The efficacy and cost effectiveness of N of 1 studies with diclofenac compared to standard treatment with nonsteroidal antiinflammatory drugs in osteoarthritis

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of combination therapy with diclofenac (50 mg) and misoprostol (Arthrotec; 200 microg twice daily) for the treatment of patients with symptomatic osteoarthritis (OA).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients with symptomatic OA of the knee, hip or hands with pain, who had less than 30 minutes of morning stiffness with no evidence of other rheumatic diseases (e.g. rheumatoid arthritis or chondrocalcinosis). In addition, the patients had to be uncertain whether current NSAID therapy was helpful. Patients were excluded if they had contraindications to NSAID, used oral steroids, were allergic to any NSAID or aspirin, or had an intolerance to diclofenac or Arthrotec. Also excluded were patients who were likely to require joint surgery in the next 6 months, and women with child-bearing potential who were pregnant, breastfeeding or not practising contraception. Other exclusions were patients with major co-morbidity or who were unable to give informed consent, and patients who had received an intraarticular injection in the last 3 months.

Setting
The setting was primary care. The economic study was conducted in Canada.

Dates to which data relate
The dates relating to the collection of effectiveness and resource use data were not reported. The price year was 1996.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were performed in the preliminary phase of the study. These suggested that 26 patients per group were needed to find a difference (≥20%) between the groups, based on a 14-mm improvement in patient global
assessment, a baseline Stanford Health Assessment Questionnaire (HAQ) of 0.9 and a standard error of the mean of 0.13, with 80% power at a 5% significance level. The patients were recruited from rheumatology practices and through a newspaper advertisement. The study sample comprised 51 patients, 24 in the N of 1 group and 27 in the conventional group. In the N of 1 group, the mean age was 59 (+/- 2.3) years and the duration of OA disease was 12.7 (+/- 2.2) years. In the conventional group, the mean age was 54 (+/- 2.4) years and the duration of OA disease was 14 (+/- 2.3) years. The baseline HAQ score was 0.84 (+/- 0.12) in the N of 1 group versus 0.92 (+/- 0.12) in the conventional group. It was not stated whether any patients were excluded from the initial study sample for any reason.

**Study design**

This was a double-blind, parallel-group, randomised clinical trial, in which the patients were randomised to conventional therapy or N of 1 trials (with crossover of placebo and study drugs). Randomisation was stratified according to the most symptomatic area of OA (hip, knee or hands). In the N of 1 group, active or placebo preparations of diclofenac were administered in a randomised, concealed allocation in balanced blocks of 2. The intervention patients received 2 weeks of placebo or diclofenac and continued for a maximum of 3 cycles (3 months). Every 4 weeks they chose which treatment they preferred. In each cycle, both the investigator and the patient were unaware of the order in which the placebo and active drugs were administered and received. All of the patients were seen monthly for 3 months and then again at 6 months. Both groups underwent the same assessment steps to ensure blinding and to avoid both performance and assessment bias. In particular, the frequency of visits in the conventional group was artificially increased to maintain concealment of treatment allocation from the research assistant. The length of follow-up was 6 months. Eight patients in the conventional group and 3 in the N of 1 group dropped out. The majority of patients dropped out due to a lack of interest, given that no new therapies were available in the trial.

**Analysis of effectiveness**

The analysis of the clinical study was conducted on an intention to treat basis. The primary outcome measure was the patient global assessment (100 mm visual analogue scale, VAS). The secondary outcome measures were:

- physician global assessment;
- the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score for lower extremity OA and HAQ score for upper extremity OA;
- the HAQ disability and pain scores;
- the Lequesne index for patients with lower extremity OA; and
- the Medical Outcome Study Short-Form-36 (SF-36).

The side effects of the therapies, as well as patient preferences, were also recorded. The study groups were comparable at baseline in terms of their demographics and disease characteristics.

**Effectiveness results**

After 6 months, 17 of 24 patients (71%) in the N of 1 group and 18 of 27 patients (67%) in the conventional group were taking NSAIDs. The NSAIDs used in the N of 1 group at 6 months were diclofenac (11 patients), naproxen (3 patients), and tenoxicam, tiaprofenic and ibuprofen (1 patient each). The NSAIDs used the conventional group were naproxen (7 patients), diclofenac (5 patients), tenoxicam (4 patients), ketoprofen and tiaprofenic acid (1 patient each). Side effects were more frequent in the N of 1 group than in the conventional group.

The average number of toxicities and adverse events per patient was 0.26 in the conventional group and 1.33 in the N of 1 group. (p=0.001).

There was a slight improvement in the HAQ disability and HAQ pain rating for the N of 1 group compared with the conventional group. However, none of these differences were statistically significant, (p>0.05).
A trend favouring the N of 1 group was found for patient global scales. No statistically significant differences were found for the other health outcomes (e.g. WOMAC, Lequesne and SF-36).

