Studie zur Wirksamkeit von Kohlblattauflagen bei Arthrose des Kniegelenks

ARTICLE *in* ZEITSCHRIFT FÜR PHYTOTHERAPIE · FEBRUARY 2016

DOI: 10.1055/s-0041-109740

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Efficacy of cabbage leaf wraps in treating symptomatic osteoarthritis of the knee – A randomized controlled trial

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FUNDING SOURCE

This work was supported by a study grant from the Karl and Veronica Carstens-Foundation. The sponsor had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABSTRACT

Objectives: Osteoarthritis of the knee is one of the most common chronic diseases among older adults. This study aimed to test the effects of cabbage leaf wraps for treating symptomatic osteoarthritis.

Methods: Patients with osteoarthritis of the knee stages II-III (Kellgren-Lawrence) were randomly assigned to 4 weeks of cabbage leaf wraps (CLW, daily 2h min.), topical pain gel (TPG, 10mg diclofenac per g, once daily min.) or usual care (UC) respectively. The primary outcome measure was pain intensity (VAS) after 4 weeks. Secondary outcomes included functional disability (WOMAC), quality of life (SF-36), self-efficacy (ASES-D), physical function (30sec CST), pressure pain sensitivity (PPT), satisfaction and safety after 4 and 12 weeks.

Results: Eighty one patients were included in this study (42 females, 65.9±10.3years). After four weeks patients in CLW reported significant less pain compared to UC (difference -12.1; 95%CI: -23.1;-1.0, p=0.033) but not to TPG (difference -8.6; 95%CI: -21.5;4.4, p=0.190). Significant effects were also found for WOMAC, SF-36, 30sec CST and PPT in CLW compared to UC. Compared to TPG effects in CLW were found for WOMAC after 4 and for quality of life after 12 weeks. Patients were satisfied with both active interventions, and except for two adverse events in both groups the applications were well tolerated.

Conclusions: Cabbage leaf wraps are more effective for knee osteoarthritis than usual care, but not compared to diclofenac gel. Therefore they might be recommended to patients with osteoarthritis of the knee. Further research is warranted.

Trial registration: ClinicalTrials.gov, registry number: NCT02027792, URL: http://clinicaltrials.gov/show/NCT02027792

KEY WORDS

Osteoarthritis of the knee; Cabbage leaf wraps; Diclofenac; Randomized Controlled Trial; Efficacy

INTRODUCTION

Osteoarthritis of the knee is among the most common chronic diseases in the elderly largely influencing daily life [1]. About one fourth of people over 55 years reported a significant knee pain episode in the last year [2]. Osteoarthritis of the knee is characterized by articular cartilage destruction in addition to underlying bony changes at the joint margins [3]. Main complaints include pain and functional impairment, severely affecting patients' quality of life [4].

Conservative symptomatic treatment mainly consists of physiotherapy and pharmacological therapy [5, 6]. Self-care guides often recommend the use of wraps and compresses [7-9] however it was criticized that high quality trials are urgently needed before any conclusions can be drawn about such treatments [5].

One such treatment which has been used for centuries is the cabbage leaf wrap [10]. Cabbage leaves, preferably from white or savoy cabbage, are applied to the painful knee joint for several hours for pain relief. The health promoting qualities of cabbage have been known for centuries [10], and they are being used for a variety of complaints, e.g. breast engorgement

[11, 12]. But no studies have yet investigated the clinical potential of cabbage leaf wraps in patients with symptomatic knee osteoarthritis.

This study aimed to investigate the effects of cabbage leaf wraps compared to usual care and a topical pain gel to improve symptoms and quality of life in patients with knee osteoarthritis.

METHODS

Ethical approval and trial registration

The trial was conducted between September 2013 and July 2014 in the Department of Complementary and Integrative Medicine in Essen, Germany. The study had been approved by the ethics committee of the University Hospital Essen (approval number: 13-5581-BO) and registered at ClinicalTrials.gov (registry number: NCT02027792), prior to patient recruitment.

Design

This was a randomized controlled three-armed parallel group trial. The intervention group was taught to apply cabbage leaf wraps themselves, whereas the control groups received either usual care or a topical pain gel, see paragraph intervention. Written instructions were given to patients to explain the applications in detail. Each group received the allocated intervention for four weeks; measurements were conducted at weeks 0, 4 and 12. At the trial's end each patient received a financial reimbursement of 20 Euro.

Patients

Patients were recruited via local newspaper advertisements, with a medical student screening interested people by phone to assess their eligibility. Patients who met the inclusion criteria were invited for assessment where they were provided with detailed written information about the study and their written informed consent was obtained. The study physician checked patients' medical histories, examined their physical health, and checked patients' medical

records, e.g. laboratory findings, X-rays or MRI results. If patients met the inclusion criteria, and did not meet any exclusion criteria, they were included in the trial.

Trial participants were required to be at least 18 years of age and to have symptomatic knee osteoarthritis at stages 2 or 3 according to the Kellgren-Lawrence classification [13] confirmed by medical records.

They also had to report at least moderate pain of 45mm or higher on a 0-100mm visual analog scale (VAS) [14], with 100mm described as " worst knee pain imaginable".

The trial exclusion criteria included pain due to secondary arthritis (e.g. after an injury, inflammatory rheumatic diseases), prior injections with cortisone (within the past 4 weeks) or hyaluronic acid (within the past 6 months), prior operations to the knee (within the past 12 months) or any severe comorbidity such as liver or kidney diseases, asthma or psychiatric disorders. Finally pregnant or lactating women, patients recently using corticosteroids or immunosuppressing drugs or other wraps and poultices for the knee were excluded.

