n Of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthritis

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Abstract

Objective—To evaluate the efficacy of paracetamol and a non-steroidal anti-inflammatory drug for symptom relief in osteoarthritis.

Design—Double blind, randomised, controlled trials in individual patients (n of 1 trials). Three treatment cycles with two weeks' each of paracetamol (1 g twice daily) and diclofenac (50 mg twice daily) prepared in identical gelatin capsules.

Setting—General practices in metropolitan Sydney, Australia.

Subjects—25 patients (median age 64 years) with pain of osteoarthritis (median duration of disease eight years) considered by their general practitioners to require regular treatment. 20 were already taking non-steroidal anti-inflammatory drugs.

Main outcome measures—Diary of pain and stiffness, function, and side effects.

Results—15 patients completed the study, five withdrew early but had made a therapeutic decision, and five dropped out very early. Results from 20 patients were analysed. Several patterns of response evolved. Eight of the 20 patients found no clear difference, symptoms being adequately controlled by paracetamol; five indicated a clear preference for the non-steroidal anti-inflammatory drug; two showed control of symptoms after their initial two weeks of the non-steroidal anti-inflammatory drug which continued throughout subsequent treatment changes; in five the non-steroidal anti-inflammatory drug may have been better but neither agent gave satisfactory control. After three months nine of the 20 patients had adequate symptom control with paracetamol alone.

Conclusions—n Of 1 studies—that is, randomised trials in individual patients—are clinically useful in deciding treatment in heterogeneous conditions which require long term symptomatic relief. In osteoarthritis many patients currently receiving or being considered for non-steroidal anti-inflammatory drugs may achieve adequate control with paracetamol.

Introduction

Osteoarthritis is the most common musculoskeletal disorder and has been recognised as the most important form of joint disease contributing to the illness burden of the community.¹ In addition to physical measures, initial and long term treatments may include analgesics such as paracetamol or non-steroidal anti-inflammatory drugs, or both. Though some people with osteoarthritis have an obvious inflammatory component, most have little or no inflammation. Despite this and the known association of non-steroidal anti-inflammatory drugs with major gastrointestinal complications of haemorrhage, perforation, and occasionally death²⁻⁴

non-steroidal anti-inflammatory drugs are widely prescribed.⁵

Elderly women suffer the highest occurrence of osteoarthritis⁶ but they also seem to be particularly prone to gastrointestinal damage associated with non-steroidal anti-inflammatory drugs.⁷⁻⁹ There is also concern that these drugs may be nephrotoxic¹⁰ and may hasten rather than deter progression of osteoarthritis.^{11,12} The toxicity associated with paracetamol overdose is well recognised.^{13,14} Isolated cases of hepatotoxicity with therapeutic doses of paracetamol (4-8 g/day) have been reported with pre-existing liver disease.^{13,15} No evidence of hepatic damage or renal insufficiency was found in one study of patients with osteoarthritis taking paracetamol (2.6 g/day) for two years.¹⁶

It seems reasonable to use non-steroidal anti-inflammatory drugs only in those patients in whom there is good evidence that these drugs are more efficacious than paracetamol in controlling pain. Results from the few trials examining this issue have been contradictory.¹⁷ Some showed no difference between treatment effects,^{18,19} but another showed significant benefit of a non-steroidal anti-inflammatory drug over analgesics.²⁰ A randomised double blind trial comparing anti-inflammatory and analgesic doses of ibuprofen (2.4 g and 1.2 g/day) with paracetamol (4 g/day) concluded that paracetamol was as efficacious as the non-steroidal anti-inflammatory drug in short term symptomatic treatment of osteoarthritis of the knee.²¹ Statistical power in that trial was low and a real difference may have been missed.²² The considerable variability in individual responses to treatment suggests that it may not be possible to extrapolate these results to each patient with osteoarthritis. n Of 1 trials have been developed to determine the most appropriate treatment choice for each patient.²³⁻²⁷

The aim of this study was to choose appropriate individual treatment for osteoarthritis in a general practice setting. The main objective was to evaluate individual patient responses to paracetamol and a non-steroidal anti-inflammatory drug (diclofenac) in terms of pain relief, immediate side effects, and general wellbeing. Minor objectives were to determine the comparative overall efficacy of paracetamol and non-steroidal anti-inflammatory drugs and to evaluate clinical usefulness by determining the proportion of patients who agreed to long term use of the treatment suggested by their results.

