Evidence for Persisting with Treatment with Paracetamol in Patients with Mild to Moderate Osteoarthritis of the Knees

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Abstract: Although paracetamol is recommended as first line pharmacological therapy for mild to moderate osteoarthritis (OA) of the knees, it is deemed to be not as efficacious as other pharmacological agents. One of the reasons could be due to poor adherence and persistence to therapy. This study examines the efficacy of the early response and the response after four weeks to paracetamol in mild to moderate OA of the knees in daily clinical practice. This is an open label study. Consecutive patients with mild to moderate OA of the knees were given 1.3 grams extended-release paracetamol three times per day for 4 weeks. Pain based on the Western Ontario and McMaster Universities (WOMAC) v3 VAS osteoathritis index was used as a measure of efficacy. Serial liver and renal profiles were done for safety monitoring. An early assessment of efficacy was done at week 1 and a later at the end of 4 weeks of therapy. The primary efficacy endpoint was a 30% reduction in global pain score at week 4 compared to baseline Analysis was done using the SPSS Version 18. Thirty patients entered the study. 73.3% were females. Mean age, BMI and duration of OA was 58.5years (SD±6.9), 28.1 kg/m2 (SD±6.4) 22.8 (SD±32.2) months respectively. The mean VAS WOMAC at baseline for pain was 35.4mm (SD±17.5). At the end of the first week of therapy, there was no difference in the WOMAC pain score compared to baseline. (95% CI -0.54-12.1, p=0.07). However by the end of 4 weeks there was a statistically significant 46.6% (95% CI 27.6-72.6, p<0.001) reduction in global pain compared to baseline. An absolute reduction of 16.5mm in global pain (95% CI 9.9-23.0, p<0.001) compared to baseline was also seen. No serious adverse events were encountered. Paracetamol used to treat OA of the knees is not efficacious in the first week of therapy. However persistence with therapy for a further three weeks results in significant reduction in pain. Therefore every effort should be made to ensure persistence with the recommended full four weeks of treatment.

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1. Introduction

Osteoarthritis (OA) of the knees is a common disorder amongst older individuals in the community.[1-2] Many present to primary care doctors with complaints of pain.[1-2] and are often prescribed non-steroidal anti-inflammatory agents (NSAIDs) or cyclo-oxygenase2 inhibitors (COX-2).[2] While these agents are efficacious, they are associated with serious adverse events especially when used for longer duration in conditions like OA of the knees.[3-4] Elderly patients tend to have more comorbidities and therefore require multiple medications. Therefore, drug interactions are more likely to occur in this group of patients.[5]

Recent studies have reported that the use of NSAIDs and COX-2 inhibitors is associated with increased cardiovascular events.[4-6] Furthermore, although paracetamol is recommended as first line treatment by various guidelines for the management of OA of the knees, it is often under-prescribed. [7-8]

Various reasons have been cited as to why paracetamol is not efficacious.[9-11] One of the reasons could be the poor adherence.[12] Regular paracetamol has to be taken four times a day and it is well known that frequent medication dosing is inversely related to adherence to therapy.[13-14] Furthermore, patients frequently do not persist with the recommended 4 weeks therapy as they tend to give up when they do not appreciate any significant reduction in pain within the first few days of taking medication, rather than persisting longer with the therapy.

A literature search produced very few studies that looked at the effect of paracetamol after the first week of therapy in the treatment of OA knees compared to the effects seen later with persistence of therapy. Two studies study examined efficacy of paracetamol compared to placebo at one week [15-16] but these studies were not extended beyond one week and thus do not allow comparisons with prolonged use. One other study did look at the efficacy of paracetamol compared to placebo at one week and six weeks but unfortunately did not report on paracetamol at week one and at week six compared to baseline.[17]

Yet another study compared efficacy of paracetamol at 2 weeks and 12 weeks and found no significant reduction in pain compared to baseline at any of these two time intervals.[18] Of note is that all

these studies used regular paracetamol that requires four times a day dosing.

We thus examined the early response and compared it to the response after 4 weeks of extended-release paracetamol in treating mild to moderate OA of the knees.