Randomization and allocation procedure

Patients were allocated to one of three groups in sequential order adopting a computer-generated (Random Allocation Software, version 1.0.0) non-stratified block randomization with varying block sizes. The trial coordinator who was not involved in patients' outcome assessments prepared sealed opaque envelopes. Envelopes were labeled according to the study participant's ID number and if patients were included in the trial, the envelope was opened in ascending order by the study physician to determine the intervention. Neither the patients nor the study physician were blinded to the intervention.

Interventions

After the baseline measurement and randomization patients received instruction and material for the respective intervention. All groups were allowed their usual care interventions except

for those listed in the exclusion criteria, but they had to record all concomitant therapies and medications in the daily log.

Cabbage leaf wraps (CLW)

Patients were instructed to apply cabbage leaf wraps once daily for four weeks. For the cabbage leaf wraps patients were advised to take 1-2 raw cabbage leaves, place it on a cutting board, cut out the hard stem, and bruise the leaves using a bottle or rolling pin. Leaves were then layered around the knee joint, fixed with a bandage and applied for at least 2 hours per day. It was suggested that the wraps were left on overnight. After removing the cabbage patients cleaned the knee with warm water. In rare cases of allergic reactions, i.e. swelling and itching sensation after application, patients were advised to resign from the application.

Topical pain gel (TPG)

This group was provided with a four week supply of a topical pain gel Voltaren® (by NOVARTIS), with its pharmacologic active agent diclofenac (10mg per g) and advised to rub in 1-4g of the gel up to four times daily for four weeks. After the study was finished, patients in this group were offered to receive instructions for the cabbage leaf wraps.

Usual care group (UC)

Patients in this group were advised to continue their usual activities and therapies including pain medication, but not to initiate any new therapeutic regimen for symptom management. After the study was finished, this group was offered to receive the cabbage leaf wraps or the topical pain gel as incentives.

Assessment

Patients' Expectation

At the assessment visit all patients rated their expectations that a cabbage leaf wrap or the topical pain gel would be successful to improve their knee pain on a 100mm VAS with 0mm described as ‘do not agree at all’ and 100mm described as ‘agree completely’.

Compliance

Compliance was determined using the daily log. Patients were considered compliant when they followed the instruction and carried out the active interventions on 80% of the days. Compliance was used for subsequent subgroup analyses.

Questionnaires

Current pain intensity was measured using a 0-100mm visual analog scale from the German Pain Questionnaire [15] with 0mm indicating ‘no knee pain at all’ and 100mm indicating ‘worst knee pain imaginable’.

Functional disability was assessed using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) [16, 17]. The WOMAC is a widely used standardized 24-item instrument to determine the impact of osteoarthritis on daily life on three subscales: pain, stiffness and physical functioning; and a global score. Each item is rated on an 11-point numerical rating scale; and the final scores range between 0 indicating ‘no complaints or difficulties’ and 10 indicating ‘extreme complaints or difficulties’.

Health-related quality of life was assessed using the Short Form 36 Health Survey Questionnaire (SF-36) [18]. This widely used comprehensive 36-item questionnaire yields an 8-scale health profile as well as two component summaries of physical and mental health-related quality of life.

Arthritis specific self-efficacy was measured using the German version of the arthritis self-efficacy short-form scale (ASES-D), an 8-item short form of the arthritis self-efficacy scale [19, 20]. The instrument is comprised of 8 items which are rated on a 10-point numerical

rating scale with 1 indicating ‘not confident at all’ and 10- indicating ‘absolutely confident’ being able to control symptoms and functional disability. The ASES-D results in one total score comprised of the average of all items [19, 20].

To measure physical function the 30-Second Chair Stand Test was applied. Patients sat in the middle of a chair and crossed their hands in front of their chest. On the signal they rose to a full standing position and sat back down again; and they repeated this as often as possible within 30 seconds. The number of full stand ups and pain intensity after the exercise were recorded [21].

Pressure pain sensitivity

Patients’ pressure pain thresholds (PPT) were measured using a digital algometer (Somedic AB, Hörby, Sweden) with a 1 cm^2 probe. Pressure was applied in increments of 40kPa/s until patients indicated a perception of pain in addition to pressure. They were measured bilaterally at three predefined sites; over the quadriceps muscle above the patella, on the pes anserinus and the lateral joint line of the knee; and unilateral at the most painful area at the painful knee. The averages of three measurements for each of these 7 locations were analyzed [22, 23].

Daily log

All patients used a log to record the intensity of their knee pain (VAS), whether they carried out the prescribed interventions and whether they took analgesics or received other osteoarthritis treatments. Analgesic consumption and concomitant treatments were analyzed by the frequency, and for analgesics also the defined daily doses were calculated [24].

Satisfaction with interventions

At the end of each phase patients were asked to judge how beneficial the respective treatment was, whether they would utilize this intervention in the future and whether they would recommend it to family or friends.

Safety

All adverse events were recorded. Patients experiencing such events were asked to see the study physician to assess their import and initiate any necessary response.

Primary and secondary outcome measures

The primary outcome measure was pain intensity after four weeks as measured by the visual analog scale (VAS). Secondary outcome measures included pain (VAS), functional disability (WOMAC), quality of life (SF-36) and self-efficacy (ASES-D) after four and 12 weeks; physical function (30 Seconds Chair Stand Test) and pressure pain sensitivity (PPT) after four weeks; and pain intensity (VAS) and medication from the daily log, compliance, satisfaction and safety.

