International Journal of Clinical Pharmacy
https://doi.org/10.1007/s11096-020-01113-1

RESEARCH ARTICLE

The impact of pharmaceutical care on the efficacy and safety of transdermal glucosamine sulfate and capsaicin for joint pain

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Received: 30 September 2019 / Accepted: 25 July 2020

Abstract

Background Arthritis is a common chronic joint disease. It progressively causes joint pain, stiffness, and disability. Glucosamine sulfate has been shown to be an effective symptom-relieving biological agent. Pharmaceutical care, including patient counseling, is very important to overcome inconsistencies in compliance and adherence. *Objective* The aim of this study is to evaluate the impact of pharmaceutical care on the efficacy and safety of transdermal glucosamine sulfate and capsaicin (TGC-Plus cream) in the management of chronic joint pain. *Settings* A rheumatology outpatient clinic, Jordan University Hospital, Amman, Jordan. *Methods* A cross sectional study with a single treatment group was conducted. One hundred (100) patients diagnosed with either osteoarthritis, rheumatoid arthritis or chronic joint pains were recruited. Patients started on TGC-Plus cream applied twice daily for duration of 12 weeks. Patients received pharmaceutical care services during the study duration. *Main outcome measure* Efficacy and safety of TGC-Plus cream in pain relief and joint function improvement (alleviating joint stiffness) the need of alternative analgesics and number of doctor's visits. *Results* There was a significant reduction of numerical pain score (7 ± 1.40 vs. 3.53 ± 2.13, $p < 0.05$), with significant reduction in the limitation of joint movement (6.18 ± 2.14 vs. 3.47 ± 2.23, $p < 0.05$) after 12 weeks. In addition, the need for analgesics and the number of doctor's visits were significantly reduced (1.99 ± 2.77 vs. 0.71 ± 1.90, $p < 0.05$), (1.11 ± 1.28 vs. 0.06 ± 0.293, $p < 0.05$) respectively. *Conclusion* Pharmacist supervised treatment with the TGC-Plus cream significantly reduces pain and enhances locomotor function in patients with chronic pain who failed to achieve adequate prior pain relief.

Keywords Glucosamine sulfate · Pharmaceutical care · Transdermal TGC plus

Impacts on practice

- Pharmacist counseling and monitoring of efficacy and safety of the transdermal glucosamine sulfate significantly improved the clinical outcomes.
- The combination of pharmaceutical care and transdermal glucosamine formulation seems to be a plausible alternative for patients with chronic joint pain who fail to achieve satisfactory pain relief otherwise.
- Pharmaceutical care plus transdermal glucosamine might be added to standard treatments of osteoarthritis and chronic joint pain to improve clinical outcomes.

Introduction

Arthritis is a degenerating joint disease that progressively cause musculoskeletal pain and disability worldwide [1]. Osteoarthritis (OA) and rheumatoid arthritis (RA) are the most common types of arthritis. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to manage arthritis symptoms [2]. Despite the widespread use of these medications to treat various pain types, they are associated with many adverse effects. The latter are dependent on the duration of NSAIDs therapy [2, 3]. Due to safety concerns, there is an urgent need to find effective and safe alternative pain treatments, especially for chronic pain. Glucosamine sulfate (GS) has been suggested to be an

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Published online: 09 August 2020

effective pain-modifying and disease-modifying biological agent [4]. Four randomized controlled clinical trials (RCTs) in which GS was compared to an NSAID, showed that GS was found to be as effective, or slightly more effective than NSAIDs [5]. Moreover, no serious adverse reactions were reported with the use of GS [5]. Further, several reports have suggested that GS might have anti-arthritic properties [6, 7]. It is believed that GS has a role in rebuilding the damaged cartilage by stimulating the production of proteoglycans by fibroblasts and chondrocytes [8]. Likewise, a plethora of experimental studies have demonstrated that GS can modulate the cytokine-mediated pathways regulating inflammation [9–11].

The efficacy of oral glucosamine supplements in reducing joint pain has been an area of debate. A network meta-analysis performed by Wandel et al. [12] in 2010 suggested that GS, chondroitin, and the two in combination, did not reduce joint pain or exert an impact on the narrowing of joint space when compared with placebo in patients with OA of hip or knee. On the other hand, a recent systematic review and meta-analysis of randomized placebo-controlled trials showed evidence of symptomatic efficacy of GS alone, or in combination with chondroitin, in the treatment of knee OA; especially their significant effect on pain relief and function improvement [13]. A randomized placebo-controlled study that included 51 RA patients, further indicated that the glucosamine administration resulted in noticeable improvements in symptoms without structural anti-rheumatic effects [14].

