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Examining the socio-demographic characteristics of osteoarthritis patients

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Abstract: This paper was conducted in order to examine not only the effect of medical treatment on pain, recovery, difficulties in vital activities, satisfaction for usual activities, stiffness, and physical function of the osteoarthritis patients, but also relationships with marital status, gender, employment and education. The effects of covariates for demographic variables and the target joints are examined for their relationships to the responses of patients. The 2x2 crossover design provided longitudinal data with 5 visits for assessments of patients both before and after each of two treatments. The questionnaires in the study addressed many areas for improvement of patients. This paper addresses 5 types of questions for responses of patients, and uses 6 types of questions as covariables. The response variables are constructed as ordinal variables with 3, 4, or 5 categories. These response variables are the amount of pain, amount of recovery, amount of pain in physical function, amount of difficulty in physical function and amount of stiffness. Methods for Generalized Estimating Equations (GEE) are used to fit regression models that appropriately account for the correlation structure of the data. The results from the analyses are interpreted through tabular summaries for pain, recovery, difficulties in vital activities, satisfaction for usual activities, stiffness, and physical function. The variables of pain, recovery, difficulties in vital activities, satisfaction for usual activities, stiffness, and physical functions of osteoarthritis patients were affected from their socio-demographic characteristics.

Key words: Arthritis; Crossover design; Longitudinal study; GEE

1. Introduction

The signs of osteoarthritis include pain in joints and reduction in movements. Physicians often provide patients with medicines to relieve the signs of this chronic disease (Stamp et al., 1989; Williams et al., 1993). There is a strong relationship between age and the disease with it usually being seen for people who are older than 40 (Amadio and Cummings, 1983). However, results of epidemiological research suggest that 10% of osteoarthritis patients have ages between 15 and 24 (Williams et al., 1993), while the prevalence is more than 80% for people older than 65 years (Bradley et al., 1991).

Osteoarthritis can be observed at 48 different joints of the body. For the study discussed in this paper, four joints (right hip, left hip, right knee and left knee) are considered since they are often the target of treatment. Accordingly, such joints are called target joints and they are relevant as covariates for analyses of responses to treatments. Non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen are commonly used as medicines to relieve pain from osteoarthritis.

Acetaminophen is often preferred for initial treatment because of its efficacy for pain reduction, low cost, and low toxicity (Holzer and Cuerdon, 1996; Eccles et al., 1998). However, an NSAID is often provided to patients who do not have pain relief from acetaminophen. In some studies to compare acetaminophen and NSAID, acetaminophen was found as effective as the NSAID or sometimes even more effective (Bradley et al., 1992, Bradley et al., 2001), and acetaminophen was also found more effective than placebo (Amadio and Cummings, 1983). There are additionally many studies in the medical literature that show that an NSAID is more effective than placebo. However, such studies address a variety of doses and some have limitations in design. There are some studies where an NSAID was found more effective than acetaminophen (Watson et al., 2000; Geba et al., 2002). Pincus et al. (2001) originally concluded from the data considered in this paper that diclofenac+200mg misoprostol twice a day provided better pain relief after 6 weeks than acetaminophen four times a day for patients with severe osteoarthritis whereas pain relief for the two treatments tended to be similar for patients with more moderate disease. In another study, patients indicated that an NSAID was the

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more useful drug for osteoarthritis compared to acetaminophen (Pincus et al., 2000). Also, adverse events were less prevalent for acetaminophen in this study.

In this paper, the effects of covariates for socio-demographic variables and the target joints are examined for their relationships to the responses of patients. Generalized Estimating Equations (GEE) are used to address the repeated measures data structure for five visits for assessments of patients both before and after each of two treatments in a 2x2 crossover design.

2. Material and methods

The study discussed in this paper had a double blind 2x2 crossover design. With this design, each patient received each of two treatments during two different time periods (Laird et al., 1992). The crossover design enables evaluation of differences between treatments for each patient and across patients for each period. An advantage of the crossover design is that it can provide more precise estimates than other designs for treatment comparisons when variation among patients is greater than within patients (Kenward and Jones, 1994; Johnson and Mercante,1996).

