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Repeated Categorical Response Data Analysis to see The Effect of a new drug "Saheli" on Breast Cancer

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Abstract

We have collected a data of a new drug "saheli" for the treatment of breast cancer. With the social, economical, educational and information evolution increasing number of women solicit medical opinion for simple pain and nodularity in breasts. There is a considerable morbidity amongst women in India on account of breast pain and nodularity. Pain is usually the most common complaint in a breast clinic followed by a lump with or without pain. Approximately 30% of women seen at surgical clinics in western countries have symptoms of breast pain. Such pain and lumpiness (absent, discrete or dominant lump) in breast is taken as a physiological aberration of normal development and involution. Mild cases can be simply treated by reassurance but sometimes it becomes troublesome enough to interfere with the quality of life or incapacitating to the extent that it interferes with the day to day activity of the woman. In such cases, it becomes mandatory for the physician to offer some form of treatment. In a study, it is reported that 85% women required no treatment after being reassured that malignant disease is absent whereas the remaining 15% requested treatment. Reassurance in the absence of a serious disease I mass I discharge in mild symptoms is very helpful and often the women will demand no further treatment.

In this research paper we have applied repeated categorical response analysis to dataset. Models are fitted for both dependent variables pain and nodularity. Estimates of parameter of model with p value are computed with the help of R. The results are discussed and presented in the form of tables and graphs.

Keywords: Breast Cancer, Saheli drug, Repeated categorical response analysis, Estimates of parameters of model, p-value.

1. Introduction

There are more than 200 types of cancer. Cancer starts when cells change abnormally and when abnormal cells divide in an uncontrolled way. Some cancers may eventually spread into other tissues. Breast cancer is now the most common cancer in most cities in India, and second most common in the rural areas. Breast cancer accounts for 25% to 32% of all female cancers in all these cities. This implies, practically, one fourth (or even approaching one thirds) of all female cancer cases are breast cancers [2].

Breast cancer starts when cells in the breast begin to grow out of control. These cells usually form a tumour that can often be seen on an x-ray or felt as a lump. The tumour is malignant (cancerous) if the cells can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. Breast cancer occurs almost entirely in women. Breast cancers can start from different parts of the breast. Most breast cancers begin in the ducts that carry milk (ductal cancers). Some starts in the glands that make milk (lobular cancers).There are also other types of breast cancer that are less common. A small number of cancers start in other tissues in the breast. These cancers are called sarcomas and lymphomas and are not really thought of as breast cancers.

With the social, economical, educational and information evolution increasing number of women solicit medical opinion for simple pain and nodularity in breasts. There is a considerable morbidity amongst women in India on account of breast pain and nodularity. Pain is usually the most common complaint in a breast clinic followed by a lump with or without pain. Approximately 30% of women seen at surgical clinics in western countries have symptoms of breast pain. Such pain and lumpiness (absent, discrete or dominant lump) in breast is taken as a physiological aberration of normal development and involution. Mild cases can be simply treated by reassurance but sometimes it becomes troublesome enough to interfere with the quality of life or incapacitating to the extent that it interferes with the day to day activity of the woman. In such cases, it becomes mandatory for the physician to offer some form of treatment. In a study, it is reported that 85% women required no treatment after being reassured that malignant disease is absent whereas the remaining 15% requested treatment. Reassurance in the absence of a serious disease I mass I discharge in mild symptoms is very helpful and often the women will demand no further treatment.

Three main theories have emerged regarding the aetiology of painful nodular breasts:

1. Increased oestrogen secretion from the ovary
2. Deficient progesterone production (or 'relative hyper-oestrogenism')
3. Hyper-prolactinaemia