A possible confounding factor to the conflicting results pertaining to GS is the hepatic first-pass metabolism, which extensively affects the pharmacokinetic profile of orally administered GS. The transdermal preparation provides an advantage of delivering active drug molecules across the skin to the blood in a sustained manner for up to six hours [15]. It was shown that transdermal preparations containing glucosamine were effective in alleviating joint pain; supporting further clinical investigation of the use of transdermal route of GS administration [15]. TGC Plus cream is a high strength formulation that contains 10% weight/weight GS salt, which is the highest concentration available on the market, and 0.025% (w/w) capsaicin to provide powerful pain-relieving effects. Clinical evidence, however, is required to confirm the anecdotal evidence of efficacy for the TGC-Plus transdermal dual active ingredient system. In addition, pharmaceutical care and role of pharmacists in patient counseling are needed to overcome inconsistencies in patient compliance and adherence.

Aim of the study

The main aim of this study was to evaluate the clinical efficacy and safety of transdermal GS preparation in reducing pain in patients with chronic joint pain and the impact of pharmaceutical care on the clinical outcomes.

Ethics approval

The deanship of academic research at The University of Jordan granted necessary approvals of the study. Reference number (1954/2017/19). Patient information was confidential.

Methods

Design of the study

This was a prospective cross-sectional study with a single treatment group to evaluate the clinical efficacy and safety of TGC-Plus cream (SANA Pharmaceuticals, Amman, Jordan). The main ingredients of this cream were 10% w/w GS and 0.025% (w/w) capsaicin. The study was carried out in a rheumatology outpatient clinic, the Jordan University Hospital (JUH), Amman, Jordan. A total of 139 individuals were approached to participate in the study. The hypothesis was that using transdermal glucosamine would be effective in reducing pain symptoms regardless of the type of chronic joint pain disease. Hence, 100 patients diagnosed with OA, RA and chronic joint pain (not diagnosed with OA or RA) at least six months prior to the study were recruited. Other inclusion criteria included prior lack of pharmaceutical care services and failure to achieve satisfactory pain relief despite treatments with at least one oral and one topical analgesic preparation for not less than seven successive days. All recruited patients were on previous oral GS supplements, at a minimum daily dose of 500 mg, for at least three weeks; without achieving satisfactory joint pain relief. A washout period of 10 days was implemented for any participant who used topical or systemic analgesic drugs within two weeks prior to commencing the study. All patients signed an informed consent form prior to commencing the study.

Patients' treatment and outcomes measured

All recruited patients ($n = 100$) were started on TGC-Plus cream applied as one gram twice daily. The treatment period lasted for 12 weeks, with a scheduled weekly follow-up and

evaluation by experienced Pharm D clinical pharmacists. This included providing pharmaceutical care to the recruited patients; consisting of full review of the patients current and past medications, providing drug utilization reviews, medication therapy management, one to one patient counseling, compliance, adherence, the need for analgesics, the number of doctor's visits and any patient concerns. The primary clinical outcomes, including the effectiveness of pain relief; joint function improvement (alleviating joint stiffness); and safety (adverse effect), were evaluated at the beginning of the study (baseline) and after 12 weeks. Pain-relieving efficacy was defined as a reduction in pain severity by at least one category (i.e. severe to moderate) on the numerical pain score tool (a score of 0–10; 0 = no pain, 10 = worst pain). Severe joint stiffness was defined as stiffness lasting at least 60 min that prevents the individual from using the affected joint. Moderate joint stiffness was defined as stiffness lasting 30 to less than 60 min with marked difficulty moving the joint. Mild joint stiffness was defined as stiffness lasting less than 30 min and finally a category "none" was defined as no joint stiffness. In addition, limitation in joint mobility (score 0–10; 0 = no limitation; 10 = most limitation), was also assessed at baseline and weekly thereafter for the duration of the treatment. Safety was evaluated through documenting adverse reactions; including skin irritation or sensitization, or any other side effects reported by patients. Figure 1 summarizes patient recruitment and measured outcomes.

Data management and analysis.

Data was presented as numbers (n) or percentage (%). Results were shown as mean ± standard deviation (SD). For the statistical analysis of the data, statistical package for social science (SPSS version 16, Chicago, USA software) was used. For comparison of two normally distributed means t-test was used. If distribution of variables was not normal, the statistical analysis was conducted using Kruskall–Wallis followed by Mann–Whitney tests. A (P) value less than 0.05 was considered statistically significant.

