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Original article

Efficacy of acetaminophen *versus* ibuprofen for the management of rotator cuff-related shoulder pain: Randomized open-label study

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ABSTRACT

Background: Shoulder pain related to the rotator cuff (RC) is one of the most common and bothersome musculoskeletal complaints. Pharmacologic treatment most often includes acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. However, data allowing comparison of the efficacy of these two drugs are very limited. We compared the therapeutic outcomes of acetaminophen and ibuprofen in the management of RC-related pain.

Methods: This was an open-label, two-center, active-control, prospective randomized clinical trial. Participants were assigned randomly to acetaminophen or ibuprofen treatment groups. The acetaminophen dose was 500 mg every 6–8 h, and it was 400–800 mg every 6–8 h for ibuprofen. The impact of the treatment was measured by Shoulder Pain and Disability Index (SPADI), Quick Disabilities of the Arm, Shoulder, and Hand (Quick-DASH) and World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaires at baseline and after 6 weeks of therapy.

Results: Thirty-three patients completed the study; 20 treated with ibuprofen and 13 with acetaminophen. Patients in both groups were comparable at baseline with regard to SPADI, Quick-DASH, and WHOQOL-BREF scores. After 6 weeks of treatment, patients receiving ibuprofen, but not acetaminophen, reported an improvement in pain severity and functional activity (as measured by SPADI and Quick-DASH). Patients taking acetaminophen, but not ibuprofen, reported improvement in the physical and environmental domains of WHOQOL-BREF scores.

Conclusions: Ibuprofen and acetaminophen provide benefits to patients suffering from RC-related pain. However, the type of improvement perceived by patients differed between these two medications.

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1. Introduction

Shoulder pain is one of the most common types of musculoskeletal pain, and is encountered frequently among athletic and non-athletic populations [Fish et al., 2011; Struyf et al., 2017]. It presents as pain and impairment of function during elevation and external rotation of the shoulder [Struyf et al., 2017; Lewis, 2016]. It is one of the most bothersome musculoskeletal complaints encountered commonly in practice [Burbank et al., 2008],

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and the most frequent condition treated by upper-extremity surgeons [Jarrett and Schmidt, 2011].

The causes of shoulder pain are multifactorial (genetics, smoking, alcohol consumption, hormonal imbalance, comorbidities, biochemical, pathoanatomical, and changes in the sensory-motor cortex) [Harvie et al., 2004; Baumgarten et al., 2010; Passaretti et al., 2016; Magnusson et al., 2007; Dunn et al., 2014; Lewis et al., 2015]. However, the major contributors to shoulder pain are strenuous exercise, excessive and repetitive overhead activities, degenerative diseases, and traumatic incidents [Fish et al., 2011; Lewis, 2016; Struyf et al., 2017].

These various causes may affect a specific area of the shoulder, known as the "rotator cuff" (RC) or the surrounding structures [Whittle and Buchbinder, 2015; Schmidt et al., 2015]. The RC plays a critical part in supporting and controlling the movements of the upper extremity of the body, including flexion, abduction, and external and internal rotations. Thus, all disorders that involve this part of the shoulder are collectively known as "rotator cuff disease" (RCD) and result in significant pain and weakness, which in turn restricts the range of motion of the shoulder and impacts negatively on the patient's quality of life (QoL) [Hopman et al., 2013; Lewis, 2016]. RCD prevalence is 10–37%, with a higher prevalence among older (≥65 years) adults [Minagawa et al., 2013]. RCD incidence ranges from 0.3% to 5.5% [Littlewood et al., 2013]. Besides older age, risk factors for RCD include repeated work above the shoulder level, obesity, smoking, diabetes mellitus, genetic background, and various anatomical abnormalities [Littlewood et al., 2013; Titchener et al., 2014; Teunis et al., 2014].