2. Matetrials and Methods

We conducted an open label study using extended-release paracetamol amongst patients presenting with osteoarthritis of the knees at a university based primary care clinic. The reason for using an open label study was to emulate a real life clinical practice scenario. Furthermore, a placebo controlled trial would be deemed to be unethical in the light of available and efficacious therapy for OA knees, especially as the patients who present to our clinic which is located in a tertiary teaching hospital are usually patients who either have more severe or of longer duration illnesses and would have had received previous treatment by other primary care doctors without much improvement. An extended-release formulation was chosen as it needs to be taken only three times daily and this in itself may enhance adherence.

Consecutive patients with mild to moderate unilateral or bilateral OA of the knees based on the American College of Rheumatology diagnostic criteria[19] were eligible for the study.

Those with inflammatory arthritis, contraindication to use of paracetamol, chronic liver disease, trauma, surgery or corticosteroid injection of knee within past 3 months, psychiatric illness, pregnancy, inability to walk unassisted or with knee effusion were excluded from the study.

This was a 4-week active treatment study in concordance with the recommendations of rheumatology societies of treatment with paracetamol for 4 weeks in mild to moderate OA knees.[19-21] However neither the guidelines nor the clinical trials for OA knees have assessed efficacy in the early stages of treatment. As we wanted to compare efficacy at early to late stage of therapy, we evaluated the patients at baseline, at the end of one week of therapy and at a final visit in week 4.

Also because of the concern of safety of prolonged use at full dose of paracetamol in the background of a high prevalence of Hepatitis B carrier in the country, liver and renal biochemistries were done after one week for safety monitoring and again at the end of 4 weeks of therapy. For those with biochemistry abnormalities, further follow-up was done one month after the active treatment had ended.

Demographic data and physical examination were done at baseline. The Western Ontario and McMaster Universities WOMAC[22] v3 VAS osteoarthritis index from 0-100 mm was applied at baseline, week 1 and week 4 for pain, function and stiffness.

Weight loss was emphasised to all overweight and obese patients. All patients were also taught knee exercise by the trained research assistant. This was provided as part of the care recommended by the various guidelines.

All patients were prescribed 1.3 Grams of extended-release paracetamol (Panadol Extend™) three times daily for 4 weeks. Efficacy of treatment was assessed by change in the WOMAC pain score at week 1 and week 4 compared to baseline.

The primary end point chosen was a 30% decrease in global pain intensity between baseline and week 4 in accordance to recommendations of a report by the Osteoarthritis Research Society International (OARSI).[23] .The secondary efficacy end point was a reduction of 10mm on the WOMAC pain score between baseline and week 1, week 1 and week 4 and baseline and week 4. This is the consensus level of response for efficacy studies of OA knees.[23] Based on a power of 80% and a two-sided α value of 5%, and a defaulter rate of 20%, the number of patients needed is 30.

Compliance was measured by a daily diary and pill count.

Analysis was done using SPSS version18 and was done on an intention to treat analysis.

Written informed consent was obtained from all patients and approval for the study was granted by the institution's University of Malaya Medical Centre Ethics Subcommittee.

3. Results

A total of 30 patients entered the study and 25 (83.3%) completed the study. Four patients attended the week 1 visit, said they felt better and did not want to continue with the study. One had diarrhoea and voluntarily withdrew from the study at week 1, although the investigators deemed that she could continue with the study. In the 25 patients who completed the study, both at week 1 and week 4, less than 4% of each outcome variable of the pain WOMAC v3 VAS score was missing.

Table 1 shows the baseline characteristics of the study patients. Majority of the patients were females and two thirds were overweight or obese. Bilateral OA was common too seen in nearly three quarters of the patients.

The results presented here are the intention to treat analysis. There was no difference in the intention to treat and per protocol analysis on the primary outcome and liver toxicity.

Table 2 shows the percentage change and Table 3 the absolute change in global WOMAC

Score in pain, stiffness and difficulty in function at week 1 and week 4 compared to baseline.

