Effect of standard dose paracetamol versus placebo as antipyretic therapy on liver injury in adult dengue infection: a multicentre randomised controlled trial

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Summary

Background Dengue is a common cause of acute liver failure in tropical countries. Paracetamol is the recommended antipyretic for dengue. Related observational studies in dengue have suggested that excessive paracetamol intake is linked to hepatic injury. We aimed to evaluate whether standard dose paracetamol as an antipyretic in dengue infection caused transaminase elevation, and to evaluate the efficacy of paracetamol.

Methods In this randomised, double-blind, placebo-controlled trial, adult participants (aged ≥18 years) with dengue, as confirmed by either positive NS1 antigen, positive dengue IgM antigen with thrombocytopenia, or positive PCR test, were enrolled at three Royal Thai Army hospitals in Thailand. Key exclusion criteria were baseline AST or ALT concentrations of more than 3 times the upper limit of normal, cirrhosis, indication of paracetamol other than dengue infection, concurrent diagnosis of other causes of fever, or pregnancy. Patients were randomly assigned (1:1), by a computer-generated block randomisation procedure (block size of six), to receive either paracetamol (500 mg) or placebo (500 mg) every 4 h when body temperature exceeded 38°C during hospitalisation. Participants and investigators were masked to treatment assignment. The primary outcome was the proportion of participants with transaminase elevation, defined as serum aspartate transaminase (AST) and alanine transaminase (ALT) concentrations of more than 3 times the upper limit of normal on recovery day, in the intention-to-treat population. Prespecified interim analyses for safety and efficacy were performed with group sequential stopping boundaries. This trial is registered with ClinicalTrials.gov, number NCT02833584.

Findings Between Sept 1, 2016, and Dec 12, 2017, 125 participants were randomly assigned to receive either paracetamol (n=63) or placebo (n=62). 123 participants were included in the intention-to-treat population. The median daily dose of study medication was 1·5 g (IQR 0·8–2·0). The study was terminated early owing to a higher incidence rate of transaminase elevation in the paracetamol group than in the placebo group (22% vs 10%; incidence rate ratio 3·77, 95% CI 1·36–10·46, p=0·011). The change of AST and ALT concentrations in the paracetamol group was higher than in the placebo group (mean difference 12·43 U/L per day, 7·16–17·71, p<0·0001 for AST; 7·40 U/L per day, 4·00–10·80, p<0·0001 for ALT). Three participants in the paracetamol group had severe dengue: two had upper gastric haemorrhage and one had acute kidney injury. No patients died or had liver failure.

Interpretation Use of standard dose paracetamol in dengue infection increased the incidence of transaminase elevation, and also overall transaminase concentrations in the absence of a counterbalancing reduced fever or pain score.

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Introduction Dengue remains a growing public health problem in many tropical countries. Around 4 billion people are estimated to be at risk, resulting in about 100 000 annual deaths. Dengue is also one of the major causes of liver failure in tropical countries. Concentrations of aspartate transaminase (AST) and alanine transaminase (ALT) are associated with the severity of the disease. Severe acute hepatitis is linked to a prolonged length of stay in hospital, mortality, bleeding, and renal failure. Although it is well known that shock and subsequent ischaemic hepatitis could result in elevated AST and ALT concentrations, AST and ALT can be elevated for many days before the onset of shock. Indeed, elevated ALT during the febrile stage has been associated with subsequent shock.

Because the use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with platelet dysfunction and severe haemorrhage, guidelines developed by WHO recommend paracetamol for antipyretics. The guidelines recommend a dose of less than 4 g daily or no more frequent than every 6 h. Nevertheless, several observational studies have shown concerning evidence among dengue patients, mostly adults. A prospective study found that transaminase elevation was significantly associated with total paracetamol intake of more than 8 g.
Research in context

Evidence before this study
Paracetamol has been used for decades as the drug of choice for antipyretics in dengue. We searched PubMed for studies of paracetamol in dengue published between inception and Aug 31, 2016, using the terms “paracetamol” OR “acetaminophen” AND “dengue”. We did not restrict our search by date or language of publication. We selected articles that assessed paracetamol and liver injury in dengue. We reviewed 27 publications and identified three observational studies. Two studies reported an association between excessive intake of paracetamol and liver injury. The other study reported an association between previous paracetamol use within 24 h and transaminase elevation.