The diagnosis of RCD usually involves evaluation of complete medical history, appropriate physical examination, and imaging (radiography, magnetic resonance imaging, ultrasound) [Bruns et al., 1997]. Treatment modalities are invasive and non-invasive approaches aimed at pain relief and restoration of function [Baysal et al., 2005]. Typically, RCD therapy begins with a course of non-invasive or conservative therapy, which includes heat or ice, exercise, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids [Whittle and Buchbinder, 2015; Boszotta and Prunner, 2004; Colegate-Stone et al., 2009]. This treatment usually lasts 6–18 weeks and results in complete recovery in 50–90% of the patients, especially if combined with physiotherapy [Cole et al., 2007].

Acetaminophen is used widely as first-line therapy for RCD given its higher tolerability in comparison with other analgesics, such as NSAIDs [Whittle and Buchbinder, 2015]. However, the American Academy of Orthopedic Surgeons recommends NSAIDs to manage RC-related pain in the absence of full-thickness tears, though admittedly the supporting evidence is inconclusive [American Academy of Orthopaedic Surgeons, 2010]. Guidelines proposed by the University of New South Wales in Australia recommend acetaminophen and NSAIDs, alone or in combination, for mild-to-moderate RC-related pain [Hopman et al., 2013].

Long-term use of NSAIDs (e.g., ibuprofen) can lead to adverse cardiovascular, cerebrovascular, and gastrointestinal effects [Fanelli et al., 2017]. Although acetaminophen is, in general, considered to be safer than NSAIDs [Fulton et al., 2015; Roberto et al., 2015], oral and topical NSAIDs are used more commonly to control RCD pain, and have shown their efficacy in relieving shoulder pain if used for a short time (4–8 weeks) in multiple randomized clinical trials [Boudreault et al., 2014; Mazieres et al., 2005]. The major problem with the use of NSAIDs for management of shoulder pain is their potential to delay tendon-to-bone healing by inhibiting cyclooxygenase-2 (COX-2) expression and, therefore, lowering the plasma concentration of prostaglandins (which are necessary for the healing of injuries) [Cohen et al., 2006]. However, this effect is not seen with acetaminophen.

Despite extensive use of acetaminophen and ibuprofen for the management of shoulder pain, no randomized controlled trials have compared the efficacy of these two drugs in the treatment of this condition [Rached et al., 2013; Boudreault et al., 2014]. Therefore, the primary objective of the present study was to compare the therapeutic outcomes (pain, functional disability, QoL) of acetaminophen and ibuprofen in the management of RC-related pain.

2. Methods

2.1. Design

The study was designed as an open label, two-center, active-control, prospective randomized clinical trial. A minimum sample size of 30 participants was calculated for power of 80% (beta = 0.2), level of significance (alpha = 0.05), large effect size (Cohen's d = 1.1), two-tailed Student's *t*-test, and a 1:1 ratio of acetaminophen to ibuprofen. However, to compensate for the possible drop-out of patients from the study, recruitment of 40 participants in each group was planned.

2.2. Study participants

Participants were assigned randomly to acetaminophen or ibuprofen treatment groups using the Internet-based Research Randomizer (www.randomizer.org).

Inclusion criteria were age ≥ 18 years and acute (≤7 days) RCD-related pain as assessed by an orthopedic surgeon and use of the Shoulder Pain and Disability Index (SPADI). Patients were asked to rate their pain on a-10 point scale; only patients scoring 0–3 ("mild" pain) and 4–8 ("moderate" pain) at baseline were enrolled.

Several exclusion criteria were established. They encompassed severe shoulder pain (score of 9–10 on SPADI), need for surgical intervention, atypical clinical features (e.g., differential diagnosis), history or presence of gastrointestinal problems (peptic or duodenal ulcer and high-risk patients on aspirin, warfarin, or corticosteroids), cardiovascular diseases (rheumatic heart disease, valvular heart disease, angina pectoris, atherosclerosis, coronary artery disease, coronary heart disease, myocardial infarction, myocarditis, pericarditis, endocarditis, cardiomyopathy, aneurysm, hypertension, peripheral arterial disease, congenital heart disease, and heart failure), cerebrovascular disease (atherosclerosis, cerebral vascular disease, stroke, and transient ischemic attack). Additional exclusion criteria were: acute or chronic kidney failure (defined as the rate of creatinine clearance ≤ 39 mL/min); liver disease resulting in increased levels of aspartate transaminase and alanine aminotransferase; taking any other NSAIDs (including aspirin) before study inclusion or previous intake of <3 days; allergy to NSAIDs or acetaminophen. Pregnant women and women not using birth control were excluded from participation in this trial. Patient recruitment started in May 2016 and ended in March 2018.