Therapy available so far addresses one or the other of these hormonal imbalances and comprise of - danazol, bromocriptine, evening primrose oil, tamoxifen and oral contraceptive pills. Danazol (100-400mg/day) is the drug most studied of all but has unacceptable androgenic side effects like weight gain acne, amennorhoea hirsutism, decrease in breast size voice change an overall incidence is 25%. Bromocriptine (2 .5 mg twice daily) has a 20% incidence of side effects of nausea dizziness; headache Evening primrose oil although devoid of any significant side effects is w1fortunately not effective in moderate and severe cases of breast pain and nodularity. Methyl xanthines and caffeine have a role in Benign Breast Disease. A meta-analysis on the trials on management of mastalgia by 3 drugs vis-a-vis Bromocriptine, Tamoxifen and Evening Primrose Oil has been done by Srivastava A (paper in pipeline) in which he has reported that, "for the trials on Bromocriptine, the chisquare test of herterogenity yielded a p=.26 indicating that the results of the 3 trials were not heterogenous. For the trials on Tamoxifen the test demonstrated no heterogeneity p=.47. For the trials on evening primrose oil the heterogeneity test yielded a p=.53. Thus a fixed model is applicable to all these trials." In a double blind, placebo control multicentric study of 555 women showed that gamolenic acid GLA efficacy did not differ !Tom that of placebo, regardless of whether or not antioxidant vitamins. In another study the efficacy of goserelinisevaluated in 147 women which proved to be beneficial in short term treatment of mastalgia. Centchroman is a time tested non steroidal anti estrogenic oral contraceptive pill developed at the Central Drug and Research Institute, Lucknow in 1980s with prolongation of menstrual cycle as the only side effect. Although its role in breast cancer has been somewhat extensively studied, no study has reported its beneficial effects in breast pain and nodularity. Anecdotal reports have claimed beneficial effects of centchoman (marketed as saheli by Hindustan Latex) in cases of breast pain, nodularity, breast cysts and fibroadenoma. Centchroman is already in market and approved for female contraception. It is an inexpensive drug. Its documented effect in mastalgia and other benign breast disorders will provide an extremely useful adjuvant for its treatment.

In this research paper, we have a dataset of two drugs "Placebo" and "Centchroman (Saheli)" of disease breast cancer. We have seen effect of both drugs on 151 patients. Placebo is given to 76

patients and Centchroman (Saheli) is given to 75 patients. We included 151 patients in the study; 75 in the drug ormeloxifene group and 76 in the placebo group. The mean (standard deviation) age of those enrolled in the drug group is 33.7 (7.45) years and in the placebo group is 32.8 (8.36) years. Thirty (19.6%) patients (18 in the drug group and 12 in the placebo group) could not complete the mandatory visit at 6 months and are considered lost to follow-up. Of the 151 patients, 121 (placebo 64, active 57) are available for efficacy analysis. Now Pain and nodularity is taken as dependent variable. Age and drug are taken as dependent variable. Then repeated response categorical data analysis has been applied to dataset and results obtained.

2. Material and Methods

2.1 Method of collection of data

We did a randomized, double-blind, placebo-controlled trial of oral ormeloxifene 30 mg, a selective oestrogen receptor modulator (SERM) or placebo twice a week for 3 months in 20–50 year old women with breast pain with or without lumpiness. Women with a discrete benign lump or cancer were excluded from the study. Serial assessments of pain on a visual analogue scale and nodularity grade on a 5-point ordinal scale were done.

A total of 151 patients were randomly allocated to two interventions using a block size of 4. This randomized, double-blind, placebo-controlled clinical trial is done during 2008–2010 at the Department of Surgery, King George's (ChhatrapatiShahujiMaharaj) Medical University, Lucknow, Uttar Pradesh, India.

Women in the age group of 20–50 years with cyclical breast pain and nodularity were considered for inclusion in the study. If the patient was more than 35 years of age, a thorough clinical examination of the breast is done followed by bi-planer mammography. Firm reassurance against cancer is given to all the subjects. After 1 month, if breast pain and nodularity persisted and the patients desired medical treatment, we offered them the opportunity to participate in this trial. Demographic variables, clinical history, general examination and breast examination were carefully recorded on a pre-designed proforma. All patients were given a simple daily breast pain self-recording chart and those with severe cyclical breast pain that continued for more than 10 days in a month were included in the study. Informed written consent is obtained from all patients.

Patients with a discrete lump, which is suspicious of cancer after clinical, imaging and cytological examination, were excluded from the study. Also patients taking alternative treatment, lactating women, those planning a pregnancy or taking other oral contraceptive pills were also excluded. Women suffering from polycystic ovarian disease, other hormonal abnormalities requiring additional investigations, and liver and kidney problems were also excluded from the study.