Results

Characteristics of the patients

The baseline characteristics of the recruited patients ($n = 100$) are presented in Table 1. Most of the patients were women (69%), with a mean age of 53 years and a mean body-mass index of 30.4 kg/m^2. Most of the patients were diagnosed with chronic pain and knee OA for an average of four years. Less than half of the patients (37%) had neuropathic pain.

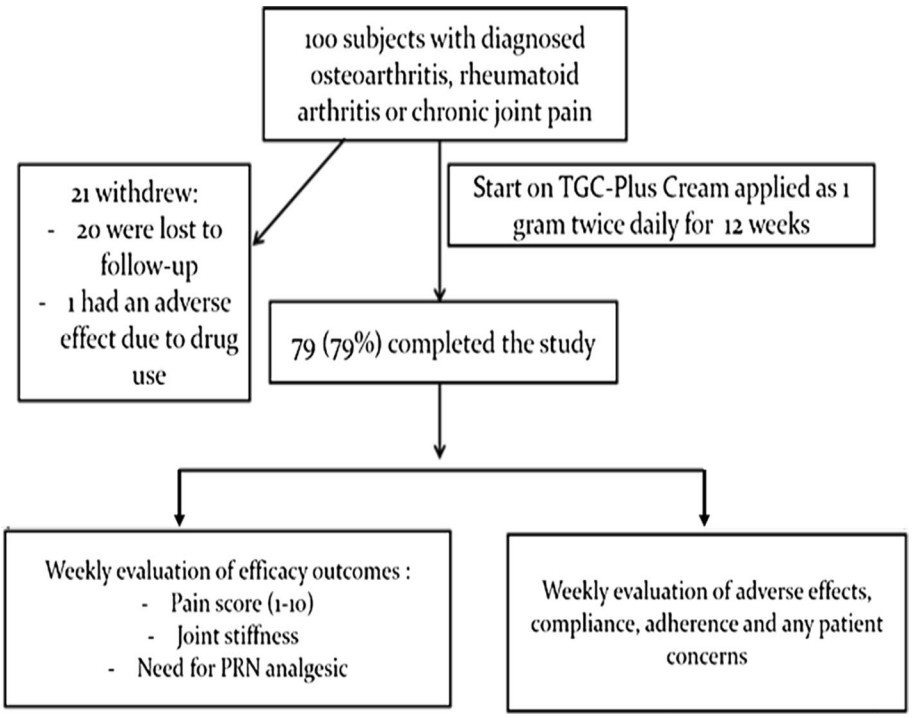

Fig. 1 Recruitment and outcomes. A total of 139 individuals were approached to participate in the study. However, 100 patients diagnosed with osteoarthritis, rheumatoid arthritis or chronic joint pain met the inclusion criteria of this study. At the end of the study, 21 individuals were lost to follow up and 79 subjects successfully completed the study

Table 1 Baseline Characteristics of the Patients

Characteristic	Recruited patients ($n=100$)
Mean Age(years) ± SD	53 ± 13.69
Gender-N (%)	
Male	31 (31)
Female	69 (69)
Marital status–N (%)	
Married	83 (83)
Single	6 (6)
Widowed	11 (11)
Mean Body-mass index (BMI) ± SD	30.4 ± 6.09
Smoking status-N (%)	
Smoker	21 (21)
Never-smoked	76 (76)
Ex-smoker	3 (3)
Education level-N (%)	
Elementary school or less	8 (8)
High school education	51 (51)
Bachelor degree or higher	41 (41)
Doing exercise-N (%)	11 (11)
Diagnosis-N (%)	
Chronic pain	49 (49)
Osteoarthritis	43 (43)
Rheumatoid arthritis	8 (8)
Average time since diagnosis(years)	4.52 ± 4.31
Affected joint-N (%)	
Knee	93 (93)
Hip	2 (2)
Wrists	3 (3)
Shoulders	1 (1)
Neck	1 (1)
Neuropathy-N (%)	37 (37)

Clinical outcomes

The clinical outcomes at the baseline of the study to the end of treatment were measured (Table 2). At the end of the study, 20 individuals were lost to follow up for personal reasons, one patient was lost to follow up due to hypersensitivity to glucosamine and 79 subjects successfully completed the study. The change in a specific clinical parameter from baseline to 12 weeks of treatment was calculated to determine the study outcomes. If the value of change in parameter is negative, it suggests a better treatment effect in terms of the clinical outcomes. As shown in Table 2, treatment with TGC-Plus cream for 12 weeks was effective in reducing pain and reducing the limitation in joint movement ($p<0.05$). In addition, the need for analgesics and the number of doctor's visits were reduced after treatment. Moreover, the value of change in effect was negative in all outcomes; suggesting that treatment with TGC-Plus cream was effective, and patients experienced a significant improvement in their symptoms when properly counseled and monitored by pharmacists. There was no need for a positive control group since the inclusion criteria included prior use of at least one topical and one oral analgesic for at least seven successive days without achieving satisfactory pain relief. For the same reason, no placebo group was needed considering that all the patients had been on at least one topical analgesic prior to the study as mentioned earlier.