Efficacy of early and late response to paracetamol

Although an early reduction in pain of 5.8mm was seen after one week of therapy, this was not statistically significant (95% CI -0.54-12.1, p=0.07). Furthermore the magnitude of pain reduction did not meet the primary efficacy end point either.

However at the end of 4 weeks of treatment, the reduction in pain was nearly 50% (CI 27.6-72.6, p<0.001) when compared to baseline. There was also a statistically significant reduction of 16.5mm (95% CI 9.9-23.0, p<0.001) on the WOMAC pain score at the end of 4 weeks compared to baseline.

Furthermore the reduction in WOMAC pain score of 10.7mm was also significant between week 1 and week 4 (95% CI 2.8-18.6, p=0.01).

A reduction in stiffness of nearly 30% and in difficulty in function of 34.9% was also seen between week 4 and baseline. There was also a statistically significant reduction of 12.3mm and 15.2mm in stiffness and difficulty in function respectively at the end of the study when compared to baseline.

Table 1: Baseline Characteristics of Study Patients (N=30)

Variable	Mean ±SD
Age (years)	58.5 (6.9)
BMI kg/m^2	28.1 (6.4)
Duration of OA (months)	22.8 (32.2)
Variable	**N (%)**
Females	22 (73.3%)
Overweight and Obese (BMI ≥25 kg/m2)	19 (63.3%)
Obesity (BMI ≥30 kg/m2)	8 (26.7%)
Bilateral OA	21 (70%)

Table 2: Percentage Reduction in WOMAC Score in pain, stiffness and difficulty in function at week 1 and week 4 compared to baseline

	% change in WOMAC VAS (95% CI)					
	Wk0-Wk1	**p**	**Wk1-W4**	**p**	**Wk0-Wk4**	**p**
Pain	**16.4 (-2.4-43.3)**	**0.071**	**35.8 (1.9-59.2)**	**0.001**	**46.6 (27.6-72.6)**	**<0.001**
Stiffness	**6.8 (-13.9-30.0)**	**0.47**	**23.7 (-12.8-41.2)**	**0.09**	**28.9 (15.0-53.4)**	**0.03**
Difficulty in Function	**18.2 (1.5-37.7)**	**0.02**	**20.5 (-2.6-49.5)**	**0.06**	**34.9 (20.5-62.5)**	**<0.001**

Table 3: Absolute Change in WOMAC pain, stiffness and difficulty in function score at baseline, week 1 and week 4

Global WOMAC Score (0-100 mm VAS)						
Mean Score (mm)				Absolute Reduction in mm (95% CI), (p value)		
	Wk 0	**Wk 1**	**Wk 4**	**Wk 0-1**	**Wk 1-4**	**Wk 0-4**
Pain	**35.4**	**29.6**	**18.9**	**5.8 (-0.54-12.1) (p=0.07)**	**10.7 (2.8-18.6) (p=0.01)**	**16.5 (9.9-23.0) (p<0.001)**
Stiffness	**42.5**	**39.6**	**30.2**	**2.9 (-6.5-12.2) (p=0.48)**	**9.4 (-1.8-20.6) (p=0.09)**	**12.3 (2.2-20.6) (p=0.03)**
Difficulty in Function	**43.5**	**35.6**	**28.3**	**7.9 (1.3-15.1) (p=0.02)**	**7.3 (-0.3-14.4) (p=0.06)**	**15.2 (7.3-23.2) (p<0.001)**

Safety and Tolerability

There were no serious adverse events encountered. Minor adverse events included dizziness (two) and diarrhoea (one).

There were also no clinically significant changes in the liver enzymes. Although there was some elevation in liver enzymes seen between baseline and at the end of week 4, none of it was raised more than twice the upper limit of normal. For those with raised liver enzymes, a follow-up was done a month after the study ended and repeat blood tests showed their enzymes had reverted to their baseline. There were also no significant changes in renal function.

