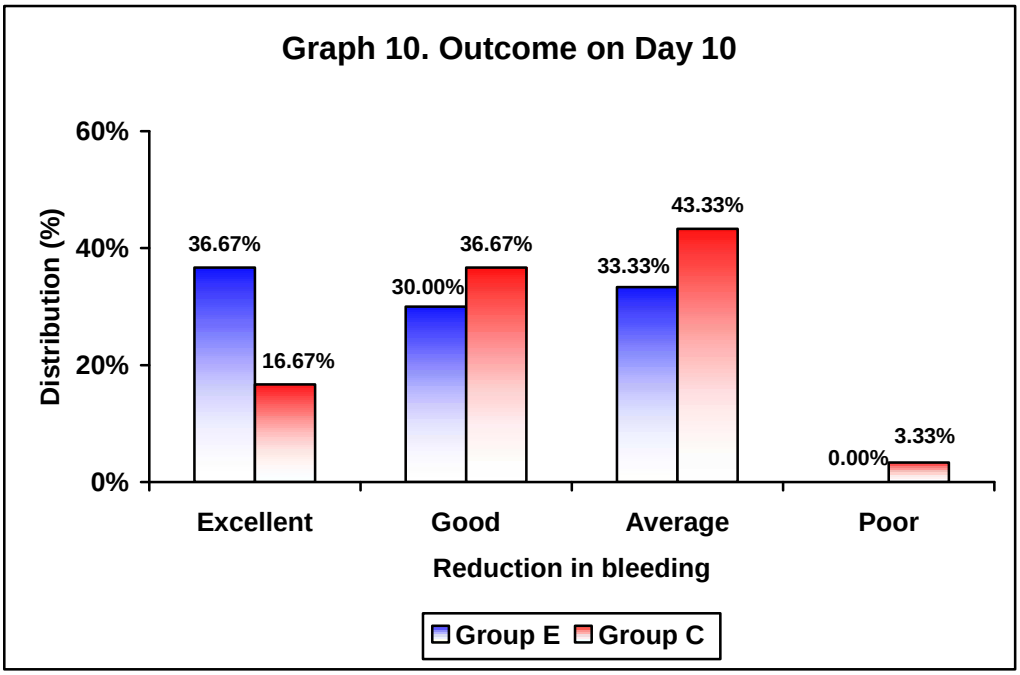


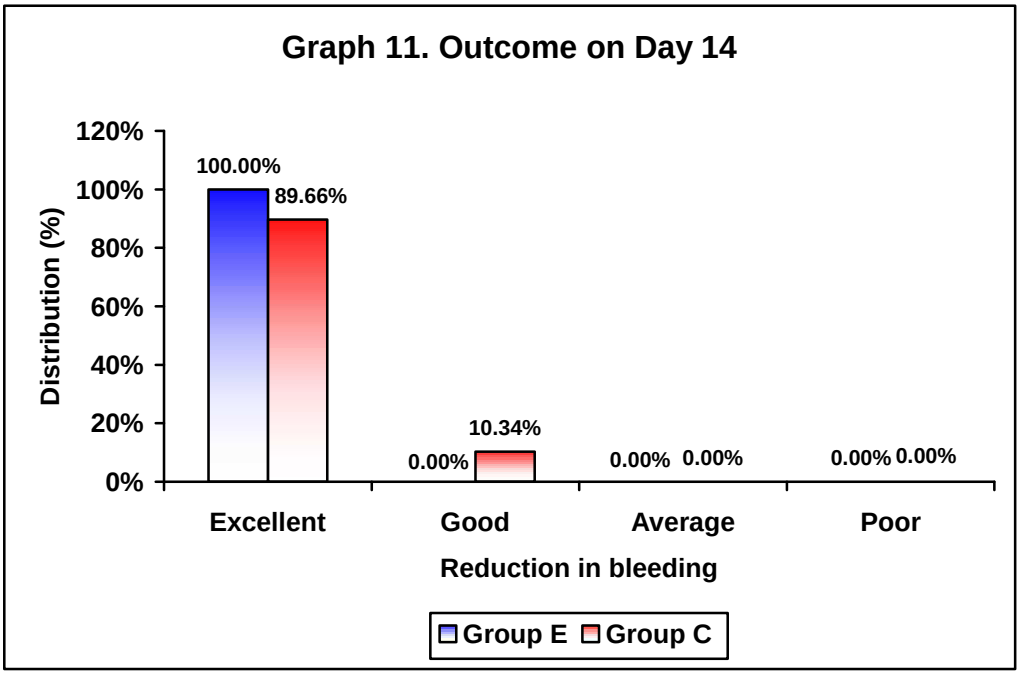
In this study proctoscopic examination revealed congestion in 53.33% of patients in group C while in patients with group E, 36.67% of patients had congestion (p=0.194).

Table 12. Reduction in bleeding during follow up

Follow up	Reduction in bleeding	Group E (n=30)		Group C (n=30)		p value
		No	%	No	%	
Day 5	Average	16	53.33	4	13.33	0.001
	Poor	14	46.67	26	86.67	
	Total	**30**	**100.00**	**30**	**100.00**	
Day 10	Excellent	11	36.67	5	16.67	0.291
	Good	9	30.00	11	36.67	
	Average	10	33.33	13	43.33	
	Poor	0	0.00	1	3.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Day 14	Excellent	27	100.00	26	89.66	0.261
	Good	0	0.00	3	10.34	
	Average	0	0.00	0	0.00	
	Poor	0	0.00	0	0.00	
	Total	**27**	**100.00**	**29**	**100.00**	


Graph 9. Outcome on Day 5
100%
80%
60%
40%
20%
0%
Distribution (%)
53.33%
13.33%
46.67%
86.67%
Average
Poor
Reduction in bleeding
Group E
Group C

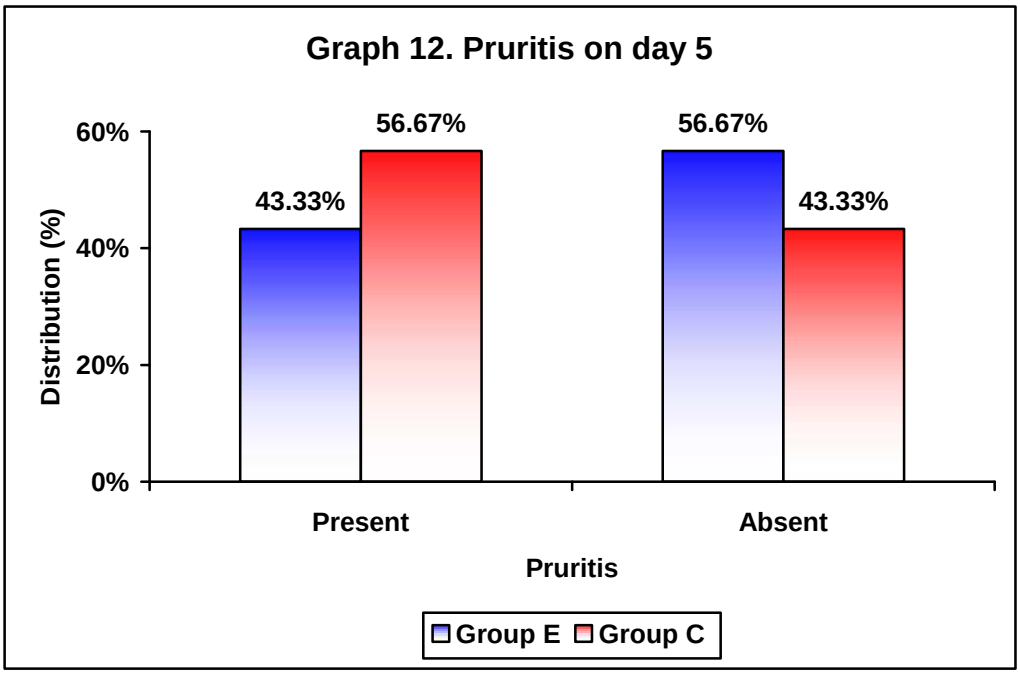

Graph 10. Outcome on Day 10
60%
40%
20%
0%
Distribution (%)
36.67%
16.67%
30.00%
36.67%
33.33%
43.33%
0.00%
3.33%
Excellent
Good
Average
Poor
Reduction in bleeding
Group E
Group C

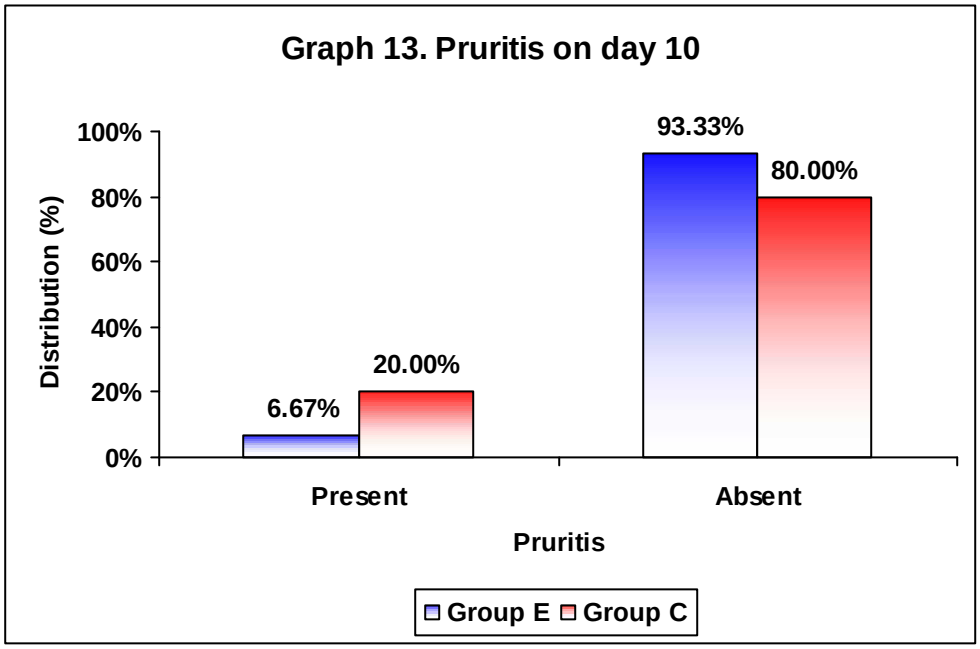


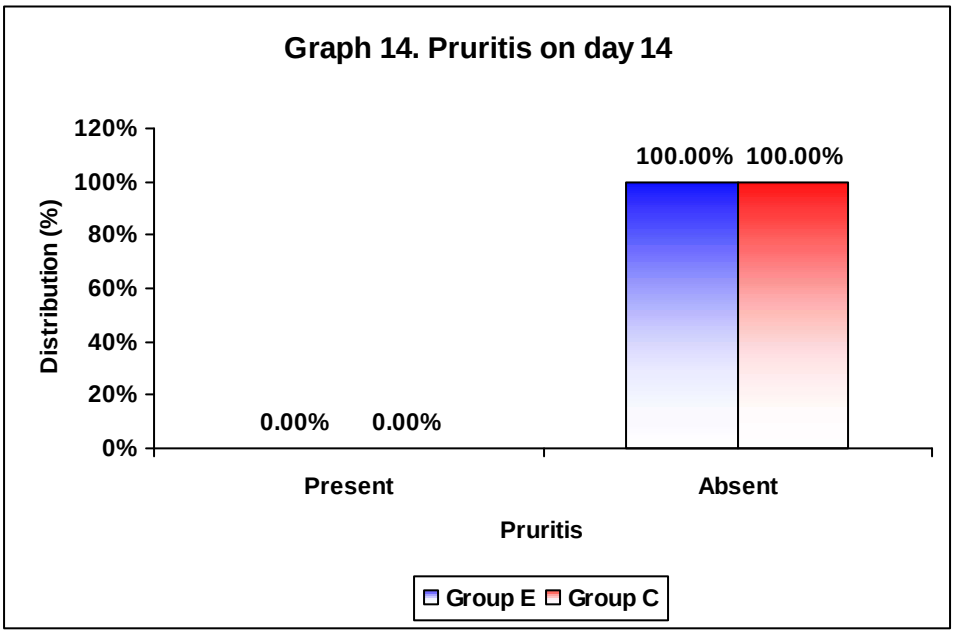
In the present study, during fifth day follow up, significantly higher number of patients in group E (53.33%) reported average reduction of bleeding compared to group C (13.33%) (p=0.001). At second follow up, 36.67% of patients in group E had excellent reduction in bleeding compared to 16.67% in group C. During third follow up all the patients in group E (100%) reported excellent reduction in bleeding compared to 89.66% but this difference between group E and C at second (p=0.291) and third follow up (p=0.261) was statistically not significant.