Subjects and methods

Patients were recruited predominantly from general practices in northern Sydney. Eighty doctors in a general practice sentinel scheme were asked to refer suitable patients. Criteria for recruitment were a clinical diagnosis of osteoarthritis with daily pain, no known contraindication to non-steroidal anti-

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inflammatory drugs, and no corticosteroid injection in the previous four weeks. The study was approved by the institutional medical research ethics committee.

The study comprised a series of randomised trials in individual patients (n of 1 trials). Each patient was treated over three four week cycles. In each cycle a non-steroidal anti-inflammatory drug (diclofenac 50 mg twice daily) was given over one period of two weeks and identically presented paracetamol (1 g twice daily) over the other. The gelatin capsules containing the study drugs were provided in bottles, one week at a time, and patients were unaware when treatment was changed. The order of drugs was randomly assigned in each cycle. The choice of initial agent was balanced in blocks of four to ensure that similar numbers of patients started the trial with each. Patients, doctors, and research assistant were all blinded with respect to which treatment patients were receiving throughout. Additional, identified paracetamol was available as an escape analgesic, to a maximum of 2 g/day. Pill counts were taken to measure compliance and assess the use of escape analgesia.

EVALUATION OF EFFICACY

At the start of the trial each patient nominated the joint that was most severely affected. When more than two joints were affected patients kept a global record. Two activities that induced pain and two that caused functional difficulty were identified in each patient by means of the Western-Ontario and McMaster University scale.²⁸

Patients completed a daily diary using separate 10 cm visual analogue scales for pain and stiffness. They were encouraged to refer to the previous day's score when marking the scale. Patients were asked to summarise their symptoms at the same time of day. Changes in ability to perform selected activities were monitored weekly by using a five point Likert scale (much better, slightly better, no change, slightly worse, much worse). Patients also kept a weekly record of changes in their global arthritis pain and global health compared with the previous week (using the same Likert scale) and a weekly checklist of 11 gastrointestinal and central nervous system complaints that are reportedly associated with non-steroidal anti-inflammatory drugs.²⁹

On completion of each trial a summary of results was prepared for discussion with the patient and general practitioner regarding future treatment. For this the weekly averages of visual analogue scores for pain and stiffness were plotted. Also provided were total reported numbers of side effects, use of escape analgesia, and an aggregate preference score, derived by using combined Likert scales each time there was a change in treatment. The joint general practitioner and patient decision on continuing treatment was recorded. Three months after the study patients were contacted by phone and asked their current treatment for osteoarthritis.

STATISTICAL ANALYSIS

Graphs of daily visual analogue scores were plotted. To avoid a carryover effect, values from the second weeks on each treatment were compared over the three cycles by a paired *t* test with two degrees of freedom. All tests for significance were one tailed to detect whether the non-steroidal anti-inflammatory drug was significantly better than paracetamol. If not, then paracetamol was considered the drug of choice. The sign test was used to assess the ratings of global arthritis severity to determine whether the assessment favoured the non-steroidal anti-inflammatory drug at times when the treatment changed. For all patients who completed the trial there were either three or four such changeovers. Use of escape analgesia and reporting of

side effects were compared between treatments by the Wilcoxon signed rank test. To assess the feasibility of combining the results of all the trials³⁰ individual treatment effects (mean difference in visual analogue score between paracetamol and the non-steroidal anti-inflammatory drug) for pain and stiffness were plotted.