Sample size calculation

For the primary outcome the average pain intensity at baseline of 59.3 ±16.2mm VAS was expected based on published data [25]. The estimated minimal clinical important difference was 19.9mm VAS. Given an effect size of d=1.045, and a two-sided 5% level t-test, 63 patients would be needed to detect this group difference with a statistical power of 90%. We planned to include 81 patients in this trial; recognizing a potential loss of analytical power due to patient withdrawal.

Statistical analysis

All analyses were based on the intention to treat population, i.e. each patient providing baseline data was included in the final analysis. Missing data were substituted with baseline data (baseline values carried forward). The analysis of the pressure pain thresholds and the chair stand test were based on the per-protocol population only.

Baseline data comparability was ensured using Student's t-tests for continuous data and x^2 test for categorical data.

The primary outcome was analyzed using an univariate analysis of covariance (ANCOVA) which modeled the post-treatment outcome as a function of treatment group (classified factor), and the respective baseline value (linear covariate). A stepwise gatekeeper analysis [26] was conducted to preserve the overall false positive rate; starting with the comparison CLW vs. UC; followed by CLW vs. TPG. Within this model the treatment effect was estimated, accompanied with a 95% confidence interval. The p-value was based on a two-sided t-test for superiority within this statistical model. For secondary outcomes the same statistical models were used, but all secondary outcomes were analyzed exploratively only. No alpha level adjustments were necessary to maintain the overall type I error rate of 5% [27, 28].

Results from the daily log were reported explorative; and no statistical analysis was conducted.

All analyses were performed using the Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, release 22.0. Armonk, NY: IBM Corp.).

RESULTS

Patients

From 207 patients initially screened by telephone, 115 patients were seen by the study physician, of whom 81 were enrolled. The most common reasons for excluding patients were not meeting the inclusion criteria, scheduling issues or lost interest in the study. Of the 81 patients enrolled, all were randomized and allocated to their intervention. During the four week intervention eight patients were lost to follow-up, three in CLW, one in TPG and four in UC. Reasons for drop outs included lost interest and adverse events. During the follow-up period another two patients were lost from UC due to time issues and lost interest. Since all patients provided baseline data, 27 patient data sets in each group could be analyzed (see figure 1 for CONSORT flowchart).

Baseline characteristics

Patients were 65.9±10.3 years on average; and 42 women and 39 men were included, see table 1. A large proportion of patients had an education below high school level, and most were retired. Only half of the patients reported receiving prior medication for symptom management, and even less had received physical therapy, surgical interventions or injections. Except for BMI no group differences were found at baseline.

Patients' Expectation

There were significant differences between the patients' expectations towards the study interventions, e.g. while the mean expectation towards CLW was 75.1±21.9mm VAS, it was 61.2±28.3mm for TPG (p=0.049).

Compliance

Figure 2 shows the percentage of compliant patients in the active groups over the study period. While compliance was highest at the beginning, it dropped to 80% in the last week. Altogether patients in both groups were highly compliant; 79.2% of CLW patients and 92% of TPG patients executed their respective intervention during the four week period on 80% of the days at least.

Outcome measures

Primary outcome measure:

At baseline, all groups had comparable pain intensity at around 40mm on a 0-100mm visual analog scale (p=0.824). Further analysis revealed a significant group difference between CLW and UC (difference -12.1, 95%CI:-23.1,-1.0, p=0.033) after four weeks, see table 2. No group difference was found between CLW and TPG (difference -8.6, 95%CI:-21.5,4.4, p=0.190), see table 3.

After four weeks eight patients in CLW, six in TPG and four in UC showed a pain reduction equally or higher than the estimated MCID [25]. After 12 weeks the corresponding numbers were eight, six and five.

Secondary outcome measures:

No difference in pain intensity between CLW and UC (difference -7.3, 95%CI:-19.0,4.3, p=0.210); or between CLW and TPG (difference -7.2, 95%CI:-20.9,6.5 p=0.290) could be found at 12 weeks.

Significant differences between CLW and UC could be found for all WOMAC scales after four and 12 weeks (table 2). When compared to TPG only the subscales pain and physical function and the global score showed significant group differences at four weeks in favor of CLW, table 3.

For quality of life the following effects were found, see table 2: physical functioning at four and 12 weeks (CLW>UC), vitality at four weeks (CLW>UC); bodily pain and the physical component summary at 12 weeks (CLW>UC). Compared to TPG the following effects were found, see table 3: physical functioning, physical role functioning, bodily pain and general health perception at 12 weeks (CLW>TPG), emotional role functioning (TP>CLW) at four weeks; and the physical component summary at four and 12 weeks (CLW>TPG).

For pressure pain thresholds significant differences were found for the quadriceps muscle and the pes anserinus with higher thresholds in CLW compared to UC; and at the quadriceps muscle compared to TPG.

The test on physical function revealed no effects on the number of stand ups, but on the pain afterwards in CLW compared to UC (table 2) or TPG (table 3).

Influence of compliance

When only compliant CLW patients were compared to UC the effect on the primary outcome remained significant (difference -12.5, 95%CI-24.7,-0.4, p=0.044). Compared to TPG however no difference was found (difference -8.2, 95%CI-21.5,5.2, p=0.223). As before no effects were found for 12 weeks (CLW vs. UC: -6.2, 95%CI-18.7,6.4, p=0.326; CLW vs. TPG: -4.9, 95%CI-18.6,8.8, p=0.475).