Table 13. Symptomatic relief - Pruritis

Follow up	Pruritis	Group E (n=30)		Group C (n=30)		p value
		No	%	No	%	
Day 5	Present	13	43.33	17	56.67	0.302
	Absent	17	56.67	13	43.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Day 10	Present	2	6.67	6	20.00	0.255
	Absent	28	93.33	24	80.00	
	Total	**30**	**100.00**	**30**	**100.00**	
Day 14	Present	0	0.00	0	0.00	1.000
	Absent	30	100.00	30	100.00	
	Total	**30**	**100.00**	**30**	**100.00**	







In this study pruritis was absent in 56.67% and 93.33% of patients in group E during first and second follow up while in group C it was absent in 43.33% and 80% respectively but, this difference was statistically not significant ($p>0.050$). At third follow up pruritis was absent in all the patients (100%) with group E and C.

CONCLUSION

It is evident from the study that Chlorhexidine mouth wash significantly reduces the incidence and the risk for development of Ventilator associated Pneumonia, compared to conventional care and the head end elevation. Though the incidence in Head end elevation Group was lesser than the conventional Group, the result was not statistically significant. Thus the Study shows a significant benefit of the intervention Chlorhexidine mouth wash in reducing the incidence, and the risk of development of VAP and thereby improving the outcome of mechanically ventilated patients in terms of lesser mortality, better survival, lesser duration of ventilation and lesser ICU stay. A multicentric stud with a larger population is recommended to support our findings.

Chapter 6

Discussion

DISCUSSION

Hemorrhoids are one of the most frequent anorectal disorders encountered in the primary care sitting. They are the most common cause of bleeding per rectum and are responsible for considerable patient suffering and disability.[91] In India approximately 40,723,288 people are reported to have hemorrhoids. 1 million new cases are reported annually, 47 per 1000 and increases with age, age group of 45-65 years.[37]

Drug treatment for various anorectal conditions has been known since ancient times. Today, modern as well as traditional drugs are being increasingly used specially in grade I and II hemorrhoids. These drugs (oral and local) are used as a part of conservative management or as an adjuvant to invasive outpatient procedures. While drug treatment is aimed at curing early grade of hemorrhoids which does not need any intervention, the role of drug therapy in advanced grades of hemorrhoids is to control the acute phase so that definitive office procedures or surgery can be scheduled at a convenient time.[91]

Numerous medications in the form of oral preparation or as local application have been proposed, used and studied since the time of Hippocrates. There are many oral antihemorrhoid preparations widely prescribed by physicians in the treatment of acute symptoms of hemorrhoids. These preparations contain semi synthetic agents or plant extracts such as escin, diosmin, and rutin related compounds that have been shown to have regulatory effects on veins, venules, and capillaries.[91]

The present study was aimed to assess the effectiveness of Euphorbia Prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin in control of bleeding haemorrhoids and to find the safety of Euphorbia Prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin.

This one year single blind randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 60 patients divided into two groups of 30 each as experimental or control group randomly by envelop method that is Group E and Group C respectively. Patients in experimental group underwent treatment with euphorbia prostrata and control group was treated with diosmin.

In the present study, the male female ratio in group E was 4:1 while in group C it was 14:1 suggesting male preponderance. Though there was male preponderance, the comparison between group E and C showed that, the sex distribution was comparable (p=0.255). In a retrospective study[91] from Nagpur to evaluate usefulness of *Euphorbia prostrate* in controlling symptoms of grade 1 and 2 symptomatic hemorrhoids on 120 patients, reported 63 were males and 57 were females.

In this study the commonest age group was 31 to 45 years in group E (73.33%) and group C (66.67%). The mean age in group E was 39.60 ± 6.52 years compared to 43.40 ± 10.11 years in group C and on comparison no statistically significant difference was observed between the two groups

(p=0.092). In a retrospective study[91] from Nagpur, the mean age of patients was 33 years (range 21-67 years). Another prospective study[92] on 1816 patients from Mumbai reported mean age of the patients as 43.43 years (range, 14-90 years). The prevalence of hemorrhoids has been estimated to be highest in those between 45 and 65 years of age.[30] An epidemiologic study by Johanson et al[31] in 1990 showed that in both sexes, peak prevalence occurred between age 45-65 years and the development of hemorrhoids before the age of 20 years was unusual.

In the present study 26.67% of the patients in group E were in service compared to 36.67% were farmers in group C. However the comparison of occupation between the two groups showed no statistically significant difference suggesting that occupation on both the groups was comparable (p=0.180).

In this study, in group E, 43.33% of the patients had duration of bleeding between 8 to 14 days compared to 36.67% of the patients in group C with duration of < 7 days. The mean duration of bleeding in group E was 14.6 ± 5.41 days compared to 12.4 ± 4.89 days in group C (p=0.109).

The most common manifestation of hemorrhoids is painless rectal bleeding associated with bowel movement, described by patients as blood drips into toilet bowl. The blood is typically bright red as hemorrhoidal tissue has direct arteriovenous communication.[49] In the present study blood stained stools were reported by 50% of patients in group E compared to 56.67% in group C. However this difference was statistically not significant (p=0.754). The presenting complaints that is, pain and pruritis were comparable in group E and C. In a retrospective study[91] on 1816 patients from Nagpur reported that, bleeding

per rectum was present in 82% of the patients. Another study[92] from Mumbai reported bleeding as the most frequent complaint at the presentation (n=1640, 89%) followed by pain (n=1470, 80%). Other symptoms were swelling, pruritus and prolapse.

With regard to the haemorroid grades, majority of the patients in group E (76.67%) and C (70%) presented with grade II haemorroids (p=0.561). On proctoscopic examination, the 10 O'clock position of haemorroids was seen in majority of the patients with group E (73.33%) and group C (80%) (p=0.542). The 7 O' clock position was noted in 56.67% of patients in group E and 53.33% in group C (p=0.795). Similar findings with regard to 7 O' clock position were reported in a study[92] from Mumbai. In this study, proctoscopic examination revealed congestion in 53.33% of patients in group C while in patients with group E, 36.67% of patients had congestion (p=0.194).

The above findings suggest that, the patients demographic characteristics such as sex and age, presenting complaints namely, bleeding pattern, pain and pruritis as reported by the patient, haemorroid characteristics like duration, grade and position were comparable in both the groups (p>0.050).

In the present study, higher number of patients in group E (53.33%) reported average reduction of bleeding compared to group C (13.33%) during fifth day follow up (p=0.001). At second follow up, 36.67% of patients in group E had excellent reduction in bleeding compared to 16.67% in group C and at third follow up all the patients in group E (100%) reported excellent reduction in bleeding compared to 89.66%. However, the difference between number of

patients reporting reduction of bleeding in group E and C at second (p=0.291) and third follow up (p=0.261) was statistically not significant. These findings suggest that, the treatment of Euphorbia prostata has significantly resulted in faster recovery from bleeding at first follow up that is on day five but further its was comparable with micronized purified flavonoid fraction of diosmin.

To date, to our knowledge, only two studies[91,92] have assessed the role of euphorbia prostata in the management of haemorroids. A study retrospective study[91] from Nagpur reported that 82% of the patients had complete cessation of bleeding at the end of two weeks amounting to a success rate of 87% and study concluded that, Euphorbia prostrata can be used as an effective and well-tolerated pharmaceutical agent in the treatment of early grades of hemorrhoids. Another prospective, open label, single arm, post marketing study[92] from Mumbai reported that, at the end of the study, bleeding was reported by 3.9% as compared to 89.3% at the baseline ($p < 0.0001$). However, the findings of this study were in agreement with these studies[91,92] to certain extent, the results could not be compared due to the methodological difference.

In this study pruritis was absent in 56.67% and 93.33% of patients in group E during first and second follow up while in group C it was absent in 43.33% and 80% respectively but, this difference was statistically not significant ($p>0.050$). At third follow up pruritis was absent in all the patients (100%) with group E and C. These findings suggest that, the symptomatic relief in terms of pruritis was high in patients who were treated with Euphorbia prostata was comparable with those who were treated with micronized purified flavonoid fraction of diosmin. A retrospective study[91] from Nagpur reported that anal

itching was relieved in 73% of patients, while anal discomfort subsided in 90% of patients. Another prospective, open label, single arm, post marketing study[92] from Mumbai reported that, significantly higher number of patients with sympatomatic relief with regard to pain, swelling and congestion at the end of the study ($p<0.001$). Global Assessment by the physician at the end of therapy showed total improvement in 27.7%, moderate in 63.2% while global Assessment by the patient showed total improvement in 27.5% and moderate improvement in 63.6%. The authors concluded that, Euphorbia Prostrata dry extract 100 mg tablets, given for 14 days in bleeding haemorrhoids patients showed maximum improvement during first 3 days of therapy and achieved total improvement in significant number of patients at the end of therapy.

Overall, this study showed the effectiveness of euphorbia prostrata in the treatment of haemorroids. The strengths of the study was the comparative study design and the limitations were smaller sample size and the bleeding and other signs such as pain were considered as reported by the patients and which would have biased the study results. Further studies with large sample size, grades of haemorroids and standardized symptomatology would explore the precise role of euphorbia prostrata in the treatment of haemorroids

SUMMARY

1. A total of 135 ventilated patients were enrolled and randomized into three groups A, B, C with 45 in each group.
2. Out of the total 135 patients, 45 patients (Group A -14, Group B-14 and Group C-17) were ventilated for < 48 hours and were excluded from the study.
3. After exclusion, the remaining 90 patients were analyzed. (Group A-31, Group B-31, Group C-28).
4. A total of 20 cases developed VAP with an overall **incidence** of 22.2%.
5. **VAP rate** was 51.5 cases for 1000 ventilation days with a total of 388 days of ventilation.
6. The incidence of VAP was lower in the interventional Groups i.e. Group B (3 cases , 9,6%) , Group C (7 cases, 25%) when compared to conventional group A (10 cases , 32.25%).
7. Incidence of VAP was significantly lesser in CHX Group B when compared with conventional Group A, with an absolute risk reduction of 22.3 %(RR: 0.333, CI: 0.1207 to 0.9209, P = 0.0341).
8. No statistically significant difference was found in the incidence when Group A was compared with the interventional groups B, C (P = 0.096) and between Group B and C (P=0.732). Similarly no difference in the incidence was found when Group A was compared with Group C (P = 0.5422).
9. VAP rate was the highest in the conventional group with 69.56 patients per 1000 ventilator days and 58.56 per 1000 ventilator days in the head end elevation group and least in the CHX group B of 24.35 patients per 1000 ventilator days.