Added value of this study
This study is, to our knowledge, the first clinical trial assessing the safety or efficacy of paracetamol in dengue. We showed a lower incidence of transaminase elevation than related studies, but paracetamol still significantly increased the incidence of transaminase elevation, without a counterbalancing reduced fever or pain score. The median daily dose of paracetamol was only 1·5 g.

Implications of all the available evidence
Paracetamol should be prescribed with caution owing to the risk for liver toxicity. In patients with dengue who are using paracetamol, transaminase concentrations should be monitored. Additional studies with the primary objective of evaluating the efficacy of paracetamol are warranted to corroborate our findings of paracetamol inefficacy.

Figure 1: Trial profile

Another retrospective study also found that paracetamol dose of more than 60 mg/kg/day before admission was significantly associated with the occurrence of hepatitis. Both studies concluded that paracetamol doses should not exceed 3 g/day, less than that recommended by WHO. A retrospective study reported that one subgroup of patients reporting previous paracetamol intake within 24 h was significantly associated with transaminase elevation. By contrast, another study found that most patients who were given paracetamol had subsequent improvement in ALT. Therefore, whether the standard dose of paracetamol causes hepatic injury in dengue remains uncertain.

Although, to date, no study has evaluated the efficacy of paracetamol in treating dengue, numerous studies have been done in various other infectious diseases. A study among children with malaria found that paracetamol reduced total fever duration for 11 h, which was not statistically significant. Another study reported a slightly lower mean body temperature in the first afternoon after paracetamol intake, without reduced disease duration. Among patients with influenza, paracetamol did not affect viral shedding, fever reduction, or overall symptoms. A study done among critically ill patients found that paracetamol significantly reduced body temperature by 0·29°C within the first 2 days without reducing mortality or duration of stay in an intensive care unit.

To provide safety and efficacy data for the use of paracetamol in dengue infection, this study aimed to assess whether standard dose paracetamol as an antipyretic in dengue infection caused transaminase elevation, and to evaluate the efficacy of paracetamol.

Methods
Study design and participants
This study was a multicentre, prospective, parallel-group, randomised, double-blind, placebo-controlled trial. Patients were enrolled from three Royal Thai Army hospitals in Thailand: Phramongkutklao Hospital (1200 beds), Ananda Mahidol Hospital (321 beds), and Fort Adisorn Hospital (30 beds).

This study was implemented in accordance with Good Clinical Practice Guidelines after protocol approval by the
institutional review board of the Royal Thai Army Medical Department. The Research Unit at Phramongkutklao Hospital oversaw the safety of the trial. The data and safety monitoring board did a formal interim analysis after the enrolment of 50% and 75% of patients. The investigators and associated research personnel collected and maintained the data. The trial statisticians performed the final analyses.

Eligible patients were aged 18 years or older and admitted to any of the three hospitals with a clinical diagnosis of dengue infection, as confirmed by either positive NS1 antigen, positive dengue IgM antigen with thrombocytopenia, or positive PCR test. Exclusion criteria included baseline AST or ALT concentrations of more than 3 times the upper limit of normal, cirrhosis, indication of paracetamol other than dengue infection, concurrent diagnosis of other causes of fever (such as malaria or heat stroke), pregnancy, being unable to take either paracetamol or tramadol by mouth, critical illness needing intubation or admission to an intensive care unit, or being unable to communicate. Full exclusion criteria are given in the appendix. Written informed consent was obtained from all participants before enrolment.

The protocol (in Thai) is available in the appendix.