2.3. Treatment protocol

Patients were randomized to receive acetaminophen or ibuprofen. Acetaminophen (500 mg, p.o.) should be taken every 6–8 h as needed for pain, but the patient can increase the dose to ≤ 1000 mg (p.o.) every 6 h if the pain is not controlled with the 500-mg dose. Emphasis was placed on instructing the patients not to exceed the dose of 4 g of acetaminophen per day. The initial dose of ibuprofen was 400–800 mg (p.o.) every 6–8 h as needed for pain. However, based on the response to and tolerance for pain, the

patient might increase the dose to ≤ 3200 mg per day. Patients were advised to remain hydrated and drink water regularly throughout the day.

We wished to compare the efficacy of the two medications in controlling pain and improving function and QoL, so these parameters were assessed at baseline and 6 weeks after treatment initiation. The latter time point was based on the fact that most patients with RC-related pain return to normal activities within 6–12 weeks [Whittle and Buchbinder, 2015].

The purpose of our study was explained to the patients in plain language, verbally and in writing. Participants were asked to sign a consent form before being enrolled in the study. Then, patients were asked to provide sociodemographic information (age, sex, education, employment status, sedentary or active lifestyle, smoking status, and monthly income). Information regarding comorbidities and medications being taken currently was obtained from electronic medical records and patient interviews.

The health literacy of study participants was assessed using the validated Arabic version of the Single Item Literacy Screener (SILS) [Al-Jumaili et al., 2015]. The SILS consists of a single question that evaluates the patient's need for help to understand medical instructions, pamphlets, or medication labels [Al-Jumaili et al., 2015]. Patients were asked to complete the Arabic version of the SPADI questionnaire. The pain index consists of five items, in which each item is rated on a 0–10 scale, and then the scores of each item are added up and then divided by the total possible score (50 points) before being multiplied by 100 for a percentage score. The disability index consists of eight items and, similarly, each item is rated on a 0–10 scale, then the total scores are added up before being divided by the total possible score (80 points) and then multiplied by 100 for a percentage score. High scores for the pain and disability indices in SPADI indicate severe pain and great impairment or disability, respectively [Alsanawi et al., 2015].

All participants completed the Quick Disabilities of the Arm, Shoulder, and Hand (Quick-DASH) questionnaire. The latter consists of 11 items, and measures the impact of the injury on upper-extremity function, with higher scores indicating a higher negative impact of the injury on upper-extremity function [Alotaibi, 2010]. Furthermore, patients were asked to complete the Arabic version of the World Health Organization Quality of Life-BREF (WHOQOL-BREF). The WHOQOL-BREF consists of 26 items which assess a patient's satisfaction with his/her life and health. The WHOQOL-BREF items cover four domains: environmental, psychological, social, and physical. Each questionnaire item is answered using a five-level Likert scale (1 = never; 2 = rarely; 3 = sometimes, 4 = often, and 5 = always) [Ohaeri and Awadalla, 2009]. SPADI, Quick-DASH, and WHOQOL-BREF questionnaires were administered before treatment initiation and after 6 weeks of therapy.

2.4. Statistical analyses

Statistical analyses were carried out using SAS v9.2 (SAS Institute, Cary, NC, USA). The chi-square test or Fisher's exact test were used (as appropriate) for comparing categorical variables. The paired *t*-test was used to compare the difference in the mean values of the self-reported outcomes in SPADI, Quick-DASH, and WHOQOL-BREF questionnaires.

2.5. Ethics approval

The study protocol was approved by the Institutional Review Board of the tertiary care hospital where the study was conducted (E-16-1834).