10. The overall mortality of ventilated patients in our study was 27.77%.
11. Statistically significant difference was observed with respect to mortality when the overall outcomes were compared between the three groups A, B, and C.
12. A statistically significant difference was observed with respect to mortality and survival of VAP between **Group A** and **Group B**.
13. There was a lesser mortality, better survival rate , lesser duration of ventilation, lesser duration of PICU stay in the Chlorhexidine Group B compared to conventional group A.
14. There was a lesser mortality, better survival rate , lesser duration of ventilation, lesser duration of PICU stay in the Head end elevation Group C compared to conventional group A.
15. A statistically significant difference was observed with respect to mortality and survival between conventional **Group A** and the interventional **Groups B + C.**
16. There was a longer duration of ventilation, a longer PICU stay and higher mortality in the conventional **Group A** compared to the interventional **Groups B+ C.**
17. On Univariate analysis, younger age, male gender, reintubation, prior ventilation, use of sedation, altered sensorium and use of uncuffed ET tube were found to be significant with the development of VAP.
18. On Multivariate analysis, male gender, Reintubation, Sedation and Altered sensorium were found to be statistically significant.

19. Patients with VAP had a significantly longer duration of ventilation, longer PICU stay, poor survival and a higher mortality in patients with VAP, when compared to patients who did not develop VAP.
20. Patients ventilated for > 96 hours had 3.75 times higher risk for development of VAP when compared with patients ventilated for < 96 hours showing a statistically significant relationship.
21. Duration of ventilation is not significantly associated with mortality.
22. The risk of mortality with late onset VAP was three times more than early onset VAP.
23. Statistically significant difference was observed with respect to duration of ventilation among VAP patients. Duration of ventilation in Group B was statistically significant compared to Group A. Similar significance was not obtained when Group A was compared with Group C and Group B with C.
24. There was a longer duration of ICU stay in patients diagnosed with VAP in Group B was compared to VAP patients in Group A and Group C.
25. Mortality rate of VAP cases was 80% among patients in the conventional group A followed by 28.5% in Group C and 0% in Group B.
26. There was a better survival rate of 66.6 % in VAP patients in the CHX group B and least in the conventional Group A (20%).
27. Culture of endotracheal secretions were positive in 41.9% of patients in Group A compared to 19.3% in Group B with the most common isolate being Pseudomonas.

Chapter 7

Conclusion

CONCLUSION

Grade I and II were the commonest haemorrhoids encountered in this study. Patients were given euphorbia prostata and micronized purified flavonoid fraction of diosmin. In Euphorbia prostata group, higher number of patients in group E (53.33%) reported average reduction of bleeding during fifth day follow up (p=0.001). At second follow up, 36.67% of patients in group E had excellent reduction in bleeding and at third follow up all the patients in group E (100%) reported excellent reduction in bleeding but the difference between number of patients reporting reduction of bleeding in group E and C at second (p=0.291) and third follow up (p=0.261) was statistically not significant.

The symptomatic relief in terms of pruritis was high in patients who were treated with Euphorbia prostrata but the difference was statistically not significant.

Hence it may be concluded that, the treatment with euphorbia prostrata significantly resulted in faster control of bleeding at first follow up on day five but further it was comparable with micronized purified flavonoid fraction of diosmin. The symptomatic relief provided by euphorbia prostrata was compared to that of micronized purified flavonoid fraction of diosmin.

BIBLIOGRAPHY

1) Ramya Srinivasan, Jeanette Asselin, Ginny Gildengorin, J. Wiener-Kronish. A Prospective Study of Ventilator-Associated Pneumonia in Children. Pediatrics 2009;123;1108

2) Bahubali. D. Gane. Ventilator associated pneumonia. International Journal of Medical Sciences and Research Jul-Sept 2013,Volume1, Issue 1

3) P.K. Patra, M. Jayashree, S. Singhi, P. Ray and A.K. Saxena. Nosocomial Pneumonia in a Pediatric Intensive Care Unit. Indian Pediatrics. volume 44july 17, 2007

4) Meghna Raju Sebastian, MD, Rakesh Lodha, MD, Arti Kapil, MD, Sushil K. Kabra, MD. Oral Mucosal Decontamination With Chlorhexidine for the Prevention of Ventilator-Associated Pneumonia in Children: A Randomized, Controlled Trial. Pediatr Crit Care Med. 2012; 13(5)

5) Shally Awasthia, Mohammad Tahazzula, Ankur Ambasta, Yogesh C. Govila, Amita Jain: Longer duration of mechanical ventilation was found to be associated with ventilator-associated pneumonia in children aged 1 month to 12 years in India. Journal of Clinical Epidemiology 66 (2013)

6) Arindam Dey and Indira Bairy. Incidence of multidrug-resistant organisms causing ventilator associated pneumonia in a tertiary care hospital: A nine months' prospective study. Ann Thoracic Med. 2007 Apr-Jun; 2(2):

7) Akash Deep, R. Ghildiyal, S. Kandian and N. Shinkre. Clinical and Microbiological Profile of Nosocomial Infections in the Pediatric Intensive Care Unit (PICU). Indian Pediatrics 2004; 41:1238-1246

8) Modi Payal , Javadekar Tanuja , Nanda Sandeep, Pandya Neelam. A study on ventilator associated pneumonia in pediatric age group in a tertiary care hospital, vadodara. National journal of medical research. Volume 2 Issue 3July – Sept 2012

9) Rakesh Lodha and SK Kabra. Diagnosis of Ventilator Associated Pneumonia: Is There a Simple Solution? Indian Pediatr 2011;48: 939-940

10) Harsh Sharmaa, Daljit Singhb, Puneet Poonib and Urmil Mohan. A Study of Profile of Ventilator-associated Pneumonia in Children in Punjab. J Trop Pediatr 2009

11) Prevention of hospital-acquired infections ;A practical guide

12) MS Tullu, CT Deshmukh, SM Baveja. Bacterial nosocomial pneumonia in Paediatric Intensive Care Unit. journal of post graduate journal .2000.vol 46

13) Noyal Mariya Joseph1, Sujatha Sistla1, Tarun Kumar Dutta2, Ashok Shankar Badhe3, Desdemona Rasitha1, Subhash Chandra Parija .Ventilator-associated pneumonia in a tertiary care hospital in India: role of multi-drug resistant pathogens. J Infect Dev Ctries 2010; 4(4):218-225

14) Noyal Mariya Joseph , Sujatha Sistla , Tarun Kumar Dutta ,Ashok Shankar Badhe , Subhash Chandra Parija . Ventilator-associated pneumonia: A review. European Journal of Internal Medicine.2010

15) Amy S. Collins. Preventing Health Care–Associated Infections Patient Safety and Quality: An Evidence-Based Handbook for Nurses: Vol. 2

16) Maha almuneef,Ziad ,memish,Hanan H. Ventilator associated pneumonia in a pediatric intensive care unit in Saudi Arabia ; A 30 month prospective surveillance.infection control and hospital epidemiology.2004:25,753-758

17) Alexis M. Elward, MD, David K. Warren, MD, Victoria J. Fraser, MD. Ventilator-Associated Pneumonia in Pediatric Intensive Care Unit Patients: Risk Factors and Outcomes. Pediatrics Vol. 109 No. 5 May 1, 2002

18) N Ismail, A Darbyshire, K Thorburn. Ventilator-associated pneumonia (VAP): a UK PICU experience. Arch Dis Child 2012;97

19) María R Becerra, José A Tantaleán, Víctor J Suárez, Margarita C Alvarado, Jorge L Candela, Flor C Urcia .Epidemiologic surveillance of nosocomial infections in a Pediatric Intensive Care Unit of a developing country. BMC Pediatrics 2010

20) Elward AM, Warren DK, Fraser VJ. Ventilator-associated pneumonia in pediatric intensive care unit patients: risk factors and outcomes. Pediatrics. 2002 May;109(5)

21) Bo Liu, Song-Qin Li, Su-Ming Zhang, Ping Xu, and Wei-Hong Zhang. Risk factors of ventilator-associated pneumonia in pediatric intensive care unit: a systematic review and meta-analysis. J Thorac Dis. 2013 August; 5(4): 525–531

22) Rosa Celia, M.D.; Antoni Torres, M.D.;Josep M. Gatell,. Nosocomial Pneumonia: A Multivariate Analysis of Risk and Prognosis. chest 1993

23) Guidelines for the management of adults with hospital acquired, ventilator acquired, and hospital associated Pneumonia .American thoracic society documents.

24) Deborah J. Cook, MD; Stephen D. Walter, PhD; Richard J. Cook, PhD; Lauren E. Griffith. Incidence of and Risk Factors for Ventilator-Associated Pneumonia in Critically Ill Patients. Ann Intern Med. 1998; 129(6):

25) Roeleveld ,D. Guijt ,E. J. Kuijper .Ventilator-associated pneumonia in children after cardiac surgery in The Netherlands. Intensive Care Med (2011) 37:1656–1663

26) Christine A'Court, Christopher S Garrard. Nosocomial pneumonia in the intensive care unit: mechanisms and significance. Thorax 1992; 47:465-473

27) Emine Alp1, Kurşat Gundoğan2, Muhammet Guven2, Murat Sungur2. Assessment of Risk Factors for Ventilator Associated Pneumonia in the Medical Intensive Care Unit. Yoğun Bakım Derg 2011; 2: 34-8

28) Emine alp,muhammet guven,orhan Y,Bilgehan aygen . Incidence, risk factors and mortality of Nosocomial Pneumonia in intensive care units: A prospective study. Annals of clinical microbiology and antimicrobials 2004 , 3:17

29) Jill Morinec, Jacalyn Iacaboni, Molly McNett . Risk Factors and Interventions for Ventilator-AssociatedPneumonia in Pediatric Patients. Journal of Pediatric Nursing (2010

30) usan E. Coffin, MD, MPH; Michael Klompas, MD; David Classen, MD, MS; Kathleen M. Arias.Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals infection control and hospital epidemiology october 2008, vol. 29, supplement 1

31) Marin H. Kollef. Ventilator-Associated Pneumonia: A Multivariate Analysis. JAMA. 1993;270(16)

32) Elizabeth Foglia, Mary Dawn Meier, and Alexis Elward. Ventilator-Associated Pneumonia in Neonatal and Pediatric Intensive Care Unit Patients. Clinical Microbiology Reviews, July 2007, p. 409–425

33) Chandler, J Hunter. Ventilator-associated pneumonia: A concise review. JICS Volume 10, Number 1, January 2009

34) Jean Chastre and Jean-Yves Fagon. Ventilator-associated Pneumonia. Am J Respir Crit Care Med Vol 165. pp 867–903, 2002

35) Bo Liu, Song-Qin Li, Su-Ming Zhang, Ping Xu, Xiang Zhang. Risk factors of ventilator-associated pneumonia in pediatric intensive care unit: a systematic review and meta-analysis. J Thorac Dis 2013; 5(4):525-531.