Oral ormeloxifene 30 mg or a placebo is given twice a week for 3 months. The active drug (saheli) is supplied by Hindustan Latex Limited and the placebo tablets by the CDRI.

2.2 Construction of variables

Breast pain and nodularity is assessed serially on initial and all subsequent visits by the same person. For pain, a visual linear analogue (VLA) scale, with a 10 cm line with markings 1 cm apart is used. The extreme left end marked as 0 denoted no pain and the extreme right end marked as 10 denoted extreme pains. Each patient is carefully explained to tick on the line at a point corresponding to her level of pain on each visit. The earlier charts were available to the patient when documenting pain at a subsequent visit.

For nodularity, the Lucknow–Cardiff scale is used [4]. This scale is a 5-point ordinal scale depicting increasing order of nodularity shown schematically in the upper outer quadrants of a paired breast. Grade 0 indicates a smooth textured breast with extreme extent of normalcy and grade 4 the maximum nodularity. There were five figures that provided a cue for the examining physician to chart nodularity in the index breast. The examining physician made a holistic interpretation of breast nodularity as a sum of areas or quadrants involved and the coarseness of nodularity. Breast nodularity is assessed longitudinally, by the same clinician on an ordinal scale of 0–4 in the breast clinic at each visit.. For the purpose of data analysis, the grades were renumbered as 1 to 5, and labelled as normal,

mild, moderate, severe and very severe, respectively. To take advantage of ordinal outcomes and summarize the association over all grades, it is informative to do the analysis using the cumulative frequencies of the nodularity grades in the two groups.

A proportional odds model for cumulative logic is applied to compare the active and placebo group which gave us the odds ratio, confidence interval and value of significance at each successive visit. At 3 months, both the active treatment and placebo were stopped. However, the blinded assessment and follow-up continued up to 6 months. This provided with a wash-out period of 3 months without any treatment or placebo.

Breast pain and nodularity were assessed at the start of the active treatment or placebo and on follow-up at 1, 2, 3 and 6 months. At each visit, photocopies of the pain and nodularity charts were available. The tablet count and self-reporting were taken as compliance. Any side-effects experienced by the patients were recorded at each visit.

3. Results and Discussion

3.1 Preliminary Analysis of Data

We have calculated mean pain score at every visit for each drug in the table below:

Table 1: Mean pain assessment at successive visits for saheli and placebo drug groups

Visit	Mean pain score	
	Placebo	**Saheli**
At initial month	5.68	6.31
After first month	5.23	4.02
After second month	4.73	2.37
After third month	4.55	1.40
After sixth month	4.66	0.98

At the initial visit, patients taking placebo drug are having mean pain score 5.68 and patients taking saheli drug are having mean pain score 6.31. There is not much difference in the mean pain score between the saheli drug and the placebo drug groups initially. However, the mean pain score in the subsequent visit decreased considerably in the saheli drug compared with the placebo group.

After first month of treatment placebo group patients and saheli group patients are having mean pain score 5.23 and 4.02 respectively.

Similarly after second month of treatment mean pain score of placebo group patients is 4.73 whereas saheli group is 2.37. There is a heavy decrease in pain in saheli drug group patients as compared to placebo drug group.

Now after third month of treatment placebo group patients and saheli group patients are having mean pain score 4.55 and 1.40 respectively.

After six month mean pain score of placebo group patients is 4.66 whereas saheli group is 0.98. We can see that, at the end of 6 months, there is an ongoing decrease in pain in the saheli drug group whereas pain recurred in the placebo group.