3. Results

3.1. Recruitment and characteristics of patients

From May 2016 to March 2018, 150 patients visited the outpatient orthopedic clinic with complaints of upper extremity-related pain. Sixty of them did not meet the inclusion criteria; 27 had a history of cardiovascular disease, and in 33 the pain was found not to be related to the RC. Fifty-seven individuals did not consent to participate in the study or were lost to follow-up, so 33 patients completed the study. Of these, 20 were treated with ibuprofen and 13 with acetaminophen (Fig. 1).

Table 1 provides the demographic and medical information of patients upon treatment initiation. The patients were middle-aged (mean age, 42.18 years) and mostly female (66.67%); there was no significant difference between the two groups. The mean body mass index indicated overweight in the ibuprofen group and obesity in the acetaminophen group, but this difference did not reach significance ($P = 0.071$). All patients said that they had a sedentary lifestyle. Almost all participants (97%) had at least high-school education, but almost half of them were unemployed. The latter was the most likely reason for the high disparity in monthly income, but its distribution was similar in both treatment groups. The vast majority of patients (90.91%) had limited health literacy, with no significant difference between the two groups. Fewer than 25% of patients were smokers, and almost 80% had no comorbidities; these values were comparable in the two groups. The reported pain intensity also did not differ between patients assigned to ibuprofen or acetaminophen treatments. On the verbal pain-intensity scale, the most frequent grades were "moderate" and "very severe", with fewer patients reporting "mild" or "severe" pain. On the numeric pain-rating scale, ranging from 0 to 10, the mean value was 6.12 ± 2.16, which reflected the level of discomfort expressed verbally.

3.2. Treatment outcomes

The intensity of pain and disability (measured by SPADI), the function of the upper extremities (measured by Quick-DASH) and QoL (measured by WHOQOL-BREF) were evaluated before treatment and 6 weeks after therapy (Table 2).

There were notable differences in the outcome of the treatment, as measured by the three questionnaires, between the two groups of patients (Table 2). Subjects receiving ibuprofen reported a significant improvement in the severity of pain (SPADI-pain) (−19.10 ± 29.62; $P = 0.01$) and functional disability (SPADI-disability) (−17.30 ± 20.54; $P = 0.002$). In contrast, patients assigned to the acetaminophen group did not show a significant benefit of the drug as measured by the SPADI questionnaire. Similarly, the data obtained with the Quick-DASH questionnaire documented that the dysfunction of upper extremities was ameliorated markedly in ibuprofen-treated patients (−13.41 ± 17.49; $P = 0.003$), but the trend toward improvement did not reach significance in the acetaminophen group (−15.04 ± 24.91; $P = 0.05$).

WHOQOL-BREF was used to evaluate the various aspects of QoL, grouped in four distinct domains: physical health, psychological, social relationship, and environmental. The scores of patients treated with ibuprofen were essentially identical at baseline and after 6 weeks in all domains covered by WHOQOL-BREF. Patients taking acetaminophen did not improve in the area of psychological welfare or social relationship, but exhibited significant improvement in perceived physical health and environmental domains by, respectively, 8.85 and 9.00 points on a 0–100 scale.