36) B M Morrow, A C Argent, P M Jeena, R J Green. Guideline for the diagnosis, prevention and treatment of paediatric ventilator-associated pneumonia. SAMJ April 2008, Vol. 98, No. 4

37) R Gillespie, Prevention and management of ventilator-associated pneumonia – the Care Bundle approach. SAJCC. November 2009, Vol. 25, No. 2

38) Marya D. Zilberberg, and Andrew F. Shorr. Ventilator-Associated Pneumonia: The Clinical Pulmonary Infection Score as a Surrogate for Diagnostics and Outcome. Clinical Infectious Diseases 2010; 51(S1):S131–S135

39) Jérôme Pugin, Raymond Auckenthaler, Nabil Mili, Jean-Paul Janssens. Diagnosis of Ventilator-associated Pneumonia by Bacteriologic Analysis of Bronchoscopic and Nonbronchoscopic "Blind" Bronchoalveolar Lavage Fluid. American Review of Respiratory Disease, Vol. 143, No. 5pt 1991

40) sachdev, k chugh, m sethi, d gupta, c wattal and g menon. Clinical pulmonary infection score to diagnose ventilator-associated pneumonia in children. Indian pediatrics. volume 48 December 17, 2011

41) Rakesh Lodha and SK Kabra. Diagnosis of Ventilator Associated Pneumonia: Is There a Simple Solution? Indian Pediatr 2011;48: 939-940

42) Jean-Claude Lacherade1, Bernard De Jonghe1, Pierre Guezennec2, Karim Debbat3, Jan Hayon Intermittent Subglottic Secretion Drainage and Ventilator-associated Pneumonia :A Multicenter Trial. Am J Respir Crit Care Med Vol 182. pp 910–917, 2010

43) Lynn Johnston MD1, John M Conly. Diagnosis of ventilator-associated pneumonia: Where do we go from here? .Can J Infect Dis Vol 14 No 2 March/April 2003

44) Noyal Mariya Joseph, Sujatha Sistla, Tarun Kumar Dutta, Ashok Shankar Badhe. Ventilator-associated pneumonia in a tertiary care hospital in India: role of multi-drug resistant pathogens. J Infect Dev Ctries 2010; 4(4):218-225

45) John D Hunter .Ventilator associated pneumonia BMJ 2012;344

46) Vani Venkatachalam, J. Owen Hendley, Douglas, Willson. The diagnostic dilemma of ventilator-associated pneumonia in critically ill children. Pediatr Crit Care Med 2011 Vol. 12, No. 3

47) Steven M. Koenig and Jonathon D. Truwit. Ventilator-Associated Pneumonia: Diagnosis, Treatment, and Prevention. Clinical Microbiology Reviews, Oct. 2006, p. 637–657

48) Ivan V. Yankov, Tonyo Il. Shmilev. Ventilator-associated pneumonias in children – diagnostic criteria, etiology and pathogenesis. Folia Medica 2012; 54(1)

49) Ilias I Siempos and Matthew E Falagas. Oral decontamination with chlorhexidine reduces the incidence of nosocomial pneumonia. Critical Care 2007, 11:402

50) Andrea Coppadoro, Edward Bittner and Lorenzo Berra. Novel preventive strategies for ventilator associated Pneumonia. Critical Care 2012, 16:210

51) Maciej Piotr Chlebicki, MD; Nasia Safdar. Topical chlorhexidine for prevention of ventilator-associated pneumonia: A meta-analysis. Crit Care Med 2007; 35:595–602

52) Anthony J. DeRiso II, MD, FCCP; Joseph S. Ladowski. Chlorhexidine Gluconate 0.12% Oral Rinse Reduces the Incidence of Total Nosocomial Respiratory Infection and Nonprophylactic Systemic Antibiotic Use in Patients Undergoing Heart Surgery. Chest1996; 109:1556-61

53) Francois fourrier,Didier dubois,Patrick. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: Double blind placebo controlled trial. Crit care med 2005,33,1728-1735

54) Susan Houston, Paul Hougland, Jacqueline J. Anderson, Mark LaRocco, Virginia Kennedy, and Layne O. Gentry. Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. American journal of critical care, November 2002, volume 11, no. 6

55) Meghna Raju Sebastian, MD, Rakesh Lodha, MD, Arti Kapil, MD, Sushil K. Kabra, MD. Oral Mucosal Decontamination With Chlorhexidine for the Prevention of Ventilator-Associated Pneumonia in Children: A Randomized, Controlled Trial. Pediatr Crit Care Med. 2012; 13(5)

56) Der Ven,Hak , Koeman ,Van ,oral decontamination with chlorhexidine reduced ventilator associated pneumonia in patients needing mechanical ventilation ≥ 48 hours. Am J Respir Crit Care Med 2006

57) Mirelle Koeman, Andre J. A. M. van der Ven, Eelko Hak, Hans C. A. Joore, Karin Kaasjager, Annemarie. Oral Decontamination with Chlorhexidine Reduces the Incidence of Ventilator-associated Pneumonia. Am J Respir Crit Care Med Vol 173. pp 1348–1355, 2006

58) Ee Yuee Chan,Annie Ruest, Maureen O Meade. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. BMJ 2007; 334:889

59) Tanmay S. Panchabhai,; Neha S. Dangayach, Anand Krishnan, Vatsal M. Kothari, Oropharyngeal Cleansing With 0.2% Chlorhexidine for Prevention of Nosocomial Pneumonia in Critically Ill Patients. CHEST 2009; 135:1150–1156

60) Lilibeth A Pineda, Ranime G Saliba and Ali A El Solh. Effect of oral decontamination with chlorhexidine on the incidence of nosocomial pneumonia: a meta-analysis. Critical Care 2006

61) Olivia Snyders, Oswell Khondowe, Janet Bell, MCur . Oral chlorhexidine in the prevention of ventilator associated pneumonia in critically ill adults in the ICU: A systematic review. SAJCC November 2011, Vol. 27, No. 2

62) Olivia Gayle Snyders. Chlorhexidine in the prevention of ventilator associated pneumonia: a systematic review. Stellenbosch University

63) Frank A Scannapieco, Jihnhee Yu, Krishnan Raghavendran Angela Vacanti . A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. Critical Care 2009, 13:R117

64) Patrique Segers, Ron G. H. Speekenbrink, Dirk T. Ubbink, Marc L. van Ogtrop, Prevention of Nosocomial Infection in Cardiac Surgery by Decontamination of the Nasopharynx and Oropharynx with Chlorhexidine Gluconate a Randomized Controlled Trial. JAMA. 2006;296:2460-2466

65) Christianne A. van Nieuwenhoven, Christine Vandenbroucke-Grauls, Frank H. van Tiel, Hans C. A. Joore, MD; Rob J. M. Strack van Schijndel. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: A randomized study. Crit Care Med 2006; 34:396–402

66) G. Li Bassi, M. Ferrer , O.T. Ranzani, Marti ,L. Berra1, L. Fernandez and A. Torres. Prevention of VAP: role of the artificial airway, body position and setting the ventilator. Eur Respir Mon 2012; 55: 153–168

67) Alexiou VG, Ierodiakonou V, Dimopoulos G, Falagas ME. Impact of patient position on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. J Crit Care. 2009 Dec; 24(4)

68) Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogué S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. Lancet. 1999 Nov 27; 354(9193):1851-8

69) Libby Keeley. Reducing the risk of ventilator acquired Pneumonia through head of bed elevation nursing in Critical Care 2007 Vol 12 No 6

70) Barbara S Niël-Weise1, Petra Gastmeier, Axel Kola, Ralf P Vonberg, Jan C Wille and Peterhans J van den Broek. An evidence-based recommendation on bed head elevation for mechanically ventilated patients. Critical Care 2011, 15:R111

71) Karen L. Johnson,Tim Meyenburg. Physiological Rationale and Current Evidence for Therapeutic Positioning of Critically Ill Patients. AACN Advanced Critical Care Volume 20, Number 3, pp.228–240

72) Mary Jo,Cindy L munro,Takeshi unoki. Ventilator associated Pneumonia: The potential critical role of emergency medicine in prevention. journal of emergency med.2010

73) Gianluigi Li Bassi and Antoni Torres. Ventilator-associated pneumonia: role of positioning. Current Opinion in Critical Care 2011, 17:57–63

74) Wilhelmina G. Melsen, Maroeska M. Rovers, Mirelle Koeman, Marc J. M. Bonten. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. Crit Care Med 2011 Vol. 39, No. 12

75) Lisa Cuccio, Ellen Cerullo, Heidi Paradis, Cynthia Padula, Cindy Rivet, Susan Steeves, Judy Lynch. An Evidence-Based Oral Care Protocol to Decrease Ventilator-Associated Pneumonia. dimens crit care nurs. 2012;31(5):301/308

76) D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E, Liberati A. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care Review. The Cochrane Library 2012, Issue 5

77) Ee Yuee Chan, Annie Ruest, Maureen O Meade, Deborah J Cook, Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. BMJ March 2007

78) Hutsaya Tantipong, Chantana Morkchareonpong, Songyod Jaiyindee, Visanu Thamlikitkul. Randomized Controlled Trial and Meta-analysis of Oral Decontamination with 2% Chlorhexidine Solution for the Prevention of Ventilator-Associated Pneumonia. Infection control and hospital epidemiology February 2008, vol. 29, no. 2

79) Venkatachalam V, Hendley JO, Willson DF. The diagnostic dilemma of ventilator-associated pneumonia in critically ill children. Pediatr Crit Care Med. 2011 May;12(3):286-96

80) Steven M. Koenig and Jonathon D. Truwit. Ventilator-Associated Pneumonia: Diagnosis, Treatment, and Prevention. clinical microbiology reviews, Oct. 2006, p. 637–657

81) Marin H. Kollef. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. Crit Care Med 2004 Vol. 32, No. 6

82) Ntoumenopoulos,J. Presneill, McElholum,J. Cade. Chest physiotherapy for the prevention of ventilator-associated pneumonia. Intensive Care Med (2002) 28:850-856

83) Renu B Pattanshetty, GS Gaude . Effect of multimodality chest physiotherapy in prevention of ventilator-associated pneumonia: A randomized clinical trial. Indian journal of critical care medicine. 2010 , Volume : 14, Issue : 2 , 70-76

84) Luis Aurelio Díaz, a Mireia Llauradó, b Jordi Rello, b,c and Marcos I. Restrepo. Non-Pharmacological Prevention of Ventilator Associated Pneumonia. Arch Bronconeumol. 2010;46(4):188-195

85) Marc J. M. Bonten, Carlo A. Gaillard, Peter W. de Leeuw, and Ellen E. Stobberingh. Role of Colonization of the Upper Intestinal Tract in the Pathogenesis of Ventilator-Associated Pneumonia. Clinical Infectious Diseases 1997; 24:309-19

Chapter 8

Summary

SUMMARY

Hemorrhoids are one of the most frequent anorectal disorders encountered in the primary care sitting. The present study was aimed to assess the effectiveness of Euphorbia Prostrata dry extract in comparison with micronized purified flavonoid fraction of diosmin in control of bleeding haemorrhoids and to find the safety of Euphorbia Prostrata dry extract.