Randomisation and masking
Participants were randomly assigned (1:1) to receive either paracetamol or placebo. A computer-generated randomisation list was prepared by an independent statistician. The list was stratified by the centre and used a block size of six. Each centre received the indistinguishable 500-mg tablets packaged in sequentially numbered containers. After confirmation that the patient met all inclusion criteria, the next available randomisation number in the centre (in chronological order) was assigned. Participants, investigators, and the medical and nursing teams were unaware of the study group assignment. Interim analyses were done by statisticians masked to treatment allocation.

Procedures
The study medications, either paracetamol or placebo, were given as one 500 mg tablet no more frequent than every 4 h whenever the measured body temperature rose to 38·5°C or higher. The use of other treatments to reduce body temperature was restricted. Tramadol was given as a 50-mg capsule every 8 h whenever the patient reported a pain score of 6 out of 10 or above. This standard dose of tramadol has not been reported to cause liver injury.10 Intravenous fluid management was given according to WHO guidelines.9

AST and ALT concentrations were measured daily using a Cobas 6000 analyser (Roche Diagnostics, Mannheim, Germany) until the recovery day, defined as the day the participant was discharged from the hospital. Participants were discharged after the resolution of fever, an increased platelet count to a safe level, and approval of the attending physicians. Axillary body temperature was measured every 4 h. Pain intensity was assessed using a visual analogue pain scale ranging from 0 to 10 points at least daily and whenever the patients reported feeling pain.

Outcomes
The primary outcome was the proportion of patients with abnormal serum transaminase concentrations, defined as a combination of AST and ALT concentrations of more than 3 times the upper limit of normal on the recovery day, in the intention-to-treat population. This outcome

| Paracetamol (n=63) | Placebo (n=60) |
|--------------------|---------------|
| Sex                |               |
| Male               | 58 (92%)      | 48 (80%)      |
| Female             | 5 (8%)        | 12 (20%)      |
| Age, years         | 27·2 (10±4)   | 27·8 (10±7)   |
| Fever duration, days| 3·6 (2·9–4·6) | 3·5 (2·8–5·1) |
| Body temperature, °C| 37·8 (1·1)    | 37·7 (1·3)    |
| Bodyweight, kg     | 63·5 (55–70)  | 63·5 (55–70)  |
| Underlying diseases| 6 (10%)       | 4 (7%)        |
| Hypertension*      | 2 (3%)        | 2 (3%)        |
| Other†             | 4 (6%)        | 2 (3%)        |
| History of paracetamol| 63 (100%)    | 60 (100%)     |
| Site               |               |
| Phramongkutklao Hospital| 45 (71%)   | 48 (80%)      |
| Fort Adisorn Hospital | 12 (19%)   | 9 (15%)       |
| Ananda Mahidol Hospital | 6 (10%)   | 3 (5%)        |
| Baseline aspartate transaminase, U/L | 53·0 (40·0–72·8) | 62·6 (45·6–90·3) |
| Baseline alanine transaminase, U/L | 36·6 (24·0–50·0) | 37·0 (25·0–57·6) |
| Haematocrit, %     | 43·8 (41·6–45·8) | 44·0 (40·4–45·9) |
| Leucocyte, ×10³/μL | 4·4 (3·6–5·4)  | 4·6 (3·7–5·6)  |
| Platelet, ×10³/μL  | 0·73 (0·46–1·15) | 0·71 (0·50–0·95) |
| Haemococoncentration‡ | 2 (3%)    | 4 (7%)        |
| Thrombocytopenia    | 32 (51%)      | 36 (60%)      |
| Dengue shock        | 0             | 0             |

| Data are n (%), mean (SD), or median (IQR). *Two participants had coexisting conditions: diabetes (n=1) and chronic obstructive disease and bladder cancer (n=1). †Other underlying diseases were hypothyroidism, asthma, dilated cardiomyopathy and cerebrovascular disease, coronary heart disease, and B-cell lymphoma (all n=1). ‡Increase in haematocrit of more than 20% on the recovery day. |

See Online for appendix

Table 1: Baseline characteristics
was analysed in prespecified subgroups based on study sites and the number of study medications used.