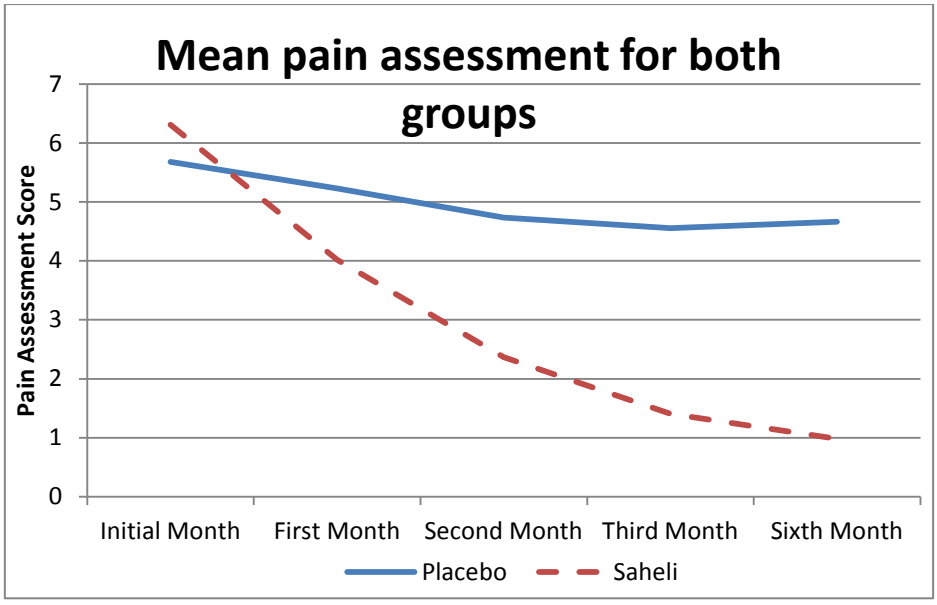

Figure 1. Mean pain assessment score for both groups

Table 2: Mean pain assessment at successive visits for drug and placebo group

Visit	Drug	Number (%) of patients in grade of nodularity					
		No	Normal	Mild	Moderate	Severe	Very Severe
At initial month	Placebo	10(15)	23(36)	23(36)	6(9)	1(2)	1(2)
	Saheli	6(11)	13(23)	20(35)	11(19)	6(11)	1(2)
After first month	Placebo	12(19)	28(44)	19(30)	5(8)	0(0)	0(0)
	Saheli	17(30)	12(21)	21(37)	4(7)	3(5)	0(0)
After second month	Placebo	14(22)	28(44)	19(30)	2(3)	1(2)	0(0)
	Saheli	24(42)	14(25)	15(26)	2(4)	2(4)	0(0)
After third month	Placebo	15(23)	26(41)	19(30)	3(5)	1(2)	0(0)
	Saheli	31(54)	17(30)	7(12)	2(4)	0(0)	0(0)
After sixth month	Placebo	14(22)	28(44)	19(30)	2(3)	1(2)	0(0)
	Saheli	37(65)	15(26)	3(5)	2(4)	0(0)	0(0)

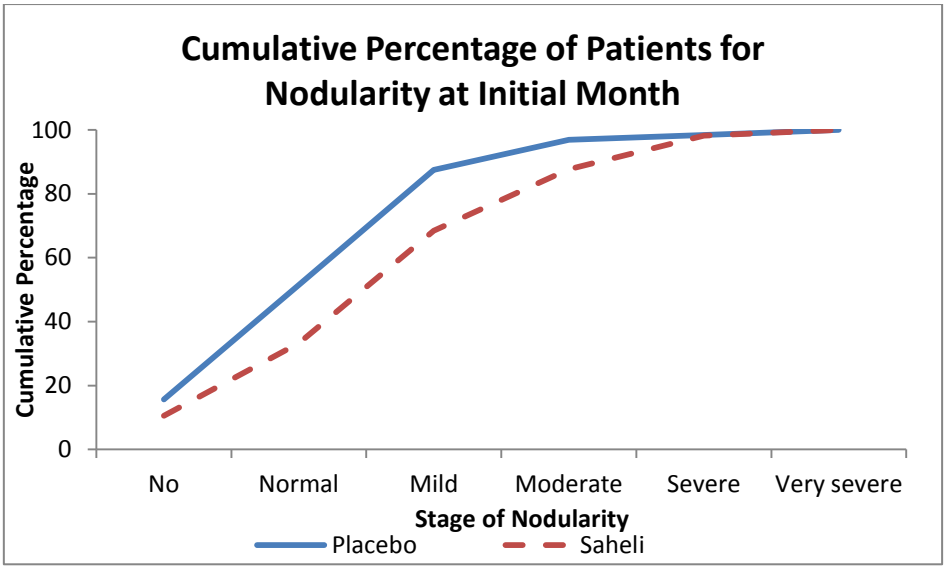

Figure-2.Cumulative percentage of patients for nodularity at initial month for both groups

In the placebo drug group at the initial month, 87% of patients are having no, normal and mild nodularity whereas 13% of patients are having moderate, severe and very severe nodularity.