Daily log

A small but consistent decline in pain intensity was found in CLW and TPG, but not in UC (figure 3a). Analysis of other drug therapies shows (figure 3b) that 10-30% of the patients used analgesics sometime during the study; with patients in the CLW tending to use fewer analgesics than the control groups. The corresponding average daily doses of analgesics were low; between 0.00 and 0.15% of recommended daily dosage (figure 3c); with lowest daily doses in CLW. The rate of concomitant treatments was less than 15%, with no overall differences between the groups (figure 3d). The most frequently used interventions were: cool pads, craniosacral therapy (TPG), heat pads, physical therapy, acupuncture, radiotherapy (CLW), mud packs, or elastic therapeutic tapes (UC).

Satisfaction with interventions

Patients reported moderate benefit of both interventions after 4 weeks (CLW: 60.3±32.8mm; TPG: 45.7±35.1mm; p=0.188) and 12 weeks (CLW: 54.3±32.8mm; TPG: 38.4±32.3mm; p=0.128). After four weeks of use 75.0% and 70.8% of patients each reported that they would consider using CLW and TPG again (x^2, p=0.5); and 79.2% and 75% would consider recommending CLW and TPG to family and friends respectively (x^2, p=0.5).

Safety

The following adverse events were recorded during the study: one patient in UC developed bronchitis, and received antibiotics. One patient in CLW complained of dry cough, which resolved after discontinuation of ACE inhibitor intake. One patient in CLW complained of itching and burning during CLW application, and stopped the treatment. The same patient reported a zoster infection during the trial; and resigned from the study. One patient in the TPG group was diagnosed with spondylolisthesis; this patient reported back problems for several years. He received orthopedic therapy. Another patient in TPG was diagnosed with gastric ulceration; and even though the patient reported gastric problems for the previous 6 months a causal relationship could not be excluded. This patient resigned from further study participation. All patients were under medical treatment at their respective physicians.

DISCUSSION

This trial found that a 4-week application of cabbage leaf wraps was more effective than usual care regarding pain, functional disability and quality of life. It was however not superior to a 4-week application of topical pain. Patients were satisfied with both interventions, and except for two adverse events in both groups the applications were well accepted and tolerated.

Scientific evidence

Even though cabbage leaf wraps are often recommended as a self-care method for knee osteoarthritis, no controlled study had investigated its efficacy. Instead, only anecdotes had been published [29, 30] of single patients claiming that they experienced substantial improvement.

Cabbage leaf wraps however have been investigated in different conditions such as breast engorgement during breastfeeding [12, 31-33]. A randomized controlled trial [32] with 120 breastfeeding women found a tendency of less breast engorgement and longer breastfeeding

when using CLW compared to usual care. The results of the study are however limited by the short application and possible baseline differences. Others [34] also found a significant relief in breast engorgement and pain after CLW, but so did those patients receiving a cold or a hot compress. A recent Cochrane review [11] concluded that evidence was insufficient to justify widespread implementation of cabbage leaf wraps among others.

But cabbage leaf wraps are not the only herbal medicine available for osteoarthritis, several studies have investigated other topical treatments including a herbal ointment [35], ginger patches [36] or patches with Traditional Chinese herbs [37, 38]. Conclusive evidence however cannot be drawn from those studies. The study by Therkleson et al. [36]for example compared two ginger preparations with each other, and no comparison to usual care or a gold standard therapy was conducted. Besides herbal medicine other topical treatments may include mud packs which according to a recent meta-analysis were effective in reducing pain in patients with knee osteoarthritis [39].

In the present trial CLW was superior to usual care but no more effective than a topical pain gel. It is not clear how much of the observed effects were actually due to non-specific effects such as expectation or placebo. Further specific effects may include effects of the cabbage herbal compounds such as flavonoids and glucosinolates with anti-inflammatory properties [7]. Caplan [40] also referred to the drawing actions of plants (absorption); however no study has yet investigated details of such actions. All in all effects of cabbage leaf wraps compared to usual care were rather small but clinically relevant.

The advantages of cabbage leaf wraps are simplicity and low costs; and the good safety profile allowing for long-term application. Patients using CLW also reported they were very satisfied, therefore they might be recommended as a complement to conventional therapy or even an alternative in cases where drugs are contraindicated. The application might only be discouraged in patients with allergies.

Strengths and limitations

The strengths of the study include the randomized study design; and the use of different comparators. The low number of drop-outs, at least in the active intervention groups, and the overall high compliance also indicated that the tested interventions were well tolerated. Also concomitant treatments and medication were evaluated as proposed by the task force of the Osteoarthritis Research Society [41, 42].

Limitations include the lack of blinding of patients and physicians. Patients in the study had mild to moderate osteoarthritis of the knee, and its validity for progressed osteoarthritis can be questioned. According to the post hoc power analysis the sample size was also too small to reliably detect the actual moderate effect size on the primary outcome measure, with a power of 1-β being smaller than 40%. The sample size required to determine a significant group difference of moderate size with a power of at least 80% and the same effect size found in this study would be more than three times the sample size that was actually used. However the difference between cabbage leaf wraps and diclofenac was smaller than the minimal clinical important difference, on which the sample size calculation was based on. In further studies other test procedure should be used to determine equality of non-inferiority of interventions. Finally the use of sequential gatekeeping analyses might be discussed controversially, as those have been primarily used to test the efficacy of different drug doses in clinical trial.

