

Efficacy of Hydroxychloroquine in Uncontrolled Type 2 Diabetes Mellitus Subjects with Adhesive Capsulitis

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ABSTRACT

Aims: The aim of this observational study is to evaluate efficacy of hydroxychloroquine in uncontrolled type 2 diabetes mellitus subjects with frozen shoulder.

Materials and methods: This was an open label, multicentre, prospective observational trial. Total 134 consecutive patients of Type 2 diabetes mellitus with adhesive capsulitis of shoulder joint were included in this study, who were inadequately control (HbA1c ≥ 7 to $\leq 10\%$) on two oral antidiabetic drugs. All the subjects were put on HYQ 400 mg OD and followed up for 24 weeks with clinical and biochemical parameters monitoring.

Results: All the 134 subjects on two oral agents (Metformin 1 gm and Glimpiride 4 mg). The mean age in males and females were 57 and 82 years respectively. The average body weight was 82.3 kg and BMI was 29 kg/m². The average duration of diabetes was 5.8 years. The mean baseline HbA1c was 8.9 %, which reduced to 7.5 % at the end of 24 weeks. The mean baseline FPG was 164 mg/dl, which was reduced to 124 mg/dl while the mean baseline PPG was 223 mg/dl which reduced to 164 mg/dl at the end of 24 weeks. Serum creatinine remained unchanged. The mean baseline hs-CRP was 5.87 mg/dl, which reduced to 1.12 mg/dl at the end of 24 weeks. There was a clinically significant change in body weight.

Conclusion: Hydroxychloroquine 400 mg once a day is an effective add-on for getting dual benefits of glycemic control and resolution of shoulder adhesive capsulitis, when appropriately used in poorly controlled type 2 diabetes

mellitus patients on dual oral agents with adhesive capsulitis.

Keywords: Hydroxychloroquine, Type 2 Diabetes, adhesive capsulitis, HbA1c.

INTRODUCTION

The musculoskeletal system can be affected by diabetes in a number of ways. The shoulder is one of the frequently affected sites. One of the rheumatic conditions caused by diabetes is frozen shoulder (adhesive capsulitis), which is a condition where the shoulder joint gradually loses mobility over a period of time, until the joint becomes immobile or "frozen." It is often very painful at first. Eventually, the condition can reverse itself but it can take 2 or 3 years for that to happen. Adhesive capsulitis is more prevalent in people who have diabetes. According to the National Institutes of Health (NIH), people with diabetes have an increased risk of developing adhesive capsulitis. Excess glucose can adhere to the cells, damaging the connective tissue which makes up the joints.

There is a consensus of opinion that poor blood sugar control and diabetes are related to microvascular and macrovascular complications of diabetes. Thomas et al.¹ showed a significant association between duration of diabetes and frozen shoulder. Hsu CL et al.² found that diabetes patients had a higher hazard of rotator cuff diseases

regardless of whether or not insulin was used. The issue as to whether enhancing glycemic control can reduce the chance of developing rotator cuff disease warrants further investigation. A 2016 meta-analysis led by Nasri Hani Zreik et al³, found that people with diabetes are five times more likely than non-diabetics to have frozen shoulder, with an overall prevalence of frozen shoulder in people with diabetes at a whopping 13.4%. According to Gupta S et al., estimated prevalence of adhesive capsulitis is 11%-30% in diabetic patients, which is considerably greater than that in non-diabetics. Adhesive capsulitis has been associated with the duration of diabetes and age with diabetics experiencing significantly greater pain and dysfunction.

Frozen shoulder treatment interventions seek to control pain and preserve movement. Physicians use pain relievers and anti-inflammatory drugs to make the patient more comfortable. Physical therapy can help in maintaining mobility of the shoulder. Disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine (HYQ), which act to weaken the immune system's effort on destroying joint tissue and causing inflammation. The anti-inflammatory effect of NSAID or steroid injection into the joint is a common practice for releasing pain and inflammation in the management of frozen shoulder and tendinitis of the rotator cuff. As a number of antidiabetic agents have been proven to have anti-inflammatory and anti-oxidative effects⁵, it is possible to find certain antidiabetic agents, such as hydroxychloroquine, might be useful in reducing shoulder disorders through various mechanisms.

Hydroxychloroquine (HCQ) improves glucose tolerance and insulin sensitivity by inhibition of insulin degradation. It slows breakdown of the internalized insulin-receptor complex and a study in obese, non-diabetic individuals reported a significant increase in insulin sensitivity index and trends toward reduced insulin resistance and insulin secretion⁷.