This one year single blind randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 60 patients divided into two groups of 30 each as experimental or control group randomly by envelop method that is Group E and Group C respectively. Patients in experimental group underwent treatment with euphorbia prostrata and control group was treated with diosmin.

In the present study, 80% of patients in group E and 93.33% of patients in group C were males. The male female ratio in group E was 4:1 while in group C it was 14:1. Most of the patients in group E (73.33%) and (66.67%) were aged 31 to 45 years. The mean age in group E was 39.60 ± 6.52 years compared to 43.40 ± 10.11 years in group C (p=0.092). The mean duration of bleeding in group E was 14.6 ± 5.41 days compared to 12.4 ± 4.89 days in group C (p=0.109). Blood stained stools were reported by 50% of patients in group E compared to 56.67% in group C (p=0.754). Most of the patients in group E (76.67%) and C (70%) presented with grade II haemorroids (p=0.561). On proctoscopic examination, the 10 O'clock position of haemorroids was seen in majority of the patients with

group E (73.33%) and group C (80%) (p=0.542) and congestion was present in 53.33% of patients in group C while in patients with group E, 36.67% of patients had congestion (p=0.194). During fifth day follow up, significantly higher number of patients in group E (53.33%) reported average reduction of bleeding compared to group C (13.33%) (p=0.001). At second and third follow up, both the groups were comparable (p>0.050). No statistically significant difference was noted with relief from pruritis (p>0.050).

Overall, treatment of euphorbia prostrata significantly resulted in faster recovery from bleeding at first follow up on day five but further its was comparable with micronized purified flavonoid fraction of diosmin. The safety of Euphorbia Prostrata dry was comparable with micronized purified flavonoid fraction of diosmin.

Chapter 9

Bibliography

BIBLIOGRAPHY

1. Sanchez C, Chinn BT. Haemorrhoids. Clin Colon Rectal Surg 2011; 24(1):5–13.

2. Johanson J F, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. Gastroenterology 1990;99:1856–7.

3. Havsteen B. Flavonoids a class of natural products with high pharmacological potency. Biochem Pharmacol 1983;32:1141-8.

4. Cintron J, Abacarian H. Benign anorectal: hemorrhoids. In: Wolff B G, Fleshman J W, editors. The ASCRS of Colon and Rectal Surgery. New York, NY: Springer-Verlag; 2007. p. 156–77.

5. Jones CB. A Comparative Study of the Methods of Treatment for Haemorrhoids. Proc Roy Soc Med 2004;67:51-3.

6. MD Laboratories. Avenida 2 Guanenas, Miranda 1220, Venezuala.

7. Thornton SC, Geibel J. Hemorrhoids. Available from: URL: http://emedicine.medscape.com/article/775407-overview Access Date: 18.04.2013

8. Marx JA, Hockberger RS, Walls RM. Rosen's Emergency Medicine: Concepts and Clinical Practice. 6th ed. Philadelphia, Pa: Elsevier; 2006.

9. Tintinalli JE, Kelen GD, Stapczynski JS. Emergency Medicine: A Comprehensive Study Guide. 6th ed., New York, NY: McGraw Hill; 2004.

10. Ibrahim AM, Hackford AW, Lee YM, Cave DR. Hemorrhoids can be a source of obscure gastrointestinal bleeding that requires transfusion: report of five patients. Dis Colon Rectum 2008;51(8):1292-4.

11. Charles MV. Surgical Treatment of Haemorrhoids. London: Springer; 2002.

12. Agbo SP. Surgical management of hemorrhoids - Case Report. J Surgi Technique 2011;3(2):68.

13. Kaidar-Person O, Person B, Wexner SD. Hemorrhoidal disease: A comprehensive review. J Am College Surg 2007;204(1):102–17.

14. Cataldo P. Hemorrhoids. Arlington Heights, IL: American Society of Colon and Rectal Surgeons; 2005.

15. Thomson WH. The nature of haemorrhoids. Br J Surg 1975;62(7):542-52.

16. Lunniss PJ, Phillips RK. Anatomy and function of the anal longitudinal muscle. Br J Surg 1992;79(9):882-4.

17. Haas PA, Fox TA, Haas GP. The pathogenesis of hemorrhoids. Dis Colon Rectum 1984;27(7):442-50.

18. Lestar B, Penninckx F, Kerremans R. The composition of anal basal pressure. An in vivo and in vitro study in man. Int J Colorectal Dis 1989;4(2):118-22.

19. Dujovny N, Quiros RM, Saclarides TJ. Anorectal anatomy and embryology. Surg Oncol Clin N Am 2004;13(2):277-93.

20. Haas PA, Fox TA, Jr. Age-related changes and scar formations of perianal connective tissue. Dis Colon Rectum 1980;23(3):160-9.

21. Gaj F, Trecca A. Hemorrhoids and rectal internal mucosal prolapse: one or two conditions? A national survey. Tech Coloproctol 2005;9(2):163-5.

22. Haas PA, Haas GP, Schmaltz S, Fox TA. The prevalence of hemorrhoids. Dis Colon Rectum 1983;26(7):435-9.

23. Goenka MK, Kochhar R, Nagi B, Mehta SK. Rectosigmoid varices and other mucosal changes in patients with portal hypertension. Am J Gastroenterol 1991;86(9):1185-9.

24. Jacobs DM, Bubrick MP, Onstad GR, Hitchcock CR. The relationship of hemorrhoids to portal hypertension. Dis Colon Rectum 1980;23(8):567-9.

25. Hosking SW, Smart HL, Johnson AG, Triger DR. Anorectal varices, haemorrhoids, and portal hypertension. Lancet 1989;1(8634):349-52.

26. Burkitt DP, Graham-Stewart CW. Haemorrhoids--postulated pathogenesis and proposed prevention. Postgrad Med J 1975;51(599):631-6.

27. Graham-Stewart CW. What Causes Hemorrhoids?a New Theory of Etiology. Dis Colon Rectum 1963;6:333-44.

28. Aigner F, Bodner G, Gruber H, Conrad F, Fritsch H, Margreiter R, et al. The vascular nature of hemorrhoids. J Gastrointest Surg 2006;10(7):1044-50.

29. Wani NA, Fazilli A, Bhat GH, Mir IS. A Retrospective Study and Evaluation of Rubber Band Ligation as a Treatment of Hemorrhoids. Indian J Practising Doctor 2009;5:

30. Mounsey AL, Halladay J, Sadiq TS. Hemorrhoids. Am Fam Physician 2011;84(2):204-10.

31. Johanson JF, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. Gastroenterology 1990;98:380–6.

32. Loder PB, Kamm MA, Nicholls RJ, Phillips RK. Haemorrhoids: pathology, pathophysiology and aetiology. Br J Surg 1994;81:946–54.

33. Gazet JC, Redding W, Rickett JW. The prevalence of haemorrhoids. A preliminary survey. Proc R Soc Med 1970;63 Suppl:78–80.

34. Lohsiriwat V. Hemorrhoids: from basic pathophysiology to clinical management. World J Gastroenterol 2012;18(17):2009-17.

35. Loder PB, Kamm MA, Nicholls RJ, Phillips RK. Haemorrhoids: pathology, pathophysiology and aetiology. Br J Surg 1994;81:946-54.

36. Pigot F, Siproudhis L, Allaert FA. Risk factors associated with hemorrhoidal symptoms in specialized consultation. Gastroenterol Clin Biol. 2005;29:1270-74.

37. Statistics by country for Hemmorrhoids. Right diagnosis. NIH publication No; 94-1447; 1994. Available from: URL: http://www.rightdiagnosis.com /h/hemorrhoids/stats-country.htm Access Date: 15.02.2013.

38. Goligher J, Duthie H, Nixon H. Surgery of the anus, rectum and colon 5. Balliere: Tindall; 1984.

39. American Gastroenterological Association medical position statement: Diagnosis and treatment of hemorrhoids. Gastroenterology. 2004;126: 1461-2.

40. Lunniss PJ, Mann CV. Classification of internal haemorrhoids: a discussion paper. Colorectal Dis 2004;6:226-32.

41. Dennison A R, Wherry D C, Morris D L. Hemorrhoids. Nonoperative management. Surg Clin North Am. 1988;68:1401–1409.

42. Holzheimer RG. Surgical Treatment: Evidence-Based and Problem-Oriented. Available from: URL: http://www.ncbi.nlm.nih.gov/books /NBK6995/#A2045 Access Date: 24.05.2013

43. Morgado PJ, Suarez JA, Gomez LG, Morgado PJ. Histoclinical basis for a new classification of hemorrhoidal disease. Dis Colon Rectum 1988; 31(6):474-80.

44. Thomson JPS, Leicester, R.J. Haemorrhoids In: Coloproctology and the pelvic floor. Senoaks: Butterworth and Co; 1985.

45. Bursics A, Morvay K, Kupcsulik P, Flautner L. Comparison of early and 1-year follow-up results of conventional hemorrhoidectomy and hemorrhoid artery ligation: a randomized study. Int J Colorectal Dis 2004;19(2):176-80.

46. Huang WS, Chin CC, Yeh CH, Lin PY, Wang JY. Randomized comparison between stapled hemorrhoidopexy and Ferguson hemorrhoidectomy for grade III hemorrhoids in Taiwan: a prospective study. Int J Colorectal Dis 2007;22(8):955-61.

47. Goenka MK, Kochhar R, Nagi B, Mehta SK. Rectosigmoid varices and other mucosal changes in patients with portal hypertension. Am J Gastroenterol 1991;86:1185-9.

48. Thomson WH. The nature and cause of haemorrhoids. Proc R Soc Med 1975;68:574-5.

49. Aigner F, Gruber H, Conrad F, Eder J, Wedel T, Zelger B, et al. Revised morphology and hemodynamics of the anorectal vascular plexus: impact on the course of hemorrhoidal disease. Int J Colorectal Dis 2009;24:105-13.

50. Harish K, Harikumar R, Sunilkumar K, Thomas V. Videoanoscopy: useful technique in the evaluation of hemorrhoids. J Gastroenterol Hepatol 2008;23:e312-7.

51. Fueglistaler P, Guenin MO, Montali I, Kern B, Peterli R, von Flüe M, et al. Long-term results after stapled hemorrhoidopexy: high patient satisfaction despite frequent postoperative symptoms. Dis Colon Rectum 2007;50(2):204-12.

52. Gupta PJ. Effect of red chili consumption on postoperative symptoms during the post-hemorrhoidectomy period: randomized, double-blind, controlled study. World J Surg 2007;31(9):1822-6.

53. Fueglistaler P, Guenin MO, Montali I, Kern B, Peterli R, von Flüe M, et al. Long-term results after stapled hemorrhoidopexy: high patient satisfaction despite frequent postoperative symptoms. Dis Colon Rectum 2007;50(2):204-12.

54. Huang WS, Chin CC, Yeh CH, Lin PY, Wang JY. Randomized comparison between stapled hemorrhoidopexy and Ferguson hemorrhoidectomy for grade III hemorrhoids in Taiwan: a prospective study. Int J Colorectal Dis 2007;22(8):955-61.