Future studies

Many self-care treatments for knee osteoarthritis are being recommended, however only a few have been scientifically evaluated. Since active coping and patient empowerment are important parts of chronic disease management, future studies should investigate the efficacy and safety of such methods. Further studies on cabbage leaf wraps may include patients with more progressed osteoarthritis stages, or patients with knee pain of other origins. A blinded comparison to other leaves without expected pharmacological effects might also shed light

into the specificity of the effect. Last but not least studies using cabbage leaf wraps as an adjunct to systemic pain therapy could reveal additional or even dose-sparing effects of the intervention.

Conclusion

Cabbage leaf wraps are more effective in the management of knee osteoarthritis than usual care, but not than topical diclofenac gel. Therefore they might be recommended to patients with osteoarthritis of the knee. Cabbage leaf wraps appear safe and may be used on the longer term. Further research is warranted.

ACKNOWLEDGEMENT

The authors want to express their gratitude towards the nurses of the inpatient ward for their support in developing this trial. They also want to thank the Karl and Veronica Carstens-Foundation for supporting the trial financially. The following individuals are also acknowledged: Jana Hochstein and Yara Lia Keldenich for help with data management, Naima Khlef for help with patient recruitment and Kathrin Cillis who assisted in the physical examinations of the patients.

AUTHOR CONTRIBUTION

Responsible for (1) conception and design: Lauche, Cramer, Al-Abtah, Dobos (2) data acquisition: Romeikat, Lauche; (3) statistical analysis: Lauche, Cramer; (4) interpretation of data: Lauche, Romeikat, Cramer; (5) drafting the manuscript: Lauche; (6) critically revising the manuscript: Lauche, Romeikat, Cramer, Al-Abtah, Saha, Dobos. All authors have given final approval of the version to be published.

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FIGURE LEGENDS

Figure 1: Consort flow chart of patient recruitment

Figure 2: Average compliance during the 4-week study period, in % of users who applied the interventions as prescribed, %±SD

Figure 3: Data from the daily log including a) pain intensity ratings during the 4-week study period, measured by a visual analog scale (mean±SE); b) relative frequency of the usage of analgesics (other than study drugs) during the 4-week study period, %±SD; c) average defined daily dose according to the WHO of concomitant analgesics, mean±SD; and d) relative frequency of concomitant therapies (other than study interventions), %±SD

TABLES

Table 1: Baseline characteristics of trial patients according to study arms: cabbage leaf wraps (CLW), topical pain gel (TPG) and usual care (UC). Comparisons between groups made by Student's t-tests for continuous data and x^2 test for categorical data.

Item	**CLW**	**TPG**	**UC**	**p**
Age in years	62.5±11.9	66.7±9.7	68.5±8.6	0.092
Gender n (female) / n (male)	12/15	15/12	15/12	0.641
BMI in kg/m^2	29.2±6.1	31.4±6.0	27.0±4.0	0.015$
Education n (%)				
< High school	15	18	19	0.681
High school	3	2	3	
University degree	9	7	5	
Employment n (%)				
Unemployed	1	4	3	0.341
Employed	11	6	5	
Retired	15	17	19	
Ethnicity n (%)				
Caucasians n (%)	27	27	27	1.000
Previous therapies				
Medication n (%)	13	16	11	0.099

Physical therapy n (%)	11	9	7	0.752
Operation n (%)	6	7	6	0.644
Injection (e.g. hyaluronic acid) n (%)	9	10	10	0.881
Rehabilitation center n (%)	0	3	3	0.172

Legend: $-Significant group difference between TPG and UC

Table 2: Results of statistical analysis between cabbage leaf wraps (CLW) and usual care (UC).

Estimated group differences from the ANCOVA and 95% Confidence Intervals (CI) are presented.

	CLW			UC			Estimated group difference between CLW and UC at week 4 (95%CI)	p	Estimated group difference between CLW and UC at week 12 (95%CI)	p
	Week 0	Week 4	Week 12	Week 0	Week 4	Week 12				
Primary Outcome										
Pain intensity (VAS)	37.0±23.1	23.7±24.4	28.8±25.7	40.3±22.7	37.9±25.1	38.0±23.8	-12.1(-23.1;-1.0)	0.033	-7.3(-19.0;4.3)	0.21
Secondary Outcomes										
Functional Disability (WOMAC)										
Pain	3.9±1.8	2.6±1.9	2.9±2.2	3.1±1.6	3.3±1.8	3.3±1.9	-1.3(-2.1;-0.5)	0.002	-1.1(-1.9;-0.3)	0.009
Stiffness	4.9±2.3	3.9±2.7	3.9±2.5	3.9±1.8	4.2±2.1	4.3±2.1	-1.1(-2.0;-0.1)	0.031	-1,1(-2.1;-0.1)	0.039
Physical Function	3.8±1.9	2.9±1.9	3.0±2.1	3.6±1.5	3.9±1.8	3.8±1.9	-1.2(-1.9;-0.4)	0.003	-1.0(-1.8;-0.1)	0.026
Global Disability	3.9±1.8	2.9±1.9	3.1±2.1	3.5±1.5	3.8±1.8	3.8±1.9	-1.2(-2.0;-0.5)	0.002	-1.0(-1.8;-0.2)	0.017
MYMOP										
Mean	3.5±0.9	3.0±1.3	2.8±1.3	3.4±0.9	3.4±0.9	3.3±0.9	-0.5(-1.0;0.1)	0.084	-0.5(-1.1;0.1)	0.073
Self-Efficacy										
Self-Efficacy (ASES)	6.4±1.6	6.9±1.9	5.9±1.6	5.8±1.9	5.6±2.1	5.4±1.8	0.8(0.0-1.7)	0.059	0.1(-0.7;0.8)	0.847
Quality of life (SF-36)										
Physical component summary	36.2±8.6	40.3±7.9	40.7±10.2	35.8±8.2	37.1±7.0	35.9±8.2	2.9(-0.3;6.1)	0.072	4.3(1.3;7.4)	0.007