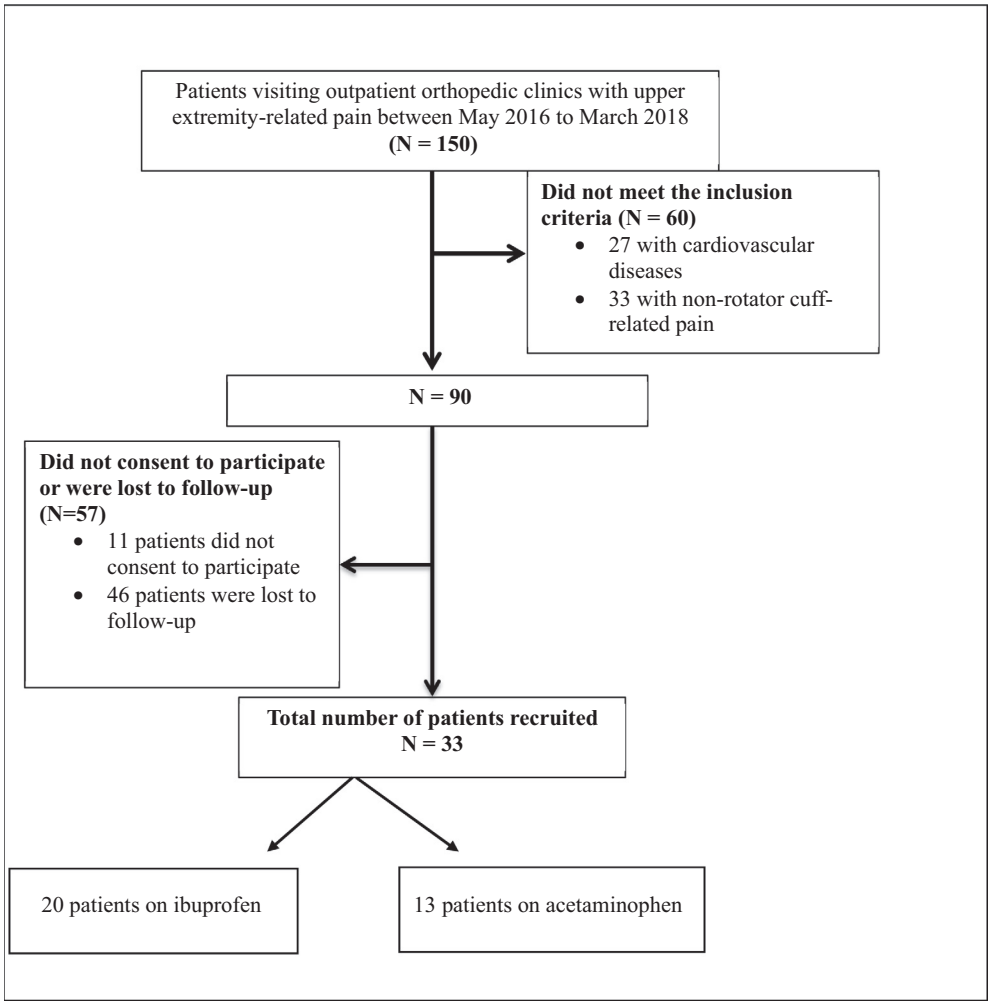

Fig. 1. Patient recruitment.

4. Discussion

Use of three instruments (SPADI, Quick-DASH, and WHOQOL-BREF questionnaires) to evaluate the impact of the treatment revealed specific areas of improvement in favor of ibuprofen or acetaminophen. In both groups, and in all three questionnaires, there was significant variability in response to these medications. Even if the mean score was improved, several patients exhibited worsening of the condition. As a result, the calculated values for standard deviation were greater than the measured mean change. However, the answer to the question of which medication provided more benefit to the patients remained elusive. Ibuprofen appeared to treat better the issues related directly to the perception of pain and, consequently, the function of upper extremities, whereas acetaminophen administration resulted in better indices for QoL.

The reason underpinning these differences in the findings based on the assessment tools used is not known, but can be explained (at least in part) by the smaller sample size in the acetaminophen group. In contrast with acetaminophen, NSAIDs such as ibuprofen inhibit the sensitization of pain receptors by blocking the inflammatory cascade [Rainsford, 2013]. Conversely, the mechanism of action of acetaminophen is complex, and includes the effects of peripheral (COX inhibition) and central (serotonergic descending neuronal pathway, L-arginine/nitric oxide pathway, and cannabinoid system) antinociception processes [Jóźwiak-Bebenista and Nowak, 2014], as well as antioxidant pathways [Prescott, 2000]. Importantly, ibuprofen has been documented to cause more adverse effects than acetaminophen [Fulton et al., 2015; Roberto et al., 2015; Whittle and Buchbinder, 2015; Fanelli et al., 2017], though recently the cardiovascular side effects of ibuprofen have been questioned [Bavry et al., 2014]. Thus, one could hypothesize that the better outcomes of acetaminophen revealed with QoL (WHOQOL-BREF) were due to the better safety profile of this medication in comparison with ibuprofen.