Results

Twenty five patients were recruited. Twenty were women and five men, and their ages ranged from 38 to 85 years (median 64). Duration of osteoarthritis ranged from one to 30 years (median eight). Nineteen patients had symptoms of osteoarthritis at more than three sites, including hip, knees, hands, feet, and spine. Twenty patients were currently taking non-steroidal anti-inflammatory drugs. Fifteen patients completed the full 12 week cycle, five withdrew early having made a decision after two cycles, and five dropped out very early (two because of intolerance of the non-steroidal anti-inflammatory drug, two because of intercurrent illness, one because of non-compliance). The table gives details of the 15 patients who completed the study. All patients took more than 90% of their trial capsules.

Figures 1-3 show examples of the daily visual analogue scores illustrating some of the patterns that evolved. These cases are presented below.

Case 13—A 60 year old woman with generalised osteoarthritis for 25 years had been taking diclofenac

FIG 1—Case 13. Daily visual analogue scores for pain and stiffness

FIG 2—Case 2. Daily visual analogue scores for pain and stiffness

FIG 3—Case 21. Daily visual analogue scores for pain and stiffness

50 mg twice daily and was concerned about possible side effects. Previous attempts to stop non-steroidal anti-inflammatory drugs had resulted in a flare up of symptoms. Figure 1 shows that her mean pain and stiffness scores were similar with each treatment, average values being slightly lower with paracetamol (table). At three of the four changeover weeks the global rating favoured the non-steroidal anti-inflammatory drug. These changes were not statistically significant, however, and the patient did not notice any clinically important change. Side effects were reported more commonly with paracetamol (table), but these were mainly headache and loss of energy. She elected to continue with regular paracetamol and achieved adequate control with paracetamol at three month follow up.

Case 2—A 77 year old woman with symptoms of osteoarthritis in both hips and one shoulder for nine years had been taking diclofenac 25 mg twice daily for more than six months but was not sure whether it was effective. Her general practitioner had suggested that she should increase the dose but she was concerned about doing so. The visual analogue scores (fig 2) showed that her symptoms were quickly controlled during the initial two weeks with the non-steroidal anti-inflammatory drug (at twice the dose she had been taking previously), and this was maintained through subsequent treatment changes. At only one of three changeovers did the global rating favour the non-steroidal anti-inflammatory drug. Side effects were minimal. Her results suggested that paracetamol would provide adequate pain relief most of the time

but that intermittent use of an anti-inflammatory dose of a non-steroidal anti-inflammatory drug might be required. At follow up at three months she was taking non-steroidal anti-inflammatory drugs daily for increasing back pain, which was a new symptom.

Case 21—A 56 year old man had a nine year history of osteoarthritis, predominantly in the left hip. His symptoms were not adequately controlled with diclofenac 25 mg twice daily and his doctor was considering changing his treatment. He had not tried paracetamol. Plots of visual analogue scores (fig 3) for both pain and stiffness showed a clear difference between treatments, rising with paracetamol and progressively falling with the non-steroidal anti-inflammatory drug. Paired *t* tests confirmed a significant mean difference in pain (3.4 cm (95% confidence interval 2.1 to 4.6); *P* = 0.003) and stiffness scores (3.6 cm (0.6 to 6.6); *P* = 0.02) between the treatments. The patient indicated a clear preference for the non-steroidal anti-inflammatory drug at each of the four changeovers (*P* = 0.06).

A clinically useful decision was made for 19 of the 20 patients who completed at least seven weeks of the study. Several patterns of response emerged—no clear difference between the two drugs (eight patients, who thought their pain was adequately controlled throughout); non-steroidal anti-inflammatory drug preferred (five patients); adequate symptom control achieved during the initial two weeks with the non-steroidal anti-inflammatory drug and maintained throughout subsequent changes in treatment (two patients); possible improvement with the non-steroidal anti-inflammatory drug but the patient not satisfied with symptom control with either agent (five cases).