Indian randomized controlled trials showed that HCQ lowers HbA1c and LDL cholesterol levels in patients with type 2 diabetes⁸.

This study is designed to access the efficacy of hydroxychloroquine in uncontrolled type 2 diabetes mellitus patients with frozen shoulder.

MATERIALS AND METHODS

This was an open label, multicentre, prospective observational trial. Total 134 consecutive patients of Type 2 diabetes mellitus with shoulder adhesive capsulitis were included for the current study, who were inadequate blood glucose control (HbA1c ≥ 7 to $\leq 10\%$) and who were already on two oral antidiabetic drugs. Details of inclusion and exclusion criteria are mentioned below-

Inclusion criteria: T2DM Patients who were having adhesive capsulitis symptoms along with HbA1C $\geq 7\%$, FPG ≥ 126 mg/dL and PPG ≥ 200 mg/dL included in the study. Body weight is ≥ 60 kg. Patients were uncontrolled on two oral hypoglycemic agents.

Exclusion criteria: Patients of frozen shoulder with altered sensorium, disturbed mental state, pregnant and lactating females. Patients of frozen shoulder on drugs known to cause hyperglycemia like Steroids, fluoroquinolones, second generation antipsychotics, calcineurin inhibitors, protease inhibitors, ART etc. Patients with renal failure, liver failure and cardiac failure. Subjects with proliferative retinopathy. Patients with trauma to shoulder joint, shoulder joint surgery and prolonged immobilization of shoulder joint.

All patients were subjected to a detailed history and thorough clinical examination including local examination by orthopaedics expert after obtaining his/her informed consent. All study participants provided written informed consent. The study was conducted using good clinical practice and in accordance with the declaration of Helsinki. The study was

carried out after an approval from the institutional ethical committee of the respective centres.

Fasting and Post prandial blood sugar, serum creatinine, hs-CRP, HbA1C, FBG, PPBG and digital x-ray of shoulder joint anterior-posterior and lateral views. We have considered the lab reports only from NABL accredit (from Govt. of India) pathological laboratories in India towards the accuracy of the reports.

On a visual analogue scale (VAS) patients' self-evaluation of pain level was also assessed at baseline at the first session and then at visits on the 12th and 24th weeks after baseline. The ability to carry out normal daily activities, strength, pain and ROM were the four subscales evaluated in VAS.

Statistical analysis was done by SPSS version 22.0. (Statistical Package for the Social Sciences, Chicago, IL), χ^2 -test, and independent t-test. Results were specified as means with standard deviation. A p-value of 0.05 or below was regarded as significant.

RESULTS

All the 134 Type 2 diabetes Mellitus patients on two oral agents (one Metformin 1 gm and other Glimpiride 2 mg or Glclazide extended release 60 mg or

Teneligliptin 20 mg or Sitagliptin 50 mg or Vildagliptin 50 mg). The mean age of patients was 57 years and 82 were males and 52 were females. The Average weight was 82.3 kg and BMI was 29 kg/m². The average duration of diabetes was 5.8 years.

Table 1. Baseline characteristics (intention-to-treat population).

Variables	N= 134
Age (yrs)	58.21 ± 8.11
Male	82 (61.2%)
Female	52 (38.8%)
Body weight (kg)	82.3±10.2
BMI (kg/m ²)	29.30 ± 4.21
Diabetes duration (yrs)	5.8±1.6
Fasting plasma glucose (mg/dl)	164±21
Post Prandial glucose (mg/dl)	223±31
HbA1c (%)	8.9±0.8
hs-CRP (mg/l)	5.87±1.2
Serum creatinine (mg/dl)	0.72±0.23

There were a clinically significant change in body weight. Body weight was came down from 82.3 kg to 80.1 kg, though the change is not statistically significant.

The mean HbA1c was 8.9 %, which reduced to 7.5 % at the end of 24 weeks (Table 2, Figure 2). The mean FBG was 164 mg/dl, which was reduced to 124 mg/dl while the mean PPBG was 223 mg/dl which reduced to 164 mg/dl at the end of 24 weeks (Table 2, Figure 1). Serum creatinine was remained unchanged. The mean hs-CRP was 5.87 mg/l, which reduced to 1.12 mg/l at the end of 24 weeks.