In the saheli drug group at the initial month, 68% of patients are having no, normal and mild nodularity whereas 32% of patients are having moderate, severe and very severe nodularity.

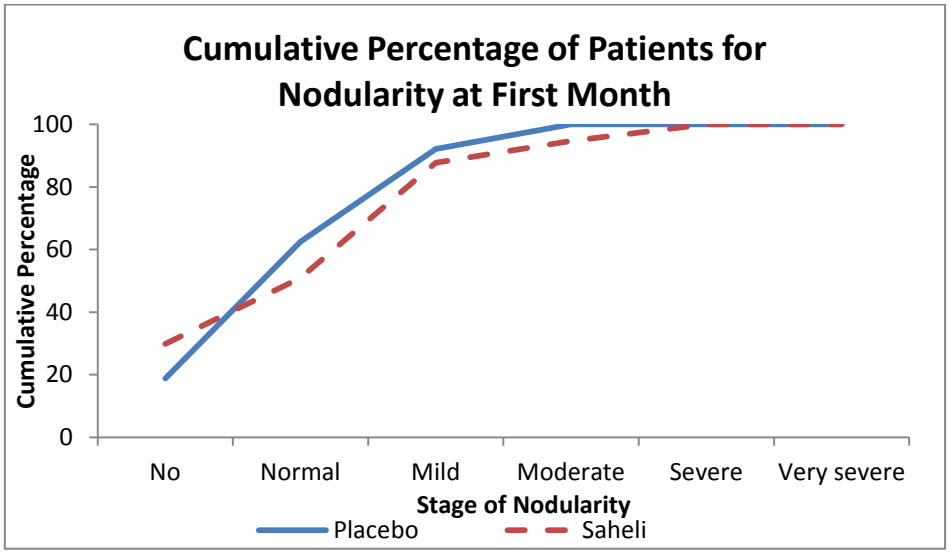

Figure-3.Cumulative percentage of patients for nodularity at first month for both groups

Similarly after first month of treatment, 92% of patients are having no, normal and mild nodularity whereas 8% of patients are having moderate, severe and very severe nodularity in patients who are taking placebo drug.

After first month of treatment, 88% of patients are having no, normal and mild nodularity whereas 12% of patients are having moderate, severe and very severe nodularity in patients who are receiving saheli drug.

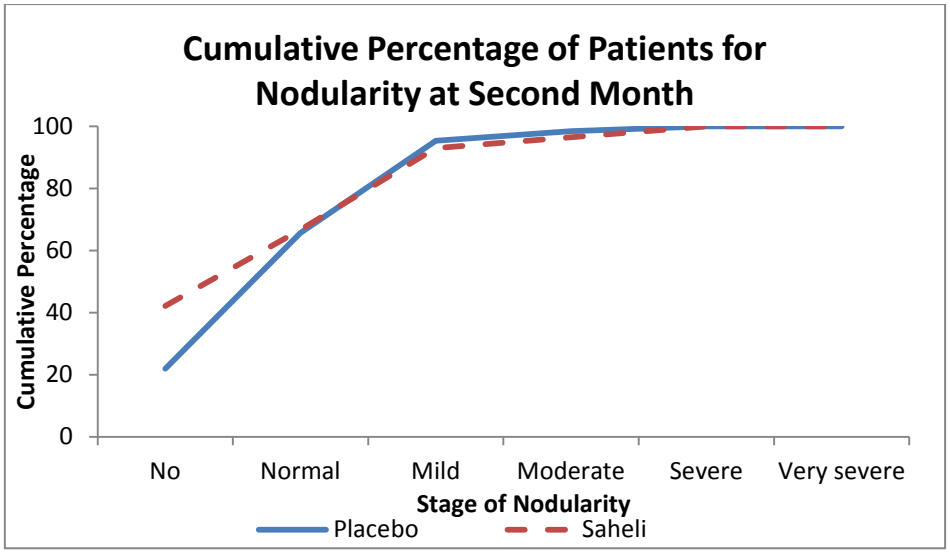

Figure4.Cumulative percentage of patients for nodularity at secondmonth for both groups

Again after second month of treatment, 95% of patients are having no, normal and mild nodularity whereas 5% of patients are having moderate, severe and very severe nodularity in patients who are taking placebo drug..

