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Research Article

A TRANSDERMAL GLUCOSAMINE FORMULATION IMPROVES OSTEOARTHRITIC SYMPTOMS IN AN OPEN CLINICAL SURVEY

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ABSTRACT

Objective: To evaluate the efficacy and safety of a new transdermal formulation of glucosamine in the treatment of osteoarthritis (OA).

Method: Forty four (44) patients with mild to moderate OA attending 16 different outpatient clinics in Singapore were recruited into the 4-week study. Three criteria were used to quantify the severity of disease activity evaluated before and after treatment with one gram (3 times daily) of Urah transdermal glucosamine (UTG) cream formulation viz: Ritchie articular index (RAI), functional disability assessment [Doctor's Evaluation of Health status (DEH)] and arthritis self-efficacy scale [Patient's Assessment Questionnaire (PAQ)].

Results: After four weeks, UTG treatment was observed to improved RAI pain score from the baseline (day 0) in all demographic group and further enhanced functional abilities. Overall, 59% of the patients had a good opinion rating for this transdermal formulation and showed beneficial effects. Efficacy appeared to be related to the site of arthritis with 100% of patients having arthritis of the shoulders reporting beneficial effects of UTG therapy as opposed to 75% of patients with ankle, wrist and elbow OA and 58% of knee OA respectively. Additionally, compliance to treatment was observed to be over 95% and there were no reports of adverse reactions and no skin irritations were observed at any time point. **Conclusion**: Urah Transdermal Glucosamine Cream significantly alleviated pain in arthritic joints when applied over four weeks suggesting an improvement in the quality of life. This results support further clinical trial into the use of transdermal route of administration of glucosamine.

Keywords: Osteoarthritis, Transdermal, Glucosamine, Route-Efficacy

INTRODUCTION

Despite recent advances in the medical sciences, arthritis, a chronic degenerative disorder of multifactorial aetiology, continues to be the most common musculoskeletal disorder in clinical practice and a leading cause of pain and handicap in many countries. Approximately 43 million Americans (ie 16.6% of the US population) are known to be afflicted by one form of arthritis or the other [1]. In Japan, Yoshimura et al reported prevalence of osteoarthritis (OA) of the knee in 25 million Japanese representing 30% of the population [2]. Zhang et al examined 1,787 Chinese residents of Beijing and reported prevalence of radiographic knee OA as 42.8% in women and 21.5% in men [3]. The high prevalence of this potentially disabling disease often translates into significant economic and socio-cultural implications to patients and the society at large, accounting for 25% of visits to primary care physicians and half of all nonsteroidal anti-inflammatory prescriptions in the United States of America [4].

Current treatment of OA is limited to palliation through the use of analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), and the cyclo-oxygenase-2 (COX-2) inhibitors [4]. The failure of these conventional medications to satisfactorily treat OA has resulted in increasing search for superior treatment options. Many OA patients resort to the use of unconventional treatment methods such as herbal or self-medication [5], spa treatments [6], and painful intra-articular injections [7].

In recent years, glucosamine has been increasingly endorsed putatively as an over-the-counter remedy for OA, with estimated annual sales exceeding $700 million in the United States alone [8]. Although several laboratory studies have shown glucosamine to be good chondro-protective agent [9], many reported human clinical studies on orally administered glucosamine formulations have not shown results complementing these laboratory findings [10]. A multicenter oral glucosamine clinical trial published in 2006 by the American National Institute of Health concludes that glucosamine and chondroitin sulphate alone or in combination did not effectively reduce pain in the overall group of patients with osteoarthritis of the knee [11]. This contrasting report between laboratory and clinical findings has done little to assuage skepticism on the therapeutic efficacy of glucosamine therapy among patients and doctors.