A potential limitation of the crossover design is the influence of carryover effects from the first period to the second period. In order to reduce the possibility of carryover effects, an interval between periods is used so as to eliminate the effect of the first period (wash-out period) for patients. The length of the washout period is defined through the design of the study. However, in some studies, some carryover effect can still remain, and unless it is negligible, consideration may need to be restricted to the first period of the study (Freeman, 1989).

2.1. The data

The data are from questionnaires used by the Department of Rheumatology of the Vanderbilt University School of Medicine, Nashville, TN, USA. Some parts of the questionnaires used the WOMAC (Western Ontario McMacter Osteoarthritis Index). There was examination of the background of the disease and the demographic status of the patients. Other questionnaires addressed the extent of the disease and how useful the assigned treatment for a period was.

The study had 5 visits. At the first visit, examination of patients identified whether they fulfilled criteria for entry to the study. Qualifying patients were asked to attend the second visit after 3-7 days without using any prohibited medicines. This 3-7 days' time is the wash-out period for medicines being used at the time of the first visit.

At the second visit, 227 patients were randomly assigned to 2 different groups in a double-blind manner so that neither the patients nor the physicians knew the assigned group. During the second visit, patients also provided responses to the questionnaires. For the six weeks between the second and third visits, one group used arthrotec (diclofenac/misoprostol) and the other group used acetaminophen. At the 3rd visit after using the assigned medicines for six weeks, the patients provided responses to the respective questionnaires and provided assessments for how useful their assigned treatment was. For the 3-7 days after the first treatment period of six weeks, the patients were required not to use any prohibited medicines so as to minimize the possibility for carryover effects (second wash-out period).

After the 4th visit where responses to questionnaires are again obtained, patients are assigned the opposite treatment to what they received for the first period. After six weeks of treatment, patients provide responses to questionnaires at the fifth visit. The first 3 visits in the study pertain to the first period of treatment, and the last two visits pertain to the second period.

The study began with 227 patients at the second visit, and 218 patients completed the first period and 181 completed the second period.

The correlation structure of the data for the respective visits is taken into account by the use of GEE methods through the GENMOD Procedure in the SAS 7.5 software.

2.2. Defining the variables

The questionnaires in the study addressed many areas for improvement of patients. This paper addresses 5 types of questions for responses of patients, and uses 6 types of questions as covariables.

The response variables are constructed as ordinal variables with 3, 4, or 5 categories. These response variables are the amount of pain, amount of recovery, amount of pain in physical function, amount of difficulty in physical function and amount of stiffness.

Some of the covariates are at the patient level and others are time varying. The patients' level covariates are age, marital status, employment, education, gender, and target joint. Marital status is only defined as married or not. Employment is defined as working, retired, and not retired but not working. Education is defined as 12 years or less and 13 to 15 years and 16 or more years. The target joint is the principal location of the osteoarthritis and is defined as right knee, left knee, right hip and left hip. The assigned treatment and its period are time-varying covariates for the 2x2 crossover design.

2.3. Statistical analysis

The independent correlation structure is used with GEE methods since it is the only structure currently available in GENMOD for models for ordinal variables. Its use also is supportive to the applicability of normal approximations for parameter estimates from the sample size of this study which is more moderate rather than clearly large. On the other hand, since there is a long wash-out period, possible low dependence is neglected.

The response variables are ordinal and so the proportional odds model is applied through cumulative logits. For each of the respective response variables, the effects of the 6 covariates are evaluated using GEE, and the results are summarized in tables.