Use of escape analgesia varied. Overall it was greater when patients were taking paracetamol than when they were taking the non-steroidal anti-inflammatory drug (median numbers of tablets taken/week 7.5 and 1.0 respectively; *P* = 0.013). Patients often reported taking paracetamol for reasons other than their osteoarthritis (headache, colds, etc). Numbers of side effects reported, other than in those people who dropped out early, were very variable. No side effect was severe, headache, loss of energy, and indigestion being the most common. These were reported as frequently with paracetamol as with the non-steroidal anti-inflammatory drug (medians 6 and 3 respectively; *P* = 0.17).

Sixteen of the 20 patients were taking non-steroidal anti-inflammatory drugs before the study. Of these, nine continued after the study and seven stopped. Three months later two of those who had continued with non-steroidal anti-inflammatory drugs had progressed to surgery and six of the seven who had

Summary of results for 15 patients who completed study

Case No	Treatment before study	Pain (mm)*			Stiffness (mm)†			Escape analgesia‡		Side effects§		Global preference		Treatment at end of study	Treatment after three months
		NSAID	Paracetamol	P (one tailed)	NSAID	Paracetamol	P (one tailed)	NSAID	Paracetamol	NSAID	Paracetamol	Changeover weeks	P (one tailed)		
2	NSAID	7.5	9.3	0.23	5.1	6.7	0.007	2.4	3.5	2	3	1/3	0.50	NSAID	NSAID
3	NSAID	50.1	54.2	0.13	57.3	59.0	0.16	0.6	1.2	3	12	3/4	0.31	NSAID	Surgery
5	NSAID	0.4	14.1	0.19	1.7	33.9	0.10	0.1	1.3	7	1	4/4	0.06	NSAID	NSAID
6	NSAID	62.5	62.1	0.63	63.2	60.8	0.74	1.8	1.6	16	15	2/4	0.69	Paracetamol	Paracetamol
7	NSAID	38.4	34.3	0.63	29.4	18.7	0.92	1.3	1.8	9	13	4/4	0.06	Paracetamol	Other¶
8	NSAID	4.8	7.2	0.14	25.1	33.7	0.22	0.7	1.0	0	1	3/4	0.31	Paracetamol	Paracetamol
9	NSAID	5.8	23.8	0.001	4.8	18.4	0.02	0	0.5	3	2	4/4	0.06	NSAID	NSAID
11	Paracetamol	4.3	5.8	0.36	2.3	2.0	0.58	0.1	0.2	9	18	2/4	0.69	NSAID	NSAID
12	None	35.0	40.5	0.33	40.0	40.9	0.44	3.8	4.1	16	12	3/3	0.12	Paracetamol	Paracetamol
13**	NSAID	12.5	9.7	0.63	21.0	19.0	0.62	0.3	0.5	3	14	3/4	0.31	Paracetamol	Paracetamol
15	NSAID	36.4	65.9	0.01	37.0	64.7	0.001	2.6	4.0	8	14	4/4	0.06	NSAID	NSAID
19	NSAID	0.8	2.1	0.11	7.8	10.8	0.25	0	0.1	0	0	3/4	0.31	Paracetamol	Paracetamol
20	Paracetamol	7.3	7.2	0.55	11.5	14.8	0.11	0	0	1	0	3/3	0.12	Paracetamol	Paracetamol
21	NSAID	9.5	43.3	0.003	9.0	45.0	0.02	0.3	0.3	1	1	4/4	0.06	NSAID	NSAID
23	NSAID	3.1	2.7	0.67	6.5	8.4	0.22	0.1	0.2	4	6	3/4	0.31	Paracetamol	Paracetamol

NSAID = Non-steroidal anti-inflammatory drug.

*Mean pain score on visual analogue scale (maximum 100 mm) taken from second week of treatment.

