To evaluate the efficacy and safety of CartiNovex plus tablet in osteoarthritis and rheumatoid arthritis

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Abstract: Interminable arthritis issue, for example, osteoarthritis (OA) and rheumatoid arthritis (RA) have in like manner an upsurge of aggravation, and oxidative anxiety, bringing about dynamic histological modifications and incapacitating indications. As of now utilized allopathic prescription (extending from painkiller executioners to natural operators) is intense, yet regularly connected with genuine, even dangerous symptoms. Utilized for centuries in customary herbalism, restorative plants are a promising option, with bring down rate of unfavorable occasions and productivity every now and again tantamount with that of traditional medications. In any case, their instrument of activity is as a rule smooth and additionally indeterminate. Despite the fact that a large number of them have been demonstrated powerful in ponders done *in vitro* or on creature models, there is a shortage of human clinical proof. This clinical trial was conducted at Liaquat National Hospital, Karachi, Pakistan. This was a single blind, placebo control phase II clinical trial. Total 200 patients were enrolled in the study, in which 110 received the CartiNovex plus tablet and 90 received the placebo. The age range of patients was 40 years to above 70 years. The sample paired t-test was applied to evaluate the significant level. Different parameters like pain on sitting or lying, morning stiffness, pain on walking, stiffness in sitting, lying or resting later in the day, getting on/off toilet, light domestic duties (such as tidying room, dusting, cooking), WOMAC score % were tested for both group i.e. CartiNovex plus group and placebo group in all parameters CartiNovex plus show significant improvement in all parameters. CartiNovex plus tablet was very effective in the management of OA and RA. The CartiNovex plus tablet was safe and well tolerated in all patients and side effects are non-significant.

Keywords: CartiNovex plus tablet, herbal treatment, osteoarthritis, rheumatoid arthritis.

INTRODUCTION

The term arthritis (joint pain) was gotten from the Greek words "artho" and "itis," which means joint and inflammation, respectively. Arthritis is a type of joint issue described by unending inflammation in at least one joints that as a rule brings about agony and is frequently disabling (Goldring, 2003, Johnson and Hunter, 2014). Arthritis incorporates more than 100 unique structures: the most widely recognized shape is osteoarthritis, however different structures incorporate rheumatoid arthritis, psoriatic arthritis, and related immune system diseases (Goldring, 2003, Johnson and Hunter, 2014). Although the reasons for these illnesses are extraordinary, their indications and medications are comparative. As osteoarthritis is a degenerative joint disease, the quantity of individuals with joint pain is likewise developing with the expansion in the maturing population (Johnson and Hunter, 2014). The overall pervasiveness of knee osteoarthritis expanded 27% from 1990 to 2010, and it influences around 10% of men and 17.9% of women over 60 years of age. The event of osteoarthritis increments with age because of the diminished ability to stifle irritation, age-related sarcopenia, and expanded bone turnover (Johnson and Hunter, 2014). Features that upsurge the risk of osteoarthritis are progressive age, sex, overweight, augmented body mass index (BMI), genetics, ethnicity, diet, trauma, certain physical or occupational activities that indicate biomechanical stress (e.g., pressure, load-bearing) across the joints (McWilliams, Leeb *et al*., 2011, Murphy, Eyles *et al*., 2016, Smith, Carter *et al*., 2004). Checking the osteoarthritis development and treatment includes torment and physical capacity evaluation for shorter examinations, and in addition joint imaging for longer investigations (1 year or more). Torment is assessed with visual simple scales