The parameter estimates from GEE are based on the odds ratio and so interpretation is straightforward and it depends on the proportional odds assumption. The proportional odds assumption is that $\boldsymbol{\beta}_k = \boldsymbol{\beta}$ for all k, simplifying the model to (Eq. 1),

$$\operatorname{logit}(\theta_{hik}) = \alpha_k + \mathbf{X}'_{hi}\boldsymbol{\beta} \quad (1)$$

For the probability $\pi_k(\mathbf{x})$ of the kth ordered category for patients with $\mathbf{x}$ as the vector of covariates, the structure of the model is shown in Eq. 2.

$$\sum_{k=1}^{j} \pi_k(\mathbf{x}) = \theta_j(\mathbf{x}) = \frac{\exp(\alpha_j + \boldsymbol{\beta}'\mathbf{x})}{(1 + \exp(\alpha_j + \boldsymbol{\beta}'\mathbf{x}))} \quad (2)$$

where α_j denotes an intercept for the j-th cumulative logit and **exp(β)** is the vector of odds ratios corresponding to the respective covariates. It should be noted that **x** includes patient level covariates as well as periods and treatments as time varying covariates. In this way, $\pi_k(\mathbf{x})$ can pertain to the respective periods for all patients with their corresponding patient level covariates. In this paper, only results that account for significant covariates are reported.

3. Results

Descriptive statistics for the distributions of the covariates are presented in Table 1 for the randomized groups according to the treatment for the first period. Also, given there are p-values for comparisons between the groups. These results support the similarity of the randomized groups for the distributions of the covariates.

Table 1: Descriptive statistics for the distributions of the covariates from the treatment groups for period 1 with p-values for comparisons between them

COVARIATES	GROUP I (treatment group)	GROUP II (control group)	p-value
Mean Age (±SEM)	62± 0.55	61±0.57	0.828
Married	58%	56%	0.789
Female	70%	71%	0.884
Working full time	23%	25%	0.758
Retired or Disabled	46%	44%	0.791
Educated less than 12 years	41%	50%	0.231

SEM: Standard error of mean

Results are interpreted through unadjusted frequency distributions for cross-tabulations of those significant covariates with treatments and the response variable.

3.1. The amount of pain

The response variable for pain severity was based on the point marked by the patient on a scale ordered from 1 to 5. Hence, the response was classified according to 5 ordered categories. The model for this response variable suggested no significant association with age, employment, education, or target joint ($p>0.05$). However, significant relationships were identified for marital status (odds ratio = 0.691, 95% confidence interval = (0.493, 0.968), p = 0.0317) and gender (odds ratio = 0.512, 95% confidence interval = (0.350, 0.750), p=0.0006). Frequency distribution which describes relationships is shown in Table 2 and Table 3.

Table 2: Distribution of amount of pain according to marital status and treatment

MARITAL STATUS	GROUP	Π_1 No Pain	Π_2	Π_3	Π_4	Π_5 Extreme Pain
Single	Treatment	0.331302	0.225995	0.218667	0.140802	0.083234
Single	Control	0.199759	0.188342	0.247610	0.211604	0.152684
Married	Treatment	0.417583	0.228027	0.188064	0.107291	0.059034
Married	Control	0.265378	0.213210	0.237756	0.172925	0.110731

According to the results in Table 2, married patients tend to have less severe pain than single patients; and patients tend to have less severe pain with study treatment than control treatment. The highest proportion with no pain was for married patients with study treatment (41.76%), and the highest proportion with extreme pain was for single patients with control treatment (15.27%).

As can be seen from Table 3, males tend to have less severe pain than females. The highest proportion with no pain was for males with study treatment (49.46%), and the highest proportion with extreme pain was for females with control treatment (14.41%).

Table 3: Distribution of amount of pain according to gender and treatment

GENDER	GROUP	Π_1 No Pain	Π_2	Π_3	Π_4	Π_5 Extreme Pain
Female	Treatment	0.334010	0.233696	0.217235	0.136116	0.078943
Female	Control	0.203347	0.197268	0.249444	0.205810	0.144130
Male	Treatment	0.494625	0.224697	0.157568	0.081039	0.042072
Male	Control	0.332499	0.233537	0.217755	0.136770	0.079439

3.2. Recovery

The response variable for recovery was based on the point marked by the patients on the scale ordered from 1 to 5, where 1 represents most light recovery. Hence, the response was classified according to 5 ordered categories. The model for this response variable suggested no significant association with marital status, education, gender, and target joint (p>0.05). A significant relationship was identified for employment with respect to retired patients versus those who were not retired but not working (odds ratio = 0.564, 95% confidence interval = (0.376, 0.845), p=0.0055), but not in comparison to working patients (odds ratio = 0.704, 95% confidence interval = (0.443, 1.119), p =0.1380). Frequency distributions which describe this relationship are shown in Table 4.