After second month visit, 92% of patients are having no, normal and mild nodularity whereas 8% of patients are having moderate, severe and very severe nodularity in patients who are taking saheli drug.

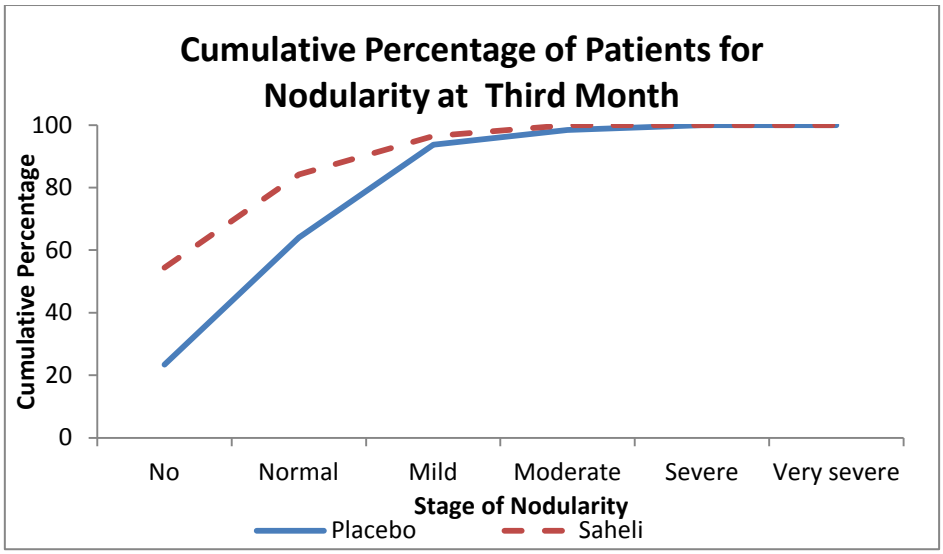

Figure5.Cumulative percentage of patients for nodularity at third month for both groups

After third month 93% of patients taking placebo drug, are having no, normal and mild nodularity whereas 7% of patients are having moderate, severe and very severe nodularity.

After third month of treatment 96% of patients taking saheli drug, are having no, normal and mild nodularity whereas 4% of patients are having moderate, severe and very severe nodularity.

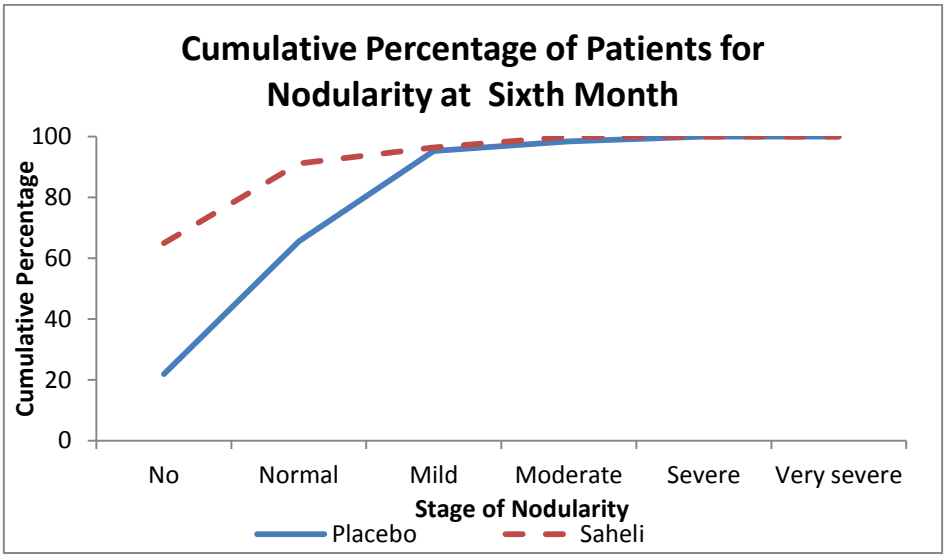

Figure-6.Cumulative percentage of patients for nodularity at sixth month for both groups

And after six month 95% of patients taking placebo drug, are having no, normal and mild nodularity whereas only 5% of patients are having moderate, severe and very severe nodularity.

