

Kirthi V, Derry S, Moore RA, McQuay HJ. Aspirin with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2010, Issue 4, Article # CD008041.

Design: Meta-analysis of randomized clinical trials

PICOS:

- Patient population: Adults with migraine with or without aura defined by International Headache Society criteria
- Intervention: Self-administered single dose of aspirin taken to treat a migraine headache when pain was of moderate or severe intensity; studies of aspirin plus an antiemetic were included, provided that both aspirin and the antiemetic were self-administered
- Comparison/control intervention: Placebo by self-administration
- Outcomes: Principal outcomes were measured 2 hours and 24 hours after drug administration; for the 2-hour mark, the major outcome was being pain-free, and the secondary outcome was having pain reduction (headache relief); for the 24-hour mark, the outcomes were sustained pain-free and sustained pain reduction, both of which had to be maintained without use of a second dose of any medication
- Study types: randomized double-blind, placebo-controlled or active-controlled studies with at least 10 participants in each arm, reporting dichotomous (success/failure) data for one of the principal outcomes

Study type and selection:

- Databases searched were MEDLINE, EMBASE, Cochrane CENTRAL, and the Oxford Pain Relief Database through 22 April 2010
- Two authors independently selected studies for inclusion, resolving disagreements through discussion with a third author
- Risk of bias was assessed with a five point scale: being randomized, adequate description of the randomization procedure, being double-blind, adequate description of the double-blinding method, and full accounting for dropouts and withdrawals from the study
- Treatment effects were reported as relative risks (RR) of success, in which RR greater than 1 indicates that aspirin is more likely to yield successful treatment of the headache symptoms
 - o Numbers needed to treat (NNT) were calculated as the number of patients who would need treatment with aspirin in order to produce one successful therapeutic outcome
- Most studies were parallel group trials; when crossover trials were included, the first-period data were used in the analysis

Results:

- 13 studies with 4222 participants, providing data on 5261 treated migraine attacks, met inclusion criteria for review and analysis; none were considered to have a high risk of bias
 - o 5 of these studies had only a placebo comparison, 4 had only an active drug comparison, and 4 had both placebo and active drug comparisons
- Aspirin doses of 900 and 1000 mg were considered sufficiently similar to combine for purposes of meta-analysis, and all comparisons were based on this dose of aspirin
- For comparisons of aspirin with placebo, 6 studies with 2027 patients reported on pain-free status at 2 hours, 4 studies with 1288 patients reported on headache relief at 1 hour, 6 studies with 2027 patients reported on headache relief at 2 hours, and 3 studies with 1142 patients reported on sustained headache relief at 24 hours
 - o Aspirin provided 2 hour pain-free status for 24% of patients, compared with 11% for placebo, for RR of 2.1
 - o Aspirin provided 1 hour headache relief for 37% of patients, compared with 15% for placebo, for RR of 2.4
 - o Aspirin provided 2 hour headache relief for 52% of patients, compared with 32% for placebo, for RR of 1.6
 - o Aspirin provided 24 hour sustained relief for 39% of patients, compared to 24% for placebo, for RR of 1.6
- For comparisons of aspirin with an active drug, 2 studies with 726 patients reported on 2 hour pain-free status compared with sumatriptan 50 mg, the same 2 studies reported on headache relief at 1 hour, and the same 2 studies also reported on headache relief at 2 hours, but neither study reported on 24 hour sustained headache relief
 - o Aspirin provided 2 hour pain-free status for 26% of patients, compared to 32% for 50 mg sumatriptan; the difference was not significant
 - o Aspirin provided 1 hour headache relief for 24% for sumatriptan, for RR of 1.6 in favor of aspirin
 - o Aspirin provided 2 hour headache relief for 51% of patients, compared with 53% for placebo; the difference was not significant
- For comparisons of a combination of aspirin with metoclopramide with placebo, 2 studies with 519 patients reported pain-free status at 2 hours; 3 studies with 726 patients reported headache relief at 2 hours, and 1 study with 257 patients reported on sustained headache relief at 24 hours
 - o Aspirin with metoclopramide provided 2 hour pain-free status for 18% of patients, compared with 7% for placebo, for RR of 2.7
 - o Aspirin with metoclopramide provided 2 hour pain relief for 52% of patients, compared with 32% for placebo, for RR of 1.6
 - o Aspirin with metoclopramide provided sustained headache relief for 37% of patients compared with 17% for placebo, for RR of 2.2
- For comparisons of aspirin with metoclopramide 10 mg with an active drug, 2 studies with 525 patients reported pain-free status at 2 hours, and the same studies reported headache relief at 2 hours