Mental component summary	54.2±10.6	54.4±10.6	51.6±12.1	55.0±9.3	53.6±9.5	54.5±10.6	1.3(-2.3;5.0)	0.467	-2.2(-6.2;1.8)	0.268
Physical functioning	51.9±23.1	59.1±21.5	60.2±24.7	53.1±18.9	50.6±16.0	52.2±18.7	9.4(3.1;15.8)	0.004	9.0(1.6;16.5)	0.019
Physical role functioning	52.8±40.6	70.4±38.6	58.3±42.7	46.3±46.6	58.3±42.3	52.8±42.9	8.3(-9.3;25.9)	0.347	0.7(-14.8;16.3)	0.924
Bodily Pain	46.9±13.2	52.5±19.1	55.9±18.9	44.8±14.2	48.7±17.2	43.6±15.7	2.4(-6.2;11.0)	0.581	10.7(3.1;18.2)	0.007
General Health Perception	62.3±20.4	65.3±19.6	66.0±21.4	63.0±13.4	61.9±13.5	60.9±13.5	4.0(-1.6;9.6)	0.159	5.7(-0.8;12.3)	0.086
Vitality	59.4±17.0	66.5±19.7	60.9±17.8	61.5±18.5	60.0±18.3	61.3±18.5	8.1(0.8;15.3)	0.030	1.4(-4.2;6.9)	0.626
Social role functioning	82.4±26.9	84.7±26.9	79.2±30.8	85.2±19.3	81.9±20.3	82.9±20.3	5.0(-2.9;13.0)	0.209	-1.2(-9.5;7.2)	0.777
Emotional role functioning	75.3±36.5	75.3±35.3	69.1±40.2	75.3±38.4	75.3±42.0	77.8±40.3	1.1(-15.1;15.1)	1.000	-8.6(-26.0;8.7)	0.323
Mental health	73.6±15.9	76.3±16.5	73.3±17.2	73.9±15.7	72.1±17.0	72.3±18.6	4.4(-2.0;10.7)	0.172	1.3(-4.1:6.8)	0.630
Chair stand test										
Number of sit ups	9.7±3.0	10.9±4.0	-	9.6±3.5	9.7±3.6	-	1.1(-0.2;2.3)	0.094	-	-
Pain	4.2±2.0	3.0±2.3	-	3.6±2.2	4.0±2.0	-	-1.4(-2.3;-0.5)	0.003	-	-
PPT										
Pain maximum	391.5±186.4	495.9±203.9	-	372.5±202.4	362.8±199.5	-	119.3(-4.9;243.4)	0.059	-	-
Quadriceps muscle	574.1±166.1	590.6±165.9	-	556.1±222.3	492.0±125.1	-	77.8(7.3;148.4)	0.033	-	-
Pes anserinus	439.0±202.0	498.1±167.7	-	375.0±194.6	343.7±175.2	-	127.1(32.8;221.5)	0.010	-	-
Lateral joint line	406.8±175.4	464.6±182.8	-	452.3±211.2	447.3±216.8	-	51.8(-56.6;160.3)	0.332	-	-

Table 3: Results of statistical analysis between cabbage leave wraps (CLW) vs. topical pain gel (TPG).

Estimated group differences from the ANCOVA and 95% Confidence Intervals (CI) are presented.

	CLW			TPG			Estimated group difference between CLW and TPG at week 4 (95%CI)	p	Estimated group difference between CLW and TPG at week 12 (95%CI)	p
	Week 0	Week 4	Week 12	Week 0	Week 4	Wee				