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(VAS), while the utilitarian hindrance with Western Ontario and McMaster Universities OA Index (WOMAC) (Dougados, 2004). Other useful assessment tools of functional impairment are Lequesne Functional Severity Index (Lequesne, Mery *et al*., 1987) and Karnofski Performance Scale Index (Johnson, Bland *et al*., 2014). Rheumatoid arthritis is a foundational provocative and dangerous joint illness with a commonness of around 1-2% of the grown-up populace worldwide (Goldring, 2003). In spite of the fact that arthritis is related with inflammation and pain, the correct reason for joint pain stays dubious, and there is no treatment for its major causes. The real objective of joint pain treatment is to diminish joint agony incited by aggravation in the joints, day by day wear and tear of joints, and muscle strains (Marcu, Otero *et al*., 2010). RA distressing 1% of the populace and producing debility and amplified hazard for cardiovascular disease, lymphoma, and death (Yang, Or *et al*., 2013), naturally connected with high phases of oxidative pressure and provocative middle people. RA is directly made do with an across the board assortment of medications stretching out from steroidal/nonsteroidal anti-inflammatory drugs (NSAID and agony executioners), to powerful organic specialists focusing on particular invulnerable and fiery pathways, for example, TNF-alpha inhibitors and interleukin-1 receptor antagonists (Smolen, Landewe *et al*., 2014). Between NSAIDs, acetaminophen is utmost commonly used in very high doses (4000mg/day). Concerning the pain killers, tramadol is exceedingly suggested, but also other opioids (e.g., morphine) (Hochberg, Altman *et al*., 2012). The biologic treatments have proven to be exceedingly fruitful and effective in the majority of RA cases, including the severe ones. Inappropriately, the use of standard drugs in arthropathies is convoyed by numerous and frequently serious side effects (Abdel-Tawab, Werz *et al*., 2011): gastrointestinal ulcerations, hemorrhagic events, and nephrotoxicity induced by NSAID (McAlindon, Bannuru *et al*., 2014); infusion hypersensitivity reactions, and auto-immune responses (e.g., lupus-like syndrome) triggered by TNF alpha inhibitors (Matucci, Cammelli *et al*., 2016); amplified risk of severe infection, distressing mainly the respiratory tract, caused by biological drugs (anakinra, rituximab, or abatacept) (Matucci, Cammelli *et al*., 2016); fatal cytopenia encouraged by methotrexate (Mameli, Barcellona *et al*., 2017); etc. Hence the transformed interest in medicines of botanical origin, which lack severe adverse effects and have a millennia-proven efficacy (Umar, Umar *et al*., 2014). These remedies may be have a valuable effect not only on the symptoms but also on the course of the disease (Akhtar, Miller *et al*., 2011). The purpose of this clinical trial was to evaluate the natural product CartiNovex for the treatment of osteoarthritis and rheumatoid arthritis. The natural product CartiNovex contains (hyaluronic acid, glucosamine sulphate, chondroitin sulphate, methyl sulfonyl methane, *colchicum luteum*, *boswellia serrata*, W*ithania somnifera*, *Smilax chinensis*, *Zingiber officinalis* and *Curcuma longa*).

MATERIALS AND METHODS

This was a randomized, placebo-controlled clinical trial with a 28-day screening period for every patient trailed by a 12-week involvement period. A total 200 patients with osteoarthritis (OA) and rheumatoid arthritis (RA) will be randomized.

The clinical impact of treatment on OA and RA will be assessed throughout clinic visits at 6 and 12 weeks, and phone contacts at 2, 4, 8 and 10 weeks, utilizing the Western Ontario and McMaster Universities Arthritis Index (WOMAC®). The WOMAC® is an approved pain scoring system and sets the standard for the patient reactions. All together not to predisposition the gathering of information, just inquiries from the approved WOMAC pain scale will be asked from patients. Clinical importance will be controlled by the final products of this trial, particularly by the clear clinical advantage versus any antagonistic occasions or any expanded obvious hazard. Safety will be evaluated by recording unfriendly occasions (through 24 hours post-measurement and at all subsequent contacts) and physical examination and vitals (Baseline, Weeks 6 and 12).

The Rheumatologist chose patients arbitrarily for CartiNovex plus tablet and placebo. 110 patients were chosen randomly from Liaquat National Hospital Karachi Pakistan. The patients were separated into two groups, test groups (CartiNovex plus) and control group (placebo), the two groups comprises 110, 90 patients respectively. Results were evaluated on the sign and symptoms of OA and RA after treatment and help in manifestations which additionally classified in various class, 1: Complete improvement, 2: Moderate improvement, 3: Mild improvement, 4: No improvement.

Selection Criteria

Test Group

The test group was treated with CartiNovex plus tablet twice a day for 12 weeks.

Control group

The control group was treated with placebo twice a day for 12 weeks.