Secondary outcomes, assessed in the intention-to-treat population, were overall serum transaminase concentrations on the recovery day and efficacy of paracetamol, consisting of mean and maximum body temperature, duration of fever, in-hospital length of stay, number of study medication used, number of tramadol used, and mean and maximum pain score.

Safety outcomes were severe dengue parameters (as defined by WHO guidelines) and mortality, assessed in the safety population (ie, all patients who received at least one dose of study treatment), as treated.

**Statistical analysis**

The primary null hypothesis was that the placebo would have the same rate of transaminase elevation as did paracetamol. Data from a meta-analysis found abnormal transaminase concentrations in 53% of patients with dengue. This trial was designed as a superiority trial with 75% power to detect a 20 percentage point absolute difference in abnormality rates (eg, 53% vs 33%) between the two study groups, with a two-sided alpha level of 0.05. 164 participants were required (82 per group). Sample size calculations are provided in detail in the appendix.

All primary and secondary analyses were done on an intention-to-treat basis while masking study group assignments. An additional post-hoc analysis was done in the per-protocol population and in prespecified subgroups of patients, based on the number of study medications used and study sites.

Data were collected using case record forms. Photocopies of the forms were sent by e-mail and transferred to an Excel spreadsheet. Validated data were transferred to STATA software (version 13.0; StataCorp, College Station, TX, USA) for statistical analyses.

Comparisons between the groups were done with Pearson’s χ² test or Fisher’s exact test, as appropriate for proportions, and with Student’s t test or Mann-Whitney U test, as appropriate for continuous outcomes. We used the generalised estimating equation for global tests of repeated measures to examine the association of the primary outcome and selected secondary outcomes (ie, transaminase elevation, transaminase concentrations, body temperature, and pain score) with treatment groups and days. The proportions were compared using generalised estimating equation for clustered data, and mean changes were compared using generalised estimating equation for progressive change. Interim analyses for safety and efficacy were done once 50% and 75% of the data were collected (ie, after the 123rd [75%] participant was discharged from the hospital). These analyses were done by an independent statistician from an independent data and safety monitoring board with group sequential stopping boundaries defined with the use of a Lan-DeMets spending function with O’Brien-Fleming monitoring boundary. The trial would not be stopped in case of futility, p values of 0.003, 0.016, and 0.031 or lower were considered to indicate statistical significance in the first, second, and final analyses, respectively. Findings from the trial were described in accordance with CONSORT guidelines. All statistical analyses were done with STATA software (version 13.0). The point estimates were naive (ie, without adjustment for bias in the interim analyses). All p values were two tailed without adjustment for the stopping rule, except for the primary outcome.

This trial is registered with ClinicalTrials.gov, number NCT02833584.

**Role of the funding source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

Between Sept 1, 2016, and Dec 12, 2017, we enrolled 125 participants, 63 of whom were assigned to paracetamol and 62 to placebo (Figure 1). On Nov 27, 2017, the second interim analysis was done by the independent data monitoring committee. Given that one group (paracetamol)
had a significantly higher rate of transaminase elevation than did the other group (placebo), the committee recommended stopping the trial (appendix). The trial was stopped on Dec 12, 2017.

Of the 125 participants enrolled, two were excluded owing to inclusion mistakes: one participant had no laboratory confirmation of dengue and another had high baseline AST and ALT concentrations (figure 1). These two patients were not given any study medication and were withdrawn from the trial within the second day after enrolment. 123 participants were included in the intention-to-treat analysis, including two participants who were given open-labelled paracetamol instead of study medications (ie, instead of placebo, as assigned). The mean age was 27·5 years (SD 10·5), 106 (86%) of 123 participants were men, and 112 (91%) participants had a positive NS1 antigen test. The baseline characteristics of the two groups did not differ (table 1). 35 (28%) of 123 participants were randomly allocated to treatment but were not treated owing to the resolution of fever. 86 participants were given study medications and included in the per-protocol analysis.

