

Extended Abstracts: Acetylsalicylic Acid (ASA)

Primary Literature

- 1) Steiner T, Lange R, Voelker M. Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. *Cephalalgia* 2003; 23(1): 59–66.

Study Objectives: The primary objective of this trial was to compare the efficacy of single-dose aspirin 1000 mg versus placebo for pain relief two hours after their ingestion in patients with moderate to severe tension type headaches (TTHs). Secondary objectives included comparing the relative efficacy of various doses of aspirin and acetaminophen to each other and placebo, and to compare tolerability of treatments.

Methods

Design: Randomized, double-dummy, controlled clinical trial

Allocation: Allocation unconcealed.

Blinding: Double-blinded (double dummy)

Follow-up period: Patients and their diary cards were followed up within 14 days after treatment.

Setting: Outpatient setting in the United Kingdom (UK); location of follow-up interviews is unclear.

Participants: (n=542) Patients were aged 16-65 and recruited from the UK general population by advertisement in general practitioner surgeries and local newspapers. Patients needed to meet the IHS diagnostic criteria for episodic TTH but not those for migraine and did not have other serious physical or mental illness or contraindications to either treatment. Exclusion criteria included women who were or might become pregnant, concomitant use of antidepressants and any medications known to interact with aspirin or acetaminophen.

Intervention: Participants were randomly allocated to the five trial treatment groups: ASA 500 and 1000 mg, paracetamol 500 and 1000 mg, and placebo. Following screening and randomization, each subject received a diary card and one dose of trial medication. Patients were instructed to treat within 8 weeks of enrolment one episode of TTH of at least moderate intensity, not improving at the time of treatment and with onset 1–12 h earlier. No prior treatment for the headache was allowed. Rescue medication was permitted after 2 hrs, and its use recorded in the diary card.

Outcomes: The primary outcomes were the difference in pain intensity on visual analog scale (VAS) at 0, 30, and 45 mins and 1, 2, 3, 4 and 24 hrs after treatment. Subjects were asked to report any adverse events (including severity and duration).

Patient follow-up: 100% of ITT population (542/542).

Main Results

For the primary endpoint of pain relief (measured by VAS) at 2 hrs after treatment, aspirin 1000 mg (75.7% response rate, $p=0.00009$), ASA 500 mg (70.3%, $P=0.0007$) and acetaminophen 1000 mg (71.3%; $P=0.011$), but not acetaminophen 500 mg (63.8%, $P=0.104$) were superior to placebo. At 54.5%, placebo response rates were higher than expected. Outcome was unaffected by headache intensity at baseline. Differences between active treatment and placebo were apparent at 30 minutes for ASA 1 g,

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and at 2 hrs for acetaminophen 100 mg and ASA 500 mg. Adverse events were reported by 13.4-18.9% of patients and tended to be mild or moderate and transient. A small excess of GI events were reported with ASA (5.8-6.3%) and acetaminophen (3.6-3.8%) compared to placebo (2.7%) was not dose related.

Conclusions

The authors concluded that aspirin 1000 mg, and perhaps to a lesser extent aspirin 500 mg and acetaminophen 1000 mg, were effective in treating moderate and severe episodic TTH. Aspirin 1000 mg also appeared to have a quicker onset than ASA 500 mg or acetaminophen 500 or 1000 mg. Both acetaminophen and ASA were thought to be well tolerated, with no serious safety concerns with either drug.

Comments/Critical Appraisal

There are several strengths to this study. Unlike many other studies involving ASA, this is a double blinded, placebo-controlled trial that permits us to directly compare ASA and acetaminophen with each other and placebo, as well as to establish causation. The IHC definition was used to clearly distinguish between TTHs and migraines. Baseline characteristics between the treatment groups were compared and appeared relatively similar. Inclusion and exclusion criteria were clearly outlined. In addition, an intention-to-treat analysis population was considered which reduces the risk of bias.