†Mean stiffness score on visual analogue scale (maximum 100 mm) taken from second week of treatment.

‡Daily mean of number of escape paracetamol tablets (500 mg) taken.

§Total number of reported side effects over six weeks with each treatment.

||Global preference in favour of non-steroidal anti-inflammatory drug at changeover (one sided *P* values).

¶Non-steroidal anti-inflammatory drug/prednisolone for different condition.

**Result of pain and stiffness obtained in only two cycles.

stopped were still not taking them. The one patient who had restarted was prescribed non-steroidal anti-inflammatory drugs and prednisolone for another condition. Of the three patients who had previously been taking paracetamol, one elected to take non-steroidal anti-inflammatory drugs even though her results did not support that decision (case 11). The patient who had not been taking anything before the study elected to take paracetamol regularly. Thus at three months equal numbers were taking non-steroidal anti-inflammatory drugs (nine) and paracetamol (nine). However, seven of the eight patients who changed treatment from baseline changed to paracetamol ($P = 0.07$, exact binomial).

Figure 4 plots the individual treatment effects as the mean difference in visual analogue scores between paracetamol and the non-steroidal anti-inflammatory drug for pain and stiffness. Only those patients with average scores > 15 mm for either pain or stiffness were included.

Twenty six general practitioners (33%) expressed interest in the study, but only 11 referred patients within the required time. At the end of the study participating doctors were contacted by phone and asked whether they considered n of 1 studies useful and whether they would use them if support services were readily available. Reaction was mixed but most thought that they were potentially useful though practically difficult.

Discussion

When considering treatment for osteoarthritis it should be remembered that physical measures such as physiotherapy, regular exercise, and aids such as walking sticks are often beneficial in controlling symptoms. Non-steroidal anti-inflammatory drugs are widely prescribed, yet published work contains no clear evidence that they provide better pain relief than paracetamol. Because of the inherent dangers associated with non-steroidal anti-inflammatory drugs, especially in elderly people, ideally they should not be prescribed without an n of 1 trial in each patient showing that they are more effective than paracetamol.

In this study n of 1 trials allowed a clinically useful decision to be made for 19 of the 25 patients. Though not an aim of the study, after three months fewer patients were taking non-steroidal anti-inflammatory drugs than at the start (16 (80%) at baseline, nine (45%) at three months). Other studies have suggested that long term treatment with non-steroidal anti-inflammatory drugs can be adequately withdrawn or replaced by simple analgesics in many elderly patients.³¹⁻³³ n Of 1 trials should prove useful as a means of withdrawing these drugs from patients who may no longer need them but who are afraid that their pain would not be controlled by paracetamol.

The distribution of individual treatment effects for pain and stiffness (fig 4) showed pronounced

FIG 4—Individual treatment effects (mean difference in visual analogue scores for pain and stiffness between two treatments (maximum ± 100 mm)). Points around zero indicate no difference. Positive points indicate preference for non-steroidal anti-inflammatory drug. Negative points indicate preference for paracetamol

Clinical implications

- Osteoarthritis affects more than 10% of the population and is one of the most frequent reasons why patients present to their general practitioner
- Non-steroidal anti-inflammatory drugs are widely prescribed but have potential for serious and expensive side effects
- Few controlled trials have examined whether simple analgesics such as paracetamol may be equally efficacious; results from group studies are contradictory and show wide individual variability
- In this series of n of 1 trials in individual patients clinically useful decisions were made for most patients
- Forty per cent of patients changed medication from baseline

variability. This may be due to real between patient differences in response or random within patient variability. In principle, as n of 1 trials give several estimates of effect for each patient they have the potential to give an estimate of between patient variability, by using analysis of variance to separate out the within patient variability. We could not use this in our series, however, because there were too few patients with results that could usefully be analysed.

Favourable comments were received from most participants. Patients came to feel that they had a better understanding of their arthritis and liked taking part in discussions of their results and future treatment. Participating doctors were generally supportive.