The mean change in AST concentrations on each day from baseline in the paracetamol group was higher than in the placebo group (mean difference 12·43 U/L per day, 95% CI 10·5–14·3, p<0·001), as was the mean change in ALT concentrations (7·40 U/L per day, 5·6–9·2, p<0·001; figure 2). On recovery day, transaminase elevation in the paracetamol group was higher than the placebo group (risk ratio [RR] 5·24, 95% CI 2·21–12·60, p=0·016; table 2). The cumulative proportion of participants with transaminase elevation were 22% in the paracetamol group and 10% in the placebo group (p=0·066). The number of patients needed to be treated with paracetamol to cause one abnormal transaminase elevation with an incidence rate ratio of 3·77 (1·36–10·46, p=0·011).

In our per-protocol analysis, transaminase elevation on recovery day in the paracetamol group was also higher than in the placebo group (RR 8·7–10, 1·16–65·0, p=0·009; appendix). The cumulative incidence of transaminase elevation was 26% in the paracetamol group and 8% for the placebo group (p=0·044; appendix). Between the two groups, the mean difference was 13·56 U/L per day (7·47–19·64, p=0·001) for AST and 10·5–14·3 U/L per day (4·05–12·54, p=0·001) for ALT, with a significantly higher rate of transaminase elevation incidence rate ratio of 3·17 (1·52–6·43, p=0·008) for 9–20 tablets of paracetamol used (incidence rate ratios vs placebo: 4·46 [1·24–15·98], p=0·022 for 4–8 tablets and 4·84 [1·52–15·39], p=0·008) for 9–20 tablets; appendix).

| Table 2: Incidence of transaminase elevation (intention-to-treat population) |
|-----------------------------|-----------------------------|-----------------------------|
| Paracetamol (n=63) | Placebo (n=60) | Risk ratio (95% CI) | p value |
| Primary outcome | Incidence rate ratio | 3·77 (1·36–10·46) | 0·011 |
| Secondary outcomes | Cumulative incidence | 14 (22%) | 6 (10%) | 2·22 (0·91–5·40) | 0·066 |
| 6 days before recovery | 0 | 0 | Insufficient sample | NA |
| 5 days before recovery | 0 | 0 | Insufficient sample | NA |
| 4 days before recovery | 0 | 1 (3%) | Insufficient sample | NA |
| 3 days before recovery | 1 (2%) | 3 (6%) | 0·31 (0·04–3·10) | 0·617 |
| 2 days before recovery | 6 (10%) | 3 (5%) | 1·90 (0·50–7·26) | 0·492 |
| 1 day before recovery | 10 (16%) | 3 (5%) | 3·17 (0·92–10·39) | 0·076 |
| Recovery day | 11 (12%) | 2 (3%) | 5·24 (1·21–22·66) | 0·016 |

Data are n (%) unless otherwise indicated. NA=not applicable.

Table 3: Efficacy analyses (intention-to-treat population)
Heterogeneity of the effect of paracetamol was not detected in subgroups according to the study sites (appendix).

Discussion
In this multicentre, randomised controlled trial, the use of paracetamol in patients with dengue significantly increased the incidence of transaminase elevation. Paracetamol intake did not affect body temperature, pain score, analgesic intake, length of stay, or duration of fever. More significant effects of transaminase elevations were also found in the per-protocol analysis, which disregarded those who did not receive study medication.

Our findings are consistent with those of related observational studies reporting an association between excessive paracetamol intake and transaminase elevation in dengue. However, in our study, even standard dose paracetamol caused transaminase elevation. The trend of increased transaminase concentrations was observed even when 4–8 tablets of paracetamol were used. This finding is consistent with numerous case reports of fulminant hepatic failure, wherein most patients reported paracetamol ingestion at a dose within the therapeutic range recommended by the US Food and Drug Administration. This effect could be explained by the downregulation of major cytochrome P-450 enzymes through pro-inflammatory cytokines found in viral induced hepatitis, resulting in altered paracetamol metabolism. However, toxic products of paracetamol are also created by these enzymes and whether the risk of liver toxicity is increased by the accumulation of paracetamol in hepatitis remains unknown.