Eligibility

Inclusion Criteria

Skilled to convey on paper educated agree to contribute in the examination, Agreeable and fit to satisfy with all investigation necessities and headings of the site ponder staff Male or female, 40 years to over 70 years of age (comprehensive). Need be mobile. File knee must be

symptomatic for more than a half year with a clinical conclusion of OA or RA. Direct to decently serious OA or RA torment in the file knee (rating of no less than 1.5 on the WOMAC Index 3.1) evaluated at screening. Direct to decently extreme OA or RA torment in the file knee (regardless of whether endless dosages of non-steroidal calming drug (NSAID), which have not changed in a month before screening, have been/are being utilized). No absence of pain (counting acetaminophen [paracetamol]) taken 12 hours preceding a viability measure. No known clinically noteworthy liver anomaly (e.g. cirrhosis, transplant, and so forth).

Exclusion Criteria

Because of medicinal survey and screening examination, the Principal Investigator considers the patient unfit for the examination. Nearness of tense emanations. Fiery or precious stone arthropathies, intense breaks, history of aseptic corruption or joint substitution in the influenced knee, as surveyed locally by the Principal Investigator. Segregated patella femoral disorder, otherwise called chondromalacia. Some other ailment or condition meddling with the free utilize and assessment of the list knee for the length of the trial (e.g. malignancy, intrinsic imperfections, spine osteoarthritis). Real damage to the file knee inside a year preceding screening. Serious hip osteoarthritis ipsilateral to the list knee. Any torment that could meddle with the appraisal of record knee torment (e.g. torment in some other piece of the lower furthest points, torment transmitting to the knee). Any pharmacological or non-pharmacological treatment focusing on OA or RA began or changed amid a month before randomization or liable to be changed amid the span of the examination. Utilization of the accompanying prescriptions:

a. No Intra Articular injected pain medications in the study knee during the study
b. No analgesics containing opioids. NSAIDs may be continued at levels preceding the study and acetaminophen is available as a rescue medication during the study from the provided supply
c. No topical treatment on osteoarthritis index knee during the study
d. No significant anticoagulant therapy (e.g. Heparin or Lovenox) during the study (treatment such as Aspirin and related anticoagulant medicine)
e. No systemic managements that may interfere with safety or efficacy assessments during the study
f. Not at all usage of corticosteroids > 10 mg prednisolone equal per day (if ≤ 10 mg prednisolone, the dose must be stable)
g. No human albumin treatment in the 3 months before randomization or throughout the duration of the study

Consent

The verbal and written consent was taken from all patients according to protocol approved by the appropriate Ethical Committee of Liaquat National Hospital and Herbion Pharmaceutical (Pvt.) Limited, Karachi, Pakistan.

Sample size

The sample size was approximately 200 patients. 110 patients were included in CartiNovex plus group and 90 patients were included in placebo group.

Adverse events

All adverse events that have been individualized or determined by patients were documented with information on the severity, onset, duration and measures related to the study drug. It was permissible the patient to willingly withdraw from the study, regardless of the reason. For patients who withdrew from the study, struggles have been done to determine the intention for desertion. Noncompliance (defined as no ingestion of less than 80.1% of medications) has not been established as a treatment failure and the reason for noncompliance.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS (version 22), sample paired T test were pragmatic and determined the statistical results. All variances were measured statistically significant by producing a p-value from test statistics. The noteworthy result with p-value less than 0.05 is considered as statistically significant.

Composition of CartiNovex plus tablet

CartiNovex plus tablet contains the powdered extract of hyaluronic acid, glucosamine sulphate, chondroitin sulphate, methyl sulfonyl methane, *Colchicum luteum*, *Boswellia serrata*, *Withania somnifera*, *Smilax chinensis*, *Zingiber officinalis* and *Curcuma longa*.

Ethical committee approval

This study is approved by the Ethical board of Herbion Pharmaceutical (Pvt.) Limited, Karachi, Pakistan.

RESULTS

A total of 200 male and female outpatients (n = 110 CartiNovex plus group; n = 90 Placebo group) were included into the study. None of patient stated any adverse or side effect of the study drug. Following symptoms of Osteoarthritis/Rheumatoid arthritis were evaluated after treatment with test drug and control drug, pain on sitting or lying, morning stiffness, pain on walking, stiffness in sitting, lying or resting later in the day, getting on/off toilet, light domestic duties (such as tidying room, dusting, cooking). Patient's age distribution; sex distribution and frequency distribution of CartiNovex plus group and placebo group are shown in fig. 1 and fig. 2 respectively.