Regarding morning and evening stiffness, treatment with TGC-Plus cream was effective in improving patient's symptoms. As shown in Fig. 2, the number of patients with mild morning stiffness at the baseline visit (16, 20.3%) was highly increased after a 12 week-treatment (30, 38%) (Fig. 2a). The numbers of patients with either moderate or severe morning stiffness were decreased after 12 weeks of treatment. A similar trend was observed for evening stiffness (Fig. 2b).

After five days of treatment most of the patients reported a noticeable reduction in joint pain (Table 3). The maximum analgesic effect was reached after 12 days of treatment. The average duration of analgesic effect, after each application, was 12 hours. TGC plus was well tolerated and only one patient of those who completed the study ($n=79$) reported mild skin irritation. On the other hand, most patients were satisfied ($n=69$, 87%) with the pharmaceutical care services provided to them along with the TGC plus treatment.

Table 2 Efficacy of treatment ($n=79$)

Outcome	Baseline	12 weeks	Change (Baseline vs. 12 weeks)	*P* value*
Mean numerical pain score (1–10) ±SD	7 ± 1.40	3.53 ± 2.13	− 3.47	1.52×10^{-28}
Limitation in joint mobility (1–10) ±SD	6.18 ± 2.14	3.47 ± 2.23	− 2.71	3.42×10^{-22}
Frequency of using additional analgesics to alleviate pain (times/week) ± SD	1.99 ± 2.77	0.71 ± 1.90	− 1.28	3.53×10^{-9}
Mean number of doctor's monthly visits	1.11 ± 1.28	0.06 ± 0.293	− 1.05	4.20×10^{-11}

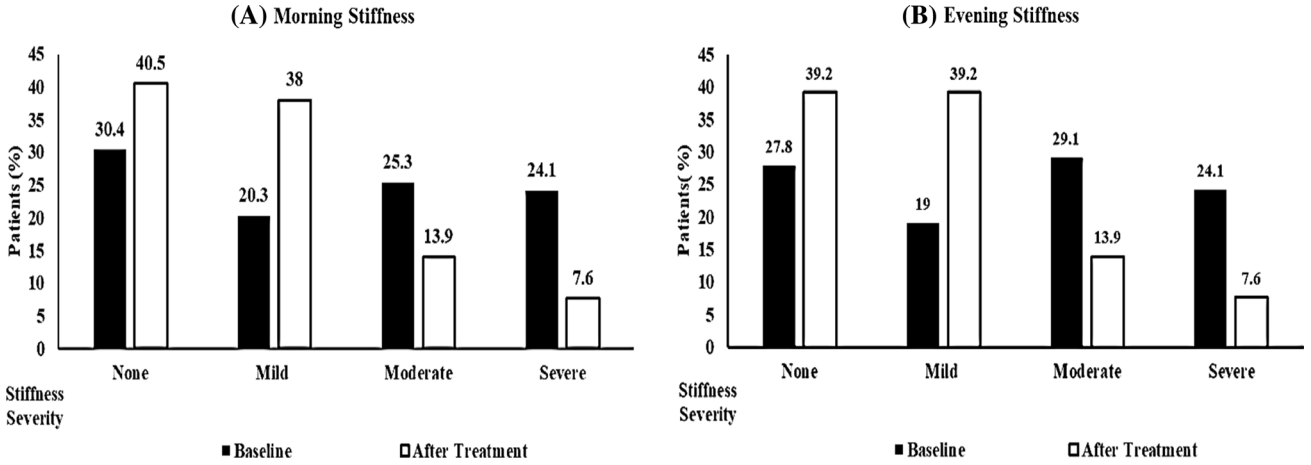

Fig. 2 Treatment effect on morning stiffness **a** and evening stiffness **b**. Percentage of patients ($n=79$) presenting with no stiffness (none), mild, moderate and severe stiffness as defined in the methods section at baseline (before treatment) and after treatment (12 weeks)

Table 3 Time efficacy of treatment

Evaluation criteria	Time (days)
Average onset of analgesic effect of TGC-Plus cream	5.43
Average duration of analgesic effect after application	0.5
Average time to maximum analgesic effect	12.1

Discussion

Transdermal glucosamine cream formulation delivers both glucosamine and capsaicin directly to joints and cartilage. Nonetheless, without pharmacist-supervised interventions the risks of inconsistencies in daily dosing, frequency, compliance and adherence to the medication could compromise the advantage of such enhanced transdermal delivery system. This is supported by the fact that 7 out of 79 patients who completed the study did use the TGC-plus cream prior to enrollment without achieving adequate relief. Those same patients achieved at least one level of pain severity reduction (at least severe to moderate or moderate to mild) in the current study.