Table 4: Distribution of recovery according to employment and treatment

Employment	GROUP	Π_1 Much better	Π_2	Π_3	Π_4	Π_5 Much worse
Retired	Treatment	0.139866	0.354884	0.322257	0.126751	0.056242
Retired	Control	0.066211	0.233012	0.361429	0.219113	0.120236
Not working	Treatment	0.223844	0.410755	0.253274	0.079618	0.032509
Not working	Control	0.111709	0.319235	0.344481	0.153031	0.071545
Working	Treatment	0.168780	0.381326	0.297803	0.106539	0.045551
Working	Control	0.081338	0.266422	0.360779	0.192809	0.098651

According to the results in Table 4, patients who were not retired but not working had better recovery than those who were retired. The highest proportion that were much better since the previous visit was for patients who were not retired but not working with test treatment (22.38%), and the highest proportion that were much worse was for retired patients with control treatment (12.02%).

3.3. Amount of pain in physical function

The response variable for pain in physical function was based on the point marked by the patient on the following scale ordered from 1 to 5. Hence, the response was classified according to 5 ordered categories. The model for this response variable suggested no significant association with age, marital status, employment, or target joint (p>0.05). However significant relationships were identified for education (odds ratio = 0.481, 95% confidence interval = (0.290, 0.795), p =0.0044) and gender (odds ratio = 0.607, 95% confidence interval = (0.408, 0.905), p =0.0142). The distributions according to education and gender are shown in Table 5 and Table 6.

Table 5: Distributions for pain in physical function according to education and treatment

EDUCATION	GROUP	Π_1 No Pain	Π_2	Π_3	Π_4	Π_5 Extreme Pain
<=12 years	Treatment	0.355855	0.307884	0.210195	0.094546	0.031520
<=12 years	Control	0.192507	0.267478	0.289487	0.180398	0.070130
13-15 years	Treatment	0.404970	0.303631	0.186581	0.079080	0.025738
13-15 years	Control	0.227023	0.285025	0.274527	0.155738	0.057687
>=15 years	Treatment	0.586157	0.248845	0.111731	0.040732	0.012535
>=15 years	Control	0.379352	0.306565	0.198741	0.086766	0.028576

According to the results in Table 5, the patients who had more than 15 years education tended to have less pain in physical function and there was less pain with test treatment than control treatment. The highest proportion with no pain was for test treatment for patients who had more than 15 years education (58.61%) and the highest proportion with extreme pain was for control treatment for patients who had less than 12 years education (7.01%).

According to the results in Table 6, males tended to have less pain in physical function. The highest proportion with no pain was for test treatment for males (50.26%), and the highest proportion with extreme pain was for control treatment for females (6.08%).

3.4. Amount of difficulty in physical function

The response variable for the amount of difficulty in physical function was based on the points marked by the patients on the following scale ordered from 1 (no difficulty) to 5 (extreme difficulty). Hence, the response was classified according to 5 ordered categories. The patients are asked to scale all 17 physical functions for 5 categories and the mean values of the responses taken into account.

The physical functions taken into account are listed below:

Table 6: Distributions for pain in physical function according to gender and treatment

GENDER	GROUP	Π1 No Pain	Π2	Π3	Π4	Π5 Extreme Pain
Female	Treatment	0.380364	0.297985	0.205878	0.086857	0.028914
Female	Control	0.220045	0.272154	0.286084	0.160872	0.060842
Male	Treatment	0.502699	0.273733	0.149914	0.055892	0.017760
Male	Control	0.317215	0.297600	0.237703	0.109629	0.037851

1. Descending stairs 2. Ascending stairs 3. Rising from sitting 4. Standing 5. Bending to floor 6. Walking on flat surface 7. Getting in/out of car 8. Going shopping 9. Putting on socks/stockings 10. Rising from bed 11. Taking off socks/stockings 12. Lying in bed 13. Getting in/out bath 14. Sitting 15. Getting on/off toilet 16. Heavy domestic duties 17. Light domestic duties