Pain on sitting or lying

Pain on sitting or lying has been recorded in participants. Participants presenting with pain on sitting or lying was observed after treatment in both groups. In CartiNovex plus group 49.09% patients show complete improvement, 21.82% show moderate improvement, 16.36% show mild improvement and 12.73% show no improvement. In Placebo group 5.56% patients show complete improvement, 11.11% show moderate improvement, 27.78% show mild improvement and 55.56% show no improvement. The overall effects of CartiNovex plus and Placebo on pain on sitting or lying after treatment is shown in table 1 and fig. 3.

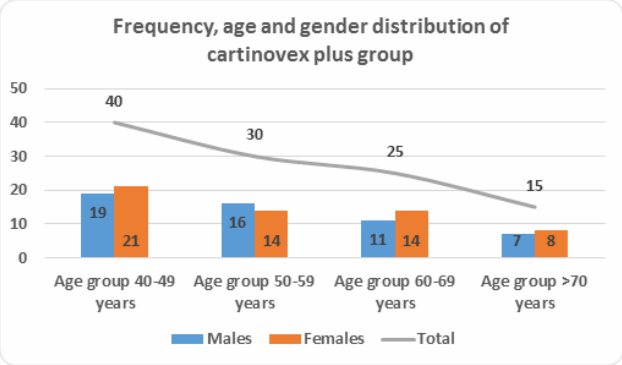

Fig 1: Frequency, age and gender distribution of CartiNovex plus group

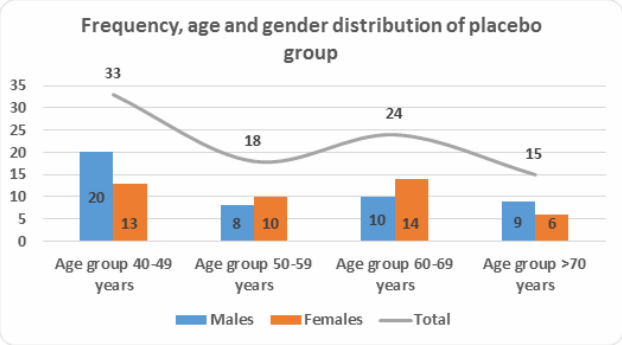

Fig 2: Frequency, age and gender distribution of placebo group.

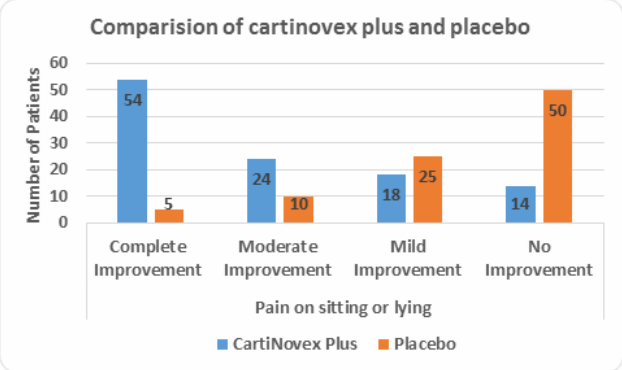

Fig 3: Comparison of pain on sitting or lying after treatment in CartiNovex plus and placebo groups

Morning stiffness

Morning stiffness has been recorded in participants. Participants presenting with morning stiffness was observed after treatment in both groups. In CartiNovex plus group 40% patients show complete improvement, 30.91% show moderate improvement, 18.18% show mild improvement and 10.91% show no improvement. In Placebo group 11.11% patients show complete improvement, 16.67% show moderate improvement, 33.33% show mild improvement and 38.89% show no improvement. The overall effects of CartiNovex plus and Placebo on morning stiffness after treatment is shown in table 2 and fig. 4.

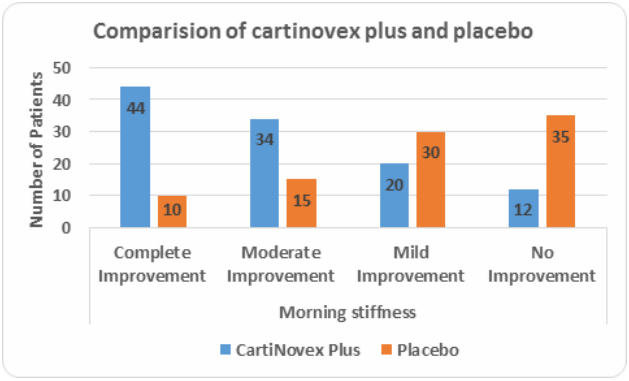

Fig 4: Comparison of morning stiffness after treatment in CartiNovex plus and placebo groups

Pain on walking

Pain on walking has been recorded in participants. Participants presenting with pain on walking was observed after treatment in both groups. In CartiNovex plus group 52.73% patients show complete improvement, 25.45% show moderate improvement, 12.73% show mild improvement and 9.09% show no improvement. In Placebo group 8.89% patients show complete improvement, 12.22% show moderate improvement, 36.67% show mild improvement and 42.22% show no improvement. The overall effects of CartiNovex plus and Placebo on pain on walking after treatment is shown in table 3 and fig. 5.