Compliance was very good with all the 25 completers achieving a compliance of between 96-98% at week 1 and 94- 96% at week 4 based on the patient's daily diary and pill count. In four of the defaulters, the compliance was between 80-86% at week 1, after which they did not wish to continue with the study as they said they felt their pain was very much reduced. The defaulter who had diarrhea took the medication for 3 days only and voluntarily withdrew from the study when reviewed at week 1

4. Discussions

Paracetamol is recommended as first line pharmacotherapy by various guidelines on the management of OA of the knees.[19-21] This study, done to reflect daily clinical practice, shows that with persistence, extended-release paracetamol given at a dose of 1.3 gram three times daily for four weeks is effective in reducing pain in patients with mild to moderate OA of the knees. It is also effective in reducing stiffness and in improving function and is safe and well tolerated. This safety and tolerability has since been confirmed in other studies when paracetamol was given for six weeks or longer.[17, 24]

Our study does not have a placebo or control arm for comparison and it can be argued that paracetamol may be no better than a placebo.[18] While it is acknowledged that the lack of a placebo or control arm is one of the limitations of our study, several randomized control trials have shown greater efficacy of paracetamol compared to placebo.[15-16,25] However, a meta-analysis[26] has shown that it is less efficacious than NSAIDs[26] providing greater support for the use of NSAIDs instead of paracetamol for OA of the knees. But many of the studies which show NSAIDs to be more effective than acetaminophen[26-28] were usually done in patients with more severe pain and longer duration of symptoms.[26-28] On the other hand, several studies have shown that there is no difference when acetaminophen, either regular or the extended formulation is compared against an NSAID.[29-30] Furthermore, the effect size seen in NSAIDs versus placebo studies is only 0.34, (95% CI 0.14-0.54) and this is not much greater than the effect size of paracetamol versus placebo[26] (effect size 0.21, 95% CI 0.02-0.41). Hence, based on our study which was done in a primary care setting and emulating daily clinical practice, there is still a case for using paracetmaol as first line pharmacotherapy especially in mild to moderate OA of the knees.

Most of the above mentioned studies compared therapies at the end of 4 weeks or longer.[17-18, 24-25, 27-29] Very few have been done to compare the effect of short term therapy.[15-16] Even fewer compared early response to response with persistent drug usage. A randomized short term study of one week[15] found significant reduction in pain with paracetamol over placebo. But another randomized short term study, also of one week, found that while paracetamol was superior to placebo, NSAIDS was superior to paracetamol.[16] Unfortunately these two studies were only for a week and thus it was not possible to examine the efficacy with longer use. A possible outcome, if there was a comparison of longer use, could be a narrowing of the differences in efficacy between NSAIDs and paracetamol. One study did examine the efficacy of paracetamol at 2 weeks and 12 weeks compared to baseline but found no difference in efficacy with prolonged use.[18] In this same study the reduction in pain was significant and seen early at 2 weeks with the use of diclofenac, suggesting an earlier onset of pain relief with NSAIDs compared with paracetamol. Because there were very few studies that compared early response to response after four weeks of paracetamol use, our study aimed to do this. Our results did show that there is significant benefit with persistent use, unlike that of one study[18] that showed that there was no significant response at 2 nor at 12 weeks compared to baseline.

Our study also shows that while there was some early reduction in pain and stiffness, this was not statistically significant. This finding does not suggest that there is no effect but that the lack of statistical significance could have been due to the small number of patients. However with persistent use of paracetamol, the improvement became greater and significant. While we studied the response after one week of therapy, this time point was an arbitrary choice. We decided to see the patient earlier rather than at the end of 4 weeks as recommended by guidelines was because we were concerned about the safety of full dosing for four weeks. This was because at the time of our study there was no available data about safety of paracetamol of longer than 2 weeks duration of use. While our study showed a statistically significant reduction in pain at the end of 4 weeks but not after one week, the

response at the end of 2 weeks or even at the end of three weeks remain unknown. In fact a meta-analysis of short term efficacy of pharmacotherapeutic interventions concluded that there was not enough data to identify a time point for maximum effect of paracetamol within a 4 week time frame for treatment of OA knees.[31] This being the case, our study helps to support the recommendation of using paracetamol for a full four weeks.