The model for this response variable suggested no significant association with employment, gender or target joint ($p>0.05$). A significant relationship was identified for age (odds ratio = 0.985, 95% confidence interval = (0.972, 0.998), p =0.0226), marital status (odds ratio = 0.653, 95% confidence interval = (0.453, 0.941), p = 0.0224) and education (odds ratio = 0.523, 95% confidence interval = (0.311, 0.877), p=0.0141). Distributions according to marital status and education are shown in Table 7 and Table 8.

Table 7: Distributions for difficulty in function according to marital status and treatment

MARITAL STATUS	GROUP	Π1 No Difficulty	Π2	Π3	Π4	Π5 Extreme Difficulty
Single	Treatment	0.412946	0.214833	0.207085	0.116038	0.049098
Single	Control	0.287430	0.204221	0.251880	0.173867	0.082603
Married	Treatment	0.518716	0.202278	0.164670	0.081736	0.032600
Married	Control	0.381969	0.215108	0.219166	0.128253	0.055504

According to the results in Table 7, married patients tend to have less difficulty than single patients, and patients tend to have less difficulty with test treatment than control treatment. The highest proportion with no difficulty was for married patients with study treatment (51.87%), and the highest proportion with extreme difficulty was for single patients with control treatment (8.26%).

Table 8: Distributions for difficulty in function according to education and treatment

EDUCATION	GROUP	Π1 No Difficulty	Π2	Π3	Π4	Π5 Extreme Difficulty
<=12 years	Treatment	0.389503	0.227039	0.211611	0.120648	0.051198
<=12 years	Control	0.253487	0.207642	0.258355	0.188462	0.092055
13-15 years	Treatment	0.492126	0.217342	0.170328	0.085894	0.034310
13-15 years	Control	0.340246	0.224907	0.230575	0.141694	0.062579
>=15 years	Treatment	0.649673	0.174068	0.109626	0.048407	0.018226
>=15 years	Control	0.496725	0.216521	0.168483	0.084566	0.033706

As can be seen from Table 8, the patients who had more than 15 years education tended to have less difficulty in physical function, particularly during test treatment (64.97%). The highest proportion with extreme difficulty in function was for patients who had less than 12 years education with control treatment (%9.21).

3.5. Amount of stiffness

The response variable for stiffness was based on the point marked by the patient on the following scale ordered from 1 to 5. Hence, the response was classified according to 5 ordered categories. The model for this response variable suggested no significant association with age, marital status, employment or target joint ($p>0.05$). However, significant relationships were identified for education (odds ratio = 0.463, 95% confidence interval = (0.261, 0.822), p =0.0086) and gender (odds ratio = 0.597, 95% confidence interval = (0.374, 0.951), p = 0.0299). Distributions according to education and gender are shown in Table 9 and Table 10.

According to the results in Table 9, patients with more than 15 years of education have less stiffness than those with fewer years. The highest proportion with no stiffness was for patients with more than 15 years of education during test treatment (47.26%) and the highest proportion with extreme stiffness was for patients with less than 12 years of education during control treatment (10.02%).

As can be seen from Table 10, males tended to have less stiffness than females. The highest proportion with no stiffness was for males during test treatment (36.57%), and the highest proportion with extreme stiffness was for females during control treatment (7.84%).

Table 9: Distributions for stiffness according to education and treatment

EDUCATION	GROUP	Π1 No Stiffness	Π2	Π3 Extreme Stiffness
<=12 years	Treatment	0.203980	0.741230	0.054790
<= 12 years	Control	0.117616	0.782120	0.100264
13-15 years	Treatment	0.293219	0.672215	0.034566
13-15 years	Control	0.177496	0.758105	0.064398
>=15 years	Treatment	0.472627	0.511069	0.016304
>=15 years	Control	0.317951	0.651169	0.030879