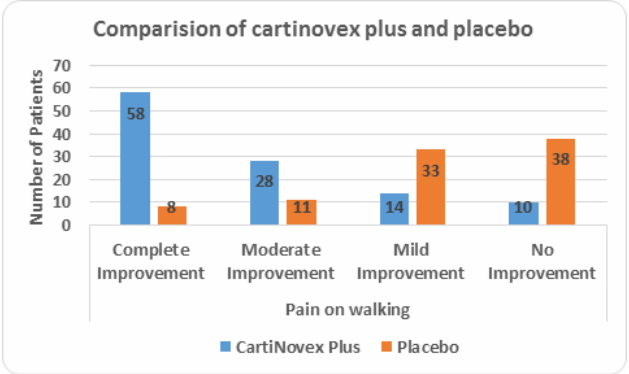

Fig 5: Comparison of pain on walking after treatment in CartiNovex plus and placebo groups

Stiffness in sitting, lying or resting later in the day

Stiffness in sitting, lying or resting later in the day has been recorded in participants. Participants presenting with stiffness in sitting, lying or resting later in the day was observed after treatment in both groups. In CartiNovex plus group 47.27% patients show complete improvement, 20.91% show moderate improvement, 18.18% show mild improvement and 13.64% show no improvement. In Placebo group 4.44% patients show complete improvement, 11.11% show moderate improvement, 33.33% show mild improvement and 51.11% show no improvement. The overall effects of CartiNovex plus and Placebo on stiffness in sitting, lying or resting later in the day after treatment is shown in table 4 and fig. 6.

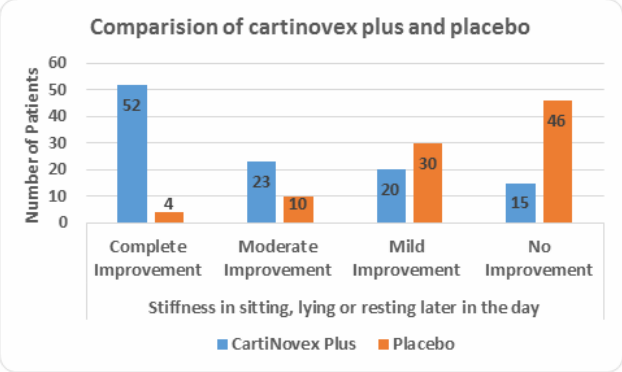

Fig. 6: Comparison of stiffness in sitting, lying or resting later in the day after treatment in CartiNovex plus and placebo groups

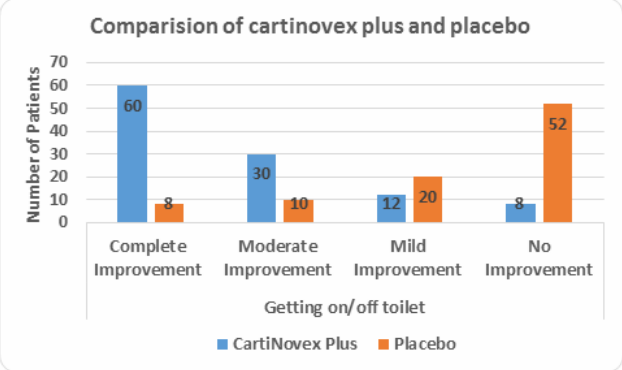

Fig. 7: Comparison of getting on/off toilet after treatment in CartiNovex plus and placebo groups