We focused on the relatively long-term effects of treatment with ibuprofen and acetaminophen. Two relevant studies comparing these two drugs in patients with soft-tissue injuries [Dalton and Schweinle, 2006; Hung et al., 2018] were restricted to 2 and 4 days of follow-up, and did not find a difference in their analgesic effects. Thus, the disparate impact of ibuprofen and acetaminophen may become apparent after treatment for an extended period of time, a protocol which would be necessary for alleviating RC-related pain.

We noted large variability in the response of patients to both medications, with several patients experiencing worsening of symptoms despite (or, possibly, because of) taking prescribed doses of medications. This finding raises a critical question of identification of the factors determining which patients are more likely to respond to treatment. Genetic factors have been shown to impact the efficacy of many therapies for various diseases [Berinstein et al., 2017; Matera et al., 2017; Politi et al., 2018;

Table 1
Baseline characteristics of the study cohort.

Characteristics	Treatment group		*P*	Total (N = 33)
	Ibuprofen (N = 20)	Acetaminophen (N = 13)		
Age (years, mean ± SD)	39.60 ± 15.93	46.15 ± 16.32	0.261	42.18 ± 16.60
Sex				
Male, n (%)	8 (40.00)	3 (23.08)	0.456	11 (33.33)
Female, n (%)	12 (60.00)	10 (76.92)		22 (66.67)
BMI (mean ± SD)	27.12 ± 5.05	30.91 ± 6.58	0.071	28.61 ± 5.91
Sedentary lifestyle, n (%)	20 (100.00)	13 (100.00)		33 (100.00)
Education				
No formal education, n (%)	0 (0)	1 (7.69)	0.191	1 (3.03)
High school, n (%)	9 (45.00)	3 (23.08)		12 (36.36)
College, n (%)	9 (45.00)	5 (38.46)		14 (42.42)
Postgraduate degree, n (%)	2 (10.00)	4 (30.77)		6 (18.18)
Health literacy				
Limited, n (%)	19 (95.00)	11 (84.62)	0.547	30 (90.91)
Adequate, n (%)	1 (5.00)	2 (15.38)		3 (9.09)
Employment status				
Unemployed, n (%)	9 (45.00)	7 (53.84)	0.802	16 (48.48)
Employed, n (%)	11 (55.00)	6 (46.15)		17 (51.52)
Monthly Income in SAR[a]				
≤3000, n (%)	4 (20.00)	5 (38.46)	0.214	9 (27.27)
>3000- ≤6000, n (%)	1 (5.00)	2 (15.38)		3 (9.09)
>6000- ≤10,000, n (%)	8 (40.00)	1 (7.69)		9 (27.27)
>10,000- ≤15,000, n (%)	2 (10.00)	3 (23.08)		5 (15.15)
>15,000- ≤20,000, n (%)	4 (20.00)	1 (7.69)		5 (15.15)
>20,000- ≤25,000, n (%)	1 (5.00)	1 (7.69)		2 (6.06)
Smoking status				
Smoker, n (%)	6 (30.00)	2 (15.38)	0.431	8 (24.24)
Non-smoker, n (%)	14 (70.00)	11 (84.62)		25 (75.76)
Comorbidities				
None, n (%)	16 (80.00)	10 (76.92)	0.139	26 (78.79)
Hypertension, n (%)	0 (0)	3 (23.08)		3 (9.09)
Dyslipidemia, n (%)	1 (5.00)	0 (0)		1 (3.03)
Major depressive disorder, n (%)	1 (5.00)	0 (0)		1 (3.03)
Asthma, n (%)	1 (5.00)	0 (0)		1 (3.03)
Diabetes mellitus, n (%)	1 (5.00)	0 (0)		1 (3.03)
Verbal pain intensity scale				
Mild	3 (15.00)	1 (7.69)	0.604	4 (12.12)
Moderate	8 (40.00)	7 (53.85)		15 (45.45)
Severe	1 (5.00)	2 (15.38)		3 (9.09)
Very severe	8 (40.00)	3 (23.08)		11 (33.33)
Numeric pain rating scale (mean ± SD)	6.15 ± 1.95	6.08 ± 2.53	0.926	6.12 ± 2.16

[a] Saudi Riyal.

Table 2
Pre- and post-treatment patient-reported outcomes scores.