- Aspirin with metoclopramide provided 2 hour pain-free status for 18% of patients, compared with 28% for 100 mg sumatriptan, for an RR of 0.63, which is equivalent to an RR of 1.6 in favor of sumatriptan (sumatriptan was more effective than aspirin with metoclopramide)
- For 2 hour pain relief, there was no difference in response to aspirin with metoclopramide (51%) and 100 mg sumatriptan (54%)
- Subgroup analyses were done for some outcomes comparing aspirin alone with aspirin plus metoclopramide
 - For two outcomes, pain-free status at 2 hours and for 24 hour sustained relief, no significant differences were calculated between aspirin alone and aspirin with metoclopramide
 - However, for 2 hour headache relief, subgroup analysis favored aspirin with metoclopramide over aspirin alone
- Another subgroup analysis did not show a difference between soluble (E.g., effervescent) preparations of aspirin and aspirin tablets
- However, another subgroup analysis showed aspirin with metoclopramide more effective than aspirin alone for relief of nausea and vomiting associated with migraine episodes
- Adverse events were slightly more frequent (172/1230; 14%) with aspirin (with or without metoclopramide) than with placebo (136/1228; 11%)

Authors' conclusions:

- Aspirin 900 or 1000 mg is an effective treatment for migraine headaches and their associated gastrointestinal symptoms
- Adding an antiemetic such as metoclopramide to aspirin may provide additional pain relief and additional relief of nausea
- Oral sumatriptan 50 or 100 mg may be comparable to aspirin for headache relief, but 100 mg of sumatriptan may be better than aspirin for complete headache relief at 2 hours; since the amount of information for the comparison of aspirin and sumatriptan is small, conclusions about their relative effectiveness must be made cautiously
- The studies are not likely to have been biased toward milder migraine headaches, since patients were recruited from headache clinics
- Most migraine patients treat their headaches before they become severe; for early treatment of headache, sumatriptan may be a better choice than aspirin in daily practice

Comments:

- As is the case with other Cochrane reviews, many studies of interventions do not consistently report the prespecified outcomes of interest to the Cochrane library; the review process may tend to provide a conservative estimate of the effectiveness of selected interventions
- Numbers needed to treat (NNT) are provided for the “statistically significant” comparisons between aspirin and other interventions; however, NNT in meta-analysis can be sensitive to differences in placebo response rates, and interpretation of NNT needs to be cautious

- Heterogeneity of effect sizes in most of the meta-analysis summaries was low, but the comparison of aspirin versus 50 mg sumatriptan involved two studies by the same author in the same year, one of which showed no difference and one of which favored sumatriptan (Diener 2004a and 2004b, Figure 5); while the statistical tests for heterogeneity fall short of statistical significance, the reason for the difference is not apparent or explored
- The number of trials of aspirin versus placebo is sufficient to be confident in its superiority
- The comparison of aspirin and sumatriptan at 2 hours is not clearly indicative of the superiority of sumatriptan, since the difference between pain-free status (sumatriptan appears better than aspirin) and headache relief (the drugs appear the same) can be sensitive to small differences in interpretation of the meaning and reporting of the two outcomes
 - o The fact that sumatriptan was superior to aspirin plus metoclopramide for pain-free status at 2 hours stands in contrast to its equivalence to aspirin without metoclopramide in those comparisons

Assessment; Adequate for strong evidence that aspirin is superior to placebo for single migraine attacks; for good evidence that addition of an antiemetic to aspirin makes it more effective for headache and associated symptoms; inadequate for evidence that sumatriptan is better than aspirin plus metoclopramide