Despite these strengths, there were some limitations to this study. Importantly, the primary endpoint of this study was the difference in pain intensity scores at 2 hrs. While a greater difference in pain intensity is certainly preferred, a larger difference does not necessarily equate to pain relief. A more clinically relevant endpoint may have been pain relief (“I am totally pain free”) at the 2 hour time point. In addition, several minor details were missing in the study, all of which are potential threats to internal validity: The method of patient allocation and randomization is not provided in the study. Some important baseline characteristics such as caffeine use were not included and may have been confounding factors. Paired statistical comparisons between baseline patient characteristics were not provided. In addition, the design of the study relies on patients to be able to distinguish between moderate TTHs and migraine, to take the active treatment when they get one, and to accurately record assessments of pain at discrete time points. Patients were also asked questions retrospectively at the 14- day follow-up interview. The potential low reliability of this data may potentially lower the study’s interval validity. The applicability of the study results may also be limited by the fact that the study only examines the efficacy of acetaminophen and ASA for a single episode, thus reducing the risk of intra-patient variability.

The external validity is bolstered by the fact that the study occurred in an outpatient setting, mimicking a real-life scenario when patients would decide to use ASA or acetaminophen for treating their TTHs. A wide age range (16-65 years old) of patients was included in the study, thus allowing us to extrapolate results to a relatively large population. However, since children < 16 and seniors > 65 were not examined in this study, we cannot necessarily apply the results to these populations. The trial also explicitly excluded pregnant and breastfeeding women.

Despite the limitations to this study, this study is one of the few high-quality RCTs comparing ASA with acetaminophen and placebo, and demonstrates that ASA 1 g is effective at reducing pain-associated with TTH and at least equivalent, and perhaps superior, to acetaminophen.

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- 2) Martínez-Martín P, Raffaelli E Jr, Titus F, et al. Efficacy and safety of metamizol vs. acetylsalicylic acid in patients with moderate episodic tension-type headache: a randomized, double-blind, placebo- and active-controlled, multicentre study. *Cephalalgia*. 2001; 21(5): 604-10.

Study Objectives

The primary objective of the study was to investigate the efficacy, safety and tolerability of oral single doses of 0.5 g and 1 g metamizol and 1 g ASA relative to placebo in episodic TTHs.

Methods

Design: Randomized, placebo- and active- controlled parallel group study

Allocation: Allocation concealed

Blinding: Double-blinded (double-dummy)

Follow-up period: N/A

Setting: 31 participating centres in Spain and Brazil; 3 included less than 4 patients

Participants: (n=360) Men and women aged between 18-65 with moderate episodic TTHs (IHS definition) were considered if they had at least 2 episodes of TTHs per month in the 3 months prior, previous pain relief with non-opioids analgesics were successful, and the first episode occurred before 50 years of age. Exclusion criteria included hypersensitivity or contraindications to treatment drugs, history of drug or alcohol abuse, more than 15 TTHs per month, prior treatment with antidepressants, anti-psychotropics, NSAIDs, anti-migraine medications or concomitant heparin or warfarin. Pregnant and nursing women were also excluded.

Intervention: Patients were randomly assigned to either 0.5 g metamizol or 1 g metamizol, 1 g ASA or placebo. Medication was given orally as single doses. The individual patient received a single treatment at the beginning of the trial for the first episode and at visit 2 for the second episode of tension-type headache. All patients were instructed to take a single dose of study medication when headache was perceived to be at least moderate. Subsequently, the patient had to record the headache pain intensity and pain relief over an observation period of 4 h in the diary provided. The decision on the type and dose of rescue medication was at the discretion of the investigator and was allowed only 2 h after intake of the investigational treatment.

Outcomes:

The primary efficacy endpoint was defined as the time interval weighted sum of pain intensity difference (SPID) from baseline on a visual analogue scale (VAS). All patients recorded the pain intensity prior to and then 30 min and 1, 2, 3 and 4 h after drug intake in the provided diary. All patients also scored pain relief on a 5-point verbal rating scale at these time-points.

Patient follow-up: 100% (360/360)

Main Results: The resulting time interval weighted mean SPID over both episodes was 12.20, 12.64, 10.56 and 8.10 for 0.5 and 1 g metamizol, 1 g ASA and placebo, respectively. All 3 active treatments had a SPID statistically superior to placebo (for ASA, $P < 0.015$). Metamizol 0.5 and 1 g were non-inferior to 1 g ASA and there was a trend towards superior efficacy of 1 g metamizol over ASA. The extent of pain

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relief was more significantly pronounced with metamizol compared to ASA up to 1 hr after one drug intake, but did not differ beyond 1 hr after administration.