Although oral ingestion continues to be the popular route of administration of glucosamine, studies have suggested that effective intra-articular concentrations may not always be achieved by oral route [12]. A number of recent studies in horses and humans have quantified the serum levels of free glucosamine after administration of clinically relevant dosages [13, 14]. These studies observed low bioavailability. They concluded that insignificant trace amounts of glucosamine enter human serum after oral ingestion and that this amount is far below any amount that could make significant therapeutic contribution. In addition to low bioavailability, oral ingestion of glucosamine compounds is limited by other side effects such as gastric irritation, nausea and gastric ulceration. A research report has suggested that though glucosamine may indeed have anti-arthritic properties but the route of administration may be the key to attaining the necessary physiological concentration of glucosamine to take full advantage of its potential effects [15]. This notion of a route-efficacy relationship in glucosamine therapy is further supported by the results of a clinical evaluation of a topical preparation containing glucosamine (30mg/g), chondroitin (50mg/g), shark cartilage 140mg/g), camphor (32mg/g) and peppermint oil (9mg/g) [16]. However, the current clinical skepticism on glucosamine seems to hamper wider clinical research on the effects of the routes of administration on glucosamine treatments.

Recently, a Transdermal Glucosamine Cream (TGC) formulation containing 80 – 100 mg/g of glucosamine compound was introduced as an alternative to oral glucosamine. However, no independent clinical evaluation on the efficacy and safety of the formulation has been reported. This survey was therefore designed as a preliminary evaluation of efficacy and safety of this new formulation of glucosamine.

MATERIALS AND METHODS

Study Design and Patients

A total of 44 patients were recruited at 16 out-patient clinics spread across Singapore. These patients had been diagnosed with OA prior to the survey by the physicians in the respective out-patient clinics. The exclusion criteria used are: known hypersensitivity to glucosamine; severe organ or systemic diseases; and open wound around the arthritic joint; pregnancy or lactating. Demographic and

baseline data collected were age, sex, occupation, history and location of pain, Ritchie articular index baseline score, information regarding other illnesses, and use of other drugs. Patients were seen weekly by the physician for 4 – 8 weeks.

Urah Transdermal Glucosamine (UTG) cream used in this study was manufactured under GMP conditions and contains 8% w/w glucosamine sulphate 2KCl. Patients were instructed to apply approximately 1 g of the cream three times daily to each of the affected joints. If both knees were affected, both were treated and evaluated. Treatment compliance was estimated by collecting finished tubes before issuing new tubes. Patients were not given specific additional instructions with regard to exercise or any restriction of activities.

Table 1: shows a modification of Ritchie articular index (mRAI) used to evaluate the status of arthritic symptom in patients

a) Modified Ritchie Articular Index (mRAI)

Pain	Score
No pain	0
Slight pain	1
Moderate pain	2
Severe pain	3

b) Patients Assessment Questionnaire (PAQ)

Pain	Score
No relief	1
Slight relief	2
Moderate relief	3
Complete relief	4

Outcome score was measured as the difference between the recruitment/baseline and the end-point score on the mRAI scale. The outcome scores are rated as Excellent (>2.5); Good (1.5 to 2.4); Fair (0.5 to 1.4); Useless (0 to 0.4) and Worse than useless (<0).

Ritchie's pain score and functional disability evaluation

At baseline and on each follow-up (weekly) visit, the investigators assessed the severity of disease activity using the modified Ritchie articular index (mRAI) [17], functional disability score [Doctor's Evaluation of Health status (DEH)] and Patient's Assessment Questionnaire (PAQ) [18], as given in Table 1a&b.

RESULTS AND DISCUSSION

The sex distribution among the 44 OA patients recruited for this survey was even (1:1 male:female ratio). Forty two (42) patients completed the minimum 4-week requirement of the clinical survey representing 95.5% compliance. Over 63% (28/44) of the patients were below the age of sixty. Over 56% (25/44) had a history of arthritis lasting less than one year duration or early stage arthritis (Table 2). The severity of arthritic symptoms before and at each follow up visits was documented and graded adopting a modification of the Ritchies Articular index and according to the Patients Assessment Questionnaire (Table 1a and b).

Over the minimum four weeks treatment period, all demographic groups of patients indicated a relative improvement of symptoms from base line and expressed favourable opinion to the use of UTG (Table 2 and 3).