Table 2: Change from baseline to 24 week study end point with Hydroxychloroquine

Parameters	Baseline	After 24 weeks	Difference	p value
Weight	82.3±10.2	80.1±11.7	2.2±2.1	0.0471
HbA1c (%)	8.9±0.8	7.5±0.5	1.4±0.5	<0.001
FPG (mg/dl)	164±21	124±18	40±19	<0.001
PPG (mg/dl)	223±31	164±24	59±26	<0.001
hs-CRP (mg/l)	5.87±1.2	1.12±1.1	4.68±1.1	<0.001
Serum creatinine (mg/dl)	0.72±0.23	0.71±0.29	0.01 ± 0.01	0.1889

Out of 134 patients included in study, right shoulder was affected in 50 patients (37.31%), left shoulder was affected in 49 patients (36.56%) and both shoulders were affected in 35 patients (26.11%). There was no significant association between right and left shoulder. Out of 134 patients, 92 patients (68.65%) were right handed and 42 patients (31.34%) were left handed. Out of 92 right handed

patients (68.65%), both shoulder were involved in 22 patients (23.91%), only right shoulder was involved in 44 patients (47.82%) and only left shoulder was involved in 26 patients (28.26%). Out of 42 left handed patients (31.34%), both shoulder were involved in 8 patients (19.04%), right shoulder were involved in 3 patients (5.98%) and only left shoulder were involved in 31 patients (75.6%).

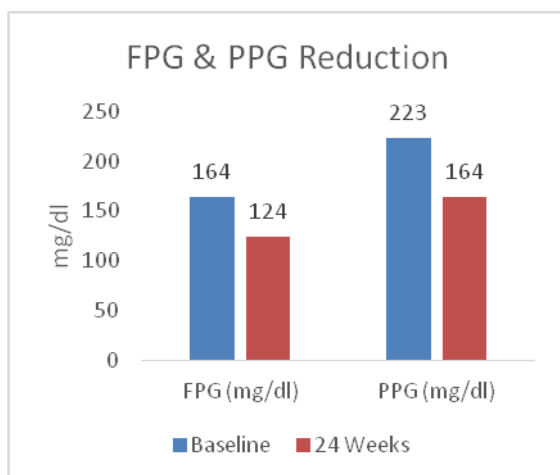


Figure 1: Reduction in FPG & PPG

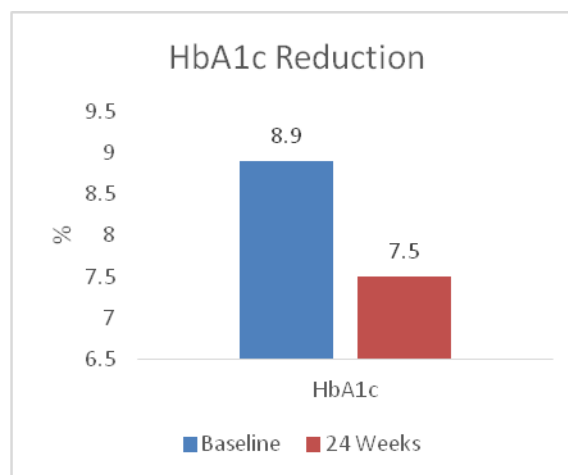


Figure 2: Reduction in HbA1c

At 24 weeks among 134 patients 45 patients whose left shoulder was affected, 48 patients whose right shoulder was affected and 32 patients whose both shoulder were affected were relieved from symptoms with improvement in digital x-ray of shoulder joint anterior-posterior and lateral. 9 patients needed additional pharmacotherapy while no patients needed corticosteroids or surgery.

There were no significant difference between the left and right shoulder groups at baseline in passive external rotation value as

demonstrated in table 3. although degree of improvement between the left and right shoulder groups was with no difference, however, passive external rotation range from baseline to the two follow-up assessments was significantly increased (Table 3). At baseline and at the first and second follow-up assessments, the passive external rotation value was not significantly different between the two groups (Table 3). At all time points in degree of improvement and by group, the active external rotation values were similar (table 3).

Table 3: VAS before and after treatment

VAS	Left Shoulder		Right Shoulder	
	Mean ± 1 SD	Med (Min–Max)	Mean ± 1 SD	Med (Min–Max)
Baseline	6.2°±2.6°	8° (2°–10°)	6.9°±2.5°	8° (0°–10°)
Change from baseline				
1st assessment	-1.9°±1.2°	-2° (-6°–0°)	-2.1°±1.3°	-2° (-6°–0°)
2nd assessment	-3.2°±2.1°	-3° (-9°–0°)	-3.5°±2.8°	-3° (-10°–2°)

*Significant within-group change from baseline, $p < 0.05$

°Shoulder range of motion measured in degrees

Mann-Whitney U test / Wilcoxon's signed rank test

HCQ was well tolerated with common treatment related adverse events being mild-moderate and included GI symptoms (5.97%) and hypoglycaemia (2.24%).