The proportion of patients with transaminase elevation in our study was lower than expected. Only 22% of patients in the paracetamol group had transaminase concentrations of more than 3 times the upper limit of normal, compared with 41% in a related observational study. A meta-analysis also reported abnormal ALT in 53% of patients with dengue haemorrhagic fever. The lower rate of transaminase elevation in our study might be explained by several reasons. First, most participants in our study were previously healthy young men, which was reported in a related study to be a significant protective factor for liver damage in dengue. Second, 29 (18%) of 163 eligible patients with transaminase elevation at baseline were excluded. Third, our strict protocol of monitoring transaminase concentrations daily and the discontinuation of study medications in the case of transaminase elevation is not routine in everyday practice. This difference prohibited the inappropriate use of paracetamol in the case of asymptomatic transaminase elevation, which was hardly monitored in related studies. Finally, higher paracetamol doses were reported in several related observational studies than in the present study. The median daily dose in this study was only 1.5 g/day (IQR 0.8–2.0), whereas as high as 4 g/day was prescribed in one related study.

Although our study was not powered to assess the efficacy of paracetamol, daily mean and maximum body temperatures did not differ between the two groups. The inefficacy of paracetamol was consistent with what has been shown in various infections, such as malaria and influenza. A meta-analysis from the Cochrane Review also concluded that paracetamol had no clear benefit in reducing fever among paediatric patients. This inefficacy might be explained by the masking effect of the tepid sponge allowed in the present trial, although the differences in the number of times that the tepid sponge was used were not significant. Tramadol, which was also allowed in our trial owing to ethical considerations, might also explain the inefficacy of paracetamol in reducing pain. More studies with the primary objective of evaluating the efficacy of paracetamol are needed.

Our trial has several limitations. First, most participants were young men without previous underlying diseases. Nevertheless, this factor helped to confirm the effect of paracetamol on the liver because paracetamol-associated acute liver failure was previously found to be more common among older, female patients. Second, all participants in our study reported a previous history of paracetamol intake, representing the real-world setting where paracetamol is commonly used by patients with dengue. The previous dose of paracetamol ingestion reported by the participants was not recorded because of the unreliability of such recall. However, baseline transaminase concentrations did not differ between groups, helping to decrease the possible effect of previous paracetamol intake on the liver, if it occurred. Third, despite the fact that dengue infection is usually treated in outpatient settings, only patients who were currently admitted to hospital were included in this study to allow for close monitoring and to avoid the effect of over-the-counter paracetamol. This inclusion might limit the generalisability of our findings in outpatient settings, in which the tepid sponge might not be used as comfortably and frequently as in wards. Fourth, although dengue commonly infects paediatric patients, this population was not included in this study.
The results should not be extrapolated to this age group. Finally, despite the significant differences in surrogate markers of transaminase concentrations, no clinical difference in hepatic failure was seen in this study. Given the 5% prevalence of acute liver failure among patients with dengue experiencing transaminase elevation, and the 22% prevalence of transaminase elevation in this study, 2920 participants would need to be assessed to achieve significant results on liver failure.

In summary, using the recommended dose of paracetamol in dengue infection increased the incidence of transaminase elevation, and overall transaminase concentrations in the absence of a counterbalancing reduction in fever or pain score. Paracetamol should be prescribed with great caution, owing to the risk of liver toxicity.

**Contributors**

VV designed and led the study and wrote the first draft of the report. VV, SN, and WC were the principal investigators of the study and the internal medicine residents and fellows at the trial sites for their support with protocol development; Picha Suwannahitatorn for Ram Rangsin, and Infectious Disease Association of Thailand for Thailand. The study medications were supplied by the Defence Physicians of Thailand Conference, April 26−28, 2018 in Pattaya.

We declare no competing interests.

**Declaration of interests**

DC coordinated trial activities. All authors critically reviewed and approved the final version.

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