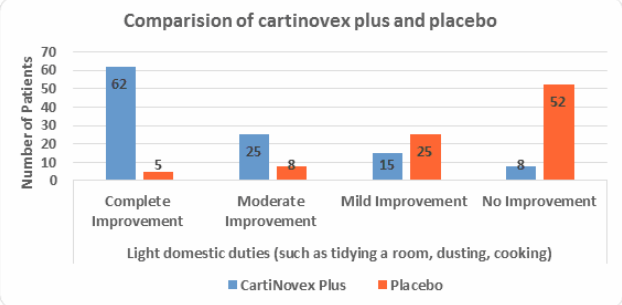

Fig 8: Comparison of light domestic duties (such as tidying room, dusting, cooking) after treatment in CartiNovex plus and placebo groups

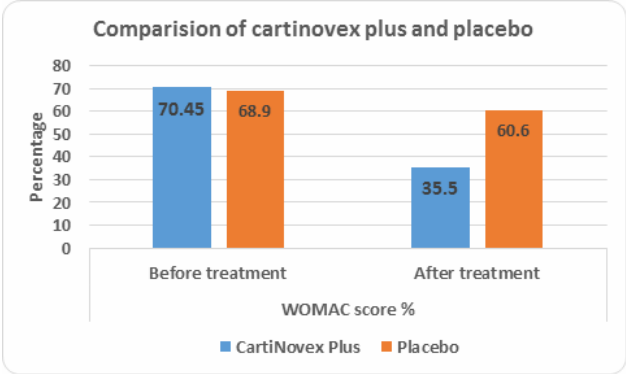

Fig. 9: Comparison of WOMAC score % before and after treatment in CartiNovex plus and placebo groups

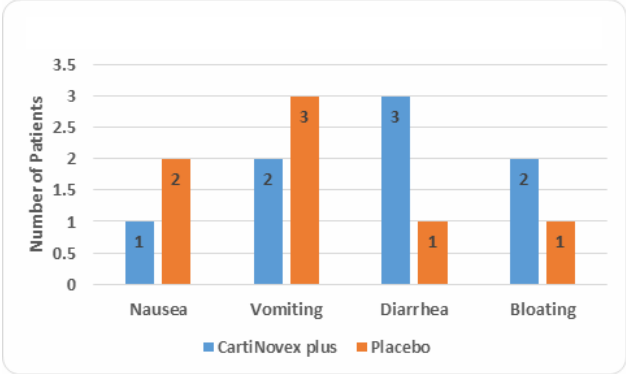

Fig. 10: Comparison of side effects in both groups

Getting on/off toilet

Getting on/off toilet has been recorded in participants. Participants presenting with getting on/off toilet was observed after treatment in both groups. In CartiNovex plus group 54.55% patients show complete improvement, 27.27% show moderate improvement, 10.91% show mild improvement and 7.27% show no improvement. In Placebo group 8.89% patients show complete improvement, 11.11% show moderate improvement, 22.22% show mild improvement and 57.78% show no improvement. The overall effects of CartiNovex plus and Placebo on getting on/off toilet after treatment is shown in table 5 and fig. 7.

Light domestic duties (such as tidying room, dusting, cooking)

Light domestic duties (such as tidying room, dusting, cooking) has been recorded in participants. In CartiNovex plus group 56.36% patients show complete improvement, 22.73% show moderate improvement, 13.64% show mild improvement and 7.27% show no improvement. In Placebo group 5.56% patients show complete improvement, 8.89% show moderate improvement, 27.78% show mild improvement and 57.78% show no improvement. The overall effects of CartiNovex plus and Placebo on light domestic duties (such as tidying room, dusting, cooking) after treatment is shown in table 6 and fig. 8.

Table 7: Comparison of pain on sitting or lying after treatment in CartiNovex plus and placebo groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P* value
Carti Novex Plus	54(49.09%)	24(21.82%)	18(16.36%)	14(12.73%)	.0001
Placebo	5(5.56%)	10(11.11%)	25(27.78%)	50(55.56%)	

Table 7: Comparison of morning stiffness after treatment in CartiNovex plus and placebo groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P* value
Carti Novex Plus	44(40%)	34(30.91%)	20(18.18%)	12(10.91%)	.0001
Placebo	10(11.11%)	15(16.67%)	30(33.33%)	35(38.89%)	

Table 7: Comparison of pain on walking after treatment in CartiNovex plus and placebo groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P* value
Carti Novex Plus	58(52.73%)	28(25.45%)	14(12.73%)	10(9.09%)	.0001
Placebo	8(8.89%)	11(12.22%)	33(36.67%)	38(42.22%)	