A limitation of our study was that it was conducted for four weeks only and efficacy for a longer duration of therapy was not evaluated. However our purpose was to emulate daily clinical practice. To be in accordance with the OA guidelines recommendations, patients are to be reviewed after four weeks of paracetamol therapy and a decision made then on further management at this time point depending on the response of the patients. Hence we did not proceed beyond the 4 weeks. It is likely that a longer study may show a continued persistence but not necessarily a further improvement in the benefit. In fact one study which compared paracetamol against placebo did not show any significant improvement at 2 weeks compared to baseline and it also did not show any further improvement at 12 weeks compared to baseline.[18]. This suggests that no further improvement can be seen after the maximum efficacy seen at four weeks is already attained.

It has to be acknowledged that the response seen in our study could have been a result of a regression to the mean or to a response shift. [32-33] However, the mean duration of OA symptoms of our study patients was nearly 2 years and not new onset OA, and it is unlikely that a regression to the mean or a response shift alone could have accounted for the response seen.

Another confounding factor would be that the reduction in pain seen in our patients could have been due to the knee exercise given to all of them. While this may be the case, we wanted to emulate best clinical practice and to be in accordance with guideline recommendations of combining non-pharmacological with pharmacological therapy. Hence we proceeded to provide knee exercise. We acknowledge that the presence of a control arm of exercise but without paracetamol, may have helped to eliminate this confounding issue. But again as these are not patients with newly diagnosed OA, it is unlikely that knee exercise alone would have accounted for the response seen. As such, inspite of all the above limitations there is still a sound reason to use paracetamol as first line as recommended by the various guidelines.

Our finding thus has implications as it adds to the dearth of data supporting persistence with paracetamol use. Our finding also suggests that it is important to remember that patients should persist and stay on treatment with paracetamol for longer, and that doctors should resist the pressure to change to another medication too soon.[34-35]

Effectiveness of paracetamol is related to adequate dosage. Doctors and other health care providers often do not use paracetamol adequately and thus paracetamol is perceived by doctors as well as patients not to be effective[7,9] Furthermore, compliance to a four times daily dosing is usually poorer than a less frequent daily dosing. Compliance to a three times a day extended preparation is excellent here. While our study shows that the treatment of OA of the knees with paracetamol is significantly efficacious, several other studies failed to show this.[17-18]One of the reasons for this difference could be the better compliance with an extended preparation seen in our study as for example versus 72% seen in another study[17]. Furthermore, many of the other studies used the regular four times a day dosing paracetamol and the studies were of a longer duration.[17-18]These factors could have contributed to the poorer compliance[12-13] and hence may have contributed to their lack of positive findings. Although it is recognized that patients in studies tend to be more compliant because of close supervision, doctors, nevertheless, should try to prescribe extended preparations in full doses as far as possible [12-13] and patients should be encouraged to take medication regularly according to the directions to reduce pain episodes.[34-35]

Given that more adverse events are associated with NSAIDs use[3-4] and that patients would forgo some degree of effectiveness for safety[36] NSAIDS are thus not necessarily superior to paracetamol, especially in patients presenting to a primary care clinic with mild to moderate OA knees. Together with the excellent safety and tolerability of using paracetamol in full dose for 4 weeks and its good safety/benefit ratio, there is still a case for advocating the use of paracetamol as first line therapy in OA of the knees.

The aim of management of OA is not to cure as this is not realistically possible, but to relieve pain, improve function and improve quality of life. This study has shown a reduction in pain severity and this is achieved with minimal adverse events with 1.3 grams of extended release paracetamol given three times daily and persisted for a full four weeks.

5. Conclusion

Paracetamol used to treat OA of the knees is not efficacious in the first week of therapy. However persistence with therapy for a further three weeks results in significant reduction in pain. Therefore

every effort should be made to ensure persistence with the recommended full four weeks of treatment.

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YCC: conceived, designed and obtained the research funding for the study. She also coordinated the study, collected and analysed the data and wrote the manuscript.
RB: participated in data collection
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NSH: participated in conception of the study
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