Conclusions: The authors concluded that a clear and consistent trend towards an earlier onset and more profound pain reduction and pain relief of either metamizol dose over 1 g ASA was observed. Metamizol and ASA were approximately equally safe and well tolerated.

Comments/Critical Appraisal

This is another well-conducted clinical trial which on the whole, demonstrates that ASA is superior to placebo, but may be less effective (in terms of time to onset and extent of pain relief) than metamizol, which is known to be a much more potent NSAID. Like Steiner et al, this trial contained many hallmarks of good clinical studies, including being double-blinded, randomized and placebo and active controlled. Unlike Steiner et al, this study clearly specified the method of randomization, allocation and blinding and is one of the few studies with ASA in this research area to do so. Drop-outs and withdrawals were accounted for and did not appear to skew the study populations. The authors also used a relatively high level of significance of $P < 0.025$ (one-sided), compared to $P < 0.05$, which reduces the risk that observed differences were due to chance. On the negative side, the baseline characteristics were stated to be similar between the four groups, however, they were not clearly laid out in a table nor were statistical procedures performed to detect differences. Sharing a similar diary method of recording events as the Steiner et al trial, this study also suffers from the same inherent problems of this study design, which including high rater subjectivity and variability, as well as potential data loss due to not documenting events or from memory loss. In addition, it also uses pain intensity as the primary index of efficacy. Again, a difference in pain intensity does not necessarily reflect a pain-free status due to the subjective nature of pain.

In terms of external validity, the inclusion criteria (18-65 years old with 2-15 TTHs per month) clearly capture a typical patient with episodic TTH. In addition, like Steiner et al, the outpatient nature of this study is highly reflective of the real clinical scenario and elevates the external validity. Of note, there were significantly more females and men in the study population (271 vs. 89). While this is justified given the higher incidence of episodic TTH in women compared to men, study results may not necessarily apply as much to men as to women. In addition, the exclusion criteria explicitly excluded concomitant use of a variety of medications, including antidepressants, antipsychotics and benzodiazepines. While this was necessary to ensure internal validity, it may not necessarily be applicable to reality as patients with episodic TTH may also present with several comorbid mental conditions such as depression.

Secondary/Tertiary Literature

- 3) Bendtsen L, Evers S, Linde M, et al. EFNS Guideline on the Treatment of Tension-Type Headache. *Eur J Neurol.* 2010, 17(11): 1318–25.

Study Objectives: To provide evidence-based or expert recommendation for different treatment procedures in TTH, including aspirin, based on literature search and the expert consensus.

Scope: Trials published in English and with adult patients (aged 18 and older) with reasonable criteria designed to distinguish TTH from migraine were considered. For drug treatments, only randomized

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placebo-controlled trials and trials comparing different treatments were included. No other restrictions in terms of patients, intervention, outcomes or duration were imposed.

Methods: All authors independently performed a literature search of the Medline, Science Citation Index and Cochrane Library databases using the keyword 'tension-type headache.' Recommendations from a review book and from the British Association for the Study of Headache were also considered. The Chairman wrote the first draft of the manuscript. He wrote three additional drafts after changes were discussed by other panel members via email. All recommendations had to be agreed upon unanimously. Recommendations were graded as level A, B or C, following the EFNS criteria.

Main Results: In the acute treatment of TTH, the authors determined that ASA has been reported in multiple studies to be more effective than placebo in doses of 1000 mg, 500 mg to 650 mg and 250 mg. Limited evidence suggested that there is a significant dose-response relationship with ASA, with 1000 mg likely being the most effective dose. One study found no difference in efficacy between solid and effervescent ASA. A review of the literature revealed that NSAIDs appear to perform consistently better than placebo; however, no one particular NSAID appears to be superior. Five studies demonstrated that NSAIDs were more effective than acetaminophen, while 3 other studies found no effect. While no differences in adverse events were found between NSAID, acetaminophen or placebo in the extracted trials, ibuprofen is associated with the fewest GI events of the NSAIDs.

Conclusions: Along with acetaminophen and other NSAIDs (ibuprofen, ketoprofen, naproxen, diclofenac), the guideline provided a Level A recommendation for aspirin 500 – 1000 mg as an acute therapy of TTH. Despite acetaminophen and NSAIDs all being considered first line, the authors suggested that ibuprofen is preferred due to its probable superiority over acetaminophen and safer side effect profile compared to other NSAIDs. The panel suggested that efficacy of simple analgesics, including acetaminophen and aspirin, tends to diminish with increasing frequency of headache. Their use may be limited to moderate TTH due to modest benefits compared to more potent treatment options.