DISCUSSION

Musculoskeletal disease is one of the most common complications in patients with diabetes, and yet is receives relatively little attention. The severity and the risks of musculoskeletal complications might not be well recognized as cardiovascular complications; however, the associated

ailments certainly inflict both physical and psychological harm on people with diabetes.

The underlying reasons in patients with DM for potentially worse outcomes and prolonged course in adhesive capsulitis are complex. Boivin et al.¹⁰ looked at the properties of the Achilles tendon of diabetic mice. They identified a significant increase in tendon diameter, and significant decreases in stiffness and elastic modulus in tendons from diabetic mice compared to controls, suggesting that altered tissue properties may account for the observed resistance of diabetics to treatment. In

addition, a consequence of visceral adiposity in DM is inflammation that occurs via several inflammatory mediators^{11, 12}. Adipocytes secrete proteins and cytokines such as tumour necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) resulting in over production of other pro-inflammatory cytokines, which in turn exacerbate inflammation. Adipocytes also release excess IL-13, which has been shown to result in hepatic fibrosis in mouse models and may thus contribute to synovial and connective tissue fibrosis. Chronic inflammation can lead to excessive accumulation of collagen and other extracellular matrix components, which may result in destruction of normal tissue architecture¹³. Production of free fatty acids (FFAs) from adipocytes also leads to up-regulation of pro-inflammatory mediators and thus overproduction of inflammatory cytokines^{14, 17, 18}. FFAs may also promote neutrophil survival and cause defective efferocytosis¹⁴. Neutrophils secrete TNF- α and IL-6, which may result in insulin resistance. Resultant hyperglycaemia interferes with the inflammatory cascade and inhibits phagocytosis of bacteria and apoptotic cells^{14, 19}. The combination of these factors could result in persistence of inflammation and limited disease resolution. Adhesive capsulitis is considered to be an inflammatory and fibrotic condition¹⁹. In the early stages of adhesive capsulitis synovial and capsular fibrosis may occur as a result of inflammation and hyper vascular synovial proliferation,^{19, 20} in part driven by increased expression of synovial vascular endothelial growth factor 2,6. Up-regulation of inflammatory mediators in the capsule have also been demonstrated^{15, 18, 19, 20}. HCQ was shown to inhibit production of TNF- α , IL-1, IL-6 and interferon- γ (IFN- γ) and other inflammatory markers in chronic inflammatory states. An improvement in CRP levels was also seen in RA patients. It also inhibits prostaglandin synthesis and leukocyte activation and migration^{21, 22}.

Chronic low grade inflammation is becoming a critical component of T2DM is recently referred to as 'metaflammation'.

Benefits of HCQ were more pronounced in patients with higher inflammatory load. Pareek et al reports 88% subjects having moderate to high hs-CRP levels (>1 mg/l). Several RCT and real world trials²³⁻²⁸, has confirmed that addition of HCQ led to significant reduction in HbA1c (0.8 - 1.8%) and other glycemic parameters which is comparable to existing oral anti-diabetic agents. Besides this, Pareek et al⁹, also confirm that HCQ also significantly reduced lipid and inflammatory parameters which are typically deranged in T2DM. Hydroxychloroquine 400 mg is approved by DCGI and recommended by RSSDI clinical practice recommendations 2017 as add-on therapy after metformin and sulfonylurea in T2DM patients.

In this trial proves that HCQ provide dual benefit by reducing glycemic parameters and provide resolution of shoulder adhesive capsulitis. Significantly improvement in symptoms observed in patients whose left and right shoulder was effected along with patients whose both shoulder were affected. Several studies already concluded that incidence of uncontrolled T2DM is high among frozen shoulder patients. This trial once again confirms the effect of HCQ in T2DM patients associated with musculoskeletal disease.

There were clinically significant changes in body weight. Body weight was come down from 82.3 kg to 80.1 kg, though the change is not statistically significant. It is very difficult to conclude that this reduction in body weight was due to addition of HCQ 400, as there was not strict diet and exercise resume was monitored during the trial period. There may be several other factors which influenced this weight change. But in earlier trials with HCQ it was observed that after addition of HCQ 400 mg there was also a significant reduction in body weight.

CONCLUSION

Physicians and diabetologists should be aware of the high prevalence of DM in

patients with AC and vice versa. Hydroxychloroquine 400 mg once a day is an effective add-on for getting dual benefits of glycemic control and resolution of shoulder adhesive capsulitis, when appropriately used in poorly controlled type 2 diabetes mellitus patients on dual oral agents with adhesive capsulitis.

Conflict of interest

The authors declare no financial support or relationships that may pose a conflict of interest.

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