						k 12				
Primary Outcome										
Pain intensity (VAS)	37.0±23.1	23.7±24.4	28.8±25.7	40.7±25.3	35.2±25.7	35.0±22.5	-8.6(-21.5;4.4)	0.190	-7.2(-20.9;6.5)	0.290
Secondary Outcomes										
Functional Disability (WOMAC)										
Pain	3.9±1.8	2.6±1.9	2.9±2.2	3.6±1.9	3.4±2.1	3.4±1.7	-1.0(-1.8;-0.2)	0.013	-0.8(-1.6;0.0)	0.060
Stiffness	4.9±2.3	3.9±2.7	3.9±2.5	4.1±2.0	3.9±2.1	4.1±1.8	-0.6(-1.5;0.4)	0.223	-0.5(-1.6;0.5)	0.305
Physical Function	3.8±1.9	2.9±1.9	3.0±2.1	4.0±1.9	3.7±1.8	3.8±1.6	-0.8(-1.5;-0.0)	0.041	-0.7(-1.4;0.1)	0.077
Global Disability	3.9±1.8	2.9±1.9	3.1±2.1	3.9±1.8	3.6±1.8	3.7±1.6	-0.8(-1.5;-0.1)	0.031	-0.7(-1.4;0.1)	0.072
MYMOP										
Mean	3.5±0.9	3.0±1.3	2.8±1.3	3.6±1.1	3.3±0.9	3.3±0.9	-0.2(-0.8;0.3)	0.416	-0.6(-1.1;-0.1)	0.031
Self-Efficacy										
Self-Efficacy (ASES)	6.4±1.6	6.9±1.9	5.9±1.6	6.6±1.7	6.2±1.4	5.2±1.5	0.9(0.1;1.6)	0.031	0.8(0.0;1.6)	0.042
Quality of life (SF-36)										
Physical component summary	36.2±8.6	40.3±7.9	40.7±10.2	35.9±10.5	35.0±9.1	33.7±9.0	5.0(1.7;8.4)	0.004	7.8(4.1;11.7)	0.0001
Mental component summary	54.2±10.6	54.4±10.6	51.6±12.1	54.2±12.1	56.2±10.8	53.3±12.5	-2.5(-6.4;1.4)	0.209	-2.5(-7.6;2.6)	0.334
Physical functioning	51.9±23.1	59.1±21.5	60.2±24.7	44.8±24.4	47.6±21.4	45.9±17.4	7.0(-0.7;14.7)	0.074	12.0(3.1;20.8)	0.026
Physical role functioning	52.8±40.6	70.4±38.6	58.3±42.7	61.1±43.5	59.3±42.8	44.4±44.0	12.5(-4.6;29.6)	0.149	22.1(3.0;41.2)	0.024
Bodily Pain	46.9±13.2	52.5±19.1	55.9±18.9	43.2±21.5	42.7±17.5	41.5±19.7	7.3(-1.7;16.3)	0.110	13.7(4.9;22.6)	0.003
General Health Perception	62.3±20.4	65.3±19.6	66.0±21.4	63.6±19.4	61.3±16.6	58.6±19.8	5.4(-0.5;11.3)	0.071	8.9(1.2;16.6)	0.024
Vitality	59.4±17.0	66.5±19.7	60.9±17.8	63.0±19.2	60.0±18.3	61.3±18.5	5.9(-2.2;13.9)	0.151	5.3(-2.4;12.9)	0.173
Social role functioning	82.4±26.9	84.7±26.9	79.2±30.8	78.7±28.8	80.6±26.5	73.1±26.6	0.6(-9.6;10.9)	0.901	3.0(-8.1;14.1)	0.588
Emotional role functioning	75.3±36.5	75.3±35.3	69.1±40.2	71.6±41.0	85.2±33.8	75.3±39.9	-16.2(-30.0;-2.5)	0.022	-11.7(-31.4;8.1)	0.241
Mental health	73.6±15.9	76.3±16.5	73.3±17.2	73.8±18.9	74.5±17.2	70.4±22.7	1.8(-4.9;8.5)	0.588	3.4(-5.5;12.2)	0.449
Chair stand test										
Number of sit ups	9.7±3.0	10.9±4.0	-	8.4±4.2	10.3±3.3	-	-0.3(-2.0;1.3)	0.670	-	-
Pain	4.2±2.0	3.0±2.3	-	4.1±2.8	4.0±2.3	-	-1.3(-2.4;-0.1)	0.033	-	-
PPT										
Pain maximum	391.5±186.4	495.9±203.9	-	378.7±186.5	399.7±179.7	-	63.9(-50.5;178.	0.260	-	-

							3)			
Quadriceps muscle	574.1±166.1	590.6±165.9	-	557.2±200.6	504.0±131.0	-	90.2(5.0; 175.5)	0.039	-	-
Pes anserinus	439.0±202.0	498.1±167.7	-	408,7±205.2	414.2±193.5	-	66.4(-32.1;164.9)	0.179	-	-
Lateral joint line	406.8±175.4	464.6±182.8	-	446.1±192.3	436.2±167.0	-	11.2 (-95.0;117.3)	0.830	-	-