Table 10: Distribution for stiffness according to gender and treatment

GENDER	GROUP	Π1 No Stiffness	Π2	Π3 Extreme Stiffness
Female	Treatment	0.255974	0.699114	0.044912
Female	Control	0.159735	0.761837	0.078428
Male	Treatment	0.365725	0.606983	0.027292
Male	Control	0.241623	0.710053	0.048324

4. Discussion

The study discussed in this paper was conducted in order to examine not only the effect of medical treatment on pain, recovery, difficulties in vital activities, satisfaction for usual activities, stiffness, and physical function of the osteoarthritis (OA) patients, but also relationships with marital status, gender, employment and education. For this purpose, methods for generalized estimating equations were used because of their applicability to non-normally distributed data. This method is applied to data obtained by questionnaire from osteoarthritis patients, for a 2x2 crossover double blind design with 5 visits.

The amount of pain was associated with marital status, and less pain was reported by married patients during test treatment. In the literature, we couldn't find any study on the relationship between the amount of pain of OA patients and marital status. But the negative psycho-social effects of living alone and pain should be kept in mind. The extent of pain was greater for female patients during control treatment. There are numerous studies supporting that finding. LeResche; Rosseland and Stubhaug studied on chronical pain showed that females complain more than the male about the pain (LeResche, 2000; Rosseland and Stubhaug, 2004). It is shown that the OA postmenaposal women who take hormonal replacement treatment have a lower thermal threshold and tolerance than the same aged females who don't take the same treatment and also the same aged males (France et al., 2004). It is found that melanacortin 1 receptor gene difference in female increase the pentazosine sensivity (Mogil et al., 2003). Those two studies can bring new point of view to biological differences but cannot explain the sociological and psychological differences.

Recovery was better for unemployed patients during test treatment and worse for retired patients during control treatment. Difficulties with vital activities were less evident for patients with less than 12 years of education during control treatment and more evident in patients with more than 15 years of education during test treatment. Pincus, Callahan, and Burkhauser mentioned that people with 12 years or less of education have a greater tendency for living with a chronic muscle disease than the people with more years of education (Pincus et al., 1987).

Pain during physical activities was greatest for females and less educated patients during control treatment. This can be explained by some reasons. Since the pain threshold and tolerance of females are low, and complaining more about pain, NSAID are more effective than paracetamol (Geba et al., 2002; Pincus et al., 2001).

For difficulties during the physical activities, age, marital status and education had significant associations. Guccione et al. mentioned that OA is the most effective disease causing disabilities on physical activities comparing the other diseases (Guccione et al., 1994). Physical disability can cause difficulties during physical activities depending on pain and other factors (Ettinger et al., 1994, Odding et al., 1998). Recently the interest on pain is focused on the other factors that might be effective on pain besides pathology. The studies on age groups showed that the pain prevalence decreases at age 60 and above (Helme and Gibson, 2001). They also mentioned that, while the pain like the pain in west decreases the pain in hip, knee and foot increases with aging. Thomas, Peat, Harris, Wilkie, and Croft found that, the pain prevalence is higher for older females than the males (Thomas et al., 2004). They also concluded that in the joints other than hip, knee and foot, they found a decrement in pain. At all age groups they mentioned the pain prevalence as 38.1% during the activities.

As another result of this study, the patients in treatment group in any age had a lower risk of getting difficulty in activities. Diclofenac was more effective than the acetaminophen. There was less difficulty in physical activities for married patients during test treatment, but there are not any other studies in the OA literature that support this association. This result might be explained through social relationships of married people being more supportive than for single people.

Also, difficulties in physical activities tended to be less extensive for patients with more than 15 years of education during test treatment.

Stiffness is an important sign in OA. The reason of stiffness in joints is not clearly known. The probable reasons of stiffness may be edema in periarticuler structures as a result of inactivity, inflammation, or thickness of capsule (Moskowitz, 1993, Bellamy and Buchannan, 1993). At the very beginning of the disease the stiffness can occur only beginning of the movement, but the duration can be longer later on. However it is never more than a half hour. There is a correlation between progression of OA and the stiffness. So a treatment can also be contributive in decreasing the stiffness and the duration of it.

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