Table 2: Shows general opinion rating of the treatment outcome

	Good opinion					Poor opinion			
	Total number	**Excellent**	**Good**	**Fair**	**Good opinion**	**Useless**	**Worse than useless**	**Poor opinion**	**Safety**
Male	22	2	4	9	68.2%	7	0	31.8%	22 (100%)
Female	22	0	4	7	50%	10	1	50%	22 (100%)
<65yr old	28	0	3	13	57.14%	12	0	42.86%	28 (100%)
>65yr old	16	2	5	3	62.5%	5	1	37.5%	16 (100%)
<1yr pain duration	25	0	3	8	44%	13	1	56%	25 (100%)
1-3yr pain duration	10	2	1	5	80%	2	0	20%	10 (100%)
>3yr pain duration	9	0	4	3	77.8%	2	0	22.2%	9 (100%)
	Total Good Opinion		**26**		**59%**	**Total poor opinion**	**18**	**41%**	

Overall, 59% of the patients had a good opinion rating for the transdermal formulation (Table 2). The most favourable opinion (80%) was expressed by patients with arthritic pain duration ranging from 1-3 years closely followed by patients with over 3 years arthritic symptoms. Fewer early stage patients (44%) who had arthritis lasting less than 1 year expressed favorable opinion when compared with later stage (1-3 years and greater than 3 years duration) patients. This finding was interesting and unexpected.

The exact reason underlining this finding is not immediately known. However, it could be related to the physical activity levels of patients as longer history of arthritis is expected to be associated with lower activity levels, being a progressing and disabling disease. Lower activity level or resting of the affected joints while applying medications could enhance recovery and regenerative ability of the joint. This deduction calls for further investigation.

Although UTG cream was found to be beneficial and relieved arthritic symptoms irrespective of the affected joint, Table 4 shows that patients with shoulder, neck or back pain expressed the highest level of satisfaction with UTG cream (100%) while those with knee symptoms were least relieved (58%). This further highlights the importance of joint activity levels and the potential regenerative ability of glucosamine. Besides the shoulder joint which connects the appendicular to the axial skeleton, the neck, back and knee are all in the axial skeleton. Expectedly, the knee carries larger passive weight than the shoulder, neck and back. This could, at least ins part, explain this observation of higher relieve for shoulder, neck, and back joints when compared to knee.

Table 3: Shows patient's demographic, treatment and outcome data

	Sex		Age range		Duration of pain before UTG treatment				Outcome	
Patient S/N	**Male**	**Female**	**≤65yrs**	**Above 65yrs**	**Less than 1yr**	**1-3yrs**	**More than 3yrs**	**Duration of treatment**	**Outcome score**	**Rating**
1	x			x		x		6 weeks	3	Excellent
2	x			x	x			4 weeks	2	Good
3	x			x		x		8 weeks	1.5	Good
4		x		x			x	6 weeks	2	Good
5	x			x		x		8 weeks	2.5	Excellent
6	x			x			x	8 weeks	2	Good
7		x		x			x	8 weeks	2	Good
8		x	x		x			8 weeks	2	Good
9	x			x			x	4 weeks	1	Fair
10	x			x		x		8 weeks	1	Fair
11	x			x	x			8 weeks	0	Useless
12		x	x		x			8 weeks	1	Fair
13	x		x		x			6 weeks	0.5	Fair
14	x		x		x			4 weeks	0.5	Fair
15	x		x		x			4 weeks	0.5	Fair
16	x		x		x			6 weeks	0	Useless
17	x			x			x	8 weeks	0	Useless
18	x		x			x		8 weeks	0.5	Fair
19		x	1				x	8 weeks	0	Useless
20	x		1				x	8 weeks	0.5	Fair
21		x	1			x		8 weeks	0	Useless
22	x		1		x			8 weeks	0.5	Fair
23	x		x			x		8 weeks	0.5	Fair
24		x	x			x		8 weeks	0.5	Fair
25	x		x		x			8 weeks	0	Useless
26		x	x		x			6 weeks	0	Useless
27		x	x		x			4 weeks	0	Useless
28	x		x		x			8 weeks	0	Useless
29		x	x		x			8 weeks	0	Useless
30		x		x	x			1 week	0	Withdrawn
31		x		x	x			1 week	0	Withdrawn
32	x		x		x			4 weeks	0	Useless
33		x	x		x			6 weeks	0.5	Fair
34		x	x		x			6 weeks	0	Useless
35	x		x		x			6 weeks	0	Useless
36	x		x		x			8 weeks	2	Good
37		x		x		x		8 weeks	0	Useless
38		x	x		x			8 weeks	0	Useless
39		x		x	x			8 weeks	-1	Worse
40		x	x		x			8 weeks	1	Fair
41		x		x			x	8 weeks	1	Fair
42		x	x			x		8 weeks	1	Fair
43		x	x				x	8 weeks	1.5	Good
44		x	x		x			8 weeks	1	Fair
TOTAL	**22**	**22**	**28**	**16**	**25**	**10**	**9**			