Our results demonstrated that the TGC-Plus cream was effective in alleviating pain, stiffness and the limitation in joint mobility in the recruited patients when combined with professional pharmaceutical care services. Interestingly, under such circumstances TGC-Plus cream was effective in alleviating joint pain regardless of the severity of the pain. Moreover, the efficacy of the TGC-Plus cream treatment was not affected by the clinical duration of joint pain prior to commencing the treatment or the patient's age or co-morbidities. Interestingly, TGC plus was effective in most patients, despite the fact that those same patients had previous combinations of oral and topical analgesics without achieving satisfactory joint pain relief.

The TGC-Plus cream was very well tolerated when used as recommended. There was only one patient, among those who completed the study, who had mild skin irritation after starting the treatment but resolved shortly after the first week. In fact, this patient admitted to applying more than the recommended dose of one gram twice daily in the first week of his treatment despite being counseled by our pharmacists on the proper administration of the drug. Clinical improvement in joint pain was documented within five days of commencing the treatment and reached the maximum pain relief after 12 days. This is an advantage over the oral preparations containing glucosamine that usually take several weeks before any clinical improvement is attained. Likewise, it's an advantage over topical or oral NSAIDs since most clinical practice guidelines recommend a 2–4-week trial of the NSAID, before judging its effectiveness or switching to another NSAID.

After reaching the maximum analgesic effect of the TGC-Plus cream, the pain relief was maintained with no reported breakthrough pain, fluctuation of its effects or therapy failure for the full duration of the treatment. This analgesic action resulted in a reduction in the average monthly doctor's visits and the weekly frequency of using additional oral analgesics for joint pain, by more than 99%. The reduction was most noticeable in patients with severe joint pain, but it was documented in all patient groups, regardless of the pain severity or the type of joint disease. In addition to the 10% w/w glucosamine sulfate salt, the TGC-Plus cream contains 0.025% (w/w) capsaicin. The latter is a powerful natural analgesic that helps in controlling peripheral nerve pain. Therefore, the efficacy of the cream in reducing joint pain in patients with neuropathies, might be attributed to dual effects of glucosamine and capsaicin.

The fact that both nociceptive and neuropathic types of pain were alleviated by a single preparation, in accordance

with professional pharmaceutical care, is a huge incentive for patient compliance and adherence. The latter was reflected by an overall patient satisfaction with the treatment that exceeded eighty seven percent, among patients who completed the study in both genders. Future work is mandated to investigate the safety and clinical benefits of administration of transdermal glucosamine sulfate either alone or in fixed-dose combinations beyond the 12-weeks period.

Strengths and limitations

The main strengths of the study were the inclusion of professional pharmaceutical care services; to maximize the benefits of TGC-Plus cream; the inclusion of patients with different chronic joint pain, with different levels of pain and the use of scores to quantify the clinical outcomes. Further, we only included patients who had not achieved satisfactory pain relief despite receiving oral and topical treatments. This population of patients is more challenging to treat in clinical practice, and alternative treatments or approaches are desperately needed. Indeed, polypharmacy and nonadherence/noncompliance issues seem to cause a rise in the prevalence of this category of patients. To our best knowledge, this is the largest clinical study to evaluate the impact of pharmaceutical care and transdermal glucosamine sulfate with capsaicin for the management of chronic refractory joint pain. The main limitation is that the study was conducted for only 12 weeks. Long term effectiveness and safety have not been evaluated.

Conclusions

The combination of professional pharmaceutical care and transdermal glucosamine sulfate-capsaicin seems to be a good alternative to NSAIDs, in alleviating joint pain in patients with OA or other chronic joint pain disorders who failed to achieve satisfactory pain relief on oral glucosamine supplements, or topical/oral analgesics and NSAIDs. TGC-Plus cream was well tolerated and resulted in statistically significant and clinically relevant improvement, with onset of action and time to maximum response, that are advantageous compared to common topical and oral NSAIDs.

Funding No external funding was needed to conduct and complete the study.

Conflicts of interest All authors stated that there was no conflict of interest regarding the study design and publication of the manuscript.

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