55. Nisar PJ, Scholefield JH. Managing haemorrhoids. BMJ 2003; 327(7419): 847-51.

56. Bat L, Pines A, Rabau M, Niv Y, Shemesh E. Colonoscopic findings in patients with hemorrhoids, rectal bleeding and normal rectoscopy. Isr J Med Sci 1985;21(2):139-41.

57. Brill AI, Fleshman JW, Jr., Ramshaw BJ, Wexner SD, Kaidar-Person O. Minimally invasive procedures: what family physicians need to know. J Fam Pract 2005;Suppl:S1-22.

58. Nelson R, Norton N, Cautley E, Furner S. Community-based prevalence of anal incontinence. JAMA 1995;274(7):559-61.

59. Talley NJ, O'Keefe EA, Zinsmeister AR, Melton LJ. Prevalence of gastrointestinal symptoms in the elderly: a population-based study. Gastroenterology 1992;102(3):895-901.

60. Walter S, Hallbook O, Gotthard R, Bergmark M, Sjodahl R. A populationbased study on bowel habits in a Swedish community: prevalence of faecal incontinence and constipation. Scand J Gastroenterol 2002;37(8):911-6.

61. Arbman G, Krook H, Haapaniemi S. Closed vs. open hemorrhoidectomy is there any difference? Dis Colon Rectum 2000;43(1):31-4.

62. Johannsson HO, Pahlman L, Graf W. Randomized clinical trial of the effects on anal function of Milligan-Morgan versus Ferguson haemorrhoidectomy. Br J Surg 2006;93(10):1208-14.

63. Murie JA, Sim AJ, Mackenzie I. The importance of pain, pruritus and soiling as symptoms of haemorrhoids and their response to haemorrhoidectomy or rubber band ligation. Br J Surg 1981;68(4):247-9.

64. Banos JE, Bosch F, Canellas M, Bassols A, Ortega F, Bigorra J. Acceptability of visual analogue scales in the clinical setting: a comparison with verbal rating scales in postoperative pain. Methods Find Exp Clin Pharmacol 1989;11(2):123-7.

65. Wabnitz DA, Nair S, Wormald PJ. Correlation between preoperative symptom scores, quality-of-life questionnaires, and staging with

computed tomography in patients with chronic rhinosinusitis. Am J Rhinol 2005;19(1):91-6.

66. Miller R, Bartolo DC, Locke-Edmunds JC, Mortensen NJ. Prospective study of conservative and operative treatment for faecal incontinence. Br J Surg 1988;75(2):101-5.

67. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. Dis Colon Rectum 1999;42(12):1525-32.

68. Acheson AG, Scholefield JH. Management of haemorrhoids. BMJ 2008;336:380-383.

69. El Nakeeb AM, Fikry AA, Omar WH, Fouda EM, El Metwally TA, Ghazy HE, et al. Rubber band ligation for 750 cases of symptomatic hemorrhoids out of 2200 cases. World J Gastroenterol 2008;14(42): 6525-30.

70. Raahave D, Jepsen LV, Pedersen IK. Primary and repeated stapled hemorrhoidopexy for prolapsing hemorrhoids: follow-up to five years. Dis Colon Rectum 2008;51(3):334-41.

71. Jayaraman S, Colquhoun PH, Malthaner RA. Stapled hemorrhoidopexy is associated with a higher long-term recurrence rate of internal hemorrhoids compared with conventional excisional hemorrhoid surgery. Dis Colon Rectum 2007;50(9):1297-305.

72. Ceci F, Picchio M, Palimento D, Calì B, Corelli S, Spaziani E. Long-term outcome of stapled hemorrhoidopexy for Grade III and Grade IV hemorrhoids. Dis Colon Rectum 2008;51(7):1107-12.

73. Alonso-Coello P, Mills E, Heels-Ansdell D, López-Yarto M, Zhou Q, Johanson JF, Guyatt G. Fiber for the treatment of hemorrhoids complications: a systematic review and meta-analysis. Am J Gastroenterol 2006;101:181-8.

74. Moesgaard F, Nielsen ML, Hansen JB, Knudsen JT. High-fiber diet reduces bleeding and pain in patients with hemorrhoids: a double-blind trial of Vi-Siblin. Dis Colon Rectum 1982;25:454-6.

75. Labrid C. Pharmacologic properties of Daflon 500 mg. Angiology. 1994;45:524-30.

76. Labrid C. A lymphatic function of Daflon 500 mg. Int Angiol. 1995;14:36-8.

77. Struckmann JR, Nicolaides AN. Flavonoids. A review of the pharmacology and therapeutic efficacy of Daflon 500 mg in patients with chronic venous insufficiency and related disorders. Angiology 1994;45:419-28.

78. Alonso-Coello P, Zhou Q, Martinez-Zapata MJ, Mills E, Heels-Ansdell D, Johanson JF, et al. Meta-analysis of flavonoids for the treatment of haemorrhoids. Br J Surg 2006;93:909-20.

79. La Torre F, Nicolai AP. Clinical use of micronized purified flavonoid fraction for treatment of symptoms after hemorrhoidectomy: results of a randomized, controlled, clinical trial. Dis Colon Rectum 2004;47:704-10.

80. Menteş BB, Görgül A, Tatlicioğlu E, Ayoğlu F, Unal S. Efficacy of calcium dobesilate in treating acute attacks of hemorrhoidal disease. Dis Colon Rectum 2001;44:1489-95.

81. Tjandra JJ, Tan JJ, Lim JF, Murray-Green C, Kennedy ML, Lubowski DZ. Rectogesic (glyceryl trinitrate 0.2%) ointment relieves symptoms of haemorrhoids associated with high resting anal canal pressures. Colorectal Dis 2007;9:457-63.

82. Perrotti P, Antropoli C, Molino D, De Stefano G, Antropoli M. Conservative treatment of acute thrombosed external hemorrhoids with topical nifedipine. Dis Colon Rectum 2001;44:405-9.

83. Smith LE, Goodreau JJ, Fouty WJ. Operative hemorrhoidectomy versus cryodestruction. Dis Colon Rectum 1979;22:10-6.

84. Johanson JF, Rimm A. Optimal nonsurgical treatment of hemorrhoids: a comparative analysis of infrared coagulation, rubber band ligation, and injection sclerotherapy. Am J Gastroenterol 1992;87:1600-6.

85. MacRae HM, McLeod RS. Comparison of hemorrhoidal treatment modalities. A meta-analysis. Dis Colon Rectum 1995;38:687-94.

86. Beattie GC, Wilson RG, Loudon MA. The contemporary management of haemorrhoids. Colorectal Dis 2002;4:450-54.

87. Lohsiriwat V, Vongjirad A, Lohsiriwat D. Value of routine histopathologic examination of three common surgical specimens: appendix, gallbladder, and hemorrhoid. World J Surg 2009;33:2189-93.

88. Burch J, Epstein D, Sari AB, Weatherly H, Jayne D, Fox D, Woolacott N. Stapled haemorrhoidopexy for the treatment of haemorrhoids: a systematic review. Colorectal Dis 2009;11:233-43.

89. Avital S, Itah R, Skornick Y, Greenberg R. Outcome of stapled hemorrhoidopexy versus doppler-guided hemorrhoidal artery ligation for grade III hemorrhoids. Tech Coloproctol 2011;15:267-71.

90. Giordano P, Nastro P, Davies A, Gravante G. Prospective evaluation of stapled haemorrhoidopexy versus transanal haemorrhoidal dearterialisation for stage II and III haemorrhoids: three-year outcomes. Tech Coloproctol 2011;15:67-73.

91. Gupta PJ. The efficacy of Euphorbia prostrata in early grades of symptomatic hemorrhoids--a pilot study. Eur Rev Med Pharmacol Sci 2011;15(2):199-203.

92. Bakshi GD, Langade DG, Desai VS. Prospective, Open Label Study of Euphorbia Prostrata Extract 100 mg in the Treatment of Bleeding Haemorrhoids Bombay Hospital J 2008;50(4):577-83.

93. Alarcon-Aguilara FJ, Roman-Ramos R, Perezgutierrez S, Aguilar-Contreras A, Contreras-Weber CC, Flores-Saenz JL. Study of the anti-hyperglycemic effect of plants used as antidiabetics. J Ethnopharmacol 1998;61:101-10.

94. Chen L, Chen R, Wei K. Constituents of tannins from Euphorbia prostrata Ait. Zhongguo Zhong Yao Za Zhi 1992;17:225-6, 255-6.

95. Rizk AM, Hammouda FM, El-Nasr MM, El-Missiry MM. Constituents of Egyptian Euphorbiaceae. Part 6: phytochemical investigation of Euphorbia geniculata Jacq. and E. prostrata Ait. Pharmazie 1978;33:540-1.

96. Monograph. Diosmin. Altern Med Rev 2004; 9: 308-11

97. Mlakar B, Kosorok P. Flavonoids to reduce bleeding and pain after stapled hemorrhoidopexy: a randomized controlled trial. Wien Klin Wochenschr 2005;117:558-60.

98. Singla AK, Pathak K. Topical antiinflammatory effects of Euphorbia prostrata on carrageenan-induced footpad oedema in mice. J Ethnopharmacol 1990;29:291-4.

99. Singla AK, Pathak K. Anti-inflammatory studies on Euphorbia prostrata. J Ethnopharmacol 1989;27:55-61.

100. MacKay D. Hemorrhoids and varicose veins: a review of treatment options. Altern Med Rev 2001;6:126-40.

101. Squadrito F, Altavilla D, Oliaro Bosso S. Double blind, randomized clinical trial of troxerutin-carbazochrome in patients with hemorrhoids. Eur Rev Med Pharmacol Sci 2000;4:21-4.

102. Hep A, Robek O, Skricka T. Treatment of hemorrhoids from the viewpoint of the gastroenterologist. Personal experience with the Ginkor Fort preparation Vnitr Lek 2000;46:282-5.

103. Quijano CE, Abalos E. Conservative management of symptomatic and/or complicated haemorrhoids in pregnancy and the puerperium. Cochrane Database Syst Rev 2005: CD004077.

104. Cholbi MR, Paya M, Alcaraz MJ. Inhibitory effects of phenolic compounds on CCl4 – induced microsomal lipid peroxidation. Expermentia 1991; 47 (2) : 195-99.

105. Singla AK, Pathak K. Anti-inflammatory studies on Euphorbia prostrata. Journal of Ethnopharmacology 1989;27:55-61.

106. Efficacy and safety and tolerability of ThankGod Relief capsule and ThankGod Anytime cream in 1 and 2 degree hemorrhoidal disease (Data on file) Panacea Biotec Ltd.

107. Arora MP, Malik VK. Double blind, placebo controlled, prospective, comparative clinical evaluation of two doses of 14395 (Flavonoids) in bleeding haemorrhoids. (Data on file) Panacea Biotec Ltd.

108. An open label, non comparative, multicentre study to assess the efficacy and safety of euphorbia prostrata tablets in haemorrhoidal disease. Data on file, Panacea Biotec Ltd.

109. Misra MC, Imlitemsu. Drug treatment of haemorrhoids. Drugs. 2005;65(11):1481-91.

110. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. Drugs 2003;63(1):71-100.