Table 4 shows opinion rating of the treatment outcome based on site of pain

Location of Pain	Total (n)	Good opinion (%)	Poor opinion (%)
Knee	33	58	42
Ankle	8	75	25
Shoulder/Neck/back	4	100	0
Wrist/Elbow	4	75	25

Of particular interest is the safety report. There were no reports of adverse reactions and no skin irritations were observed at any time point. This further underlines the advantages of transdermal over oral route of administration. Similarly, the high level of compliance observed in this survey could be due to the absence of gastrointestinal side effects often reported for acidic formulations.

The use of micelle and nanotechnology in enhancing bioavailability of poorly soluble drugs is gaining popularity in research and the pharmaceutical industry [19-21]. This has provided therapeutic agents that could be administered to patients via routes other than the traditional oral or parenteral routes. One such alternative route that could be very beneficial for therapeutic agents with traditionally low bioavailability is the transdermal route of administration. Observed advantages of the transdermal route of administration over the oral route and hypodermic injections includes: 1) improved control of the rate of direct delivery into the bloodstream as it bypasses the gastrointestinal enzymes and significant first pass effect, 2) smaller peak-to-valley fluctuation in plasma concentration especially when patches are adopted and 3) improved patient compliance as they are generally painless and causes little or no discomfort [22, 23]. These factors could account for the discrepancies in the therapeutic efficacy of glucosamine between laboratory and clinical studies reported previously. Aghazadeh-Habashi et al studied the

pharmacokinetics and bioavailability of glucosamine and concluded that orally administered glucosamine has rapid but low absorption and is widely distributed and efficiently cleared. They further stated that the gut rather than liver is the organ mainly responsible for the low bioavailability of glucosamine and that the limited absorption of glucosamine suggests a transport dependent absorption. They went further to state that food does not significantly affect the bioavailability of glucosamine [24]. This suggest a high first pass metabolism as will be expected for many supplements, being normal part of the human metabolic chain, with well established degradation pathways.

In the present clinical survey, we found a new transdermal glucosamine formulation, Urah TGC, to be effective in relieving symptoms of arthritis. If this clinical observation is further established in a double blind studies, this could open the way for a new era of glucosamine research and therapy. Being a clinical survey, direct comparison of these results with previous studies are difficult due to differences in methodology. However, the results presented here are consistent with earlier reports by Cohen et al [16] which concludes that topical application of glucosamine and Chondroitin sulphate was effective in relieving the pain of OA of the knee and improvement was evident in 4 weeks. Taken together, our survey and that study lean credence to a route-efficacy relationship in the use of glucosamine for the treatment of OA.

The current clinical survey is not without limitations. Being a survey, there is a need to conduct a double blind study on this product as well as enlarge the cohort and protocol. However, being the first study to evaluate patient response to this new transdermal formulation in this community, the survey achieved its main objectives and thus paves the way for more detailed studies.

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APPENDIX

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