Self-reported measure	Treatment group							
	Ibuprofen (N = 20)				Acetaminophen (N = 13)			
	Baseline	6-week follow-up	Mean difference*	*P*	Baseline	6-week follow-up	Mean difference*	*P*
SPADI								
Pain	56.90 ± 18.61	37.80 ± 28.27	−19.10 ± 29.62	0.01	61.69 ± 19.80	40.62 ± 24.69	−21.08 ± 34.89	0.050
Disability	40.75 ± 21.53	24.47 ± 20.01	−17.30 ± 20.54	0.002	46.35 ± 26.21	30.00 ± 25.33	−16.35 ± 39.84	0.165
Quick-DASH	41.82 ± 18.40	28.41 ± 22.30	−13.41 ± 17.49	0.003	42.83 ± 21.89	27.80 ± 18.84	−15.04 ± 24.91	0.050
WHOQOL-BREF								
Environmental	63.90 ± 10.73	64.05 ± 12.85	0.15 ± 8.00	0.934	57.46 ± 20.07	66.46 ± 20.03	9.00 ± 12.68	0.025
Psychological	65.90 ± 13.80	62.45 ± 11.29	−3.45 ± 10.59	0.162	63.69 ± 17.26	67.00 ± 14.36	3.31 ± 15.16	0.447
Social	52.40 ± 21.57	51.15 ± 23.51	−1.25 ± 17.56	0.754	58.54 ± 29.22	61.92 ± 25.91	3.38 ± 24.43	0.626
Physical	54.35 ± 11.62	56.30 ± 9.45	1.95 ± 10.52	0.417	52.38 ± 11.79	61.23 ± 7.81	8.85 ± 10.67	0.011

Data are the mean ± SD.
* An improvement is reflected by a negative value of mean difference in SPADI and Quick-DASH, and by a positive value of mean difference in WHOQOL-BRE.

Yamamoto and Yano, 2018], and provide the basis for the development of "personalized medicine" [Di Paolo et al., 2017; Kent et al., 2018; Zhou at al., 2018]. Our results support the necessity of further research into the possibility of introducing personalized medicine into pain management.

We did not evaluate the efficacy of the combination of ibuprofen and acetaminophen. A recent study addressing the potential benefit of simultaneous administration of acetaminophen and the NSAID diclofenac demonstrated that acetaminophen was not inferior to diclofenac or the combination of diclofenac and acetamino-

phen [Ridderikhof et al., 2018]. However, those drugs were administered for only a few days, as opposed to the long-term treatment provided to the patients in our study. Thus, the potential benefits of multimodal analgesia in chronic shoulder pain must be addressed in future research. Multimodal approaches to pain management could reduce the risks associated with opioid monotherapy [Savarese and Tabler, 2017; Erdogan Kayhan et al., 2018]. The latter frequently leads to drug addiction and abuse of opioids, a problem that, although at a level markedly lower than that in Western countries, also affects the population of Saudi Arabia [Martins and Ghandour, 2017; Al-Maharbi et al., 2018].

The limitations of our investigation must be considered when evaluating data and conclusions. This was a two-center study, and it was underpowered due to the small number of enrolled eligible patients. This was mainly due to sociocultural factors that played a part in patients misunderstanding clinical trials as well as the public perception that such studies carry a high risk of injury [Chalela P et al., 2014; Lee GE et al., 2016]. Moreover, the number of participants differed significantly between the two arms of the treatment. It was not feasible to create a dosage form of the analgesic that would keep the investigators and participants blinded. Furthermore, a placebo was not used for ethical reasons. In addition, adherence, the number of doses, or dose used by patients to manage pain were not reported. Finally, the adverse effects of medications were not reported, which limited full evaluation of treatment efficacy.

5. Conclusions

Our data provide good insight into the value of acetaminophen *versus* ibuprofen in the management of RC-related shoulder pain and, as such, encourage researchers and healthcare providers to examine this relationship on a large scale with a more robust study design.

Disclosure

The authors of this study have nothing to disclose concerning possible financial/personal relationships with commercial entities that may have a direct/indirect interest in the subject matter of this study.

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