**Clinical conclusions**

The effectiveness analysis suggested that there were no statistically significant differences in the main health outcomes between the two therapies. Although a trend in favour of N of 1 patients was found for HAQ scores and patient global scales, N of 1 patients experienced significantly more adverse events in comparison with patients taking conventional therapy.

**Measure of benefits used in the economic analysis**

No summary benefit measure was used in the economic analysis because there was no statistically significant difference between the groups in terms of outcome measures. Therefore, it appears that a cost-minimisation analysis has been conducted. However, as the health outcomes were left disaggregated, the study could also be considered a cost-consequences analysis.

**Direct costs**

Discounting was not relevant since the costs were incurred during 6 months. The unit costs were not presented separately from the quantities of resources used. Only the time spent by nurses and physicians was reported separately from their costs. The health services included in the economic evaluation were medications for OA, laboratory tests, treatment of side effects, and the physicians' and nurses' time for visits. The cost/resource boundary of the analysis reflected the societal perspective adopted in the study. The source of the cost data was not reported. Resources use was estimated from the actual data evaluation alongside the clinical trial. The price year was 1996 and there was no inflation adjustment.

**Statistical analysis of costs**

Standard statistical analyses were conducted to test the statistical significance of differences between the groups in the estimated total costs.

**Indirect Costs**

The indirect costs associated with the patients' time, time of a driver (if indicated) and travel time were included in the study since a societal perspective was adopted. No discounting was applied due to the short time horizon of the analysis. The quantities of resources used were derived from individualised data estimated from the sample of patients included in the effectiveness study. The costs came from the US Bureau of Labor Statistics for both working and non working patients. The time amounts were converted to costs using the patient's salary, hourly wage, or an appropriate conversion for homemakers or retired people. The unit costs were not presented separately from the quantities of resources used, but the patient's time spent for visits was presented. The price year was 1996.

**Currency**

Canadian dollars (Can$).

**Sensitivity analysis**

No sensitivity analyses were performed.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.
Cost results
When all visits were included (including those artificially generated in the conventional group), the total costs were Can$494.32 (+/- 266.06) in the conventional group and Can$551.39 (+/- 154.02) in the N of 1 group, (p=0.3650).

When only completers were considered, the total costs were Can$533.48 (+/- 175.33) in the conventional group and Can$565.39 (+/- 143.37) in the N of 1 group, (p=0.5308). However, if protocol-generated visits were removed from the conventional group, then the costs for patients receiving standard care were significantly lower than for patients in the N of 1 group, both for all patients and for completers only, (p<0.01).

Synthesis of costs and benefits
The costs and benefits were not combined, as there was no statistically significant difference in either the costs or outcomes between the two groups.

Authors’ conclusions
The use of N of 1 trials of non-steroidal anti-inflammatory drugs (NSAIDs) for patients with osteoarthritis (OA) did not result in significant improvements in clinical outcomes or reductions in costs. When artificially generated visits were excluded in the conventional group, the use of N of 1 trials was statistically more costly.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. The selection of standard NSAID therapy reflected usual care for patients with OA. You should decide whether this represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a clinical trial, which was appropriate for the study question. A particular design was adopted to fit the characteristics of the disease under evaluation and to verify the study hypothesis. The internal validity of the analysis was further enhanced by several factors. For example, the performance of power calculations, the application of a double-blind method for outcome assessment, the use of intention to treat, and the baseline comparability of the two groups of patients. An identical assessment was carried out in both groups to reduce potential bias. However, since the participants were volunteers, it was unclear whether the study sample was representative of the study population. Further, the dropout rate was high. Finally, the study may have had insufficient power to detect statistically significant differences in all outcome measures.

Validity of estimate of measure of benefit
No summary benefit measure was used in the study because a cost-minimisation analysis was conducted. Given that the health outcomes were left disaggregated, the study could also be classified as a cost-consequences analysis.

Validity of estimate of costs
The authors stated explicitly the perspective adopted in the study and it appears that all the relevant categories of costs were included. The price year was reported, which would facilitate reflation exercises in other settings. Statistical tests were conducted when the estimated costs were compared. However, the cost estimates were not varied in a sensitivity analysis. The source of the direct costs was not reported and the quantities of resources used were not presented separately from the unit costs. The analysis of costs was conducted both on an intention to treat basis and including treatment completers only.

Other issues
The authors made some comparisons of their findings with those from other studies whose results were not clearly reported. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not conducted. Therefore, the external validity of the analysis was low. The authors noted some limitations to the
validity of the analysis. The study referred to patients with OA not responding to standard therapy and this was reflected in the authors' conclusions.

Implications of the study
The study results suggested that N of 1 trials of NSAIDs are not cost-effective in patients with OA. However, the conclusions of the study were affected by the small sample size considered in the analysis.

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Other publications of related interest


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