111. Struckmann JR. Clinical efficacy of micronized purified flavonoid fraction: an overview. J Vasc Res 1999;36 Suppl 1:37-41.

Annexures

Annexure I

ANNEXURE I – CONSENT FORM

Title of Research Study: TO STUDY EUPHORBIA PROSTRATA DRY PLANT EXTRACT Vs MICRONISED PURIFIED FLAVONOID FRACTION OF DIOSMIN EFFECTIVENESS IN TREATMENT OF BLEEDING HAEMORRHOIDS IN PATIENTS ATTENDING A TERTIARY CARE HOSPITAL - A RANDOMISED CONTROL STUDY.

Principal Investigator:-
Dr. ****** ******
Professor
Department Of General Surgery,
J. N. Medical College, Belgaum.

Co-investigator:-
Dr. ******** ******
Post Graduate Student,
Department Of General Surgery,
J. N. Medical College, Belgaum.

You are requested to participate in a study that is an attempt to find out the effectiveness of Euphorbia prostrata plant extract as compared to micronized purified flavonoid fraction of diosmin. Diosmin was the drug of choice for the treatment of bleeding haemorrhoids. Its main content is flavonoid. This new drug Euphorbia Prostrata is found to have flavonoid, phenolic acid and tannin .Studies have shown that Euphorbia Prostrata is more effective in controlling bleeding haemorrhoids The dosage of this drug is also convenient (OD dose of 500mg) as compared to diosmin. Hence this study is being conducted so as to include Euphorbia Prostrata in the regular treatment regimen.

About 60 patients with bleeding haemorrhoids will be enrolled in this study. This study will be conducted by Dr. ***** ********, Post Graduate in Department of Surgery, under the direct supervision and guidance of Dr. **** *******, Professor, Department of Surgery, J. N. Medical College, Belgaum.

You need to be eligible, meeting all the selection criteria to participate in this study. You should be willing to provide information about yourself.

If you agree to participate in this study, you will be randomly allotted into a group (A or B) and accordingly receive either the standard treatment (micronized purified fraction of diosmin) or the newer treatment (Euphorbia Prostrata).

After the commencement of treatment you will be followed up on day 5, 10, 14 and checked for improvement in the bleeding.

The benefits of the procedure under study is early cessation of bleeding if the drug is found to be effective.

There is no additional risk compared to the standard method of treatment.

Taking part in the study will not affect the cost of treatment i.e. it will be almost similar to the cost of standard procedure. In the event that you become injured as a result of taking part in this study, treatment will be offered to you or you will be given information about where to receive medical care: but you/your insurance company will be responsible for the costs. However, no reimbursement, compensation or free medical care will be given.

Every effort will be made to protect the confidentiality of the information you provide. This means that the researchers will not let anyone, not a part of the study, see the information you provide. Only Dr. ***** ******* and Dr. ****** ******* will have access to the information collected. Results of this study may be published but your name will not be revealed.

Taking part in this study is voluntary; you may choose not to enroll in this study. Your decision will not change the present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital, Belgaum.

If you have any queries about the study, you may contact Dr. ***** ****** (Contact No.- ***** ******) or Dr. ****** *******, Professor, Dept. of Surgery, JNMC, Belgaum (Contact No.- ****** ******). In case you need any further information regarding your rights as a study participant, you may contact Chairman of Institutional Ethics Committee (Contact No.- ****** *******).

CONSENT TO PARTICIPATE IN THE STUDY

I Mr./Ms._____ have been explained about the research study, the need of the study, the diagnostic intervention, their risks, benefits and alternatives available in my own vernacular language.

I voluntarily agree to participate in this study by signing up this form below. I may withdraw at any time from this study. I am not giving any of my legal rights by signing up this form. My signature / thumb impression below indicates that I have read or information in the consent been explained to me including the risks and benefits and have cleared my doubts.

In case of any queries, you can contact the following:

Dr. **** ********
Postgraduate student,
Department of Gen. Surgery,
J. N. Medical College,
KLE University, Belgaum – 10.
Contact No.- ****** *******.

Dr. **** ********
Professor,
Department of Gen. Surgery,
J. N. Medical College,
KLE University, Belgaum-10.
Contact No.- ****** ******

Dr. *** *******
Chairman,
Institutional Ethics Committee,
J. N. Medical College,
KLE University, Belgaum – 10.
Contact No.- ***** ******

Name of the participant:

Signature / Thumb impression of the study participant:

Name of the witness:

Signature of witness:

Name of investigator:

Signature of the investigator

Date:

Place:

Annexures

Annexure II

ANNEXURE II – PROFORMA

Title: TO STUDY EUPHORBIA PROSTRATA DRY PLANT EXTRACT Vs MICRONISED PURIFIED FLAVONOID FRACTION OF DIOSMIN EFFECTIVENESS IN TREATMENT OF BLEEDING HAEMORRHOIDS IN PATIENTS ATTENDING A TERTIARY CARE HOSPITAL - A RANDOMISED CONTROL STUDY.

Name:

Address:

Age:

Sex: IP No.:

Occupation: Socio-Economic Status:

HISTORY

When did the patients experience bleeding PR:

Amount of bleeding:

Associated features : Pain / Pruritis / Congestion.

Past History:

Family History:

GENERAL PHYSICAL EXAMINATION:

Built and Nourishment:

Pallor / Icterus / Cyanosis / Clubbing / Edema / Lymphadenopathy :

Vital Signs: PR: BP: Temp:

PER RECTAL EXAMINATION:

INSPECTION:

PROCTOSCOPIC EXAMINATION:

Day 5:

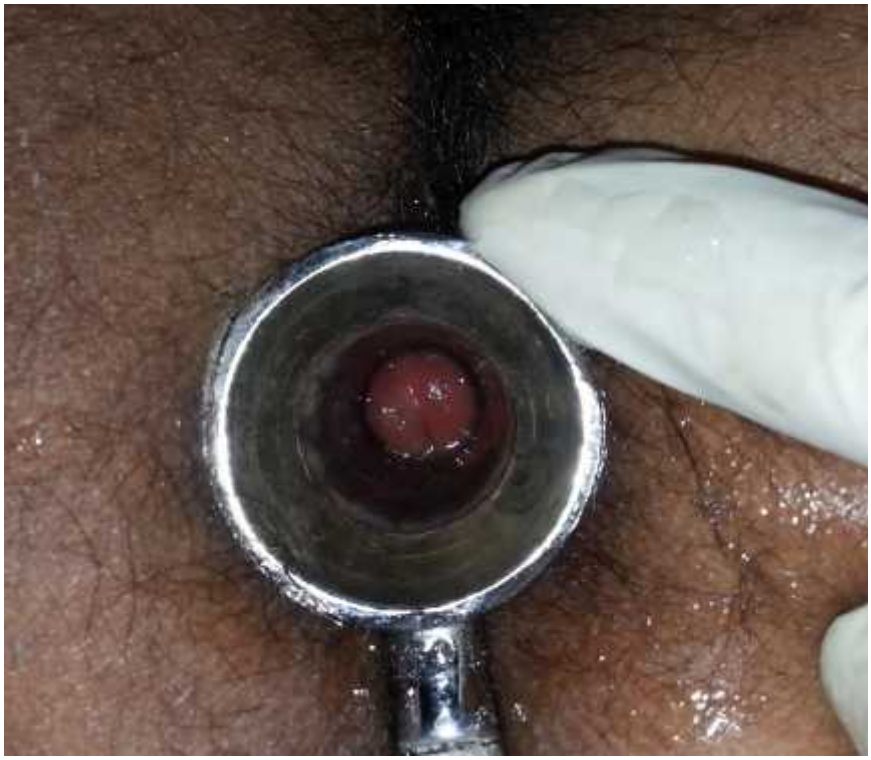
Day 10:

Day 14:

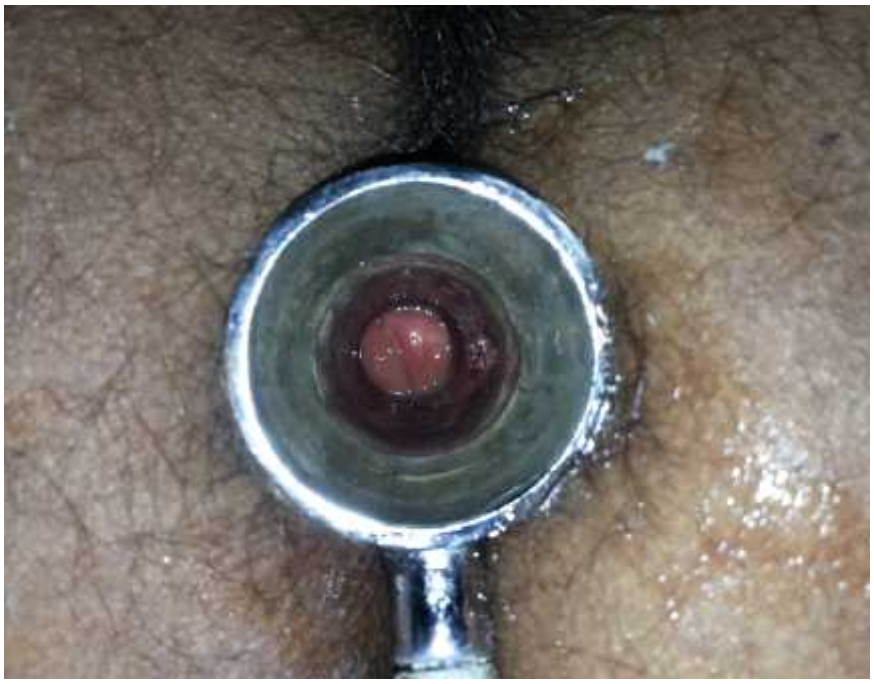
Annexures

Annexure III

ANNEXURE III – PHOTOGRAPHS



Photograph 3. Haemorrhoid – Pretreatment with Euphorbia prostrata



Photograph 4. Haemorrhoid – Post treatment (day 14) with Euphorbia prostrata

ANNEXURE IV - MASTER CHART - GROUP E

Serial Number	IP Number	Age (Years)	Sex	Occupation	History									General physical examination												Proctoscopic examination					Outcome					
								Features													Vitals											Day 5		Day 10		Day 14	
																						BP				Position									
					Bleeding PR	Duration (Days)	Amount	Pain	Pruritis	Congesion	Past history	Family history	Built and nourishment	Pallor	Icterus	Cyanosis	Clubbing	Oedema	Lymphadenopahy	Pulse rate (bpm)	Systolic (mm Hg)	Diastolic (mm Hg)	Temperature	Haemorroids	3 O' Clock	7 O' Clock	10 O' Clock	Congestion	Reduction in bleeding (%	Pruritis	Reduction in bleeding	Pruritis	Reduction in bleeding	Pruritis
1	2076808	32	M	B	+	10	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	80	120	80	AF	II	+	-	+	+	10%	+	80%	-	100%	-
2	2058586	40	F	F	+	12	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	80	120	78	AF	II	+	-	+	-	40%	-	60%	-	100%	-
3	2211380	34	M	S	+	7	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	78	114	80	AF	II	-	+	-	+	30%	+	80%	-	100%	-
4	2035798	40	M	F	+	12	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	80	120	70	AF	I	-	-	+	+	10%	-	80%	-	100%	-
5	2034158	41	M	S	+	14	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	80	110	80	AF	II	-	+	+	+	20%	+	40%	-	100%	-
6	2211217	38	M	B	+	18	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	82	120	78	AF	II	+	-	+	-	10%	+	50%	-	100%	-
7	2066723	36	F	HW	+	14	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	80	110	70	AF	II	+	-	-	-	40%	-	70%	-	100%	-
8	2076112	52	M	F	+	11	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	80	110	80	AF	I	-	+	+	+	40%	-	90%	-	100%	-
9	2085288	52	M	B	+	7	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	78	110	70	AF	II	-	-	+	-	40%	-	60%	-	100%	-
10	2194741	43	F	HW	+	11	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	80	110	70	AF	I	-	+	+	-	40%	+	70%	-	100%	-
11	1937345	40	M	S	+	20	BSS	+	+	-	-	-	MD	-	-	-	-	-	-	74	110	78	AF	II	-	+	+	-	40%	+	50%	+	100%	-
12	1735253	38	M	S	+	7	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	82	120	76	AF	II	-	+	+	-	30%	-	50%	-	100%	-
13	1939079	54	M	S	+	18	BSS	-	+	-	+	-	MD	-	-	-	-	-	-	80	110	70	AF	II	+	-	+	+	50%	-	70%	-	100%	-
14	1924521	32	M	B	+	7	BSS	+	+	-	-	-	MD	-	-	-	-	-	-	84	120	78	AF	II	-	+	-	-	40%	-	80%	-	100%	-
15	1932460	34	M	W	+	21	5D	+	-	-	-	-	WB	-	-	-	-	-	-	78	120	78	AF	I	-	+	+	-	40%	-	80%	-	100%	-
16	2194465	40	M	W	+	19	10D	+	+	-	-	-	MD	-	-	-	-	-	-	80	120	78	AF	II	-	+	-	+	50%	-	100%	-	-	-
17	1924574	39	M	W	+	15	15D	+	-	-	-	-	WB	-	-	-	-	-	-	82	120	80	AF	II	-	-	+	-	40%	-	70%	-	100%	-
18	1933208	48	F	HW	+	14	5D	+	-	-	-	-	MD	-	-	-	-	-	-	80	120	72	AF	II	+	-	+	-	10%	+	50%	-	100%	-
19	2034573	39	M	B	+	7	5D	+	-	-	+	-	MD	-	-	-	-	-	-	80	110	80	AF	II	+	+	-	+	20%	-	40%	-	100%	-
20	2042862	41	M	S	+	28	5D	+	-	-	-	-	MD	-	-	-	-	-	-	82	120	80	AF	I	-	+	-	+	40%	+	60%	-	100%	-
21	2066596	30	M	F	+	11	10D	+	-	-	-	-	MD	-	-	-	-	-	-	80	120	80	AF	II	-	-	+	-	10%	+	40%	-	100%	-
22	2066705	39	M	F	+	12	15D	+	-	-	-	-	MD	-	-	-	-	-	-	70	120	80	AF	II	+	-	+	-	30%	+	50%	-	100%	-
23	1734618	40	M	W	+	14	SFB	+	-	-	-	-	MD	-	-	-	-	-	-	74	120	80	AF	II	+	+	-	-	40%	-	100%	-	-	-
24	2193649	32	M	B	+	12	SFB	+	+	-	-	-	WB	-	-	-	-	-	-	78	124	80	AF	II	-	+	+	-	40%	-	60%	-	100%	-
25	1880115	30	M	S	+	21	SFB	+	-	-	-	-	MD	-	-	-	-	-	-	76	120	78	AF	II	+	+	-	-	20%	+	40%	-	100%	-
26	1933284	50	M	S	+	22	SFB	+	-	-	+	-	MD	-	-	-	-	-	-	74	120	80	AF	II	-	+	+	+	40%	-	100%	-	-	-
27	1983202	39	F	HW	+	14	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	80	120	70	AF	I	-	-	+	+	10%	-	80%	-	100%	-
28	1866288	36	M	W	+	18	5D	+	-	-	-	-	WB	-	-	-	-	-	-	78	120	78	AF	I	-	+	+	-	20%	+	80%	-	100%	-
29	2076868	46	F	HW	+	20	5D	+	-	-	-	-	MD	-	-	-	-	-	-	80	120	72	AF	II	+	-	+	-	10%	+	50%	+	100%	-
30	1723498	34	M	B	+	21	SFB	+	+	-	-	-	WB	-	-	-	-	-	-	78	124	80	AF	II	-	+	+	-	40%	-	60%	-	100%	-

ANNEXURE IV - MASTER CHART - GROUP C

Serial Number	IP Number	Age (Years)	Sex	Occupation	History								General physical examination											Proctoscopic examination				Outcome					
								Features												Vitals					Position				Day 5		Day 10		Day 14	
					Bleeding PR	Duration (Days)	Amount	Pain	Pruritis	Congesion	Past history	Family history	Built and nourishment	Pallor	Icterus	Cyanosis	Clubbing	Oedema	Lymphadenopahy	Pulse rate (bpm)	(mm Hg) Systolic	(mm Hg) Diastolic	Temperature	Haemorroids	3 O' Clock	7 O' Clock	10 O' Clock	Congestion	Reduction in bleeding (%	Pruritis	Reduction in bleeding	Pruritis	Reduction in bleeding	Pruritis
1	2076101	40	M	B	+	7	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	80	110	80	AF	I	-	-	+	-	30%	+	100%	-	-	-
2	2505057	40	M	F	+	7	15D	+	-	-	-	-	MD	-	-	-	-	-	-	80	110	80	AF	II	-	+	+	-	30%	-	50%	-	100%	-
3	1932435	40	M	B	+	14	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	74	110	80	AF	I	+	-	+	+	20%	+	40%	+	70%	-
4	2034451	35	M	S	+	10	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	74	120	70	AF	I	+	-	+	-	30%	+	60%	-	100%	-
5	1633853	48	M	S	+	7	BSS	+	-	-	-	-	WB	-	-	-	-	-	-	80	120	82	AF	II	-	+	-	-	10%	+	30%	+	60%	+
6	2066614	38	M	B	+	7	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	80	120	80	AF	I	+	+	-	+	30%	-	80%	-	100%	-
7	2073216	31	M	B	+	14	BSS	-	+	-	-	-	WB	-	-	-	-	-	-	80	120	70	AF	II	+	+	-	-	30%	-	50%	-	100%	-
8	2193811	40	M	F	+	18	BSS	-	-	-	-	-	MD	-	-	-	-	-	-	72	118	72	AF	II	+	-	+	+	40%	-	60%	-	100%	-
9	2066738	40	M	S	+	7	BSS	-	-	-	-	-	MD	-	-	-	-	-	-	80	110	82	AF	II	-	-	+	+	20%	+	50%	-	100%	-
10	1932503	40	M	F	+	10	BSS	+	-	-	+	-	WB	-	-	-	-	-	-	80	20	70	AF	II	-	+	+	-	10%	+	50%	+	100%	-
11	2066550	44	M	S	+	7	BSS	+	-	-	-	-	WB	-	-	-	-	-	-	80	118	82	AF	II	-	+	+	-	10%	+	80%	-	100%	-
12	1211322	32	M	S	+	14	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	80	110	80	AF	I	-	+	+	+	30%	-	80%	-	100%	-
13	2086154	50	M	F	+	7	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	80	120	70	AF	II	+	-	+	+	20%	-	50%	-	100%	-
14	1924548	61	M	F	+	14	BSS	+	+	-	+	-	PB	+	-	-	-	-	-	68	110	68	AF	I	-	+	+	-	20%	+	70%	-	100%	-
15	2085211	47	M	F	+	20	BSS	+	+	-	-	-	MD	-	-	-	-	-	-	78	110	80	AF	II	-	+	+	-	20%	+	50%	-	100%	-
16	2076152	42	F	HW	+	20	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	80	110	80	AF	II	-	+	+	-	40%	-	60%	-	100%	-
17	2194365	40	M	W	+	14	5D	-	+	-	-	-	MD	-	-	-	-	-	-	82	120	80	AF	I	+	-	+	+	30%	-	50%	-	100%	-
18	1735279	40	M	B	+	14	5D	-	+	-	-	-	MD	-	-	-	-	-	-	78	110	80	AF	II	-	+	+	+	20%	+	60%	-	100%	-
19	2211279	50	M	F	+	20	5D	-	+	-	-	-	MD	-	-	-	-	-	-	72	110	80	AF	II	-	+	+	+	40%	-	60%	-	100%	-
20	2076099	42	M	B	+	7	10D	+	+	-	-	-	MD	-	-	-	-	-	-	80	120	80	AF	II	+	-	+	-	30%	+	60%	-	100%	-
21	1939109	47	M	S	+	15	10D	+	-	-	-	-	MD	-	-	-	-	-	-	76	130	80	AF	II	-	+	+	+	20%	-	60%	-	100%	-
22	2076475	43	M	S	+	7	15D	+	-	-	-	-	MD	-	-	-	-	-	-	76	110	80	AF	II	+	-	+	+	30%	-	50%	-	100%	-
23	2193631	50	M	F	+	15	15D	+	-	-	-	-	WB	-	-	-	-	-	-	80	120	70	AF	II	+	-	-	-	30%	-	60%	-	100%	-
24	1735378	58	M	F	+	7	SFB	+	+	-	+	-	PB	-	-	-	-	-	-	70	150	90	AF	II	+	+	-	+	30%	+	40%	+	100%	-
25	2086154	33	M	B	+	20	SFB	+	-	-	-	-	WB	-	-	-	-	-	-	76	120	70	AF	II	+	-	+	+	30%	+	50%	+	100%	-
26	2076096	32	M	S	+	7	SFB	-	+	-	-	-	WB	-	-	-	-	-	-	80	110	80	AF	II	-	+	+	+	10%	+	50%	-	100%	-
27	1924470	80	M	F	+	20	SFB	+	-	-	-	-	MD	-	-	-	-	-	-	76	110	70	AF	II	+	-	+	-	20%	+	60%	-	100%	-
28	2198268	39	M	B	+	14	BSS	+	-	-	-	-	MD	-	-	-	-	-	-	74	110	80	AF	I	+	-	+	+	20%	+	40%	+	70%	-
29	1942698	31	F	HW	+	14	BSS	-	+	-	-	-	MD	-	-	-	-	-	-	80	110	80	AF	I	-	+	+	+	30%	+	80%	-	100%	-
30	1953002	49	M	F	+	15	15D	+	-	-	-	-	WB	-	-	-	-	-	-	80	120	70	AF	II	+	-	-	-	40%	-	60%	-	100%	-

Annexures

Annexure IV

ANNEXURE IV – MASTER CHART

+	-	Present
-	-	Absent
AF	-	Afebrile
B	-	Business
BP	-	Blood pressure
bpm	-	Beats Per Minute
BSS	-	Blood Stained Stools
D	-	Drops
F	-	Farmer
F	-	Female
HW	-	House Wife
IP Number	-	In patient number
MD	-	Moderately Built
mm Hg	-	Millimeter of mercury
M	-	Male
PB	-	Poorly Built
SFB	-	Slow Flow Of Blood
S	-	Service
WB	-	Well Built
W	-	Worker