After the six month 96% of patients taking, are having no, normal and mild nodularity whereas only 4% of patients are having moderate, severe and very severe nodularity.

Table 3: Odds ratio and significance value of nodularity at each visit

Visit	Odds Ratio (C.I.)	p value
At initial month	3.231 (1.278, 8.170)	0.013
After first month	1.652 (0.494, 5.528)	0.414
After second month	1.535 (0.328, 7.169)	0.586
After third month	0.545 (0.096, 3.096)	0.007
After sixth month	0.739 (0.119, 4.531)	< 0.001

In the first or initial pre-treatment visit somewhat higher grades of nodularity are present in the placebo drug group than in the saheli drug group. However, there is no significant difference ($p = 0.414$ and $p=0.56$) in the first and second follow-up visits in both the groups.

After second month of treatment again placebo drug group patients are having higher grade of nodularity than saheli drug patients group insignificantly, as $p = 0.586$.

Significant difference ($p = 0.007$) is noticed at the end of the third month while on saheli drug treatment.

Assessment of nodularity at 6 months in the two groups showed that the effect of the active drug still persisted and is significant as $p < 0.001$.

3.2 Repeated Ordinal Response Data Analysis on Pain

Pain of each patient has been measured between scales 1 to 10. For this analysis we have categorized it in six states 1 to 6; 1. no (if pain is 0), 2. normal (if pain is 0.1 to 2), 3. mild (if pain is 2.1 to 4), 4. moderate (if pain is 4.1 to 6), 5. severe (if pain is 6.1 to 8) and 6. very severe (if pain is 8.1 to 10)at initial month, first month, second month, third month and sixth month.

Here pain is treated as ordinal variable, means normal is higher than no pain, mild is higher than normal, moderate is higher than mild, severe is higher than moderate and very severe is higher than severe. Pain is treated as dependent variable with five categories and five times measurement. Drug (placebo and saheli), age and time are treated as independent variable and analysed on R using geepack package [8]. The results are given below:

Table 4: Parameter estimates of model for pain

Independent Variables	Coefficient (B)	p value
Drug	- 0.996	0.153
Time	- 0.299	0.029
Age	- 0.048	0.407

Placebo is less effective on pain than saheli drug because of B = - 0.996 < 0. This coefficient is insignificant as p value is 0.514.

Pain is decreasing by time as B = - 0.299 < 0 with p value = 0.029 (< 0.05) implies that this coefficient is significant.

Similarly younger age patients have less pain than older insignificantly as B = - 0.048 with p value = 0.407 (> 0.05).

3.3 Repeated ordinal response data analysis on nodularity

Here nodularity is treated as ordinal variable, means normal is higher than no pain, mild is higher than normal, moderate is higher than mild, severe is higher than moderate and very severe is higher than severe. Nodularity is treated as dependent variable with five categories and five times measurement. Drug (placebo and saheli), age and time are treated as independent variable and again analysed on R using geepack package [11]. The results are given below:

Table 5: Parameter estimates of model for nodularity

Independent Variables	Coefficient (B)	p value
Drug	- 4.704	< 0.001
Time	- 31.401	< 0.001
Age	- 324.520	< 0.001

Placebo is less effective on pain than saheli drug because of B = - 4.704 < 0. This coefficient is significant as p value is less than 0.001.

Pain is decreasing by time as B = - 31.401 < 0 with p value less than 0.001 (< 0.05) implies that this coefficient is significant.

Similarly younger age patients have less pain than older insignificantly as B = - 324.52 with p value less than 0.001 (< 0.05).

4. Conclusion

Overall we can say that saheli drug is more effective on pain than placebo drug. Thus placebo drug can be replaced by saheli drug.

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