In this study n of 1 trials were useful in avoiding unnecessary treatment with non-steroidal anti-inflammatory drugs in many patients with osteoarthritis. This was in a select group of patients, most of whom had generalised osteoarthritis and were already taking non-steroidal anti-inflammatory drugs. We recommend wider use of n of 1 trials to test whether each patient being considered for a non-steroidal anti-inflammatory drug will truly obtain greater benefit than from the use of a safer agent such as paracetamol.

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Commentary: n Of 1 trials may be useful for informed decision making

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Statisticians and clinicians are often parodied as being at opposite ends of a spectrum. On the one hand, statisticians are interested in the effect of treatment only "on average" and they assume that either the treatment works for everyone to a greater or less degree or it works for no one. A clinician, on the other hand, has the immediacy of a patient sitting in front of him or her and wants to know whether the treatment will work for that particular patient. The controversy surrounding so called n of 1 trials, or trials in single subjects, rises largely because of this polarity.^{1,2} March *et al* show n of 1 trials possibly offer a useful methodology for informed decision making. Their paper is an interesting example of an n of 1 trial comparing a non-steroidal anti-inflammatory agent with paracetamol in individual patients with osteoarthritis and could be a model for doctors trying to decide treatment in their patients.

A useful commentary on n of 1 trials was given by Senn, who pointed out that statisticians cannot afford to get on the moral high ground about them.³ One of the most famous statisticians of all time, R A Fisher (after whom the F test is named), described a classic n of 1 trial. This was to decide whether a woman could detect whether milk had been added before or after a tea infusion. She was given a number of cups of tea to taste, in random order.

The study has been extensively discussed and there are many important lessons to be drawn. The first is the importance of randomisation within the subject. The treatments were not simply alternated. The second is that the question was not whether women in general could detect the difference between milk added before and after but whether one particular woman, 70 years ago in Rothamsted, Hertfordshire, could detect the difference.

Another point is that the statistical inference depends very much on the design of the study. Do you tell the subject how many cups of tea she is expected to taste and what proportion have milk added first? In fact, as Senn pointed out, it is better for the subject to know the design in advance.³ If Fisher's subject had not known the design it would have been impossible to

compute the probability of her obtaining any particular result on the assumption that she was guessing (the null hypothesis).

It is worth noting that public health intervention studies, such as the effect of seat belt legislation, are often n of 1 studies, as they have no independent control group. They do not, however, arouse undue controversy. Single case studies seem to be more popular in other disciplines, such as psychology, rehabilitation, and applied behavioural research, possibly because of the more individualistic nature of treatment, and there are many such reports.⁴

Serial data and conventional statistics

A common belief is that when data are measured serially the observations are not independent and so conventional statistical methods cannot be applied. This is not necessarily so. Consider randomly generated numbers purporting to be blood pressure recordings at five minute intervals 20 minutes before and 20 minutes into a psychological stress test. Values are 67, 68, 71, 68, 72, 80, 87, 78, 78, and 79 mmHg. Correlating adjacent observations yields $r=0.60$, $P<0.01$, whereas for the first five observations $r=-0.27$ and for the second five $r=-0.16$ (both $P>0.5$). The correlation is induced by the change in pressure after the first five observations, but around the two readings before and after intervention the observations are plausibly independent. This type of design is probably best analysed by a simple plot, though a two sample *t* test or a permutation test might validly be applied in this case.

Figure 3 in the paper by March *et al* shows clearly the benefit of the non-steroidal agent over paracetamol for a particular patient without the need for a statistical test. Indeed, the statistical analysis of such studies may be complex. Time series methods can occasionally be applied,⁵ though often there are insufficient data for valid conclusions to be drawn. The analysis also includes some of the most controversial or difficult issues in statistics, such as the analysis of crossover trials and sequential analysis. If trials are to be