Figure 1

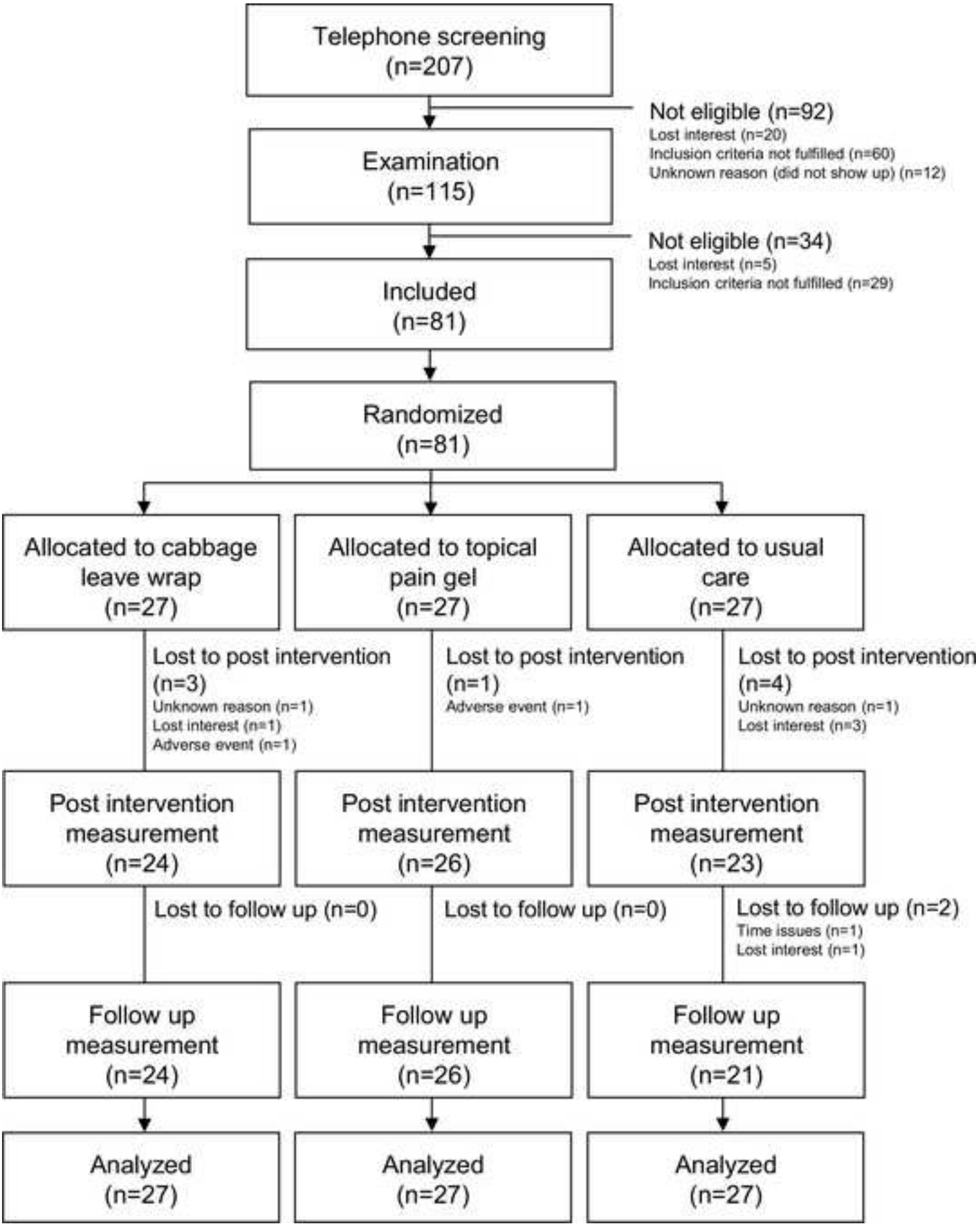

Figure 2

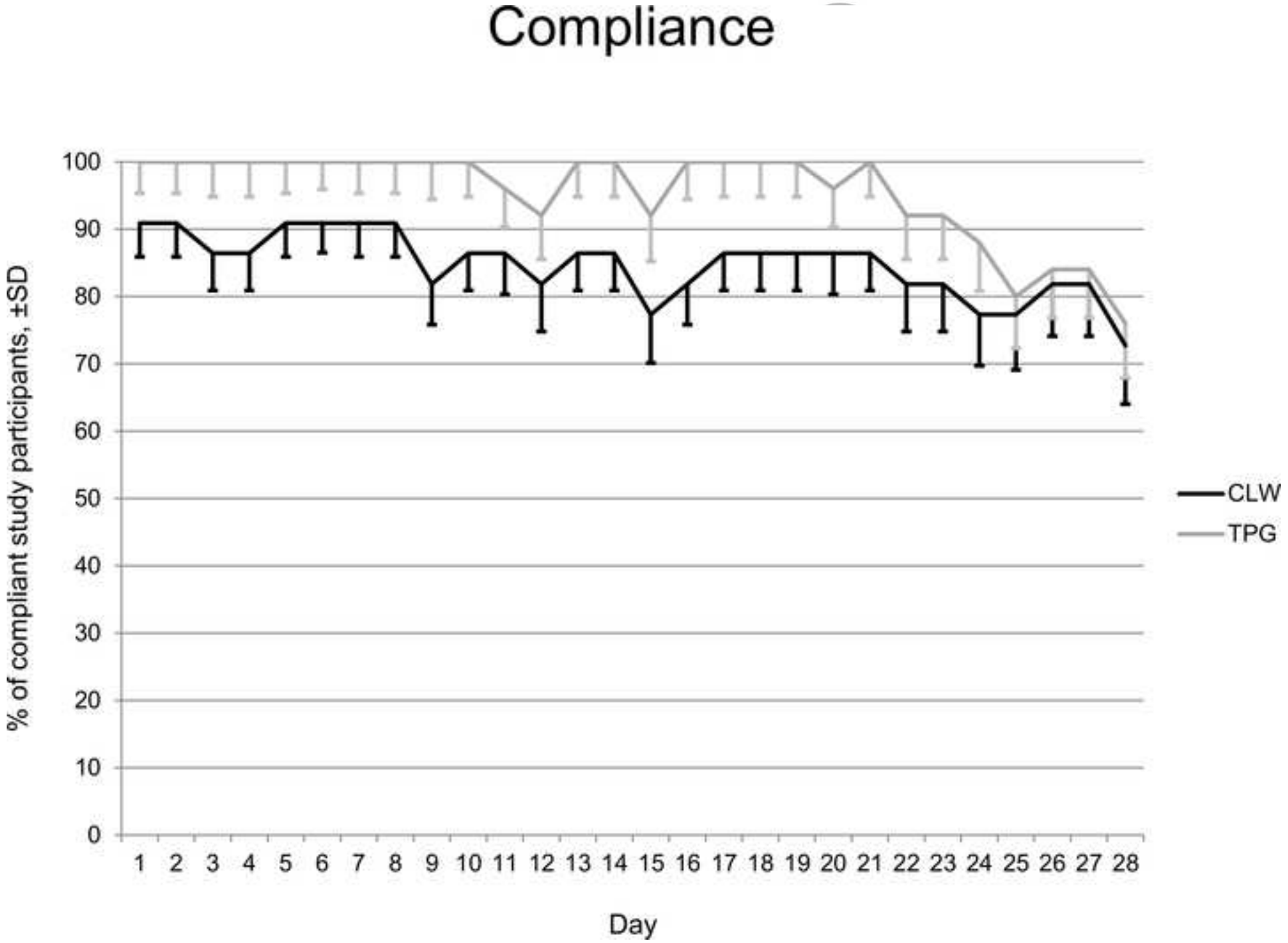

Figure 3