Comments/Critical Appraisal

The internal validity of this guideline is elevated by the systematic approach that has been utilized to develop the guideline recommendations. For example, the search strategy was transparent and could be replicated. Keyword terms used were inclusive. Literature searches were conducted independently, thus increasing objectivity and reducing potential inter-reviewer bias. In terms of the extracted studies, only randomized placebo- and comparator- controlled trials were considered; this represents the highest level of evidence possible for any individual trial. Search strategy and definitions for recommendation levels conducted were those standardized to all other EFNS guidelines.

On the other hand, internal validity of this guideline may be threatened by the fact that the limitations of individual studies were not discussed. Although the level of evidence was assigned to each recommendation, a review of the references reveals that the quality of the studies supporting these recommendations was highly variable. Increased discussion of this variability or application of a systematic way to rate the quality of the individual trials (see **BELOW**) may have enhanced the internal validity of this guideline even further.

In terms of external validity, potential limitations to applicability of the data include the fact that only adult data is considered, and only English trials were abstracted. This means that results are not

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directly applicable to pediatric and senior populations. In addition, studies from different countries of value may have been excluded from the analysis.

- 4) Verhagen AP, Damen L, Berger MY, et al. Is any one analgesic superior for episodic tension-type headache? *J Fam Pract* 2006(12); 55:1064–72.

Study Objectives: To describe and assess the data from randomized controlled trials regarding the efficacy and tolerability of analgesics for the treatment of acute TTH episodes in adult patients.

Scope: The selection criteria for studies were as follows: Only RCTs including analgesic medicine used in the treatment or management of TTH conducted among adult patients (aged 18 years or older), with reasonable criteria designed to distinguish TTH from migraine, were selected. The use of a specific set of diagnostic criteria was not required, but TTH diagnoses had to be based on at least some of the distinctive features of TTH (ex. bilateral, no nausea or vomiting, mild or moderate intensity, or no exacerbation by exercise). Main outcome measures were pain relief or recovery over 2 to 6 hours.

Methods: Medline and EMBASE were searched from inception to January 2005 using the terms *tension-type headache*, *tension headache*, *stress headache*, or *muscle contraction headache* together with the search strategy for identifying RCTs. The Cochrane Controlled Trials Register was searched using the words *tension headache* or *tension-type headache* or *muscle contraction headache*. Additional strategies for identifying trials included searching the reference lists of review articles and included studies. Studies were selected using the selection criteria described above: in brief, only RCTs involving adults and treatment options for acute TTH were included. Of the 1878 RCTs retrieved, 41 met the inclusion criteria and were included in the systematic review. Two authors independently rated the methodological quality of the included trials using the Delphi list. Extraction of data from the original reports was performed by 1 author and checked by a second. Disagreements were resolved by consensus. Extracted information included (if available) demographic data, detailed description of the intervention and control (ie, dose given, study duration, rescue medication), data on pain relief or recovery, and information on adverse effects measured during a treatment period of 2 to 6 hours. Quantitative and qualitative analysis of the extracted data was performed.

Main Results:

Compared to placebo, NSAIDs, including ASA, were significantly more effective for short-term pain relief. Pool relative risk for adverse effects did not differ. Relative to acetaminophen, 6 high-quality quality studies demonstrated that NSAIDs were not significantly more effective than acetaminophen for acute TTH treatment. Seven studies compared different types of RCTs comparing NSAIDs, of which two involved aspirin. The authors found no significant differences in the efficacy of NSAIDs, including aspirin; non-significant differences in relative risk of TTH were found in the two ASA trials. In terms of tolerability, naproxen and zomepirac were associated with more centrally mediated adverse effects than aspirin, naproxen and ketoprofen. However, the systematic review found that, based on one trial, aspirin was associated with more gastrointestinal complaints than ibuprofen. Fatigue and cramps were also more common with ketoprofen, naproxen and zomepirac than with ibuprofen.