Table 7: Comparison of stiffness in sitting, lying or resting later in the day after treatment in CartiNovex plus and placebo groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P* value
CartiNovex Plus	52(47.27%)	23(20.91%)	20(18.18%)	15(13.64%)	.0001
Placebo	4(4.44%)	10(11.11%)	30(33.33%)	46(51.11%)	

Table 7: Comparison of getting on/off toilet after treatment in CartiNovex plus and placebo groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P* value
CartiNovex Plus	60(54.55%)	30(27.27%)	12(10.91%)	8(7.27%)	.0001
Placebo	8(8.89%)	10(11.11%)	20(22.22%)	52(57.78%)	

Table 7: Comparison of light domestic duties (such as tidying room, dusting, cooking) after treatment in CartiNovex plus and placebo groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P* value
CartiNovex Plus	62(56.36%)	25(22.73%)	15(13.64%)	8(7.27%)	.0001
Placebo	5(5.56%)	8(8.89%)	25(27.78%)	52(57.78%)	

Table 7: Comparison of WOMAC score % before and after treatment in CartiNovex plus and placebo groups

Level of Improvement	Before treatment	After treatment	*P* value
CartiNovex Plus	70.45%	35.5%	.0001
Placebo	68.9%	60.6%	

WOMAC score % has been recorded in participants. In CartiNovex plus group before treatment WOMAC score % was 70.45 and after treatment was 35.5%. In placebo group before treatment was 68.9% and after the treatment it was 60.6%. The overall effects of CartiNovex plus and Placebo on WOMAC score % before and after treatment is shown in table 7 and fig. 9.

Side effects

Some patients show side effects in both groups which are not significant. Side effects are shown in fig 10.

DISCUSSION

In spite of the fact that the specific biochemical reason of OA stays unidentified, it is connected with irritation in articular ligament, which can cause strange joint structure in the knee and hip and it is went with torment. The most widely recognized medications are analgesics and NSAIDs (Suokas, Sagar *et al*., 2014). Be that as it may, the medications have genuine unfavorable occasions in the gastrointestinal tract and cardiovascular system (Schnitzer, 2006). Consequently, herbal medications that can moderate the agony and aggravation have been

researched as potential essential or assistant treatments for easing joint inflammation side effects. Madhu *et al*. (Madhu, Chanda *et al*., 2013) stated in his study the use of curcumin and chondroitin sulfate for the treatment of OA. This investigation had four groups: placebo treatment, turmeric, chondroitin sulfate, and turmeric plus chondroitin sulfate. Turmeric and chondroitin sulfate both gave huge advantages by the two PVAS and WOMAC score, with turmeric performing fundamentally better. The most imperative commitment of this investigation, in any case, might be that it showed intense mitigating or potentially pain-relieving benefits for turmeric segments other than curcumin. Turmeric (C. longa) has a long history of safe use as sustenance and it has for quite some time been utilized as in calming treatment in Chinese and Ayurvedic medicine (He, Yue *et al.,* 2015). CartiNovex plus tablet contains the combination of curcumin and other potent anti-inflammatory herbal drugs due to that CartiNovex plus tablet showed very effective results in the treatment of both OA and RA with non-significant side effects.

CONCLUSION

OA and RA are the disease of old age and it is progressive in nature. CartiNovex plus shows the decrease in the progression of OA and RA and improve the life style of the patients compared with placebo group. It is a potential herbal drug for the patient of OA and RA. Its efficacy in reducing pain, physical function, and quality of life among OA and RA patients has been tested in this study. The effects of CartiNovex plus on OA and RA can be accredited to its ability to prevent apoptosis of chondrocytes due to inflammation predominantly, and oxidative stress to a lesser extent. The result of this study proved that CartiNovex plus tablet was very effective in the treatment of OA and RA. The CartiNovex plus tablet was safe and well tolerated in all patients and none of the patient reported any side effect. Large scale clinical trials with imaging studies are suggested for better understanding the use of CartiNovex plus as an alternate safe and cost-effective treatment for OA and RA.

ACKNOWLEDGEMENTS

We would like to thanks Mr. Nadeem Khalid CEO Herbion Pharmaceutical, Mr. Aamir Shahzad, Mr. Shariq Naveed, Mr. Mahmmod Sadiq, Mr. Sajjad Khan, Mr. Faheem, Mr. Naeem Akhtar, and all the staff of Liaquat National Hospital and all others who help to complete this study.

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