Conclusions: The authors concluded that acetaminophen and NSAIDs, such as aspirin, are effective in treating acute TTH symptoms. An effective and well-tolerated dose of either of these two medications is a reasonable choice for treating patients with episode TTH. However, the authors suggest that ibuprofen is a prudent first choice due to its efficacy and favorable side effect profile. For patients

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allergic to NSAIDs or on concomitant warfarin, the use of acetaminophen is suggested. Only 35% of included RCTs were deemed to be of high quality.

Comments/Critical Appraisal:

This systematic review contains most of the elements of what one would consider a well-performed systematic review: The rationale was well established and the objectives were clearly identified. The eligibility criteria and information sources were readily available and rationale for the search strategy were aptly described so it could be repeated, though perhaps limits used could have been identified. The rationale for study selection was provided with a narrow focus on only RCTs and studies involving adult patients. Two authors independently screened titles and abstracts for eligibility and, unlike the European guideline (above), rated study quality using a validated criteria (Delphi list). An objective third party resolved disputes between the two authors, which occurred. Methods of qualitative and quantitative analysis were explained. Tables clearly lay out the results of individual trials in terms of whether they are low or high quality and indicate the relative risk of comparisons made. A summary of studies was provided, as well as a discussion of limitations, conclusion and funding sources. Even more, the systematic review examined the risk of potential bias with studies, including the potential for selection bias and from funding sources. Overall, this systematic review was well conducted and meets the majority of elements from the PRISMA checklist used to evaluate systematic reviews and meta-analyses.

In terms of external validity, the authors exclusively looked at high quality RCTs to draw conclusions and a mere 35% of studies were rated as high quality (6/10 on the modified Delphi list). This low percentage speaks to the many methodological shortcomings of studies assessing the efficacy of analgesics in TTHs. Since the medications, including ASA, have only been evaluated in 1 or 2 high quality trials, the conclusions presented are not definitive and the authors admit that generalizability of findings may be limited.

Other Literature Types

5) Farinelli I and Martelletti P. Aspirin and tension-type headache. *J Headache Pain*. 2007; 8(1):49-55.

Source Description: This narrative review in the peer-reviewed *Journal of Headache and Pain* discusses the role of ASA in the treatment of episode TTH. Published in January 2007 (with last revisions received on December 19, 2006), the review delves into the various historical and current uses of aspirin, proposed mechanisms of action and unique features of ASA compared to other NSAIDs including the ability to induce lipoxins. In-text referencing is used throughout the article to support assertions. In addition to the above, the literature regarding the use of ASA in the treatment of TTHs and migraines is summarized. The authors, both of whom represent the Sapienza University of Rome, also describe a new formulation of ASA.

Summary: With respect to the clinical utility of ASA in treating TTH, the authors conclude that aspirin is useful for acute treatment of pain relief due to its low cost, availability and lack of a requirement for a prescription. The authors review the literature supporting the use of ASA with focus on Steiner et al.'s study (see above) which suggested that ASA 1 g is more effective than ASA 500 mg and acetaminophen 500 mg or 1000 mg at treating TTHs. Two other small RCTs showing beneficial outcomes with ASA in treating TTHs are also briefly discussed. The authors review pharmacokinetic evidence that suggests a new formulation of ASA, composed of dry granules, is faster acting than standard ASA tablets with

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similar efficacy and adverse effects. In general, the authors conclude the role of ASA in headache therapy has not been sufficiently investigated and further studies are warranted.

Comments/Critical Appraisal: To the best of this writer's knowledge, this is the only narrative review or other literature which focuses on the multiple facets of ASA in TTH, including its role in treatment as well as potential mechanisms of action. In terms of how the review addresses the efficacy of ASA, it very much affirms the other information sources presented in the extended abstract that call ASA is a relatively safe and effective first line option for acute treatment of moderate TTHs. Due to its focus on ASA and in particular, the study lead by Steiner et al, the generalizability of the findings in this review is limited. Without any mention of the relative efficacy of ASA compared NSAIDs, it is difficult to ascertain the place in therapy of ASA by reading this review alone. In addition, it is difficult to make strong recommendations for the use of ASA, as this review dose, after discussing mainly just one efficacy trial. In addition to limitations in external validity, the internal validity of this review is also questionable, as it is unclear whether the author has included all relevant trials pertaining to the role of ASA in treating TTHs.
